Health technology assessment of imaging technologies for breast cancer screening and follow-up
Koleva-Kolarova, Rositsa Georgieva

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Chapter 7.
General discussion
Breast cancer is one of the most commonly diagnosed cancers worldwide and a leading cause of mortality amongst women. Many European countries have successfully implemented population-wide screening programmes with the aim to detect cancer as early as possible so adequate treatment could be applied and ultimately survival could be improved. Despite the wider implementation of regular breast cancer screening programmes, whether the resulting mortality reductions, regarded as the principal benefit of the service screening programmes, outweigh the harms associated is still a controversial discussion with no sound conclusion. Amongst the controversial areas which are most often debated are the natural history of the disease which relates to the proportion of the overdiagnosed and overtreated tumours, the characteristics of the screening test (sensitivity and specificity of mammography, tomosynthesis, and magnetic resonance imaging (MRI) in relation to breast density, and the impact of different types of treatment (surgery and systemic (neo) adjuvant therapies) on the survival of breast cancer patients, and their synergistic or possibly competitive effects which lessen the need for screening.

**Natural history of breast cancer**

In general, the natural course of breast cancer includes the progression of breast epithelial cells to ductal carcinoma in situ (DCIS) and then to invasive disease or directly to invasive disease. However, it has been proven that not all DCIS would actually progress to an invasive tumour and become clinically significant. In addition, there is a proportion of tumours detected by the screening mammography that are indolent and would never progress (some of them may actually regress naturally) or become clinically evident in a woman’s lifetime. The proportion of the DCIS which is considered clinically insignificant and the indolent tumours are usually referred to as overdiagnosis. Defining and quantifying overdiagnosis is challenging and there
are three important perspectives which can be used in this process.\textsuperscript{5} From a patients’ perspective cancers detected by screening which would not have become clinically evident in a woman’s lifetime in the absence of screening are considered overdiagnosis.\textsuperscript{6} The statistical perspective provides a more technical definition according to which the cases whose lead time exceeds their remaining years of life are considered overdiagnosis.\textsuperscript{7} From a social perspective overdiagnosis occurs when the patients are given diagnosis of a condition which is not a false positive but carries an unfavourable benefit-harm ratio.\textsuperscript{8} So far there is no consensus on the degree of overdiagnosis nor the most appropriate methodological approach to estimate it.\textsuperscript{9-11} Barratt and Jacklyn reported that in contemporary screening programmes 15-30\% of breast cancers detected in women who regularly attend screening were overdiagnosed.\textsuperscript{5} These estimations were based on data from randomised controlled trials and well conducted observational studies. Lower, as well as much higher estimates were reported from studies with high risk of bias.\textsuperscript{5,8} Another issue associated with overdiagnosis is overtreatment as women with overdiagnosed breast cancers would receive treatment similar to that of the women with actual disease.\textsuperscript{5} Overtreatment results in side effects, lowering the quality of life of the women and unnecessary costs.\textsuperscript{9-11} Overdiagnosis and resulting overtreatment have great implications for the clinical and cost-effectiveness of regular breast cancer screening programmes as they can impact negatively the health and quality of life of patients which are being given unnecessary tests, some of which invasive and potentially causing complications, and treatments which can be risky and causing adverse effects.

\textit{The characteristics of the screening test}

Ideally a screening test should be both very sensitive and specific to detect disease while it has not yet exhibited clinical symptoms. In addition, a screening test should be affordable, non-
invasive and easily available. Mammography is relatively cheap and affordable, non-invasive and available in Western Europe. Mammography has high specificity (>95%)\textsuperscript{12} for detecting breast cancer which would benefit the women who actually have the disease. However, when screening in large asymptomatic population groups the high specificity of the test may result in a considerable number of false positive results which would cause distress in the screened women and incur additional unnecessary imaging tests, invasive biopsies and even treatment. Mammography has shown further limitations, i.e. lower sensitivity (75.8%)\textsuperscript{13}, especially in women with dense breast tissue which resulted in a proportion of cancers being underdiagnosed in the screening setting and treated when clinically evident. To overcome these shortcomings introducing complementary imaging with ultrasound and magnetic resonance imaging are being suggested and studies on the potential of replacing mammography by digital tomosynthesis are being performed.

**The available treatment**

According to the ESMO guidelines the treatment options for women diagnosed with primary early stage breast cancer include surgery (lumpectomy or mastectomy) with or without radiotherapy and (neo) adjuvant systemic therapy.\textsuperscript{14} Both screening and treatment options for primary and advanced breast cancer have improved over time, thus the observed reduction in the mortality from the disease is jointly attributable to the advances in imaging technologies and adjuvant therapies; however, it is yet unclear and debatable what the exact contribution of regular screening and treatment to the mortality reduction from breast cancer is.\textsuperscript{15-19} Modelling studies have analysed the issue and reported that advances in systemic therapies for breast cancer have decreased the absolute benefit of regular screening but not the relative benefit due to their impact on survival from the disease\textsuperscript{17}, and estimated the contribution of adjuvant
therapies to breast cancer mortality reduction to be ranging from 12% to 20.9%, while the reduction in the mortality rates attributable to screening was predicted to be from 7.5% to 22.7%\textsuperscript{18,19}, concluding that adjuvant systemic therapy and screening reduced breast cancer mortality in similar amounts.\textsuperscript{19} Recent studies have sparked even greater controversies claiming that the contribution of mass mammography to mortality reduction from breast cancer was overestimated\textsuperscript{10,15,16} and did not exceed mortality reduction achieved by physical examination\textsuperscript{15}, and other factors than screening\textsuperscript{16}, in particular improved systemic therapies\textsuperscript{10}, contributed to the reduction of breast cancer death risks. These finding were also confronted and argued, mainly for its methodological approaches.\textsuperscript{11} Such recent developments suggested that systemic treatments could have synergistic and even competitive effects to regular screening on the mortality reduction from breast cancer, however, the short- and long-term adverse effects of these treatment and their costs should not be underestimated.

\textbf{How to tackle the uncertainties and controversies in breast cancer screening?}

Given the uncertainties and controversies surrounding breast cancer screening at present the question of utmost importance to be answered is: “Is regular breast cancer screening here to stay?” The best way to answer this question would be to perform one or preferably more randomised controlled trials. However, it will take a long period of time and large groups of participants to evaluate the effects on mortality reduction from the disease and the potential benefits and harms associated with regular mammographic screening. One way to evaluate regular mammographic screening without having to wait long or unethically withdraw access to mammography to women who are already entitled to it, is to apply decision analytical models and perform health technology assessment analyses.
The role of health technology assessment and decision analytical models

Increasingly, health technology assessment is recognised as a standard part or tool for policy makers to decide on the implementation and the reimbursement of innovative technologies in health care. Decision analytical models provide the opportunity to evaluate health interventions and compare scenarios to find the optimum policy without having to trial each variant. Models can extrapolate the results of randomised controlled trials to different population sub-groups and provide health technology assessment of different health services and programmes. Decision analytical models are often used alongside randomised controlled trials to inform decision making. Decisions concerning whether to implement or abolish a health intervention have large budgetary impact and consequences for the population involved, hence, they pose stringent requirements on the reliability and the accuracy of the model outcomes.

In this thesis we critically reviewed other published models for breast cancer screening with multiple applications and critically assessed their outcomes by comparing them to randomised controlled trials and cost-effectiveness acceptability thresholds. After this we applied our approach to evaluate new screening regimens for primary breast cancer patients with earlier starting ages and one-stop shop imaging (positron emission tomography and computed tomography (PET/CT) for diagnosing and treatment selection for patients suspected with distant relapse. For this purpose, a previously published and validated simulation decision analytical model was modified and applied.

Assessment of decision analytical models applied to inform decision making in regular breast cancer screening

Various decision analytical tools have been modelled and applied to study breast cancer screening of the general population. As the outcomes of these models are fundamentally
important to policy makers, healthcare professionals and patients alike, their reliability and accuracy is crucial and should be subjected to continuous assessment.

Models are always a simplification of the real world and as such are prone to pitfalls. Current modelling in breast cancer was found to bear high risk of bias in their output mainly due to unsystematically selected input data, modelling assumptions regarding the natural history of the disease and lack of external validation. As a result, models with multiple applications tended to overestimate the effect of regular breast cancer screening on mortality reduction from the disease (Chapter 2). Such overestimations can have substantial impact on the healthcare budgets and on the screened population, thus, more stringent requirements should be posed on models’ accuracy and reliability. It is difficult to quantify which of the afore mentioned issues contributed the most to the risk of bias and overestimation in mortality reduction, therefore, we assumed that the selection of input data, the modelling assumptions, the lack of external validation, and the omission of potential harms of screening in the analysis were equally important.

**Implications for future modelling methodology and research**

Primary data in the field of breast cancer screening in terms of large randomised controlled trials is unlikely to be produced due to the associated costs, follow-up periods and ethical considerations. Therefore, it can be expected that the role and the involvement of decision analytical models to inform decision making for breast cancer screening will increase. In addition, performing health technology assessment and economic evaluation of new regimens and novel imaging modalities for breast cancer prior to their wide clinical implementation is warranted. Therefore, future modelling should focus on selecting a modelling type that is flexible and produces stable outcomes. Systematically evaluated data should be used for
calibrating the input parameters of simulation models. Regarding the natural history of breast
cancer and how it should be modelled, the application of aggregated incidence together with
individual risk factors and allowing for variable lead times depending on the type of tumour
could overcome some of the issues current modelling is faced with, e.g. lack of agreement on
how to model the biological behaviour of ductal carcinomas in situ and their progression to
invasive breast cancer or regression to indolent tumours, e.g. overdiagnosis and associated
overtreatment. Further, model validation should ensure that the model is representing
sufficiently the system which was built to represent and evaluate. As model outcomes are
affecting the decision whether to adopt a new technology and disseminate it widely into clinical
practice, this calls for a higher validation status and external validation is regarded as being the
superior approach. In order to ensure that sufficient validations efforts are made, a unified and
transparent approach on model validation reporting should be adopted.

Health technology assessment of alternative population breast cancer screening
scenarios

Currently the recommended starting age of population breast cancer screening is 50 years, but
there are debates that women may benefit from regular screening starting from an earlier age.
Previous economic evaluations have found that there were screening regimens starting from
earlier ages which have demonstrated value for money, however, there was no sound
recommendation regarding their implementation. Therefore, an economic analysis of three
breast cancer screening scenarios starting from 46, 48 and 50 years, respectively, were assessed
to report on the potential benefits, harms and cost-effectiveness (Chapter 3). The number of
additional expected harms was relatively small in both alternative scenarios (e.g. 46 and 48)
and the difference in the incremental cost-effectiveness ratios (ICERs) was not large,
introducing two additional screening rounds to the current biennial breast cancer screening in the Netherlands is justifiable from a cost-effectiveness and benefit-harms point of view.

**Health technology assessment of novel imaging modalities for follow-up and treatment selection**

Prognosis after primary breast cancer is usually favourable, however, around 10% of the patients will actually develop distant relapse within the 5 years after initial diagnosis and treatment.\(^{24,25}\) Currently metastatic breast cancer is considered amenable to palliative rather than curative intent, however, earlier diagnosis of distant relapse could improve the quality of life of these patients by decreasing the potential delay in treatment and relief of symptoms.\(^{26}\) Novel combined PET/CT with different tracers offer a one-stop shop diagnostic imaging for distant relapse after primary breast cancer which can overcome the shortcomings of conventional imaging techniques and potentially guide and monitor treatment selection and response. As these imaging modalities contribute to the increasing costs in health care, prior evaluation of their efficiency and effectiveness is warranted.

As standard work-up imaging for detecting distant recurrence after initial breast cancer screening could be inconclusive regarding the diagnosis the potential of new imaging modalities should be explored. PET/CT with 16\(\alpha\)-[18F]fluoro-17\(\beta\)-oestradiol (FES) or 2-[18F]fluoro-2-deoxy-D-glucose (FDG) tracers have already established its clinical value for resolving clinical dilemma in suspected distant relapse after primary breast cancer,\(^{27,28}\) however, their cost-effectiveness in diagnosing and personalising treatment in metastatic breast cancer is yet to be determined. The application of PET/CT with FES and FDG tracers as an upfront one-stop shop diagnostic modality decreased the number of performed imaging tests and the number of false positive results in women symptomatic for distant recurrence (Chapter 145...
However, both PET/CT diagnostic strategies incurred additional costs as compared to the standard diagnostic work-up. The FES-PET/CT strategy was most beneficial in terms of avoided invasive biopsies and decreased false-negative results (Chapter 4).

In addition, FES-PET/CT may guide therapeutic decision making as it provided insights in oestrogen receptor status and potential heterogeneity herein, and thus could reduce costs resulting from ineffective therapy. FES-PET/CT could provide more information regarding metastatic recurrence than conventional approach, and might have added value in therapy selection, individualised treatment and follow-up resulting in increase of survival, however, the cost-effectiveness of this approach has to be established. Results from randomised controlled trials showed that the application of non-hormonal targeted therapies in patients with metastatic breast cancer prolonged the overall survival and the progression-free survival of these patients, however, the extent to which their life was prolonged is not yet clear. Therefore, a meta-analysis was performed to assess the median contribution of targeted therapies to overall and progression-free survival. The application of non-hormonal targeted therapies prolonged the median overall survival and progression-free survival of receptor-positive metastatic breast cancer patients by means of months. The pooled data showed a large variation in the minimum and maximum ranges of overall and progression-free survival for both the targeted therapy and the comparator arms, as well as per receptor status and line of treatment. As these therapies are costly, determination of the receptor status of the tumours is important for personalised selection of therapy, decreasing the proportion of patients who will not respond and containing costs (Chapter 5).

In the last decades, these new therapies account for substantial increase in healthcare expenditures for metastatic breast cancer treatment and the cost-effectiveness in terms of monetary units spent per life-year-gained and quality adjusted life years varies largely. In these analyses the variables that have a significant impact on the cost-effectiveness estimations
are the price of the therapies, and the survival benefit and gain in quality adjusted life years. Therefore, it is important to use diagnostic imaging and select the patients that would benefit the most from these therapies. The potential cost-effectiveness of applying PET/CT with FES and 89-zirconium-(89Zr)-trastuzumab tracers for treatment selection in metastatic breast cancer patients was evaluated in Chapter 6. The results from our analyses demonstrated that the decision analytical model was most sensitive to changes in the proportion of inconclusive and unobtainable biopsies, and the sensitivity and the specificity of the PET/CT imaging modalities. The intervention pathway yielded higher costs to evaluate receptor status of the MBC disease and select treatment than the care as usual pathway. The number of LYG was also higher in the intervention pathway, provided sensitivity and specificity were sufficiently high. The application of PET/CT with FES and 89Zr-trastuzumab tracers for selecting the first-line therapy in MBC had the potential to be cost-effective with ICERs ranging from €71,000 to €80,000 per LYG when the sensitivity and specificity of PET/CT with FES and 89Zr-trastuzumab tracers were at least 77.1% and 80% (aiming at the lowest sensitivity), or – starting with low values of specificity: 80% and 76.7%, respectively. This study was a proof of concept analysis of the potential cost-effectiveness of PET/CT for first-line treatment selection in metastatic breast cancer and as such it had its limitations. One of these is the omission of quality-adjusted life years (QALYs) in the analysis. Quality of life is an important measure of successful treatment in women with metastatic breast cancer and if PET/CT can select more precisely the group of women who would benefit from targeted treatment we may expect a greater gain in QALYs. However, currently we do not have a reliable method to evaluate the change in QALYs as a result of applying PET/CT for treatment selection. Another limitation is partial probabilistic sensitivity analysis which was performed on the sensitivity and specificity of PET/CT and the risk of unobtainable biopsy. As mentioned, the results of the model were highly dependent on the changes in these parameters, therefore, only these
parameters were varied and their effect on the main outcome measure (ICER) was assessed. Thirdly, we chose not to perform an early health technology assessment or headroom analysis, mainly due to the limited availability of reliable data from dedicated randomised controlled trials such as IMPACT. Data on inconclusive and unobtainable biopsies, metastasis site progression-free and overall survival with regards to the site of the distant relapse, sensitivity and specificity of PET/CT per site and size of the metastatic lesion is very important in determining the uncertainty in the outcome measure. Therefore, reference is made to the expected results from the recent IMPACT trial which could be used to precise the input parameters and estimate the uncertainty in the calculated ICER.

**Implications for future breast cancer screening and follow-up research**

**Updating the screening recommendations for breast cancer**

Epidemiological evidence shows prominent increase in the breast cancer incidence above 45 years of age and results from modelling studies suggest that starting regular breast cancer screening earlier is cost-effective. However, expanding the starting age of breast cancer screening even lower (below 45 or 40 years of age) would further increase the expected harms, especially the radiation induced tumours as BEIR VII is exponentially higher at lower ages, and thus costs of screening. In addition, recent analyses have demonstrated that systemic treatments have nearly equal effect as compared to regular screening on the mortality reduction from breast cancer.\(^{10,15-19}\) Emerging novel imaging modalities like tomosynthesis could also improve breast cancer screening outcomes and reshape cost-effectiveness\(^{32}\) thus contributing to the mortality decline from the disease. Since costs of systematic therapies and novel screening modalities need further consideration, clinical studies along with modelling
evaluations are needed in order to assess the most optimal cost-benefit ratio and rethink the starting age and the screening interval for breast cancer. Decision analytical studies need to model not only the expected effect of new screening technologies but also the combined effect of treatment and screening.

**Updating the recommendations for breast cancer follow-up**

We demonstrated that PET/CT with different tracers could potentially decrease time to diagnosis and treatment selection in patients with metastatic breast cancer. PET/CT could also have a positive impact on quality of life by decreasing the delay in relief of symptoms and the negative effect on patients’ health resulting from ineffective treatment. Future research should focus on addressing the impact of PET/CT on treatment decision making in first and second line metastatic breast cancer from both clinical and health economics point of view. Although PET/CT with different tracers represents a promising advancement in the field of breast cancer follow-up, barriers to its more widespread use also exist (excluding FDG-PET/CT). This is mainly due to the lack of clinical studies to prospectively validate its role in different clinical contexts, similar to the studies undertaken with FDG-PET/CT. The value of PET/CT as a component in a multimarker approach to prognostication and management must be further understood and explored. Data from all these efforts is needed to support regulatory approvals and guideline recommendations. Clinical data is needed which would examine the particular benefits of combined PET/CT with different tracers in diagnosing different type of metastatic lesions (bone, lung, brain, liver, etc.) and treatment selection with respect to their receptor status. In addition, larger studies are needed to clarify the generalisability of the modality’s reported benefits, particularly given the high associated costs and limited availability in most institutions and settings.33
References:


