Effectiveness of different regimens after the treatment for primary breast cancer

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

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Executive summary

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Executive summary

Background

Survival following breast cancer treatment is increasing. A key question is, therefore, how best to follow up patients after completion of primary treatments. There is considerable debate about the role and optimal organisation of the follow-up of patients following treatment for primary breast cancer. Data indicate that the early detection of ipsilateral breast tumour recurrence or ipsilateral second primary cancer [ipsilateral breast tumour recurrence (IBTR)] in the treated breast and detection of new primary cancers in the contralateral breast [metachronous contralateral breast cancer (MCBC)] is beneficial in terms of survival. This raises the question as to how best to identify ipsilateral local recurrence of disease and new contralateral primary breast cancer at the earliest possible stage. Surveillance mammography is directed towards the detection of IBTR and MCBC. However, the optimal frequency of mammographic surveillance and the length of follow-up are unclear.

Objectives

1. Identify feasible management strategies for surveillance and follow-up of women after treatment for breast cancer in a UK setting.
2. Determine the effectiveness of differing surveillance and follow-up regimens after treatment for breast cancer.
3. Estimate the costs of differing surveillance and follow-up regimens after treatment for breast cancer.
4. Estimate the cost-effectiveness of differing surveillance and follow-up regimens after treatment for breast cancer.
5. Identify future research needs.

Methods

The work comprised a survey of UK breast surgeons and radiologists to identify current UK surveillance mammography regimens and inform feasible alternative regimens. In addition, we undertook two discrete systematic reviews to determine the clinical effectiveness of differing surveillance mammography regimens carried out after treatment for primary breast cancer on patient health outcomes and the test accuracy of surveillance mammography in the detection of IBTR and MCBC. Sensitive search strategies of several major bibliographic databases were conducted from 1990 to mid 2009. We undertook statistical analysis of individual patient data [West Midlands Cancer Intelligence Unit (WMCIU) Breast Cancer Registry and Edinburgh data sets] and economic modelling using the systematic reviews results, existing data sets, and focused searches for specific data analysis to determine the effectiveness and cost–utility of differing surveillance regimens. We developed an economic model in the form of a Markov model to represent the alternative surveillance regimens modelled at varying surveillance intervals. Parameter estimates for the Markov model were determined from a survey of existing data sets, a series of systematic reviews, and focused searches for specific data.

Results

Survey

We received responses from 17% (183/1048) of those surveyed, 64% were surgeons and 35% radiologists and were based in 105 NHS trusts across the UK. The majority initiate surveillance mammography 12 months post surgery for women who have had breast-conserving surgery (BCS) (87%) and for women who have had a mastectomy (79%). Annual surveillance mammography was the most commonly reported surveillance mammography frequency for women after breast-conserving surgery (BCS) or after mastectomy (72% and 53%, respectively), with biennial mammography the next most frequently reported (12% and 30%, respectively). Most (74%, 136/182) discharge women from surveillance mammography and they do this most frequently 10 years after surgery. The majority (82%, 148/180) do discharge from clinical follow-up and most frequently at 5 years. Just over half (55%, 98/179) responded that they discharge women to the NHSBSP if eligible. Combining initiation, frequency and duration of surveillance mammography resulted in 54 differing surveillance regimens for women after BCS and 56 for women following mastectomy. The most commonly followed four regimens for women after BCS or after mastectomy are to initiate surveillance mammography 12 months after surgery, conduct annual surveillance mammography with indefinite duration (12%, 19/154, 7%, 10/136 respectively); or discharge from both clinical and mammographic surveillance at 5 years (14%, 22/154, 10%, 13/136 respectively); or 10 years (12%, 18/154, 11%, 15/136 respectively) after surgery or discharge from clinical follow-up at 5 years with continued mammographic surveillance until 10 years (13%, 20/154, 8%, 11/136 respectively). Our findings suggest that, although common patterns in surveillance mammography practice exist, there is considerable variation in the combinations of start, frequency, duration and discharge from surveillance mammography. Our findings reflect the different guidance given by the various professional organisations with an interest in surveillance after breast cancer, in combination with the local protocols of the respondents.

Systematic reviews

Eight studies, involving 3775 women, were included in the systematic review of clinical effectiveness. Although none of the tests of interest was used for the same purpose (i.e. routine or non-routine surveillance) in all studies, results suggest that the use of surveillance mammography offers a survival benefit compared with a surveillance regimen that does not include surveillance mammography.

Nine studies, involving 3724 women, were included in the systematic review of test performance. For the detection of IBTR in routine surveillance where there was no prior suspicion of recurrence, the highest sensitivity was shown for magnetic resonance imaging (MRI) and combined MRI/clinical examination at 100%, whereas the highest specificity was shown for surveillance mammography alone (97%) although this was obtained in a highly select population. Clinical examination alone had the lowest sensitivity (50%) and surveillance mammography with clinical examination had the lowest specificity (67%). For the detection of IBTR in patients for whom there was a suspicion of recurrence, sensitivity of tests varied from 50% (surveillance mammography) to 100% (MRI) and specificity ranged from 31% (ultrasound) to 96% (MRI). In the detection of MCBC in routine surveillance, sensitivity ranged from 0% (clinical examination) to 100% for the combination of surveillance mammography, clinical examination, ultrasound and MRI. Specificity ranged from 50% for surveillance mammography, MRI or clinical examination to 99% for the combination of surveillance mammography and ultrasound. Again, the highly selected nature of the population should be borne in mind in the context of these results.

Analyses of the WMCIU and Edinburgh data sets

The analyses showed that IBTR has an adverse effect on survival that is independent of known risk factors. Furthermore, in those women experiencing a second tumour (either IBTR or MCBC) the size of this second tumour is important, with those women with tumours of > 20 mm in diameter being at a significantly greater risk of death than those with no recurrence or those whose tumour was < 10 mm in diameter.

Economic evaluation

The results of the economic model should be considered exploratory and interpreted with caution given the paucity of data available to inform the economic model. In the base-case analysis, the strategy with the highest net benefit, and therefore the most likely to be considered cost-effective, was surveillance mammography alone, provided every 12 months at a societal willingness to pay for a quality-adjusted life-year (QALY) of either £20,000 or £30,000. The incremental cost-effectiveness ratio for surveillance mammography alone every 12 months compared to no surveillance was £4727. This result holds for women previously treated for their primary cancer with either breast-conserving surgery or mastectomy or for women who suffer IBTR. The results of the model are sensitive to changes in the incidence of recurrent cancer. When the expected incidence is increased towards the maximum that could be expected (approximately 0.008 per annum) clinical surveillance plus mammography has an incremental cost per QALY of approximately £30,000. As the surveillance interval and incidence increase regimens that are more costly but more effective (proxied by the MRI plus clinical surveillance) may also have incremental costs per QALY < £30,000. This suggests that there may be some scope for research into alternative technologies that could be used for surveillance.

We did not conduct probabilistic sensitivity analysis due to statistically imprecise and limited data. We did conduct both one-way and multiway sensitivity analyses, however. Sensitivity analysis included varying the probability of cancer, inflating the risk of death from cancer, inflating the risk of cancer progression in undiagnosed or untreated cancers, varying diagnostic accuracy of the surveillance tests and varying costs and age.

The results of the model were sensitive to incidence and other factors, for example age, tumour characteristics, etc., which might define women with greater or lesser likelihoods of developing an IBTR or MCBC. These results suggest that a more intensive follow-up of women with greater likelihood of IBTR or MCBC may be worthwhile. Conversely, for women with less likelihood of IBTR or MCBC it may be more cost-effective for surveillance to be performed less often (every 2 or 3 years) with mammography alone. As the surveillance interval and incidence increase, strategies that are more costly, but more effective, may also have incremental costs per QALY below typical threshold values.

Limitations

Despite considerable and rigorous methods adopted for both systematic reviews, we found few studies meeting our inclusion criteria, none of which were a randomised controlled trial (RCT). The limited and variable nature of the data available precluded any quantitative analysis. There was no useable evidence contained in the Breast Cancer Registry database to assess the effectiveness of surveillance mammography directly. As few data were available, the economic results need to be treated cautiously. In particular, a series of simplifying assumptions were made about disease progression and prognosis of recurrent cancers. We took care to err on the side of caution when making these assumptions, however, in order to minimise the possibility of overestimating the value of surveillance. Furthermore, few data relevant to the UK were available on health-state utilities. We assumed that the data used were applicable to the UK and the health states modelled.

Conclusions

Implications for service provision

Surveillance is likely to improve survival, with a strategy of mammography alone, every 12–24 months, appearing to have the highest net benefits. The evidence base on which to recommend any change in current practice is relatively weak, however. Careful consideration should be given to stratification of patients to ensure maximum benefit to ensure optimal use of resources, with those women with a greater likelihood of developing IBTR or MCBC being offered more comprehensive (e.g. mammography and clinical follow-up) and more frequent surveillance (every 12 months). The greatest net benefit for women with the lowest likelihood of IBTR or MCBC is mammography only every 3 years. Although there may be arguments for delivering a varying surveillance regimen this would present challenges and, without provision of information and reassurance, might be a source of unnecessary anxiety for patients.

Suggested research priorities

- The utility of the national data sets could be improved. In addition to the nationally agreed collection, it would be extremely valuable to record details of mode of detection for IBTR or MCBC; the frequency of the clinical and mammographic surveillance regimens, and how this varies over time; and whether a woman's IBTR or MCBC was detected during routine surveillance or as a result of it causing symptoms for the patient.
- There is a need for high-quality, direct head-to-head studies comparing the diagnostic accuracy of tests used in the surveillance population. Further primary work should also consider whether the use of existing technologies, such as MRI, which may have better performance, could be worthwhile for patients at high risk of IBTR or MCBC. An economic analysis should form part of such work.
- Further economic evaluation modelling should compare differing mixed regimens of clinical follow up, delivered in lower cost settings, combined with surveillance mammography in the long term. This would be important to inform further primary research (e.g. an RCT) which could then focus on regimens that appeared most promising.
- A definitive RCT would be ideal and, although costly, could focus on those women at higher risk of IBTR or MCBC. The interventions considered might include mammography and MRI, for those at the highest risk, or surveillance mammography of 1 year versus a longer time interval, for example 3 years. Such a trial might also compare more sophisticated surveillance regimens, which vary not only in terms of the frequency of mammography but also in terms of the frequency and setting of clinical follow-up. An economic evaluation should form part of any RCT.

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/47/01. The contractual start date was in June 2008. The draft report began editorial review in February 2010 and was accepted for publication in September 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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