



Cohort Study

The effectiveness of mammography surveillance after treatment of primary breast cancer: A single centre retrospective cohort study

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ARTICLE INFO

Keywords:

Breast
Cancer
Mammogram
Surveillance
Detection
Recurrence

ABSTRACT

Introduction: There is a little evidence that routine follow-up of patients treated for early breast cancer (BC) to detect ipsilateral breast tumour recurrence (IBTR), or contralateral breast cancer (CBC), is either effective or offers any mortality benefits. We report our experience of following patients with early BC for recurrences and new primaries in order to determine the role of mammogram surveillance.

Methods: Single centre, retrospective primary observational study was designed. Patients who had BC during year 2001–2006 were included and followed for a minimum of ten years. Patients were divided based on the modalities of detecting BC in to screen detected group and clinically detected one i.e. symptomatic BC. These two groups were compared.

Results: Total number of patients considered for analysis was 2530 (screen detected BC - 703 patients and symptomatic BC - 1827 patients). The rate of recurrence including regional and distant metastasis in screen detected BC group was 8% (57/703) and 2% (43/1827) in symptomatic one. However, the prevalence of IBTR/CBC in the whole cohort was 2% (62/2530). Mammography surveillance identified 60% (37/62) of patients who had IBTRs/CBCs.

Mammography surveillance detected 85% (29/34) of all IBTRs/CBCs in the **screen detected BC group**. In contrast, it picked up only 29% (8/28) in the other group (Chi squared 20.5 $p < 0.005$).

Conclusions: Mammography surveillance is efficient for the screen detected BC group but not for the symptomatic one. Hence, it is worth suggesting different follow-up strategies for both groups. Further studies are therefore recommended.

1. Introduction

Breast cancer is the most common cancer in women [1]. The 5-year survival rate for invasive breast cancer is 85% [2]. Approximately 20% of patients will develop a systemic recurrence and die within 5 years. Moreover, in patients who undergo breast-conserving therapy (BCT), ipsilateral breast tumour recurrence (IBTR) occurs in 1–2% of patients each year and contralateral breast cancer (CBC) occurs at a rate of up to 0.8% each year [3–5].

There is a little evidence that routine follow-up of patients treated for early breast cancer, in order to detect recurrence or a new primary disease, is either effective or offers any mortality benefit. Furthermore, there is lack of high-level evidence to support decisions about the

frequency, timing, and duration of mammography surveillance.

Literature review from 1990 onwards, the year of introduction of the national breast screening program in United Kingdom (UK) [6], showed that follow-up programs based on a regular physical exam and yearly mammogram appear to be as effective as the more intensive approaches [7–9]. The contribution of routine clinical examination (CE) for the detection of potentially treatable relapse was challenged several times. Montgomery and colleagues found recommendations for CE follow-up was based on weak evidence [10,11]. Additionally, there is also a paucity of evidence on the relative effectiveness of mammography in combination with other imaging such as MRI in follow up surveillance. These studies showed that additional imaging could result in unnecessary surgical procedures [12]. Some Studies reported that MRI and

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Received 25 February 2021; Received in revised form 27 March 2021; Accepted 30 March 2021

Available online 9 April 2021

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mammography, combined with CE are most sensitive for detection of recurrences. However, none of these studies reported survival benefits over mammography only based surveillance [13].

Currently, most of the breast units in the UK follow patients with an annual mammography for five years or until the age of 50, after which patients enter the national screening program [14]. In 2013, the American Society of Clinical Oncology (ASCO) updated their clinical practice guidelines for follow-up. They recommended post-treatment mammogram to be obtained 1 year after the initial mammogram and at least 6 months after completion of radiation therapy; thereafter a yearly mammographic evaluation should be performed [15].

There are no data from randomised controlled trials demonstrating any benefit from mammography surveillance and therefore guidelines are based on expert opinion [16,17]. It was shown by non-randomised retrospective study that mammographic follow-up allowed early detection of relapse in the asymptomatic phase, which improved prognosis relatively to symptomatic relapses [18]. Moreover, it was reported by the SEER database that early detection of CBC was associated with a mortality reduction compared with cases of CBC diagnosed at more advanced stages which supports the survival benefit of follow up with mammography [19].

It is now accepted that IBTR has an adverse influence on patient survival [20]. If patients experience IBTR, 40–50% will have further recurrence or develop distant disease subsequently. Therefore, the early detection of recurrence may be beneficial in terms of survival [21].

The **objective** of this study is to assess the rate of detection of IBTRs/CBCs by mammography, and to compare this rate between patients whose original tumour was detected by screening and those who presented symptomatically.

2. Methods

2.1. Registration and ethics

Research registry was undertaken through ISRCTN (Registration Unique Identifying number; ISRCTN37620362) [22].

The work has been reported in line with the STROCSS criteria [23].

Formal ethics committee clearance was not needed, as this was a service evaluation project.

2.2. Cohort study design

This is a single centre, retrospective primary observational study. All patients diagnosed with primary BC from 2001 to 2006 were identified using the cancer database at the Breast unit in Cambridge University Hospitals, NHS Foundation Trust, UK.

All patients were followed up for at least **10 years** or until the development of a second cancer (i.e. IBTR or CBC). Demographics and details of both primary and second cancers were documented.

2.3. Cohort groups

Patients were divided in to **two groups** according to mode of presentation of their BC (screen detected vs clinically detected) and mode of the diagnosis of their recurrences/new primaries (by mammogram or clinically).

2.4. Participants and outcomes

Details of patient's who had recurrences/new primaries such as age, histopathology of cancer, time of recurrence and mode of detection were collected and analysed.

IBTR is defined as any tumour in the same breast that was treated by conservative breast surgery for BC. On the other hand **CBC** is defined as any tumour in the other breast, after treatment of BC (Both breast conservative surgery and mastectomy were included).

The following patients were **excluded**: patients with distant metastasis or regional recurrence (chest wall, mastectomy scar or axilla), patients who were lost to follow-up or had no records, patients who died because of reasons other than breast cancer during ten years of follow-up and who were recurrence-free at the time of death.

2.5. Statistical methods

χ^2 test was used to determine differences between subject groups. *P* value was considered significant if < 0.05 . No power calculation done for this study, as the data were retrospective and observational.

3. Results

From January 2001 to June 2006 a total of **2552 patients** had BC. Twenty-two patients had no records or were lost during follow-up and were hence excluded from the analysis. The cohort was divided into two groups according to the primary method of diagnosis, 703 patients had screen-detected breast cancer and 1827 patients presented symptomatically. 2% (62/2530) had IBTRs/CBCs in both groups. Moreover mammography surveillance identified 60% (37/62) of them.

The **median age of recurrence** was 69 (range 50–75) in the screen-detected BC group and 68 (45–90) in the symptomatic one.

The IBTRs/CBCs in the **screen and clinically detected BC** groups were 8% (57/703) and 2% (43/1827) respectively. **Table 1** shows summary of IBTRs/CBCs in both groups.

Screen-detected BC represented 55% (34/62) of all patients who had another cancer. The remaining 45% (28/62) of patients belonged to the symptomatic group.

Furthermore, mammography surveillance detected 85% (29/34) of all IBTRs/CBCs that developed in screen-detected BC group. On the other hand only 28% (8/28) of them in clinically detected group were picked up by mammogram. In fact the majority of this group i.e. 72% (20/28), presented clinically as they did first time (**Table 2**) ($p < 0.005$).

Pathology of 25 patients who developed IBTRs/CBCs that were missed by mammogram and detected clinically is illustrated in **Table 3**.

For those who were diagnosed by mammogram, 72% (21/29) of them had their IBTRs/CBCs picked up in the first five years of follow-up for screen-detected BC patients. However, the opposite was the case for symptomatic group. As only 37% (3/8) of them were detected in the first five years of follow-up by mammogram (**Fig. 1**).

4. Discussion

Our study showed that mammography surveillance of patients who were treated for primary BCs is of a value. It detected 60% of patients who had IBTRs or CBCs.

Interestingly, when we divided patients in to two main groups, **symptomatic and screen detected BCs**, mammography surveillance was of more value in detecting IBTRs/CBCs in the screen-detected BC group than in the symptomatic one. Mammography surveillance picked up 85% of IBTRs/CBCs in the screen-detected BCs group that represent 55% of all patients who had IBTRs/CBCs in the cohort. On the other hand, mammogram showed only 28% in the symptomatic group. This difference was statistically significant ($p < 0.005$).

Table 1
Summary of IBTRs/CBCs in screen and clinically-detected BC group.

| | Screen detected BC group (n = 57) | Clinically detected BC group (n = 43) |
|------------|--------------------------------------|--|
| IBTR | 21/57 (37%) | 25/43 (58%) |
| CBC | 13/57 (23%) | 3/43 (7%) |
| Regional | 3/57 (3%) | 11/43 (26%) |
| recurrence | | |
| Systematic | 20/57 (35%) | 4/43 (9%) |
| recurrence | | |

Table 2

Detection modes of IBTRs/CBCs.

| | Screen detected BC group n = 34 (%) | Clinically detected BC group n = 28 (%) |
|----------------------------------|--|--|
| IBTRs/CBCs detected by mammogram | 29/34 (85%) | 8/28 (28%) |
| IBTRs/CBCs detected clinically | 5/34 (15%) | 20/28 (72%) |

Table 3

Pathology of IBTRs/CBCs detected clinically.

| IBTRs/CBCs Pathology | | | | | | |
|----------------------|------|------|-----|-----|--------|-------|
| PBCs Pathology | DCIS | LCIS | IDC | ILC | Others | Total |
| DCIS | – | – | 4 | – | 1 | 5 |
| LCIS | – | – | – | – | – | – |
| IDC | – | – | 17 | – | – | 17 |
| ILC | – | – | 1 | 2 | – | 3 |
| Others | – | – | – | – | – | – |
| Total | – | – | 22 | 2 | 1 | 25 |

PBC- Primary Breast Cancer, DCIS –Ductal Carcinoma In Situ, LCIS –Lobular Carcinoma In Situ, IDC-Invasive ductal carcinoma, ILC-Invasive Lobular Carcinoma.

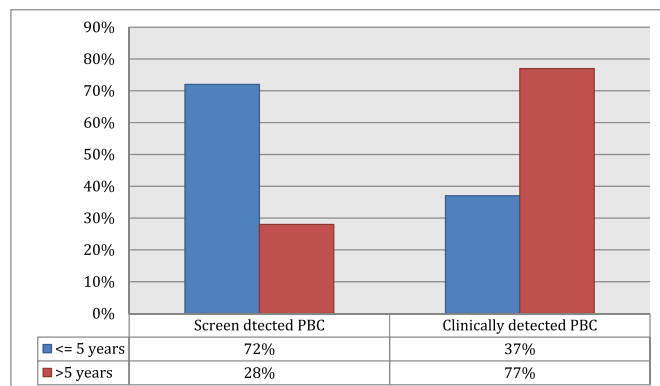


Fig. 1. Mammogram detected recurrences in relation to time of presentation PBC- Primary Breast Cancer.

Despite of the small number of recurrences/new primaries (n = 62), our study has shown that it is justified to consider the mode of detecting primary BCs as one of characteristics to personalise follow-up strategies. The stratification of patients based on how likely they are to get IBTRs/CBCs, in order to ensure the maximum benefit and the optimal use of resources was already recommended by Robertson and colleagues [13]. However none has clearly mentioned before in the literature that mammographic detection rate might be affected by the mode of primary BCs presentation. Furthermore, there was no mention of using the mode of detecting BCs as a possible guide to stratify the follow-up strategy.

Our results demonstrated that 72% of the IBTRs/CBCs that were detected by mammography in the screen-detected group were found in the first five years of follow up. On the other hand, in the symptomatic group, 77% of them presented after five years of mammography surveillance. There was no explanation for such contrasting results. The small number of this cohort may have implications on how much these results could reflect an actual trend. Hence it is difficult to make any comments or recommendations regarding the duration of follow-up or its frequency. Furthermore it is statistically insignificant (p = 0.067).

From our literature review we could not find a study that compares the effect of different intervals on detecting recurrence and its stage. Furthermore there is paucity of strong evidences on the ideal duration of follow up. Most guidelines recommend either 12 monthly or 6–12

monthly surveillance following completion of adjuvant therapies. These recommendations were based on expert opinion due to the paucity of supporting data. Arasu et al. recommended continuing doing semi-annual surveillance [24] when other studies concluded that interval of 6 months is of low value [25,26]. Optimal duration and interval for mammogram follow-up stays uncertain [27]. Customising follow up duration and frequency to patients was suggested. Higher risk patients may benefit from annual mammography while triennial mammography may suffice as a cost-effective strategy for lower risk patients [13,15,27, 28]. Ciatto and colleagues supported long term follow up of patients for 10 years [29]. The on going Mammo 50 trial that aims to investigate the optimum frequency and duration of follow up mammograms in patients older than 50 should provide evidence that will contribute to the debate. It is likely to produce useful data as it is multi-centric, randomised, controlled, phase III trial [30].

In our study, patients who had cancers that were missed by mammogram were analysed in depth, the characteristics (type, grade, LVI and receptor status) of both primary BC and/CBCs were studied, in order to find out whether these characteristics played a role in being missed by mammograms. For instance it is well known that mammography has limitation in detecting invasive lobular cancer and often underestimates the disease [31]. However, our findings showed no specific tumour characteristics that explained why IBTRs/CBCs were missed by mammograms.

Breast tissue high density is another factor to be blamed for missing tumours in mammograms. In our study, there was a limitation for accessing the radiology films to assess the density of the breast tissue of patients who had IBTRs/CBCs missed by mammogram, as films were not available in majority of the patients who were missed by mammogram. Therefore, age was considered as a guide of breast density, based on the fact that young patients have more dense breasts, which may reduce the efficacy of a mammogram [32]. We found no observed difference in the age groups of patients who had IBTRs/CBCs, regardless of whether they were detected by mammogram or clinically at the time of presentation. Hence, breast density was not considered as a factor that contributed to missing recurrence or CBC in this study.

We acknowledged few limits of our study that can be underlined. One of them is being from a single centre. This may lead to under estimation of real status. Another one is loss of follows ups, absence of records and loss of data all contributed to loss of participants; 3% of BCs were excluded due to absent records.

Having recognised the limitation of this study, it is still worth recommending, that follow-up surveillance for screen-detected BC patients should be with a mammogram, more frequently, for a longer duration, and with less clinical visits. On the other hand, patients who present with palpable primary BC should be followed clinically with less frequent mammograms and a shorter duration. Further study is therefore recommended.

5. Conclusion

Mammogram follow-up is efficient for the screen-detected group but not for the clinically detected once. Hence, it is worth suggesting different follow-up strategies for both groups after further study on larger number of patients.

Ethics approval

Not required.

Author contribution

Study concepts: WT Study design: WT, SL Data acquisition: WT.

Quality control of data and algorithms: WT,SL.

Data access: JB.

Data analysis and interpretation: WT, SL Statistical analysis: WT, SL.

Manuscript preparation: WT. Manuscript revision: SL, JB.
All authors approved the final version submitted.

Consent

Not applicable.

Research registration unique identifying number

ISRCTN37620362
<https://doi.org/10.1186/ISRCTN37620362>.

Guarantor

W Taher.

Funding

None.

Data statement

The database used and/or analysed during the current study are not publicly available, but can be available from the corresponding author on reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

None.

Acknowledgement

Khalid Hureibi: manuscript preparation and revision. Asmaa Al Allak: Data analysis and interpretation.

Cambridge Breast Cancer Research Clinical Informatics; Ternent, S. on behalf of CBCR clinical informatics: Database collection and provision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102272>.

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