**Survival and disease characteristics of *de novo* versus recurrent metastatic breast cancer in a cohort of young breast cancer patients**

**Running title: Metastatic breast cancer in young patients**

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**Abstract**

BACKGROUND: It is not clear how the pathology, presentation and outcome for patients who present with *de novo* metastatic breast cancer (dnMBC) compare to those who later develop distant metastases. DnMBC is uncommon in younger patients. We describe these differences within a cohort of young patients in the UK.

METHODS: Women aged 40 years or younger with a first invasive breast cancer were recruited to the prospective POSH national cohort study. Baseline clinicopathological data were collected, with annual follow-up. Overall survival (OS) and post-distant relapse-free survival (PDRS) were assessed using Kaplan-Meier curves.
RESULTS: 862 patients were diagnosed with metastatic disease. DnMBC prevalence was 2.6% (76/2977). Of those with initially localised disease, 27.1% (786/2901) subsequently developed a distant recurrence. Median follow-up was 11.00 years (95% CI 10.79-11.59). Patients who developed metastatic disease within 12 months had worse OS than dnMBC patients (HR 2.64; 1.84-3.77). For PDRS, dnMBC was better than all groups, including those who relapsed after five years. Of dnMBC patients, 1.3% had a g*BRCA1* and 11.8% a g*BRCA2* mutation.

CONCLUSIONS: Young women with dnMBC have better PDRS than those who develop relapsed metastatic breast cancer. A gBRCA2 mutation was overrepresented in dnMBC.

**Background**

Breast cancer is the most common neoplasm in women, with over 55,000 new diagnoses per year in the UK(1). The vast majority of patients present with disease localised to the breast and axillary lymph nodes and are treated with the aim of cure, but for the 6 to 7% who present with *de novo* metastatic disease (dnMBC) treatment is usually with palliative intent(2, 3). Overall, the median survival of those with metastatic breast cancer (MBC) is 2 to 3 years(4), although the range is wide, with some patients with ER+ or HER2+ disease living much longer. Most MBC survival analyses are retrospective, with a median age of 53-65 (with less than 15% of participants being aged under 40)(5-7).

A number of studies to date have shown a longer survival time following diagnosis of metastases for those presenting with dnMBC, compared to those who later develop distant metastases after initial treatment for early breast cancer (recurrent MBC; rMBC)(6, 8-10). In a retrospective multicenter study evaluating 815 consecutive patients with MBC in the Netherlands from 2007 to 2009, this was only true for rMBC patients with a metastasis-free interval (MFI) of less than 24 months (7).

The phenotype of breast cancer for those with dnMBC is unclear. Compared to rMBC cases, more favourable pathological features have been reported, such as a lower frequency of “triple negative carcinomas(6, 8). However, more aggressive features have also been documented, such as larger tumours, and an increased frequency that are Grade 3 (6). However, with median follow up length of less than five years, interpretation of these studies is limited by the omission of late ER+ve recurrences.

Data regarding clinical presentation has also yielded varying results. A higher prevalence of bone involvement in the dnMBC group at diagnosis has been reported in two studies; one reported an equal prevalence of brain metastases and the other reported fewer brain metastases compared to those with rMBC(7, 8). Another study also found a lower prevalence of brain metastases, but a similar prevalence of bone involvement (6). Locoregional management in patients with dnMBC is the subject of ongoing debate as results from retrospective studies have been confounded by selection bias and the results from randomised trials are been conflicting(11).

Published studies on dnMBC have been limited by their retrospective nature (with the risk of survival bias) or by small patient numbers and short follow-up periods. None have complete germline *BRCA* status or evaluate a specific age group. of the incidence of breast cancer in young women (aged less than 40) is low, , but increasing(12). Young women are more likely to have breast cancer with adverse biological features, including higher grade, absence of hormone receptors, lymph node involvement and vascular invasion(13). Young age has been consistently shown to be an adverse prognostic factor, with a higher risk of distant recurrence(12). Although young women present more frequently with stage III disease, dnMBC is found infrequently (1% of those aged under 40 in one retrospective study) (14). The POSH study, a prospective observational study of almost 3000 patients aged 40 years or younger with a first diagnosis of invasive breast cancer (13) provides a unique opportunity to study the natural history of dnMBC in young women. Patients were recruited between 2000 and 2008 in the UK. A wealth of clinicopathological data is available for these patients, including body mass index and ethnicity, and genotyping for germline *BRCA* mutation status has been performed on the vast majority (>94%). This is an important variable to study as *BRCA mutation* status is increasingly being incorporated in decision making regarding optimal treatment(12). We aimed to characterise the clinical features, pattern of disease progression and survival of young breast cancer patients who present with metastatic disease, compared to those who later develop distant metastases, in a large prospective cohort genotyped for germline *BRCA1/2*.

**Methods**

Prospective Outcomes in Sporadic *versus* Hereditary breast cancer (POSH) is a multicenter prospective observational cohort study of young women diagnosed with breast cancer in the United Kingdom. The detailed study protocol was published in 2007 (15). The study received approval from the South West Multi-center Research Ethics Committee (MREC 00/6/69). Written informed consent was obtained from all participants.

*Patients*

In total, 3021 female patients were recruited from 127 UK hospitals. Patients were eligible if they were diagnosed with an invasive breast cancer between January 1, 2000 and January 31, 2008 at an age of 40 years or younger. Patients were excluded if they had a previous invasive malignancy (excluding non-melanomatous skin cancer), Patients were consented within 12 months of initial diagnosis. All patients received treatment according to local protocols. Patients with confirmed distant metastatic disease at diagnosis (stage M1) according to the local site comprised the dnMBC cohort. Tissue diagnosis of metastatic disease was not mandated by the study. Patients who initially had localised disease (stage M0) but developed distant metastatic disease within the follow-up period (according to site reporting) comprised the rMBC cohort. Tissue diagnosis of metastatic disease was not mandated by the study. Patients without metastatic disease at any time were not included in this analysis.

*Data collection*

Information regarding personal characteristics, tumour pathology, stage and treatment received were collected from medical records at study entry. Family history was collected by questionnaire. Pathology and imaging data were verified with copies of original reports. Follow-up data including date and site of disease recurrence were obtained from medical records at 6 months, 12 months and thereafter annually until death or loss to follow-up. Follow-up interval was determined according to local standards; no imaging or other investigation was mandated by this study, as it was observational. Patients were flagged in the National Health Service Medical Research Information Service to facilitate automatic notification of date and cause of death. This study presents analyses conducted on follow-up data received until 26 June 2016.

*Biological testing*

Estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor status of primary tumours were determined from routine diagnostic pathology reports. Hormone receptor concentrations equivalent to an Allred score of 3 or more were categorised as positive. Tissue microarray (TMA) immunohistochemical staining was used to supplement missing information regarding receptor status.

DNA for genotyping was extracted from whole blood samples collected at recruitment. A multiplex amplicon-based library preparation system, Fluidigm Access Array (Fluidigm UK, Cambridge, UK) was used to sequence a panel of breast cancer susceptibility genes, including *BRCA1/2* and *TP53.* Illumina HiSeq2500 Next Generation Sequencing Platform was utilized (Illumina, Little Chesterford, UK). If patients met current UK guidelines for genetic testing, multiplex ligation probe analysis was used to ensure mutations consisting of large exonic deletions or duplications were not missed. Pathogenic variants were confirmed by Sanger sequencing. Those with variants of unknown significance were classified as *BRCA-*negative.

*Statistical methods*

Statistical analyses were performed according to a pre-specified statistical analysis plan (Supplementary Information) as per STROBE guidelines.

The primary objective was the comparison of overall survival (OS) of patients with dnMBC with that of patients with rMBC with a MFI of less than 12 months (early12). OS was defined as the time from date of diagnosis to death from any cause. MFI was defined as the time from date of diagnosis to date of first distant relapse (as reported by study site).

Secondary objectives included the comparison of OS and post distant relapse free survival (PDRS) of patients with dnMBC with that of patients with rMBC with a MFI of less than 24 months (early24). PDRS was defined as time from date of diagnosis of first distant metastases (date of diagnosis of primary tumour for patients with dnMBC) to death from any cause. Other secondary objectives included the comparison of PDRS of patients with dnMBC versus early12 patients and the description of clinicopathological features in patients with dnMBC and those with rMBC in four cohorts (recurrent disease within 12 months, within 24 months, between 24 and 60 months, and after 60 months). Patient and tumour characteristics included ethnicity, body mass index (BMI), germline *BRCA* status, first site of metastasis and primary tumour grading/receptor status. Time to event outcomes were described using Kaplan-Meier curves and analysed using Cox regression models; stratified Cox models or flexible parametric survival models were used in cases where hazards were time varying. All multivariable analyses were adjusted for age at diagnosis, BMI, grade, tumour size, pathological N stage, ethnicity, and ER and HER2 tumour status. Further objectives included the comparison of OS of dnMBC patients who had breast conserving surgery (BCS), nodal surgery only or mastectomy vs. those who had no surgery and assessment of correlation between MFI and PDRS in rMBC patients using the survcorr command in R. Statistical analyses were carried out using Stata v15.1 and RStudio v1.1.456.

The study size and power calculations are discussed in the study protocol(13).

**Results**

A total of 3021 eligible women were recruited to the POSH study. For this study, 44 women were excluded (42 were aged 41-50 years and 2 had missing primary tumour data). Of the 2977 women included, 862 (29.0%) were diagnosed with metastatic disease and comprise the analysis population. There were 76 women (2.6%) who presented with dnMBC. As of June 2016 , the distant recurrence rate amongst the 2901 women with localised disease at presentation is 27.1% (n=786). Median follow-up of the analysis population was 11.00 years (95% CI 10.79 to 11.59; n=862).

Of patients with rMBC, 70 (8.9%) developed metastases within 12 months of diagnosis (early12). There were 268 women (34.1%) who developed metastatic disease within 24 months of their first diagnosis (early24), 360 (45.8%) within 24 to 60 months (early24-60) and 158 (20.1%) after 60 months (late).

*Baseline clinicopathological data*

For the 862 women diagnosed with metastatic disease, clinicopathological data can be seen in Table 1. The proportion of patients that were very young (aged 30 or less) decreased with time to relapse amongst rMBC patients (18.6% for early12, 6.3% for late relapse). The largest proportion of *BRCA1* mutation carriers was found in the early24 group (8.6%; 23/268). The largest proportion of *BRCA2* mutation carriers was found in the dnMBC group (11.8%; 9/76); there was only one *BRCA1* mutation in this group (1.3%;1/76).

On review of tumour characteristics, ER-positivity was positively correlated with later time of relapse: 45.3% of early24, 72.4% of early24to60 and 84.2% of late relapse cases (69.3% of dnMBC). HER2 positivity was highest in the dnMBC cohort with 47.9%, vs. 32.4% in the early24 group and 24.3% in the late relapse group. The median maximum tumour size was largest in the dnMBC group at 35mm, compared to 25mm in the late relapse group. The proportion of cases with Grade 3 disease was inversely proportional with time to relapse amongst the rMBC group: 87.0% of early12 and 47.4% of the late relapse group (63.2% of dnMBC).

The early12 group had a high proportion of adverse tumour characteristics, including Grade 3 disease (87.0%), LVI (76.9%) and node-positivity (83.8%). The number of involved lymph nodes was more than 10 in a quarter of cases (25.0%) and over a third of cases were triple negative (34.3%).

*Survival*

Patients who relapsed within 12 months had a significantly worse OS than the dnMBC group (Figure 1A), with a HR for death of 2.64 (1.84-3.77; p=<0.001). For those who relapsed after 24 months, the OS varied over time, consistent with the delay from diagnosis to metastatic disease (clearly the HR for death at 2 years was very small). However, results from the time-varying regression model show that by 5 years the risk of death for those who relapsed between 24 and 60 months was increased compared to the dnMBC group with a 5yr HR of 1.55 (1.10 – 2.18; p=0.013) and 10yr HR 2.21 (1.02 – 4.77; p=0.044) (Figure 1B, S2A). Similarly the time-varying regression model shows that, for those who relapsed after 60 months, the risk of death at 5 years was very small, but compared to the dnMBC group the 10yr HR was 1.74 (0.80 – 3.78; p=0.160) (Figure 1B, S2B). There was longer PDRS for dnMBC compared to all other groups who developed metastases, including those with late relapse after 60 months (HR 2.67; 1.92-3.71, p<0.001) (Figure 2A, 2B). The hazard ratio for PDRS for early12, compared to dnMBC, decreased over time (Figure 2C).

We assessed for a correlation between time from initial diagnosis to metastatic relapse (metastasis-free interval; MFI) and PDRS and found a very slight positive Rho correlation coefficient of 0.045 (95% CI: -0.023 to 0.113)suggesting there is not a close correlation between these two factors.

A multivariable analysis was performed to assess for factors related to duration of survival in those with dnMBC vs. early12. For OS (Table 2), early12 patients maintained a significantly worse OS compared to dnMBC after adjustment for other factors (HR 3.76; 2.22-6.38; p<0.001). Positive nodes were found to be associated with significantly longer survival (HR 2.29; 1.17-4.47; p=0.015) whilst patients with HER2 positive tumours were at reduced risk of death (HR 0.500; 0.311-0.802; p=0.004). Similar results were also found in the multivariable analyses for PDRS.

For early24 patients (Table 3), PDRS was worse compared to dnMBC patients after adjustment for other factors at 2 and 5 years (HR 2.53; 1.50-4.27; p<0.001 and HR 2.42; 1.39-4.22; p=0.0019). Again, positive nodes were found to be a significant risk of earlier distant relapse (HR 1.42; 1.05-1.93; p=0.024) whilst patients with HER2 positive tumours had longer survival (HR 0.66; 0.51-0.86; p=0.002). ER-positive status was protective for disease relapse at 2 years compared to ER-negative (HR 0.50; 0.38-0.67; p<0.001), but not at 5 or 10 years.

*Sites of metastases*

Regarding sites of metastases (at any time during disease course), patients in the dnMBC and early12 groups were most likely to have widespread (bone, visceral and brain) disease with 26.3% and 21.4% respectively, compared to 13.6% in the late relapse group. Patients with dnMBC had the highest prevalence of brain metastases (39.5%), which decreased with time to relapse (24.3% in the late relapse group). The proportion with bone metastases correlated with time to relapse amongst those with rMBC: 54.3% of the early12, up to 71.4% with late relapse (71.1% of the dnMBC group). Visceral metastases were equally prevalent throughout all groups.

When the first site of metastases was evaluated, bone only or nodal only disease at presentation was most common in the dnMBC group (30.3% and 15.8% respectively). Visceral metastases at presentation of metastatic disease were less common in the dnMBC group (52.6%) and most common in the early24to60 group (66.8%). Bony metastases at presentation were present in 50% of the early12 group, increasing to 60.4% of the late relapse group (57% of dnMBC). Brain metastases at presentation decreased with time to relapse amongst the rMBC cohort: 18.6% of early12 and 8.7% of late relapses (1.3% of dnMBC).

*Treatment*

Amongst dnMBC patients, 65.8% (50/76) had local surgery. Survival was better in those who had surgery, with a univariable HR of 0.41 (0.24-0.68, p=<0.001) and 5-year OS of 44.6% (42.24-46.94) vs. 15.27% (7.85-24.97) (Figure 3). Patients were treated with palliative cytotoxic chemotherapy in 98.7% of the dnMBC group versus 71.4% in the early12 group and 70.3% in the late relapse group. Palliative hormone therapy was also highest in the dnMBC group (68.4%), whereas it was given in 28.6% of patients who relapsed within 12 months and 61.4% of patients with a late relapse. Palliative radiotherapy was also administered at the highest rate in the dnMBC group, with 76.3% of patients receiving it, compared to 60.0% in the early12 group and 50.0% in the late relapse group.

Discussion

This is the largest prospective study to evaluate metastatic disease in the young onset breast cancer population. We have shown that young women who develop secondary metastatic disease, even if greater than five years after diagnosis, have shorter survival time following diagnosis of metastases compared to those who present with *de novo* metastatic disease. When survival from initial diagnosis (OS) was compared, this was superior for those with dnMBC, compared to those who developed relapsed disease within 24 months.

In this study, nearly a third (27.1%) of women developed metastatic recurrence after presenting with localised disease. Only 2.6% of this cohort had metastatic disease at presentation, lower than the national (unselected age) estimate of 6-7% from Cancer Research UK (1). Late stage at diagnosis is reported to be more common in women aged greater than 80 and so this likely contributes to the higher figure nationally (1, 14). It is also possible that there was an element of selection bias, as oncologists may have chosen to recruit patients with metastatic disease to an interventional study rather than an observational one. However, a retrospective Swedish study found only 1% of patients aged less than 40 presented with metastases, with this figure increasing successively in each age cohort (up to 10% for those aged greater than 80) (14). In other retrospective studies of women in the same age group the *de novo* rate was 3.0-3.9%, not dissimilar to what is reported here(16-18).

With regards to the identification of *de novo* disease, at the time of recruitment further preoperative imaging would only have been performed if the patient had symptoms suggestive of metastatic disease or possibly because of clinically positive axillary nodes or a large primary tumour. NICE guidelines from 2009 advised that patients with early breast cancer should only undergo staging for metastatic disease in the presence of symptoms(19). CT would not have been particularly common in this context; screening for occult metastases would more typically have involved chest radiographs, liver ultrasound and bone scintigraphy(20). Therefore women diagnosed with *de novo* disease at the time of the POSH study are more likely to have had adverse tumour features clinically or concerning symptoms. Given that we have shown younger patients to have a high rate of node-positivity and more advanced T-stage, in addition to ER-negativity, it is possible that they were more likely to have baseline imaging. At the present time, there is no difference in recommended staging or follow-up for younger patients(12). One retrospective study found that a baseline PET/CT scan upgraded 15% of young, asymptomatic patients with early-stage breast cancer to stage IV(21). Given the better survival for *de novo* patients here, compared to those who relapsed within 24 months and the more adverse biology in young patients, age should be incorporated into clinicians’ decision making with regards to baseline imaging. A randomised controlled trial would be required to identify whether routine imaging for metastatic disease at baseline would improve survival for young patients.

A third of women who developed metastatic disease (34.1%) relapsed within 24 months of diagnosis. This group had a significantly worse OS compared to those who presented with metastatic disease. For PDRS, outcomes were better for *de novo* disease compared to all relapsed groups, including those who relapsed late (after 5 years). It might be assumed that late relapsing disease is inherently indolent but this study challenges that assumption. Review of long-term survivorship with metastatic disease shows 10-year OS rates of 12.45% (95% CI 5.81-21.76) for dnMBC patients, but only 1.73% (0.55-4.24) for patients who relapsed within 24 months (Figure 1B). It is hypothesized that the selection pressure of adjuvant therapy results in the emergence of subclones with mutations conferring resistance to further cytotoxic/hormonal treatment. Another possibility is that women with *de novo* disease may have been treated more aggressively, e.g. with local therapy for oligometastatic disease.

The *de novo* cohort had a remarkably high prevalence of HER2-positive tumours (47.9%). The number of HER2+ cases in this group may contribute to the improved survival seen with dnMBC, given previous reports of long-term responses to trastuzumab in a proportion of patients with HER2+ MBC (22). However, not all HER2+ patients received trastuzumab, reflective of the era during which POSH was recruited. In general, baseline tumour characteristics were adverse in the early relapse group, with the greatest proportion of T2/3, node-positive and LVI tumours.These features may account for the worse prognosis in this group. The late relapse group was marked by ER-positivity (84.2%, vs. 41.4% in the early12 group), node-negativity (31.4% vs. 16.2%) and smaller median tumour size (25mm vs 32mm). Despite this, they still had a shorter PDRS than those with *de novo* disease, suggesting that chemotherapy or hormone therapy -resistant clones play a role in the poorer prognosis of recurrent disease. Future work to determine the differences at a genomic/transcriptonomic level between de novo and recurrent metastatic lesions may improve the precision of treatment for patients with recurrent disease.

It has been hypothesized that there is a different pattern of metastatic spread between patients with primary and secondary metastatic breast cancer. In fact the *de novo* group had the highest proportion of widespread (bone, visceral and brain) metastases during their disease course (26.3%), although this may be reflective of their longer survival and resultant time to allow dissemination. In addition, their widespread metastases may have produced symptoms that resulted in their *de novo* disease being detected with imaging at diagnosis. The prevalence of HER2-positivity in this group may also account for this. The late relapse group was the least likely to develop brain metastases during the course of their disease (24.3%); proportions were similar for the dnMBC and early12 groups (39.5 and 38.6% respectively). However, only one of the dnMBC patients (1.3%) had brain metastases at diagnosis, compared to 18.6% of the early12 group. This may reflect clinicians being more likely to perform a baseline CT brain in patients with recurrent, as opposed to newly diagnosed, breast cancer. Young age has previously been associated with an increased risk of brain metastases; the prevalence in this entire cohort was nearly a third (32.3%)(12). Clinicians should be vigilant for central nervous system symptoms in young women during follow-up for breast cancer. There is no clear evidence that the sites of distant disease explains the differing prognosis between relapse categories; it seems more likely that the underlying biology influences metastatic sites, which determines whether or not a patient presents with *de novo* disease.

This cohort is unique not only for its age but for completeness of *BRCA* gene mutation testing. It was notable therefore that a relatively large proportion of patients with *de novo* disease (11.8%) had a *BRCA2* mutation, whereas just one (1.3%) had a *BRCA1* mutation. Although the 69.3% ER-positivity rate in this group may explain this to some extent, the ER-positivity was higher in the early24to60 and late relapse groups with a lower BRCA2 prevalence (5.8% and 6.3% respectively). Across the cohort of 862 patients with metastatic disease, the BRCA2 mutation rate was 5.6%; the rate was 5.0% across the POSH cohort as a whole (excluding dnMBC patients) (23). The reason for such a large proportion of dnMBC cases having a *BRCA2* mutation is unclear; it is possible that a family history of breast and ovarian cancer in *BRCA2* mutation carriers meant they were more vigilant regarding symptoms of metastatic disease. Additionally, 57% of the dnMBC cohort had bone metastases at presentation (in common with 69.3% being ER+ve, the common phenotype arising from a *BRCA2* mutation); perhaps bone pain in a young woman is a red flag symptom that resulted in early imaging. This might enrich the dnMBC with *BRCA2* mutation carriers. Our results would suggest that further studies using *BRCA* germline testing in young women with dnMBC are warranted.

Primary surgery in patients with *de novo* metastatic breast cancer remains a debated issue. At present decisions are made on a case-by-case basis and there are no clear guidelines. To date, there are two prospective randomized controlled trials (RCTs) evaluating survival benefit for locoregional surgery in patients with dnMBC, with conflicting results. A single-institution study in India showed no improvement in OS, while a Turkish study showed a prolonged OS of around nine months for those who had surgery(24, 25). Interpretation of these studies is limited by a number of factors and the question has not been conclusively answered(11). In this study we have shown an improved survival in those who had surgery (n=50) vs. those who didn’t (n=26), with a univariable HR of 0.41 (p=<0.001), but this outcome is susceptible toselection bias as locoregional treatment was presumably more likely to occur if disease was apparently relatively indolent, less widespread and the patient’s performance status was good. For exampleThis is supported by the fact that 70% of the surgery group and 27% of the no-surgery group had ER+ disease. Of the surgery group, 24% had nodal-only disease at diagnosis, compared to 0% in the no-surgery group. This is in keeping with a previous study showing that surgery is less likely to take place if patients have a high tumour burden(26). The results here indicate that primary surgery is unlikely to be detrimental in selected cases, but a randomized prospective trial in the modern era is required to be more definitive.

Almost all women with *de novo* disease received palliative cytotoxic chemotherapy (98.7%), an unsurprising finding given they had not previously been exposed to systemic treatment. The dnMBC cohort was also most likely to receive palliative hormone therapy, radiotherapy and trastuzumab. The groups least likely to receive palliative chemotherapy were the early12 and late relapse groups (71.4% and 70.3% respectively). In the early12 group, this may be related to lack of recovery from toxicity following recent adjuvant/neoadjuvant chemotherapy, radiotherapy and surgery. Physicians may also have chosen not to treat refractory disease with further systemic treatment. Amongst the late relapse group, 84.2% of whom were ER-positive, most patients received hormone therapy (61.4%). This is likely to reflect tumour burden, in addition to the distribution o/f metastatic disease. It may also be that the late relapses were perceived as more indolent. They experienced less brain metastases compared to the dnMBC group (24.3% vs. 39.5%) but a similar proportion of visceral metastases (77.9% vs. 75.0%). In fact, the poor PDRS of the late relapse group compared to dnMBC would indicate that alternative treatment strategies are needed for this cohort.

The potential limitations of this study include its age. As a result there have been changes in systemic options available, although most patients in this study were treated with anthracycline +/- taxane chemotherapy and approximately half received trastuzumab if HER2+(13). There is an increasingly proactive approach to staging investigations, including the use of advanced imaging, such as positron emission tomography. This may mean that more patients are now diagnosed with occult metastases at presentation, affecting the characteristics of the *de novo* group. Finally, we cannot rule out a degree of selection bias during POSH recruitment. However, as detailed previously, POSH participants recruited from England represented 23% of the available population during the recruitment period and comparison with cancer registry data confirmed that the cohort is representative of the wider population(23). The strengths of this study include the large cohort size and complete germline *BRCA* testing. There are few missing data (with HER2 status missing in only 5.7% of cases) and long follow-up, with only a small number of patients lost to follow-up.

Conclusion

This is the first report to describe patterns of metastatic disease in a large prospective cohort of young onset breast cancer patients with a long follow-up period and complete *BRCA* germline testing. We have shown that women aged 40 or less with *de novo* metastatic breast cancer have better survival following onset of metastatic disease than those with develop secondary breast cancer. Despite more favourable baseline tumour characteristics, patients who developed late onset metastatic disease had a worse PDRS than *de novo* patients, indicating that chemotherapy resistant clones and/or perceived poor fitness due to prior therapies have a significant impact on prognosis. A notable proportion of women with dnMBC had a germline *BRCA2* mutation; this has not previously been highlighted in the literature.

Additional information

*Ethics approval and consent to participate*

Written informed consent was obtained from all participants and the study was performed in accordance with the Declaration of Helsinki. Ethical approval was granted in 2000 (MREC 00/6/69) and the study was approved for recruitment as part of the UK National Cancer Research Network (NCRN) portfolio in 2002, subsequently the NIHR portfolio.

*Availability of data and material*

The datasets generated during and/or analysed during the current study are not publically available.

*Conflict of interest*

ERC declares honoraria from Roche. DME declares honoraria from AstraZeneca and Pierre Fabre. All other authors declare no competing interests.

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*Authors’ contributions*

HM, DE, EC and TM participated in the study conception and design. HM, DE, EC and TM wrote the manuscript. HM, LD and TM performed data analysis and interpretation. All authors approved the final draft.

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Supplementary information is available at the British Journal of Cancer’s website.

References

1. Cancer Research UK. [Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive>.

2. T. Lee, Isaacs C. Treatment of primary breast tumors in de novo metastatic breast cancer. Clin Adv Hematol Oncol. 2014;12(12):820-7.

3. L. Cortesi, Toss A., Cirilli C., Marcheselli L., Braghiroli B., Sebastiani F., et al. Twenty-years experience with de novo metastatic breast cancer. Int J Cancer. 2015;137(6):1417-26.

4. N. U. Lin, Thomssen C., Cardoso F., Cameron D., Cufer T., Fallowfield L., et al. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: Surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013;22(3):203-10.

5. S. K. Chia, Speers C. H., D'Yachkova Y., Kang A., Malfair-Taylor S., Barnett J., et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer. 2007;110(5):973-9.

6. J. A. Malmgren, Mayer M., Atwood M. K., Kaplan H. G. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010. Breast Cancer Res Treat. 2018;167(2):579-90.

7. D. J. Lobbezoo, van Kampen R. J., Voogd A. C., Dercksen M. W., van den Berkmortel F., Smilde T. J., et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer. 2015;112(9):1445-51.

8. U. Guth, Magaton I., Huang D. J., Fisher R., Schotzau A., Vetter M. Primary and secondary distant metastatic breast cancer: two sides of the same coin. Breast. 2014;23(1):26-32.

9. S. Dawood, Broglio K., Ensor J., Hortobagyi G. N., Giordano S. H. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol. 2010;21(11):2169-74.

10. W. D. den Brok, Speers C. H., Gondara L., Baxter E., Tyldesley S. K., Lohrisch C. A. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. Breast Cancer Res Treat. 2017;161(3):549-56.

11. F. Poggio, Lambertini M., de Azambuja E. Surgery of the primary tumour in patients presenting with de novo metastatic breast cancer: to do or not to do? ESMO Open. 2018;3(1):e000324.

12. F. Cardoso, Loibl S., Pagani O., Graziottin A., Panizza P., Martincich L., et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012;48(18):3355-77.

13. E. Copson, Eccles B., Maishman T., Gerty S., Stanton L., Cutress R. I., et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study. J Natl Cancer Inst. 2013;105(13):978-88.

14. J. Brandt, Garne J. P., Tengrup I., Manjer J. Age at diagnosis in relation to survival following breast cancer: a cohort study. World J Surg Oncol. 2015;13:33.

15. D. Eccles, Gerty S., Simmonds P., Hammond V., Ennis S., Altman D. G., et al. Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH): study protocol. BMC Cancer. 2007;7:160.

16. H. Fredholm, Eaker S., Frisell J., Holmberg L., Fredriksson I., Lindman H. Breast cancer in young women: poor survival despite intensive treatment. PLoS One. 2009;4(11):e7695.

17. J. L. Gnerlich, Deshpande A. D., Jeffe D. B., Sweet A., White N., Margenthaler J. A. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg. 2009;208(3):341-7.

18. E. H. Kheirelseid, Boggs J. M., Curran C., Glynn R. W., Dooley C., Sweeney K. J., et al. Younger age as a prognostic indicator in breast cancer: a cohort study. BMC Cancer. 2011;11:383.

19. N. Chand, Cutress R. I., Oeppen R. S., Agrawal A. Staging Investigations in Breast Cancer: Collective Opinion of UK Breast Surgeons. Int J Breast Cancer. 2013;2013:506172.

20. T. Barrett, Bowden D. J., Greenberg D. C., Brown C. H., Wishart G. C., Britton P. D. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer. 2009;101(9):1522-8.

21. C. C. Riedl, Slobod E., Jochelson M., Morrow M., Goldman D. A., Gonen M., et al. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med. 2014;55(10):1578-83.

22. P. Murthy, Kidwell K. M., Schott A. F., Merajver S. D., Griggs J. J., Smerage J. D., et al. Clinical predictors of long-term survival in HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 2016;155(3):589-95.

23. E. R. Copson, Maishman T. C., Tapper W. J., Cutress R. I., Greville-Heygate S., Altman D. G., et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018.

24. R. Badwe, Hawaldar R., Nair N., Kaushik R., Parmar V., Siddique S., et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol. 2015;16(13):1380-8.

25. A. Soran, Ozmen V., Ozbas S., Karanlik H., Muslumanoglu M., Igci A., et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Ann Surg Oncol. 2018;25(11):3141-9.

26. J. Barinoff, Schmidt M., Schneeweiss A., Schoenegg W., Thill M., Keitel S., et al. Primary metastatic breast cancer in the era of targeted therapy - Prognostic impact and the role of breast tumour surgery. Eur J Cancer. 2017;83:116-24.

Figure legends

## Figure 1A – OS for dnMBC vs. early12; reference category: dnMBC.

Figure 1B – OS for dnMBC vs. early24, early24 to 60 and late60+; reference category: dnMBC.

## Figure 2A – PDRS for dnMBC vs. early12; reference category: dnMBC.

## Figure 2B – PDRS for dnMBC vs. early24, early24 to 60, and early 60+; reference category: dnMBC.

Figure 2C - Time-varying HR for PDRS for dnMBC vs. early12; reference category: dnMBC.

## Figure 3 – OS by surgical type (dnMBC patients only); reference category: no surgery.