Soutien scientifique au Collège d'Oncologie: mise à jour des recommandations de bonne pratique pour la prise en charge du cancer du sein

KCE reports 143B

Centre fédéral d'expertise des soins de santé
Federaal Kenniscentrum voor de Gezondheidszorg
2010

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Comment citer ce rapport?

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Modifications		Impact		
		On the results of the research	*On the conclusion of the scientific report*	*On the recommendations of the report*
Chapter 2.3.3	A regular update of the full guideline takes a lot of time and is not cost-effective. Therefore, the decision was made to regularly update specific parts of the guideline based on alert messages given by the members of the GDG. In October 2011, members of the GDG proposed to update the thresholds adopted for systemic treatment modalities (endocrine therapy, anti-HER2 therapy and chemotherapy).	No	No	No
Chapter 2.8	As part of the standard KCE procedures, an external scientific validation of the report was conducted by three independent experts. This validation was done in September 2010 (first edition) and in December 2011 (second edition).	No	No	No
Chapter 3.5.4.3	The 12th St Gallen International Breast Cancer Conference (2011) Expert Panel adopted a new approach for the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes within the breast cancer spectrum. The systemic treatment recommendations mainly recommend endocrine therapy alone for patients with clinicopathologically classified 'Luminal A' disease (except in defined high-risk cases), chemoendocrine therapy for 'Luminal B', the addition of anti-HER2 therapy in the presence of 'HER2 positivity', and a reliance on chemotherapy for most patients with 'Triple negative' disease (e.g. those with invasive ductal carcinoma)	No	No	No

PRÉFACE

En publiant des recommandations de bonne pratique en matière de diagnostic et de traitement du cancer du sein en 2007, nous soulignions l'importance de la mise à jour régulière de celles-ci, tant il est vrai que la littérature scientifique et la pratique médicale évoluent de manière rapide, et que le cancer du sein continue à toucher un grand nombre de femmes.

Le KCE tient donc ses promesses et revoit aujourd'hui ses recommandations en matière de prise en charge du cancer du sein sur base de tout ce qui est paru depuis 2007 et, comme toujours, après avoir évalué soigneusement ces nouvelles données scientifiques et avoir discuté en réunion multidisciplinaire ce qu'il fallait en retirer comme nouvelles lignes de conduite en pratique clinique.

Ce rapport en annonce un autre, également prévu depuis 2007 et qui présentera des indicateurs permettant d'évaluer dans quelle mesure ces recommandations sont suivies et si elles conduisent à améliorer la qualité des soins, ce qui est finalement le but de ce travail. Ce rapport ne se prononce pas sur le rapport coût-efficacité des innovations qui apparaissent dans cette recommandation, ni sur le caractère justifié ou non de leur éventuel remboursement. Cela représente en soi un travail complémentaire, qui ne fait habituellement pas partie d'une recommandation de bonne pratique.

Cette entreprise de longue haleine a demandé la participation et la collaboration de nombreux spécialistes de la littérature scientifique et de la pratique clinique. Nous les en remercions chaleureusement. Comme par le passé, le Collège d'Oncologie a également contribué au rapport depuis sa conception et contribuera à sa diffusion, notamment à travers son site web. Nous sommes certains que ces efforts coordonnés se traduiront par une amélioration de la qualité de vie de toutes les femmes qui sont affectées par cette pénible maladie.

Jean Pierre CLOSON
Directeur général adjoint

Raf MERTENS
Directeur général

Résumé

INTRODUCTION

Le présent document est une mise à jour de la recommandation de bonne pratique clinique (RBP) sur le cancer du sein, publiée en 2007. Il couvre un vaste éventail de thèmes allant du diagnostic au suivi. La recommandation concerne essentiellement les femmes souffrant d'un cancer du sein invasif à un stade précoce ou avancé. Les hommes souffrant d'un cancer du sein ne sont pas inclus dans cette recommandation. Le dépistage de la population ne fait pas partie du champ d'application de la présente RBP mais sera étudié de manière exhaustive dans un rapport futur, de même que la surveillance et le traitement des femmes exposées à un risque accru de cancer du sein en raison d'antécédents familiaux.

Toutes les recommandations se fondent sur l'efficacité clinique en tenant compte des préférences et de la qualité de vie des patientes; aucune analyse du rapport coût-efficacité n'a été réalisée. Cette recommandation a pour vocation d'être utilisée par tous les prestataires de soins impliqués dans la prise en charge des patientes atteintes de ce cancer.

MÉTHODOLOGIE

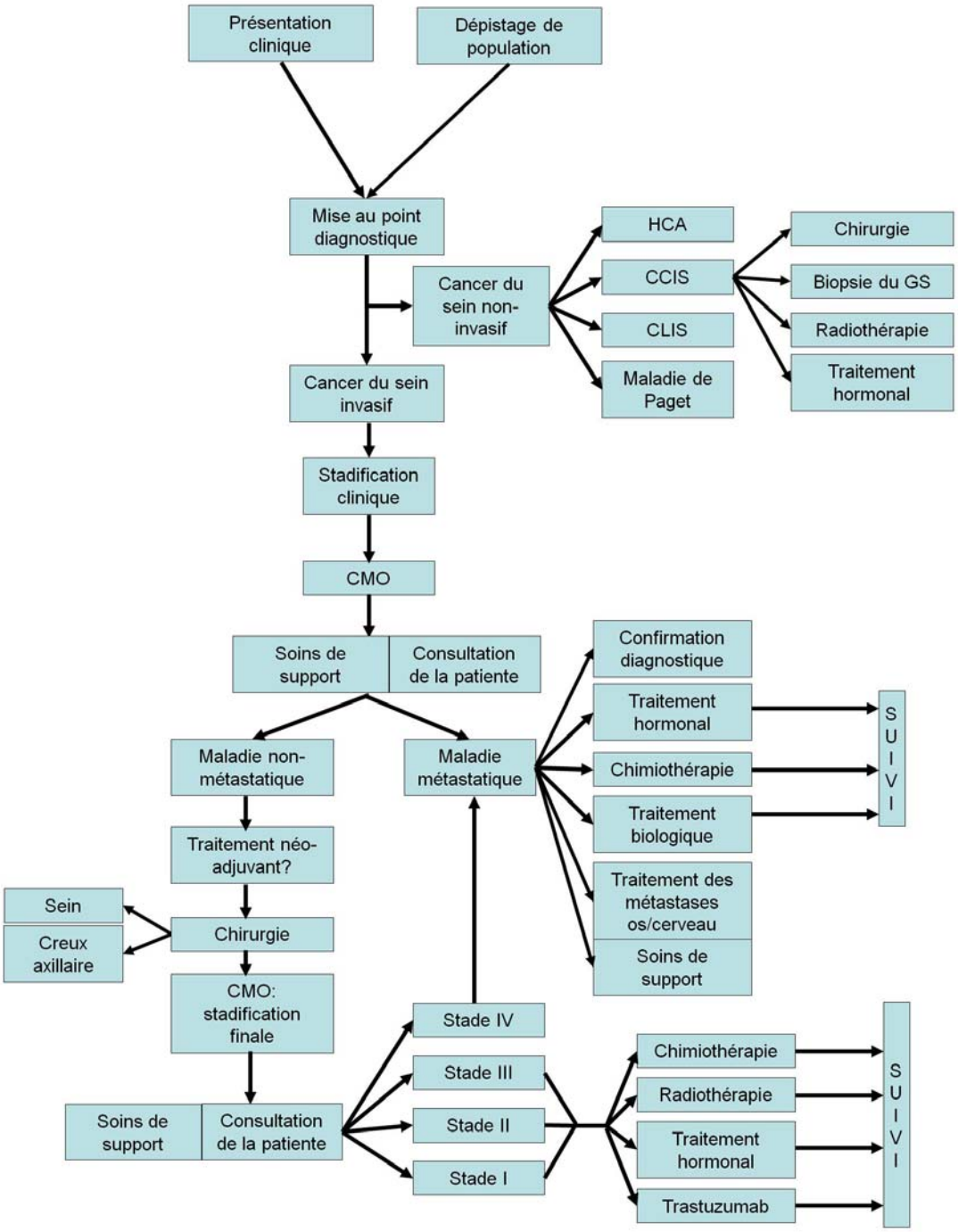
Le Groupe de Développement des Recommandations pour le cancer du sein a suivi une procédure méthodique pour l'élaboration des recommandations, en appliquant la méthodologie ADAPTE. Dans un premier temps, les questions cliniques centrales ont été formulées avec l'aide de cliniciens. Ensuite, nous avons recherché les recommandations (inter)nationales existantes dans Medline, Embase, le National Guideline Clearinghouse, les sites internet d'organisations d'élaboration de recommandations et les sites internet d'organisations en oncologie. Les 47 recommandations retenues ont été évaluées en termes de qualité par deux examinateurs indépendants en utilisant l'instrument AGREE. Ces recommandations ont été sélectionnées en se fondant sur leur qualité globale. Ensuite, pour chaque question clinique, les 20 recommandations sélectionnées ont été mises à jour avec les preuves complémentaires identifiées dans Medline, la Cochrane Database of Systematic Reviews et la Database of Abstracts of Reviews of Effects (DARE). Un niveau de preuve a été attribué à chaque recommandation initiale et à chaque étude complémentaire en utilisant le système GRADE. Toutes les recherches de littérature ont été conduites entre mars et décembre 2009, et mises à jour en janvier 2010.

Sur la base des preuves obtenues, les recommandations finales ont été élaborées par un groupe multidisciplinaire (i.e. les auteurs du présent document). Une révision de ces recommandations a été réalisée par des experts extérieurs en utilisant une procédure officielle. Les conflits d'intérêt ont été actés.

RECOMMANDATIONS FINALES[a]

Vous trouverez les détails des recommandations dans le rapport scientifique qui suit le présent résumé. Toutes les recommandations figurent sous les titres et sous-titres correspondant à des chapitres et sections spécifiques de chaque chapitre. Ci-dessous, l'algorithme général est présenté.

ALGORITHME GÉNÉRAL



Note HCA : hyperplasie lobulaire atypique ; CCIS : carcinome canalaire in situ ; CLIS : carcinome lobulaire in situ ; GS : ganglion sentinelle ; CMO : consultation multidisciplinaire en oncologie

a Le KCE reste seul responsable des recommandations faites aux autorités publiques

DIAGNOSTIC DU CANCER DU SEIN

Triple évaluation

Recommandations	Niveau de preuve
Toutes les patientes doivent subir un examen clinique.	1C
En présence d'une anomalie localisée, les patientes doivent subir une mammographie et/ou une échographie suivie d'une biopsie et/ou d'une ponction cytologique à l'aiguille fine.	1C
Dans les cas où l'examen clinique et l'imagerie sont pathognomoniques (BIRADS 2) d'une lésion bénigne (autrement dit, un kyste), la biopsie/cytologie n'est pas obligatoire.	Avis d'expert
Une lésion considérée comme maligne après l'examen clinique, l'imagerie ou la cytologie seule doit, lorsque c'est possible, obtenir une confirmation histopathologique de la malignité avant toute procédure chirurgicale.	1C
Une mammographie à double vue doit être réalisée dans le cadre de la triple évaluation (évaluation clinique, imagerie et prélèvement tissulaire) dans un service spécialisé en imagerie du sein.	1C
Comme pour les femmes plus âgées, les jeunes femmes présentant des symptômes mammaires et une forte suspicion de cancer du sein doivent être évaluées au moyen de la triple évaluation pour exclure ou poser un diagnostic de cancer.	1C

Imagerie par résonance magnétique (IRM)

Recommandations	Niveau de preuve
Les preuves sont insuffisantes pour utiliser l'IRM en routine pour le diagnostic du cancer du sein. L'IRM peut être envisagée dans des situations cliniques spécifiques lorsque les autres modalités d'imagerie ne sont pas fiables ou se sont révélées peu concluantes, ou si des indications montrent que l'IRM est utile (cancer du sein cliniquement palpable et occulte à la mammographie, patientes au stade clinique cT0N+, cancers associés à une mutation d'un gène BRCA, diagnostic de récidive).	1C
Aux fins d'une caractérisation définitive des lésions mammaires, l'IRM ne peut pas remplacer la biopsie.	1B

Scintimammographie 99mTc-MIBI (SMM)

Recommandation	Niveau de preuve
Les preuves sont insuffisantes pour utiliser en routine la scintimammographie 99mTc-MIBI aux fins du diagnostic et de la stadification du cancer du sein. La scintimammographie 99mTc-MIBI peut être envisagée dans des situations cliniques spécifiques, lorsque les autres modalités d'imagerie ne sont pas fiables ou se sont révélées peu concluantes, et si des indications montrent que la scintimammographie 99m Tc-MIBI est utile.	1C

La tomographie par émission de positrons (PET Scan)

Recommandation	Niveau de preuve
Le PET scan est insuffisamment précis pour être recommandé dans le diagnostic du cancer du sein comme une alternative à la biopsie.	1B

Evaluation des récepteurs hormonaux

Recommandations	Niveau de preuve
Les récepteurs d'œstrogène et les récepteurs de progestérone (ER/PgR) doivent être évalués pour tous les carcinomes canalaires in situ (CCIS) et les cancers du sein primitifs invasifs.	1B
L'expression de la protéine HER2 confirmée par l'amplification génique si elle est positive devrait, si cela est possible, être évaluée dans tout cancer du sein primitif invasif, au moment du diagnostic et au moment de la récidive.	1B

Marqueurs tumoraux

Recommandation	Niveau de preuve
Il n'existe pas de preuves de qualité suffisante pour inclure les marqueurs tumoraux (les cellules tumorales circulantes [CTC], CA 15-3, CA 27.29, ACE et Cathepsin D) dans l'élaboration du diagnostic du cancer du sein primitif.	2C

STADIFICATION DU CANCER DU SEIN

Tests de stadification en routine

Recommandations	Niveau de preuve
L'utilisation du scanner osseux, de l'échographie du foie et de la radiographie du thorax chez les femmes présentant un cancer du sein de stade I ne contribue guère au traitement et ne peut être recommandée en routine.	2C
Chez les patientes asymptomatiques atteintes d'un CCIS, le scanner osseux, l'échographie du foie et la radiographie du thorax en routine ne sont pas indiqués dans la stadification de base.	2C

Imagerie par résonance magnétique (IRM)

Recommandations	Niveau de preuve
L'utilisation en routine de l'IRM mammaire n'est pas recommandée dans le cadre de l'évaluation préopératoire des patientes dont la biopsie a prouvé qu'elles étaient atteintes d'un cancer du sein invasif ou d'un CCIS, sauf dans les situations suivantes :	1C
• S'il existe une différence à propos de l'étendue de la maladie sur la base de l'examen clinique, de la mammographie et de l'échographie pour la planification du traitement ;	2C
• En cas de carcinome lobulaire invasif ;	1C
• Dans les cas où, en raison de la densité mammaire, l'examen mammographique ne permet par d'exclure une maladie multicentrique et bilatérale.	2C
Pour la stadification M (métastases osseuses ou viscérales), une IRM/CT peut être envisagée.	2C

Echographie axillaire

Recommandation	Niveau de preuve
L'échographie axillaire avec ponction cytologique à l'aiguille fine des ganglions lymphatiques axillaires dont on soupçonne une malignité est recommandée.	2C

La tomographie par émission de positrons (PET scan)

Recommandations	Niveau de preuve
Le recours au PET scan dans la stadification des ganglions lymphatiques axillaires pour le cancer du sein n'est pas recommandé. La sensibilité du PETscan est inférieure à celle du curage axillaire et de la biopsie du ganglion sentinelle.	1B
Le PET scan peut être utile aux fins de l'évaluation de la maladie métastatique dans les tumeurs du sein localement avancées avec une chance élevée de maladie (micro- ou macro) métastatique.	Avis d'expert
L'utilité du PET scan pour la détection des métastases osseuses étant peu concluante, le scanner osseux reste la technique à privilégier.	2C

TRAITEMENT DES TUMEURS MAMMAIRES NON INVASIVES

Lésions précurseurs et lésions à haut risque

Recommandations	Niveau de preuve
La prise en charge de lésions précurseurs est de préférence débattue dans un contexte multidisciplinaire.	Avis d'expert
Face à une hyperplasie lobulaire atypique ou à une métaplasie cylindrique atypique (MCA) à proximité des marges d'un spécimen d'exérèse, une nouvelle résection n'est pas nécessaire.	Avis d'expert
Lorsque le carcinome lobulaire in situ ou l'hyperplasie canalaire atypique est présent dans les marges d'exérèse, une nouvelle exérèse n'est pas recommandée.	Avis d'expert
Lorsque l'on découvre dans une biopsie une hyperplasie lobulaire atypique/ un carcinome lobulaire in situ, une métaplasie cylindrique atypique ou une prolifération intracanalaire atypique - réminiscence d'une hyperplasie canalaire atypique-, l'exérèse diagnostique est recommandée.	Avis d'expert
Lorsque l'on découvre dans une biopsie, un carcinome lobulaire in situ pléomorphe ou un carcinome lobulaire in situ avec comédonécrose, une exérèse totale avec marges saines est recommandée, et le traitement antihormonal et/ou la radiothérapie représente(nt) également une option.	Avis d'expert
Une mammographie annuelle de suivi est indiquée après un diagnostic de carcinome lobulaire in situ ou d'hyperplasie canalaire atypique.	2C

Carcinome canalaire in situ

Chirurgie

Recommandations	Niveau de preuve
Les patientes présentant un CCIS mammaire de haut grade de malignité et/ou palpable et/ou de grande envergure qui sont candidates pour une chirurgie mammaire conservatrice doivent se voir proposer le choix entre une exérèse locale large ou une mastectomie, après une information correcte. En cas de tumeur multicentrique, une exérèse locale large n'est pas recommandée.	1B
Chez les femmes atteintes d'un CCIS, la mastectomie, avec ou sans reconstruction immédiate, reste une option acceptable pour les patientes désireuses d'optimaliser le contrôle local ou d'éviter la radiothérapie.	1B
Les techniques de réparation oncoplastiques doivent être proposées aux patientes traitées par chirurgie mammaire conservatrice dans le but d'optimiser les résultats esthétiques.	1C
La reconstruction mammaire immédiate doit être discutée avec toutes les patientes auxquelles on recommande une mastectomie, à l'exception des cas où des comorbidités importantes excluent cette option.	1C
Lorsqu'une exérèse locale large est pratiquée chez les femmes atteintes d'un CCIS, une marge d'exérèse radiale minimale de 2 mm est habituellement recommandée, avec examen pathologique.	1C
Le curage axillaire n'est pas recommandé chez les patientes atteintes d'un CCIS.	1C

La biopsie du ganglion sentinelle

Recommandations	**Niveau de preuve**
La biopsie du ganglion sentinelle n'est pas recommandée chez les patientes avec un diagnostic préopératoire de CCIS ayant opté pour une chirurgie mammaire conservatrice, sauf si elles sont considérées à haut risque de maladie infiltrante. Le groupe de patientes à haut risque comprend celles qui présentent une masse palpable ou des micro-calcifications étendues.	1B
Des données sont disponibles pour appuyer le recours à la biopsie du ganglion sentinelle dans le CCIS de haut grade de malignité, dans le cas où une mastectomie avec ou sans reconstruction immédiate est prévue. L'âge, le sexe ou l'obésité ne constituent pas des critères d'exclusion pour la biopsie du ganglion sentinelle.	1A

Radiothérapie

Recommandation	**Niveau de preuve**
Après une chirurgie conservatrice du CCIS, on peut envisager de faire l'impasse sur la radiothérapie lorsque le risque de récidive locale est considéré comme très faible et après une discussion avec l'équipe multidisciplinaire.	1A

L'hormonothérapie

Recommandation	**Niveau de preuve**
Le traitement hormonal adjuvant est recommandé chez les patientes souffrant de CCIS avec récepteurs de l'œstrogène positifs.	1A

Maladie de Paget

Recommandations	**Niveau de preuve**
La chirurgie mammaire conservatrice avec excision du complexe aréole-mamelon suivie d'une radiothérapie devrait être proposée au lieu de la mastectomie aux patientes présentant une Maladie de Paget sans cancer du sein invasif sous-jacent.	2C
Les techniques de réparation oncoplastiques doivent être proposées aux patientes souffrant de maladie de Paget qui sont traitées par chirurgie mammaire conservatrice, dans le but d'optimiser les résultats esthétiques.	1C

Cancer du sein invasif précoce

Recommandation	**Niveau de preuve**
Le cas de toutes les patientes atteintes d'un cancer du sein doit être débattu au sein d'une équipe multidisciplinaire, et ce avant tout traitement.	Avis d'expert

Traitement néo-adjuvant

Recommandation	**Niveau de preuve**
Chez les patientes présentant des tumeurs unifocales opérables de trop grande taille pour proposer une chirurgie mammaire conservatrice, une régression du volume de la tumeur avec un traitement systémique néo-adjuvant peut être envisagée.	1A

Chirurgie mammaire

Recommandations	**Niveau de preuve**
La chirurgie mammaire conservatrice suivie d'une radiothérapie offre les mêmes avantages en termes de survie que la mastectomie radicale modifiée chez les femmes atteintes d'un cancer du sein au stade I ou II qui sont candidates pour la chirurgie mammaire conservatrice.	1A
Les techniques de réparation oncoplastiques doivent être proposées aux patientes qui sont traitées par chirurgie mammaire conservatrice, dans le but d'optimiser les résultats esthétiques.	1C
La reconstruction mammaire immédiate après une mastectomie offre les mêmes avantages en termes de survie que la mastectomie sans reconstruction.	1C
Le choix de la chirurgie doit être personnalisé pour chaque patiente souffrant d'un cancer du sein au stade I ou II qui doit être pleinement informée de toutes les options chirurgicales.	1A

Chirurgie axillaire

Recommandations	**Niveau de preuve**
La biopsie du ganglion sentinelle n'est pas recommandée en cas de: 1. cancer du sein invasif T2 étendu (c.à.d. > 3 cm) ou T3-4; 2. cancer du sein inflammatoire; 3. présence de ganglions lymphatiques axillaires suspects palpables; 4. présence de tumeurs multiples ; et de troubles potentiels du drainage lymphatique après une chirurgie axillaire récente ou une large béance causée par la biopsie après exérèse de la tumeur.	1A
Chez les femmes atteintes d'un cancer du sein primitif de moins de 3 cm et dont les ganglions sont négatifs aux examens cliniques et échographiques, une biopsie du ganglion sentinelle doit être pratiquée.	1A
Un examen pathologique péri-opératoire du ganglion sentinelle est recommandé. En cas de macrométastases (>2 mm), une dissection du ganglion axillaire de niveau I et II est indiquée. En cas de micrométastases (0.2-2 mm), la dissection axillaire est recommandée jusqu'à ce que l'on dispose des résultats finaux des essais cliniques prospectifs en cours, même si, selon certains experts, cette décision devrait également tenir compte d'autres facteurs de risque (par exemple, l'utilisation en tant que nomogramme).	1A Avis d'expert
Si la biopsie du ganglion sentinelle est impossible, une dissection du ganglion axillaire de niveau I et II est indiquée.	1A
Il ne faut pas proposer de traitement axillaire ultérieur aux patientes ne présentant que des cellules tumorales isolées dans leurs ganglions sentinelles.	1C

Thérapie adjuvante

Recommandations	**Niveau de preuve**
Si la chimiothérapie et la radiothérapie adjuvantes sont indiquées, la chimiothérapie devrait être administrée d'abord.	1A
Il est recommandé de débuter la chimiothérapie ou la radiothérapie adjuvante dans les 8 semaines qui suivent la chirurgie.	1C

Radiothérapie

Recommandations	**Niveau de preuve**
Chez les patientes présentant un cancer du sein précoce, l'irradiation adjuvante est indiquée après une chirurgie mammaire conservatrice.	1A
La radiothérapie adjuvante de la paroi de la cage thoracique après une mastectomie doit être proposée aux patientes souffrant de cancer du sein précoce invasif et à risque élevé de récidive locale, incluant quatre ganglions lymphatiques axillaires positifs ou plus, ou avec des marges d'exérèse positives.	1A
Jusqu'à ce que les données provenant d'un essai randomisé de grande envergure, actuellement en cours, soient disponibles, la radiothérapie après une mastectomie doit être proposée aux patientes présentant 1-3 ganglions positifs.	1A
Une irradiation de la chaîne mammaire interne doit être discutée avec l'équipe multidisciplinaire.	Avis d'expert
Le volume cible de la radiothérapie adjuvante percutanée est déterminé pour l'ensemble du sein et de la paroi thoracique adjacente. La dose est d'approximativement 50 Gray, fractionnés de la manière traditionnelle (1.8-2.0 Gray) avec un complément d'irradiation localisé (ou boost) dans le lit tumoral.	1A
Un complément d'irradiation localisé (ou boost) dans le lit tumoral peut être proposé aux patientes souffrant d'un cancer du sein précoce invasif et à risque élevé de récidive locale, après une chirurgie mammaire conservatrice avec des marges d'exérèse saines et une radiothérapie de tout le sein.	2A
La radiothérapie axillaire doit être discutée au cas par cas avec l'équipe multidisciplinaire.	1A

Traitement systémique

Recommandation	**Niveau de preuve**
Le choix du traitement systémique adjuvant du cancer du sein invasif doit être fonction de la sensibilité hormonale, du profil de risque de la tumeur, de l'âge de la patiente, de son statut ménopausique et de ses comorbidités.	1A

Chimiothérapie

Recommandations	**Niveau de preuve**
Chez les patientes souffrant d'un cancer du sein au stade I-III, les régimes de prédilection sont ceux à base d'anthracyclines, avec ou sans taxanes.	1A
Chez les patientes souffrant de cancer du sein à ganglion lymphatique positif, les régimes de prédilection sont les régimes standards à base d'anthracyclines et de taxanes.	2A
Chez les patientes souffrant de cancer du sein HER-2 positif qui reçoivent du trastuzumab, un régime séquentiel à base d'anthracyclines et de taxanes est recommandé dans le but de diminuer la dose totale d'anthracyclines et, partant, de réduire la cardiotoxicité.	Avis d'expert
Les patientes qui reçoivent un régime adjuvant de type anthracycline–taxane doivent faire l'objet d'une surveillance rapprochée pour la neutropénie fébrile. - Un traitement prophylactique primaire par G-CSF (facteurs de croissance granulocytaire) est préconisé si le risque de neutropénie fébrile est supérieur ou égal à 20%. - Une prophylaxie secondaire avec le CSF (facteurs de croissance hématopoïétique), est recommandée chez les patientes ayant eu une complication neutropénique lors d'un précédent cycle de chimiothérapie.	1A
Chez les patientes présentant un cancer du sein, une chimiothérapie hautement dosée avec transplantation de cellules souches ne peut pas être recommandée.	1A
Chez toutes les femmes en âge de procréer, les problèmes liés à la fertilité doivent toujours être débattus avant l'instauration d'un traitement anticancéreux.	1C
La chimiothérapie durant la grossesse n'est pas contre-indiquée après 14 semaines de gestation.	2C

L'hormonothérapie

Recommandations	Niveau de preuve
Les patientes pré-ménopausées souffrant d'un cancer du sein à récepteur hormonal positif doivent recevoir un traitement hormonal adjuvant par tamoxifène pendant 5 ans avec ou sans analogue de la LHRH.	1A
Les patientes pré-ménopausées souffrant d'un cancer du sein au stade I ou II qui ne peuvent pas prendre de tamoxifène doivent recevoir un analogue de la LHRH.	1A
Les patientes post-ménopausées souffrant d'un cancer du sein à récepteur hormonal positif doivent recevoir un traitement hormonal adjuvant : - avec du tamoxifène (pendant 5 ans), - ou avec de l'anastrozole (pendant 5 ans) ou du letrozole (pendant 5 ans), - ou avec du tamoxifène (pendant 2 - 3 ans), suivi d'un inhibiteur de l'aromatase (pour un total de 5 ans de thérapie hormonale), - ou avec un inhibiteur de l'aromatase (pendant 2 ans), suivi de tamoxifène (pour un total de 5 ans de thérapie hormonale).	1A
Chez les patientes post-ménopausées présentant des tumeurs à récepteur hormonal positif qui ont terminé cinq années de traitement adjuvant par tamoxifène, une prolongation de traitement avec un inhibiteur de l'aromatase (d'une durée pouvant atteindre 5 ans) doit être envisagée en cas de ganglion lymphatique positif ou de ganglion négatif à haut risque (pT2 ou Niveau III).	1A

Trastuzumab

Recommandations	Niveau de preuve
Un traitement adjuvant d'une année avec le trastuzumab est recommandé chez les patientes souffrant d'un cancer du sein HER2-positif, à ganglion positif ou à ganglion négatif à haut risque (taille de la tumeur > 1 cm), ayant une fraction d'éjection du ventricule gauche ≥ 55% et sans facteur de risque cardiovasculaire important, ayant reçu une chimiothérapie.	1A
Pendant le traitement avec le trastuzumab, la fonction cardiaque devrait être surveillée tous les 3 mois.	1A

Biphosphonates

Recommandation	Niveau de preuve
Les biphosphonates ne doivent pas encore faire partie du traitement adjuvant du cancer du sein.	1A

TRAITEMENT DU CANCER DU SEIN MÉTASTATIQUE

Approche multidisciplinaire

Recommandations	Niveau de preuve
Le traitement du cancer du sein métastatique doit être débattu au sein d'une équipe multidisciplinaire et les préférences de la patiente doivent toujours être prises en considération.	Avis d'expert

Diagnostic du cancer du sein métastatique

Marqueurs tumoraux

Recommandations	Niveau de preuve
Aux fins de la surveillance des patientes souffrant de maladie métastatique durant le traitement actif, on peut avoir recours aux marqueurs tumoraux CA 27.29, CA 15-3 ou ACE, en conjonction avec l'imagerie diagnostique, l'historique et l'examen physique.	2C

Biopsie des lésions métastatiques

Recommandations	Niveau de preuve
Lorsqu'elles sont accessibles, les lésions métastatiques doivent faire l'objet d'une biopsie et d'une réévaluation des récepteurs d'œstrogène, de progestérone et les récepteurs HER2.	1B
Tant chez les patientes pré-ménopausiques que post-ménopausiques, le statut HER2 doit être utilisé pour identifier les patientes qui sont le plus susceptibles de bénéficier d'un traitement avec trastuzumab dans le contexte d'une maladie métastatique.	1B

Traitement systémique

Traitement hormonal et antagonistes du récepteur de l'oestrogène

Recommandations	Niveau de preuve
Chez les patientes pré-ménopausiques atteintes d'un cancer du sein métastasique à récepteur hormonal positif ou inconnu, la suppression de la fonction ovarienne en association avec le tamoxifène constitue la thérapie de première ligne de prédilection.	1A
Chez les patientes post-ménopausiques atteintes d'un cancer du sein métastasique à récepteur hormonal positif ou inconnu, le traitement de première ligne consiste en l'administration d'inhibiteurs de l'aromatase de la troisième génération (anastrozole, letrozole, exemestane) ou de tamoxifène. Le choix de l'agent doit tenir compte du traitement hormonal adjuvant reçu par la patiente. En traitement de deuxième ligne, le recours à un inhibiteur de l'aromatase de la troisième génération ou au Fulvestrant est recommandé.	1A
Fulvestrant peut être envisagé en traitement de substitution aux inhibiteurs de l'aromatase de la troisième génération chez les femmes post-ménopausiques souffrant d'un cancer du sein métastatique à récepteurs hormonaux positifs (récepteurs de l'œstrogène et/ou récepteurs de la progestérone) ayant récidivé après un traitement adjuvant au tamoxifène ou ayant progressé durant un traitement adjuvant au tamoxifène pour maladie à un stade avancé.	1B

Chimiothérapie

Recommandations	Niveau de preuve
La chimiothérapie chez les patientes souffrant de cancer du sein métastatique est indiquée dans les cas suivants : - tumeurs réfractaires aux hormones ou tumeurs à récepteurs hormonaux négatifs - maladie à progression rapide ou symptomatique - maladie mettant en jeu le pronostic vital	Avis d'expert
Le choix entre la polychimiothérapie et la chimiothérapie séquentielle avec un seul agent doit tenir compte du pronostic, du degré de performance, de la nécessité de contrôler rapidement les symptômes et des profils de toxicité, le but ultime étant d'optimiser la durée et la qualité de vie.	Avis d'expert
Les régimes à base d'anthracycline et/ou de taxane doivent être préférés en tant que traitement de première ligne, tenant compte de la chimiothérapie adjuvante reçue et du temps de survie sans maladie.	1A
Dans le cas de patientes présentant une résistance à l'anthracycline ou chez qui le traitement a échoué, qui n'ont pas encore reçu de taxane, et pour lesquelles on envisage une nouvelle chimiothérapie, un traitement à base de taxane (en monothérapie ou en association avec gemcitabine ou capecitabine) doit être utilisé, en tenant compte de la qualité de vie, de la toxicité, des caractéristiques de la maladie et de la facilité d'administration.	1A

Traitement biologique

Recommandation	Niveau de preuve
Le trastuzumab, avec/sans chimiothérapie non basée sur les anthracyclines ou thérapie endocrinienne, constitue le traitement de choix de tous les cancers du sein métastatiques HER-2 positifs, sauf en présence de contre-indications cardiaques au trastuzumab.	1A

Traitement des métastases osseuses

Recommandations	Niveau de preuve
Les biphosphonates doivent être utilisés en routine en association avec un autre traitement systémique chez les patientes présentant un cancer du sein métastatique avec métastases osseuses lytiques multiples ou symptomatiques.	1A
Chez les patientes présentant des métastases osseuses douloureuses ou menaçantes, la radiothérapie constitue le traitement de prédilection, si elle est faisable.	1A

Traitement des métastases au cerveau

Recommandation	Niveau de preuve
Les patientes présentant une seule ou un petit nombre de métastases au cerveau potentiellement résécables peuvent être traitées par radiochirurgie ou avec une chirurgie suivie d'une radiothérapie de la totalité du cerveau. La radiothérapie de l'ensemble du cerveau peut être proposée aux patientes pour lesquelles la chirurgie ou la radiochirurgie n'est pas adéquate.	2C

TRAITEMENT DE LA RÉCIDIVE LOCORÉGIONALE

Recommandations	Niveau de preuve
Une récidive locale dans la paroi de la cage thoracique doit être traitée de préférence par une chirurgie et une radiothérapie adjuvante, lorsque cela est possible.	1C
Une récidive locale après un traitement conservateur du sein doit être traitée par mastectomie.	1C
Le traitement systémique d'une récidive locorégionale totalement réséquée doit être débattu au sein de l'équipe multidisciplinaire.	Avis d'expert

SOINS DE SUPPORT AUX PATIENTES SOUFFRANT DE CANCER DU SEIN

Recommandations	Niveau de preuve
Les patientes atteintes d'un cancer du sein doivent être informées du risque de développer un œdème lymphatique après chirurgie ou radiothérapie et doivent se voir proposer un accès rapide à un service spécialisé en œdème lymphatique.	1A
La kinésithérapie de mobilisation après un curage axillaire doit être recommandée.	1A
Un entraînement physique comprenant des exercices spécifiques pour la fatigue liée au cancer peut être recommandé après un traitement pour un cancer du sein.	1A
Le traitement hormonal de substitution pour la ménopause est contre-indiqué chez les femmes atteintes d'un cancer du sein.	1B
Un soutien psychologique devrait être disponible pour toutes les patientes diagnostiquées avec un cancer du sein.	1A
Une équipe de soins palliatifs doit évaluer toutes les patientes présentant une maladie non contrôlée dans le but de prévoir une stratégie de gestion des symptômes.	1C

SURVEILLANCE DES PATIENTES ATTEINTES DE CANCER DU SEIN

Recommandations	**Niveau de preuve**
Une mammographie annuelle avec/sans échographie doit être pratiquée durant les 10 premières années dans le but de déceler des récidives ou des secondes tumeurs primitives chez les patientes ayant suivi un traitement préalable pour un cancer du sein, y compris un CCIS.	1C
Un monitoring intensif (test CBC, marqueurs tumoraux, radiographie du thorax, scanners osseux, échographie du foie et CT scan) n'est pas recommandé dans la surveillance en routine du cancer du sein.	1A
L'IRM ne doit pas être proposée en routine en guise d'examen de surveillance post-thérapeutique aux patientes ayant été soignées pour un cancer du sein précoce invasif ou un CCIS, sauf dans les cas suivants : - Cancer lobulaire infiltrant - Patientes très jeunes (< 35 ans) - Cancers associés à une mutation BRCA - Si la tumeur primitive n'a pas été visualisée à la mammographie / échographie - Dans des situations cliniques particulières où les autres modalités d'imagerie ne sont pas fiables ou sont restées peu concluantes.	1C
Des consultations de suivi peuvent être offertes tous les 3 à 4 mois durant les deux premières années suivant le diagnostic, tous les 6 mois jusqu'à 5 ans après le diagnostic et tous les ans après 5 ans.	Avis d'expert

APPROCHE MULTIDISCIPLINAIRE POUR LES PATIENTES ATTEINTES D'UN CANCER DU SEIN

Recommandation	**Niveau de preuve**
Toutes les femmes avec un diagnostic potentiel ou connu de cancer du sein devraient bénéficier du soutien d'une infirmière spécialisée en cancer du sein à toutes les étapes du diagnostic, du traitement et du suivi.	1B

CANCER DU SEIN ET GROSSESSE

Recommandation	**Niveau de preuve**
Le cancer du sein ne constitue pas une contre-indication à la grossesse ou à l'allaitement par la suite, mais la question doit faire l'objet d'une discussion au cas par cas.	2C

PARTICIPATION AUX ESSAIS CLINIQUES

Recommandation	**Niveau de preuve**
Compte tenu des évolutions très rapides au niveau des données probantes dans le cancer du sein, les cliniciens doivent encourager les patientes atteintes d'un cancer du sein à participer aux essais cliniques.	Avis d'expert

IMPLÉMENTATION, EVALUATION ET ACTUALISATION

Implémentation

La mise en œuvre de la présente recommandation doit être assurée par le Collège d'Oncologie. Un outil de mise en œuvre en ligne, similaire aux outils ayant accompagné les recommandations précédentes, doit être développé. Cet outil doit se baser sur l'algorithme général des recommandations.

Contrôle de qualité

Sur base de ces recommandations, des indicateurs de qualité ont été développés pour évaluer leur mise en œuvre. Les résultats de l'évaluation pilote de ces indicateurs seront publiés dans un prochain rapport.

Actualisation des recommandations

Compte tenu des preuves qui se modifient rapidement, et sur base d'une pré-évaluation de la littérature, les présentes recommandations devront être mises à jour régulièrement (p.ex. deux fois par an). Dans l'intervalle, lorsque des données probantes importantes sont publiées, elles seront mentionnées sur le site internet du Collège d'oncologie.

Scientific Summary

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ABBREVIATIONS

95% CI	95 percent confidence interval
ADH	Atypical ductal hyperplasia
AHRQ	Agency for Healthcare Research and Quality
ALH	Atypical lobular hyperplasia
ALND	Axillary lymph node dissection
ASCO	American Society of Clinical Oncology
AUS	Axillary ultrasonography
BCS	Breast conserving surgery
BRCA	Breast cancer gene
CBO	Dutch Institute for Healthcare Improvement
CCO	Cancer Care Ontario
CDSR	Cochrane database of systematic reviews
CEA	Carcinoembryonic antigen
CMF	Cyclophosphamide, methotrexate, fluorouracil
CPG	Clinical practice guideline
CT	Computed tomography
DARE	Database of Abstracts of Reviews of Effects
DCIS	Ductal carcinoma in situ
DFS	Disease free survival
ER	Estrogen receptor
FAC	Cyclophosphamide, doxorubicin, fluorouracil
FEA	Flat epithelial atypia
FEC	Cyclophosphamide, epirubicin, fluorouracil
FNAC	Fine needle aspiration cytology
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
FP	False positive
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRT	Hormone replacement therapy
HTA	Health technology Assessment
IQR	Inter quartile range
LCIS	Lobular carcinoma in situ
LHRHa	Luteinising-hormone releasing hormone agonist
LVI	Lymphovascular invasion
MBC	Metastatic breast cancer

MDT	Multidisciplinary team
MeSH	Medical Subject Headings
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
NPV	Negative Predictive Value
OR	Odds Ratio
OS	Overall survival
PET	Positron-emission tomography
PFS	Progression free survival
PgR	Progesterone receptor
PLCIS	Pleomorphic lobular carcinoma in situ
PPV	Positive predictive value
PVI	Peritumoral vascular invasion
RCT	Randomised controlled trial
RFS	Recurrence free survival
RR	Risk ratio
SE	Standard error
Se	Sensitivity
SIGN	Scottish Intercollegiate Guidelines Network
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SMM	Scintimammography
Sp	Specificity
SR	Systematic review
SUV	Standard Uptake Value
TP	True Positive
TPA	Tissue polypeptide antigen
TPS	Tissue polypeptide specific antigen
US	Ultrasonography
WBS	Whole Body Scan
WLE	Wide Local Excision

1 INTRODUCTION

1.1 SCOPE

In the present chapter, the clinical practice guideline (CPG) on breast cancer, published in 2007, is updated[1]. This guideline is the result of a collaboration between the College of Oncology and the KCE. The CPG will cover a broad range of topics: diagnosis, staging, treatment, reconstructive surgery, supportive therapy and follow-up. It primarily concerns women with invasive early or advanced breast cancer. It is intended to be used by all care providers involved in the care for these women.

Early breast cancer is subdivided into two major categories: in situ disease, mainly in the form of ductal carcinoma in situ (DCIS), and invasive cancer. Both are heterogeneous diseases with very variable appearances, biology and clinical behaviour[2]. Advanced breast cancer includes locally advanced breast cancer and breast cancer with metastases[3].

Screening is beyond the scope of this CPG. Population-based screening will be fully addressed in a future report, as well as the surveillance and the treatment of women with an increased risk of breast cancer due to family history.

1.2 EPIDEMIOLOGY

In 2006, the most common type of cancer in women in Europe was breast cancer (429 900 cases, 13.5% of all cancer cases)[4]. In Belgium, 9 405 new breast cancers were diagnosed in 2005. In Belgium as in Europe, breast cancer is the most frequent cause of death by cancer in women (20.6% of all cancer deaths)[5]. However, a favourable pattern in breast cancer mortality in the EU-25 was observed after 1989, leading to a fall in overall rates from 21.3/100 000 in 1990 to 18.9/100 000 in 2000[6]. This decline has been attributed to the combined effect of earlier detection and improved adjuvant treatment.

Only 5% to 7% of breast carcinomas are diagnosed in women who are younger than 40 years of age[7]. However, at this age, women had the worst 5-year cancer specific survival (69.7%) and a poor 5-year disease-free survival (60.8%) compared with all older age groups[8].

Breast cancer risk increases with age. Because of the ageing of the European population, the absolute number of deaths from breast cancer is still rising (130 000 in 2004, 132 000 in 2006)[4]. According to the Belgian Cancer Registry (2008)[5], more favourable stages (stage I and II) are found in the age group submitted to screening (50-69 years), only 15% in this group having advanced tumour stages (stage III or IV). On the contrary, older females present with more advanced stage tumours (25% with stage III or IV tumours). Survival rates depend on the stage of disease at diagnosis. At stage 0 (carcinoma in situ), the five-year survival rate is 100%. Five-year survival rates for women with stage IV (cancer has spread beyond the breast) are only 16%[9].

2 METHODOLOGY

2.1 GENERAL APPROACH

As for the previous CPGs developed within the collaboration between the College and the KCE, the present CPG was developed by adapting (inter)national CPGs to the Belgian context (www.kce.fgov.be). This approach was recently structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers[10]. The ADAPTE methodology generally consists of three major phases (www.adapte.org):

1. **Set-up Phase:** Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).
2. **Adaptation Phase**: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.
3. **Finalization Phase**: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

2.2 CLINICAL QUESTIONS

The CPG addresses the following clinical questions:

1. What diagnostic tests are the most effective to confirm the diagnosis of breast cancer?
   a. Triple test approach: clinical examination / mammography / pathology
   b. MRI
   c. MIBI scintimammography
2. What diagnostic tests are necessary to investigate the extent of the breast cancer?
   a. Sentinel biopsy
   b. Chest X-ray
   c. Ultrasonography of the liver
   d. Bone scintigraphy
   e. Biochemical and tumour markers; hormonal receptors
   f. CT scan of the thorax
   g. PET scan
3. What is the most effective treatment strategy for:
   a. Non-invasive breast cancer (ductal carcinoma in situ, Paget's disease)
   b. Early-stage invasive breast cancer
   c. Locally-advanced invasive breast cancer
   d. Metastatic breast cancer
   e. Locoregional recurrence of breast cancer

4. What is the place of supportive treatment of breast cancer, including erythropoesis stimulating proteins, biphosphonates, physiotherapy, physical training, psychological support and hormonal substitution?
5. What is the place of reconstructive surgery in the treatment of breast cancer?
6. What is the most effective strategy for the follow-up of patients with breast cancer?

2.3 SEARCH FOR EVIDENCE

2.3.1 Clinical practice guidelines

2.3.1.1 Sources

A broad search of electronic databases (Medline, EMBASE), specific guideline websites and websites of organisations in oncology (Table 1) was conducted.

Table 1: Searched guideline websites and websites of organisations in oncology

Alberta Heritage Foundation For Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
American Society of Clinical Oncology (ASCO)	http://www.asco.org/
American College of Surgeons (ACS)	http://www.facs.org/cancer/coc/
Cancer Care Ontario	http://www.cancercare.on.ca/english/home/
CMA Infobase	http://mdm.ca/cpgsnew/cpgs/index.asp
Guidelines International Network (GIN)	http://www.g-i-n.net/
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/
National Guideline Clearinghouse	http://www.guideline.gov/
National Cancer Institute	http://www.cancer.gov/
Haute Autorité de Santé (HAS)	http://bfes.has-sante.fr/HTML/indexBFES_HAS.html
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/

2.3.1.2 Search terms

For Medline (OVID) the following MeSH terms were used in combination: breast, breast diseases, neoplasms, breast neoplasms, breast tumour, breast carcinoma, breast malignant, breast metastases. These MeSH terms were combined with a standardised search strategy to identify CPGs (Table 2).

Table 2: Standardised search strategy for CPGs.

Database	Search strategy
Medline	guideline [pt] OR practice guideline [pt] OR recommendation* [ti] OR standard* [ti] OR guideline* [ti]

2.3.1.3 In- and exclusion criteria

Both national and international CPGs on breast cancer were searched. A language (English, Dutch, French) and date restriction (2006 – 2009) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

2.3.2 Additional evidence

For each clinical question, the evidence – identified through the included CPGs – was updated by searching Medline, the Cochrane Database of Systematic Reviews and DARE from the search date of the CPG on. For those clinical questions where no CPG was available, the search was extended to the inception date of the respective databases. A combination of appropriate MeSH terms and free text words was used (appendix 1).

An iterative approach was followed. For therapeutic interventions, systematic reviews and randomized controlled trials (RCT) were included. However, for diagnostic interventions we also searched for observational studies in case no systematic review or RCT was found. Inclusion criteria for the diagnostic studies were: prospective cohort study design (or RCT), ability to construct a 2x2 table, no partial verification, description of reference standard.

All searches were run between March and December 2009, and updated in January 2010.

The identified studies were selected based on title and abstract. For all eligible studies, the full-text was retrieved. In case no full-text was available, the study was not taken into account for the final recommendations.

2.3.3 Guideline update

A regular update of the full guideline takes a lot of time and is not cost-effective. Therefore, the decision was made to regularly update specific parts of the guideline based on alert messages given by the members of the GDG.

In October 2011, members of the GDG proposed to update the thresholds adopted for systemic treatment modalities (endocrine therapy, anti-HER2 therapy and chemotherapy). The algorithm used in the previous edition of the guideline was a result of the eleventh St. Gallen expert consensus meeting, organized in 2009[11]. In 2011, during the 12th St. Gallen expert consensus meeting, this algorithm was updated[12] (see 3.5.4.3. Systemic therapy). Therefore, it was considered necessary to update the algorithm in this guideline too.

2.4 QUALITY APPRAISAL

2.4.1 Clinical practice guidelines

In total, 47 CPGs were identified. All were quality appraised by two independent reviewers (SS, JV) using the AGREE instrument (www.agreecollaboration.org). Disagreement was discussed face-to-face. At the end, agreement was reached for all CPGs, and 20 CPGs were included. In appendix 3, an overview is provided of all aggregated dimension scores of the identified CPGs.

2.4.2 Additional evidence

The quality of the retrieved systematic reviews and RCTs was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl). The methodological quality of the diagnostic accuracy studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist, which is a standardised instrument endorsed by the Cochrane Collaboration[13].

2.5 DATA EXTRACTION AND SUMMARY

For each included CPG the following data were extracted: searched databases and search terms, search date, publication year, in- and exclusion criteria, quality appraisal, availability of evidence tables, the consistency between the evidence and its

interpretation, and the consistency between the interpretation of the evidence and the recommendations.

For each systematic review, the search date, publication year, included studies and main results were extracted. For RCTs and longitudinal studies, the following data were extracted: publication year, study population, study intervention, and outcomes. All evidence tables are reported in appendix 4.

The seventh edition of the TNM Classification of Malignant Tumours (appendix 7) was used to describe and categorize cancer stages and progression[14].

For each clinical question, the recommendations from the identified CPGs and the additional evidence were summarized in evidence tables. A level of evidence was assigned to each recommendation and additional study using the GRADE system (see appendix 2).

2.6 FORMULATION OF RECOMMENDATIONS

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (SS and JV). This first draft together with the evidence tables was circulated to the guideline development group 2 weeks prior to the face-to-face meetings. The guideline development group met on 4 occasions (March 24th 2009, November 10th 2009, November 26th 2009 and January 12th 2010). Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared. A grade of recommendation was assigned to each recommendation using the GRADE system. The second draft was once more circulated to the guideline development group for final approval.

Composition of the guideline development group

Expert	Field of expertise
Fatima Cardoso	Medical Oncology
Claire Bourgain	Pathology
Birgit Carly	Surgery
Marie-Rose Christiaens	Medical Oncology
Véronique Cocquyt	Medical oncology
Eric Lifrange	Gynaecology
Patrick Neven	Gynaecology
Pierre Scaillet	Radiotherapy
Jean-Christophe Schobbens	Gynaecology
Mireille Van Goethem	Medical imaging
Geert Villeirs	Medical imaging

2.7 EXTERNAL EXPERT MEETING

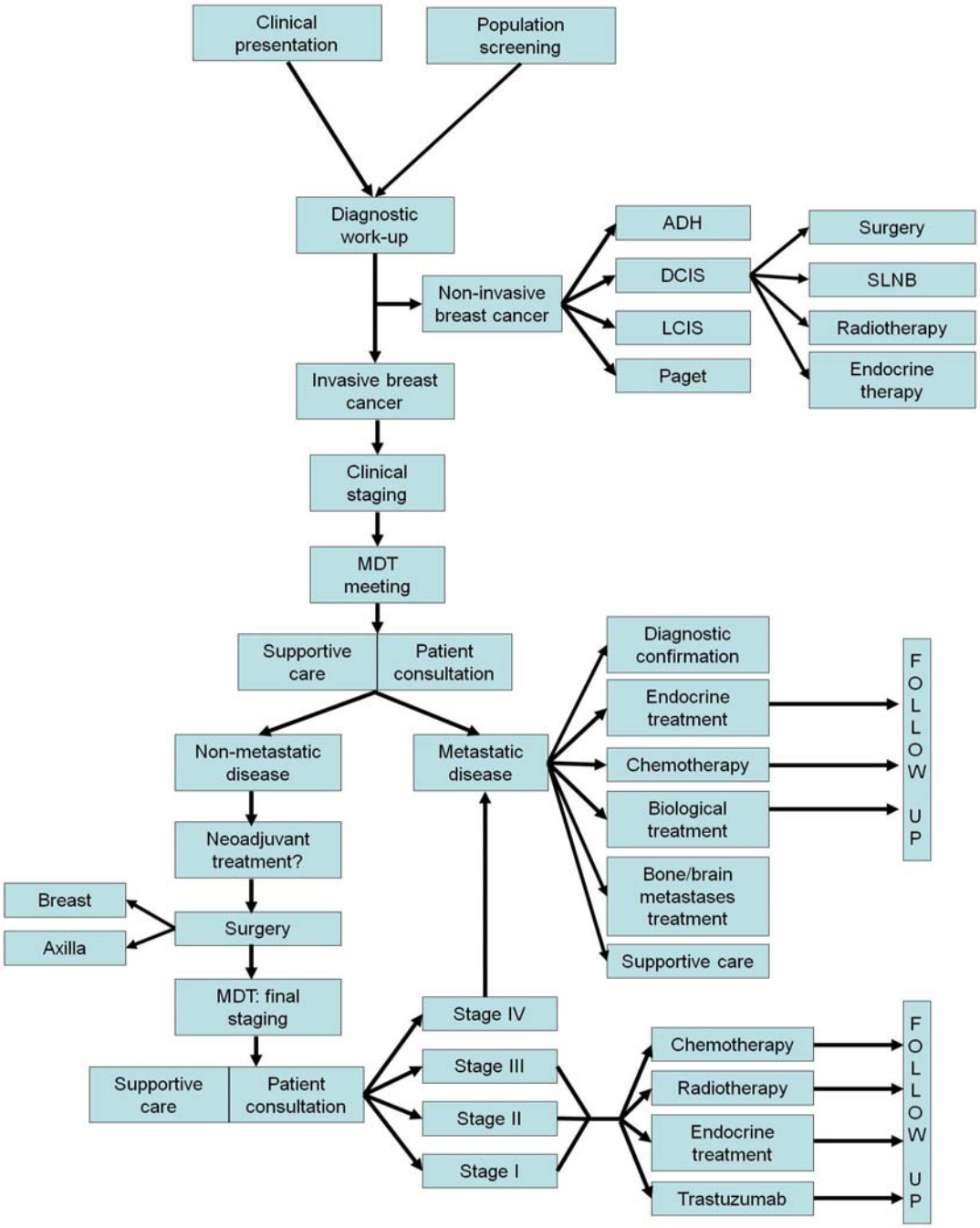
External experts received the recommendations 10 days prior to the expert meeting. As a preparation of the meeting all invited experts were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the experts were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case an expert disagreed with the recommendation (score '1 or '2'), (s)he was asked to provide appropriate evidence. All scores were then anonymized and summarized into a median score, minimum score, maximum score and % of 'agree' -scores (score '4' and '5') to allow a targeted discussion (see appendix 5). The recommendations were then discussed during a face-to-face meeting on September 15th 2010. Based on this discussion a final draft of the recommendations was prepared. In appendix 5, an overview is provided on how the comments of the external experts were taken into account.

2.8 FINAL VALIDATION

As part of the standard KCE procedures, an external scientific validation of the report was conducted by three independent experts. This validation was done in September 2010 (first edition) and in December 2011 (second edition). Following this validation procedure, some recommendations were finally adapted, if strong scientific arguments supported a change in the formulation (see appendix 6).

3 FINAL RECOMMENDATIONS

3.1 GENERAL ALGORITHM



Note. ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; SLNB: sentinel lymph node biopsy; MDT: multidisciplinary team

3.2 DIAGNOSIS OF BREAST CANCER

3.2.1 Triple assessment

The diagnosis of breast cancer relies on the so-called triple assessment, including clinical examination, imaging (comprising mammography and/or ultrasonography [US])[15, 16] and sampling of the lesion with a needle for histological/cytological assessment[17, 18]. The choice between core biopsy and/or a fine needle aspiration cytology (FNAC) depends on the clinician's, radiologist's and pathologist's experience[19-21].

In the SIGN guideline two-view mammography (cranio-caudal and oblique projections) was recommended as part of the triple assessment[18]. However, additional views (rolled views, magnifications, extra incidence views, etc.) can be left at the radiologist's discretion. Indeed, a supplementary latero-lateral view (three-view mammography) is not needed in all circumstances.

Younger age (i.e. < 40 years) has been associated with delay in referral for investigation of breast symptoms. Therefore, if a young woman presents with breast symptoms, she should also be evaluated with the triple assessment approach[22].

Recommendations

- **All patients should have a clinical examination (1C evidence).**
- **Where a localised abnormality is present, patients should have mammography and/or ultrasonography followed by core biopsy and/or fine needle aspiration cytology (1C evidence).**
- **In cases where clinical examination and imaging are pathognomonic (BIRADS 2) of a benign lesion (i.e. cyst), biopsy/cytology is not mandatory (expert opinion).**
- **A lesion considered malignant following clinical examination, imaging or cytology alone should, where possible, have histopathological confirmation of malignancy before any surgical procedure takes place (1C evidence).**
- **Two-view mammography should be performed as part of triple assessment (clinical assessment, imaging and tissue sampling) in a unit specialized in breast imaging (1C evidence).**
- **As for older women, young women presenting with breast symptoms and a strong suspicion of breast cancer should be evaluated by means of the triple assessment approach to exclude or establish a diagnosis of cancer (1C evidence).**

3.2.2 Magnetic resonance imaging (MRI)

Prospective cohort studies showed that MRI is a sensitive procedure for the diagnosis of breast cancer, with sensitivities ranging from 86 – 98%[23-25]. In a recent meta-analysis including 44 diagnostic studies, Peters et al.[26] reported pooled weighted estimates of sensitivity and specificity of 90% (95%CI 88% - 92%) and 72% (95%CI 67% - 77%), respectively. However, the performance of breast MRI was influenced by the prevalence of cancer in the studied population and by the number of criteria used to differentiate benign from malignant lesions. Breast MRI also demonstrated a higher sensitivity to diagnose early BRCA-associated breast cancer than mammography (86% vs. 48%, p=0.02), albeit without an association with an improved survival[27]. Similar results were obtained in two other studies with higher sensitivies and specificities for MRI compared to mammography[28, 29] and US[29].

Nevertheless, for definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI. In some specific cases, such as clinically palpable and mammographically occult breast cancer, patients with positive lymph nodes without an obvious tumour or diagnosis of recurrence, MRI can be useful[30].

Recommendations

- **There is insufficient evidence to routinely use MRI for the diagnosis of breast cancer. MRI can be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful (clinically palpable and mammographically occult breast cancer, cT0N+ patients, BRCA-associated cancers, diagnosis of recurrence) (1C evidence).**
- **For definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI (1B evidence).**

3.2.3 99mTc-MIBI scintimammography (SMM)

Numerous observational studies have shown that SMM is a procedure with a moderate sensitivity (ranging from 58 – 93%) and specificity (71 – 91%) for the diagnosis of breast cancer[23, 24, 31-36]. In 2007, the Medical Advisory Secretariat (Ontario Ministry of Health and Long-Term Care)[37] published a meta-analysis of 49 studies reporting higher diagnostic performance results (Se: 84%, Sp: 81%, PPV: 84% and NPV: 76%), indicating a moderate effectiveness of SMM in differentiating benign and malignant breast lesions. However, this evidence does not permit to advocate the routine use of SMM for the diagnosis of breast cancer. SMM may play a role as a third-line adjunctive technique in the evaluation of breast abnormalities, in particular when other imaging modalities are not reliable or were inconclusive. Overall, the same specific indications for MRI can also be applied to SSM (clinically palpable and mammographically occult breast cancer, cT0N+ patients, diagnosis of recurrence).

Two prospective cohort studies directly compared MRI and SSM for the diagnosis of breast cancer[23, 24], showing that MRI is a slightly more sensitive procedure.

Recommendation

- **There is insufficient evidence to routinely use 99mTc-MIBI scintimammography for the diagnosis and staging of breast cancer. 99mTc-MIBI scintimammography can be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that 99mTc-MIBI scintimammography is useful (1C evidence).**

3.2.4 PET Scan

The KCE recently published a Health Technology Assessment report on the use of PET scan[38]. This report was in part based on a high-quality HTA report published by the NCCHTA[39] assessing the clinical effectiveness of PET. Management decisions relating to diagnosis, staging/restaging, recurrence and treatment response were evaluated. The NCCHTA 2007 report included one systematic review conducted by AHRQ in 2001[40], and further updated by the AHRQ in 2006[9]. This systematic review was of high quality, but the quality of the included studies was moderate. The objective of the systematic review was to determine if the available non-invasive diagnostic tests (PET, MRI, US, SMM) are sufficiently accurate to exclude malignancy, avoiding women with an abnormal mammogram to undergo biopsy. Ninety-six publications were included: 9 on PET (8 WBS, 1 gamma camera), 45 on SMM, 19 on MRI and 8 on US. Some publications reported data for more than one test. The reference standard was histopathology obtained after biopsy for all studies. Patients considered were those who had suspicious breast lesions (abnormal mammogram and/or physical examination and/or US examination). For suspicious lesions, sensitivity of diagnostic tests was higher for MRI (92%) than for US (86%) or PET (82%)[9]. On the other hand, specificity was higher for PET (78%) than for MRI (72%) or US (66%). For non-palpable lesions, only scintimammography was studied, yielding a sensitivity of 68% and a specificity of 85%.

The authors concluded that MRI is a more valuable tool than PET for the diagnosis of breast cancer. However, if a <2% risk of having breast cancer with a negative diagnostic test is considered, an acceptable level of risk for a diagnostic test to reliably preclude biopsy, none of these tests was sufficiently accurate to replace biopsy for women at average risk of breast cancer.

For non-palpable lesions, data were insufficient to estimate the accuracy of PET, MRI or US. SMM was not sufficiently accurate to avoid biopsy. For palpable lesions, data were insufficient to estimate the accuracy of PET, MRI, US and SMM.

The additional primary study retrieved by the NCCHTA 2007[39] compared PET and MRI in 36 women with suspicious lesions on mammography or clinical examination. In this study, PET yielded lower sensitivity than MRI (76%, 95%CI 52-91% vs. 95%, 95%CI 74-99%) and a similar specificity (73%, 95%CI 45-91%). PET was less accurate to detect smaller lesions (< 10 mm).

The systematic review conducted by Bourguet et al. (2006)[41] reported that PET is not indicated in the diagnosis of breast cancer.

Recommendation

- **PET scanning is insufficiently accurate to be recommended for diagnosis of breast cancer as an alternative to biopsy (1B evidence).**

3.2.5 Hormonal receptor assessment

In 2007, the American Society of Clinical Oncology[42] updated its 1996 recommendations for the use of tumour markers in breast cancer. This update also encompassed assessment of oestrogen receptors (ER) and progesterone receptors (PgR). Recommendations related to ER and PgR assessment are supported by data from The Early Breast Cancer Trialists' Collaborative Group [EBCTCG] 2005[43] and other clinical studies[44-46]. In 2010, a guideline jointly produced by the American Society of Clinical Oncology and College of American Pathologists was published that confirmed the utility of ER and PgR status assessment in all invasive breast cancer women[47]. However, the authors reported that up to 20% of the current determinations of ER and PgR testing worldwide were potentially inaccurate, due to false positive and false negative results[47]. They developed recommendations for optimal immunohistochemical (IHC) ER/PgR testing performance (available on http://www.asco.org/guidelines/erpr; accessed on September 28th 2010).

Breast cancer patients with tumours that are ER-positive and/or PR-positive have lower risks of mortality after their diagnosis compared to women with ER- and/or PR-negative disease[48]. More importantly, ER and PgR status are predictive of benefit from endocrine treatment (tamoxifen, chemical ovarian ablation, aromatase inhibitors and fulvestrant) in both the adjuvant and metastatic settings[49]. An emerging topic is the potential role of hormone receptor determination in the management of DCIS. The addition of tamoxifen to the lumpectomy followed by breast radiation therapy is supported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial[50, 51] which showed a significant decrease in the recurrence of both in situ and invasive breast cancer in the tamoxifen group, with no impact on overall survival. However, another large randomized trial of adjuvant tamoxifen in DCIS, the United Kingdom Coordinating Committee on Cancer Research trial[52], failed to show an advantage for the tamoxifen-treated group in either the recurrence of breast cancer or overall survival.

The treatment of patients with advanced breast cancer is also guided by a number of factors including the hormone receptor (ER and PR) status and the expression of HER2 of the primary tumour or the metastases. If the receptor status of the primary tumour is unknown and further analysis is not possible, it may be necessary to biopsy the metastatic disease, particularly if the results would influence treatment planning[3, 42].

HER2 is a member of the epidermal growth factor receptor (EGFR) family. The amplification of the HER2 gene or the overexpression of its protein is observed in 20% to 30% of human breast cancers and is associated with a poor prognosis in patients with primary breast cancer[53]. Amplification and/or overexpression of HER2 in breast cancer is associated with a number of adverse prognostic factors. HER2 status is of great clinical value in breast tumours for the identification of those patients who are eligible for trastuzumab or lapatinib therapy. Moreover, level II evidence suggests that overexpression of HER2 identifies patients who have greater benefit from anthracycline-based adjuvant therapy[42].

Recommendations

- **Estrogen receptors and progesterone receptors (ER/PgR) should be measured on all ductal carcinomas in situ (DCIS) and primary invasive breast cancers (1B evidence).**
- **HER2 protein expression, and if positive confirmed with gene amplification, should be evaluated in every primary invasive breast cancer at the time of diagnosis and at the time of recurrence whenever possible (1B evidence).**

3.2.6 Tumour markers

There is no good evidence (only from very low quality observational studies) to support the routine use of biochemical tests for the diagnosis of breast cancer, including tumour markers such as circulating tumour cells (CTC), CA 15-3, CA 27.29, CEA and Cathepsin D[54-57].

CA 15-3 and CA 27.29 are well-characterized assays that allow the detection of circulating MUC-1 antigen in peripheral blood. Several studies supported the prognostic relevance of this circulating marker in early-stage breast cancer[58-61]. However, its role in the management of early-stage breast cancer is unclear[62, 63]. It has yet to be determined that MUC-1–based serum markers are helpful in making treatment decisions in this setting.

Recommendation

- **There is no good evidence to include tumour markers (circulating tumour cells [CTC], CA 15-3, CA 27.29, CEA and Cathepsin D) in the diagnosis of primary breast cancer (2C evidence).**

3.3 STAGING OF BREAST CANCER

3.3.1 Routine staging tests

There is no good evidence to support the pre-treatment routine screening for metastatic disease in asymptomatic women with early operable breast cancer (i.e. cT1-2, N0-1)[18, 64, 65].

Imaging investigations including chest X-ray, bone scan, liver US, and chest and liver CT have a low diagnostic yield and are not indicated in asymptomatic women with ductal carcinoma in situ and pathological stage I disease. They should be used only when clinically indicated (e.g. symptoms of lung disease, a palpable liver, abnormal liver function tests, bone pain or bony tenderness). Serological tests for cancer-specific antigens, such as CEA and CA 15-3, are non-specific and unreliable as indices of active disease[54-57, 62, 63].

However, observational data have shown that specific subsets of patients (e.g. triple negative patients, young patients) harbour a higher risk of distant metastases[66, 67], and should therefore be staged more aggressively.

The conclusions above are confirmed by the results of a recent observational study that reported an overall detection rate of 6.3% for skeletal metastases by bone scintigraphy, 0.7% for liver metastases by liver US, and 0.9% for lung metastases by chest X-ray[68].

Of course, these results should be interpreted with caution because of the retrospective study design.

Recommendations

- **The use of bone scanning, liver ultrasonography and chest radiography in women with stage I breast cancer has a very low yield and cannot be recommended routinely (2C evidence).**
- **In asymptomatic women with DCIS, routine bone scanning, liver ultrasonography and chest radiography are not indicated as part of baseline staging (2C evidence).**

3.3.2 Magnetic resonance imaging (MRI)

There is insufficient evidence to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes. There is also little evidence on which to base any recommendation on the use of MRI in the assessment of the breast in patients with a diagnosis of pure DCIS.

Breast MRI demonstrated moderate to high sensitivity (75-100%) and specificity (82-100%) in detecting multicentric tumour foci in fibroglandular or dense breasts[69, 70]. MRI will detect additional mammogram-occult foci greater than 2 cm from the index cancer in +/- 10% of women[71, 72]. Contrast-enhanced MRI has the lowest false negative rate in detecting invasive lobular carcinoma and has the highest accuracy in measuring the size of the invasive lobular carcinoma[73]. MRI has been shown to detect occult invasive breast cancers with a sensitivity of 97%-100%.

Combined mammography, clinical examination and MRI were more sensitive than any other individual test or routine triad[74]. However, all these results need to be interpreted with caution because of the methodological limitations of the studies and the small sample sizes.

Nevertheless, the increased use of breast MRI at the time of diagnosis and staging is one potential reason for the increased rate of mastectomy[75]. Breast MRI is increasingly being used to exclude the presence of multifocal or multicentric breast cancer in the ipsilateral breast, but also to identify mammographically occult contralateral breast cancers in women who present with unilateral invasive breast cancer. MRI can improve the detection of cancer in the contralateral breast when added to a thorough clinical breast examination and mammographic evaluation at the time of the initial diagnosis of breast cancer. The increased cancer detection rate is associated with a false positive rate of 10.9% and a relatively low risk of detecting benign disease on biopsy (9.4%)[76]. In a recent meta-analysis[77], MRI identified additional tumour foci in 16% (95%CI 6-34%) of patients newly diagnosed with breast cancer and led to a change in surgical therapy in 8% to 33% of patients, most commonly resulting in mastectomy that would not have been performed otherwise. MRI detected contralateral lesions in a substantial proportion of women, but did not reliably distinguish benign from malignant findings. Relatively high incremental cancer detection rates may be due to selection bias and/or overdetection.

Houssami et al.[78] identified 19 studies (n=2 610) in a meta-analysis to determine the accuracy and impact of breast MRI in the context of local staging, with a focus on detection of multifocal and/or multicentric cancer not identified on conventional imaging. MRI detected additional disease in 16% of women with breast cancer. The accuracy differed according to the reference standard (p=0.16), from 99% to 86% as the quality of the reference standard increased. The overall summary estimate for positive predictive value (PPV) was 66% (95%CI 52-77%). True positive to false positive ratio was 1.91 (95%CI 1.09–3.34). Due to MRI-detected lesions, conversion from wide local excision (WLE) to mastectomy was 1.1% (95% CI 0.3–3.6%), while conversion from WLE to more extensive surgery was 5.5% (95%CI 3.1–18.3%). The authors concluded that MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer. There is a need to reduce the false positive rate in MRI detection.

The COMICE trial (Comparative Effectiveness of Magnetic Resonance Imaging in Breast Cancer)[79] evaluated whether adding a MRI scan to conventional triple assessment (mammogram, US and biopsy) assisted loco-regional staging, and thereby reduced re-operation rates, for patients with primary breast cancer scheduled for wide local excision. In this trial, the MRI group of women was more likely to proceed to mastectomy instead of the previously planned wide local excision (7% vs. 1%), with no difference in re-operation rates (19% in both groups, OR 0.96, 95% CI 0.75–1.24) within 6 months after randomization. The results of the COMICE trial suggest no significant benefit in terms of reduction in re-operation rates by the addition of MRI to conventional triple assessment for this patient group.

MRI is also able to detect previously unidentified metastases, including those that were non-skeletal[3]. When the field was extended to include the pelvis, CT had a higher diagnostic accuracy in detecting bone metastases than scintigraphy[3].

Recommendations

The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS (1C evidence), except in the following situations:

- **if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment (2C evidence);**
- **in invasive lobular cancer (1C evidence);**
- **in cases where breast density does not allow to exclude multicentric and bilateral disease by mammographic assessment (2C evidence).**

For M-staging (visceral or bone metastases), MRI/CT can be considered (2C evidence).

3.3.3 Axillary ultrasonography

For patients with early invasive breast cancer, staging of the ipsilateral axilla is essential for deciding what local and systemic treatments are subsequently required[2].

Two prospective cohort studies showed that axillary ultrasonography (AUS) is a specific procedure for the detection of axillary lymph nodes[80, 81]. Altinyollar et al. performed US of the axillary, infraclavicular and supraclavicular region in 100 consecutive patients with breast cancer[80]. Specificity and sensitivity for detecting metastatic lymph nodes were 92% and 79% respectively. In the study of Podkrajsek et al., 165 patients with breast cancer and clinically negative axilla underwent AUS (and US-guided fine-needle aspiration biopsy if suspicious lymph nodes)[81]. A specificity and sensitivity of 89% and 58% were found.

NICE[2] included 8 case series and one meta-analysis[82] with pooled estimates based on 16 case series. The staging performance of US-guided FNAC showed a mean sensitivity of 43% and a mean specificity of 100%, a PPV of 99% and a negative predictive value (NPV) of 72%. The meta-analysis included only patients in whom it was possible to obtain biopsy material by US; the pooled sensitivity was 75.0% and the pooled specificity was 98.3%.

Recommendation

- **Axillary ultrasonography with fine needle aspiration cytology of axillary lymph nodes suspicious for malignancy is recommended (2C evidence).**

3.3.4 PET scan

In the KCE report on the use of PET scan[38], one systematic review and four additional primary studies evaluated PET for staging axillary lymph nodes. Two studies used axillary lymph node dissection (ALND) with sentinel lymph node biopsy (SLNB) as reference standard, one study used only ALND and the fourth study used ALND or SLNB plus ALND. When ALND was used as reference, PET yielded a sensitivity that ranged between 40% and 93%, with a specificity that ranged between 87% and 100%. When ALND + SLNB were used as reference standard, sensitivity decreased to 20-50%, while specificity did not change (82-100%). Since prevalence of node-positive disease approximated 33-64%, 36-67% patients with negative PET would have undetected axillary disease if further tests were not undertaken.

The systematic review conducted by Sloka et al.[83] included 19 studies for staging axillary lymph nodes in patients with breast cancer. Due to the high heterogeneity between studies, planned meta-analysis was not performed. Particularly, reference standards were quite different between studies (histology via ALND, SLNB, histology + ALND, SLNB + histology via ALND). In 3 high-quality studies, i.e. studies with broad generalisability and no significant flaws in research methods, sensitivity ranged between 61% and 94%, while specificity ranged between 80% and 98%.

Four additional primary studies[84-87] were retrieved by our own literature search. Ueda et al.[86] included 183 patients with primary operable breast cancer that underwent PET/CT and AUS followed by SLNB and/or ALND for axillary staging. Using visual assessment of PET/CT images, PET/CT yielded a sensitivity of 58% (95%CI 44-70%) and a specificity of 95% (95%CI 89-98%). When a cut-off of SUV was set at 1.8, sensitivity and specificity were 36% (95%CI 24-49%) and 100% (95%CI 96-100%), respectively. On the other hand, the diagnostic performance of AUS was not so different, with a sensitivity of 54% (95%CI 31-55%) and a specificity of 99% (95%CI 95-100%). With the combination of PET/CT (visual assessment) and AUS, sensitivity and specificity changed to 64% (95%CI 51-76%) and 94% (95%CI 88-97%) respectively.

Veronesi et al.[87] enrolled 236 patients with breast cancer and clinically negative axilla undergoing PET/CT before surgery. In all patients, SLNB was carried out after identification through lymphoscintigraphy. Patients also underwent ALND in cases of positive FDG-PET or positive SLNB. The results of PET scan were compared with histopathology of SLNB and ALND. In all, 103 out of the 236 patients (44%) had metastases in axillary nodes. Sensitivity of PET/CT was low (37%, 95%CI 28-47%), but specificity was acceptable (96%, 95%CI 91-99%). Comparatively, sensitivity and specificity of SLNB were 96% (95%CI 90-99%) and 100% (95%CI 96-100%), respectively.

Gil-Rendo et al.[84] conducted a prospective study including 275 women with breast cancer. In a first group (150 women), ALND was performed regardless of PET results. In a second group (125 women), the axillary examination was complemented by SLNB only in women without pathological axillary uptake on PET scan. In the first group, the sensitivity and specificity of PET for detecting axillary lymph nodes were 90% (95%CI 83-97%) and 98% (95%CI 93-99%) respectively. PET detected axillary involvement in 64 of 71 patients (7 false negatives) and correctly diagnosed 78 of 79 patients without axillary metastases.

Finally, Kumar et al.[85] conducted a prospective study in 80 women with a histological diagnosis of breast cancer and clinically negative axillary lymph nodes, in order to assess the diagnostic efficacy of PET in detecting axillary lymph nodes. Overall, 36 out of the 80 patients (45%) had metastases in axillary lymph nodes. Sensitivity of PET was very low (44%, 95%CI 28-62%), whereas specificity was good (95%, 95%CI 83-99%).

Shie et al.[88] conducted a systematic review comparing PET and bone scintigraphy for the detection of bone metastases from breast cancer. Three studies presented patient-based data, whereas the other 3 studies reported lesion-based data. Reference standards were CT, MRI or bone biopsy with clinical follow-up longer than 6 months. The pooled patient-based sensitivity and specificity of PET were 81% (95%CI 70-89%) and 93% (95%CI 84-97%), respectively. For bone scan, the pooled sensitivity was 78% (95%CI 67-86%), while specificity was 79% (95%CI 40-95%).

In addition to this high-quality review, 15 small comparative studies or case series were identified. These were generally of poor to medium quality and many were retrospective studies.

One prospective[89] and one retrospective cohort study[90] were identified that studied the role of PET scan in the evaluation of metastatic breast cancer. Nakai et al.[90] compared the diagnostic efficacy of PET and bone scintigraphy for the evaluation of osteoblastic bone metastases in patients with breast cancer. The sensitivity and specificity of bone scintigraphy were 78% (95%CI 64-88%) and 82% (95%CI 65-92%) respectively, and those of PET were 80% (95%CI 66-89%) and 88% (95%CI 71-96%) respectively. Uematsu et al.[89] compared PET scan to bone scanning with SPECT for the evaluation of bone metastases. In the lesion-by-lesion analysis (n = 900), the sensitivity and specificity were 85% and 99% respectively for SPECT, and those of PET were 17% and 100% respectively (95% CI were not provided). However, both studies suffered from methodological flaws. In the study of Nakai et al., the reference standard was not applied to all included patients[90], whereas the study of Uematsu et al. only included 15 patients[89].

MRI and FDG-PET were equal to or better than scintigraphy in visualising bone metastases, other than osteoblastic lesions, but whole body MRI was better than FDG-PET in detecting distant metastases, particularly in abdominal organs, brain and bone.

Recommendations

- **The use of PET in staging axillary lymph nodes for breast cancer is not recommended. PET sensitivity is inferior to axillary node dissection and sentinel node biopsy (1B evidence).**
- **PET scan can be useful for the evaluation of metastatic disease in locally advanced breast tumours with a high chance of (micro- or macro) metastatic disease (expert opinion).**
- **Inconclusive evidence was identified on the use of PET for the detection of bone metastases (2C evidence) and therefore, bone scan is still the technique of choice.**

3.4 TREATMENT OF NON-INVASIVE BREAST TUMOURS

3.4.1 Early precursor and high-risk lesions

Since precursor lesions, such as atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH) and (small cell) lobular carcinoma in situ (LCIS), have a small chance of progression and a very slow progression rate, they are usually considered as indicators of increased risk[64]. Therefore, when ALH/LCIS is found within or near the margins of a wide excision specimen, re-excision is not necessary[91, 92]. On the other hand, clear margins do not exclude the presence of residual ALH/LCIS elsewhere in the breast.

The presence of ALH/LCIS in a core biopsy has a totally different meaning. Since only a minority of ALH/LCIS is associated with microcalcifications, these lesions are not visible on imaging, and hence are not the targeted lesion, but merely a coincidental finding.

Multidisciplinary discussion is essential as the abnormality identified radiologically may not be represented in the core biopsy[92]. Furthermore, at present it is not yet known whether ALH/LCIS diagnosed via a targeted core biopsy of a mammographic abnormality carries the same (low) risk as ALH/LCIS encountered serendipitously in an excision specimen. Therefore, these cases must be managed cautiously, and a surgical diagnostic excision might be considered. Following a diagnosis of ALH/LCIS – even if completely excised – careful follow-up is indicated[64]. As these lesions are only recognized to constitute a separate entity for about a decade, no large follow-up studies are available. Indeed, such lesions were until recently considered as DCIS and treated accordingly. Many authorities advise to continue to do so. This means that when these lesions are encountered in a core biopsy, complete excision is advocated.

If margins are not free, re-excision may be considered. Following surgical excision, radiotherapy and hormonal therapy may be administered.

Recommendations

- **Management of early precursor lesions is preferably discussed in a multidisciplinary setting (expert opinion)**
- **When atypical lobular hyperplasia or flat epithelial atypia is present near the margins of an excision specimen, re-excision is not necessary (expert opinion).**
- **When lobular carcinoma in situ or atypical ductal hyperplasia is present in the margins, re-excision is not recommended (expert opinion).**
- **When atypical lobular hyperplasia / lobular carcinoma in situ, flat epithelial atypia or an atypical intraductal proliferation reminiscent of atypical ductal hyperplasia, is found in a core biopsy, diagnostic excision is recommended (expert opinion).**
- **When pleomorphic lobular carcinoma in situ or lobular carcinoma in situ with comedonecrosis is found in a core biopsy, complete excision with negative margins is recommended, and anti-hormonal treatment and/or radiotherapy are an option (expert opinion).**
- **Annual follow-up mammography after a diagnosis of lobular carcinoma in situ or atypical ductal hyperplasia is indicated (2C evidence).**

3.4.2 Ductal carcinoma in situ

DCIS or intraductal carcinoma is most commonly diagnosed as a result of detection of microcalcifications on mammography. It is usually not palpable. By definition, it is confined to the duct system of the breast, so it is not associated with metastases.

3.4.2.1 Surgery

1. Different well-established surgical procedures for the treatment of early breast cancer are available to eradicate the primary tumour and any local extension[93]: wide local excision (excision of a tumour with a margin free of both invasive and in situ disease), segmental excision or sector resection (as above, but the excision incorporates tissue from the nipple right out to the periphery of the breast in a segmental shape), quadrantectomy (involves a similar excision to segmental excision but a whole quadrant of the breast is removed), and mastectomy (refers to removal of the entire breast). Wide local excision, partial mastectomy, quadrantectomy and segmentectomy are usually referred to as breast conserving surgery (BCS).
2. Our recommendations are completely based on existing guidelines[2, 18, 94, 95]. One additional meta-analysis of clinical trials that examined BCS with RT for the treatment of DCIS was identified[96]. However, due to the absence of a quality appraisal of the included studies, this meta-analysis was not considered here.
3. The choice of BCS versus total mastectomy (with the option for reconstruction) is based on a sub-analysis of a RCT and a meta-analysis of observational studies[18], that showed similar mortality rates at 5 years for both procedures.
4. Multicentricity and residual disease (positive margins) are contraindications for local wide excision[64]. Complete resection of the lesion should be achieved. Indeed, studies have shown that positive or indeterminate resection margins increase the risk of local recurrence[95].
5. The best available evidence for the optimal surgical resection margin was drawn from 32 observational studies described in the NICE guideline[2]. There was no consistency whether to use wide tumour-free resection margins or smaller margins together with radiotherapy. Most studies agree that margins containing tumour cells are associated with local recurrence or bear the risk of residual cancer. There is agreement that the risk of local recurrence is reduced with very

wide margins, e.g. more than 10 mm of tumour-free tissue. Nevertheless, the wider the margin, the more breast tissue is removed and the greater the detrimental effect on cosmesis. When margins of 2 mm or more are achieved, local recurrence rates of 2% (with radiotherapy) to 11% (without radiotherapy) are reported[2].

6. Immediate breast reconstruction is an acceptable procedure that does not disadvantage patients compared to delayed reconstruction. With respect to psychological outcomes, one systematic review of observational studies suggested that better psychological outcomes are achieved in patients treated with immediate reconstruction compared to delayed reconstruction[97]. Further observational studies reported similar findings[98, 99]. High rates of acceptable cosmetic results were also reported by observational studies. Two systematic reviews of observational studies[97, 100] suggested that immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction. In the same way, no reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those receiving delayed reconstruction.
7. By definition, DCIS is pre-invasive and does not have the potential to spread to regional lymph nodes[101]. However, a significant proportion of patients with larger volume and higher grade DCIS diagnosed on imaging and core needle biopsy will be found to have invasive disease. Therefore, these women will need an assessment of regional lymph nodes status. Axillary clearance can be considered only for large or stage III DCIS[64, 94, 95].

Recommendations

- **Women with high-grade and/or palpable and/or large DCIS of the breast who are candidates for breast conserving surgery should be offered the choice of local wide excision or mastectomy after the patient is correctly informed. In case of multicentricity local wide excision is not recommended (1B evidence).**
- **In women with DCIS, mastectomy with or without immediate reconstruction remains an acceptable choice for women preferring to maximize local control or to avoid radiotherapy (1B evidence).**
- **Oncoplastic repair techniques should be offered to patients treated with breast conserving surgery to maximise cosmesis (1C evidence).**
- **Immediate breast reconstruction should be discussed with all patients being advised to have a mastectomy, except when significant comorbidities preclude this option (1C evidence).**
- **When local wide excision is performed in women with DCIS, a minimum of 2 mm pathological radial excision margin is usually recommended (1C evidence).**
- **Axillary clearance is not recommended for women with DCIS (1C evidence).**

3.4.2.2 Sentinel lymph node biopsy

SLNB is a targeted technique to identify and remove the sentinel lymph node(s) (SLN), causing minimal disruption to the axilla. SLNB is a less invasive axillary staging technique than ALND and has been shown to reduce the complication rate[2].

Currently, there is insufficient evidence to support the routine use of SLNB in patients with DCIS. Ansari et al.[101] conducted a meta-analysis (of observational studies) of the incidence of SLN metastases in patients with DCIS. This analysis showed that the frequency of SLN positivity in patients with a preoperative diagnosis of DCIS ranged from 0 to 16.7%. The estimate for the incidence of SLN metastases in patients with a preoperative diagnosis of DCIS was 7.4% (95% CI 6.2- 8.9%) compared with 3.7% (95%CI 2.8-4.8) in patients with a definitive (postoperative) diagnosis of DCIS alone. This was a significant difference with an odds ratio of 2.11 (95%CI 1.15-2.93).

There was no evidence to suggest a correlation between the rate of positive SLN and DCIS grade or DCIS size. It was not possible to reliably estimate from the studies identified the proportion of patients with DCIS and positive SLN who had further axillary nodal involvement, because of the small numbers of patients in the series. None of the selected studies (all retrospective) reported changes to treatment plans as a result of staging by SLNB.

Evidence on a subset of patients with a biopsy diagnosis of DCIS who were at high risk of an invasive component was reviewed and suggested that a palpable mass, a mammographic mass, a high-grade DCIS and a large size were associated with a significant risk of invasive disease in the final resection specimen[101]. SLNB can be considered for high-grade DCIS, when mastectomy with or without immediate reconstruction is planned[102, 103].

Recommendations

- **Sentinel lymph node biopsy is not recommended in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease. Patients at high risk include those with a palpable mass or extensive micro-calcifications (1B evidence).**
- **Data are available to support the use of sentinel lymph node biopsy for high-grade DCIS, when mastectomy with or without immediate reconstruction is planned (1A evidence). Age, gender or obesity are no exclusion criteria for SLNB.**

3.4.2.3 Radiotherapy

In a Cochrane systematic review, Goodwin et al. evaluated the addition of RT to BCS for the treatment of DCIS[104]. Four RCTs involving 3 925 women were reviewed. Meta-analysis confirmed a statistically significant benefit from the addition of RT on all ipsilateral breast events (hazard ratio [HR] 0.49; 95%CI 0.41-0.58, p<0.00001), ipsilateral invasive recurrence (HR 0.50; 95%CI 0.32-0.76, p=0.001) and ipsilateral DCIS recurrence (HR 0.61; 95%CI 0.39-0.95, p=0.03). All analyzed subgroups benefited from addition of RT, including women having small DCIS lesion (less than 10mm). Nine women require treatment with RT to prevent one ipsilateral breast recurrence.

However, no difference in 8-year and in 10-year overall survival was found in 2 RCTs (NSAPB and EORTC respectively) between patients treated for DCIS with local excision alone or local excision plus radiotherapy (95% in both groups).

Recommendation

- **After a breast-conserving treatment of DCIS, omitting radiotherapy could be considered when the risk of local recurrence is estimated to be very low and after discussion in the multidisciplinary team meeting (1A evidence).**

3.4.2.4 Endocrine therapy

The systematic literature review conducted by CCO[105] retrieved two randomized trials that investigated the use of tamoxifen in patients with DCIS who had undergone BCS and adjuvant radiotherapy. The NSABP B-24 trial compared tamoxifen versus placebo in 1 804 women[50, 51] while the UKCCCR trial included 1 576 patients[52].

The NSABP B-24 trial[50, 51] randomized women with DCIS after surgery to 5 years of tamoxifen or placebo. The cumulative 7-year incidence of ipsilateral or contralateral breast malignancy was lower for patients in the tamoxifen group versus those in the placebo group (10% vs. 17%, p=0.0003). The overall 7-year survival rate was 95% for both groups. The recurrence rate in those with negative margins (74% of all patients) was lower and the effect of tamoxifen less substantial. A subgroup analysis on ER-positive DCIS (77% of all patients) was done. The risk ratio (RR) of recurrent or new breast pathology with tamoxifen was 0.41 (95%CI 0.25-0.65).

Results also indicated that adjuvant tamoxifen is optimally given for a period of about 5 years, the majority of patients being disease-free at the time they discontinue tamoxifen.

In the UKCCCR trial[52], 1 576 patients were included, with 794 patients receiving tamoxifen and 782 not. Only 34% of the tamoxifen group and 32% of the no-tamoxifen group received radiation. Of the 794 patients randomized to receive tamoxifen, 11% stopped taking the drug prematurely. After a median follow-up of 52.6 months, there was no statistically significant difference in the occurrence of ipsilateral (6% vs. 4%, p=0.23) or contralateral (1% vs. 2%, p=0.30) invasive carcinoma or DCIS, but there was a difference in the overall incidence of DCIS (ipsilateral and contralateral combined) (HR 0.68; 95%CI 0.49-0.96) favouring the tamoxifen group.

The benefits and harms of endocrine therapy should be discussed with women with DCIS, and treatment decisions should be based on individual circumstances.

Recommendation

- **Adjuvant hormonal therapy can be considered for patients with ER positive DCIS (1A evidence).**

3.4.3 Paget's disease

Paget's disease of the breast is an eczema-like change in the skin of the nipple, almost always caused by an underlying breast cancer (either DCIS or invasive cancer)[2].

The NICE guideline (2009)[2] reviewed 11 observational studies providing data on breast cancer recurrence in patients treated with mastectomy or BCS for Paget's disease. In a prospective study, 61 patients with Paget's disease without associated invasive disease were treated with a cone excision and radiotherapy[106]. At a median follow-up of 6.4 years, 4 patients developed a local recurrence. One patient with an invasive local recurrence died of disseminated breast carcinoma. The 5-year local recurrence rate was 5.2% (95%CI 1.8 – 14.1%). In rare and selected cases, such as Paget's disease limited to the nipple or surrounding skin, radiotherapy alone may be sufficient[107]. In these cases, surgery could be avoided.

In 3 out of 4 studies in which survival data were reported for both mastectomy and BCS, post-mastectomy breast cancer-specific survival was superior[108-111]. A single study statistically compared survival following mastectomy or BCS and found no statistical difference in breast cancer-specific survival at 15 years following treatment[112].

However, these cases should first be discussed in the Multidisciplinary team (MDT).

Patients with Paget's disease and underlying DCIS or invasive breast cancer should be treated according to the respective recommendations (see above).

Recommendations

- **Breast conserving surgery with removal of the nipple–areolar complex followed by radiotherapy should be offered as an alternative to mastectomy in patients with Paget's disease without underlying invasive breast cancer (2C evidence).**
- **Oncoplastic repair techniques should be offered to patients with Paget's disease treated with breast conserving surgery to maximise cosmesis (1C evidence).**

3.5 TREATMENT OF EARLY INVASIVE BREAST CANCER

For all women with early invasive breast cancer, treatment may consist of the following components[2]:

- neoadjuvant systemic therapy
- surgery to the breast and surgery to the axilla
- locoregional radiotherapy
- adjuvant chemotherapy
- adjuvant endocrine treatment if hormone receptor positive.

However, this treatment is multidisciplinary and should therefore be discussed on an individual basis in the multidisciplinary team.

Recommendations

- **All patients with breast cancer should be discussed within a multidisciplinary team before any treatment (expert opinion).**

3.5.1 Neoadjuvant treatment

A Cochrane review[113] aimed to assess the effectiveness of preoperative chemotherapy in women with operable breast cancer. This review, identifying 14 RCTs involving 5 500 women, revealed no difference in overall survival and disease-free survival for women receiving either preoperative or postoperative chemotherapy (HR 0.98; 95%CI 0.87-1.09; p=0.67; no heterogeneity). Preoperative treatment increases the possibility for BCS because of shrinkage of the tumour before surgical intervention (RR 0.82; 95%CI 0.76-0.89), yet at the associated cost of slightly increased locoregional recurrence rates (HR 1.12; 95%CI 0.92- 1.37; p=0.25; no heterogeneity). Pathological complete response was associated with better survival than residual disease (HR 0.48; 95%CI 0.33-0.69; p < 0.0001). This review suggests safe application of preoperative chemotherapy for downstaging in the treatment of women with early stage breast cancer[113].

Recommendations

- **In patients with unifocal operable tumours too large for breast conserving surgery, downstaging with neoadjuvant systemic therapy can be considered (1A evidence).**

3.5.2 Surgery to the breast

Several RCTs compared BCS (followed by loco-regional radiation therapy) with total mastectomy and found no difference in survival between the two procedures[18, 114-117]. Yang et al.[117] carried out a meta-analysis to determine the effectiveness of BCS or mastectomy for stage I or stage II breast cancer. Globally, 18 RCTs of moderate quality including a total of 9 388 patients were analysed. The meta-analysis showed that the overall survival at 3, 5, 10, 15 and 20 years and the locoregional recurrence rate at 3, 5, 15 and 20 years were not significantly different between the two groups, but 10-year locoregional recurrence rate increased in the group with BCS. The sensitivity analysis indicated that both overall survival and locoregional recurrence rate were not statistically different between the BCS group and the mastectomy group. Blichert-Toft et al.[114] reported similar results from the 20-year follow-up of the Danish randomized DBCG-82TM protocol. The main analyses were conducted on a subgroup of 793 correctly randomized patients. The 10-year recurrence free survival and 20-year overall survival based on the intention-to-treat principle did not reveal significant differences in outcome between BCS vs. mastectomy (p=0.95 and p=0.10, respectively). In conclusion, long-term data indicate that BCS (followed by loco-regional radiation therapy) in eligible patients proves as effective as mastectomy both regarding local tumour control, recurrence free survival and overall survival.

Breast reconstruction involves the use of a prosthesis or tissue from elsewhere in the body to rebuild a breast shape following mastectomy. Immediate breast reconstruction occuring at the time of initial surgery results in less surgical interventions. Delayed reconstruction requires a subsequent surgical procedure once a woman has recovered from initial surgery and any other adjuvant treatment. This may be a better choice for some women who need radiation to the chest area after mastectomy[93]. Our literature review did not identify any studies comparing the effectiveness of immediate compared with delayed breast reconstruction. Some evidence regarding local recurrence and surgery was available in the SIGN guideline (2003)[18], whereas the NICE guideline (2009)[2] retrieved one systematic review of observational studies[97] suggesting that better psychological outcomes are associated with immediate reconstruction compared to delayed reconstruction. Subsequently published observational studies[98, 99] suggested that psychological outcomes are generally good following immediate reconstruction. No reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those who receive delayed reconstruction[2].

All patients eligible for BCS should be fully informed about both options before the choice of surgery is made.

Recommendations

- **Breast-conserving surgery followed by radiotherapy offers the same survival benefits as modified radical mastectomy in women with stage I or II breast cancer who are candidates for breast-conserving surgery (1A evidence).**
- **Oncoplastic repair techniques should be offered to patients treated with breast conserving surgery to maximise cosmesis (1C evidence).**
- **Immediate breast reconstruction after mastectomy offers the same survival benefits as mastectomy without reconstruction (1C evidence).**
- **The choice of surgery must be tailored to the individual patient with stage I or II breast cancer, who should be fully informed of the surgical options (1A evidence).**

3.5.3 Surgery to the axilla

Axillary surgery is currently required for adequate staging and treatment of early invasive breast cancer. The aims of axillary surgery are to eradicate local disease thereby minimising local recurrence and possibly influencing survival, and to determine prognosis in order to guide adjuvant therapy. Axillary surgery includes techniques, such as SLNB, ALND or axillary sampling[2, 93].

A large amount of evidence is available on the use of SLNB in breast cancer[2, 64, 103]. In 2004, ASCO identified 1 RCT, 4 meta-analyses and 60 controlled trials[103]. A well-conducted systematic review and meta-analysis of 69 studies was further undertaken by Kim et al.[102] with data from over 8 000 patients. The overall SLN localisation rate was 96.4%, the pooled estimate of the false negative rate was 7.0% (95%CI 5.2%-8.8%), the mean proportion of patients with positive SLNs was 42% and the post-test probability negative was 4.6%.

SLNB is indicated in women with primary breast cancer less than 3 cm and clinically and ultrasonographically negative nodes[64, 102, 103]. Appropriately identified patients with negative results from SLNB, when done by an experienced surgeon, do not need completion ALND[103].

The sentinel node is positive if any tumour deposit in the node or in the afferent or efferent lymph vessels is found. Tumour deposits are categorized as isolated tumour cells (<0.2 mm), micrometastases (0.2–2 mm), or macrometastases (>2 mm)[118].

Isolated cancer cells detected by pathologic examination of the SLN with use of specialized techniques are currently of unknown clinical significance and are not a required part of SLN evaluation for breast cancer at this time. This recommendation is based on a large body of mainly observational evidence[103].

Since 2008, in the AMAROS trial, isolated tumour cells are also considered to be sentinel node negative and do not require further axillary treatment[118].

If the SLN contains macrometastases, ALND level I and II is indicated[2, 118]. Also, for invasive tumours > 3 cm or for cN+ tumours, an ALND level I and II is mandatory. For micrometastases, prospective clinical trials are ongoing (AMAROS trial and IBCSG-23-01 trial). Both trials are investigating treatment following identification of a positive SN/micrometastases from SNB. Preliminary results from AMAROS indicated that further nodal involvement in patients with macrometastases, micrometastases, and isolated tumor cells undergoing an ALND was 41, 18, and 18%, respectively[118]. Until final results from both trials are presented, axillary dissection is recommended.

For some experts, the decision for axillary dissection in the presence of micrometastases in the SLN depends on other risk factors. For example increased tumor size, more than one positive sentinel lymph node, lymphovascular invasion in the primary tumor, and lobular histology (used as a nomogram) also have statistically significant predictive value. However, if a SLNB is impossible, an ALND level I and II is indicated[64].

In the NICE guideline (2009)[2], two RCTs reported no significant differences in overall survival between groups given ALND or axillary sampling with regional lymph node radiotherapy for lymph node-positive patients; similarly there was no significant difference in overall survival between the groups receiving SLNB with ALND and SLNB or ALND only in SLN-positive patients. Finally, there were no differences between these groups for locoregional recurrences or axillary recurrences.

Mansel et al. reported on a RCT that examined arm morbidity and quality of life after SLNB or standard axillary treatment in 954 women with early-stage clinically node negative breast cancer[119]. Both outcomes were statistically better in the group allocated to SLNB.

In the ACOSOG trials Z0010 and Z0011, the authors compared results obtained with completion ALND (cALND), either concurrently with SLNB (n=425 patients) or at a second procedure (n=578)[120]. Lymph node recovery and long-term complications were similar after either delayed or immediate cALND for patients with metastasis to SLNs. Patients who underwent immediate cALND experienced more short-term morbidity (at 30 days) in terms of axillary paresthesia (51% vs. 35%; p<.000) and impaired range of motion (49% vs. 36%; p<.0001). However, improvement was reported at 1 year. With respect to staging and complications, there is no clear detriment for patients with a positive SLN who undergo a second procedure for cALND. The ACOSOG trial Z0011, a phase III trial, tested the use of ALND in clinically node negative patients having one or two positive SLN undergoing breast conserving surgery and classical radiotherapy. The publication of the final results will give important information on how to handle a positive sentinel node.

Both the ASCO[103], UK[2] and European guidelines[121] contain a section on the pathologic evaluation of SLNs. A clear discussion can also be found in the CBO guideline (in Dutch)[64].

Recommendations

- **Sentinel lymph node biopsy is not recommended for (1A evidence):**
  - **large T2 (i.e. > 3 cm) or T3-4 invasive breast cancers;**
  - **inflammatory breast cancer;**
  - **in the presence of suspicious palpable axillary lymph nodes;**
  - **multiple tumours; and possible disturbed lymph drainage after recent axillary surgery or a large biopsy cave after tumour excision.**
- **In women with primary breast cancer less than 3 cm and with clinically and ultrasonographically negative nodes, a sentinel lymph node biopsy should be performed (1A evidence).**
- **Peri-operative pathology examination of SLN is recommended. For macrometastases (>2 mm), axillary lymph node dissection level I and II is indicated (1A evidence). For micrometastases (0.2-2 mm) until final results of ongoing prospective clinical trials are available, axillary dissection is recommended taking into consideration other risk factors (for example used as a nomogram) (expert opinion).**
- **If a sentinel lymph node biopsy is impossible, an axillary lymph node dissection level I and II is indicated (1A evidence).**
- **Patients found to have only isolated tumour cells in their sentinel lymph nodes should not be offered further axillary treatment (1C evidence).**

3.5.4 Adjuvant therapy

3.5.4.1 Sequencing of adjuvant therapy

In a recent Cochrane review of RCTs evaluating different sequencing of chemotherapy and radiotherapy, no significant differences were found between the various methods of sequencing adjuvant therapy in terms of survival, distant metastases or local recurrence[122]. However, radiotherapy before chemotherapy was associated with a significantly increased risk of neutropenic sepsis (OR 2.96, 95%CI 1.26 - 6.98) compared with chemotherapy before radiotherapy. Therefore, if both adjuvant chemotherapy and radiotherapy are indicated, the chemotherapy should be given first.

Evidence from a meta-analysis of 8 observational studies suggests that locoregional recurrence is more likely if radiotherapy is delayed more than 8 weeks following surgery (OR [interval>8 weeks : interval ≤ 8 weeks] 1.62; 95%CI, 1.21 - 2.16) corresponding to an increase in the 5-year loco-regional recurrence rate from 5.8% in those patients treated within 8 weeks to 9.1% in those patients treated between 9 and 16 weeks after surgery[123].

Similar results were obtained in a retrospective analysis of 2 594 patients receiving adjuvant chemotherapy for stage I and II breast cancer. Five-year OS rates were 84%, 85%, 89%, and 78%, (log-rank p=0.013); RFS rates were 74%, 79%, 82%, and 69% (log-rank p=0.004) for patients starting chemotherapy 4 weeks or fewer, more than 4 to 8 weeks, more than 8 to 12 weeks, and more than 12 to 24 weeks after surgery, respectively. Lohrisch et al.[124] concluded that 5 year-RFS and 5 year-OS seem to be compromised by delaying chemotherapy more than 12 weeks after definitive surgery.

However, there is conflicting evidence about the higher impact of delaying chemotherapy according to the hormonal receptor status (ER negative or ER positive)[124-127].

Recommendations

- **If adjuvant chemotherapy and radiotherapy are indicated, the chemotherapy should be given first (1A evidence).**
- **It is recommended to start adjuvant chemotherapy or radiotherapy within 8 weeks of completion of surgery (1C evidence).**

3.5.4.2 Radiotherapy

The recommendation to give adjuvant radiotherapy to patients treated with BCS is based on the systematic review of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) and subsequent RCTs[18, 64, 128]. Ten trials reported a substantial and significant reduction in local recurrence (mainly in the conserved breast) after adjuvant radiotherapy (p<0.00001). The recurrence rate ratio, comparing those allocated radiotherapy with those not, was about 0.3 in every trial, corresponding to a proportional reduction of 70%[128]. The proportional risk reduction for breast cancer mortality is much less extreme, but highly significant (breast cancer death rate ratio 0.83, SE 0.05, 95%CI 0.75–0.91, 2p=0.0002), indicating a reduction of about one-sixth in the annual breast cancer mortality rate[128].

However, the effect on mortality of radiotherapy of the thoracic wall following mastectomy is less clear[18]. In a systematic review of the EBCTCG of 34 RCTs involving approximately 20 000 women, no reduction of all-cause mortality or breast cancer mortality was found with radiotherapy after mastectomy alone or mastectomy plus axillary clearance[18]. However, radiotherapy did reduce all-cause mortality and breast cancer mortality after mastectomy plus axillary sampling. A recent RCT showed a clear survival benefit of radiotherapy in premenopausal women with node-positive breast cancer treated with modified radical mastectomy and adjuvant chemotherapy[129].

In their large overview of all EBCTCG trials conducted since 1995, Clarke et al.[44] reported that for women with mastectomy, axillary clearance, and node-positive disease, the 5-year local recurrence risks, irradiated versus control, were 4% versus 16% for women with 1-3 involved nodes (reduction 12%, SE 2) and 12% versus 26% for women with 4+ involved nodes (reduction 14%, SE 2). The 15-year local recurrence risk reduction differed more substantially, however, and was 14% and 20% for women with 1-3 and for those with 4+ involved nodes, respectively. The paper published by Overgaard et al.[130] on a subgroup of the DBCG 82 b&c trials confirmed the effectiveness of radiotherapy for women with less than 4 involved nodes. Radiotherapy reduced the 15-year loco-regional failure rate from 51% to 10% (p<0.001) in 4+ positive node patients and from 27% to 4% (p<0.001) in patients with 1-3 positive nodes. Similarly, the 15-year survival benefit after radiotherapy was significantly improved in both patients with 1-3 positive nodes (57% vs. 48%, p=0.03) and in patients with 4+ positive nodes (21% vs. 12%, p=0.03). However, in women having at least two out of three unfavourable criteria (>3 positive nodes, tumour size >5 cm, Grade 3 malignancy), a large absolute reduction in 5-year local recurrence probability (36%) did not translate into any reduction in 15-year breast cancer mortality (0%)[131].

As no RCT evaluated the harm/benefit ratio obtained with post-mastectomy irradiation for only one positive node, this treatment has to be discussed with the patient, taking into account prognostic characteristics of the tumour, the positive node's size, woman's age, her desire to have a breast reconstruction and cardiotoxicity of RT. Altogether, these issues may be clarified in the prospective randomized international SUPREMO trial including patients with 1–3 positive lymph nodes (ISRCTN61145589).

The role of internal mammary chain irradiation is unclear at the moment[132], and is currently being investigated in the EORTC 22922/10925 trial[133]. Patients eligible for internal mammary chain irradiation are to be discussed in the MDT.

For breast cancer patients having primary BCS or mastectomy, the commonest schedule used internationally involves 25 fractions of 2 Gy to a total dose of 50 Gy[2]. The aim of conventional fractionation at 2 Gy per fraction is to minimise late tissue damage whilst maximising tumour control. However, some trials are testing the delivery of an effective dose of radiation in a shorter period in order to increase patient throughput and convenience for rural patients[134, 135]. Two high-quality RCTs[134, 136] were evaluated in a systematic review[137]. Whelan et al. compared two different fractionation regimes (42.5 Gy in 16 fractions and 50 Gy in 25 fractions) while Owen et al.[134] compared three fractionation regimens (39 Gy in 13 fractions, 42.9 Gy in 13 fractions, and 50 Gy in 25 fractions). Hypofractioned radiotherapy did not appear to affect local recurrence free survival (absolute difference 0.4%, 95%CI -1.5% to 2.4%), breast appearance (RR 1.01, 95%CI 0.88 to 1.17), survival at five years (RR 0.97, 95%CI 0.78 to 1.19), late skin toxicity at five years (RR 0.99, 95%CI 0.44 to 2.22), and late radiation toxicity in sub-cutaneous tissue (RR 1.0, 95%CI 0.78 to 1.28). The START Trialists' Group also conducted a RCT comparing two radiotherapy schedules in women with early breast cancer (pT1-3a pN0-1 M0): 50 Gy in 25 fractions of 2.0 Gy over 5 weeks (n=1 105 women) or 40 Gy in 15 fractions of 2.67 Gy over 3 weeks (n=1 110 women)[135]. After a median follow up of 6.0 years (IQR 5.0–6.2) the rate of local-regional tumour relapse at 5 years was 2.2% (95% CI 1.3–3.1%) in the 40 Gy group and 3.3% (95%CI 2.2 to 4.5%) in the 50 Gy group. The authors concluded that fewer, larger fractions are at least as safe and as effective as the 'standard' schedule of 50 Gy in 25 fractions. However, a median follow-up of 5 years is too short to allow assessment of all potential late normal tissue effects such as cardiac damage[135]. The length of follow-up and the evidence are currently insufficient to identify one optimal fractionation schedule.

To reduce the risk of local recurrence after radiotherapy, an additional boost dose of radiation to the tumour bed can be considered. NICE[2] reported results from the European Organisation for Research and Treatment of Cancer trial EORTC 22881–10882, in which participants, younger than 70 years old, were randomised to a boost radiotherapy dose of 16 Gy to the original tumour bed or no boost. RCT data were consistent in the finding that a boost dose to the tumour bed reduced local recurrence (4.3% in 'boost' arm vs. 7.3% in 'no boost' arm), but had little effect on overall survival. Nevertheless, fibrosis and teleangiectasia tended to be worse in the boost group[138].

Veronesi et al. assessed the role of axillary radiotherapy in the treatment of node negative early breast cancer[139]. No significant differences were found between the axillary radiotherapy group and group receiving no axillary treatment in terms of local recurrence and disease-free survival. In a RCT of Louis-Sylvestre et al., no difference in long-term survival was found after axillary radiotherapy vs. axillary dissection in patients with clinically node-negative invasive breast cancer[140]. Based on these data, axillary radiotherapy cannot be considered routine practice and should be discussed in the MDT on an individual basis.

Recommendations

- **In patients with early breast cancer, adjuvant irradiation is indicated after breast conserving surgery (1A evidence).**
- **Adjuvant chest wall radiotherapy after mastectomy should be offered to patients with early invasive breast cancer and a high risk of local recurrence including four or more positive axillary lymph nodes or involved resection margins (1A evidence).**
- **Until data from a large ongoing randomized trial become available, radiotherapy after mastectomy should be offered to patients with 1-3 positive nodes (1A evidence).**
- **Internal mammary chain irradiation is to be discussed in the multidisciplinary team meeting (expert opinion).**
- **The target volume of percutaneous adjuvant radiotherapy encompasses the entire breast and the adjoining thoracic wall. The dose amounts to approximately 50 Gray fractionated in the conventional manner (1.8-2.0 Gray) with an additional local boost (1A evidence).**
- **An additional beam boost to the site of local excision can be offered to patients with early invasive breast cancer and a high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy (2A evidence).**
- **Axillary radiotherapy should be discussed on an individual basis in the multidisciplinary team (1A evidence).**

3.5.4.3 Systemic therapy

Classification of patients for therapeutic purposes

The 12th St Gallen International Breast Cancer Conference (2011) Expert Panel adopted a new approach for the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes within the breast cancer spectrum[12]. For systemic therapy, recommendations were formulated for each of the biological subtypes, since these already incorporate many of the risk factors and response predictors previously considered separately. However, gene expression array information is not always simple to obtain. Consequently, a simplified classification has been adopted. Subtypes defined by clinicopathological criteria are similar to but not identical to intrinsic subtypes and represent a convenient approximation. This approach, summarized in Table 3, uses an immunohistochemical definition of estrogen and progesterone receptors, the detection of overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2) oncogene, and the Ki-67 labeling index[141], a marker of cell proliferation, as the means of identifying tumour subtypes[12].

The classification of breast tumours according to the intrinsic subtypes is helpful for estimating the prognosis of breast cancer patients[142]. Nevertheless, there are no data from phase III trials on their role as predictive tools for chemotherapy benefit.

Table 3. Surrogate definitions of intrinsic subtypes of breast cancer[142, 143]

Intrinsic Subtype	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** ER and/or PgR positive[144] HER2 negative[145] Ki-67 low (<14%)*	This cut-off point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping[143]. Local quality control of Ki-67staining is important.
Luminal B**	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high **'Luminal B (HER2 positive)'** ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Genes indicative of higher proliferation are markers of poor prognosis in multiple genetic assays[146]. If reliable Ki-67 measurement is not available, some alternative assessment of tumour proliferation such as grade may be used to distinguish between 'Luminal A' and 'Luminal B (HER2 negative)'. Chemotherapy, endocrine and anti-HER2 therapy may be indicated.
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent	Quality of HER2 testing is of paramount importance
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	Approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype but 'triple negative'*** also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low(er) risks of distant recurrence. Staining for basal keratins[147] although shown to aid selection of true basal-like tumours, is considered insufficiently reproducible for general use.

Note. This table is based on Goldhirsch et al. (2011)[12], adapted by our GDG

*This cut-off point is derived from comparison with gene array data as a prognostic factor[143]. Optimal cut-points in Ki-67 labelling index for prediction of efficacy of endocrine or cytotoxic therapy may vary.

**Some cases over-express both luminal and HER2 genes.

*** The heterogeneous subtype includes adenoid cystic, juvenile secretory (good prognosis), medullary (intermediate prognosis), and metaplastic (either low grade, with good prognosis; or high grade, with poor prognosis) carcinomas, for which no generalizations can be proposed[148].

Table 4. Systemic treatment recommendations for subtypes.

'Subtype'	Type of therapy	Notes on therapy
'Luminal A'	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status or other indicator of risk).
'Luminal B (HER2 negative)'	Endocrine ± cytotoxic therapy	Inclusion and type of cytotoxics may depend on tumor load and characteristics including level of endocrine receptor expression and patient preference.
Luminal B (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2	Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.
'Triple negative (ductal)'	Cytotoxics	
'Special histological type'*		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine nonresponsive	Cytotoxics	Medullary** and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

Note. This table is based on Goldhirsch et al. (2011)[12], adapted by our GDG

*Special histological types: Endocrine responsive (cribriform, tubular, and mucinous); Endocrine nonresponsive (apocrine, medullary, adenoid cystic and metaplastic).

** Medullary carcinoma has a better outcome than other triple negative tumors, but this was mainly in cohorts where patients received chemotherapy. Medullary carcinoma is probably highly chemosensitive. One study of metaplastic tumors without adjuvant chemotherapy showed 10y overall survival around 65% which indicates intrinsic risk of relapse without chemotherapy. The value of adjuvant chemotherapy for these tumors is insufficiently studied[149].

The systemic treatment recommendations summarized in Table 4 mainly recommend endocrine therapy alone for patients with clinicopathologically classified 'Luminal A' disease (except in defined high-risk cases), chemoendocrine therapy for 'Luminal B', the addition of anti-HER2 therapy in the presence of 'HER2 positivity', and a reliance on chemotherapy for most patients with 'Triple negative' disease (e.g. those with invasive ductal carcinoma)[12].

Recommendation

- **The choice of the adjuvant systemic treatment for invasive breast cancer should be driven by the hormonal sensitivity, risk profile of the tumour, age, menopausal status and comorbidities of the patient (1A evidence).**

Chemotherapy

In a combined analysis of 2 RCTs, Arriagada et al. found a better 10-year disease-free survival in early breast cancer patients (stage I – III) treated with adjuvant anthracycline-based chemotherapy compared to patients not treated with chemotherapy (65% vs. 60%, p=0.01)[150]. Also, the 10-year distant metastasis rates were significantly better in the active treatment group (23% vs. 28%, p=0.02). However, the 10-year local recurrence rate did not differ significantly between the two treatment groups[150].

Hutchins et al. found a slightly better 10-year overall survival rate in node-negative breast cancer patients treated with adjuvant FAC (cyclophosphamide, doxorubicin, fluorouracil) compared to those treated with adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) (85% vs. 82%, p=0.03)[151]. However, disease-free survival did not differ significantly, and FAC was associated with greater toxicity. In node-positive breast cancer patients, adjuvant FEC (cyclophosphamide, epirubicin, fluorouracil) was associated with a better 10-year relapse-free survival (52% vs. 45%, p=0.007) compared to adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil)[152]. Toxicity associated with FEC was acceptable.

High level evidence concluded to the superiority of anthracyclines-based chemotherapy on CMF in moderate or high risk breast cancer patients. The EBCTCG 2005 systematic review reported the superiority of anthracycline-based regimens to standard CMF regimens, in reducing breath cancer death rate by about 38% (SE 5) for women younger than 50 years of age and by about 20% (SE 4) for those of age 50–69 years, largely irrespective of the use of tamoxifen and of oestrogen receptor (ER) status, nodal status, or other tumour characteristics[43]. Eljertsen et al.[153] concluded that anthracycline-based therapy also resulted in an improvement in both disease free survival (HR 0.84; 95%CI 0.71 – 0.99) and overall survival (HR 0.79; 95%CI 0.66 – 0.94) at the 10-year follow-up. Toxicity associated with anthracyclines-based chemotherapy was considered acceptable with adverse events including nausea and vomiting, alopecia, mucositis. The risk of secondary leukaemia and congestive heart failure was similar in both chemotherapy regimens.

However, for patients with HER2 positive breast cancer who receive anti-HER2 therapy, the risk of cardiotoxicity is greatest when trastuzumab is used concurrently with anthracyclines (doxorubicin or epirubicin)[154]. Huybrechts et al. concluded that trastuzumab and anthracyclines should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring[154]. The pooled efficacy data of one year of trastuzumab was stronger when trastuzumab was administered concurrently with a taxane after anthracycline chemotherapy. Disease-free survival was significantly improved with a RR 0.49 (95%CI 0.41 – 0.57)[154].

In a pooled analysis of 9 RCTs, Bria et al. found significant differences in favour of taxanes in terms of disease-free survival in the overall (RR 0.86; 95%CI 0.81 – 0.90) and lymph node-positive population (RR 0.84; 95%CI 0.79 – 0.89), and in terms of overall survival in the overall (RR 0.87; 95%CI 0.81 – 0.83) and lymph node-positive population (RR 0.84; 95%CI 0.77 – 0.92)[155]. Further studies which reported overall survival also showed improved overall survival with use of the taxanes[156, 157]. A meta-analysis including 12 studies (N=22 379 participants, N=3 329 deaths) also showed a significant reduction in the risk of death for taxane-based treatment (HR 0.85, 95%CI 0.79 - 0.91, p<0.00001)[158]. The inclusion of a taxane in an anthracycline-based regimen should be considered[2, 159]. However, neutropenia and febrile neutropenia were identified as occurring more frequently in patients in the taxane groups than in the control groups. Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who have a high risk of febrile neutropenia based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. Clinical trial data support the use of CSF when the risk of febrile neutropenia is in the range of 20%

or higher[160]. Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome[160].

In a recent systematic review of Farquhar et al. – based on the results of 13 RCTs – no evidence was found to support the routine use of high-dose chemotherapy with autologous stem-cell transplantation in women with early poor-prognosis breast cancer[161]. At six years there was no statistically significant difference between the groups in event-free survival. With respect to overall survival, there was no statistically significant difference between the groups at any stage of follow up. However, morbidity was more common and more severe in the high-dose group[161].

Fertility may be transiently or permanently affected by cancer treatment or only become manifest later on through premature ovarian failure. Before the induction of the cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists[162].

For pregnant women with breast cancer, neoadjuvant or adjuvant anthracycline-based chemotherapy (FAC) can be given with minimal risks (premature labour and foetal wastage) to the foetus during the second or third trimester[163-165]. Anthracyclines need to be fractionated. Data on the immediate and long-term effects of chemotherapy on the child remain limited[163]. However, two year data did not demonstrate adverse events on the children[166, 167]. Until now, the use of newer therapeutic agents, such as docetaxel and paclitaxel, in pregnant patients is limited to case reports[165, 168, 169]. Given the potential foetal toxicity of methotrexate, CMF should not be used during pregnancy.

Recommendations

- **For patients with Stage I-III breast cancer, preferred regimens are standard anthracycline-based regimens with or without a taxane (1A evidence).**
- **For patients with lymph node-positive breast cancer, preferred regimens are standard anthracycline and taxane-based regimens (2A evidence).**
- **For patients with HER-2 positive breast cancer who receive trastuzumab, a sequential regimen of anthracyclines and taxanes is recommended to decrease the total dose of anthracyclines and hence reduce the cardiotoxicity (expert opinion).**
- **Women receiving an adjuvant anthracycline–taxane regimen should be closely monitored for febrile neutropenia.**
  - **Primary prophylactic G-CSF (granulocyte colony-stimulating factor) is recommended if risk of febrile neutropenia is 20% or higher (1A evidence).**
  - **Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (1A evidence).**
- **In patients with breast cancer, high-dose chemotherapy with stem-cell transplantation cannot be recommended (1A evidence).**
- **For all women within child bearing age, fertility issues should always be discussed before the induction of breast cancer therapy (1C evidence).**
- **Chemotherapy during pregnancy is not contraindicated after 14 weeks of gestation (2C evidence).**

Endocrine therapy

Adjuvant treatment with tamoxifen substantially improves the 15-year survival of premenopausal women with ER-positive tumours and of women whose tumours are of unknown ER status[43]. For ER-positive disease only, 5 years of adjuvant tamoxifen reduces the mortality rate by 31%, largely irrespective of the use of chemotherapy and

of age (<50, 50-69, ≥ 70 years), progesterone receptor status, or other tumour characteristics. Five years of treatment is significantly more effective than 1-2 years of tamoxifen[43]. For women with ER-negative and PR-negative tumours, adjuvant tamoxifen must not be given.

In a recent systematic review of Sharma et al., 4 RCTs were identified that studied the addition of LHRH agonists (mainly goserelin) to adjuvant hormonal therapy in premenopausal women with early breast cancer[170]. Overall, these studies demonstrated the efficacy of adjuvant goserelin with or without tamoxifen, in reducing the risk of recurrence and delaying the death. The evidence is insufficient to support LHRH agonists over chemotherapy, or vice versa, regarding recurrence-free survival and overall survival, but LHRH agonists have fewer or less severe adverse effects.

The authors concluded that combined tamoxifen and LHRH agonists may be regarded as a treatment option for premenopausal women with endocrine-responsive disease.

Hackshaw et al.[171] published 12 years follow-up data of 2 700 premenopausal women with operable stage I or II breast cancer, recruited for the ZIPP trial (Zoladex In Premenopausal Patients), evaluating the LHRH agonist goserelin and tamoxifen, given for 2 years. They concluded that 2 years of goserelin treatment was as effective as 2 years of tamoxifen treatment until 15 years after starting therapy. In women who did not take tamoxifen, there was a large benefit of goserelin treatment on survival and recurrence (8.5 fewer breast cancer deaths vs. no goserelin). In women who did take tamoxifen, there was a marginal benefit when goserelin was added (possibly 2.6 fewer deaths). This confirmed previous results, indicating that the addition of tamoxifen and goserelin to adjuvant chemotherapy significantly improved disease-free survival (HR=0.74; 95%CI 0.56 – 0.99; p=0.04)[172].

Aromatase inhibitors (anastrozole, exemestane and letrozole) are alternative options to tamoxifen for ER-positive invasive breast cancer in postmenopausal women[2, 173]. Switching to adjuvant anastrozole from adjuvant tamoxifen showed a statistically significant improvement in disease-free survival (HR 0.66; 95%CI 0.44-1.00; p=0.049), and improved overall survival (HR 0.53; 95%CI 0.28-0.99; p=0.045) compared with continuing on tamoxifen[174]. A meta-analysis of the ABCSG-8 (The Austrian Breast and Colorectal Cancer Study Group), ARNO-95 (German Adjuvant Breast Cancer Group Arimidex/Nolvadex), and ITA (The Italian Tamoxifen Arimidex) trials found improvements in disease-free survival (HR 0.59; 95%CI 0.48-0.74; p<0.0001), distant recurrence-free survival (HR 0.61, 95%CI 0.45-0.83, p=0.002), and overall survival (HR 0.71; 95%CI 0.52-0.98; p=0.04) for women who switched to anastrozole[175]. However, consistent advantage in overall survival has not been observed, particularly for other aromatase inhibitors and in other treatment settings. Moreover, evidence indicates that patients treated with aromatase inhibitors experience a higher incidence of fractures and an increased loss of lumbar spine and hip bone mineral density[2].

The Intergroup Exemestane Study (IES) (n=4 742) compared two to three years of tamoxifen followed by exemestane with two to three years of tamoxifen followed by further tamoxifen, each to a total of five years of adjuvant hormone therapy[176, 177]. At a median follow-up of 55.7 months, disease-free survival was significantly improved in the exemestane arm (HR 0.76; 95%CI 0.6-0.88), but overall survival did not. Overall survival was only significantly improved in ER-positive women (HR 0.83, 95% CI 0.69-1.00 in favour of switching to exemestane).

The Breast International Group (BIG) 1-98 trial compared letrozole versus tamoxifen in 8 028 women. After a median follow-up of 51 months, patients treated with letrozole had significantly better disease-free survival versus those treated with tamoxifen (HR 0.82; 95%CI 0.71-0.95). There was also significant benefit as to time-to-recurrence and time-to-distant-recurrence with letrozole. Overall survival was not significantly different. The Breast International Group (BIG) 1-98 trial also compared 2 years of treatment with one agent followed by 3 years of treatment with the other[178]. At a median follow-up of 71 months after randomization, disease-free survival was not significantly improved with either sequential treatment as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05; 99% CI 0.84-1.32; HR for letrozole followed by tamoxifen, 0.96; 99%CI 0.76-1.21). The updated analysis of monotherapy showed that

there was a non-significant difference in overall survival between women assigned to treatment with letrozole and those assigned to treatment with tamoxifen (HR for letrozole, 0.87; 95%CI 0.75-1.02; p = 0.08).

Patients who started tamoxifen at baseline should consider a switch to an oral aromatase inhibitor after 2-3 years of tamoxifen therapy, especially if they are at high-risk for recurrence (node positive, grade 3, HER2 positive, LVI or large tumour size).

The MA-17 trial showed that extended adjuvant treatment with letrozole (after 5 years of standard tamoxifen treatment) significantly reduces the risk of recurrent breast cancer regardless of the patient's nodal status or receipt of prior chemotherapy[173, 179]. Above this, letrozole was associated with a significant improvement in overall survival in women with node-positive disease.

In the absence of good clinical data, but as a matter of precaution, it is current practice to give adjuvant hormonal treatment after chemotherapy and not concomitantly[180]. Albain et al.[181] supported this recommendation, reporting that chemotherapy with CAF (cyclophosphamide, doxorubicin, and fluorouracil) plus tamoxifen given sequentially was more effective adjuvant therapy for disease free survival and overall survival in postmenopausal patients with endocrine-responsive, node-positive breast cancer than is tamoxifen alone.

Recommendations

- **Premenopausal patients with hormone receptor positive breast cancer should receive adjuvant endocrine treatment with tamoxifen for 5 years with or without an LHRH analogue (1A evidence).**
- **Premenopausal women with stage I or II breast cancer who cannot take tamoxifen, should receive a LHRH analogue (1A evidence).**
- **Postmenopausal patients with hormone receptor positive breast cancer should receive adjuvant endocrine treatment with either (1A evidence):**
  - **tamoxifen (for 5 years),**
  - **anastrozole (for 5 years) or letrozole (for 5 years),**
  - **or tamoxifen (for 2 - 3 years) followed by an aromatase inhibitor (to a total of five years of hormone therapy),**
  - **or aromatase inhibitor (for 2 years) followed by tamoxifen (for a total of 5 years).**
- **Postmenopausal women with hormone receptor positive tumours who have completed five years of adjuvant tamoxifen therapy should be considered for extended treatment with an aromatase inhibitor (for up to 5 years) if node-positive or high-risk node-negative (pT2 or grade III) (1A evidence).**

Trastuzumab

The humanised monoclonal antibody trastuzumab targets the extracellular domain of HER2. Its use in the adjuvant therapy of HER2-positive breast cancer reduces the risk of relapse by about 50% and the risk of death by about 30%[2]. Dahabreh et al.[182] conducted a systematic review and meta-analysis to compare treatment outcomes for HER2–positive breast cancer patients receiving adjuvant chemotherapy with or without trastuzumab. The authors identified five trials reporting outcomes on 13 493 women. Fixed-effects analysis showed higher disease-free survival for trastuzumab treated patients (RR 0.62; 95%CI 0.56–0.68), lower mortality (RR 0.66; 95%CI 0.57–0.77), lower locoregional recurrence (RR 0.58; 95% CI 0.43–0.77), and lower distant recurrence (RR 0.60; 95%CI 0.52–0.68). However, in the trastuzumab arm, patients had a higher risk for congestive heart failure (RR, 7.60; 95%CI, 4.07–14.18) and for left ventricular ejection fraction decline (RR, 2.09; 95%CI, 1.84–2.37). A higher risk for central nervous system metastasis as the first recurrence event (RR, 1.60; 95%CI, 1.06–2.40) was also reported in this group.

Recently, the KCE published a report on the use of trastuzumab as an adjuvant treatment in women with early-stage breast cancer[154]. According to the identified

evidence, the authors concluded that – based on the criteria from the HERA trial (T > 1cm and/or previously chemotherapy)[183, 184] – a 1 year treatment with adjuvant trastuzumab is usually effective in women with early-stage HER2 FISH-positive breast cancer, a left ventricular ejection fraction of ≥ 55% and without cardiovascular exclusion criteria[154]. However, this treatment was not found to be cost-effective in all cases (stage I patients over 60 years, stage II patients over 70 years, and stage III patients over 80 years). A nine weeks treatment with adjuvant trastuzumab according to the criteria from the FinHer trial was found to be cost-saving[154]. It should be stressed, however, that the optimal treatment regimen and duration is unknown at present.

A safety and efficacy meta-analysis identified an increased risk of grade III-IV congestive heart failure, asymptomatic left ventricular ejection fraction and brain metastases with trastuzumab compared with controls, along with prolonged disease-free survival, prolonged distant disease-free survival and prolonged overall survival with trastuzumab[185]. In view of the safety profile of trastuzumab, cardiac function should be monitored during treatment with trastuzumab[154].

ASCO and the College of American Pathologists recently published a guideline on HER2-testing in invasive breast cancer[186]. Besides a practical testing algorithm, this guideline also contains an interesting discussion on HER2-testing variation and tissue handling requirement. An analogue discussion can be found in the European guidelines[121].

It is important to note that, based on the phase III multicenter study BCIRG 006, in 2008 the US Food and Drug Administration approved a new treatment consisting of the chemotherapeutic agents Taxotere® (docetaxel) and carboplatin combined with Herceptin® (trastuzumab) (TCH) for the adjuvant treatment of HER2-positive early breast cancer. This regimen is not currently approved by the European Medicines Agency (EMA).

Recommendations

- **One year treatment with adjuvant trastuzumab is indicated for women with HER2-positive, node-positive or high-risk node-negative breast cancer (tumour size > 1 cm), having a left ventricular ejection fraction of ≥ 55% and without important cardiovascular risk factors who received chemotherapy (1A evidence).**
- **During treatment with trastuzumab, cardiac function should be monitored every 3 months (1A evidence).**

Biphosphonates

A recent systematic review identified 3 RCTs examining the use of bisphosphonates in the treatment of women with breast cancer but without clinically evident bone metastases. No risk reduction for the development of skeletal metastases was found, but a significant heterogeneity was found among the 3 studies[187]. In terms of survival, the combined results indicated that adjuvant clodronate may improve survival, again with significant heterogeneity among the three studies[187]. There are insufficient data to support the use of bisphosphonates in women without metastatic bone involvement or without tumour-induced hypercalcemia[188, 189]. However, different results can be expected in the near future, leading to potentially reconsider this conclusion.

Recommendation

- **Biphosphonates should not yet be part of the adjuvant treatment of breast cancer (1A evidence).**

3.6 TREATMENT OF METASTATIC BREAST CANCER

3.6.1 Multidisciplinary approach

The management of women with metastatic breast cancer is complex and can include endocrine therapy, chemotherapy and biological therapy. Above this, supportive and palliative care will also be needed for these patients[3]. Treatment choices are made according to patients' expectations and preferences, the risks of toxicity and the probable benefits in terms of improving symptoms, quality of life or survival[3].

However, the treatment is multidisciplinary and should therefore be discussed on an individual basis in the multidisciplinary team.

Recommendation

- **The treatment of the metastatic breast cancer should be discussed within a multidisciplinary team and patient preferences should always be taken into account (expert opinion).**

3.6.2 Diagnosis of metastatic breast cancer

3.6.2.1 Tumour markers

For monitoring patients with metastatic disease during active therapy, CA 27.29, CA 15-3 or CEA can be used in conjunction with diagnostic imaging, history, and physical exam. Present data are insufficient to recommend the use of CA 15-3, CA 27.29 or CEA alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA 15-3, CA 27.29 or CEA may indicate treatment failure. Caution should be used when interpreting a rising CA 27.29, CA 15-3 or CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur[42], specially with endocrine therapy.

Recommendation

- **For monitoring patients with metastatic disease during active therapy, CA 27.29, CA 15-3 or CEA can be used in conjunction with diagnostic imaging, history, and physical exam (2C evidence).**

3.6.2.2 Biopsy of metastatic lesions

Histological or cytological verification of metastatic disease should be done whenever possible. The biopsy of metastatic lesions allows to confirm the presence of a metastatic tumour (in cases of doubt), to characterize the biological markers associated with tumour recurrence and to define the treatment planning. In such cases, a reassessment of the ER and PgR status by standardized immunohistochemistry (IHC) and of Her-2/neu status by IHC or fluorescence in situ hybridization (FISH) have to be included in the diagnostic work-up[188,34].

Recommendations

- **Metastatic lesions should be biopsied whenever accessible and ER, PgR and HER2 reassessed (1B evidence).**
- **In both pre- and postmenopausal patients, HER2 status should be used to identify patients most likely to benefit from Trastuzumab in metastatic disease settings (1B evidence).**

3.6.3 Systemic treatment

3.6.3.1 Endocrine therapy and ER antagonists

In premenopausal patients with HR+ or HR-unknown metastatic breast cancer, suppression of ovarian function in combination with tamoxifen is the first-line hormonal therapy[17, 64]. This recommendation is based on a meta-analysis of 4 RCTs, in which a significant survival benefit (HR 0.78, p=0.02) and progression-free survival benefit (HR 0.70, p=0.0003) was found in favour of the combined treatment[190].

In a recent systematic review including 6 RCTs, aromatase inhibitors were found to have a clear advantage in overall response rate, clinical benefit, and time to progression over tamoxifen as first-line hormonal treatment in postmenopausal patients with metastatic breast cancer[191]. Overall survival did not differ significantly. These results confirm the recommendations of CBO[64], the German Cancer Society[17], Cancer Care Ontario[192] and the Central European Cooperative Oncology Group[188]. However, tamoxifen remains an acceptable alternative as first-line treatment. Based on data from RCTs, following tamoxifen failure, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) or fulvestrant are recommended for second-line treatment for post-menopausal patients with HR-positive metastatic breast cancer based upon the more favourable side-effect profile[188, 192].

Flemming et al.[193, 194] reported results from two phase III, multicentre RCTs comparing fulvestrant versus anastrozole in patients with prior metastatic or adjuvant endocrine therapy. No significant differences were observed between fulvestrant and anastrozole therapy arms for time-to-progression (primary endpoint), objective response rate, time-to-treatment failure, clinical benefit, and overall survival (median follow-up ranging from 15.1 to 27.0 months). No significant differences in tolerability measures were identified between therapy arms with the exception of a higher incidence of joint disorders (including arthralgia, arthrosis, and arthritis) for patients treated with anastrozole (12.8% vs. 8.3%, p = 0.0234).

Flemming et al.[193, 194] also reported the results of the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) (n = 693)[195] comparing fulvestrant with exemestane in women with HR-positive breast cancer recurring after prior adjuvant non-steroidal aromatase inhibitor (NSAI) therapy (during or within 6 months of discontinuation) or progressing during prior NSAI therapy for advanced disease. At a median follow-up of 13 months, there were no significant differences for median time-to-progression (primary endpoint), objective response rate, clinical benefit rate, or duration of response. Fulvestrant and exemestane were both well tolerated, with no significant differences noted across any adverse events.

Recommendations

- **In premenopausal patients with hormone receptor-positive or hormone receptor unknown metastatic breast cancer, suppression of ovarian function in combination with tamoxifen is the first-line hormonal therapy of choice (1A evidence).**
- **In postmenopausal patients with hormone receptor-positive or hormone receptor unknown metastatic breast cancer, first-line treatment consists of third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) or Tamoxifen. The choice of the agent should take into consideration the adjuvant endocrine therapy received. As second-line treatment, the use of a third generation aromatase inhibitor or Fulvestrant is recommended (1A evidence).**
- **Fulvestrant may be considered as alternative therapy to third-generation aromatase inhibitors for metastatic breast cancer in postmenopausal women with hormone receptor-positive (ER+ and/or PgR+) breast cancer that has recurred after prior adjuvant tamoxifen therapy or progressed during prior tamoxifen therapy for advanced disease (1B evidence).**

3.6.3.2 *Chemotherapy*

Chemotherapy is indicated for women with hormone refractory or HR-negative metastatic breast cancer, rapidly progressive disease or symptomatic disease, or with life-threatening disease (e.g. diffuse lung or liver metastases, massive bone marrow metastases with pancytopenia)[64]. Multiple systematic reviews exist evaluating different chemotherapy regimens for women with metastatic breast cancer[161, 196-198].

A systematic review of 43 randomized trials (n = 9 742 women) suggests that polychemotherapy is associated with higher response rates and longer progression-free survival and a modest improvement in overall survival compared to single-agent treatment, but produces more adverse events including a decrease in white blood cell count, increased hair loss and nausea and vomiting[196]. On the other hand, the only major RCT[199] comparing sequential monotherapies with combined anthracyclines and taxanes did not demonstrate improved survival or quality of life with the latter approach, despite increased response rates[188]. In the absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control[200], sequential use of single cytotoxic agents is preferred to combination chemotherapy in metastatic disease. Patient- and disease related factors should be considered to choose between combination and sequential single-agent chemotherapy for MBC[200].

Anthracycline- and/or taxane-based regimens are to be preferred as first-line treatment in symptomatic patients and/or those with rapidly progressive disease[188]. The combined use of anthracyclines and taxanes increased objective response rate and time-to-progression in some trials. Moreover, overall survival was improved in two RCTs[201, 202]. A higher treatment-related toxicity was reported.

Polychemotherapy compared to single-agent therapy obtained slightly superior results in overall survival in metastatic breast cancer women pretreated with anthracycline. In one phase III trial[203], the combination of capecitabine plus docetaxel resulted in significantly superior efficacy in time-to-disease progression (HR 0.65; 95%CI 0.54-0.78; median, 6.1 vs. 4.2 months), overall survival (HR 0.77; 95%CI 0.63-0.94; median, 14.5 vs. 11.5 months), and objective tumour response rate (42% vs. 30%, p=0.006) compared with docetaxel. The combination resulted in significantly increased hematologic and non-hematologic toxicity. Another randomized phase III trial compared paclitaxel plus gemcitabine with paclitaxel[204]. The combination regimen was associated with an improved overall survival (18.6 months versus 15.8 months; log-rank p = 0.0489, with an adjusted Cox hazard ratio of 0.78 [95% CI 0.64-0.96; p = 0.0187]), a longer time-to-progression (6.14 vs. 3.98 months; log-rank p = 0.0002) and a better response rate (41.4% vs. 26.2%; p = 0.0002). The gemcitabine/paclitaxel arm was also associated with increased pain relief and better quality of life. However, there was more grade 3 to 4 neutropenia on combined therapy and grade 2 to 4 fatigue and neuropathy were slightly more prevalent. Data from these two RCTs demonstrated that the combination of a taxane with capecitabine or gemcitabine is superior to taxane alone in increasing overall survival in patients with metastatic breast cancer[188].

A randomized phase III trial compared docetaxel plus gemcitabine (DG) with docetaxel plus capecitabine (DC) and showed similar efficacy in terms of progression-free survival (median PFS was 8.05 months [95% CI, 6.60 to 8.71] for DG and 7.98 [95% CI, 6.93 to 8.77] for DC), tumour response rate (32% in both arms) and overall survival. Time-to-failure was longer and non-hematologic toxicity was significantly lower in the DG arm[205]. However, severe hematologic toxicity rates (grades 3 to 4 leukopenia) were higher in DG group (78% vs. 66%; p=0.025), as was the transfusion rate (DG, 17%; CD, 7%; p=0.0051).

Very few randomized phase III trials have addressed optimal selection of treatment after failure of taxanes and/or anthracyclines. Chan et al.[206] conducted a large non-systematic review evaluating the relative efficacy of capecitabine and vinorelbine alone or in combination in metastatic breast cancer. They identified 6 capecitabine and 2 vinorelbine phase III trials, numerous phase II monotherapy studies and 35 phase I/II studies exploring capecitabine–vinorelbine combination therapy (1 with trastuzumab in HER2-positive MBC). For the majority of patients, capecitabine monotherapy appeared to be the more effective agent for metastatic breast cancer women with prior taxane exposure or who are unsuitable for taxane therapy. Treatment options should take into account prior therapy, comorbidities, tolerability and patient preferences. Combination regimens of capecitabine and vinorelbine potentially improve efficacy compared with monotherapy, but at the cost of increased toxicity. Such regimens need further evaluation against effective sequential, monotherapy strategies before they can be recommended for routine use[206].

Recommendations

- **Chemotherapy for patients with metastatic breast cancer is indicated for the following conditions (expert opinion):**
  - **hormone refractory or HR- tumours**
  - **rapidly progressive disease or symptomatic disease**
  - **life threatening disease**
- **The choice between polychemotherapy and sequential single agent chemotherapy should take into account the prognosis, performance status, need for rapid symptom control and toxicity profiles with the ultimate goal of optimizing quality and quantity of life (expert opinion).**
- **Anthracycline- and/or taxane based regimens are to be preferred as first-line treatment depending on adjuvant chemotherapy received and disease-free interval (1A evidence).**
- **In patients with anthracycline-resistance or failure and taxane-naive, considered for further chemotherapy, taxane-based treatment (monotherapy or combination of a taxane with gemcitabine or capecitabine) should be used, taking into account quality of life, toxicity, characteristics of the disease and the ease of administration (1A evidence).**

3.6.3.3 Biological therapy

Trastuzumab

Trastuzumab is only used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated test[3].

In a pivotal, randomized phase III trial performed in patients with HER-2/neu overexpressing metastatic breast cancer, first-line treatment with the combination of trastuzumab plus chemotherapy has been shown to result in a significantly higher tumour response rate and significantly prolonged overall survival as compared with chemotherapy alone[188]. Numerous RCTs have shown the advantage of adding trastuzumab to chemotherapy with taxanes[188]. This was confirmed by a RCT that showed that the combination of trastuzumab and docetaxel is superior to docetaxel alone as first-line treatment of patients with HER2-positive metastatic breast cancer in terms of overall survival, response rate, response duration, time to progression, and time-to-treatment failure, although combination treatment was complicated by a higher risk of cardiotoxicity[207]. In this trial, survival was longest for the group who received trastuzumab and docetaxel concomitantly from the start of treatment (median OS, 31.2 months), indicating that that earlier treatment with trastuzumab could lead to the improvement in survival. Patients have to undergo baseline measurement of cardiac function prior to trastuzumab–based therapy and continue cardiac surveillance while continuing treatment[188].

An important phase III trial investigated if trastuzumab treatment should be continued beyond progression[208]. Patients with HER2-positive breast cancer progressing during treatment with trastuzumab with a taxane were randomly assigned to receive capecitabine alone or in combination with trastuzumab. Continuation of trastuzumab plus capecitabine showed a significant improvement in overall response (OR 2.50; p=0.0115) and time-to-progression (HR 0.69; 95%CI 0.48 - 0.97; two-sided log-rank p=0.0338) and a trend to improved survival (25.5 months vs. 20.4 months; HR 0.76; p=0.13) compared with capecitabine alone. Continuation of trastuzumab beyond progression was not associated with increased toxicity. In another phase III trial, women with HER2-positive, locally advanced or metastatic breast cancer previously treated with anthracycline-, taxane-, and trastuzumab-containing regimens were randomized to lapatinib plus capecitabine or capecitabine alone[209]. The addition of lapatinib to capecitabine prolonged time-to-progression (HR 0.57; 95% CI 0.43-0.77; p < 0.001) and was associated with a trend towards improved overall survival (HR 0.78; 95% CI 0.55-1.12; p = 0.177).

It is striking to note that the optimal sequencing of anti-HER2 agents is currently unknown.

Bevacizumab

Very recently, meta-analyses of RCTs were published (after our literature search), examining the benefits of bevacizumab in HER2-negative metastatic breast cancer patients[210, 211]. Combination of bevacizumab and chemotherapy resulted in a small but statistically significant improvement in progression-free survival and tumour response rate compared with chemotherapy alone. The pooled HR for overall survival did not show significant advantages for the use of bevacizumab compared to placebo. Meta-analyses suggested benefits of a carefully managed bevacizumab-containing treatment for patients with histologically or cytologically confirmed HER2-negative metastatic breast cancer not received previously receiving cytotoxic therapy.

Recommendation

- **Trastuzumab with/without non-anthracycline-based chemotherapy or endocrine therapy is the treatment of choice of all HER2 positive metastatic breast cancer except in the presence of cardiac contra-indications for the use of Trastuzumab (1A evidence).**

3.6.4 Treatment of bone metastases

Extensive evidence has shown the effectiveness of biphosphonates in patients with breast cancer and multiple lytic bone metastases in terms of pain reduction, reduction of skeletal events, improvement of the quality of life, and time-to-progression[3, 18, 64]. Although most trials evaluated treatment given for about 2 years, no data are available on optimal duration of biphosphonate treatment[188]. These findings were confirmed by a recent systematic review of Pavlakis et al. including 21 RCTs[187]. In patients with painful or threatening bone metastases, radiotherapy remains the treatment of choice[3, 18, 64].

Recommendations

- **Biphosphonates should be routinely used in combination with other systemic therapy in patients with metastatic breast cancer with multiple or symptomatic lytic bone metastases (1A evidence).**
- **In patients with painful or threatening bone metastases, radiotherapy is the treatment of choice, if feasible (1A evidence).**

3.6.5 Treatment of brain metastases

Some patients with metastatic breast cancer will develop symptomatic brain metastases, usually at multiple sites. The main treatment options include surgery and radiotherapy. Surgery is only considered for patients who have a solitary metastasis or a limited number of brain metastases; this applies to the minority of patients. Most patients will subsequently be treated with whole brain radiotherapy (WBRT) which may improve their symptoms and function. More recently, treatment with stereotactic radiosurgery was considered as an acceptable alternative to resection or to radiotherapy alone for patients with brain metastases. Retrospective studies suggest clinical effectiveness in younger patients and those with good performance status[3].

Recommendation

- **Patients with a single or small number of potentially resectable brain metastases can be treated with radiosurgery or with surgery followed by whole brain radiotherapy. Whole brain radiotherapy should only be offered to patients for whom surgery or radiosurgery is not appropriate (2C evidence).**

3.7 TREATMENT OF LOCOREGIONAL RELAPSE

In case of a local recurrence in the thoracic wall, a complete excision of the tumour should be aimed for[17, 64]. Small recurrences in the scar can be removed by wide excision in healthy tissue. Large chest-wall recurrences can be treated by chest wall resection. If no radiotherapy has been performed as part of the primary therapy, radiotherapy should be performed postoperatively[17, 64]. However, in the presence of unfavourable risk factors, an additional course of (small-volume) radiotherapy may be given postoperatively even in patients who have received prior adjuvant radiotherapy. This should first be discussed in the MDT. In patients with a local recurrence after breast conserving treatment, salvage mastectomy is recommended[64]. However, for some cases BCS may be an option. Few trials exist on the use of systemic treatment for a locoregional recurrence that has been completely excised[64]. Therefore, this should be discussed in the MDT for each individual patient.

Recommendations

- **A local recurrence in the thoracic wall should be treated preferentially with surgery and adjuvant radiotherapy whenever possible (1C evidence).**
- **A local recurrence after breast-conserving treatment should be treated by a mastectomy (1C evidence).**
- **Systemic treatment for a completely excised locoregional recurrence should be discussed in the multidisciplinary team (expert opinion).**

3.8 SUPPORTIVE CARE FOR PATIENTS WITH BREAST CANCER

For symptomatic anaemia (haemoglobin <11 g/dl), erythropoietin and erythrocyte transfusions are reasonable options. For acute symptoms and in case of non-responsiveness to erythropoesis-stimulating proteins, erythrocyte transfusions can be administered[188].

Patients with metastatic breast cancer may develop lymphoedema following surgery or radiotherapy, or due to the pathological changes associated with progressive localised disease[3]. Early identification and management of the swelling is important, but there are no agreed diagnostic tests and assessment methods[3]. A Cochrane review of Badger et al. identified 3 RCTs examining the use of physical therapies for the reduction and control of lymphoedema of the limbs[212].

Only one of these RCTs (a crossover study of manual lymph drainage followed by self-administered massage versus no treatment) exclusively included women with unilateral lymphoedema of the upper limb following treatment for breast cancer. No extra benefit of manual lymph drainage was found[212].

One meta-analysis was identified on the use of physical exercise in breast cancer patients[213]. The authors identified 14 RCTs with important heterogeneity and small sample sizes. Physical exercise was found to be associated with statistically significant improvements in quality of life and physical functioning[213]. Meta-analysis of data from 28 RCTs[214] showed a highly significant effect of exercise compared with controls on fatigue reduction both in cancer patients in general (n = 2 083 participants), and in a large sub-group of patients with breast cancer (n = 1 172 participants). Since the review included all forms of exercise, a specific regime, intensity or duration can not be recommended[3].

There are no clear and uniform data as to whether the use of conventional hormonal replacement therapy (HRT) alleviates menopausal symptoms or alters outcomes in women with breast cancer treated with endocrine agents[18, 64, 215]. In the HABITS trial, a clinically and statistically significant increased risk of a new breast cancer event was reported in patients receiving menopausal HRT after a median follow-up of 4 years[216]. Therefore, this treatment cannot be recommended after treatment for breast cancer[216].

A systematic review of Edwards et al. identified 5 RCTs examining the use of psychological interventions for women with metastatic breast cancer[217]. The authors concluded that there was insufficient evidence to advocate group therapy for all women diagnosed with metastatic breast cancer. Numerous additional RCTs on group interventions[218-223], individual interventions[224-231], couple and family interventions[232-234], and computer- and telephone-based interventions[235-237] were identified. The psychological interventions included strategies to reduce stress, improve mood, alter health behaviours, and maintain adherence to cancer treatment and care. These interventions were reported to have positive impact on different outcomes such as stress and depression, dietary and smoking habits, breast cancer recurrence and overall survival. However, many of these trials were hampered by methodological limitations and small sample sizes, and reporting on outcomes was heterogeneous. Nevertheless, psychological support should be available to all patients diagnosed with breast cancer[3, 18].

The management of uncontrolled disease needs to be individualised and will usually involve a combination of treatments. A team approach is therefore very important and will include nurses, surgeons, oncologists and psychologists. A palliative care team should assess all patients with uncontrolled disease in order to plan a symptom management strategy[3].

Recommendations

- **Women with breast cancer should be informed about the risk of developing lymphoedema following surgery or radiotherapy and should be offered rapid access to a specialist lymphoedema service (1A evidence).**
- **Physiotherapy for mobility after axillary clearance should be recommended (1A evidence).**
- **Physical training including specific exercises for cancer-related fatigue can be recommended after treatment for breast cancer (1A evidence).**
- **Menopausal hormonal replacement therapy is contraindicated in women with breast cancer (1B evidence).**
- **Psychological support should be available to all patients diagnosed with breast cancer (1A evidence).**
- **A palliative care team should assess all patients with uncontrolled disease in order to plan a symptom management strategy (1C evidence).**

3.9 SURVEILLANCE OF PATIENTS WITH BREAST CANCER

Local recurrences or second primaries in the treated breast can be detected clinically or mammographically[3, 18, 62, 64]. Mammography is the gold standard method of imaging for cancer detection, but no evidence was identified to suggest the optimal frequency of this procedure. In current practice, mammography is offered once yearly after treatment for breast cancer. Since there is no evidence that performing diagnostic tests such as X-rays and scans to screen for distant metastases improves survival, these tests should not be performed in asymptomatic women[18, 62, 64].

There is no evidence that breast MRI improves outcome when used as a breast cancer surveillance tool during routine follow-up in asymptomatic patients. The decision to use breast MRI in high-risk patients should be made on an individual basis depending on the complexity of the clinical scenario[62].

The frequency of follow-up consultations is not extensively studied, and therefore mainly based on expert opinion. Follow-up consultations can be provided every 3 to 4 months in the first two years after diagnosis, every 6 months until 5 years after diagnosis, and every year after 5 years[64].

Studies are currently comparing different forms of follow-up such as traditional hospital follow-up with telephone follow-up by specialist nurses[238]. Such studies highlight the importance to consider who will organise and execute the follow-up (specialists in a breast clinic, general practitioner, breast care nurse specialist,…), if it is possible to transfer the surveillance of breast cancer patients from the hospital to the community and which training and resources are needed in the future.

Recommendations

- **Yearly mammography with/without ultrasound should be used during the first 10 years to detect recurrence or second primaries in patients who have undergone previous treatment for breast cancer, including DCIS (1C evidence).**
- **Intensive surveillance monitoring (CBC testing, tumour markers, chest x-ray, bone scans, liver ultrasound and computed tomography) is not recommended for routine breast cancer surveillance (1A evidence).**
- **MRI should not be offered routinely as a post-treatment surveillance test in patients who have been treated for early invasive breast cancer or DCIS, except in the following situations (1C evidence):**
  - **Lobular invasive cancer**
  - **Very young patients (< 35 years)**
  - **BRCA associated cancers**
  - **If initial tumour was not seen at mammography/ultrasound**
  - **In specific clinical situations where other imaging modalities are not reliable, or have been inconclusive**
- **Follow-up consultations can be provided every 3 to 4 months in the first two years after diagnosis, every 6 months until 5 years after diagnosis, and every year after 5 years (expert opinion)**

3.10 MULTIDISCIPLINARY APPROACH OF PATIENTS WITH BREAST CANCER

There is evidence that a multidisciplinary breast clinic provides an accurate and effective means of establishing a correct diagnosis in women referred with breast symptoms[18]. A multidisciplinary clinic will usually involve breast clinicians, radiologists and cytologists. Above this, all women with a potential or known diagnosis of breast cancer should have access to a breast care nurse specialist for information and support at every stage of diagnosis and treatment[18]. One RCT reported that telephone follow-up by specialist nurses (consultation with structured intervention and mammography according to hospital policy) can be suitable for women at low to moderate risk of recurrence and those with long travelling distances or mobility problems, and decreases the burden on busy hospital clinics, with no physical or psychological disadvantage[238].

Recommendation

- **All women with a potential or known diagnosis of breast cancer should have access to a breast care nurse specialist for information and support at every stage of diagnosis, treatment and follow- up (1B evidence).**

3.11 BREAST CANCER AND PREGNANCY

In a recent population-based descriptive study, women aged <45 with a diagnosis of breast cancer who subsequently conceived were identified[239]. Subsequent pregnancy was associated with improved overall survival. However, due to the observational nature of the study, these results should be interpreted with caution. Nevertheless, breast cancer is not considered a contraindication for a later pregnancy or breastfeeding[240]. This should be individually discussed.

Recommendation

- **Breast cancer is not a contraindication for a later pregnancy or breastfeeding, but should be individually discussed (2C evidence).**

3.12 PARTICIPATION IN CLINICAL TRIALS

The inclusion of breast cancer women in research protocols should always be considered, particularly when the curative options are poor, i.e. in the metastatic setting.

Recommendation

- **In view of the rapidly changing evidence in the field of breast cancer, clinicians should encourage women with breast cancer to participate in clinical trials (expert opinion).**

4 IMPLEMENTATION AND UPDATING OF THE BREAST CANCER GUIDELINE

4.1 IMPLEMENTATION

The implementation of the present guideline will be led by the College of Oncology. An online implementation tool – similar to the tools accompanying previous guidelines (https://portal.health.fgov.be/portal/page?_pageid=56,10338450&_dad=portal&_schema=PORTAL) – will be developed. The tool will be based on the general algorithm of this guideline.

4.2 QUALITY CONTROL

Based on this guideline, quality indicators were developed to evaluate its implementation. The results of the pilot test of these indicators will be reported in a subsequent report.

4.3 GUIDELINE UPDATE

In view of the changing evidence, and based on a pre-assessment of the literature, this guideline should be regularly updated (e.g. 2 times per year). In the meanwhile, when important evidence becomes available, this will be mentioned on the website of the College of Oncology. Indeed, already during the finalisation of this guideline, numerous new studies became available.

5 APPENDICES

APPENDIX 1: SEARCH STRATEGIES

BREAST CANCER

1. breast/ or breast diseases/
2. Neoplasms/
3. 1 and 2
4. exp Breast Neoplasms/
5. (breast$ adj5 neoplas$).tw.
6. (breast$ adj5 cancer$).tw.
7. (breast$ adj5 carcin$).tw.
8. (breast$ adj5 tumo$).tw.
9. (breast$ adj5 metasta$).tw.
10. (breast$ adj5 malig$).tw.
11. exp Carcinoma, Ductal, Breast/
12. or/4-11

SEARCH FILTER SYSTEMATIC REVIEW

1. meta-analysis.pt,ti,ab,sh.
2. 1 or (meta anal$ or metaanal$).ti,ab,sh.
3. (methodol$ or systematic$ or quantitativ$).ti,ab,sh.
4. ((methodol$ or systematic$ or quantitativ$) adj (review$ or overview$ or survey$)).ti,ab,sh.
5. (medline or embase or index medicus).ti,ab.
6. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
7. or/3-6
8. 7 and review.pt,sh.
9. 2 or 8

SEARCH FILTER RANDOMISED CONTROLLED TRIALS

1. Randomized controlled trials/
2. Randomized controlled trial.pt.
3. Random allocation/
4. Double blind method/
5. Single blind method/
6. Clinical trial.pt.
7. exp clinical trials/
8. or/1-7
9. (clinic$ adj trial$1).tw.
10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
11. Placebos/
12. Placebo$.tw.
13. Randomly allocated.tw.
14. (allocated adj2 random).tw.
15. or/9-14
16. 8 or 15
17. Case report.tw.
18. Letter.pt.
19. Historical article.pt.
20. Review of reported cases.pt.
21. Review, multicase.pt.
22. or/17-21
23. 16 not 22
24. 8 or 23

DIAGNOSTIC STUDIES

1. exp "Sensitivity and Specificity"/
2. sensitivity.tw.
3. specificity.tw.
4. ((pre-test or pretest) adj probability).tw.
5. post-test probability.tw.
6. predictive value$.tw.
7. likelihood ratio$.tw.
8. Prospective Studies/
9. or/1-8

HISTOPATHOLOGIC EXAMINATION

1. "prognos*".ti,ab.
2. first.ti,ab.
3. episode.ti,ab.
4. 2 and 3
5. cohort.ti,ab.
6. 1 or 4 or 5
7. pathology.mp. or Pathology/ or Pathology, Clinical/ or Pathology, Surgical/
8. Lymph Nodes/
9. (resection adj margin$).mp.
10. Neoplasm Invasiveness/
11. Neoplasm Staging/ or TNM.mp.
12. Neoplasm Recurrence, Local/
13. R0.mp.
14. R1.mp.
15. Frozen Sections/
16. or/7-15
17. 6 and 16

FOLLOW-UP

1. Follow-Up Studies/
2. follow-up.ti,ab.
3. followup.ti,ab.
4. follow up.ti,ab.
5. monitoring.ti,ab.
6. surveillance.ti,ab.
7. or/1-6
8. office visit.ti,ab.
9. physician visit.ti,ab.
10. physical examination.ti,ab.
11. frequency.ti,ab.
12. length.ti,ab.
13. Office Visits/
14. Physical Examination/
15. or/8-14
16. 7 and 15

RECURRENT DISEASE

1. Recurrence/
2. Neoplasm Recurrence, Local/
3. recurren$.tw.
4. or/1-3

APPENDIX 2: GRADE SYSTEM[241]

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

APPENDIX 3: AGREE SCORES OF IDENTIFIED GUIDELINES

Source	Title	Standardised Score#						Final Appraisal
		I	II	III	IV	V	VI	
NICE 2009	Early and locally advanced breast cancer: diagnosis and treatment	100%	75%	98%	96%	78%	83%	Recommended
NICE 2009	Advanced breast cancer: diagnosis and treatment	100%	75%	98%	96%	78%	83%	Recommended
ASCO 2007	American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer	89%	50%	67%	79%	28%	50%	Recommended with modifications
ASCO 2006	American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer	100%	67%	88%	75%	56%	50%	Recommended with modifications
ASCO 2006	American Society of Clinical Oncology 2006 Update of the Breast Cancer Follow-Up and Management Guidelines in the Adjuvant Setting	78%	67%	74%	83%	61%	50%	Recommended with modifications
CCO 2007	Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer: A Clinical Practice Guideline	100%	67%	93%	71%	50%	100%	Recommended
CCO 2006	Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline	100%	62%	95%	75%	17%	100%	Recommended
CCO 2008	The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: Guideline Recommendations	100%	63%	98%	79%	11%	100%	Recommended
CCO 2007	The Role of Gemcitabine in the Management of Metastatic Breast Cancer: A Clinical Practice Guideline	100%	46%	93%	62%	0%	100%	Recommended
CCO 2006	The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer: A Clinical Practice Guideline	100%	38%	93%	67%	6%	100%	Recommended
Alberta Medical Association 2007	The Early detection of Breast Cancer	67%	29%	19%	83%	0%	0%	Not recommended
CCO 2006	The Role of HER2/neu in Systemic and Radiation Therapy for Women with Breast Cancer: A Systematic Review	100%	50%	83%	67%	0%	100%	Recommended with modifications

Source	Title	Standardised Score#						Final Appraisal
		I	II	III	IV	V	VI	
SOGC 2006	Progesterone-Only and Non-Hormonal Contraception in the Breast Cancer Survivor: Joint Review and Committee Opinion of the Society of Obstetricians and Gynaecologists of Canada and the Society of Gynecologic Oncologists of Canada	67%	0%	24%	58%	0%	0%	Not recommended
CCO 2006	Diagnostic Imaging in Breast Cancer	100%	33%	69%	71%	0%	100%	Recommended with modifications
NCCN 2009	Breast Cancer	83%	71%	62%	100%	17%	83%	Not recommended
ACR 2006	American College of Radiology Appropriateness Criteria – Stage I Breast Carcinoma	83%	25%	29%	46%	33%	0%	Not recommended
ACS 2007	American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography	94%	29%	38%	58%	33%	0%	Not recommended
ICSI 2008	Health Care Guideline: Diagnosis of Breast Disease	61%	42%	57%	96%	78%	50%	Not recommended
NHS HDL 2007	Scottish referral guidelines for suspected cancer	67%	25%	2%	29%	28%	0%	Not recommended
FNCLCC 2007	Recommandations pour la Pratique Clinique : Saint Paul de Vence 2007 «cancers du sein»	100%	54%	83%	75%	50%	100%	Recommended with modifications
FNCLCC 2006	Utilisation de la TEP-FDG dans les cancers du sein, de l'ovaire et de l'utérus - Bulletin de synthèse de veille 2005	100%	17%	86%	62%	0%	50%	Recommended with modifications
NICE 2006	Familial breast cancer - The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care	100%	50%	81%	79%	100%	0%	Recommended with modifications
ESMO 2008	Primary breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up	67%	17%	38%	58%	6%	25%	Not recommended
ESMO 2008	Locally recurrent or metastatic breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up	67%	25%	33%	58%	11%	25%	Not recommended
ABS 2007	Oncoplastic breast surgery - A guide to good practice	78%	42%	17%	50%	72%	75%	Not recommended
CCO 2008	Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations	100%	54%	98%	75%	0%	100%	Recommended with modifications

Source	Title	Standardised Score#						Final Appraisal
		I	II	III	IV	V	VI	
UMHS 2007	Guidelines for clinical care : Common breast problems	89%	25%	21%	62%	33%	67%	Not recommended
ACP 2007	Screening Mammography for Women 40 to 49 Years of Age: A Clinical Practice Guideline from the American College of Physicians	100%	46%	64%	79%	11%	100%	Recommended with modifications
NSGC 2007	Risk Assessment and Genetic Counseling for Hereditary Breast and Ovarian Cancer: Recommendations of the National Society of Genetic Counselors	78%	54%	50%	54%	39%	50%	Not recommended
ADA 2007	Breast cancer and oncology nutrition	28%	21%	55%	71%	11%	0%	Not recommended
CECOG 2007	Second consensus on medical treatment of metastatic breast cancer	94%	21%	67%	62%	0%	8%	Recommended with modifications
EUSOMA 2006	The role of complementary and alternative medicine in the management of early breast cancer: Recommendations of the European Society of Mastology (EUSOMA)	83%	33%	0%	25%	0%	50%	Not recommended
ASCO 2006	Recommendations From an International Expert Panel on the Use of Neoadjuvant (Primary) Systemic Treatment of Operable Breast Cancer: An Update	72%	21%	29%	21%	0%	50%	Not recommended
ASCO 2006	Breast Carcinoma during Pregnancy - International Recommendations from an Expert Meeting	78%	17%	36%	33%	0%	8%	Not recommended
NOS and NCRI Breast Cancer Study Group 2008	Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group	89%	46%	45%	67%	0%	100%	Not recommended
ISGO 2007	Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology	94%	37%	62%	42%	11%	50%	Not recommended
ASCO 2006	American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients	100%	75%	69%	50%	39%	50%	Recommended
CCO 2006	Management of Ductal Carcinoma in Situ of the Breast: A Systematic Review	100%	75%	100%	75%	28%	100%	Recommended

APPENDIX 4: EVIDENCE TABLES BY CLINICAL QUESTION

DIAGNOSIS

Triple assessment

No additional evidence found

Diagnosis with MRI

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Peters et al. 2008	[26]	July 2005	Women who have small lesions detected at mammographic screening (non palpable lesions)	CE-MRI Reference: Histologic analysis / mammographic and clinical follow-up > 2 years	Diagnostic performance of MR imaging	Pooled weighted estimates of : - sensitivity: 0.90 (95% CI: 0.88, 0.92) - specificity: 0.72 (95% CI: 0.67, 0.77) The performance of breast MRI was influenced by the prevalence of cancer in the studied population (23%-84%; p = 0.05) and the number of criteria used to differentiate benign from malignant lesions (p=0.02). ➔ For definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI.	Search strategy in Medline: January 1985 → March 2005 Search in PubMed, DARE, Cochrane database (July 2005) Quality appraisal with QUADAS 44 studies published between 1993 and 2004 were included in the meta-analysis	SR and meta-analysis	High

Diagnosis with scintimammography

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
MAS 2007	[37]	January 2007	Patients with palpable breast tumors OR patients with either palpable tumors or indeterminate or suspicious XMM findings OR patients with dense breast tissues	Scintimammography (SMM) versus US Standard: surgical histopathology	Se, Sp, PPV, NPV, adverse effects for SMM and US.	SMM alone : meta-analysis of 49 studies Se: 84% Sp: 81% PPV: 84% NPV: 76% SMM Versus US: Meta-Analysis on Paired Data (5 comparative studies) In the SROC plot, the area under the curve as a measure of discriminatory power showed minimal difference between the 2 techniques (94% for SMM and 93% for US). Conclusion: SMM is as effective as US in differentiating benign and malignant breast lesions. However, there may be a role for SMM as a third line adjunctive technique in the evaluation of breast abnormalities, in particular where breast US examination is inconclusive because of dense breast tissue or architectural distortion resulting from previous surgery or radiation treatment.	Literature search for the period 1992-2002, since the potential use of SMM in breast cancer was discovered in 1992, and the first conducted study was published in 1994. The 2007 update included English- and French-language health technology assessments and English-language studies published from mid-October 2002 to January 31, 2007. Excluded were case reports, comments, editorials, and letters.	SR and meta-analysis of 49 studies on SMM published between 1994 and 1999 with data on 4 540 breast lesions	Moderate

Diagnosis with PET scan

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[3]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.	2 SR (Shie 2008, Isasi 2005) and 15 small comparative studies or case series (Abe 2005, Altehoefer 2001, Bradley 2000, Bristow 2008, Cook 1998, Engelhard 2004, Eubank 2001, Eubank 2004, Fueger 2005, Haubold-Reuter 1993, Kamby 1987, Nakai 2005, Schirrmeister 1999, Schmidt 2008 and Ternier 2006)	Studies used to formulate these recommandation are based on PET and not on PET-CT→ non reliable	Very low

	Population	Index test	Results	Comments
HTA reports				
NCCHTA 2007[39]	Patients who have an abnormal mammogram or palpable breast mass and have been referred for breast biopsy	**FDG-PET** Reference standards: cytological aspiration and histopathology	One systematic review identified (AHRQ 2001): already included in previous KCE report. Additional primary study (Heinisch 2003) compared PET and MRI in 36 women with suspicious lesions on mammography or clinical examination. PET Se 76% (95% CI: 52% - 91%) Sp 73% (95% CI: 45% - 91%) MRI Se 95% (95% CI: 74% - 99%) Sp 73% (95% CI: 45% - 91%)	Good-quality HTA *Search date*: Aug 2005 *Databases*: Medline, EMBASE, Cochrane Library, HTA database, DARE, individual contacts through INAHTA Meta-analysis using random-effects Trials only include patients with suspicious mammograms or palpable masses, so prevalence is high and mean tumour size was large. Hence, report states that evidence is required in other patients.
AHRQ 2006[9]	Patients who have suspicious breast lesions (abnormal mammogram and/or physical examination and/or ultrasound examination)	**FDG-PET** Comparators: MRI, US, scintimammography Reference standard: biopsy	*Objective*: to determine if available non invasive diagnostic test (PET/MR/US/scintimammography) are sufficiently accurate to exclude malignancy, avoiding women with an abnormal mammogram to perform biopsy. 69 publications were included: - 9 of 18-FDG PET scanning (8 WBS, 1 gamma camera). - 45 of scintimammography (SCM) - 19 of MRI - 8 of ultrasound	High quality HTA Search date : April 2005 Databases: PubMed, EMBASE, Clinical Trials, Cochrane Databases, ECRI databases, CRISP, Controlled Trials, Database of Abstracts of Reviews of Effectiveness (DARE), U.S. Centers for Medicare & Medicaid Services.

	Population	Index test	Results	Comments
			Some publications reported data for more than one technology *For suspicious lesions* Se: PET (82.2%); MRI (92.5%); US (86.1%) Sp: PET (78.3%); MRI (72.4%); US (66.4%) *For non palpable lesions* Se: SCM (68.7%) Sp: SCM (84.8%) In USA, after an abnormal mammogram, women have a level of risk of cancer = 20%. All technologies could reduce the need for biopsy (a) but each would miss some cancers (b). At this average risk level, in 1 000 women with: - a negative PET scan, 924 (a) but 76 (b) - a negative SCM, 907 (a) but 93 (b) - a negative MRI, 962 (a) but 38 (b) - a negative US, 950 (a) but 50 (b) Future studies could overturn these findings. *Conclusion*: MRI is a more valuable tool than PET to give a diagnosis (higher sensitivity and higher NPV). However, if a less than 2% risk of having breast cancer with a negative diagnostic test is considered an acceptable level of risk for a diagnostic test to reliably preclude biopsy, none of these tests was sufficiently accurate to replace biopsy for women at average risk of breast cancer. For non palpable lesions, data were insufficient to estimate the accuracy of PET, MRI or US. SCM was not sufficiently accurate to avoid biopsy. For palpable lesions, data were insufficient to estimate the accuracy of PET, MRI, US and SCM.	The quality of all of the studies was moderate.

Systematic reviews				
Bourguet 2006[41]	Patients with suspicion of breast cancer	**FDG-PET**	No change since 2003. *Standard*: PET is not indicated in the diagnosis of breast cancer (evidence level A).	Update of a previous systematic review (2003) Literature search in Medline (2003-November 2005) + OVID alerts Language restrictions: French and English

STAGING

Magnetic Resonance Imaging (MRI)

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
MRI							
NICE 2009	2	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 who are candidates for breast cancer surgery	The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or ductal carcinoma in situ (DCIS).	There is insufficient evidence (a) to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes, and (b) on which to base any recommendation on the use of MRI in the assessment of the breast with a diagnosis of pure DCIS. MRI can complement mammography in guiding surgical treatment of DCIS by providing a better description of tumour size and detection of additional malignant lesions (Francescutti 2002; Shiraishi 2003; Menell 2005). However, data need to be interpreted with caution because of the limitations of the studies, low evidence levels and small sample sizes.	2 case control studies and 4 case series, with a relatively high degree of consistency in results.	Low
NICE 2009	2	July 2008	Women and men with newly diagnosed invasive	Offer MRI of the breast to patients with invasive breast cancer: - if there is discrepancy regarding the	Breast MRI: moderate to high sensitivity (75-100%) and specificity (82-100%) in detecting multicentric tumour foci in fibroglandular or	one SR, 9 case control studies and 11 case series, with a relatively high	Moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
			adenocarcinoma of the breast of clinical stages 1, 2 and 3 who are candidates for breast cancer surgery	extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment - if breast density precludes accurate mammographic assessment - to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer.	dense breasts (BCBS-TEC Review 2004, Del et al. 2007). MRI will detect additional mammogram-occult foci greater than 2 cm from the index cancer in +/- 10% of women (Schnall et al. 2005, Deurloo et al. 2006). Contrast enhanced MRI has the lowest FN rate in detecting invasive lobular carcinoma and has the highest accuracy in measuring the size of the invasive lobular carcinoma (Boetes et al. 2004). MRI has been shown to detect occult invasive breast cancers with the sensitivity of 97%-100%. Combined mammography, clinical examination and MRI were more sensitive than any other individual test or routine triad (Chung et al. 2005). Axillary lymph nodes can be evaluated as part of an MRI-mammography study (Kvistad et al. 2004). Patients' treatment was changed to mastectomy based on MRI findings in 7% of the patients (BCBS-TEC Review 2004, Blair et al. 2006, Bremner et al. 2007, Del et al. 2007, Schelfout 2004). Preoperative MRI of the breast is effective in patients with histopathologically verified breast cancer, for local staging (Fischer et al. 2004).	degree of consistency in results	

NICE 2009	[3]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	Assess the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI).	Two systematic reviews (Isasi et al. 2005 and Shie et al. 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008, Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005, Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	There was insufficient evidence to support the choice of one imaging modality over another Other than the SR, papers were of poor to medium quality and many were retrospective studies.	Very Low
NICE 2009	[3]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	Assess the presence and extent of metastases in the bones of the axial skeleton using bone windows on a CT scan or MRI or bone scintigraphy.	Two systematic reviews (Isasi et al., 2005 and Shie et al., 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008, Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005, Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	There was insufficient evidence to support the choice of one imaging modality over another Other than the SR, papers were of poor to medium quality and many were retrospective studies.	Very Low
NICE 2009	[3]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	Assess proximal limb bones for the risk of pathological fracture in patients with evidence of bone metastases elsewhere, using bone scintigraphy and/or plain radiography.	Two systematic reviews (Isasi et al. 2005 and Shie et al., 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008, Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005,	There was insufficient evidence to support the choice of one imaging modality over another Other than the SR, papers were of poor to medium	Very Low

					Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	quality and many were retrospective studies.	
NICE 2009	[3]	July 2008	Women and men with invasive adenocarcinoma of the breast of clinical stage 4	Use MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example, if there are lytic metastases encroaching on the spinal canal).	Two systematic reviews (Isasi et al., 2005 and Shie et al., 2008) and 15 small comparative studies or case series (Abe et al. 2005, Altehoefer et al. 2001, Bradley et al. 2000, Bristow et al. 2008, Cook et al. 1998, Engelhard et al. 2004, Eubank et al. 2001, Eubank et al. 2004, Fueger et al. 2005, Haubold-Reuter et al. 1993, Kamby et al. 1987, Nakai et al. 2005, Schirrmeister et al. 1999, Schmidt et al. 2008 and Ternier et al. 2006) formed the evidence base for the topic on imaging to determine disease extent. GDG consensus	There was insufficient evidence to support the choice of one imaging modality over another Other than the SR, papers were of poor to medium quality and many were retrospective studies.	Very Low
CCO 2006	[242]	September 2004	Candidates for breast cancer surgery	Subsets of patients that may benefit from MRI: - Women with clinically palpable and mammographically occult breast cancer. - Women with metastatic adenocarcinoma to axillary lymph nodes, with an unknown primary. - Extent of disease needs better delineation, e.g. women with lobular carcinoma. - Patients who require re-excision because of positive surgical margins. - Patients with a high risk of multifocal disease.	Five case series examined imaging of the breast with ultrasound or MRI to determine the extent of disease prior to surgery (Snelling 2004, Park 2003, Schelfout 2004, Liberman 2003, Zhang 2002). Snelling (2004; n=111; prev=24%) compared whole breast ultrasound with clinical measurement for differentiating tumours larger than 3 cm from smaller ones (gold standard: pathology). Low sensitivity for both modalities (26% vs. 30%) but higher overall accuracy using whole-breast ultrasound (94% versus vs. 83%).	Low evidence → consensus between panel members	Very Low

				MRI should not be used as a substitute for detailed mammographic or sonographic work-up of any abnormalities detected at a routine screening or as a substitute for the clinical or image-guided core biopsy of mammographic, sonographic, or clinical abnormalities	Park (2003; n=183) found high sensitivity (100%) but moderate (67%) specificity for breast sonography for the detection of multifocal or diffuse disease. Three case series examined imaging of the breast with MRI compared to other imaging modalities (Schelfout 2004, Liberman 2003, Zhang 2002) Schelfout (n=170) compared MRI, ultrasound and mammography in the detection of multifocal, multicentric, and bilateral disease. He found high specificity (100%) for all modalities, with high sensitivity for MRI (95% to 100%) but low to moderate sensitivity for ultrasound (9% to 56%) and mammography (18% to 56%). Liberman (n=70; prev=27%) reported only 53% positive predictive value of MRI in detecting cancer in the ipsilateral breast. Zhang (n=54; prev=37%) found the combination of ultrasound and mammography to have a low sensitivity (26%) but high specificity (100%) compared to the MRI high sensitivity (100%) and good specificity (85%).		

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Houssami et al. 2008	[78]	June 2007	Women diagnosed with breast cancer	MRI Reference: Histologic analysis	Accuracy of MRI in detection of additional tumour foci multifocal (MF) and/or multicentric (MC)	MRI detects additional disease in 16% of women with breast cancer. Se and Sp were only graphically provided per study, and were not meta-analysed. The accuracy differs according to the reference standard (p=0.16), from 99% to 86% as the quality of reference standard increases. The overall summary estimate for PPV was 66% (95% CI: 52% to 77%). TP:FP ratio was 1.91 (95% CI: 1.09 – 3.34) Due to MRI-detected lesions, conversion from wide local excision to mastectomy was 1.1% (95% CI: 0.3 – 3.6%), from WLE to more extensive surgery was 5.5% (95%CI: 3.1 – 18.3%). ➔ MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer. There is a need to reduce FP in MRI detection.	Search strategy in Medline: 1966 → June 2007 19 studies were included for a total of 2 610 patients; 8 of them were also included in Peters et al. 2008	SR and meta-analysis	High

Hormonal receptors

Hormonal receptors	Source	Recommendations	Supporting evidence	Level of evidence
Estrogen receptors and progesterone receptors (ER/PgR)				
Estrogen receptors and progesterone receptors (ER/PgR)	ASCO 2007[42]	ER and PgR should be measured on every primary invasive breast cancer and may be measured on metastatic lesions if the results would influence treatment planning. In both pre- and post-menopausal patients, steroid hormone receptor status should be used to identify patients most likely to benefit from endocrine forms of therapy in both the early breast cancer and metastatic disease settings. For patients with DCIS who are candidates for hormonal therapy, data are insufficient to recommend routine measurement of ER and PgR for therapy recommendations.	Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005 Clark et al. 1983 Ravdin et al. 1992 Diaz et al. 2005	Moderate-High
HER2				
HER2 evaluation in breast cancer	ASCO 2007[42]	HER2 expression and/or amplification should be evaluated in every primary invasive breast cancer either at the time of diagnosis or at the time of recurrence, principally to guide selection of trastuzumab in the adjuvant and/or metastatic setting.	Colomer et al. 1997, 2000 Fehm et al. 1997 Hayes et al. 1993 Leitzel et al. 1992, 1995 Lipton et al. 2000, 2002, 2003 Stender et al. 1997 Yamauchi et al. 1997	Moderate-High
HER2 to define prognosis for early stage breast cancer patients in the absence of systemic therapy	ASCO 2007[42]	Not recommended	Slamon et al. 1987 Pik et al. 1990 Van de Vijver et al. 1988 Stender et al. 1997 Kandl et al. 1994 Willsher et al. 1996 Mehta et al. 1998 Fehm et al. 1998 Leitzel et al. 2001	Moderate-High

HER2 to determine sensitivity to endocrine therapy	ASCO 2007[42]	There are insufficient data to support the use of HER2 in tissue (or serum) as a predictor of response to endocrine therapy : Not recommended	Berry et al. 2000 Bianco et al. 2000 Elledge et al. 1998 Love et al. 2003 Ellis et al. 2001 Dowsett et al. 2005, 2006	Moderate - High
	CCO 2006[53]	**Tamoxifen:** The evidence does not support a recommendation against tamoxifen therapy in HER2/neu-positive patients. While it is possible that tamoxifen is more effective in HER2/neu-negative patients, there is still sufficient evidence that it is effective in HER2/neu-positive patients as well. **Aromatase inhibitors:** The current evidence does not support a definitive recommendation regarding aromatase inhibitor therapy and HER2/neu status. **Ovarian ablation:** The current evidence does not support a definitive recommendation regarding ovarian ablation and HER2/neu status.	**Tamoxifen:** Knoop et al. 2001 De Placido et al. 2003 Jakesz et al. 2002 Blanco et al. 1998 Rydén et al. 2005 Swedish Breast Cancer Cooperative Group 1996 Stal et al. 2000 **Aromatase inhibitors:** Lipton et al. 2003 Ellis et al. 2001 Smith et al. 2005 Eiermann et al. 2001 **Ovarian ablation:** Jakesz et al. 2002 Love et al. 2002, 2003	High
HER2 to determine sensitivity to chemoendocrine therapy	CCO 2006[53]	The current evidence does not support a definitive recommendation regarding chemoendocrine therapy and HER2/neu status.	Ravdin et al. 1998	Low
HER2 to predict response to taxane-based therapy	ASCO 2007[42]	It is not recommended to use HER2 guiding use of taxane chemotherapy in the adjuvant setting.	Baselga et al. 1997 Gianni et al. 1997 Hayes et al. 2006 Volm et al. 1999 Harris et al. 2006 Konecny et al. 2004	Moderate-High
	CCO 2006[53]	The current evidence does not support a definitive	Sjostrom et al. 1999, 2002	Moderate-High

		recommendation regarding taxane chemotherapy and HER2/neu status.	Hamilton et al. 2000 Konecny et al. 2004 Paridaens et al. 2000 Luck et al. 2000 Learn et al. 2005 Lin et al. 2004 Martin et al. 2005	
HER2 to determine sensitivity to anti-HER2-based therapy	ASCO 2007[42]	High levels of tissue HER2 expression or HER2 gene amplification should be used to identify patients for whom trastuzumab may be of benefit for treatment of breast cancer in the adjuvant or metastatic disease settings.	Seidman et al. 2004 Buzdar et al. 2005 Joensuu et al. 2006 Piccart-Gebhart et al. 2005 Romond al. 2005 Slamon et al. 2005	High
HER2 to determine sensitivity to radiation therapy	CCO 2006[53]	The current evidence does not support a definitive recommendation regarding radiation therapy and HER2/neu status.	No paper found	Low
Utility of HER2 for predicting response to specific chemotherapeutic agents	ASCO 2007[42]	Level II evidence (prospective therapeutic trials in which marker utility is a secondary study objective) suggests that overexpression of HER2 (3+ by protein or > 2.0 FISH ratio by gene amplification) identifies patients who have greater benefit from anthracycline-based adjuvant therapy. If a clinician is considering chemotherapy for a patient with HER2 positive breast cancer, it is recommended that an anthracycline be strongly considered, assuming there are no contraindications to anthracycline therapy. In the context of trastuzumab therapy, there is Level I evidence (single, high-powered, prospective, randomized controlled trials specifically designed to test the marker or a meta-analyses of well-designed studies) that a non-anthracycline regimen may produce similar outcomes. At present, the Update Committee does not recommend that HER2 be used to guide use of taxane chemotherapy in the adjuvant setting.	- CMF-based regimens: Allred et al. 1992 Berns et al. 1995 Gusterson et al. 1992 Miles et al. 1999 - Anthracyclines : Baselga et al. 1997 Di Leo et al. 2002 Harris et al. 2004 Järvinen et al. 2000 Knoop et al. 2005 O'Malley et al; 2006 Carter et al. 2006 Mano et al. 2007 - CMF / anthracyclines Paik et al. 2000 Gianni et al. 1997 Pritchard et al. 2006	Moderate-High
	CCO 2006[53]	Patients with HER2/neu-positive breast cancer should be	Paik et al. 1998, 2000	High

		considered for chemotherapy containing an anthracycline instead of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or melphalan and 5-fluorouracil (PF) chemotherapy	Di Leo et al. 2001, 2002, 2005 Vera et al. 1999 Petruzelka et al. 2000 Moliterni et al. 2003 Fisher et al. 1989, 1990 Pritchard et al. 2002 Levine et al. 1998 De Laurentiis et al. 2001 De Placido et al. 1995 Knoop et al. 2005 Colozza et al. 2002, 2005 Del Mastro et al. 2004 Rodenhuis et al. 2003, 2005 Thor et al. 1998 Arnould et al. 2003 Bonneterre et al. 2003	
Circulating extracellular domain of HER-2	ASCO 2007[42]	Measuring circulating extracellular domain of HER2 is not currently recommended for any clinical setting.	Nunes et al. 2001 Esteva et al. 2002 Volas et al. 1996 Leitzel et al. 1995 Yamauchi et al. 1997 Lipton et al. 2003 Burstein et al. 2003	Low

Tumour markers

Tumour markers	Source	Recommendations	Supporting evidence	Level of evidence
uPA and PAI				
uPA and PAI as a marker for breast cancer (prognosis)	ASCO 2007[42]	uPA/PAI-1 measured by ELISAs on a minimum of 300 mg of fresh or frozen breast cancer tissue may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer. IHC for these markers is not accurate, and the prognostic value of ELISA using smaller tissue specimens has not been validated. Low levels of both markers are associated with a sufficiently low risk of recurrence, especially in hormone receptor positive women who will receive adjuvant endocrine therapy, that chemotherapy will only contribute minimal additional benefit. Furthermore, CMF-	Duffy 2002 Duffy et al. 1988 Foekens et al. 1994 Look et al. 2002 Jänicke et al. 2001 De Witte et al. 1998 Pedersen et al. 1999 Bouchet et al. 1994, 1999 Eppenberger et al. 1998 Harbeck et al. 2002	Low

		based adjuvant chemotherapy provides substantial benefit, compared to observation alone, in patients with high risk of recurrence as determined by high levels of uPA and PAI-1.	Zenzoum et al. 2003	
Multiparameter gene expression analysis for breast cancer				
Multiparameter gene expression analysis for breast cancer	ASCO 2007[42]	In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX™ assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX™ may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (CMF) than from tamoxifen. There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens. The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint™ assay, the "Rotterdam Signature," and the "Breast Cancer Gene Expression Ratio" are under investigation.	- Oncotype DX™ assay Paik et al. 2004, 2006 Hable et al. 2004 Hornberger et al. 2005 Esteva et al. 2005 - MammaPrint van 't Veer et al. 2002 van de vijver et al.2002 Dai et al. 2005 Breast International Group Buyse et al. 2006 Desmedt et al. 2007 Jenssen et al. 2005 Ransohoff 2004 Espinosa et al; 2005 - Rotterdam Signature Wang et al. 2005 Foekens et al. 2006 - Breast Cancer Gene Expression Ratio Goetz et al. 2006 Jansen et al. 2007	Low
Markers of proliferation				
Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation	ASCO 2007[42]	Present data are insufficient to recommend measurement of Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation to assign patients to prognostic groupings. DNA low cytometry-based proliferation markers are not recommended for breast cancer	Colozza et al. 2005 Mandard et al. 2000	Low

Cyclin E				
Cyclin E as markers for breast cancer	ASCO 2007[42]	Present data are insufficient to recommend use of whole length or fragment measurements of cyclin E for management of patients with breast cancer.	Keyomarsi et al. 2002 Wang et al. 2006 Porter et al. 2006	Low
Proteomic analysis for breast cancer	ASCO 2007[42]	Present data are insufficient to recommend use of proteomic patterns for management of patients with breast cancer.	Hu et al. 2005 Fowler et al. 2004 Becker et al. 2004 Li et al. 2002 Vlahou et al. 2003 Pawlik et al. 2005, 2006 Sauter et al. 2005 Wulfkuhle et al. 2002 Jacquemier et al. 2005 Abd El-Rehim 2005 Makretsov et al. 2004 Nielsen et al. 2004	Low
Bone marrow micrometastases				
Bone marrow micrometastases as markers for breast cancer	ASCO 2007[42]	Present data are insufficient to recommend assessment of bone marrow micrometastases for management of patients with breast cancer.	Braun et al. 2005	Low
Circulating tumor cell assays				
Circulating tumor cell assays as markers for breast cancer	ASCO 2007[42]	The measurement of circulating tumor cells (CTC) should not be used to make the diagnosis of breast cancer or to influence any treatment decisions in patients with breast cancer. Similarly, the use of the recently FDA-cleared test for CTC (Cell Search, Veridex) in patients with metastatic breast cancer cannot be recommended until further validation confirms the clinical value of this test.	Gaforio et al. 2003 Weigelt et al. 2003 Cristofanilli 2004, 2005 Hayes et al. 2006 Budd et al. 2006	Low
CA 15-3 and CA 27.29				
CA 15-3 and CA 27.29 as screening, diagnostic or staging tests or for detecting recurrence	ASCO 2007[42]	CA 15-3 and CA 27.29 are not recommended as Markers for Breast Cancer as screening, diagnostic or staging tests or for detecting recurrence.	Ebeling et al. 2002 Gion et al. 2002 Kumpulainen et al. 2002 Martin et al. 2006 Molina et al. 2003, 2005 Khatcheressian et al. 2006	Low
CA 15-3 and CA 27.29 to contribute to decisions regarding therapy for metastatic	ASCO 2007[42]	For monitoring patients with metastatic disease during active therapy, CA 27.29 or CA 15-3 can be used in conjunction with diagnostic imaging, history, and physical exam. Present data are	Ebeling et al. 2002 Gion et al. 2002 Kumpulainen et al. 2002	Low

breast cancer		insufficient to recommend use of CA 15-3 or CA 27.29 alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA 15-3 or CA 27.29 may be used to indicate treatment failure. Caution should be used when interpreting a rising CA 27.29 or CA 15-3 level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.	Martín et al. 2006 Molina et al. 2003	
Carcinoembryonic antigen				
CEA for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy	ASCO 2007[42]	CEA is not recommended for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy.	There is no change from the guideline published in 2000. No relevant studies were identified from the review of the review of literature conducted for this topic.	Low
CEA to contribute to decisions regarding therapy for metastatic breast cancer	ASCO 2007[42]	For monitoring patients with metastatic disease during active therapy, CEA can be used in conjunction with diagnostic imaging, history, and physical exam. Present data are insufficient to recommend use of CEA alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CEA may be used to indicate treatment failure. Caution should be used when interpreting a rising CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.	Guadagni et al. 2001 Tondini et al. 1988 Basuyau et al. 2000 Cheung et al. 2001 Coveney et al. 1995 Deprés-Brummer et al. 1995 Lauro et al. 1999 Robertson et al. 1999 Söletormos et al. 2000 Yildiz et al. 2004	Low
P53				
P 53	ASCO 2007[42]	Present data are insufficient to recommend use of p53 measurements for management of patients with breast cancer. *Note.* p53 abnormalities are associated with either resistance or sensitivity to different therapeutic agents. However, most studies analyzing p53 have not taken therapy into consideration, and the results may be strongly biased in one direction or the other, depending on the agents in question.	Olivier et al. 2006 Pharoah et al. 1999	Low
Cathepsin D				
Cathepsin D	ASCO 2007[42]	Cathepsin D is not recommended as a marker for breast cancer	Foekens et al. 1994 Billgren et al. 2002	Low

Abbreviations. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; QA, quality assurance.

Axillary ultrasonography

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 who are candidates for breast cancer surgery	Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered. Ultrasound-guided needle biopsy of abnormal lymph nodes using FNAC or core biopsy has the potential to provide the required definitive cytological or histological proof of a positive result on which to base treatment decisions.	The proportion of cases in whom it was possible to visualise axillary lymph nodes on ultrasound was of 76% (mean) but it varied widely, with a range 35% to 99%. The remaining proportion represents patients for whom ultrasound does not add any information (Altinyollar et al. 2005, Brancato et al. 2004, Damera et al. 2003, Deurloo et al. 2003, Dixon et al. 1992, Esen et al. 2005, Nori et al. 2005, Podkrajsek et al. 2005). The meta-analysis included only patients in whom it was possible to obtain biopsy material by ultrasound, the pooled sensitivity was 75.0% and the pooled specificity was 98.3%. The staging performance of 'grey scale' ultrasound alone showed a mean sensitivity of 62%, a mean specificity of 87% (Altinyollar et al. 2005, Bartonkova et al. 2006, Brancato et al. 2004, Chandawarkar and Shinde 1997, Esen et al. 2005, Heusinger et al. 2005, Lee et al. 1996, Hergan et al. 1996, Sato et al. 2004 and Van Rijk et al. 2006). The staging performance of 'grey scale' ultrasound plus colour doppler ultrasound showed a mean sensitivity of 65% and a mean specificity of 89% (Couto et al. 2004, Dixon et al. 1992, Esen et al. 2005, Lee et al. 1996, Nori et al. 2005, Perre et al. 1996, Podkrajsek et al. 2005, Walsh et al. 1994). The staging performance of ultrasound guided fine needle aspiration cytology (FNAC) showed a mean sensitivity of 43% and a mean specificity of 100%, a positive predictive value of 99% and a negative predictive value of 72% (Brancato et al. 2004, Damera et al. 2003, De Kanter et al. 2006, Deurloo	8 case series studies and one meta-analysis (Alvarez et al. 2006) which pooled estimates based upon 16 case series studies NICE (2009), Brancato et al. (2004), Davies et al. (2006) and Genta et al. (2007) conducted cost-effectiveness studies about pretreatment ultrasound plus needle biopsy in staging early breast cancer patients	Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					et al. 2003, Lemos et al. 2005, Podkrajsek et al. 2005, Stewart et al. 2006, Van Rijk et al. 2006). Sahoo et al. (2007) reported that 70% of patients with positive ultrasound FNAC were spared the additional step of SLNB while Somasunder et al. (2006) reported that 47% of patients with positive ultrasound FNAC were spared SLNB. Cost-effectiveness studies (NICE 2009, Brancato et al. 2004, Davies et al. 2006 and Genta et al. 2007) concluded that ultrasound plus needle biopsy seemed to be a cost effective staging strategy when compared to SLNB, without translating their results in QALYs gains. However, this health gain is attainable because both the reduction in the number of patients undergoing SLNB and the fact that, ultrasound plus needle biopsy is a less invasive staging procedure when compared to SLNB, can translate in sufficient gains in quality of life.		

Positron emission tomography (PET)

	Population	Index test	Results	Comments
HTA reports				
NCCHTA 2007[39]	Extent of tumour in ALN in patients with confirmed primary breast malignancy, no palpable ALN metastases (cN0) and no evidence of distant metastases	**FDG-PET** Reference standards: ALND ALND + SNB	One systematic review (BCBSA 2003) already included in previous KCE report, and four additional primary studies (Fehr 2004, Lovrics 2004, Wahl 2004, Zornoza 2004). ALND as ref.: PET Se = 40–93% PET Sp = 87–100% ALND + SNB as ref.: PET Se = 20–50% PET Sp = 82–100%	Good-quality HTA *Search date*: Aug 2005 *Databases*: Medline, EMBASE, Cochrane Library, HTA database, DARE, individual contacts through INAHTA Meta-analysis using random-effects

			Prevalence of node-positive disease = 33–64%, so 36–67% patients with PET negative would have axillary disease undetected if further tests were not undertaken. *Conclusion*: PET cannot be used to avoid ALND in patients with clinically N0 axillae, because of unacceptably low sensitivity. With this level of false negatives, if patients did not go on to have standard diagnostic tests, modelling suggests that under-treatment would be associated with absolute difference in 10-year survival of 8.2%. *Recommendation*: PET cannot be reliably used to avoid ALND.	
Systematic reviews				
Sloka 2007[83]	Patients with breast cancer	**FDG-PET** Reference standards: Histology via ALND / SNB / histology / histology + ALND / SNB +histo via ALND	**19 studies for staging axillary lymph nodes were considered in this systematic review.** In 3 high-quality studies (of which 2 were already included in previous KCE report: Wahl 2004, Zornoza 2004), i.e. studies with broad generalizability to a variety of patients and no significant flaws in research methods (Wahl 2004, Zornoza 2004, Greco 2001): - sensitivity : 61 – 94% - specificity : 80 – 98% *Recommendation:* Authors recommend that further studies be performed that control for contributory variables (patient position, etc) in order to explain the variability of study results. Avoid older studies (< 1992) due to the increased accuracy of new scanners.	Literature search in December 2005 (MEDLINE, Current Contents and EMBASE) restricted to English, Spanish and French language articles. Due to the high heterogeneity between studies, meta-analysis was not performed.
Bourguet 2006[41]	Patients with breast cancer	**FDG-PET**	**1 primary study (Zornoza 2004):** already included in previous KCE report. No change since 2003: PET is unable to detect microscopic lymph node metastasis. *Option*: PET enables documentation of loco-regional invasion and metastatic spread in the initial staging of invasive breast cancer (evidence level B2). *Recommendation*: the place of PET in the initial staging of invasive breast cancer remains to be established.	Update of a previous systematic review (2003) Literature search in Medline (2003-November 2005) + OVID alerts Language restrictions: French and English

	Population	Index test	Outcome	Results	Comments
FDG-PET					
Ueda 2008[86]	183 patients having primary breast cancer proven by core needle biopsy who are operable	**FDG-PET/CT** Comparator: axillary US Standard reference: ALND and/or SNB	Diagnostic performance of PET/ CT and AUS in assessing axillary status: Se and Sp	18-FDG PET/CT - visual assessment: Se: 58% (95% CI: 44% - 70%) Sp: 95% (95% CI: 89% - 98%) - SUV cut-off point 1.8 Se: 36% (95% CI: 24% - 49%) Sp: 100% (95% CI: 96% - 100%) AUS Se: 54% (95% CI: 31% - 55%) Sp: 99% (95% CI: 95% - 100%) Visual assessment of 18F-FDG uptake combined with AUS Se: 64% (95% CI: 51% - 76%) Sp: 94% (95% CI: 88% - 97%) Conclusion: performance of 18F-FDG PET/CT was almost equivalent to that of AUS for detecting of ALN involvement in patients with primary breast cancer. Sensitivity was low in both cases. The combination of these 2 exams slightly increased sensitivity. When it is difficult to judge the axillary staging using AUS alone, metabolic approach of 18F-FDG PET/CT for axillary staging would enable a much more confident diagnosis.	Prospective study Possibility of review bias: unclear
Veronesi 2007[87]	236 patients with breast cancer and clinically negative axilla	**FDG-PET** Comparator: SNB	Diagnostic performance of PET and SNB in assessing axillary status: Se and Sp	103 out of the 236 patients (44%) had metastases in axillary nodes 18 FDG-PET: Se: 37% (95% CI: 28% - 47%)	Prospective study conducted from September 2003 to April 2005 in Italy

	Population	Index test	Outcome	Results	Comments
		Standard reference: ALND		Sp: 96% (95% CI: 91% - 99%) SNB: Se: 96% (95% CI: 90% - 99%) Sp: 100% (95% CI: 96% - 100%) Conclusion: The high specificity of PET indicates that patients who have a PET-positive axilla should perform an ALND rather than an SNB for axillary staging. In contrast, when FDG-PET is negative at the axilla, its reliability is very low and axillary SNB becomes imperative.	
Gil-Rendo 2006[84]	150 women with breast cancer: histologically proven carcinoma of the breast with clinically and ultrasonographically non-suspicious axillary lymph nodes, eligible for primary treatment by breast conservation or mastectomy	**FDG-PET** Standard reference: ALND	Diagnostic performance of PET in assessing axillary status: Se and Sp	In the first group of 150 women who had preoperative PET and ALND, the sensitivity and specificity for detecting axillary status were: Se: 90% (95% CI: 83% - 97%) Sp: 98% (95% CI: 93% - 99%) PET detected axillary involvement in 64 of 71 patients (7 false negatives) and correctly diagnosed 78 of 79 patients without axillary metastases. Conclusion: The high sensitivity and the high specificity of PET suggest that FDG uptake in the axilla could be an indication for full ALND without previous SLNB	Prospective study on 275 women (2 subgroups). In a first group (150 women), ALND was performed regardless of PET results with the aim of evaluating the Se and Sp of the technique. In a second group (125 women), the axillary examination was complemented by SLNB only in those with no pathological axillary uptake on the FDG-PET scan.
Kumar 2006[85]	80 women with a histological diagnosis of breast cancer and clinically negative axillary nodes	**FDG-PET** Standard reference: SLNB or ALND	Diagnostic performance of PET in assessing axillary status: Se and Sp	36 out of the 80 patients (45%) had metastases in axillary nodes 18 FDG-PET: Se: 44% (95% CI: 28% - 62%) Sp: 95% (95% CI: 83% - 99%) Conclusion: FDG PET cannot replace histological staging using SLNB in patients with	Prospective study in USA

	Population	Index test	Outcome	Results	Comments
				breast cancer. The high specificity of PET indicates that patients who have a PET-positive axilla should perform an ALND rather than an SLNB for axillary staging. In contrast, FDG-PET showed poor sensitivity in the detection of axillary metastases, confirming the need for SLNB in cases where PET is negative in the axilla.	

TREATMENT OF NON INVASIVE BREAST CANCER

Ductal carcinoma in situ

Surgery

Sentinel lymph node biopsy

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 having breast conserving surgery	Do not perform SLNB routinely in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease. Patients at high risk include those with a palpable mass or extensive microcalcifications. Offer SLNB to all patients who are having a mastectomy for DCIS.	Ansari et al. (2008) conducted a meta-analysis (of observational studies) of the reported data on the incidence of SLN metastasis in patients with DCIS. This analysis reported SLNB results in patients with the diagnosis of DCIS. The analysis showed the frequency of sentinel lymph node positivity in patients with a preoperative diagnosis of DCIS ranged from 0 to 16.7%. With an overall positivity incidence of 7 ·4%. Postoperative overall positivity incidence was 3.7%. There was no evidence to suggest that a pattern exists between the rate of positive sentinel lymph nodes and DCIS grade. There was no evidence to suggest that a pattern exists between the rate of positive sentinel lymph nodes and DCIS tumour size.	GDG consensus	Moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					It was not possible to reliably estimate the proportion of patients with DCIS and positive sentinel lymph nodes who have further axillary nodal involvement from the studies identified, because of small numbers of patients in the series. None of the selected studies (all retrospective) reported changes to treatment plans as a result of staging by SLNB.		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008	Women and men with newly diagnosed DCIS having breast conserving surgery	For all patients treated with breast conserving surgery for DCIS a minimum of 2 mm radial margin of excision is recommended with pathological examination. Re-excision should be considered if the margin is less than 2 mm after discussion of the risks and benefits with the patient.	Observational studies (Bijker et al. 2001; Boland et al. 2001 and 2003; Boyages et al. 1999; Cabioglu et al. 2007; Chan et al. 2001; Cheng et al. 1997; Denoux et al. 2001; Dillon et al. 2007; Goldstein et al. 1998, 1999, 2000; Hetelekidis et al. 1999; Holland et al. 1998; Kell and Morrow 2005; Macdonald et al. 2005 and 2006; Neuschatz et al. 2001 and 2002; Ratanawichitrasin et al. 1999; Rodrigues et al. 2002; Sahoo et al. 2005; Sigal-Zafrani et al. 2004; Silverstein et al. 1994, 1997 and 1999; Silverstein and Buchanan 2003; Solin et al. 2005; Tunon-de-Lara et al. 2001; Vargas et al. 2005; Vicini et al. 2001; Wong et al. 2006; Yau et al. 2006). There is no consistency regarding: - the optimal tumour free tissue margin - whether wide margins can and whether they should replace radiotherapy		Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					- which of the two should most be avoided. There is consistency that the risk of local recurrence is reduced with very wide margins, e.g. more than 10 mm of tumour-free tissue.		
NICE 2009	[2]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 having mastectomy	Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant comorbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally.	These recommendations are based on limited clinical evidence from observational studies and on GDG consensus that immediate reconstruction is an acceptable procedure that does not disadvantage patients compared to delayed reconstruction. *Psychological outcomes* SR (Fischbacher 2002): better psychological outcomes arise in patients treated with immediate reconstruction compared to delayed reconstruction. Observational studies (Drucker-Zertuche and Robles-Vidal 2007 and Gendy et al. 2003): psychological outcomes are generally good following immediate reconstruction. *Cosmetic results* Observational studies (Anderson et al. 2004; Drucker-Zertuche and Robles-Vidal 2007; Gendy et al. 2003; Cordeiro et al. 2004 and Vandeweyer et al. 2003) report high rates of acceptable cosmetic results between 80% and 96% whereas in one study (Knottenbelt et al. 2004) the reported rate is only 20%.	GDG consensus	Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Rate of complications Two SR (Fischbacher 2002 and Javaid et al. 2006): immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction. A third less rigorous review (Taylor et al. 2005) found similar rates of capsular contraction between immediate and delayed reconstruction with implants, but with a trend for unfavourable results with immediate autologous tissue reconstruction. *Delay to start adjuvant therapy* No reliable evidence was identified on whether immediate breast reconstruction following mastectomy delays the start of adjuvant chemotherapy or radiotherapy. *Recurrence or survival* No reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those who receive delayed reconstruction. *Patients satisfaction* Evidence from observational studies suggests that in general, patients are satisfied with their reconstructed breasts following either immediate reconstruction, or delayed reconstruction.		

Radiotherapy

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008	Women with DCIS	Offer adjuvant radiotherapy to patients with DCIS following adequate breast conserving surgery and discuss with them the potential benefits and risks.	4 RCTs: Bijker et al. 2006 (EORTC); Fisher et al. 1998 (NSABP); Emdin et al. 2006 (SweDCIS); Houghton et al. 2003 (UKCCCR); Holmberg et al. 2008 (update of the original SweDCIS RCT) Systematic reviews: Boyages et al. 1999; Fonseca et al. 1997; Shelley et al. 2006; Baxter et al. 2005; Smith et al. 2006 *All ipsilateral breast recurrence* 4 RCTS: pooled HR 0.49; 95%CI 0.41 to 0.59; p<0.00001 → favoured RT Individual trial results were all consistent with the pooled HR *Ipsilateral invasive recurrence* 2 RCTS (NSABP and UKCCCR) HR 0.64; 95%CI 0.38 to 1.06; p<0.08 *Ipsilateral DCIS recurrence* 2 RCTS (NSABP and UKCCCR) HR 0.64; 95% CI 0.41 to 1.01; p=0.05 Lower rates of ipsilateral recurrence in the radiotherapy arm when considering either invasive ipsilateral recurrence or non-invasive ipsilateral recurrence (Bijker et al. 2006; Fisher et al. 1998; Houghton et al. 2003) *Disease-free survival* EORTC: 10-year metastasis free survival 96% in both groups	A Cochrane SR (Goodwin et al. 2009) meta-analysed results obtained from these 4 RCTs Meta-analysis used Kaplan-Meier curves	High

					Contralateral breast events were similar in both RT and control groups for all trials. *Overall survival* NSABP (8y FU): 94% (BCS) vs. 95% (BCS+RT) EORTC (10y FU): 95% in both groups SweDCIS: not reported UKCCCR: not reported No significant long-term toxicity from RT was found. No information about short-term toxicity from RT or quality of life data were reported.		

Endocrine therapy

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008	Pre-menopausal women with ER-positive DCIS	Do not offer adjuvant tamoxifen after breast conserving surgery to patients with DCIS.	*Ipsilateral local recurrence* There is evidence from one placebo controlled RCT (NSABP B-24 trial-Fisher et al. 1999) that in patients treated for DCIS with lumpectomy and adjuvant radiotherapy, adjuvant tamoxifen reduces the risk of ipsilateral local recurrence by 30% and contralateral breast cancer by 50%. *Any breast cancer event* The risk at 5 years of any breast cancer event in the tamoxifen arm was 8% and in the placebo arm, 13%. One subsequent RCT with a less rigorous design found no similar benefit arising from tamoxifen (UKCCCR trial-Houghton et al., 2003). The UKCCCR trial examined the use of tamoxifen versus no adjuvant therapy		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					following complete local excision of DCIS (without radiotherapy) and found no benefit arising from tamoxifen, except in terms of subsequent DCIS in either breast: this risk was reduced by 30%. The risk of any breast event in the tamoxifen arm at 56 months was 12% (UKCCCR) and in the control arm, 15%. *Disease-free survival vs overall survival* The NSABP B-24 trial found that Tamoxifen and radiotherapy improved disease-free survival at 5 years (87%) compared to placebo and radiotherapy (83%), but with no difference between groups for overall survival.		
CCO 2006	105	March 2006	Women with DCIS	Women should be informed of the option of five years of tamoxifen therapy and of the potential toxicities and benefits associated with tamoxifen.	Two trials : the NSABP B-24 trial with a median follow-up of 6.9 years, and the UKCCCR trial (see above).		High

Paget's disease

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	2	July 2008	Women and men with Paget's disease of the nipple	Offer breast conserving surgery with removal of the nipple–areolar complex as an alternative to mastectomy. Offer oncoplastic repair techniques to maximise cosmesis.	11 observational studies (Sutton et al. 1999; Bijker et al. 2001; Dixon et al. 1991; Duff et al.1998; Howard et al. 1989; Nicolosai et al. 1996; Polgar et al. 2002; Zurrida et al. 1993; Estabrook et al. 1996 and Marshal et al. 2003) show higher rates of recurrence following breast conserving surgery compared to mastectomy, but no study provided a statistical analysis. In 3 out of 4 studies in which survival data were reported for both mastectomy and breast conserving surgery, post-	There was no strong evidence that survival of these patients would be adversely affected by having breast conserving surgery rather than mastectomy	Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					mastectomy breast cancer-specific survival was superior (Dixon et al. 1991; Howard et al. 1989; Polgar et al. 2002 and Sutton et al. 1999). A single study statistically found no statistical difference in breast cancer-specific survival at 15 years following treatment (Chen et al. 2006). Cosmesis was assessed in one study only (Marshall et al., 2003) including 31 patients. These were rated as: excellent, 10 (32%; 4 patients underwent nipple reconstruction); good, 18 (58%); fair, 3 (10%).		

TREATMENT OF INVASIVE NON-METASTATIC BREAST CANCER

Primary systemic (Neoadjuvant) therapy

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Early breast cancer							
NICE 2009	[2]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast	- Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery. - Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation.	Three systematic reviews (Hind et al. 2006; Mieog et al. 2007 and Trudeau et al. 2005) and a review providing updated results of two RCTs (Rastogi et al. 2008). *Primary endocrine therapy vs. surgery* One SR (Hind et al., 2006) of RCTs in patients > 70 years. - no significant difference in overall survival - surgery + endocrine therapy vs. endocrine therapy alone: significant effect for breast cancer specific survival. *Preoperative or postoperative chemotherapy* A Cochrane SR (Mieog et al. 2007) and Rastogi et al. (2008) *Overall survival rates* HR of 0.98 (95% CI, 0.87 to 1.09; p= 0.67; no heterogeneity). *Breast conservation rates* No difference as long as surgery remains part of the treatment even after complete tumour regression HR, 1.12; 95% CI, 0.92 to 1.37; p= 0.25; no heterogeneity. *Adverse effects* Preoperative chemotherapy was associated with fewer adverse effects.	Mieog et al. (2007): Data were based on 1 139 estimated deaths in 4 620 women Women with operable breast cancer - TNM stage T1c, T2, T3, N0 to 2, and M0	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Locally Advanced or Inflammatory Breast Cancer							
NICE 2009	[2]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast	Offer local treatment by mastectomy (or in exceptional cases, breast conserving surgery) followed by radiotherapy to patients with locally advanced or inflammatory breast cancer who have been treated with chemotherapy.	A Cochrane review and two systematic reviews (Mieog et al. 2007; Shenkier et al. 2004; Pouillart et al. 1981). One RCT (Bucholz et al., 2006), retrospective studies (Huang et al. 2004; McGuire et al. 2007) and GDG consensus. No difference in overall survival was observed when comparing different radiotherapy regimens (Bucholz et al. 2006 and Shenkier et al. 2004) A higher rate of loco-regional recurrence was reported in patients who received radiotherapy without surgery after primary chemotherapy (Mieog et al. 2007 and Mauri et al. 2005).		High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Preoperative aromatase inhibitor (AI) and cyclooxygenase-2 (COX-2) inhibitor									
Chow 2009	[243]	NA	Postmeno-pausal women with invasive breast cancer (clinical size of tumor ≥3 cm) with ER- and/or PgR positive status	- Group A: exemestane 25mg/d + celecoxib 400mg twice daily; n=30 - Group B: exemestane 25mg/d; n=24 - Group C: letrozole 2.5mg/d, n=28	Tumour size Clinical response (CR, PR, NR)	All groups showed clinical responses (58.6% for group A, 54.5% for group B and 62.0% for group C) and decrease in tumor area (61.8% for group A, 58.1% for group B and 55.7% for group C). → all of the three anti-aromatase therapies are effective and safe but the serum levels of CA15.3 dropped more significantly when anti-aromatase therapy was combined with celecoxib.	No precision about blinding No ITT	RCT	Moderate

Surgery

Surgery to the breast

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Lee et al. 2009	[244]	July 2007	Breast cancer women	Mastectomy with (immediate or delayed) recontruction vs. mastectomy without reconstruction	Quality of life Body image Sexuality	Patient-reported outcomes of breast reconstruction after mastectomy are similar to outcomes of mastectomy without reconstruction. *Results from high quality studies* Equivalent or poorer quality of life, body image, or sexual outcomes in women who had mastectomy with reconstruction, compared with women who had mastectomy only (Rowland 2000, Nissen 2001, Arora 2001, Janz 2005). Postoperative quality of life was poorer for women who had reconstruction, adjusted for preoperative quality of life (Nissen 2001).	Search in Medline (using PubMed), PsycINFO, CINAHL and the Cochrane Library 28 studies were included The majority of the studies had limitations (study design, methodology, selection bias, sensitivity of measures, power, and appropriateness of decisions).	SR	Low
Yang 2008	[117]	NA	Women with stage I or stage II breast cancer	Breast conserving surgery (BCS); n = 5 359 vs. Mastectomy (M); n = 4 038	Overall survival Locoregional recurrence	*Three-year overall survival* 9 RCTs: 92.8% (BCS) vs. 94.4% (MT) OR (fixed effect model) 0.84, 95% CI 0.63–1.12, p = 0.24 *Five-year overall survival* 12 RCTs: 82.6% (BCS) vs. 83.5% (MT) OR (fixed effect model) 0.97, 95% CI 0.84–1.11, p = 0.64 *Ten-year overall survival* 8 RCTs: 69.7% (BCS) vs. 69.3% (MT)	Among RCTs, some authors referred to adopted BCS as quadrantectomy plus axillary dissection, while others adopted tumourectomy plus axillary dissection The methodo-	SR and MA of 18 RCTs	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						OR (fixed effect model) 1.09, 95% CI 0.97–1.23, p = 0.16 *Fifteen-year survival* 6 RCTs: 56.2% (BCS) vs. 58.6% (MT) OR (random effects model) 0.90, 95% CI 0.80–1.02, p = 0.10 *Twenty-year OS* 5 RCTs: 44.1% (BCS) vs. 45.0% (MT) OR (random effects model) 1.09, 95% CI 0.95–1.25, p = 0.23 *Three-year locoregional recurrence rate* 5 RCTs: 3.2% (BCS) vs. 1.9% (MT) OR (random effects model) 1.52, 95% CI 0.40–5.69, p = 0.54 *Five-year survival locoregional recurrence* 10 RCTs: 7.4% (BCS) vs. 7.1% (MT); OR (random effects model) 1.19, 95% CI (0.77–1.85), p = 0.44 *Ten-year locoregional recurrence rate* 8 RCTs: 10.4% (BCS) compared with 8.0% (MT); OR (random effects model) 1.55, 95% CI (1.05–2.30), p = 0.03 *Fifteen-year locoregional recurrence rate* 2 RCTs: 7.1% (BCS) vs. 3.6% (MT); OR (random effects model) 1.59, 95% CI (0.84–2.98), p = 0.15	logical quality of several included RCTs was only moderate or poor.		

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						Twenty-year locoregional recurrence rate 4 RCTs: 11.6% (BCS) vs. 10.1% (MT); OR (random effects model) 1.89, 95% CI (0.48–7.50), p = 0.37 The subgroup analysis showed that the overall survival in 3, 5, 10, 15 and 20 years and the locoregional recurrence rate in 3, 5, 10 and 20 years were not statistically significantly different between groups for patients with tumors up to 5 cm in diameter. Also the overall survival in 3, 5, 10, 15 and 20 years and the locoregional recurrence rate in 3, 5, 10 and 20 years were not statistically significantly different between groups for patients with tumors 2 cm or smaller			
Blichert-Toft 2008	[114]	NA	Women with operable invasive breast carcinoma	Breast conserving surgery (BCS); n = 381 vs. Mastectomy (M); n = 350	Long-term efficacy of BCS vs. M Overall survival (OS) Recurrence free survival (RFS)	Patients with BCS received radiotherapy within 2-4 weeks after surgery In mastectomy group, only high-risk patients received radiotherapy All high-risk patients received adjuvant systemic therapy 10-year recurrence free survival and 20-year overall survival : no significant differences between groups (p=.95 and p=.10	Median follow-up time : 19.6 years (17.1 – 23.3 years) Some problems with randomization No blinding	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						respectively). No differences in recurrences as a first event between groups (p=.27). BCS is as effective as mastectomy regarding tumour control, RFS and OS.			
Petit et al. 2008	[245]	April 1997-December 2001	677 patients with invasive breast cancer	Total mastectomy and complete axillary dissection - immediate breast reconstruction (IBR) in 518 patients - Patey mastectomy without reconstruction (even delayed) in 159 patients (NoIBR)	Disease free survival (DFS) and overall survival (OS)	Median follow up was 70 months (range 15–114) for IBR group and 71 months (range 13–109) for NoIBR group. The local recurrence rate was 5.2% for the group of IBR and 9.4% for the mastectomy group (NoIBR). The regional metastases rate was 1.4 vs. 1.3%. The rate of distant metastases was 13.9 vs. 16.4%. Contra-lateral breast tumor was observed in 1.5 vs. 1.3%. Death rate was 10.4 vs. 16.4%. *Overall survival* IBR vs. NoIBR: HR 1.03 (95% C.I. 0.61–1.75) *Disease-free survival* IBR vs. NoIBR: HR 0.99 (95% C.I. 0.67–1.47).	An adjuvant medical treatment was given according to the biological characteristics of the tumor and lymph node status with the same protocol delivered to the two groups. No radiotherapy. Clinical follow up every 6 months (Rx/ year or more, mammo on the contra-lateral breast only and bilateral US examination). Liver, bone and thorax /year with the biological markers. Survival curves were estimated	Case-control study	Low

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
							using the Kaplan-Meier method and the Log-rank test + Cox proportional hazard regression model		

Surgery to the axilla

Sentinel lymph node biopsy

CPG ID	Ref	Search date	Population	Recommendation	*Supporting evidence*	Comments	Level of evidence
NICE 2009	[2]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 having breast conserving surgery	Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. SLNB is the preferred technique.	*Invasive breast cancer SLNB versus axillary clearance or axillary sampling* Evidence on SLNB comes both from RCTs and case series studies (Agarwal et al. 2005; Blanchard et al. 2003; BMJ Clinical Evidence 2005; Carlo et al. 2005; Clarke et al. 2004; Cody et al. 1999; Cox. et al. 2000; Cserni et al. 2002; Fleissig et al. 2006; Giuliano et al. 1997; Haid et al. 2002; Imoto et al. 2004; Julian et al. 2004; Katz et al. 2006; Kim et al. 2006; Kokke et al. 2005; Krag et al. 2001 and 2007; Langer et al. 2004, 2005; Leidenius 2004; Lucci et al. 2007; Mansel et al. 2006; Naik et al. 2004; Purushotham et al. 2005; Reitsamer et al. 2004; Rietman et al. 2003; Ung et al. 2004; Veronesi et al. 2003, 2006; Zavagno et al., 2005a, b and 2008). A well conducted systematic review and meta-analysis of 69 studies was undertaken by Kim, Giuliano and Lyman (2006) with data from over 8 000 patients. The overall sentinel lymph node localisation rate was 96.4%, the pooled estimate of FN rate was 7.0%, the mean proportion of patients with positive sentinal lymph nodes was 42% and the post test probability negative was 4.6%.		High

					From other studies, the sentinel lymph node localisation rate ranged from 81.4% to 100% (mean 94.0% and median 94.9%) The false negative rate of SLNB ranges from 0% to 10.7% (mean 5.8%, median 5.9%) The accuracy of SLNB ranges from 94.6% to 100% (mean 97.7% with a median of 98.3%) The prevalence of axillary disease has a mean of 39.1%, median 35.4% and a range from 28.8% to 57.6%. The evidence on morbidity, including lymphoedema, favours SLNB over axillary clearance. The ALMANAC RCT and the RCT by Purushotham et al. (2005) found little evidence, by ITT, that a difference exists in psychological morbidity between patients treated by SLNB compared to axillary clearance. *Axillary sampling as staging surgery* 15 studies evaluated axillary sampling as staging surgery in early breast cancer: two RCTs (Chetty et al., 2000 and Forrest et al., 1995) and 13 case series studies (Hadjiminas and Burke, 1994; Rampaul et al. 2004; Tanaka et al. 2006; Thompson et al. 1995; Mathew et al. 2006; Sato et al. 2001; Ishikawa et al. 2005; Narredy et al. 2006; Macmillan et al. 2001; Hoar and Stonelake, 2003; Gui et al. 2005; Cserni, 1999 and Kingsmore et al. 2003).		

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Langer 2009	[246]	January 2000 - December 2003	659 early stage breast cancer patients (pT1 and pT2 ≤ 3 cm, cN0)	SLNB frozen section Reference: Histopathology (H&E and ICT)	identification of SLN macro-metastases	SLN were identified in 98.3% of all patients. The accuracy of frozen section was 90.1%. Se: 70% (95% CI: 63.2% - 73.9%) Sp: 100% (95% CI: 98.9% - 100%) A delayed completion of ALND can be avoided in 98% of these patients. 96% of patients with SLN micro-metastases or isolated tumor cells undergoing delayed completion ALND did not benefit from the second operation as ALND specimens were free of macro-metastases. → the routine use of SLN frozen section in early stage breast cancer patients is recommended.		Prospective study	Low
Canavese 2009	[247]	1998 - 2001	248 consecutive patients randomized in 2 arms	- SLNB and ALND (ALND arm) - SLNB + ALND if SLNB positive (SLNB arm)	Overall survival Axillary recurrence	*Diagnostic accuracy of ALND* Se: 45%; 95%CI: 25.1% - 67.3% Sp: 85%; 95%CI: 75.7% - 91.2% *Risk ratio of SNB vs ALND* RR=0.87; 95%CI 0.38 – 2.01 *5-year Event free survival* ALND arm: 89.8% (95%CI: 86.9%-92.7%) SLNB arm: 94.5% (95% CI: 90.9% - 98.1%) Log rank p = 0.715 *5-year overall survival* ALND arm: 97.2% (95%CI: 95.4% -	Non-inferiority trial having to analyze 2750 patients → underpowered study The diagnostic accuracy is uncorrectly reported in the paper Median follow-up: 5.5 ± 1.4 years	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						92.7%) SLNB arm: 97.2% (95%CI: 95.4% - 92.7%) Log rank p = 0.697			
Motomura 2008	[248]	January 2000 – September 2006	631 consecutive patients with clinical T1 breast cancer with clinically negative nodes	SLNB - If positive intraoperatively → immediate ALND - If positive by final pathologic results → subsequent ALND <u>Reference</u>: Histopathology (H&E / H&E and ICT)	Accuracy of imprint cytology for the intra-operative diagnosis of sentinel node metastases	*Imprint cytology for the diagnosis of sentinel node metastases* Se: 84.6% (95%CI: 77% - 90.1%) Sp: 96.6% (95%CI: 94.5% - 97.1%) Overall accuracy: 94.1% Only 20 (3.2%) patients required a second axillary operation in the present study.	Patients with multiple primary tumors, nonpalpable breast cancer, prior axillary surgery, or pregnancy were excluded.	Prospective study	Low

Axillary lymph node dissection

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008	Women and men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 having breast conserving surgery	Offer further axillary treatment to patients with early invasive breast cancer who: − have macrometastases or micrometastases shown in a sentinel lymph node − have a preoperative ultrasound-guided needle biopsy with histologically proven metastatic cancer. The preferred technique is ALND because it gives additional staging information. Do not offer further axillary treatment to patients found to have only isolated	RCT evidence: Chetty et al. 2000, Forrest et al. 1995; Veronesi et al. 2003. - no significant differences in overall survival between groups given axillary dissection or axillary sampling with regional lymph node radiotherapy for lymph node-positive patients - no significant difference in overall survival between the groups receiving SLNB and axillary dissection and SLNB or axillary dissection only in SLNB-positive patients - no differences between these	Of the included studies only one (Calhoun et al., 2005) provides data for recurrence and survival. All patients were alive at a mean follow-up of 80.5 months (6 years, 8 months).	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				tumour cells in their sentinel lymph nodes. These patients should be regarded as lymph node-negative.	groups for locoregional recurrences or axillary recurrences SR: Cserni et al. 2004 and Degnim et al. 2003 The pooled estimate for the rate metastatic nonsentinel lymph nodes in patients with sentinel lymph node metastases of size 2 mm or less was 20.2% (95% CI 15.5%-24.9%) when the sentinel lymph node metastases are detected by H&E staining, and 9.4% (95% CI 6.2%-12.6%) when the sentinel lymph node metastases are detected by immunohistochemistry techniques Observational studies: de Widt-Levert et al. 2003; Goyal et al. 1990; Bolster et al. 2007; Calhoun et al. 2005; Houvenaeghel et al. 2006; Katz et al. 2006; van Rijk et al. 2006 and Viale et al. 2005. The mean proportion of patients with metastatic non-sentinel lymph nodes is 10% for sentinel lymph node isolated tumour cells, 17.7% for sentinel lymph node micrometastases and 53.2% for sentinel lymph node macrometastases.		

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Droeser et al. 2009	[249]	2006	Women undergoing mastectomy or breast conserving surgery + ALND	Volume-controlled drainage (VCD) vs no/short-term drainage (NoD)	Seroma formation Wound infection	*Seroma formation* VCD vs NoD: RR 0.44, 95% CI 0.24–0.80, p for heterogeneity <0.001	Search in Pubmed, EMBASE and the Cochrane library for RCTs inclusion	SR and MA	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
				after ALND	Length of hospital stay	*Wound infection* VCD vs NoD: RR 1.23, 95% CI 0.70–2.16, p for heterogeneity = 0.8 *Length of Stay (1 RCT)* VCD vs NoD: weighted mean difference 1.50, 95% CI 1.23–1.76, days, p for heterogeneity <0.001	6 RCTs including a total of 561 patients: 299 in volume-controlled group vs 262 in no/ short-term drainage group 4 RCTs did not report concealed treatment allocation. No patients or care givers blinding. Blinded outcome assessment was not reported in any of the trials. Overall, the quality of included trials was considered to be fair		
Olson 2008	[120]		1 003 patients with breast cancer metastasis to the sentinel lymph nodes (SLNs)	Completion axillary lymph node dissection (cALND): - concurrently with SLNB (n=425) - in a second procedure (n=578)	Complications (axillary seroma, paresthesia, arm morbidity and range of motion, and lymphedema)	<u>Immediate cALND versus delayed cALND</u> *Axillary paresthesia (at 30 days)*: 51% v 35%; p<.0001 *Impaired ROM (at 30 days)*: 49% v 36%; p<.0001 Improvement reported at 1 year.		Large prospective cohort study	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						Lymphedema (at 6 months) 13% v 10%; *p* not significant), no difference at 1 year.			

Adjuvant therapy planning

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
All patients with early invasive breast cancer							
NICE 2009	[2]	July 2008	Women with early invasive breast cancer	- Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded. - Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. - Decisions should be made following discussion of these factors with the patient.	GDG consensus and expert position		Low
All patients with early breast cancer							
NICE 2009	[2]	July 2008	Women with early breast cancer	Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments.	***Sequencing of adjuvant therapies*** *Concurrent adjuvant chemotherapy/ radiotherapy versus chemotherapy followed by radiotherapy*: High-quality evidence from RCTs (Hickey et al. 2006; Calais et al. 2005) - no difference in terms of local recurrence [OR (concurrent: sequential) 1.30; 95% CI 0.45 to 3.77; p=0.63], distant metastases [OR (concurrent:sequential) 1.43 95% CI 0.86 to 2.37, p=0.16] and overall survival. - no difference with regard to some toxic effects [fever (OR 1.27, 95% CI 0.79 to 2.03, p=NS), cardiac		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					complications (OR 1.73, 95% CI 0.50 to 5.96, p= NS), neutrophil toxicity (OR 0.89, 95% CI 0.63 to 1.27, p= NS) or platelet toxicity (OR 0.89, 95% CI 0.39 to 2.06, p=NS)]; - oesophageal toxicity (OR 1.44, 95% CI 1.03 to 2.02, p=0.03), haematological toxicity (OR 1.43, 95% CI 1.01 to 2.03, p = 0.04) and skin toxicity (OR 1.46, 95% CI 1.00-2.14), p=0.05) were significantly lower with sequential therapy; - nausea and vomiting was significantly less common with concurrent therapy (OR 0.70, 95% CI 0.50 to 0.98, p= 0.04) - Late toxic effects (subcutaneous fibrosis, telengectasia, skin pigmentation, and breast atrophy) are more common following concurrent therapy than sequential therapy. - in the subgroup of lymph node-positive patients, local recurrence-free survival is higher following concurrent therapy than sequential therapy (p<0.035). Subsequent RCT (Toledano et al., 2007): no statistically significant differences between the sequential therapy group and the concurrent therapy group - in 5-year rates of disease-free survival (80% and 80% respectively; p=0.83, Log-rank test), recurrence-free survival (92% and 95% respectively; p=0.76, Log-rank test) and overall survival (90% and 91% respectively; p=0.76, Log-rank test).		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					- no difference in local recurrence-free survival in the node-negative subgroup of patients between the sequential therapy group (93%) and the concurrent therapy group (93%; p=0.81, Log-rank test). - in the node-positive subgroup local recurrence-free survival was statistically significantly worse in the sequential therapy group (91%) compared to the concurrent therapy group (97%; p=0.02, Log-rank test; HR 0.61, 95% CI 0.38-0.93). *Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy*: RCT evidence (Hickey et al. 2006): - no difference in terms of distant metastases [HR (RT first:CT first) 0.82, 95% CI 0.49 to 1.36, p=0.44] and overall survival [HR (RT first:CT first) 0.85, 95% CI 0.51 to 1.40, p=0.52]. - higher rate of neutropenic sepsis in patients who receive radiotherapy before chemotherapy [OR (RT first: CT first) 2.96, 95% CI 1.26 to 6.98, p=0.02] - no difference for other toxicity outcomes [skin toxicity [OR (RT first: CT first) 1.48, 95% CI 0.68 to 3.26, p=NS], subcutaneous toxicity [OR (RT first: CT first) 2.05, 95% CI 0.50 to 8.40, p=NS], pneumonitis [OR (RT first: CT first) 11.47, 95% CI 0.63 to 209.7, p=NS], lymphoedema [OR (RT first: CT first) 0.11, 95% CI 0.01 to 2.02, p=NS] and brachial plexopathy [OR (RT first: CT first) 3.02, 95% CI 0.12 to 74.98,		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					p=NS]. - However, treatments in the included trials were given a decade ago on average (based on CMF) and the chemotherapy regimens may not be considered optimal today. Secondly, surgical outcomes in the trials might be considered unacceptable today. There is currently no information regarding the optimum sequencing of radiotherapy with taxanes or with trastuzumab. *Early versus late chemotherapy*: RCT evidence from the International Breast Cancer Study Group (1997) suggests there is no difference in 5-year disease-free survival or overall survival arising from early chemotherapy given over the first three months following surgery versus delayed chemotherapy given between 9 and 15 months following surgery. ***Interval between surgery and start of adjuvant therapy*** *Interval from surgery to radiotherapy*: Disease-free and overall survival were not adversely affected by increasing delay to the start of radiotherapy in the first three months after surgery (Benchalal et al. 2005; Jobsen et al. 2006 and Mikeljevic et al. 2004) whereas overall survival was adversely affected in those whose radiotherapy was delayed for at least 5 to 6 months after surgery (Mikeljevic et al. 2004).		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Interval from surgery to chemotherapy: Increasing delay to the start of adjuvant chemotherapy in the first 3 months after surgery was not associated with poorer disease-free or overall survival (Cold et al. 2005; Colleoni et al. 2000; Lohrisch et al. 2006; Sanchez et al. 2007 and Shannon et al. 2003). Colleoni et al. (2000) reported that disease-free survival was adversely affected by delays of three or more weeks in the sub-group of women with ERnegative disease. Another study reported that disease-free and overall survival were adversely affected only when the start of chemotherapy was delayed until at least three to six months after surgery (Lohrisch et al., 2006).		

Radiotherapy

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Breast conserving surgery							
NICE 2009	[2]	July 2008	Women with early invasive breast cancer	Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy.	Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (Clarke et al. 2005) + additional data (Liljegren 2002; Rutqvist et al. 2003 and Vinh-Hung and Verschraegen 2004). One RCT (Ford et al. 2006) and one retrospective cohort study from the US SEER database (Vinh-Hung et al. 2003). *Cosmetic outcomes* Two systematic reviews reported (Liljegren 2002 and Mul et al. 2007), one RCT (Johansen et al. 2002) and one non-randomised study (Duetsch and Flickinger, 2003). *Quality of life outcomes* RCTs (Lee et al. 2008; Rayan et al. 2003 and Whelan et al. 2000), a survey (Back et al. 2005). Four guidelines: two Canadian (Shelley and Trudeau 2002 and Whelan et al. 2003), one American (Morrow et al. 2002) and one recent German DEGRO guideline (Sautter-Bihl et al. 2007). → postoperative radiation decreased the risk of local recurrence + moderate reduction in breast cancer deaths and overall mortality after 15 years.		High

Post-Mamectomy Radiotherapy							
NICE 2009	[2]	July 2008	Women with early invasive breast cancer	- Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins. - Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an intermediate risk of local recurrence into the current UK trial (SUPREMO) assessing the value of postoperative radiotherapy. Patients at an intermediate risk of local recurrence include those with one to three lymph nodes involved, lymphovascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40 years. - Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node-negative).	Meta-analyses of RCTs: EBCTCG (Clarke et al. 2005), Gebski et al. 2006; Killander et al. 2007; Kyndi et al. 2008 and Whelan et al. 2000. Danish Breast Cancer Cooperative Group (Nielsen et al. 2006 and Overgaard et al. 2007) Van de Steene et al. 2000; Bartelink 2000; Bellon et al. 2006; Fisher et al. 2002; Gustavsson et al. 1999; Hojris et al. 2000; Hojris et al. 1999; Recht et al. 2001; et al. Smith 2006 and Truong 2004. *Loco-regional recurrence* Reduction of locoregional recurrence. The absolute reduction in local recurrence was greater in lymph node-positive than lymph node-negative disease (17% versus 4%). *Mortality* Reduction in 15 year all cause mortality of 4.2% (for lymph node-negative) and 4.4% (for lymph node-positive). *Prognostic factors for survival* Significant factors reducing survival were a tumour size > 21 mm), number of involved lymph nodes, extracapsular invasion, and site of local recurrence (Nielsen et al. 2006).		High

Dose fractionation							
NICE 2009	2	July 2008	Women with early invasive breast cancer	Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy.	Systematic reviews compared hypofractionated radiotherapy with no radiotherapy (EBCTCG 2002 and Gebski et al., 2006). RCT (Owen et al., 2006; START A and B 2008; Whelan et al., 2002 and Yarnold et al., 2005). Trials (Bates 1998; Goel et al., 2000 and Taher et al., 2004). *Rates of local recurrence* No difference between conventional 50 Gy fractions and hypofractionated schedules *Distant relapse* Lower in the hypofractionated schedules *Rates of disease-free survival and overall survival* Improved in the hypofractionated schedules *Cosmetic outcomes* Less consistent results		High
Breast boost							
NICE 2009	2	July 2008	Women with early invasive breast cancer	- Offer an external beam boost to the site of local excision to patients with early invasive breast cancer and a high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy. - If an external beam boost to the site of local excision following breast conserving surgery is	RCTs (EORTC 22881-10882; Poortmans et al. 2004) and non-randomised studies → a boost dose to the tumour bed reduced local recurrence but had little effect on overall survival A joint SR on cost effectiveness of radiotherapy + external beam		High

				being considered in patients with early invasive breast cancer, inform the patient of the side effects associated with this intervention, including poor cosmesis, particularly in women with larger breasts.	radiotherapy boost to the site of local excision after breast conserving surgery. ➔ the addition of a radiotherapy boost after breast conserving surgery and radiotherapy on early breast cancer patients with stage 1 and 2 tumours and negative margins does not seem to be cost effective		
Radiotherapy to nodal areas							
NICE 2009	[2]	July 2008	Women with early invasive breast cancer	- Do not offer adjuvant radiotherapy to the axilla or supraclavicular fossa to patients with early breast cancer who have been shown to be histologically lymph node negative. - Do not offer adjuvant radiotherapy to the axilla after ALND for early breast cancer. - If ALND is not possible following a positive axillary SLNB or four-node sample, offer adjuvant radiotherapy to the axilla to patients with early breast cancer. - Offer adjuvant radiotherapy to the supraclavicular fossa in patients with early breast cancer and four or more involved axillary lymph nodes. - Offer adjuvant radiotherapy to the supraclavicular fossa to patients with early breast cancer and one to three positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status. - Do not offer adjuvant radiotherapy to the internal mammary chain to patients with early breast cancer who have had breast surgery.	Studies comparing surgery and regional lymph node irradiation with mastectomy and axillary dissection or mastectomy only (Fisher et al., 2002; Overgaard et al., 1999; Ragaz et al., 2005 and Wallgren et al., 1986); Studies comparing breast conserving surgery with or without axillary dissection or axillary radiotherapy (Louis-Sylvestre et al., 2004; Pejavar et al., 2006, and Veronesi et al., 2005); Studies applying radiation to the internal mammary lymph nodes (Arriagada et al., 1988; Grabenbauer 2004; Kaija and Maunu 1995; Obedian and Haffty 1999; Vinod and Pendlebury, 1999); Retrospective studies (Livi et al. 2006; Grills et al. 2003; Fortin et al. 2006 and Tai et al. 2007).		

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
James ML 2008	[137]	June-November 2006	Women with early breast cancer who had undergone breast conserving surgery.	Unconventional versus conventional fractionation	(1) local-recurrence free survival (2) breast appearance (3) survival at five years (4) late skin toxicity at 5 years	Unconventional fractionation (delivering radiation therapy in larger amounts each day but over fewer days than with conventional fractionation) did not appear to affect: (1) local-recurrence free survival (absolute difference 0.4%, 95% CI -1.5% to 2.4%), (2) breast appearance (risk ratio (RR) 1.01, 95% CI 0.88 to 1.17), (3) survival at five years (RR 0.97, 95% CI 0.78 to 1.19), (4) late skin toxicity at five years (RR 0.99, 95% CI 0.44 to 2.22), (5) late radiation toxicity in sub-cutaneous tissue (RR 1.0, 95% CI 0.78 to 1.28).	Two RCTs were included and reported on 2 644 women (Owen et al., 2006; Whelan et al., 2002) Both RCTs were included in NICE 2009	SR	High
Holli 2009	[250]	NA	Women > 40 years having ≤20 mm, node negative, PgR positive (n=264)	Breast irradiation Vs. not after BCS and ALND		*Time to local recurrence* HR 0.36; 95%CI 0.20 - 0.65; p = 0.0007 *Overall survival* HR 0.63; 95% CI 0.35 to 1.12; p= 0.11	Randomisation computer program No blinding ITT analysis Median FU of 12.1 years (6 years follow-up: Holli 2001)	RCT	Moderate

Chemotherapy

For early and locally advanced breast cancer

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008		- Offer docetaxel to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen. - Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer.	Cochrane review (Ferguson et al. 2007) HTA report (Ward et al. 2007) meta-analysis (De Laurentiis et al. 2008) pooled analysis (Bria et al. 2006) 2 RCTs (Kummel et al. 2006; Piedbois et al. 2007) 1 RCT from an abstract (Ellis et al. 2007) *With taxanes* Improved overall and disease-free survival *With docetaxel* More frequent (febrile) neutropenia	Sparano et al. (2008) showed that weekly paclitaxel was more effective than 3 weekly docetaxel. This trial also showed no difference between 3 weekly docetaxel and 3 weekly paclitaxel. This trial was found when updating the evidence searches.	High
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	The following taxane-containing regimens are considered reasonable treatment options for the target population: - Six cycles of three-weekly docetaxel, doxorubicin, and cyclophosphamide (DAC) (75/50/500 mg/m^2) - Four cycles of doxorubicin and cyclophosphamide (AC) (60/600 mg/m^2) followed by four cycles of paclitaxel (175 mg/m^2 or 225 mg/m^2 every three weeks or 175 mg/m^2 every two weeks with granulocyte	Randomized controlled phase III trials		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				colony-stimulating factor [G-CSF]). - Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m^2) These regimens are recommended over their non–taxane-containing counterparts (six cycles of FAC, four cycles of AC, or six cycles of FEC-100), as they have been shown to be superior in efficacy.			
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Six cycles of three-weekly DAC (75/50/500 mg/m^2) is recommended over six-cycles of three-weekly FAC (500/50/500 mg/m^2).	Breast Cancer International Research Group (BCIRG) 001 trial (Martin et al. 2005) Meta-analysis on 5 trials: Martin et al. 2005, Gianni et al. 2005, Goldstein et al. 2005, Kümel et al. 2006, Crown et al. 2006 Anthracycline–taxane regimens compared to their non-taxane containing counterparts. *Disease free survival* HR=0.82 (95% CI 0.71 to 0.94), with little statistical heterogeneity (χ2 test for heterogeneity p=0.16, I^2 = 39.1%). *Overall survival* HR= 0.84 (95% CI 0.66 to 1.08), with evidence of statistical heterogeneity (χ2 test for heterogeneity p=0.02, I^2 = 65.1%).	n=1 491 women	High
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive	The inclusion of a taxane in sequence with an anthracycline-based regimen should be considered. The following regimens have been specifically studied in comparison to	Meta-analysis on 6 trials: Crown et al. 2006, Henderson et al. 2003, Martín et al. 2005, Rodriguez-Lescure et al. 2004, Buzdar et al. 2002, Mamounas et al. 2005,		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
			breast cancer.	their non–anthracycline-containing counterparts and are recommended. - Four cycles of three-weekly AC (60/600 mg/m^2) followed by four cycles of three-weekly paclitaxel (175 mg/m^2 or 225 mg/m^2) is recommended over four cycles of three-weekly AC alone (60/600 mg/m^2). - Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m^2) is recommended over six cycles of FEC-100 alone.	Roché et al. 2004 *Disease free survival* HR=0.80 (95% CI 0.75 to 0.86) *Overall survival* HR=0.83 (95% CI 0.76 to 0.91). No statistical heterogeneity in either estimate (I^2=0% for both estimates).		
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Women in the target population should be considered for dose-dense therapy with doxorubicin and cyclophosphamide followed by paclitaxel. In practice, four cycles of two-weekly AC (60/600 mg/m^2) followed by four cycles of two-weekly paclitaxel (175 mg/m^2) (AC→ T) is more commonly used due to a shorter duration of treatment. G-CSF (days three to 10 of each cycle [a total of seven doses] at 5 µg/kg rounded to either 300 µg or 480 µg total dose) should be given in combination with four cycles of two-weekly AC→ T to prevent neutropenia.	Intergroup (INT) C9741 trial (Citron et al. 2003, Hudis et al. 2005) *Disease free survival* Significantly improved in women who received G-CSF and four cycles of two-weekly A→T→C or AC→T compared with women who received the same regimens every three weeks at a median follow-up of 69 months (HR 0.80, 95% CI 0.62 to 0.96, p=0.018). At a median follow-up of 36 months, the absolute difference in four-year DFS was 7% (p=0.010)	N = 1 973 women	High
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Four cycles of three-weekly docetaxel and cyclophosphamide (75/600 mg/m^2) (DC) is recommended over four cycles of three-weekly AC (60/600 mg/m^2).	U.S. Oncology (USON) 9735 trial (Jones et al. 2001, 2005) *Disease free survival* Significantly improved in women treated with DC versus those treated with AC	RCTs	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					(HR 0.67, absolute difference at five years 6%, p=0.015). *Overall survival* No significant difference (HR 0.76, absolute difference at five years 3%, p=0.131).		
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Prophylactic G-CSF (granulocyte colony-stimulating factor) should be considered in patients receiving concurrent anthracycline /taxane regimens.	Breast Cancer International Research Group (BCIRG) 001 trial (Martin et al. 2005): DAC versus FAC *grade 3+ neutropenia* 65.5% vs. 49.3%, p<0.001 *grade 3+ anemia* 4.3% vs. 1.6%, p=0.003 *febrile neutropenia* 24.7% vs. 2.5%, p<0.001	RCTs	High
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Women receiving an adjuvant anthracycline–taxane regimen should be closely monitored for febrile neutropenia. In those who experience febrile neutropenia while receiving DAC, G-CSF (granulocyte colony-stimulating factor) should be administered with subsequent docetaxel infusions. Alternatively, a dose reduction should be considered.	GEICAM 9906 trial (Martín et al. 2005, Rodriguez-Lescure et al. 2004) : FEC→T vs FEC *grade 3+ neutropenia* 20.5% vs. 30%, p=significant *grade 3+ leucopenia* 7.4% vs. 10.6%, p=significant *febrile neutropenia* 5.1% vs. 9.3%, p=0.004 PACS 01 trial (Roché et al. 2004): FEC→D versus FEC	RCTs	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					febrile neutropenia 4.6% vs. 1%, p=0.001		
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	The Breast Cancer DSG considers the following G-CSF regimen (granulocyte colony-stimulating factor) to be reasonable for either prophylaxis for or treatment of febrile neutropenia: day three to ten of each cycle (a total of seven doses) at 5 µg/kg rounded to either 300 µg or 480 µg total dose.	CALGB 9344 trial (Henderson et al. 2003): AC→T vs AC *hematologic toxicity* Fewer occurrences during the paclitaxel cycles of the AC→T arm than during the equivalent cycles of AC in the AC-only arm. INT C9741 trial (Citron et al. 2003, Hudis et al. 2005) : dose-dense AC→T versus standard AC→T *grade 3+ neutropenia* 5.9% vs. 12%, p not reported. *grade 2+ anemia* 23% 8%, p<0.0001) NB. patients receiving dose-dense therapy in this trial received G-CSF prophylaxis.	RCT	High
CCO 2006	[159]	May 2006	Women with T 1-3, operable, node-positive breast cancer.	Women receiving a taxane regimen should also be monitored for other toxicities, including diarrhea, stomatitis, amenorrhea, asthenia, myalgia, paresthesia, and leukopenia.	USON 9735 trial (Jones et al. 2001, 2005): DC vs AC *Febrile neutropenia* 6% vs. 3%, p=0.03	RCT	High

Abbreviations: doxorubicin and cyclophosphamide [AC]; 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC]; 5-fluorouracil, epirubicin, and cyclophosphamide [500/100/500mg/m2] [FEC-100]; cyclophosphamide, epirubicin, 5-fluorouracil [75/60/100mg/m2] [CEF].

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
EBCTCG 2008	[251]	1985-2008	Pre-menopausal and post-menopausal women with ER-poor early breast cancer	1) Non-taxanes based polychemo-therapy vs. not 2) Tamoxifen vs. not Chemotherapy denotes prolonged adjuvant trt with various standard combinations of older drugs: eg, about six courses of CMF (45% of randomised women) or about six courses of FAC or FEC (31% of randomised women) None of the regimens studied were taxane-based or deliberately myeloablative.	Recurrence Breast cancer mortality Death from any cause	**Polychemotherapy vs not (with or without Tamoxifen)** *Recurrence (treatment versus control recurrence rate ratios)* <u>Age < 50 years (1 907 women, 15% node-positive)</u> - Ratio: 0 ·61 [SE 0 ·07] - the 10-year risks were: o recurrence 33% vs 45% (ratio of 10-year risks 0 ·73, 2p<0 ·00001), o breast cancer mortality 24% vs 32% (ratio 0 ·73, 2p=0 ·0002), o death from any cause 25% vs 33% (ratio 0 ·75, 2p=0 ·0003). <u>Age 50-59 years</u> - Ratio: 0.68 [SE 0.06] <u>Age 60–69 years</u> - Ratio: 0 ·82 [SE 0 ·07] In women aged 50–69 years (3 965 women, 58% node-positive), the 10-year risks were: o recurrence 42% vs 52% (ratio 0 ·82, 2p<0 ·00001), o breast cancer mortality 36% vs 42% (ratio 0 ·86, 2p=0 ·0004), o death from any cause 39% vs 45% (ratio 0 ·87, 2p=0 ·0009).	6 000 women with ER-poor breast cancer in 46 trials of polychemotherapy versus not (typically about six cycles; trial start dates 1975–96, median 1984) 14 000 women with ER-poor breast cancer in 50 trials of tamoxifen versus not (in presence / absence of poly-chemotherapy; trial start dates 1972–93, median 1982).	SR et MA of RCTs	High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						Few were aged 70 years or older. Tamoxifen had little effect on recurrence or death in women who were classified in these trials as having ER-poor disease, and did not significantly modify the effects of polychemotherapy. → the older adjuvant polychemo-therapy regimens were safe (ie, had little eff ect on mortality from causes other than breast cancer) and produced substantial and definite reductions in the 10-year risks of recurrence and death.			
Albain 2009	[181]	NA	1 558 post-menopausal women with hormone-receptor-positive, node-positive breast cancer	CAF followed by tamoxifen (CAF-T) Vs. CAF with concurrent tamoxifen (CAFT)	DFS OS Toxicity	*Disease free survival* HR 0 ·84, 0 ·70–1 ·01; p=0 ·061 *Overall survival* HR 0 ·90, 0 ·73–1 ·10; p=0 ·30 *Toxicity* Neutropenia, stomatitis, thromboembolism, congestive heart failure, and leukaemia were more frequent in the combined CAF plus tamoxifen groups	13 years of follow-up Randomization : allocation by a central software program; 2:3:3 ratio to receive tamoxifen alone, CAF-T, or CAFT Stratification by number of involved nodes (1–3 vs ≥4), PgR status (positive vs negative), and interval from surgery (≤6 weeks vs >6 weeks).	Phase III RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
							Unblinded patients and treating physicians		
Amadori 2008	[252]	NA	Women <70 y with node negative breast cancer after surgery (mammectomy or quadran-tectomy) + radiotherapy (n= 281)	Adjuvant CMF 6 cycles Vs. no further treatment	Relapse Death	*Relapse* HR 0.75 (95%CI 0.50-1.13) ; p =0.17 *Death* HR 0.80 (95%CI 0.48-1.33) p = 0.38 + retrospective subgroup analysis	FU 12 years Randomisation by permuted block No blinding ITT and per protocol analysis Previous publication in Amadori 2000 (same RCT)	RCT	Moderate
De Azambuja 2008	[253]	NA	Women ≤70 y with node positive breast cancer after modified radical mastectomy or lumpectomy plus AND Tamoxifen if post menop and HER+ Radiotherapy mandatory for BCS Post-mastectomy optional (n=777)	6 cycles of CMF Vs. 8 cycles of EC (epirubicin low dose) Vs. 8 cycles HEC (high dose epirubicin + cyclophosphamide)	Event free survival Overall survival Toxicity	*15 years event free survival (EFS)* CMF: 45% / EC: 39% / HEC 50% HEC vs EC: HR 0.77 (95%CI 0.60-0.98) HEC vs CMF HR 0.90 (NS) EC vs CMF HR 0.86 (NS) *15 years overall survival (OS)* No difference *Cardiac toxicity* Significantly more frequent with HEC than CMF (p =0.006), but no more than EC (=0.21).	Randomisation by central assignment No blinding ITT analysis Follow up 15 years	RCT	Moderate

Eljertsen 2008	[153]		1 224 women with reseceted unilateral invasive carcinoma of the breast and no signs of metastases	9 cycles of three-weekly IV CMF Vs. 9 cycles of three-weekly IV CEF	DFS OS Toxicity	*10 years disease free survival (DFS) CEF vs. CMF* HR 0.84 (95% CI 0.71–0.99) *10 years overall survival (OS)* HR 0.79 (95% CI 0.66–0.94) *Toxicity* CEF: more nausea and vomiting (P < 0.01), conjunctivitis, stomatitis, alopecia Cardiac and thromboembolic events : similar incidence in the CEF (4.8%) and CMF (4.3%) groups.	ITT analysis 10 years follow-up and per protocol analysis	Phase III RCT	Moderate
Ellis 2009	[254]	NA	4162 patients with node positive or high risk node negative early breast cancer Who underwent a mastectomy or wide local excision	Experimental group: 4 cycles FEC followed by 4 cycles docetaxel Vs. control group: -either FEC: 8 cycles FEC -either E-CMF: 4 cycles epirubicin followed by 4 cycles CMF	DFS Toxicity	*5-year disease-free survival* Experimental group: 75 ·6% (95% CI 73 ·7–77 ·5) Control group: 74 ·3% (72 ·3–76 ·2) Absolute difference 1.3% (-2.2 to 4.8) HR 0 ·95, 95%CI 0 ·85–1 ·08; p=0 ·44. More patients with grade 3 or 4 adverse event in the experimental group (p<0 ·0001) The most frequent events were neutropenia (937 events vs 797 events), leucopenia (507 vs 362), and lethargy (456 vs 272).	Randomisation by computer-generated permuted block randomisation No blinding ITT analysis Median follow up of 62 months	RCT	Moderate
Francis 2008	[255]	NA	Patients with lymph node positive breast cancer T1-T3	- Sequential docetaxel (doxorubicin / docetaxel / CMF);	Disease free survival	*5-year disease free survival* - in control arms: 73% (95% CI 70% to 75%). - docetaxel vs. Control : HR =	Randomisation: minimization procedure with stratification	RCT	Low (reduced power)

			who underwent mastectomy or BCS (n = 2887)	- concurrent docetaxel (doxorubicin + docetaxel / CMF) Vs. control: - Sequential control (doxorubicin / CMF) - concurrent control (doxorubicin + CMF);		0.86, 95% CI = 0.7 -1.00; p = .05). - sequential docetaxel vs. concurrent docetaxel : HR = 0.83, 95% CI = 0.69 - 1.00) - sequential docetaxel vs. sequential control arm: HR = 0.79, 95% CI = 0.64 - 0.98.	No blinding ITT analysis Median follow up 5 years Reduced power of the study after 5 years and chance not excluded		
Gianni 2008	[256]	NA	Operable breast cancer T2-T3, N0-N1, M0 (n= 1355) Surgery: mastectomy or BCS	- Arm A: Surgery / doxirubin / CMF - Arm B: Surgery / paclitaxel + doxorubin / CMF - Arm C: paclitaxel + doxorubin / CMF / surgery	Disease free survival	*Disease free survival at 76 months* Arm B versus arm A HR = 0.73; 95% CI = 0.57 to 0.97 p = .03 Arm B versus arm C HR = 1.21; 95% CI = 0.92 to 1.60 P = .18	Randomisation: minimization procedure with stratification No blinding ITT analysis Median follow up 76 months	RCT	Moderate
Goldstein 2008	[257]		Operable breast cancer with 1 to 3 involved lymph nodes or tumor > 1 cm with negative nodes (n= 2882) After surgery: lumpectomy or mastectomy and ALND	Doxorubicin + AC Vs. Doxorubicin + AT / hormone therapy for ER+ and/or PR+ tumors.	Disease free survival Overall survival	*5 years disease-free survival* 85% in both arms For AC versus AT: HR = 1.02 (95% CI 0.86 - 1.22; p = .78). *5 years overall survival* 91% v 92% Grade 3 neutropenia associated with fever or infection occurred more often with AT (26% v 10%; p < .05).	Randomisation: permuted blocks No blinding ITT analysis Median follow-up of 79.5 months	RCT	Moderate

Jones 2009	[258]	NA	Operable breast cancer > 1 cm and < 7 cm, T1-3, M0 (n = 1016) After lumpectomy + AND or modified radical mastectomy	AC Doxorubicin + cyclophosphamide Vs. TC Docetaxel + cyclophosphamide	Disease free survival Overall survival	TC superior *7 years Disease free survival* HR 0.74; 95% CI 0.56 to 0.98 *7 years Overall survival (OS)* HR 0.69; 95% CI 0.50 to 0.97	Randomisation (method not described) No blinding ITT analysis (5 years follow-up: previous publication Jones 2006)	RCT	Moderate
Lee 2008	[259]	NA	209 women with axillary node positive, stage II/III breast cancer	Docetaxel/capecitabine (TX) Vs. anthracycline-containing regimen, doxorubicin/ cyclophosphamide (AC) followed by surgery and cross-over to the other treatment	Pathologic complete response (pCR) Disease free survival Overall survival Toxicity	*pCR* 21% TX vs. 10% AC, p = 0.024 *Disease free survival (DFS)* not significant *Overall survival (OS)* not significant TX was associated with less nausea and vomiting, but more stomatitis, diarrhea, myalgia, and skin/nail changes than AC.	Randomisation on block size No blinding ITT analysis Median follow-up of 37 months	RCT	Moderate
Martin 2008	[260]	NA	Women with lymph node – positive disease after BCS (n= 1246)	FEC Vs. FEC / paclitaxel (FEC-P)	Disease free survival Overall survival	*5-year disease-free survival (DFS)* HR = 0.77, 95% CI = 0.62 to 0.95; p = 0.022 in favour of FEC-P *Overall survival* HR = 0.78, 95% CI = 0.57 to 1.06; p = 0.110	Randomisation by computer program No blinding ITT analysis Median follow-up of 66 months	RCT	Moderate
Muss 2009	[261]	NA	Women ≥65 years; stage I, II, IIIA, or IIIB breast cancer (n = 600)	Standard chemotherapy (CMR or cyclophosphamide + doxorubicin)	Disease recurrence Death	*Disease recurrence or death* HR in the capecitabine group was 2.09 (95% confidence interval, 1.38 to 3.17; P<0.001) after a median FU of 2.4 years	Randomisation (method not described) No blinding	RCT	Low

				Vs. capecitabine			ITT analysis Median follow-up of 66 months Test of the non inferiority of capecitabine		
Taucher 2008	[262]	NA	High-risk endocrine non-responsive breast cancer patients (n= 203)	Pre- operative chemotherapy containing CMF Vs. postoperative chemotherapy CMF	Recurrence-free survival Overall survival	*9 years recurrence-free survival* HR 0.7, 0.51–0.95; P = 0.024 in favour of post op. *9 years overall survival* HR 0.8, 0.56–1.13; p = 0.213.	Randomisation (method not described) No blinding No ITT analysis Median follow-up of 9 years	RCT	Low
Tokuda 2008	[263]	NA	97 patients < 56 years with stage I to IIIB breast cancer involving 10 or more axillary lymph nodes	standard arm (STD): cyclophosphamide, oxorubicin, and 5-fluorouracil / tamoxifen Vs high-dose arm (HDC): cyclophosphamide, doxorubicin, and 5-fluorouracil / tamoxifen + cyclophosphamide and thiotepa	Recurrence-free survival Overall survival	*5-year Relapse-free survival* 37% (STD) and 52% HDC (P= □0.17) *5 year Overall survival* 62% (STD) and 63% (HDC) (P=□0.78).	Randomisation by minimisation No blinding ITT analysis Median follow-up of 63 months 31% of arm HDC did not undergo HDC	RCT	Low
Watanabe 2009	[264]	NA	Node negative high risk breast cancer (n= 773)	2 years UFT (uracil-tegafur) Vs. CMF	Recurrence-free survival Overall	*5-year Relapse-free survival* 88% (CMF) and 87.8% (UFT) HR 0.98, 0.66–1.45; P = 0.92	Randomisation by minimisation No blinding	RCT	Moderate

					survival	*5 year Overall survival* 96% (CMF) and 96.2% (UFT) HR 0.81, 0.44–1.48; P = 0.49	ITT analysis (?) Median follow-up of 6.2 years		
Zander 2008	[265]	NA	307 patients with primary breast cancer and ≥10 axillary lymph nodes after mastectomy or BCS + AND	After four cycles of epirubicin and cyclophosphamide - Standard-dose chemotherapy (SD-CT): CMF - Vs high-dose chemotherapy (HD-CT): cyclophosphamide, thiotepa and mitoxantrone followed by stemcell transplantation	Recurrence-free survival Overall survival	*Recurrence free survival (6.1 years)* HR = 0.80 ; 95%CI 0.59-1.08, p = 0.15. for HD-CT versus SD-CT *Overall survival (6.1 years)* HR = 0.84 ; 95%CI 0.59 - 1.20, p = 0.33. for HD-CT versus SD-CT	Randomisation (method not described) No blinding No ITT analysis Median follow-up of 6.1 years	RCT	Low

Note. C=cyclophosphamide, M=methotrexate, F=5-fluorouracil, A=doxorubicin [also called adriamycin], and E=epirubicin.

Endocrine therapy for early and locally advanced disease

Ovarian suppression/ablation

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[2]	July 2008	Pre-menopausal women with ER-positive early breast cancer	Do not offer adjuvant ovarian ablation/ suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy. Offer adjuvant ovarian ablation/ suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it.	*Ovarian ablation or suppression versus none*: One meta-analysis (EBCTCG 2005): ovarian ablation/suppression beneficial compared to none in terms of recurrence (respective rates 47% and 52%, p<0.0001) and breast cancer mortality (respective rates 40% and 44%, p<0.004), both assessed at 15 years follow-up. *Ovarian ablation and the role of chemotherapy*: One meta-analysis (EBCTCG 1998), randomised trials (Nomura et al. 1999; Thomson et al. 2002), and 1 RCT (Kaufmann et al. 2007): no benefit where adjuvant chemotherapy is given. *LHRHa versus no systemic therapy:* A meta-analysis (n=338; Cuzick et al. 2007): no difference in recurrence or survival, comparing LHRH agonists with no systemic therapy. A well conducted RCT (Love et al. 2008): 5 and 10 year disease free survival and overall survival rates improved following adjuvant oophorectomy and tamoxifen. *LHRHa versus chemotherapy*: No difference in terms of recurrence and survival (Cuzick et al. 2007).	This guideline includes a Cochrane Systematic Review (Sharma et al. 2008)	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					LHRHa plus tamoxifen versus LHRH alone or tamoxifen alone: Reduction in recurrence and mortality with combined treatment (Sharma et al. 2008). No difference in a meta-analysis (Cuzick et al. 2007). *LHRHa with or without tamoxifen in addition to chemotherapy*: Cochrane Review (Sharma et al. 2008) and meta-analysis of randomised trials (Cuzick et al. 2007): recurrence and mortality are reduced. *LHRHa with or without tamoxifen versus chemotherapy*: Cochrane Review (Sharma et al. 2008) and meta-analysis of randomised trials (Cuzick et al. 2007): same effectiveness in terms of recurrence and mortality *Side effects and quality of life*: ovarian ablation, ovarian suppression and chemotherapy each have adverse side effects and each can induce menopausal symptoms, including amenorrhoea (Brunt et al. 2004; Groenvold et al. 2006; Schmid et al. 2007; Love et al. 1999; Sharma et al. 2008 and Celio et al. 2002).		

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Hackshaw 2009	[171]	NA	Premenopausal women or aged under 50 years with operable stage I or II breast cancer, confined to one breast; to have no evidence of distant metastases and regardless of ER status	- Goserelin and tamoxifen (n=1800) - Goserelin or not (n = 910; some received elective tamoxifen) for 2 years.	Event free survival Overall survival Risk of recurrence Risk of dying from breast cancer	Goserelin was associated with a risk reduction in all four endpoints *EFS event* HR 0.82; 95%CI 0.73-0.92; p=.001 *Overall mortality* HR 0.83; 95%CI 0.71-0.96; p=.013 *Risk of recurrence* HR=0.81; 95%CI 0.71-0.92;p=.001 *Breast cancer mortality* HR 0.82; 95% CI 0.70-0.96; p=.03 **Goserelin without Tamoxifen** *EFS* 33% of risk reduction *Overall mortality* 29% of risk reduction *Recurrence* 34% risk reduction *Breast cancer mortality* 29% risk reduction **Goserelin with Tamoxifen** *EFS* 8% of risk reduction *Overall mortality* 10% of risk reduction	The ZIPP collaboration (Zoladex in pre-menopausal patients) includes four unblinded, randomised, multicentre trials Median follow-up: 12 years (26 545 persons-years)	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						Recurrence 9% risk reduction *Breast cancer mortality* 11% risk reduction **Tamoxifen vs Goserelin** Two years of goserelin treatment was as effective as 2 years of tamoxifen treatment 15 years after starting therapy. In women who did not take tamoxifen, there was a large benefit of goserelin treatment on survival and recurrence (8.5 fewer breast cancer deaths vs no goserelin) In women who did take tamoxifen, there was a marginal potential benefit on these outcomes when goserelin was added (possibly 2.6 fewer deaths).			

Aromatase inhibitors / Tamoxifen

For premenopausal women

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Rossi 2008	[266]	NA	Premenopausal women with early breast cancer	Tamoxifen (20mgdaily) + triptorelin (3.75mg IM every 4 weeks) for 5 years; n=51 Letrozole (2.5 mg/d) + triptorelin (3.75 mg IM every 4 weeks) for 5	Endocrine changes	Letrozole + triptorelin (± zoledronate) induced a stronger suppression of median E2 serum levels (P = .0008), LH levels (P = .0005), and cortisol serum levels (P < .0001) compared with tamoxifen + triptorelin. Median FSH serum levels were suppressed in both groups, but such	Triptorelin= gonadotropin releasing hormone (GnRH) agonists that produce postmenopausal-like plasma estrogen concentrations	RCT	High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
				years; or Letrozole + triptorelin (as above) + zoledronic acid (4 mg by 15-minute IV every 6 months) for 5 years; n=30		suppression was lower among patients receiving letrozole, who showed significantly higher median FSH serum levels (P < .0001). No significant differences were observed for testosterone, progesterone, ACTH, androstenedione, and dehydroepiandrosterone between the two groups of patients. → letrozole could be more effective than tamoxifen as adjuvant hormonal treatment for premenopausal patients with endocrine responsive breast cancer			

For postmenopausal women

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Postmenopausal women with early invasive breast cancer							
NICE 2009	[2]	July 2008	Postmenopausal women with ER-positive early invasive breast cancer	- Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk* should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated. - Offer an aromatase inhibitor, either exemestane or anastrozole instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low-risk* and who have been treated with tamoxifen for 2−3 years.	*Anastrazole* Boccardo et al. 2005; Buzdar et al. 2006; Buzdar and Cuzick 2006; Dowsett et al. 2005; Forbes et al. 2008; Hind et al. 2007; Howell et al. 2005; Jakesz et al. 2005; Kaufmann et al. 2007. Disease-free survival: - significantly increased with anastrazole compared to tamoxifen either as first line adjuvant treatment or after tamoxifen. - prior chemotherapy (CMF, anthracyclines or taxanes) reduces the	High quality RCTs	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				- Offer additional treatment with the aromatase inhibitor letrozole for 2−3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years. - The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women. - The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.	disease-free survival advantage of anastrozole. - in hormone receptor-positive patients: DFS favoured in the anastrozole group - in the hormone receptor-negative subgroup: no difference (Forbes et al., 2008). Overall survival: - no difference either as first adjuvant treatment or after tamoxifen. - ><: Kaufmann et al. (2007b) showed a significant improvement in survival for patients in the anastrozole group when the benefits of switching to anastrozole after 2 years of tamoxifen treatment were compared with continuing on tamoxifen for 5 years. Risk of disease recurrence: - significantly reduced in all ER-positive patients with anastrozole and independently of nodal status, tumour size or prior chemotherapy; - 5 years of adjuvant tamoxifen (with or without the aromatase inhibitor, amino-glutethimide, for the first 2 years of therapy) + 3 years of anastrozole, DFS statistically improved with significantly fewer recurrences compared to no further treatment - statistically fewer patients on anastrozole experienced distant disease recurrence (Forbes et al. 2008, Kaufmann et al. 2007).		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Risk of contralateral breast cancer: - significantly reduced only if anastrozole is given as first line adjuvant treatment; - not significantly different if given after tamoxifen. Time to progression: - significantly increased for ER-positive/PR-negative tumours. Adverse events: - significant increased risk of bone fracture with anastrazole compared to tamoxifen. - significant increased risk of endometrial cancer, deep venous and venous thromboembolic events and ischaemic cerebrovascular events with tamoxifen compared to anastrozole. *Letrozole* BIG 1-98 trial: letrozole vs tamoxifen in the initial adjuvant setting (Crivellari et al. 2008; Coates et al. 2007; Hind et al. 2007; Thurlimann et al. 2005; Rasmussen et al. 2008) – **Follow-up: 60 months** MA-17 trial: letrozole vs placebo in the extended adjuvant setting following standard adjuvant treatment with tamoxifen (Goss et al. 2005 and 2007; Hind et al. 2007; Ingle et al. 2006 and Muss et al. 2008)		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Disease-free survival: - significantly improved with letrozole compared to tamoxifen for lymph node-positive tumours - significant improvement with letrozole compared to placebo. Over time (6 months to 4 years) the difference in the risk of progression significantly increased in the letrozole group compared to the placebo group - improved in the placebo arm of the MA-17 trial who subsequently received letrozole Overall survival: - not statistically different between letrozole and tamoxifen - not statistically different between letrozole and placebo - patients in the placebo arm of the MA-17 trial who subsequently received letrozole: the overall survival adjusted hazard ratio was 0.30 for the letrozole arm. Risk of contralateral breast cancer: - did not report statistically significant results; letrozole vs tamoxifen: 0.4% vs 0.7% - no difference for time to recurrence ; letrozole vs placebo. Adverse events: - fewer thromboembolic events with letrozole compared with tamoxifen but higher risk of bone fracture and some cardiac events.		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					- Differences were not significant for thromboembolic or cardiac adverse events - higher incidence of osteoporosis but no difference in the fracture rate with letrozole compared to placebo - time to any disease recurrence was significantly decreased with letrozole compared to tamoxifen or placebo - no significant difference between letrozole and tamoxifen with respect to quality of life - disease-free survival for ER-positive/PR-positive tumours was significantly increased with letrozole compared with placebo. - disease-free survival significantly improved with letrozole compared to placebo in lymph node-positive and lymph node-negative women. *Exemestane* Coombes et al. 2004 and 2007; Eisen et al. 2008 and Hind et al. 2007. Disease-free survival: - significantly increased with exemestane compared with tamoxifen, and nodal status did not affect outcome. - significantly increased for women with ER-positive histology regardless of PR status. Overall survival: - not significantly different between		

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					exemestane or tamoxifen or between exemestane and placebo - modest improvement in overall survival for patients who switch to exemestane after 2–3 years on tamoxifen Adverse events: - significant increase in bone fractures with exemestane - risk of contralateral breast cancer was significantly decreased with exemestane - endocrine events decreased for all women with no difference between exemestane or tamoxifen.		
CCO 2008	[173]	May 2007	Postmenopausal women with early-stage, hormone receptor-positive breast cancer.	• Adjuvant tamoxifen (20 mg daily for five years) remains an acceptable option for the treatment of women with hormone receptor-positive, early-stage breast cancer. • Adjuvant anastrozole (1.0 mg daily for five years) or letrozole (2.5 mg daily for five years) is an acceptable alternative to five years of adjuvant tamoxifen therapy. • Adjuvant tamoxifen (20 mg for two to three years) followed by switching to either adjuvant exemestane (25 mg daily, to a total of five years of hormone therapy) or adjuvant anastrozole (1mg daily, to a total of five years) therapy is also an acceptable alternative to five years of tamoxifen.	Nine randomized controlled trials (ATAC Trialists Group 2002, 2005; BIG 1-98 Collaborative Group 2005; Coates 2007; Coombes 2004, 2007; Boccardo 2005; Jakesz 2005; Goss 2005; Mamounas 2006) and one meta-analysis (Jonat 2006) **ATAC study** (n=9 366): tamoxifen versus anastrozole versus tamoxifen + anastrozole – FU: 68 months (5.7 years) *disease-free survival* significantly improved in the anastrozole group versus the tamoxifen group (HR: 0.87; 95% CI, 0.78 to 0.97; p=0.03). The absolute difference in four-year disease-free survival estimates was 2.4% (86.9% with anastrozole versus [vs.] 84.5% with tamoxifen).	All major trials under review were multicentre trials	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				• Adjuvant letrozole (2.5 mg daily for five years) should be considered for women who have completed five years of adjuvant tamoxifen therapy.	Additional benefit was seen for time to recurrence (TTR) and time to distant recurrence (TDR) with anastrozole. Overall survival was not significantly different. **A meta-analysis of the ABCSG-8, ARNO-95, and ITA trials** : improvements for women who switched to anastrozole *disease-free survival* HR, 0.59; 95% CI, 0.48 to 0.74; p<0.0001 *distant recurrence-free survival* HR 0.61, 95% CI 0.45 to 0.83, p=0.002 *overall survival* HR, 0.71; 95% CI, 0.52 to 0.98; p=0.04 **Other RCTs:** see NICE 2009		
CCO 2008	[173]	May 2007	Postmenopausal women with early-stage, hormone receptor-positive breast cancer.	Women receiving aromatase inhibitors should be monitored for changes in bone mineral density.	ATAC and BIG 1-98 trials TEAM International trial (Tamoxifen and Exemestane Adjuvant Multicenter substudy) IES ABCSG-8/ARNO-95 MA.17 trial See NICE 2009 (adverse events)	RCTs	High
CCO 2008	[173]	May 2007	Postmenopausal women with early-stage, HR positive breast cancer.	Due to the lack of evidence, no recommendation for the use of aromatase inhibitors based on HER2/neu status can be made at this time.	No eligible trials on the efficacy of aromatase inhibitors according to HER2/neu status were identified.		Low

Note. * Low-risk patients are those in the EPG (excellent prognostic group) or GPG (good prognostic group) in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. High-risk patients are those in groups PPG (poor prognostic group) with 53% or VPG (very poor prognostic group) with 39%.

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Aromatase inhibitors in postmenopausal women with early breast cancer									
Big 1-98 2009	[178]	NA	Postmenopausal women with ER-positive or PgR positive early breast cancer	- 5 years of tamoxifen - 5 years of letrozole - 2 years of treatment with one agent followed by 3 years of trt with the other.	DFS OS	*Disease-free survival* HR for tamoxifen followed by letrozole: 1.05 (99% CI: 0.84 to 1.32) HR for letrozole followed by tamoxifen: 0.96 (99% CI: 0.76 to 1.21). *Overall survival* HR for letrozole: 0.87 (95% CI: 0.75 to 1.02; p = 0.08). *Safety* - thromboembolic events: higher incidence with tamoxifen regimens than with letrozole (4.1 to 4.9% vs. 2.4%, P<0.001). - stroke and transient cerebral ischemic: similar rates between groups (1.7 to 1.9% and 1.4%, respectively; P = 0.74). - cardiac events: similar rates (6.1 to 7.0% and 5.7%, respectively; P = 0.45). Vaginal bleeding, hot flashes and night sweats occurred more frequently with tamoxifen whereas arthralgia and myalgia were more frequent with letrozole. Sequential treatment with letrozole and tamoxifen did not improve	71 months follow-up	RCT (randomized, phase 3, double-blind trial)	High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						disease-free survival as compared with letrozole monotherapy. *Update for monotherapy* The 5-year overall survival was 91.8% in the letrozole group and 90.9% in the tamoxifen group (hazard ratio, 0.87; 95% CI: 0.75 to 1.02; P = 0.08)			
Eastell 2008		NA	Postmenopausal women with localized early breast cancer	- Anastrazole (1 mg/d): n=57 - Tamoxifen (20 mg/d): n=51	Lumbar spine and total hip bone mineral density (BMD)	108 women included in the primary analysis. Follow-up: 5 years *Anastrozole group* Decrease in median BMD in lumbar spine (- 6.08%) and total hip (- 7.24%) *Tamoxifen group* Increase in median BMD in lumbar spine (+ 2.77%) and total hip (+ 0.74%). No patients with normal BMD at baseline became osteoporotic at 5 years. → Anastrozole is associated with accelerated bone loss over the 5-year treatment period. However, patients with normal BMD would not appear to require specific monitoring	Comparison before and 5 years after treatment	Prospective substudy of the ATAC trial	High
Hadji 2009		NA	Postmenopausal women with ER- and/or PgR positive invasive	- Exemestane (25 mg/d): n=78 - Tamoxifen (20	Lumbar spine and total hip bone mineral density	*Exemestane group* Decrease in median BMD in lumbar spine (- 2.8%) and total hip (- 2.2%)	Blinding not reported Follow-up : 12	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
			primary breast cancer (stage I, IIa, IIb, IIIa, T1-3, N0-2, M0)	mg/d): n=83	(BMD)	*Tamoxifen group* Increase in median BMD in lumbar spine (+ 0.5%) and total hip (0.4+%) No differences in BMD for neck femur. →The rapid increase of bone loss with exemestane then stabilized after 6- and 12 month treatment.	months		

Trastuzumab

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Trastuzumab							
NICE 2009	[2]	July 2008	Women with HER2-positive early invasive breast cancer	*Neo adjuvant setting* No recommendation in regards to neoadjuvant trastuzumab use can be made at this time. *Adjuvant setting* Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2- positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable. *Dosage* Prefer one of the following schedules: - sequentially, after the completion of a minimum	Two papers from the HERA trial (Herceptin Adjuvant) (Smith et al., 2007 and Suter et al., 2007) One joint-analysis of the NSABP B-31 trial (National Surgical Adjuvant Breast and Bowel Project), B-31 trial and the NCCTG N9831 trial (North Central Cancer Treatment Group) (Romond et al. 2005) Two papers which considered cardiac dysfunction in the NSABP B-31 (Tan-Chiu et al. 2005) and NCCTG N9831 (Perez et al. 2008) A meta-analysis of cardiotoxicity with adjuvant trastuzumab (Bria 2008)	A large volume of economic evidence was identified on the cost effectiveness of trastuzumab in the adjuvant setting. Ten economic evaluations were reviewed in detail (Garrison et al., 2007; Kurian et al., 2007; Lidgren et al., 2007; Liberato et al., 2007; Millar and Millward 2007; Dedes et al., 2007;	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				of four cycles of chemotherapy; - concurrently with a taxane as part of an AC-paclitaxel (AC fi T + H), AC-docetaxel - (AC fi D + H) or docetaxel and carboplatin regimen (D + Pla + H; weekly trastuzumab schedule only); - concurrently with either: vinorelbine or docetaxel prior to FEC (V/D+H fi FEC), or with paclitaxel prior to AC (T + H fi (AC)/(AC + H)). Favoured a weekly dosage schedule when trastuzumab offered concurrently with a taxane. A loading dose of 4 mg/kg of adjuvant trastuzumab should be offered on week one for all concurrent regimens. *Target populations* Trastuzumab should be offered for one year to all women with HER2/neu-positive, node-positive, and to a lesser extent, high-risk node-negative breast cancer (tumour size >1 cm) N.B. The definition of 'high-risk' node negative differed somewhat across trials *Cardiac monitoring* Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following: – a left ventricular ejection fraction (LVEF) of 55% or less – a history of documented congestive heart failure – high-risk uncontrolled arrhythmias	From the FinHer trial (Joensuu et al. 2006) From the ECOG E2198 trial (Budzar et al. 2007) One small trial (Buzdar et al. 2007) *Trastuzumab group* - Improved overall survival, disease free survival and distant recurrence event-free survival - Higher incidence of cardiac end points (severe congestive heart failure (CHF), symptomatic CHF and confirmed left ventricular ejection fraction (LVEF) drop)	Neyt et al., 2006; Neyt et al., 2008; Norum et al., 2007 and Shiroiwa et al., 2008). One SR (Mardanas et al. 2008) published after NICE guideline included same RCTs	

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				– angina pectoris requiring medication – clinically significant valvular disease – evidence of transmural infarction on electrocardiograph (ECG) – poorly controlled hypertension. Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman. *Single-agent trastuzumab therapy* No recommendation follows for single-agent trastuzumab therapy as no trials under review addressed this choice of therapy.			
NICE 2009	[3]	July 2008	Women with advanced breast cancer	For patients who are receiving treatment with trastuzumab for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.	A prospective post RCT study (Tripathy et al. 2004), five retrospective case series (Fountzilas et al. 2003; Gelmon et al. 2004; Garcia-Saenz et al. 2005; Montemurro et al. 2006 and Stemmler et al. 2005) and a phase II study (Bartsch et al. 2006). No significant improvements in survival, safety or efficacy for women with disease progression who continued TRZ combined with different chemotherapies.		Moderate

CCO 2006	[267]	May 2006	Women with HER2/neu-overexpressing breast cancer	Trastuzumab should be offered for one year to all patients with HER2-positive node-positive or node-negative, tumour greater than 1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.	Herceptin Adjuvant (HERA) trial (Piccart-Gebhart et al. 2005): the addition of one-year trastuzumab following (neo)adjuvant chemotherapy vs observation after chemotherapy Significant improvement in terms of disease-free survival (DFS) (HR 0.54, 95% CI 0.43 to 0.67), recurrence-free survival (HR 0.50, 95% CI 0.40 to 0.63), and distant-disease-free survival (HR 0.40, 95% CI 0.40 to 0.66). National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial and the North Central Cancer Treatment Group (NCCTG) N9831 trial (Romond et al. 2005): the addition of one-year trastuzumab concurrent with adjuvant paclitaxel following adjuvant doxorubicin and cyclophosphamide vs. no trastuzumab Significant improvement to in terms of DFS (HR 0.48, p-value 3x10-12), time-to-first-distant-recurrence (TTR) (HR 0.47, p-value 8x10-10), and overall survival (OS) (HR 0.67, p-value 0.015).		High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Dahabreh 2008	[182]	June 2007	(HER)-2 positive and resectable breast cancer women (early stage)	Adjuvant chemotherapy with trastuzumab vs. adjuvant chemotherapy without trastuzumab	Disease-free survival (DFS) Mortality (death from any cause) Locoregional recurrence Distant recurrence Central nervous system (CNS) recurrence Class III/IV congestive heart failure (CHF) Significant decline in left ventricular ejection fraction (LVEF)	Five eligible trials were identified, reporting outcomes on 13 493 women: NSABP B-31 trial, NCCTG 9831, HERA, FinHer and BCIRG 006 trial. *Disease-free survival* Longer for trastuzumab treated patients (risk ratio [RR], 0.62; 95% CI, 0.56–0.68). *Mortality* Lower for trastuzumab treated patients (RR, 0.66;95%CI, 0.57–0.77), *Locoregional recurrence* Lower for trastuzumab treated patients (RR, 0.58; 95% CI, 0.43–0.77) *Distant recurrence* Lower for trastuzumab treated patients (RR, 0.60; 95% CI, 0.52–0.68). *Congestive heart failure* Higher risk for patients receiving trastuzumab (RR, 7.60; 95% CI, 4.07–14.18) *Left ventricular ejection fraction decline* Higher risk for patients receiving trastuzumab (RR, 2.09; 95%CI, 1.84–2.37).	Literature search in MEDLINE, the Cochrane central register of controlled trials, the online proceedings of the ASCO, and the online proceedings of the San Antonio Breast Cancer Symposium Meta-analyse used Mantel-Haenszel method with fixed-effects models to estimate pooled point estimates with their CIs. Random-effects models were used in a sensitivity analysis. All analyses were performed according to the intention-to-treat principle No evidence of significant between-study heterogeneity or inconsistency for	SR and MA of RCTs	High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						Central nervous system metastasis as the first recurrence event Higher risk for patients receiving trastuzumab (RR, 1.60; 95% CI, 1.06–2.40) A new trial was finally included in the analysis (PACS 04 trial) without modyfing the results. DFS 0.63 (0.59–0.69) p<.0001 Mortality 0.66 (0.57–0.77) p<.0001 Locoregional recurrence 0.60 (0.46–0.78) p=.0002 Distant metastasis 0.62 (0.55–0.70) p<.0001 CHF 7.32 (4.02–13.32) p<.0001 LVEF decline 2.09 (1.84–2.36) p<.0001	the primary outcome, DFS (I^2 = 35.8%; Q = 4.67; p = .198)		
Untch 2008	[268]	NA	HER2-positive breast cancer women	standard chemotherapy + trastuzumab (n=1703 women) vs. standard chemotherapy + observation (n= 1698 women)	Magnitude of trastuzumab treatment effect on disease free survival (DFS) in different subgroups identified by their nodal status and their hormone receptor status	The overall hazard ratio (HR) for trastuzumab versus observation was 0.64 [95% CI 0.54–0.76; P < 0.0001]. *Three-year DFS (n; HR; 95%CI)* **Nodal status** Negative (1099; 0.59; 0.39-0.91) 1-3 positive nodes (976; 0.61; 0.43-0.87) ≥ 4 positive nodes (953; 0.64; 0.49-0.83) **Hormone receptor status** ER- / PgR- (1627; 0.63; 0.50-0.78) ER- / PgR+ (172; 0.77; 0.34-1.74) ER+ / PgR- (460; 0.82; 0.50-1.34) ER+ / PgR+ (984; 0.63; 0.43-0.93)	Analysis of subgroups from the HERA trial. Subgroup analyses must be interpreted with caution due to the increased likelihood of false-positive and false-negative results Median follow-up was 23.5 months.	Sub-analyses of a RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						Estimated improvement in 3-year DFS in subgroups ranged from +11.3% to +0.6%. Patients with the best prognosis (those with node-negative disease and tumors 1.1–2.0 cm) had benefit similar to the overall cohort (HR 0.53, 95% CI 0.26–1.07; 3-year DFS improvement +4.6%, 95% CI 24.0% to 13.2%).			

Assessment and Treatment for Bone Loss

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Ovarian suppression/ablation							
NICE 2009	[3]	July 2008		- Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they: o are starting adjuvant aromatase inhibitor treatment o have treatment-induced menopause o are starting ovarian ablation/suppression therapy. - Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pretreatment menopausal status. For prescription of biphosphonates, please refer to NICE guideline 'Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group' (2008)	A consensus position statement from a UK Expert Group. Cancer Treatment Reviews (2008).		Guideline of high quality (assessed with AGREE)

TREATMENT OF METASTATIC BREAST CANCER

Endocrine therapy

Aromatase inhibitors

Pre-menopausal women

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[3]	July 2008	Premenopausal women with ER-positive advanced breast cancer	Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.	A moderate quality systematic review (Klijn et al. 2001) and one RCT (Klijn et al. 2000) reported a survival benefit for combination therapy over single agents in pre-menopausal patients with metastatic breast cancer. GDG consensus for peri-menopausal women.		Moderate
NICE 2009	[3]	July 2008	Men with ER-positive advanced breast cancer.	Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer.	Two small retrospective case series (Ribeiro 1983 and Patterson et al. 1980) and GDG consensus		Low
CECOG 2007	[188]	May 2005	Premenopausal women	Tamoxifen, ovarian function suppression, or a combination of both are suitable options for endocrine treatment of premenopausal patients.	Three small randomized studies have compared the combination of tamoxifen and LHRH agonist versus LHRH agonist alone (Boccardo et al. 1994; Jonat et al. 1995; Klijn et al. 2000). A small meta-analysis combined these data and suggested that combination of LH-RH agonist and tamoxifen may be superior to LH-RH agonist alone in all analyzed efficacy parameters (OS, PFS, RR) (Klijn et al. 2001). At present, there are insufficient data on the use of aromatase inhibitors or fulvestrant in premenopausal patients. If aromatase inhibitors are considered, they definitely should be given in conjunction with some form of ovarian function suppression.		Moderate

Post-menopausal women

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009	[3]		Post-menopausal women with MBC	Offer an aromatase inhibitor (either non-steroidal or steroidal) to: o postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy o postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.	The evidence base for this topic comprises one guideline (Eisen et al. 2004), five systematic reviews (Mauri et al. 2006; Gibson et al. 2007; Ferretti et al. 2006; Klijn et al. 2001 and Crump et al. 1997), five RCTs (Chia et al. 2008; Mouridsen et al. 2007; Taylor et al. 1998; Klijn et al. 2000 and Goss et al. 2007) a pooled analysis of RCT data (Howell et al. 2005) and a small, low quality comparative study (Catania et al. 2007a).		High
CECOG 2007	[188]	May 2005	postmenopausal patients with hormone receptor-positive MBC	Based upon the more favorable toxicity profile, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) is recommended as first-line treatment for postmenopausal patients with hormone receptor-positive MBC, but tamoxifen remains a valuable option.	**First-line endocrine therapy** *anastrozole versus tamoxifen* Two randomized phase III trials compared anastrozole with tamoxifen (Bonneterre et al. 2000, 2001; Nabholtz 2000, 2003). →TTP : no difference between anastrozole and tamoxifen *letrozole versus tamoxifen* A randomized phase III trial compared letrozole to tamoxifen (Mouridsen et al. 2001, 2003). →TTP and ORR : better results with letrozole →OS : no difference between letrozole and tamoxifen *exemestane versus tamoxifen* A randomized phase III trial compared exemestane and tamoxifen (Paridaens et al. 2003) →TTP and ORR: better results with exemestane *Fulvestrant versus tamoxifen* A randomized phase III study compared fulvestrant and tamoxifen (Howell et al. 2004)		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					→ ORR and TTP : no difference between fulvestrant and tamoxifen → OS: better results with tamoxifen		
CECOG 2007	188	May 2005	postmenopausal patients with hormone receptor-positive MBC	Following tamoxifen failure, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) or fulvestrant are recommended for second-line treatment for post-menopausal patients with hormone receptor-positive MBC based upon the more favorable side-effect profile.	**Second line endocrine therapy** Following failure of tamoxifen, the following studies have been performed: *third generation aromatase inhibitors versus progestins or aminoglutethimide* Randomized phase III studies showed the superiority of 3rd generation aromatase inhibitors versus progestins or aminoglutethimide (Buzdar et al. 1996, 1998, 2001; Goss et al. 1999; Dombernowsky et al. 1998) *anastrozole versus letrozole* A phase III study found no difference in TTP and OS in the intent to treat analysis and ORR favored letrozol (Rose et al. 2003) *anastrozole versus fulvestrant* Two randomized phase III studies showed no significant difference in terms of ORR and TTP (Osborne et al. 2002; Howell et al. 2002, 2005).		High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Campos 2009	269	NA	Postmenopausal women with invasive breast cancer with visceral metastases (liver / lung)	- Anastrozole (1mg/d); n=64 - Exemestane (25 mg/d); n=64 ≥ 8 weeks	Response rate in visceral disease (CR / PR) Clinical benefit TTP	*Overall tumour response rate* Anastrozole: 15.6% (95% CI: 7.8 – 26.9%) Exemestane: 10.9% (95% CI: 4.5 – 21.3%) *Overall clinical benefit* Anastrozole & Exemestane: 32.8% (95% CI: 21.6 – 45.7%)	Blinding?	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
					Duration of clinical benefit Overall survival	*Median duration of overall response* Anastrozole: 85.1 weeks (22.9 – 166.7) Exemestane: 109.9 weeks (21.6 – 131.3) *Median TTP* Anastrozole: 4.24 months Exemestane: 3.71 months *Median survival* Anastrozole: 33.3 months Exemestane: 30.5 months → efficacy and tolerability of AI in this group of patients			
Paridaens 2008	[270]	NA	Postmenopausal women with ER- and/or PgR positive metastatic or locally advanced breast cancer	- Exemestane (25 mg/d): n=164 - Tamoxifen (20 mg/d): n=176	Overall response rate Progression free survival	*Progression free survival* HR: 0.84 (95% CI: 0.67 – 1.05) in favour of exemestane *Percentage of patients without disease progression* Exemestane: 66% (95% CI: 59.3% - 73.1%) at 6 months; 41.7% (95% CI: 34.5% - 48.9%) at 12 months *Tamoxifen:* 49.5% (95% CI: 42.2% - 56.6%) at 6 months; 31.2% (95% CI: 24.4% - 37.9%) at 12 months	Median follow-up: 29 months Update analysis at 49 months No evidence of blinding	RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						Overall survival No differences between arms (log-rank p=.821) At 49 months, HR 1.13 (95% CI: 0.85 - 1.50) →Exemestane is an effective treatment for women with metastatic breast cancer and offers significant early improvement in TTP but without impact on OS			
Dirix 2008	[271]	NA	Postmenopausal patients with hormone-sensitive breast cancer and measurable disease who had progressive disease after treatment with tamoxifen	- exemestane 25 mg/d; n=55 - exemestane 25 mg/d + celecoxib 400 mg twice daily; n=56	Clinical benefit rate Tolerability Objective response rate TTP Duration of clinical benefit	*Clinical benefit rate* Exemestane: 48.98% Exemetane + celecoxib: 47.06% *Median TTP* Exemestane: 20.0 weeks Exemetane+celecoxib: 23.4 weeks *Median survival time* Exemestane: 74.1 weeks Exemetane+celecoxib: 73.9 weeks *Duration of clinical benefit* Exemestane: 49.1 weeks Exemetane+celecoxib: 96.6 weeks Both treatments were generally well tolerated.	Blinding?	Phase II RCT	Moderate
Johnston 2008	[272]	NA	Postmenopausal women with ER-positive advanced breast cancer that had progressed after tamoxifen	- letrozole (2.5 mg/d) + tipifarnib 300 mg (TL); n=80 - letrozole (2.5 mg/d) + placebo (L); n=40	Response rate (CR / PR) TTP Tolerability	*Letrozole + tipifarnib* Response rate: 30% (95% CI; 20–41%) *Letrozole + placebo* Response rate: 38% (95% CI; 23–55%) There was no significant difference in response duration, time to disease	Tipifarnib = Farnesyltransferase inhibitors (FTIs) Tipifarnib has been shown to inhibit the growth of human breast cancer cell	phase II RCT	Moderate

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
					Clinical benefit rate (proportion of patients who achieved response or stable disease for at least 24 weeks) Overall survival	progression or survival. Clinical benefit rates were 49% (TL) and 62% (L). → Adding tipifarnib to letrozole did not improve objective response rate in this population of patients with advanced breast cancer	lines in vitro		

ER antagonists

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
ER antagonists							
CCO 2008	[193]	June 2008	Post-menopausal women with locally advanced or metastatic breast cancer	Fulvestrant is NOT recommended as an alternative to tamoxifen for first-line therapy of locally advanced or metastatic breast cancer in post-menopausal women who have had no prior endocrine or cytotoxic therapy for advanced disease and no recent adjuvant endocrine therapy (within previous twelve months).	One superiority, Phase III, multicentre RCT (Howell et al. 2004) : fulvestrant 250 mg IM q (every) monthly vs. tamoxifen 20 mg daily for first-line metastatic therapy of locally advanced or metastatic breast cancer in postmenopausal women (n=587). - no significant differences with respect to TTP, tumour response to treatment, or quality of life (QOL). - no significant difference for TTP in ER+ and/or PgR + group. - overall survival in favour of tamoxifen (38.7 vs. 36.5 months, HR 1.29, 95% CI 1.01-1.64, p=0.04). - time-to-treatment-failure (TTF) in favour of tamoxifen (7.8 vs. 5.9 months, HR 1.24, 95% CI 1.03-1.50, p=0.026) - tolerability: hot flashes (24.7% vs. 17.7%, p=0.0501, tamoxifen vs.	A systematic review conducted by Flemming et al. (2009) reported the same results coming from the same trials	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					fulvestrant).		
CCO 2008	[193]	June 2008	Post-menopausal women with locally advanced or metastatic breast cancer	Fulvestrant may be considered as alternative therapy to anastrozole for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant tamoxifen therapy or progressed on prior tamoxifen therapy for advanced disease. Factors that may influence the choice of fulvestrant versus anastrozole therapy include a slightly decreased, although still significant, incidence of joint disorders and the potential for improved compliance with fulvestrant.	Two superiority, Phase III, multicentre RCTs (European Open-Label Trial 0020 and U.S. Double-Blind Trial 0021): fulvestrant 250 mg IM q monthly vs. anastrozole 1 mg daily in patients who had received prior adjuvant tamoxifen therapy, or tamoxifen for advanced disease. Combined analyses (n=851) found: - No significant difference for TTP, TTF, ORR, clinical benefit rate (CBR; the sum of complete response + partial response + stable disease) and OS (Howell et al. 2005). - Superiority of Fulvestrant was not supported (Howell et al. 2005). - No significant differences between therapy arms with respect to ORR or CB across subpopulations of patients with or without visceral metastases (Mauriac et al. 2003). - Non-inferiority of fulvestrant to anastrozole (5.5 vs. 4.1 months, HR 0.95, 95% CI 0.82-1.10). The secondary endpoint of ORR also confirmed non-inferiority (Howell et al. 2005). - Duration of response (DOR) was significantly longer for fulvestrant vs. anastrozole when analyzed for all randomized patients (ratio of average response durations = 1.30, p<0.01), or just for responders (16.7 vs. 13.7 months; p-value not reported) (Dodwell et al. 2006). - Tolerability : higher incidence of joint	The U.S. Double-Blind Trial 0021 used a double-dummy, double-blinding approach whereby patients were given both placebo and actual therapy simultaneously, whereas the European Open-Label Trial 0020 did not blind patients or investigators to therapy + Methodological weaknesses were reported 18.4% of patients in the combined population were ER/PgR unknown or ER/PgR-negative, but analyses were not stratified by hormone-receptor status	Moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					disorders for those taking anastrozole (8.3% vs. 12.8%, p=0.0234, fulvestrant vs. anastrozole, respectively)		
CCO 2008	[193]	June 2008	Post-menopausal women with locally advanced or metastatic breast cancer	Fulvestrant may be considered as alternative therapy to exemestane for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (during or within six months of discontinuation) or progressed on prior NSAI therapy for advanced disease. Factors that influence the choice of fulvestrant versus exemestane therapy include the potential for improved compliance in favour of fulvestrant.	Evaluation of Faslodex vs. Exemestane Clinical Trial (EFECT) is one superiority Phase III, multicentre, double-blind, double-dummy RCT (Chia et al. 2008) comparing a fulvestrant loading-dose regimen (500 mg IM day 0, 250 mg IM on days 14 and 28, and 250 mg IM injection q monthly thereafter) with exemestane 25 mg orally [po] daily in women with HR+ breast cancer that has recurred or progressed on prior NSAI therapy. At the time of a planned final analysis (median follow-up 13 months; n=693): - The median TTP in both groups was 3.7 months (HR 0.93, 95% CI 0.819-1.133, p=0.65). Adjusting for covariates made little difference (HR 0.968, 95% CI 0.822-1.141). - The ORR (7.4% vs. 6.7%, OR 1.12, 95% CI 0.578-2.186, p=0.736) and CBR (32.2% vs. 31.5%, OR 1.03, 95% CI 0.72-1.487, p=0.853) did not differ significantly between fulvestrant and exemestane treatment groups respectively. - According to an abstract at the 2007 San Antonio Breast Cancer Symposium (SABCS), median OS was not significantly different between treatment arms (24.3 vs. 23.1 months, HR 1.012, 95% CI 0.833-1.229, p=0.9072 in favour of fulvestrant) at a median follow-up of 20.9 months	Only 10% of women enrolled received their previous AI as adjuvant therapy, thus limiting the generalizability of results for this population	Moderate-High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					(Chia et al. 2007). - Good tolerability in both arms with no significant differences in the incidence of adverse events.		
CCO 2008	[193]	June 2008	Post-menopausal women with locally advanced or metastatic breast cancer	The recommended dose of fulvestrant for the treatment of locally advanced or metastatic breast cancer is 250 mg IM every month OR a loading dose schedule of 500 mg IM day 0,250 mg IM on days 14 and 28, and 250 mg IM injection q monthly thereafter. Factors that may influence the choice of a loading dose include a shortened time to reach steady state (within one month vs. three to six months for standard dosage) although this may require further verification.	Two Phase III trials comparing fulvestrant vs. anastrozole (Trial 0020 and Trial 0021): fulvestrant was administered at 250 mg IM q monthly (28 +/- 3 days) as either two separate 2.5 ml injections (Trial 0020) or as a single 5 ml injection (Trial 0021). The latter approach was also used in the study by Howell et al. (2004). A randomized pharmacokinetic study (Robertson 2003) and a pharmaco-kinetic analysis of Trial 0020 and Trial 0021 (Robertson et al; 2004), both comparing a single 5 ml injection with two separate 2.5 ml injections for the delivery of a 250 mg fulvestrant dose, found no difference in pharmacokinetics or tolerability. In a Phase III trial comparing fulvestrant to exemestane (EFECT Trial; Chia et al. 2008), a loading dose schedule of fulvestrant was used (500 mg on day 0, 250 mg on day 14, 250 mg on day 28, and every 28 days thereafter). There are several currently active Phase III trials that are using this fulvestrant loading dose schedule (Southwest Oncology Group [SWOG]-S0226, Fulvestrant and Anastrozole Clinical Trial [FACT], Study of Faslodex, Exemestane and Arimidex [SOFEA];	Pharmacokinetic studies – no comparison with other dosages	Moderate

Chemotherapy

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Combination versus sequential chemotherapy							
NICE 2009	[3]	July 2008		On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.	One large RCT (Sledge et al. 2003): combining anthracycline and taxane, rather than giving the drugs sequentially in either order, resulted in a better tumour response and superior time to progression but did not improve median overall survival. Consistently, adverse events due to combined therapy were reported as being more numerous or of greater severity.		High
CECOG 2007	[188]	May 2005		The choice between polychemotherapy and sequential single agent chemotherapy should take into account the prognosis, performance status, symptom control and toxicity profiles with the ultimate goal of optimizing quality and quantity of life.	One Phase III RCT of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer (Sledge et al. 2003). →no gain in survival or quality of life with the combination despite increased response rates		High
Combined versus single chemotherapy regimes							
NICE 2009	[3]	July 2008		Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.	Evidence for comparing single chemotherapy with combined chemotherapy comprised one very high quality systematic review (n > 7,000 study participants) (Carrick et al. 2005) a systematic review (Takeda et al. 2007) three RCTs (Eijertsen et al. 2004; Pacilio et al. 2006 and Martin et al. 2007) and two post-study papers published from the pivotal trial by		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					O'Shaughnessy et al. 2002 (Leonard et al. 2006 and Miles et al. 2004).		
Optimal first-line chemotherapy							
CECOG 2007	188	May 2005		No definitive recommendation for optimal first-line chemotherapy for patients with MBC can be given. - Anthracycline- and/or taxane based regimens are to be preferred as first-line treatment in symptomatic patients and/or those with rapidly progressive disease. - In patients who have received anthracyclines and/or taxanes in the adjuvant or neoadjuvant setting this strategy may have to be modified in the future. - Reintroduction of anthracyclines and taxanes in patients relapsing more than a year after completion of adjuvant therapy or, alternatively, other regimens in patients with shorter disease-free periods may be considered.	Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer (Keller et al. 2004) Phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer (O'Brien et al., 2004) Pegylated liposomal doxorubicin (doxil) (Safra et al., 2000) Two randomized studies have demonstrated improved OS (Jassem et al. 2001; Bonneterre et al. 2004). These benefits were achieved at the cost of higher treatment-related toxicity.		High
Gemcitabine							
NICE 2009	3	July 2008		Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.	This recommendation is from 'Gemcitabine for the treatment of metastatic breast cancer', NICE technology appraisal guidance 116 (2007).		
CCO 2007	273	August 2005	Women with metastatic	The combination of gemcitabine and docetaxel may be considered as an alternative to capecitabine and docetaxel for first- or second-line	One randomized phase III study (Chan 2005)	Abstract form only	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
			breast cancer	chemotherapy in patients where the toxicity of the capecitabine and docetaxel regimen is a concern.	Combination of gemcitabine (1000 mg/m2 on days one and eight) and docetaxel (75 mg/m2 on day one) every 21 days vs. combination of capecitabine (1250 mg/m2 twice a day for 14 days) and docetaxel (as above) every 21 days No difference in terms of objective response rate (ORR), progression-free survival (PFS), duration of response, or time-to-progression (TTP). However, patients receiving gemcitabine plus docetaxel experienced significantly less hand-foot syndrome, diarrhea, and mucositis than those receiving capecitabine plus docetaxel.		
	[273]			For patients with metastatic breast cancer who have received prior (neo)adjuvant anthracycline therapy, the combination of gemcitabine plus paclitaxel is superior compared to paclitaxel alone as first-line chemotherapy.	One RCT (Albain et al. 2004, Moinpour et al. 2004, O'Shaughnessy et al. 2003) Combination of gemcitabine (1250 mg/m2 of on days one and eight) and paclitaxel (175 mg/m2 on day one) every 21 days to the same dosage and schedule of paclitaxel without gemcitabine in patients with metastatic breast cancer who had previously received adjuvant or neoadjuvant anthracycline chemotherapy. That trial found a significantly superior ORR (40.8% versus		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					22.1%, p<0.0001), median TTP (5.2 months versus 2.9 months, HR=0.650, 95% CI 0.524 to 0.805), and overall survival (18.5 months versus 15.8 months, HR 0.775, 95% CI 0.627 to 0.959) in patients treated with the combination regimen.		
	273			Single-agent gemcitabine is NOT recommended for women with metastatic breast cancer who are being considered for first-line single-agent anthracycline chemotherapy.	One randomized phase III study (Feher et al. 2005) Epirubicin (35 mg/m2 on days one, eight, and 15) vs. gemcitabine (1200 mg/m2 on days one, eight, and 15) every 28 days in postmenopausal patients aged 60 or older. No significant differences in terms of time to response and duration of response. Epirubicin was significantly better than gemcitabine in terms of ORR (40.3% versus 16.4%, p<0.0001), TTP (6.1 months versus 3.4 months, p=0.0001), and overall survival (19.1 months versus 11.8 months, p=0.004).		High
	273			The combination of gemcitabine, epirubicin, and paclitaxel (GET) is NOT recommended as first-line chemotherapy for women with metastatic breast cancer who are being considered for anthracycline-based combination chemotherapy	One randomized controlled trial (Zielinski et al. 2005) Combination of gemcitabine (1000 mg/m2 on days one and four), epirubicin (90 mg/m2 on day one), and paclitaxel (175 mg/m2 on day one) vs. combination of 5-	Patients were required to have had one prior non-anthracycline adjuvant chemotherapy.	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					fluorouracil (500 mg/m2), epirubicin (90 mg/m2), and cyclophosphamide (500 mg/m2), all on day one. Both combinations used a 21-day cycle. No significant differences in terms of ORR, TTP, or OS Significantly higher haematological toxicities, polyneuropathy, and mucositis in the gemcitabine-containing arm.		
Post-anthracycline-exposure (anthracycline resistance or failure)							
NICE 2009	[3]	July 2008		For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contra-indicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence: – first line: single-agent docetaxel – second line: single-agent vinorelbine or capecitabine – third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).	A health economic analysis that compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens, for patients who are anthracycline resistant or for whom anthracycline therapy is contraindicated Vinorelbine: 2C evidence Capecitabine: 2C evidence Taxanes: 1A evidence The most cost-effective treatment sequence based on a threshold of £30,000 per QALY was docetaxel-capecitabine- vinorelbine. The ICER for this sequence was estimated to be £23,332 per QALY. When applying a threshold of £20,000 per QALY, the most cost-effective sequence was docetaxel-	The costs considered in the analysis were those relevant to the NHS, and included; drug acquisition costs, administration costs, cost of assessment and follow-up, cost of treating adverse events, cost of supportive and palliative care.	

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					capecitabine.		
CECOG 2007	[188]	May 2005		In patients with anthracycline-resistance or failure, considered for further chemotherapy, taxane-based treatment (monotherapy or combination of a taxane with gemcitabine or capecitabine) should be used, taking into account quality of life, toxicity, characteristics of the disease and the ease of administration.	*Paclitaxel* Nabholtz et al. 1996; Winer et al. 2004; Perez et al. 2001 Seidman et al. 1998 *Docetaxel* Mouridsen et al. 2002; Jones et al. 2005; Kuroi et al. 2003 *Nanoparticle albumin paclitaxel* (ABI-007, Abraxane). Gradishar et al. 2005 *Docetaxel plus capecitabine* O'Shaughnessy et al. 2002 *Paclitaxel plus gemcitabine* Albain et al. 2004 *Docetaxel plus gemcitabine vs docetaxel plus capecitabine* Chan et al. 2005	Phase III RCTs	High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Carrick 2009	[196]	First search in 2003 Update in November 2008	Women with metastatic breast cancer	Single chemotherapy agents that include cyclophosphamide, fluorouracil, epirubicin, lomustine and ifosamide vs. polychemo-therapy	Overall survival Time-to-progression Response rate Toxicity	*Overall survival* HR 0.88; 95%CI 0.83-0.93, p<0.00001 in favour of multiple agents (vs. single agent) HR 0.82; 95%CI 0.75-0.89, p<0.00001 in favour of multiple agents (vs. single agent taxane) HR 0.94; 95%CI 0.86-1.02, p=0.15 (multiple agents vs. single agent anthracycline)	Search in Cochrane Breast Cancer Group Specialised Register + conference proceedings Compared to the first review (2004), 6 new trials were added (Albain 2004, GEICAM 2007, Norris 2000; O'Shaughnessy 2001; Stockler 2006, Thomas	SR including 43 RCTs (9 742 women)	High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						No significant heterogeneity between trials (X^2 = 48.56, 35 df, p=0.06). *Time to progression* HR 0.78, 95%CI 0.74 - 0.82, p<0.00001 in favour of multiple agents (vs. single agent) but Heterogeneity was statistically significant (X^2= 71.88, 26 df, p<0.00001; I^2=64%). *Overall response* RR 1.29, 95%CI 1.14 -1.45, p<0.0001 in favour of multiple agents (vs. single agent) but Heterogeneity was statistically significant (X^2=177.93, 45 df, p<0.00001, I^2 =75%). *Toxicity* Higher toxicity level for : - white cell count: RR of 1.49; 95% CI 1.24 to 1.79, p<0.0001. There was evidence of heterogeneity (X^2 = 607.34, 34 df, p< 0.00001, I^2 = 94%) There was no statistically significant difference between the groups for alopecia (RR 1.12, 95%CI 0.81 to 1.54, p=0.48) or for nausea and vomiting (RR 1.29, 95% CI 0.96 to 1.74, p=0.09). There was evidence of heterogeneity (X^2= 394.44, 20 df, p<0.00001, I^2 = 95%) and (X^2 =	2008) as 2 trials previously classified as 'ongoing' (Ejlertsen 2004; Heidemann 2004). Two RCTs included in the first review (Keller 2004; Liu 1986) were excluded on the basis of further assessment during the update		

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
						172.40, 29 df, p< 0.00001, I^2 = 83%) respectively. The findings of this review are not necessarily applicable to some of the more modern single agents including, docetaxel, paclitaxel and capecitabine for example.			
Chan 2009	[205]		Patients with locally advanced breast cancer or MBC	Docetaxel plus gemcitabine (DG) with docetaxel plus capecitabine (DC)	Progression-free survival Tumour response rate Overall survival Toxicity	*Progression-free survival* median PFS was 8.05 months [95% CI, 6.60 to 8.71] for GD and 7.98 [95% CI, 6.93 to 8.77] for CD *Tumour response rate* 32% in both arms *Overall survival* No difference : p=0.983 *Time-to-failure* Longer in the DG arm (p=0.053) *Non-hematologic toxicity* Significantly lower in the DG arm *Hematologic toxicity* Rates for grades 3 to 4 leukopenia were higher in DG group (78% vs. 66%; p=0.025) as transfusions (DG, 17%; CD, 7%; p=0.0051).	Blinding of randomization and assessment were not reported	Phase III RCT	Moderate

Trastuzumab

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CECOG 2007	[188]	May 2005		The use of first-line trastuzumab as either monotherapy or in combination with non-anthracycline-based chemotherapy was strongly recommended in patients with HER-2/neu protein overexpressing (3+ by IHC) or Her-2/neu FISH positive MBC regardless of age, prior adjuvant chemotherapy, or sites of metastatic disease. For patients with newly diagnosed MBC that is both hormone receptor positive and HER-2/neu positive, hormonal options should be explored first.	Randomized phase III trial (Slamon et al. 2001): trastuzumab plus chemotherapy vs. chemotherapy alone → significantly higher ORR and prolonged OS A phase II trial (Marty et al. 2005): docetaxel with or without trastuzumab has shown benefit in OS. A series of phase II trials (Burstein et al. 2003; Jahanzeb et al. 2002; O'Shaughnessy et al. 2004; Sledge 2003; Pegram and Slamon 1999; Burris et al. 2004; Leyland-Jones et al. 2003): Trastuzumab + other cytotoxic drugs including vinorelbine, platinum compounds, capecitabine and gemcitabine		High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Von Minckwitz 2009	[208]	NA	Patients with HER-2–positive breast cancer that progresses during treatment with trastuzumab	Capecitabine alone (C group; n=78) OR Capecitabine with continuation of trastuzumab in 3-week cycles (C/T group; n=78)	Time-to-progression Overall survival Overall response rates	*Time to progression* C group: median 5.6 months C/T group: median 8.2 months HR 0.69 (95% CI, 0.48 to 0.97; two-sided log-rank p= .0338). *Overall survival rates* C group: 20.4 months (95% CI, 17.8 to 24.7) C/T group: 25.5 months (95% CI,	German Breast Group 26/Breast International Group 03-05 trial Random assignment was stratified by pretreatment No investigator	RCT	High

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
					Toxicity	19.0 to 30.7) (p= .257). *Overall response rates* C group: 27.0% C/T group: 48.1% odds ratio, 2.50; p= .0115). *Toxicity* Continuation of trastuzumab beyond progression was not associated with increased toxicity.	blinding Kaplan-Meier product-limit method Sensitivity analyses Follow-up: 15.6 months		

Treatment of metastases

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Bone metastases							
NICE 2009	[3]	July 2008	Women with advanced breast cancer	- Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain. - The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication. - Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain. - An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery	Three systematic reviews (Pavlakis et al. 2005; Martinez-Zapata et al. 2006 and Sze et al. 2002), a guideline (Warr et al. 2002), five RCTs (Tripathy et al. 2004; Hartsell et al. 2005; Salazar et al. 2001; Wardley et al. 2005 and Rasmusson et al. 1995), two comparative or cohort studies (Weinfurt et al. 2004 and Pecherstorfer et al. 2006) and six case series (Broos et al.1993; Gerszten et al. 2005; Gristina et al. 1983; Scarantino et al. 1996; Borojevic et al. 1999 and Durr et al. 2002). Bisphosphonates had little impact on overall survival, but could reduce pain and the occurrence of skeletal events.		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Four papers offered good evidence on the role of radiotherapy in bone metastases, including a Cochrane review (Sze et al., 2002) and three RCTs (Hartsell et al., 2005; Salazar et al., 2001 and Rasmussen et al., 1995)		
Brain metastases							
NICE 2009	[3]	July 2008	Women with advanced breast cancer	- Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease. - Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis. - Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy. - Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate.	Retrospective case series Surgery (Pieper et al. 1997 and Wroski et al. 1997), stereotactic radiosurgery (Combs et al. 2004; Lederman et al. 2001; Amendola et al. 2000; Firlik et al. 2000; Levin et al. 2002; Akyurek et al. 2007 and Muacevic et al., 2004), chemotherapy (Rivera et al. 2006; Rosner et al. 1986; Boogerd et al. 1992; Franciosi et al. 1999; Oberhoff et al. 2001; Lassman 2006 and Trudeau 2006) and whole brain radiotherapy (WBRT) (Bartsch et al. 2006; Fokstuen et al. 2000; Korzeniowski and Szpytma 1987; Lentzsch et al. 1999; Liu et al. 2006; Ogura et al. 2003 and Mahmoud-Ahmed et al. 2002; Viani et al. 2007 and Johansen et al. 2008).		Low

MANAGEMENT OF COMPLICATIONS OF LOCAL TREATMENT

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Lymphoedema							
NICE 2009	[3]	July 2008	Women with early invasive breast cancer	- Inform all patients with early breast cancer about the risk of developing lymphoedema and give them relevant written information before treatment with surgery and radiotherapy. - Give advice on how to prevent infection or trauma that may cause or exacerbate lymphoedema to patients treated for early breast cancer. - Ensure that all patients with early breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service.	RCTs: Bendz and Fagevik, 2002; Box et al., 2002a and 2002b; Cave and Jones, 2006 and Cheema et al., 2008. Observational studies: Cordero et al., 2003; Coward, 1999; Karki et al., 2001, 2004; Lane 2005 and Sandel et al., 2005.		High
NICE 2009	[3]	July 2008	Women with advanced breast cancer	- Assess patients with lymphoedema for treatable underlying factors before starting any lymphoedema management programme. - Offer all patients with lymphoedema complex decongestive therapy (CDT) as the first stage of lymphoedema management. - Consider using multi-layer lymphoedema bandaging (MLLB) for volume reduction as a first treatment option before compression hosiery. - Provide patients with lymphoedema with at least two suitable compression garments. These should be of the appropriate class and size, and a choice of fabrics and colours should be available.	A guideline (Harris et al. 2001), one very high quality systematic review (Moseley et al. 2007), two systematic reviews of less quality (Kligman et al. 2004 and Rinehart-Ayres et al. 2007), four randomised trials (Didem et al. 2005; Irdesel and Kahraman 2007; Badger et al. 2004 and Johansson et al. 2005) and six case series or phase II studies (Vignes et al. 2007; Hamner and Fleming 2007; Sitzia et al. 2002; Kim et al. 2007; Koul et al. 2007 and Fiaschi et al. 1998).		

Arm mobility							
NICE 2009	[3]	July 2008	Women with early invasive breast cancer	- All breast units should have written local guidelines agreed with the physiotherapy department for postoperative physiotherapy regimens. - Identify breast cancer patients with pre-existing shoulder conditions preoperatively as this may inform further decisions on treatment. - Give instructions on functional exercises, which should start the day after surgery, to all breast cancer patients undergoing axillary surgery. This should include relevant written information from a member of the breast or physiotherapy team. - Refer patients to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility after breast cancer treatment.	RCTs: Wingate et al. 1989; Dawson et al. 1989; Gerber et al. 1992; Le Vu et al. 1997; Na et al. 1999; Bendz and Fagevik 2002; Box et al. 2002; Gordon et al. 2005; Johannsson 2005; Lauridsen et al. 2005; Sandel et al. 2005; Wang et al. 2005; Kilbreath et al. 2006; Beurskens et al. 2007; Cinar et al. 2008.		High
Cancer-related fatigue							
NICE 2009	[3]	July 2008	Women with advancedb reast cancer	- Offer all patients with advanced breast cancer for whom cancer-related fatigue is a significant problem an assessment to identify any treatable causative factors and offer appropriate management as necessary. - Provide clear, written information about cancer-related fatigue, organisations that offer psychosocial support and patient-led groups. - Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue.	Two systematic reviews (Minton et al. 2007 and Cramp and Daniel, 2008) one on drug therapies and one on exercise regimes, together with two RCTs (Headley et al. 2004 and Bordeleau et al. 2003) and a poor quality case series (Carson et al. 2007). ➔ no significant effect of progestational steroids, including megesterol acetate. Meta-analysis of data from 28		High

					RCTs (Cramp and Daniel, 2008) ➔ highly significant effect of exercise		
Uncontrolled local disease							
NICE 2009	3	July 2008	Women with advanced breast cancer	- A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms. - A wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team. - A palliative care team should assess all patients with uncontrolled local disease in order to plan a symptom management strategy and provide psychological support.	Low patient number case series (Bower et al. 1992; Kuge et al. 1996; Lund-Nielsen et al. 2005; Kumar et al. 1987; Kolodziejski et al. 2005; Faneyte et al. 1997 and Pameijer et al. 2005), the majority of which were retrospective		Low
Menopausal symptoms							
NICE 2009	3	July 2008	Women with early invasive breast cancer	- Discontinue HRT in women who are diagnosed with breast cancer. - Do not offer HRT (including oestrogen/progestogen combination) routinely to women with menopausal symptoms and a history of breast cancer. HRT may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed. - Offer information and counselling for all women about the possibility of early menopause and menopausal symptoms associated with breast cancer treatment. - The selective serotonin re-uptake inhibitor antidepressants paroxetine and fluoxetine may be offered to women with breast cancer for	Systematic reviews: Antoine et al. 2007; Bordeleau et al. 2007; Carpenter et al. 2007; Col et al. 2005; Deng et al. 2007; Ganz et al. 2000; Goodwin et al. 2008; Hickey et al. 2005; Kenemans et al. 2005; Kimmick et al. 2006; Kroiss et al. 2005; Loprinzi et al. 2007; MacLennan et al. 2004; Modelska et al. 2002; Mom et al. 2006; Nedrow et al. 2006; Nelson et al., 2006; Pritchard et al. 2002; Royal College of Obstetricians and Gynaecologists et al. 2006; Thompson et al. 2008; Tremblay et al. 2008; von Schoultz et al. 2005 and Walji et al. 2007.	Some SR included studies of women without breast cancer	

				relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen. - Clonidine, venlafaxine and gabapentin should only be offered to treat hot flushes in women with breast cancer after they have been fully informed of the significant side effects. - Soy (isoflavone), red clover, black cohosh, vitamin E and magnetic devices are not recommended for the treatment of menopausal symptoms in women with breast cancer.			
Anaemia							
CECOG 2007	[188]	May 2005	Women with MBC	- Supportive treatment with erythropoesis stimulating proteins can be considered for the maintenance of quality of life in the case of symptomatic anemia including disease- or treatment-associated fatigue. - For acute symptoms and in the case of non responsiveness to erythropoesis stimulating proteins, erythrocyte transfusions should be administered. - In contrast, in patients undergoing cytotoxic treatment, erythropoesis stimulating proteins should not be administered for the prevention of anemia or to reach high hemoglobin targets.	Leyland-Jones et al. 2005		Low
Leukopenia							
CECOG 2007	[188]	May 2005	Women with MBC	- In the case of chemotherapy-associated myelosuppression or a history of recurrent febrile neutropenia following previous chemotherapy, the use of myeloid colony stimulating factors can be considered. - If the anticipated febrile neutropenia rate is high (>20% according to NCCN guidelines,	GDG consensus		Low

				>40% according to ASCO guidelines, the primary prophylactic use of myeloid colony stimulating factors should be considered.			
Psychosocial support							
CECOG 2007	[188]	May 2005	Women with MBC	- Psychosocial support should be available to patients with MBC. No recommendation of an optimal type of intervention, an optimal timing or the duration of such interventions can be formulated.	GDG consensus		Low

Hormone replacement therapy

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Holmberg 2008	[216]	NA	Post-menopausal women previously treated for breast cancer	Hormone replacement therapy (n=221) vs. best management of menopausal symptoms without hormones (n=221)	New breast cancer event Distant Metastasis – Free and Overall Survival	*New breast cancer event* HT arm: 39 women experienced a new breast cancer event vs. 17 women in the control group HR = 2.4; 95%CI = 1.3 to 4.2. Cumulative incidences at 5 years were 22.2% in the HT arm and 8.0% in the control arm. *Distant Metastasis – Free and Overall Survival* HT arm: 6 deaths + 6 women with distant metastases. Control arm: 5 deaths + 4 women with distant metastases. The difference in distant metastasis – free survival was not statistically significant (p = 0.51, log-rank test). → After extended follow-up, there was a clinically and statistically significant increased risk of a new breast cancer event in survivors who took HT	More women in the HT arm than the control arm had had hormone receptor–positive cancer (62.3% vs 54.5%). No blinding Possibility of information bias related to possibly more vigorous follow-up and diagnosis of events in the HT arm. However, identical number of follow-up visits in the two groups Median follow-up: 4 years	Randomized, non- placebo-controlled noninferiority trial (HABITS)	Moderate

Psychological intervention

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Andersen 2008	[218]	NA	Women with regional breast cancer surgically treated	Assessment + Psychologic intervention (n=114) Versus Assessment alone (n=113)	Breast cancer recurrence Breast cancer related death	Intervention: 26 sessions in small groups, led by 2 psychologists (39 hours over 12 months); muscle relaxation, problem solving for common difficulties, identifying supportive family members or friends, improving dietary habits, strategies to cope with treatment side effects… Median Follow-up: 11 years *Breast cancer recurrence* HR 0.55 (95%CI 0.32-0.96; p=0.034) *Breast cancer related death* HR 0.44 (95% CI 0.22-0.86; p=0.016) *Overall survival* HR=0.51 (95% CI 0.28-0.93; p=0.028)	No blinding Patients were paid per assessment Cox proportional Hazards analysis for survival	RCT	Moderate

SURVEILLANCE (FOLLOW-UP)

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
History/physical examination							
ASCO 2006	[62]	March 2006	Patients with breast cancer	History/physical examination is recommended every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually	The GIVIO Investigators 1994 Rosselli et al. 1994	No recent prospective studies evaluating alternative clinical follow-up schedules for surveillance. The current recommendations are the same as the original 1997 guidelines.	Moderate
Patient education regarding symptoms of recurrence							
ASCO 2006	[62]	March 2006	Patients with breast cancer	Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, abdominal pain, dyspnea or persistent headaches	A meta-analysis (De Bock et al. 2004) of 12 studies (n=5 045 patients): • 40% (95% CI, 35% - 45%) of patients with locoregional recurrences were diagnosed during routine clinic visits or routine testing • 60% developed symptomatic recurrences before their scheduled clinical visits.	SR and meta-analysis	Moderate
Referral for genetic counseling							
ASCO 2006	[62]	March 2006	Patients with breast cancer	Women at high risk for familial breast cancer syndromes should be referred for genetic counselling. Criteria to recommend referral include the following: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer	US Preventive Services Task Force 2005	Recommendation statement	Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				diagnosed before the age of 50 years; two or more first- or second degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative			
Breast self-examination (BSE)							
ASCO 2006	62	March 2006	Patients with breast cancer	All women should be counseled to perform monthly breast self-examination Women should be made aware that monthly BSE does not replace mammography as a breast cancer screening tool.	A large comparative study (Thomas et al. 2002; n > 260 000 Chinese women) <u>BSE vs no surveillance</u> *Efficacy of BSE alone* No survival benefit in the group BSE. Similar cumulative breast cancer mortality rates through 10 years of follow-up (risk ratio=1.04; 95% CI, 0.82 to 1.33; p=.72) More benign breast lesions diagnosed in the BSE group	Routine screening mammography was not available.	Moderate
Mammography							
NICE 2009	3	July 2008	Women	Offer annual mammography to all patients with early breast cancer, including DCIS. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years.	Two systematic reviews of observational studies *Ipsilateral local recurrence* Proportion detected by follow-up mammography between 8%-50% (Grunfeld et al., 2002 and McGahan and Noorani 2000) and median values of 26% (McGahan and Noorani, 2000) and 27% (Grunfeld et al., 2002).		Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Temple et al. 1999: Se: 38%-74%; Sp: 39%-60%. *Contralateral breast cancer* Proportion detected by follow-up mammography between 8%-80% (Grunfeld et al., 2002 and McGahan and Noorani, 2000) and median values of 36% (McGahan and Noorani, 2000) and 45% (Grunfeld et al., 2002). Physical examination plus mammography (Temple et al., 1999): Se: 81%-88% Sp: 96.5%-99.9% For DCIS, 2 retrospective studies (Liberman et al., 1997 and Weng et al., 2000).		
ASCO 2006	[62]	March 2006	Patients with breast cancer	Women treated with breast-conserving therapy should have their first post-treatment mammogram no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained every 6 to 12 months for surveillance of abnormalities. Mammography should be performed yearly if stability of mammographic findings is achieved after completion of locoregional therapy.	Grunfeld et al. 2002	Observational study (Included in NICE 2009)	Low
CCO 2006				Indicated			
Coordination of care							

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
ASCO 2006	[62]	March 2006	Patients with breast cancer	Continuity of care for breast cancer patients is encouraged and should be performed by a physician experienced in the surveillance of cancer patients and in breast examination including the examination of irradiated breasts; if follow-up is transferred to a PCP, the PCP and the patient should be informed of the long-term options regarding adjuvant hormonal therapy for the particular patient; this may necessitate referral for oncology assessment if a patient is receiving adjuvant endocrine therapy.	Grunfeld et al. 1995, 1996, 1999, 2006; Gulliford et al. 1997 Institute of Medicine and National Research Council, Committee on Cancer Survivorship 2005	Well designed RCT involving 296 women receiving follow-up for breast cancer in specialist oncology and surgical clinics in Great Britain IoM proposed a shared-care model that could be integrated across different specialties	High
Pelvic examination							
ASCO 2006	[62]	March 2006	Patients with breast cancer	Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians	No	See literature on 'Tamoxifen'	Low
Intensive surveillance monitoring							
ASCO 2006	[62]	March 2006	Patients with breast cancer	Intensive surveillance monitoring (CBC testing, chest x-ray, bone scans, liver ultrasound and computed tomography) is not recommended for routine breast cancer surveillance.	**Intensive monitoring** Meta-analysis of 2 well-designed RCTs (The GIVIO Investigators 1994; Rosselli et al. 1994) involving a total of 2 563 women: regular clinical visits *vs* intensive surveillance *Overall Survival* HR=0.96; 95% CI, 0.80 to 1.15 *Disease-free survival* HR=0.84;95%CI, 0.71 to 1.00 *5-year mortality* No statistical difference	Intensive surveillance includes clinical visits, bone scans, liver US, chest x-rays, and laboratory testing	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					In The GIVIO Investigators (1994): higher percentage of asymptomatic metastases was found in the intensive surveillance group compared with the control group (31% v 21%, respectively) → no improvement in survival. **Routine blood tests** Palli et al. 1999 Rojas et al. 2005 **CT scans** 2 retrospective studies : Drotman et al. 2001 ; Hurria et al. 2003		Low Low
FDG-PET scanning							
NCC-HTA 2007			Patients with breast cancer and clinical suspicion of recurrence (with arm pain or other symptoms referable to the brachial plexus)	FDG-PET Reference standard: histopathology/follow-up	One systematic review (BCBS 2003) and one additional primary study (Goerres 2003) both included in previous KCE report.	See above	
ASCO 2006	[62]	March 2006	Patients with breast cancer	FDG-PET scanning is not recommended for routine breast cancer surveillance	2 retrospective cohort studies (Vranjesevic et al. 2002, Kamel et al. 2003) 1 meta-analysis of 16 studies comprising 808 patients (Isasi et al. 2005):		Low High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					- pooled sensitivity: 90% (95% CI, 86.8% to 93.2%) - pooled false-positive rate: 11% (95% CI, 86.0% to 90.6%).		
Breast MRI							
NICE 2009	2	July 2008	Women with early invasive breast cancer or DCIS.	Do not offer ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS.	7 diagnostic studies of follow-up MRI (Aichinger et al., 2002; Bone et al., 1995; Buthiau et al., 1995; Coulthard et al., 1999; Heywangkobrunner et al., 1993; Preda et al., 2006 and Viehweg et al., 1998). Se MRI: 85.7%-100%. Sp MRI: 82%-100%		Low
ASCO 2006	62	March 2006	Patients with breast cancer	There is no evidence that breast MRI improves outcomes when used as a breast cancer surveillance tool during routine follow-up in asymptomatic patients. Breast MRI is not recommended for routine breast cancer surveillance.	Kuhl et al. 2005 Leach et al. 2005	2 prospective cohort studies in women at high risk for breast cancer based on family history	Low
Re-assessment of ER and HER2 status							
NICE 2009	2	July 2008	Patients with advanced breast cancer with ER/PR and HER2 status known in primary tumour	Patients with tumours of known oestrogen receptor (ER) status whose disease recurs should not have a further biopsy just to reassess ER status.	17 observational studies all of which compared paired (from the same patient) biopsy or FNA samples from primary and locoregional or metastatic tumour tissue. HER2 (Niehans et al. 1993; Shimizu et al. 2000; Gancberg et al. 2002; Carlsson et al. 2004; Regitnig et al. 2004; Gong et al. 2005; Zidan et al. 2005; Lorincz et al. 2006; Rom et al. 2006; Pectasides et al. 2006; Tapia et al. 2007 and Santinelli et	Papers were concerned with identifying the rate of status change but did not address overall survival, time to progression or quality of life. Approximately 15% of patients showed a change in ER status, from positive to negative,	Low
				Patients with tumours of known human epidermal growth factor receptor 2 (HER2) status whose disease recurs should not have a further biopsy just to reassess HER2 status.			
				Assess ER and HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess			

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				ER and HER2 status.	al. 2008) and/or ER (Spataro et al. 1992; Johnston et al. 1995; Lower et al. 2005; Rom et al. 2006; Shimizu et al. 2000 and Brankovic-Magic et al. 2002)	comparing primary with locoregional or metastatic tumour samples. 93% of patients tested for HER2 status showed no change between paired samples.	

Abbreviations; PCP, primary care physician; FDG-PET,18Ffluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging.

Study ID	Ref	Search date	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Beaver 2009	[238]	NA	Women treated for breast cancer who were at low to moderate risk of recurrence.	Traditional hospital follow-up (consultation, clinical exam and mammo-graphy as per hospital policy) Versus Telephone follow-up by specialist nurses (consultation with structured intervention and mammography according to hospital policy).	Psychological morbidity (anxiety, general health), participants' needs for information, participants' satisfaction, clinical investigations ordered, and time to detection of recurrent disease.	No difference in anxiety and in number of investigations ordered but higher satisfaction in the telephone group (intention to treat P<0.001). Recurrences were few (4.5%), with no differences between groups for time to detection (median 60.5 (range 37-131) days in hospital group v 39.0 (10-152) days in telephone group; P=0.228).	Trial registration National Cancer Research Institute 1477.	Equivalence RCT	High

APPENDIX 5: RESULTS OF EXTERNAL EXPERT MEETING

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
Diagnosis	Triple assessment	All patients should have a full clinical examination	1	C	5	4	5	100%		No change
		Where a localised abnormality is present, patients should have mammography and/or ultrasonography followed by core biopsy and/or fine needle aspirate cytology	1	C	5	3	5	83%	if no certain diagnosis is made	No change
		In cases where clinical examination and imaging are pathognomonic of a benign lesion (i.e. cyst), biopsy/cytology is not mandatory	Expert opinio		5	3	5	83%	but follow-up should be scheduled; in doubt MRI should be performed.This is especially the case in genetica	To define 'pathognomonic' as BIRADS 2
		A lesion considered malignant following clinical examination, imaging or cytology alone should, where possible, have histopathological confirmation of malignancy before any surgical procedure takes place	1	C	5	4	5	100%		No change
		Two-view mammography should be performed as part of triple assessment (clinical assessment, imaging and tissue sampling) in a unit specialized in breast imaging	1	C	5	4	5	100%		No change
		Young women presenting with breast symptoms and a strong suspicion of breast cancer should be evaluated by means of the triple assessment approach to exclude or establish a diagnosis of cancer	1	C	5	3	5	83%	What makes difference with other women?	Young women should not form an exception on the general rule for triple assessment
	MRI	There is insufficient evidence to routinely use MRI for the diagnosis of breast cancer. MRI can be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful (clinically palpable and mammographically occult breast cancer, cT0N+ patients, diagnosis of recurrence	1	C	5	1	5	67%	MRI should be used in genetically predisposed women	No change : genetically predisposed women are beyond the scope of this project
		For definitive characterization of breast lesions, biopsy cannot yet be replaced by MRI	1	B	5	5	5	100%		No change
	99mTc-MIBI scintimammography (SMM)	There is insufficient evidence to routinely use 99mTc-MIBI scintimammography for the diagnosis and staging of breast cancer. 99mTc-MIBI scintimammography can be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that 99mTc-MIBI scintimammography is useful	1	C	5	5	5	100%	Dangerous High radiation hazard	
	PET scan	PET scanning is insufficiently accurate to be recommended for diagnosis of breast cancer as an alternative to biopsy	1	B	5	5	5	100%		
	Hormonal receptor assessment	Estrogen receptors and progesterone receptors (ER/PgR) should be measured on all ductal carcinomas in situ (DCIS) and primary invasive breast cancers	1	B	5	5	5	100%		
		HER2 protein expression and/or gene amplification should be evaluated in every primary invasive breast cancer at the time of diagnosis and at the time of recurrence whenever possible	1	B	5	4	5	100%	This should be gene amplification, not IHC	
	Tumour markers	There is no good evidence to include tumour markers (circulating tumour cells [CTC], CA 15-3, CA 27.29, CEA and Cathepsin D) in the diagnostic work-up of primary breast cancer	2	C	5	2	5	60%	not for diagnosis	

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
Staging	Routine staging tests	There is no evidence for pre-treatment routine bone scanning, liver ultrasonography and chest radiography, or tumour markers for asymptomatic patients with negative clinical findings, unless there is at least clinical stage II disease and/or neoadjuvant treatment is considered, or a mastectomy is planned	2	C	4	2	5	60%	Grade 3 lesions should have these exams in stage I	
		In asymptomatic women with DCIS, routine bone scanning, liver ultrasonography and chest radiography are not indicated as part of baseline staging	2	C	5	1	5	80%		
	MRI	The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS, except in the following situations:	1	C	5	1	5	60%		
		• if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment	2	C	5	5	5	100%		
		• in invasive lobular cancer	1	C	5	3	5	83%		
		• in cases where breast density does not allow to exclude multicentric disease by mammographic assessment	2	C	5	3	5	83%	AND THE OTHER BREAST	
		There is no good evidence to perform a preoperative breast MRI in each case of a breast cancer diagnosis with a dense mammographic appearance	2	C	3,5	1	5	50%		
		For M-staging (visceral or bone metastases), MRI/CT can be considered	2	C	5	4	5	100%		
	Axillary ultrasonography	Axillary ultrasonography with fine needle aspiration cytology of axillary lymph nodes suspicious for malignancy is recommended before preoperative systemic treatment	2	C	5	3	5	83%	what is the sensitivity of axillay ultrasonography?negative results does not always mean pN0.	
	PET scan	The use of PET in staging axillary lymph nodes for breast cancer is not recommended. PET sensitivity is inferior to axillary node dissection and sentinel node biopsy	1	B	5	3	5	83%		
		PET scan can be useful for the evaluation of metastatic disease of invasive breast cancer	1	C	5	5	5	100%		
		Inconclusive evidence was identified on the use of PET for the detection of bone metastases and therefore, bone scan is still the technique of choice	2	C	5	3	5	80%		

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
Treatment of non invasive breast tumours	***Early precursor and high-risk lesion***	Management of early precursor lesions is preferably discussed in a multidisciplinary setting	expert opinion		5	4	5	100%		
		When atypical lobular hyperplasia or flat epithelial atypia is present near the margins of an excision specimen, re-excision is not necessary	expert opinion		5	4	5	100%		
		When lobular carcinoma in situ or atypical ductal hyperplasia is present in the margins, re-excision is recommended	expert opinion		5	4	5	100%		
		When atypical lobular hyperplasia / lobular carcinoma in situ, flat epithelial atypia or an atypical intraductal proliferation reminiscent of atypical ductal hyperplasia, is found in a core biopsy, diagnostic excision is recommended	expert opinion		5	5	5	100%		
		When pleomorphic lobular carcinoma in situ or lobular carcinoma in situ with comedonecrosis is found in a core biopsy, complete excision with negative margins is recommended, and anti-hormonal treatment as well as radiotherapy is an option	expert opinion		5	3	5	75%	references??	
		Annual follow-up mammography after a diagnosis of lobular carcinoma in situ or atypical ductal hyperplasia is indicated	2	C	5	5	5	100%		
	Surgery	Women with high-grade and/or palpable and/or large DCIS of the breast who are candidates for breast conserving surgery should be offered the choice of local wide excision or mastectomy after the patient is correctly informed. In case of multicentricity local wide excision is not recommended	1	B	5	5	5	100%		
		In women with DCIS, mastectomy with or without immediate reconstruction remains an acceptable choice for women preferring to maximize local control or to avoid radiotherapy	1	B	5	5	5	100%		
		Immediate breast reconstruction should be discussed with all patients being advised to have a mastectomy, except when significant comorbidities preclude this option	1	C	5	5	5	100%		
		When local wide excision is performed in women with DCIS, a minimum of 2 mm radial margin of excision is usually recommended with pathological examination	1	C	4,5	2	5	75%	Margin?	
		Axillary clearance is not recommended for women with DCIS	1	C	5	4	5	100%	Sentinel might be recommended?	
	Sentinel lymph node biopsy	Sentinel lymph node biopsy is not recommended in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease. Patients at high risk include those with a palpable mass or extensive micro-calcifications	1	B	5	2	5	80%	see above / Because size should matter in decision for SN/ is this also true for large high grade DCIS? What is the sensitivity of SNB for large tumors?	
		Data are available to support the use of sentinel lymph node biopsy for high-grade DCIS, when mastectomy with or without immediate reconstruction is planned. Age, gender or obesity are no exclusion criteria for SLNB	1	A	5	3	5	80%		

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
	Radiotherapy	Radiotherapy should be part of the breast-conserving treatment of DCIS	1	A	4,5	4	5	100%	also for small, low grade DCIS, with free margins?	
	Endocrine therapy	Adjuvant hormonal therapy is recommended for patients with ER positive	1	A	4,5	1	5	75%	What is the evidence and what icost-benefit ?	
					4,5	4	5	100%		
	Paget's disease	Breast conserving surgery with removal of the nipple–areolar complex followed by radiotherapy should be offered as an alternative to mastectomy in patients with Paget's disease without underlying invasive breast cancer	2	C	5	4	5	100%		
		Oncoplastic repair techniques should be offered to patients with Paget's disease treated with breast conserving surgery to maximise cosmesis	1	C	5	4	5	100%		
	Early invasive breast cancer	All patients with breast cancer should be discussed within a multidiscipl	expert opinion		5	4	5	100%		
	Neoadjuvant treatment	In patients with unifocal operable tumours too large for breast conserving surgery, downstaging with neoadjuvant systemic therapy should be considered	1	A	5	3	5	80%	the responses of invasive lobular cancer to neoadjuvant chemotherapy are very low, as well as the rate of breast conserving surgery. Therefore, pts with ILC are no good candidates for neoadjuvant chemotherapy.	
	Surgery to the breast	Breast-conserving surgery followed by radiotherapy offers the same survival benefits as modified radical mastectomy in women with stage I or II breast cancer who are candidates for breast-conserving surgery	1	A	5	5	5	100%		
		Immediate breast reconstruction after mastectomy offers the same survival benefits as mastectomy without reconstruction	1	C	5	5	5	100%		
		The choice of surgery must be tailored to the individual patient with stage I or II breast cancer, who should be fully informed of the options	1	A	5	5	5	100%		
	Surgery to the axilla	Sentinel lymph node biopsy is not recommended for:	1	A	5	5	5	100%	Specify "alone, without axillary clearance because SNB in addition to clearance helps !!!	
		1. large T2 (i.e. > 3 cm) or T3-4 invasive breast cancers;			5	5	5	100%		
		2. inflammatory breast cancer;			5	5	5	100%		
		3. in the presence of suspicious palpable axillary lymph nodes;			5	5	5	100%		
		4. multiple tumours; and possible disturbed lymph drainage after recent axillary surgery or a large biopsy cave after tumour excision			5	5	5	100%		
		In women with primary breast cancer less than 3 cm and with clinically and ultrasonographically negative nodes, a sentinel lymph node biopsy should be performed	1	A	5	4	5	100%	Should be proposed with informed consent	

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
		Peri-operative pathology examination of SLN is recommended. For macrometastases (>0.2 mm), axillary lymph node dissection level I and II is indicated (1A evidence). For micrometastases (0.2-2 mm) until final results of ongoing prospective clinical trials are available, axillary dissection is recommended, although for some experts this decision should also take into consideration other risk factors (for example used as a nomogram)	expert opinion		5	4	5	100%		No change
		If a sentinel lymph node biopsy is impossible, an axillary lymph node dissection level I and II is indicated	1	A	5	5	5	100%		No change
		Patients found to have only isolated tumour cells in their sentinel lymph nodes should not be offered further axillary treatment. These patients should be regarded as lymph node-negative	1	C	5	4	5	100%		No change
	Adjuvant therapy	If adjuvant chemotherapy and radiotherapy are indicated, the chemotherapy should be given first	1	A	5	4	5	100%	or concommittant	No change
		Adjuvant chemotherapy or radiotherapy should be started maximum within 8 weeks of completion of surgery	1	C	5	4	5	100%	This does not mean that if later this should be dropped	To reformulate : It is recommended to start adjuvant chemotherapy or radiotherapy within 8 weeks of
	Radiotherapy	In patients with early breast cancer, adjuvant irradiation is indicated after breast conserving surgery	1	A	5	5	5	100%		No change
		Adjuvant chest wall radiotherapy after mastectomy should be offered to patients with early invasive breast cancer and a high risk of local recurrence including four or more positive axillary lymph nodes or involved resection margins	1	A	5	5	5	100%	Add size above 5 cm (T3), or large T2 3-5 cm with additional risk factors (multifocality, multicentricity, high grade)	No change
		Until data from a large ongoing randomized trial become available, radiotherapy after mastectomy should be offered to patients with 1-3 positive nodes	1	A	5	5	5	100%		No change
		Internal mammary chain irradiation is to be discussed in the multidisciplinary team meeting	expert opinion		5	5	5	100%		No change
		The target volume of percutaneous adjuvant radiotherapy encompasses the entire breast and the adjoining thoracic wall. The dose amounts to approximately 50 Gray fractionated in the conventional manner (1.8-2.0 Gray) with an additional local boost	1	A	5	4	5	100%	For selected patients, alternative schemes like 42,56 Gy in 16 fractions or 40 Gy in 15 fractions are possible. (reference START, Whelan, …)	No change
		An additional beam boost to the site of local excision can be offered to patients with early invasive breast cancer and a high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy	2	A	5	5	5	100%		No change
		Axillary radiotherapy should be discussed on an individual basis in the multidisciplinary team	1	A	5	4	5	100%	Should be done if N+	No change
	Systemic therapy	The choice of the adjuvant systemic treatment for invasive breast cancer should be driven by the hormonal sensitivity, risk profile of the tumour, age, menopausal status and comorbidities of the patient	1	A	5	5	5	100%		No change

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
	Chemotherapy	For patients with Stage I-III breast cancer, preferred regimens are standard anthracycline-based regimens with or without a taxane	1	A	5	5	5	100%		No change
		For patients with lymph node-positive breast cancer, preferred regimens are standard anthracycline and taxane-based regimens	2	A	5	5	5	100%		No change
		For patients with HER-2 positive breast cancer who receive trastuzumab, a sequential regimen of anthracyclines and taxanes is recommended to decrease the total dose of anthracyclines and hence reduce the cardiotoxicity	expert opinion		5	5	5	100%		No change
		Women receiving an adjuvant anthracycline–taxane regimen should be closely moni	1	A	5	5	5	100%	G-CSF recommendation by age	No change
		a. Primary prophylactic G-CSF (granulocyte colony-stimulating factor) is recommended if risk of febrile neutropenia is 20% or higher			5	4	5	100%	This guideline 20% is too vague	No change
		b. Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy			5	5	5	100%		No change
		In patients with breast cancer, high-dose chemotherapy with stem-cell transplantation cannot be recommended	1	A	5	5	5	100%		No change
		For all women within child bearing age, fertility issues should always be discussed before the induction of breast cancer therapy	1	C	5	5	5	100%		No change
		Chemotherapy during pregnancy is not contraindicated after 14 weeks of gestation	2	C	5	4	5	100%		No change
	Endocrine therapy	Premenopausal patients with hormone receptor positive breast cancer should receive adjuvant endocrine treatment with tamoxifen for 5 years with or without an LHRH analogue	1	A	5	5	5	100%	The LHRH agonist should be 3 years; 5 years of TAM is a minimum	No change
		Premenopausal women with stage I or II breast cancer who cannot take tamoxifen, should receive a LHRH analogue	1	A	5	5	5	100%		No change
		Postmenopausal patients with hormone receptor positive breast cancer should receive adjuvant endocrine treatment with either: - tamoxifen (for 5 years), - anastrozole (for 5 years) or letrozole (for 5 years), - or tamoxifen (for 2 - 3 years) followed by an aromatase inhibitor (to a total of five years of hormone therapy), - or aromatase inhibitor (for 2 years) followed by tamoxifen (for a total of 5 years).	1	A	5	4	5	100%	tamoxifen 10 years if node positive (or switch AI); the switch strategies should not be recommended; they are historical artifacts	No change
		Postmenopausal women with hormone receptor positive tumours who have completed five years of adjuvant tamoxifen therapy should be considered for extended treatment with an aromatase inhibitor (for up to 5 years) if node-positive or high-risk node-negative (pT2 or grade III)	1	A	5	5	5	100%		No change
	Trastuzumab	One year treatment with adjuvant trastuzumab is indicated for women with HER2-positive, node-positive or high-risk node-negative breast cancer (tumour size > 1 cm), having a left ventricular ejection fraction of ≥ 55% and without important cardiovascular risk factors who received chemotherapy	1	A	5	5	5	100%		No change
		During treatment with trastuzumab, cardiac function should be monitored every 3 months	1	A	5	5	5	100%		No change

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
Treatment of metastatic breast cancer	Multidisciplinary approach	The treatment of the metastatic breast cancer should be discussed within a multidisciplinary team and patient preferences should always be taken into account	expert opinion		5	4	5	100%	drop "always"; if unreasonable not	No change
	Diagnosis	For monitoring patients with metastatic disease during active therapy, CA 27.29, CA 15-3 or CEA can be used in conjunction with diagnostic imaging, history, and physical exam	2	C	5	4	5	100%		No change
		Metastatic lesions should be biopsied whenever accessible and ER and PgR reassessed	1	B	5	4	5	100%	And also HER2 FISH	No change
		In both pre- and postmenopausal patients, HER2 status should be used to identify patients most likely to benefit from endocrine forms of therapy in metastatic disease settings	1	B	5	1	5	60%	Does not make sense / error! Hormone receptor status should be used ….from endocrine forms of therapy . HER-2 status should be used to identify patients for anti HER-2 treatment.	Replace 'endocrine forms of therapy' by 'Trastuzumab'
	Systemic treatment *Endocrine therapy*	In premenopausal patients with hormone receptor-positive or hormone receptor unknown metastatic breast cancer, suppression of ovarian function (e.g. with LHRH analogs, bilateral oophorectomy, irradiation of the ovaries) in combination with tamoxifen is the first-line hormonal therapy of choice	1	A	5	5	5	100%	irradiation of ovaries is outdated	Delete examples of mathods used to suppress the ovarian function
		In postmenopausal patients with hormone receptor-positive or hormone receptor unknown metastatic breast cancer, first-line treatment consists of third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) or Tamoxifen. The choice of the agent should take into consideration the adjuvant endocrine therapy received. As second-line treatment, the use of a third generation aromatase inhibitor or Fulvestrant is recommended	1	A	5	5	5	100%		No change
		Fulvestrant may be considered as alternative therapy to third-generation aromatase inhibitors for metastatic breast cancer in postmenopausal women with hormone receptor-positive (ER+ and/or PgR+) breast cancer that has recurred after prior adjuvant tamoxifen therapy or progressed during prior tamoxifen therapy for advanced disease	1	B	5	4	5	100%		No change
		Fulvestrant may be considered as alternative therapy to exemestane for metastatic breast cancer in postmenopausal women with hormone receptor-positive (ER+ and/or PgR+) breast cancer that has recurred after prior adjuvant non-steroidal aromatase inhibitor therapy (during or within six months of discontinuation) or progressed during prior non-steroidal aromatase inhibitor therapy for advanced disease	1	B	5	4	5	100%	not the same?	This recommendation is too precise --> not necessary : to delete

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
	Chemotherapy	Chemotherapy for patients with metastatic breast cancer is indicated for the following conditions : - hormone refractory or HR- tumours - rapidly progressive disease or symptomatic disease - life threatening disease	expert opinion		5	5	5	100%		No change
		The choice between polychemotherapy and sequential single agent chemotherapy should take into account the prognosis, performance status, need for rapid symptom control and toxicity profiles with the ultimate goal of optimizing quality and quantity of life	1	A	5	5	5	100%		No change
		Anthracycline- and/or taxane based regimens are to be preferred as first-line treatment depending on adjuvant chemotherapy received and disease-free interval	1	A	5	5	5	100%		No change
		In patients with anthracycline-resistance or failure and taxane-naive, considered for further chemotherapy, taxane-based treatment (monotherapy or combination of a taxane with gemcitabine or capecitabine) should be used, taking into account quality of life, toxicity, characteristics of the disease and the ease of administration	1	A	5	5	5	100%		No change
		For patients pretreated with anthracyclines and taxanes, capecitabine monotherapy is the preferred treatment	1	A	4,5	3	5	75%	or navelbine?	This recommendation is too precise --> not
	Biological therapy	Trastuzumab with/without non-anthracycline-based chemotherapy or endocrine therapy is the treatment of choice for first-line therapy of all HER2 positive metastatic breast cancer except in the presence of cardiac contra-indications for the use of Trastuzumab	1	A	5	2	5	75%	treatment with lapatinib is also possible, in combination with capecitabine in pts pretreated with antrac and taxanes in adjuvant setting	To delete: 'for first-line therapy'
		In patients progressing on taxane plus Trastuzumab given in the metastatic setting, anti-HER2 therapy (Trastuzumab or lapatinib) should be continued in combination with capecitabine	1	A	4,5	4	5	100%	or other chemo	This recommendation is too precise --> not necessary : to delete
		For patients with HER-2 negative metastatic breast cancer bevacizumab associated with a taxane can be offered as first line therapy	1	A	5	4	5	100%		No change
	Treatment of bone metastases	Bisphosphonates should be routinely used in combination with other systemic therapy in patients with metastatic breast cancer with multiple or symptomatic lytic bone metastases	1	A	5	5	5	100%	This should also be included in adjuvant setting	No change
		In patients with painful or threatening bone metastases, radiotherapy is the treatment of choice, if not yet received	1	A	5	5	5	100%		No change
	Treatment of brain metastases	Patients with a single or small number of potentially resectable brain metastases can be treated with radiosurgery or with surgery followed by whole brain radiotherapy. Whole brain radiotherapy should only be offered to patients for whom surgery or radiosurgery is not appropriate	2	C	5	4	5	100%		No change

Dimension	Item	Recommendation(s)	GOR	LoE	Med	Min	Max	%4-5	Comments	Decision
Treatment of locoregional relapse		A local recurrence in the thoracic wall should be treated preferentially with surgery and adjuvant radiotherapy whenever possible	1	C	5	5	5	100%		No change
		A local recurrence after breast-conserving treatment should be treated by a mastectomy	1	C	5	5	5	100%		No change
		Systemic treatment for a completely excised locoregional recurrence should be discussed in the multidisciplinary team	expert opinion		5	5	5	100%		No change
Supportive care		Biphosphonates should not yet be part of the adjuvant treatment of breast cancer	1	A	5	2	5	80%	There is evidence in favor!	No change
		Supportive treatment with erythropoesis stimulating proteins can be considered in patients with symptomatic anaemia. For acute symptoms or in case of failure of erythropoesis-stimulating proteins, erythrocyte transfusions can be administered	1	C	4,5	2	5	75%	Not in adjuvant setting	To delete : the second sentence
		Women with breast cancer should be informed about the risk of developing lymphoedema and should be offered rapid access to a specialist lymphoedema service	1	A	5	5	5	100%		No change
		Physiotherapy for mobility after axillary clearance should be recommended	1	A	5	5	5	100%		No change
		Physical training including specific exercises for cancer-related fatigue can be recommended after treatment for breast cancer	1	A	5	5	5	100%		No change
		Menopausal hormonal replacement therapy is contraindicated in women with breast cancer	1	B	5	5	5	100%		No change
		Psychological support should be available to all patients diagnosed with breast cancer	1	A	5	5	5	100%		No change
		A palliative care team should assess all patients with uncontrolled disease in order to plan a symptom management strategy	1	C	5	5	5	100%		No change
Surveillance of patients		Yearly mammography with/without ultrasound should be used to detect recurrence or second primaries in patients who have undergone previous treatment for breast cancer, including DCIS	1	C	5	5	5	100%		To add: during the first 10 years
		Intensive surveillance monitoring (CBC testing, chest x-ray, bone scans, liver ultrasound and computed tomography) is not recommended for routine breast cancer surveillance	1	A	5	4	5	100%		No change
		MRI should not be offered routinely as a post-treatment surveillance test in patients who have been treated for early invasive breast cancer or DCIS, except in the following situations: - Lobular invasive cancer - Very young patients (< 35 years) - BRCA associated cancers - If initial tumour was not seen at mammography/ultrasound	1	C	5	4	5	100%		To add : the same categories than for MRI in diagnostic setting and "when other imaging techniques do not allow to obtain a reliable diagnosis"
		Follow-up consultations can be provided every 3 to 4 months in the first two years after diagnosis, every 6 months until 5 years after diagnosis, and every year after 5 years	expert opinion		4	2	5	80%	This is severe overshooting / 3-6 months (instead 3-4) initially for good prognosis	No change

APPENDIX 6: DECISIONS TAKEN DURING THE VALIDATION MEETINGS

Dimension	Item	Recommendation(s)	Decision
Diagnosis	Triple assessment	All patients should have a full clinical examination	Delete 'full' since all clinical examinations encompass the same examination
	MRI	There is insufficient evidence to routinely use MRI for the diagnosis of breast cancer. MRI can be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful (clinically palpable and mammographically occult breast cancer, cT0N+ patients, diagnosis of recurrence	Add here : MRI is useful for BRCA associated cancers (references to add)
	Hormonal receptor assessment	HER2 protein expression and/or gene amplification should be evaluated in every primary invasive breast cancer at the time of diagnosis and at the time of recurrence whenever possible	HER2 protein expression, and if positive, gene amplification…
	Tumour markers	There is no good evidence to include tumour markers (circulating tumour cells [CTC], CA 15-3, CA 27.29, CEA and Cathepsin D) in the diagnostic work-up of primary breast cancer	Only for diagnostic and not 'diagnostic work-up'
Staging	Routine staging tests	There is no evidence for pre-treatment routine bone scanning, liver ultrasonography and chest radiography, or tumour markers for asymptomatic patients with negative clinical findings, unless there is at least clinical stage II disease and/or neoadjuvant treatment is considered, or a mastectomy is planned	To replace by 'The use of re is no evidence for pre-treatment routine bone scanning, liver ultrasonography and chest radiography, or tumour markers for asymptomatic patients with negative clinical findings, unless there is at least clinical stage II disease and/or neoadjuvant treatment is considered, or a mastectomy is planned in women with stage I breast cancer has a very low yield and cannot be recommended routinely (2C evidence)' since the last sentence is not 2C evidence.
	PET scan	PET scan can be useful for the evaluation of metastatic disease of invasive breast cancer	If you leave it this way, PET will be considered/done in a lot of patients (while you mention p 24 that even bone scan .. are not necessary); To replace by ' PET scan can be useful for the evaluation of metastatic disease in locally advanced breast tumors with a high chance of (micro- or macro)metastatic disease'
Treatment of non invasive breast tumours	***Early precursor and high-risk lesion***	When pleomorphic lobular carcinoma in situ or lobular carcinoma in situ with comedonecrosis is found in a core biopsy, complete excision with negative margins is recommended, and anti-hormonal treatment as well as radiotherapy is an option	Replace 'anti-hormonal treatment as well as radiotherapy is an option' by 'anti-hormonal treatment and/or radiotherapy is an option'
	Early invasive breast cancer		
	Surgery to the axilla	Patients found to have only isolated tumour cells in their sentinel lymph nodes should not be offered further axillary treatment. These patients should be regarded as lymph node-negative	Since 'These patients should be regarded as lymph node-negative' is controversial (This has been seriously challenged by a recent paper "N Engl J Med. 2009 Aug 13;361(7):653-63.), delete this sentence
Treatment of metastatic breast cancer	Diagnosis	Metastatic lesions should be biopsied whenever accessible and ER and PgR reassessed	To add 'and HER2'; HER2 status can change in metastatic lesions, and this can have important therapeutic impact (herceptin in case HER2 becomes positive)
	Biological therapy	For patients with HER-2 negative metastatic breast cancer bevacizumab associated with a taxane can be offered as first line therapy	Bevacizumab is controversial --> to delete this recommendation
	Treatment of bone metastases	In patients with painful or threatening bone metastases, radiotherapy is the treatment of choice, if not yet received	'if not yet received'. This is not correct. If a patient received eg 1x8 Gy on vertebra 2y ago with excellent effect, and now again pain, new radiotherapy is first choice.--> if feasible
Supportive care		Biphosphonates should not yet be part of the adjuvant treatment of breast cancer	To replace in 'adjuvant setting'
		Supportive treatment with erythropoesis stimulating proteins can be considered in patients with symptomatic anaemia. For acute symptoms or in case of failure of erythropoesis-stimulating proteins, erythrocyte transfusions can be administered	To delete this recommendation --> FDA that now warns for use of EPO in adjuvant setting since there are data that relapse rate is higher in case of EPO !!

APPENDIX 7 : TNM CLINICAL CLASSIFICATION

T – Primary tumor

Tx Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

- Tis (DCIS) Ductal carcinoma in situ
- Tis (LCIS) Lobular carcinoma in situ
- Tis (Paget) Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.

T1 Tumor 2 cm or less in greatest dimension

- T1mi Microinvasion 0.1 cm or less in greatest dimension

Microinvasion is the extension of cancer cells beyons the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion (do not use the sum of all individual foci). The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

- T1a More than 0.1 cm but not more than 0.5 cm in greatest dimension
- T1b More than 0.5 cm but not more than 1 cm in greatest dimension
- T1c More than 1 cm but not more than 2 cm in greatest dimension

T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumor more than 5 cm in greatest dimension

T4 Tumor of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)

Note: Invasion of the dermis alone does not qualify as T4. Chest wall includes ribs, intercostals muscles, and serratus anterior muscle, but not pectoral muscle

- T4a Extension to chest wall (does not include pectoralis muscle invasion only)
- T4b Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
- T4c Both 4a and 4b, above
- T4d Inflammatory carcinoma

Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

N – regional lymph nodes

Nx Regional lymph nodes cannot be assessed (e.g. previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral Level I, II axillary lymph node(s)

N2 Metastasis in ipsilateral Level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary lymph nodes(s) in the absence of clinically evident axillary lymph node metastasis

- N2a Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
- N2b Metastasis only in clinically detected* internal mammary lymph nodes(s) and in the absence of clinically detected axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident Level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

- N3a Metastasis in infraclavicular lymph node(s)
- N3b Metastasis in internal mammary and axillary lymph nodes
- N3c Metastasis in supraclavicular lymph node(s)

*clinically detected = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine-needle aspiration biopsy with cytological examination. Confirmation of clinically detected metastatic disease by fine-needle aspiration without excision biopsy is designated with an (f) suffix, e.g., cN3a(f).

Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g., cN1. Pathological classification (pN) is used for excision or sentinel lymph node only in conjunction with a pathological T assignment.

M- Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

pTNM Pathological Classification

pT- Primary tumour

A case can be classified pT if there is only microscopic tumour in a margin. The pT categories correspond to the T categories.

Note: When classifying pT the tumour size is a measurement of the invasive component. If there is a large in situ component (e.g., 4 cm) and a small invasive component (e.g., 0.5 cm), the tumour is coded pT1a.

pN – Regional Lymph nodes

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (Level I). Such a resection will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

- pNx: Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathological study)
- pN0: No regional lymph node metastasis*.

*Isolated tumor cell clusters (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by immunohistochemistry or by routine HeE stains. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross-section. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification and should be included in the total number of nodes evaluated.

- pN1: Micrometastasis; or metastasis in 1-3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastasis detected by sentinel lymph node biopsy but not clinically detected*

  - pN1mi: micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
  - pN1a metastasis in 1-3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension
  - pN1b internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected*
  - pN1c metastasis in 1-3 axillary lymph nodes and internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected*

- pN2: Metastasis in 4-9 ipsilateral axillary lymph nodes, or in clinically detected* ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis

  - pN2a metastasis in 4-9 axillary lymph nodes, including at least one larger than 2 mm.
  - pN2b metastasis in clinically detected* internal mammary lymph node(s), in the absence of axillary lymph node metastasis

- pN3: Metastasis as described below:

  - pN3a metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes
  - pN3b metastasis in clinically detected* internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
  - pN3c metastasis in ipsilateral supraclavicular lymph node(s)

- *clinically detected is defined as detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine-needle aspiration biopsy with cytological examination.
- Not clinically detected is defined as not detected by clinical examination or by imaging studies (excluding lymphoscintigraphy).

pM – Distant Metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0, T1*	N1mi	M0
Stage II A	T0, T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1*, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note: *T1 includes T1mi

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