

Interval cancers and bilateral cancers at breast cancer screening

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Valorisation

Introduction

Breast cancer is still one of the leading causes of cancer related death among women worldwide. In 2018 breast cancer was diagnosed in about 2.1 million women, according to the World Health Organisation (WHO), and approximately 627,000 women died due to breast cancer in that year. Detecting breast cancer at an earlier stage will allow a more effective treatment and will thus result in a decrease in mortality and morbidity. The latter is the main goal of breast cancer screening. In the Netherlands, breast cancer screening has contributed substantially to the reduction of the breast cancer mortality in the last three decades. Since its introduction in 1989 multiple adjustments have been made in the Dutch screening programme to improve its effectiveness. From a double read single mammography, breast cancer screening has switched to a two-view mammography with blinded double-reading. One of the latest changes is the introduction of full-field digital mammography (FFDM), which has replaced screen-film mammography (SFM).

There are several quality indicators available for the evaluation of breast cancer screening. The most prominent ones are the cancer detection rate (CDR), positive predictive value (PPV) of referral and the interval cancer rate (ICR). Together these three indicators provide information about the balance between detecting as many malignancies as possible while minimizing the number of false positive referrals. Interval cancers are cancers that are not detected by screening in the window between two subsequent screens. Reducing the number of interval cancers is very important, as these cancers have a much poorer prognosis than screen-detected cancers.

Relevance of this thesis

In this thesis, one of our aims was to evaluate the effects of the transition from SFM screening to FFDM screening, with the main focus on interval cancers. One of the studies in this thesis showed an increased cancer detection rate (CDR) during implementation of FFDM screening, accompanied by a higher referral rate. This resulted in a decreased interval cancer rate (ICR) and a higher programme sensitivity. This study also covered the second round of FFDM screening and showed that the CDR remained higher during the second round when compared to SFM screening. The referral rate, however, also remained higher, resulting in a lower PPV of referral. Therefore it is important to know if this decrease in ICR contain the more aggressive interval cancers, and not only the low grade malignancies. Therefore in this thesis we analysed the characteristics of interval cancers diagnosed during the transition from

SFM to FFDM. After the first round of digital screening an increased proportion of interval cancers was not visible on the latest screening mammogram. However, this phenomenon did not persist after the second round of FFDM screening. Besides a slightly lower proportion of invasive ductal cancers among interval cancers, no differences were seen in tumour characteristics and the extent of the surgical treatment (i.e., breast-conserving surgery or mastectomy) during the implementation of digital screening. If FFDM screening would have filtered out more smaller and insignificant tumours and thus mainly would have caused overtreatment, one would have expected that the introduction of FFDM resulted in relatively more interval cancers with a poor prognostic profile. As this was not the case, the increase in CDR is expected to have a relevant positive effect on overall breast cancer mortality and morbidity.

In our opinion, these findings justify the introduction of FFDM screening, especially when taking into account the improved logistics (e.g. easier access to images, storage capacity) and increased editing options (e.g. windowing and enlarging), compared to SFM screening. It is obvious that it is important to keep the referral rate as low as is reasonably achievable. However, even after the introduction of FFDM screening, the referral rate in the Netherlands is still relatively low compared to those observed in other countries (Table 9.1). Therefore, the advantage of an increased CDR and a decline in ICR outweighs the increase in referral rate and the lower PPV.

Most of the breast cancers in a systematically screened population are detected by screening. However, about 20% of breast cancers are diagnosed in between two subsequent screening rounds. As these interval cancers have a poorer prognostic profile than screen-detected cancers, it is of paramount importance to further improve the quality of the screening in order to decrease the interval cancer rate. This thesis describes tumour characteristics of interval cancers prior, during and after the transition from SFM to FFDM screening. We found that digital screening did not decrease the proportion of “missed” interval cancers, which are the cancers that (in retrospect) were visible on the last screening mammogram and thus should have been referred. Therefore, we conclude that there is still room for improvement of breast cancer screening. Future possibilities to obtain this improvement may include personalisation of screening and the implementation of Artificial Intelligence as a complementary tool for screen radiologists. Another possible improvement of breast screening could be digital breast tomosynthesis (DBT), however if DBT can reduce the interval cancer rate is still a point of discussion.

This thesis also focused on women who were referred more than once for the same mammographic lesion. We found a significant increase in these repeated referrals from 1.2% prior to the transition from SFM to FFDM to 2.2% during the transition and

2.8% after the transition. This increase came along with a decline of the PPV of referral of repeatedly referred lesions, from 35.1% before to 14.8% after the transition from SFM to FFDM. Despite an obvious delay in the diagnosis of breast cancer after delayed referrals, these cancers showed more favourable prognostic features than interval cancers. We feel that these findings are of particular interest for screening radiologists, especially to increase the awareness of the probability of breast cancer being present in repeatedly referred mammographic abnormalities. As indicated, these abnormalities should not be automatically dismissed because “it was already there”, but they should be referred once more for re-evaluation when they remain suspicious or show growth, architectural changes, increased density or increased suspicious calcifications.

We also looked at blinded (BDR) versus non-blinded double reading (NBDR) of screening mammograms and its effect on surgical treatment. Clinical evidence shows that BDR increases the sensitivity of breast cancer detection and it is therefore superior to NBDR. We investigated whether the two reading strategies yielded differences in surgical procedures. We found no significant differences in surgical treatment of screen-detected breast cancers after BDR or NBDR. We found, however, a higher rate of breast conserving surgery (BCS) in women with interval cancer after NBDR compared to BDR. This is probably due to the higher detection rate at BDR screening. BDR shows no significant changes in chosen surgical therapy and other studies show an increase in biopsy procedures and referrals and slightly more complex logistics of blinded double reading. These issues should be taken in consideration by screening organisations and screen radiologists when deciding which reading strategy to follow.

Bilateral interval cancers are a small subgroup of all breast cancers at screening mammography and, to our knowledge, no prior studies on bilateral interval cancers have been performed. For the most effective and efficient treatment of breast cancer it is important to determine the extent of the disease. Therefore, it is necessary to know whether or not a contralateral malignancy is present at the time of treatment decision. This study therefore aimed to give insight in the incidence and characteristics of bilateral interval cancers. We found that 3.2% of all interval cancers were bilateral. Among invasive interval cancers, bilateral interval cancers were more often of lobular histology and more often had a low grade (grade I) differentiation than unilateral interval cancers. They also were larger (more often stage 2 or higher) than bilateral screen-detected cancers. As stated before, this study may also increase the awareness of bilateral (interval) breast cancer being present in screened women and it also underlines the importance of including MRI in pre-operative work-up of selected cases, especially when dealing with invasive lobular tumours. The use of MRI

for the work-up of invasive lobular breast malignancy has already been incorporated in European guidelines.