Proposal for risk stratified follow up of patients with breast cancer in the Yorkshire and Humber Region – South Yorkshire, Bassetlaw & North Derbyshire.

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Introduction.

Breast cancer outcomes are improving steadily with 5 year survival rates now over 80% and very low rates of loco-regional recurrence, quoted at 0.2 to 0.5% per year in the latest studies. These advances are multifactorial and due to improvements in surgery and adjuvant therapies, combined with earlier diagnosis due to screening.

As a result of this success, there is a large population of women who are long term breast cancer survivors. They may suffer an array of adverse effects from their breast cancer diagnosis and treatment. These may be severe and life changing or of more minor impact, but all cause concern and may require advice, reassurance or active therapy.

Routine follow up has not been shown to confer a survival benefit for women affected by breast cancer. It may provide psychological reassurance, allow opportunities to manage treatment related side effects, manage ongoing therapies (such as adjuvant anti-oestrogens and bisphosphonates) and ensure that appropriate breast imaging surveillance is in place. In addition post-operative issues such as cosmetic concerns, lymphoedema and psychological issues may be identified and treatment offered. It is therefore important that follow up is not merely considered to be for the purpose of detecting recurrence.

It is recommended that all women have a follow up consultation after the completion of primary treatment to review their holistic needs, ensure they are aware of their ongoing treatment recommendations, define their follow-up schedule and are offered a 'recovery package'. Education and information provision about adverse events and the symptoms and signs of recurrence should be provided.

Risk stratified follow up should be tailored to the likely needs of the patient, both in terms of the likelihood of treatment related side effects and the risks of recurrence.

Metastatic Recurrence

For the majority of women who develop recurrence, this will be in the form of metastatic disease, (20-25% over 10 years) which is substantially more common than local recurrence (<5% over 10 years). Routine scans and monitoring of serum tumour markers have never been shown to be advantageous in the earlier detection of metastatic recurrence as there is no survival advantage[1, 2]. Similarly clinical examination does not usually identify this type of recurrence at clinic visits with the majority presenting symptomatically between visits. Therefore the purpose of follow up is not for the early detection of metastatic disease, even in high risk women. Services should have rapid access facilities for urgent referral back into the system, if metastatic disease is suspected.

Local and Regional Recurrence

Local and regional recurrence (LRR) may potentially be treated with curative intent, and therefore timely diagnosis may be of value in prolonging life[3] and hence imaging surveillance is routine, although the optimal duration and frequency of such surveillance is currently being evaluated by trials such as Mammo 50[4].

Rates of local and regional recurrence (LRR) are falling and are now 0.2-0.5% per year with modern multimodal therapy[5, 6]. There are 2 broad types of LRR, which differ significantly in their prognostic impact. Women with local recurrence after mastectomy, where the disease tends to be linked with high risk primary cancer (aggressive biology, vascular invasion, advanced stage, high grade) and is often associated with metastatic recurrence[7]. This is thought to be due to residual dermal lymphatic permeation remaining after surgery and adjuvant therapy. In these women the recurrence usually presents as cutaneous

nodularity, usually within the first 2 to 3 years after therapy (60-85% occur within the first 3 years[8]), is often linked to synchronous metastatic recurrence[7] and, if not systemically disseminated, may be challenging to treat/cure locally.

Local recurrence after breast conservation is usually much more variable in timing and prognostic impact and may occur decades after surgery, especially in women with low risk disease. Although it is thought to have adverse prognostic significance[9] there are some subgroups where outcomes are good[10]. It is thought to be due to residual foci of microscopic disease within the breast which was not excised at primary surgery and did not respond to adjuvant radiotherapy and systemic therapy. It is much less likely to be associated with metastatic disease and may cured by mastectomy. This type of recurrence may present symptomatically between clinic visits with a change in the scar, breast contour deformity, a new lump or, more usually, via follow up mammography[11].

The risk of local recurrence varies between patients. Risk factors include positive margins[12-14], high grade disease[15] certain high risk immune-phenotypes (triple negative and Her-2 positive cancer[16]), vascular invasion[17], omission of adjuvant radiotherapy or systemic therapy and young patient age[16]. Many of these risk factors will more than double the rate of local recurrence relative to the UK average. The risk of recurrence tends to be in the first few years in patients with high risk disease, where it has more adverse prognostic significance[16] but may occur over several decades in women with low risk (low grade, ER+) disease. There are on line calculators which may be used to estimate LRR risk such as IBTR![18]. For women with DCIS only, recurrence risk is minimal after mastectomy (1%) but higher after conservation surgery and risk may be predicted using a range of scoring algorithms such as the modified van Nuy's Prognostic Index[19] and more recently with DCIS arrays[20]. The risk is once again dependant on tumour size, biology, margin status, adjuvant therapy and age.

Treatment Related Adverse Events.

A major cause of concern and reduced quality of life for breast cancer survivors are treatment related side effects. The majority of these may be treated and should be actively enquired about so that treatment may be offered.

Some side effects are transient and usually resolve spontaneously (radiotherapy induced breast inflammation, chemotherapy induced hair loss), with management offered during the treatment phase. Some only occur later. Examples include depression, anxiety, lymphoedema, menopausal symptoms, joint pain and cosmetic concerns. An appointment after completion of active treatments is therefore beneficial.

Risk Stratified Imaging Follow-up

For most women, mammographic screening after breast conservation surgery is advised on a yearly or biennial basis for 5 years after diagnosis. There is evidence that early detection of local recurrence may have a survival advantage with recurrences of 10mm having better survival rates than those with 20mm tumours[3].

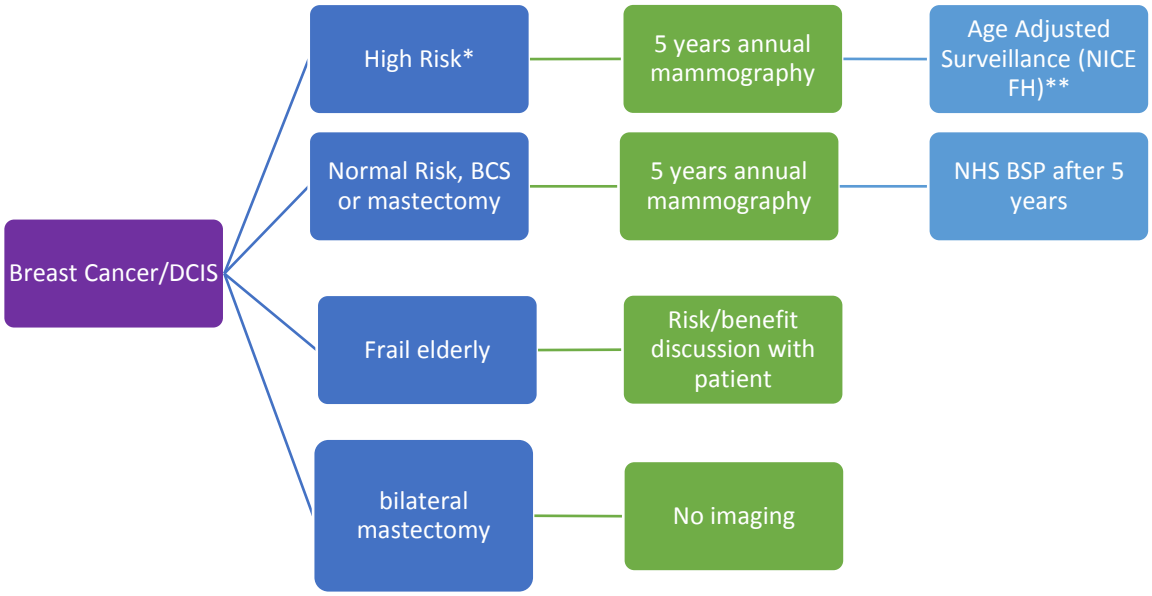
Thereafter routine 3 yearly screening via the NHS BSP is advised unless they are at an increased familial risk, when they may be offered extended enhanced screening as per the NICE Familial breast cancer guidelines[21]. Women who are known BRCA gene carriers have a 4 fold increased risk of developing a new contralateral primary cancer and a 10-25% increased risk of an IBTR compared to non-BRCA carriers[22] and hence surveillance for these women should be more frequent up to age 70 (unless they have had bilateral mastectomy in which case they will require no formal breast imaging).

There are also a small minority of women who may theoretically benefit from MRI surveillance if they have had a mammographically occult primary cancer and have dense breasts. MRI is the most sensitive modality for the detection of invasive breast tumour recurrence[3] compared to clinical examination and mammography but is not currently funded by the NHS for this indication.

For women who have had a mastectomy for their primary cancer, mammographic surveillance is simply enhanced screening of their contralateral breast. For older women who are over the age of normal screening, and especially those who are frail or suffer with significant co-morbidities, there is little logic in arranging contralateral breast mammography. This should be discussed on a case by case basis with the patient.

For women who have had breast conservation, imaging of the affected breast is performed to look for local recurrence. This is usually performed annually for 5 years, followed by

routine triennial screening via the NHS BSP. The below diagram shows the algorithm for breast imaging following a breast cancer diagnosis.



Anti-oestrogen therapy

All women with ER positive breast cancer are offered a minimum of 5 years of anti-oestrogen treatment. This is in the form of tamoxifen (plus or minus GnRH agonist injection) for premenopausal women or an aromatase inhibitor (AI) if post-menopausal. For women with high risk cancers, these treatments may be extended to 10 years. Whilst patients currently being commenced on therapy will have treatment plans that specify whether 5 or 10 years of therapy is appropriate, women diagnosed more than 2 years ago may not be aware of the benefits of extended adjuvant therapy and review at 5 years allows the opportunity for review of their ideal therapy duration. Patients who have undergone premature ovarian suppression or started on an AI should have a DEXA scan and appropriate bone health management. The recommendation for DEXA scans needs to take into account concurrent use of adjuvant bisphosphonates to prevent recurrence and patients receiving adjuvant bisphosphonates do not routinely require DEXA scanning.

Adjuvant BPs

Post-menopausal women with invasive breast cancer at sufficient increased risk (>12% 10 year risk of breast cancer death) will be offered a bisphosphonate for 3 years duration in order to reduce the risk of bone recurrence and improve breast cancer survival. Refer to local guidelines for the recommended bisphosphonate regimen and schedule.

Risk Stratified Clinical Follow-Up

As mentioned above clinical follow up has little value for the diagnosis of metastatic recurrence and rarely identifies local recurrence which is usually identified after symptomatic self-referral or by routine imaging. Imaging is much more sensitive than clinical examination in this respect. One large Dutch study found that 262 imaging tests versus nearly 1400 clinical examinations were needed to diagnosis one LRR[11]. However women may have a range of clinical concerns and side effects relating to their adjuvant therapy and suffer side effects from their surgery, radiotherapy or chemotherapy.

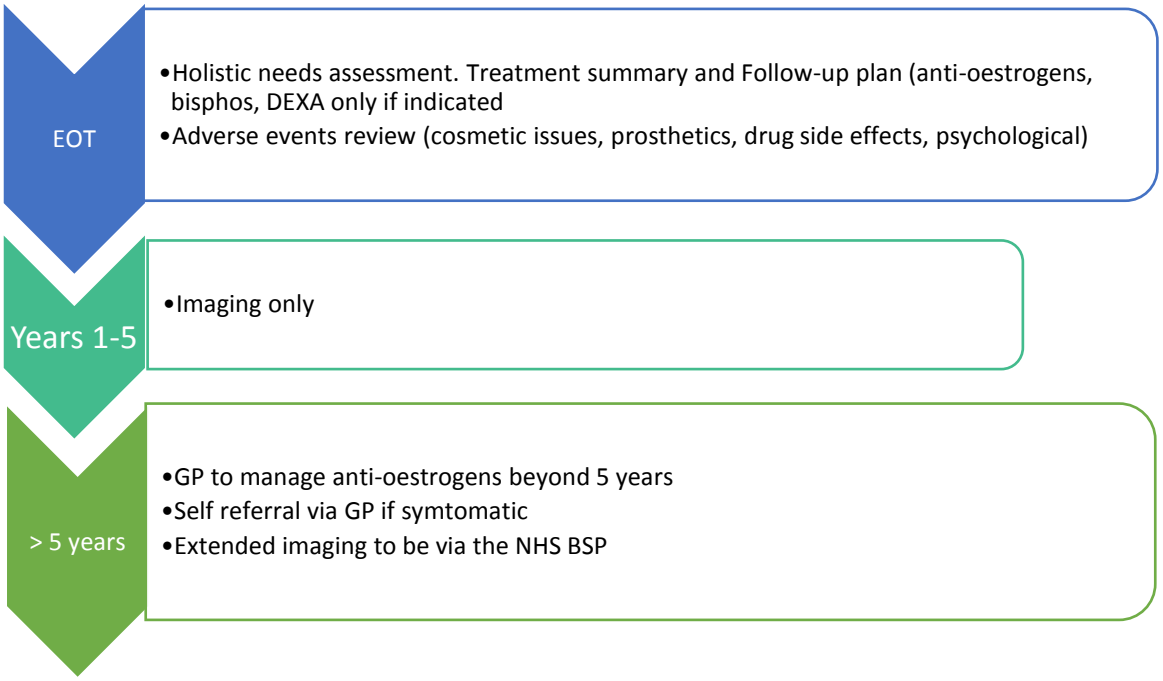
The recommendation is to see all women on completion of treatment (end of treatment [EOT] appointment) to review the follow-up plan, ensure they have no side effects from their anti-oestrogens or their previous treatments, ensure they have appropriate mammographic surveillance arranged and ensure they have no major psychological issues or informational needs.

A low risk group of women who are unlikely to benefit from clinical follow up for their breast cancer may be discharged at this end of treatment appointment from clinical follow up if they have no ongoing problems following therapy. This group include:

- Patients who have had lower risk cancers for metastatic recurrence *(NPI <3.4 if ER negative and <4.4 if ER positive), and if Oncotype testing has been performed (in ER+ve, HER2-ve , node negative patients), those patients with lower-risk Recurrence score (<25)*
- Low risk for loco-regional recurrence (ER+ve, <2cm, HER2-ve, node negative, clear margins)
- DCIS only
- No serious adverse events at their end of treatment appointment

- Patients whose life expectancy is likely to be low due to non-breast cancer causes (extreme old age, frailty, severe co-morbidities, prior diagnosis of terminal non-breast cancer) regardless of breast cancer risk.

A schematic for low risk clinical follow up is shown below:

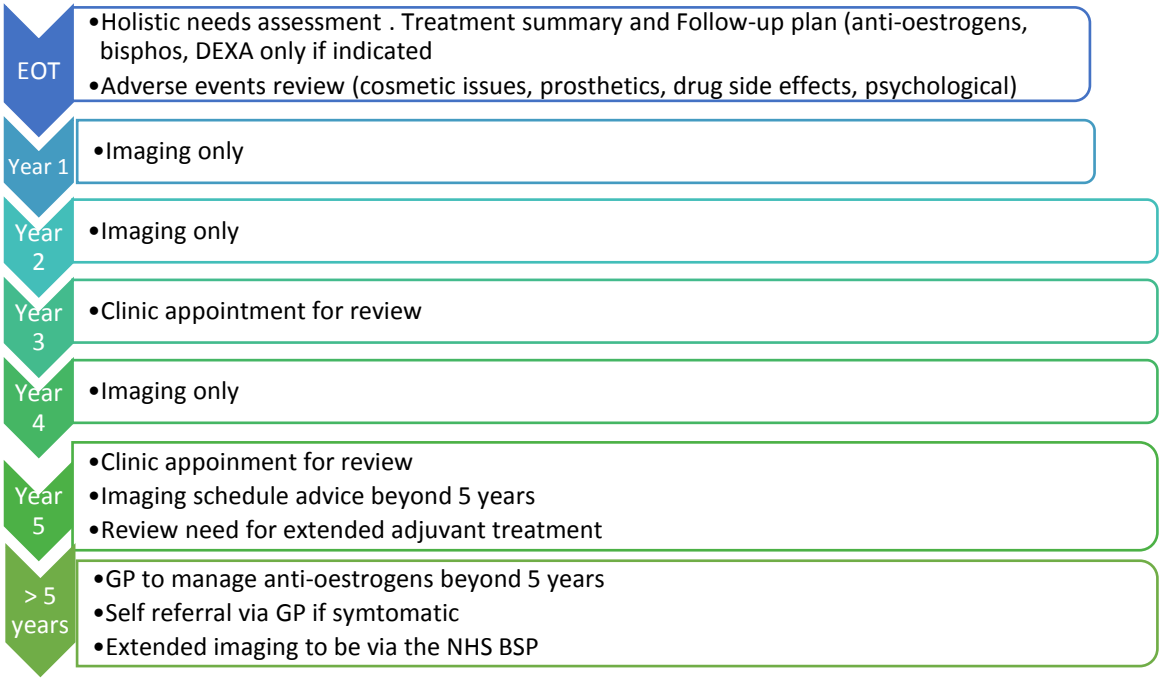


Patients who are likely to benefit from face to face consultation at 3 and 5 years will follow the standard clinical follow up pathway. These patients include:

- Higher risk patients (all chemotherapy and biological therapy, axillary clearance surgery)
- Young patients with possible fertility issues
- Patients who struggled psychologically with diagnosis or treatment or have a history of mental health problems, or patients with learning difficulties where self-care may be a concern
- Patients who did not comply with standard management
- Patients who suffer side effects from their cancer therapy and would benefit from ongoing review (cardiac problems after chemotherapy, significant breast or arm oedema, post-operative pain etc).

Patients will be seen at 3 and 5 years post diagnosis, as most NHS trusts have the facilities to book appointments up to 2 years in advance. At 5 years they will be discharged to the care of the GP with instructions about whether they require ongoing anti-oestrogen therapy. The GP will manage longer term therapy beyond 5 years.

A schematic for standard clinical follow up is shown below:



References

1. Bornhak S, Heidemann E, Herschlein HJ, Simon W, Merkle E, Widmaier G, Ernst R, Greulich M, Bittner R, Kieninger G *et al*: **Symptom-oriented follow-up of early breast cancer is not inferior to conventional control. Results of a prospective multicentre study**. *Onkologie* 2007, **30**(8-9):443-449.
2. Joseph E, Hyacinthe M, Lyman GH, Busch C, Demps L, Reintgen DS, Cox CE: **Evaluation of an intensive strategy for follow-up and surveillance of primary breast cancer**. *Ann Surg Oncol* 1998, **5**(6):522-528.
3. Robertson C, Arcot Ragupathy SK, Boachie C, Dixon JM, Fraser C, Hernandez R, Heys S, Jack W, Kerr GR, Lawrence G *et al*: **The clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer: systematic reviews registry database analyses and economic evaluation**. *Health Technol Assess* 2011, **15**(34):v-vi, 1-322.
4. Dunn JA, Donnelly PK, Marshall A, Wilcox M, Watson E, Young A, Balmer C, Ramirez M, Hartup S, Maxwell AJ *et al*: **Follow-up in early breast cancer--a surgical and radiological perceptive**. *Clin Oncol (R Coll Radiol)* 2014, **26**(10):625-629.
5. van Laar C, van der Sangen MJ, Poortmans PM, Nieuwenhuijzen GA, Roukema JA, Roumen RM, Tjan-Heijnen VC, Voogd AC: **Local recurrence following breast-conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population-based cohort of 1143 patients**. *Eur J Cancer* 2013, **49**(15):3093-3101.
6. Bodilsen A, Offersen BV, Christiansen P, Overgaard J: **Pattern of relapse after breast conserving therapy, a study of 1519 early breast cancer patients treated in the Central Region of Denmark 2000-2009**. *Acta Oncol* 2016, **55**(8):964-969.
7. Willner J, Kiricuta IC, Kolbl O: **Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis**. *Int J Radiat Oncol Biol Phys* 1997, **37**(4):853-863.
8. Jager JJ, Volovics L, Schouten LJ, de Jong JM, Hupperets PS, von Meyenfeldt MF, Schutte B, Blijham GH: **Loco-regional recurrences after mastectomy in breast cancer: prognostic factors and implications for postoperative irradiation**. *Radiother Oncol* 1999, **50**(3):267-275.
9. Anderson SJ, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, Geyer CE, Jr., Wickerham DL, Costantino JP, Wolmark N: **Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer**. *J Clin Oncol* 2009, **27**(15):2466-2473.
10. Miles RC, Gullerud RE, Lohse CM, Jakub JW, Degnim AC, Boughey JC: **Local recurrence after breast-conserving surgery: multivariable analysis of risk factors and the impact of young age**. *Ann Surg Oncol* 2012, **19**(4):1153-1159.
11. Geurts SM, de Vegt F, Siesling S, Flobbe K, Aben KK, van der Heiden-van der Loo M, Verbeek AL, van Dijck JA, Tjan-Heijnen VC: **Pattern of follow-up care and early relapse detection in breast cancer patients**. *Breast Cancer Res Treat* 2012, **136**(3):859-868.
12. Vos EL, Siesling S, Baaijens MHA, Verhoef C, Jager A, Voogd AC, Koppert LB: **Omitting re-excision for focally positive margins after breast-conserving surgery does not impair disease-free and overall survival**. *Breast Cancer Res Treat* 2017, **164**(1):157-167.
13. Rivere AE, Chiasson KF, Corsetti RL, Fuhrman GM: **An Assessment of Margins after Lumpectomy in Breast Cancer Management**. *Am Surg* 2016, **82**(2):156-160.
14. Houssami N, Macaskill P, Marinovich ML, Morrow M: **The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis**. *Ann Surg Oncol* 2014, **21**(3):717-730.

15. Truong PT, Lesperance M, Culhaci A, Kader HA, Speers CH, Olivotto IA: **Patient subsets with T1-T2, node-negative breast cancer at high locoregional recurrence risk after mastectomy**. *Int J Radiat Oncol Biol Phys* 2005, **62**(1):175-182.
16. Rezai M, Kraemer S, Kimmig R, Kern P: **Breast conservative surgery and local recurrence**. *Breast* 2015, **24 Suppl 2**:S100-107.
17. Truong PT, Yong CM, Abnousi F, Lee J, Kader HA, Hayashi A, Olivotto IA: **Lymphovascular invasion is associated with reduced locoregional control and survival in women with node-negative breast cancer treated with mastectomy and systemic therapy**. *J Am Coll Surg* 2005, **200**(6):912-921.
18. Sanghani M, Truong PT, Raad RA, Niemierko A, Lesperance M, Olivotto IA, Wazer DE, Taghian AG: **Validation of a web-based predictive nomogram for ipsilateral breast tumor recurrence after breast conserving therapy**. *J Clin Oncol* 2010, **28**(5):718-722.
19. Silverstein MJ: **The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast**. *Am J Surg* 2003, **186**(4):337-343.
20. Solin LJ, Gray R, Baehner FL, Butler SM, Hughes LL, Yoshizawa C, Cherbavaz DB, Shak S, Page DL, Sledge GW, Jr. *et al*: **A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast**. *J Natl Cancer Inst* 2013, **105**(10):701-710.
21. Excellence NIfHaC: **Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer**. Published date: June 2013 Last updated: August 2015.
22. Pierce LJ, Phillips KA, Griffith KA, Buys S, Gaffney DK, Moran MS, Haffty BG, Ben-David M, Kaufman B, Garber JE *et al*: **Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy**. *Breast Cancer Res Treat* 2010, **121**(2):389-398.