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EDITORIAL

Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery

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Abstract
Purpose Inflammatory breast cancer (IBC) is rare and associated with a poor prognosis. Following neoadjuvant chemotherapy or endocrine therapy, the multidisciplinary team selected a small number of patients for breast-conservation therapy (BCT). The aim of this study was to determine the outcome of IBC patients treated with BCT in Edinburgh.
Methods Between January 1999 and December 2013, thirty-five women with IBC were treated by BCT. The median follow-up was 80 months.
Results The 5-year actuarial survival for the 35 patients was 70.3 %. Median survival for 20 neoadjuvant chemotherapy patients was 12.9 years (95 % CI 7.6, 18.1), and for 14 patient neoadjuvant endocrine therapy patients, it was 11.8 years (95 % CI 1.1, 22.6) ($p = 0.34$). Five patients developed locoregional recurrence (LRR) between 11 and 72 months after BCT (median 37 months). Three had breast only recurrence, one patient had both breast and axillary recurrence, and one developed axillary recurrence. The 5-year LR-free survival was 87.5 % (95 % CI 76.0, 99.0). In 4 of the 5 patients with LRR, systemic metastases were diagnosed within 6 months and survival post-LRR in these 4 patients was short.
Conclusion IBC is not an absolute contraindication to BCT. LRR in patients after BCT appears part of widespread recurrent disease rather than inadequate local treatment. Multicentre data should be collected to confirm that women with IBC who have a good response to systemic therapy may be offered BCT in the knowledge that in a larger series our observations are confirmed.

Keywords Inflammatory breast cancer · Treatment outcomes · Breast-conserving therapy · Edinburgh Breast Unit · IBC · BCT · IBC for BCT

Introduction

Inflammatory breast cancer (IBC) is rare and associated with a poor prognosis. The term IBC was first used by Lee and Tannenbaum in 1924 [1]. Haagensen in 1956 described IBC as a clinicopathologic entity characterised by diffuse erythema (a third or more of the breast) and oedema (*peau d'orange*) often without an underlying localised mass [2]. A short history of less than 6 months is one of the diagnostic criterion of IBC. A characteristic pathologic feature of IBC is the presence of tumour cells in numerous lymphatics under the skin. According to the WHO classification in 2012, a diagnosis of IBC can be made if typical clinical and/or characteristic histological features are present [3]. Most IBCs are cancers of no special type but there is no characteristic phenotype with regards to ER, PR and HER2 receptors.

In 2011, a consensus panel stated that management should be multimodal with neoadjuvant chemotherapy followed by a modified radical mastectomy and radiotherapy [4]. More

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recently, an IBC working group produced management guidelines and included the statement that in selected cases responding well to primary systemic therapy, a breast-conservation approach may be considered [5]. The Edinburgh Breast Unit manages patients with IBC with primary systemic therapy; either chemotherapy or in post-menopausal women with ER-rich cancers (Allred scores 7 or 8) neoadjuvant endocrine therapy is used. Following assessment of response, and discussion at the multidisciplinary meeting, our unit has selected appropriate patients for breast-conservation therapy (BCT) over the past 20 years. The aim of this study was to determine the outcome of IBC patients treated with BCT in Edinburgh.

Patients and methods

The Edinburgh Breast Unit has comprehensive databases with data entered prospectively on patient and tumour characteristics including pathology data. A review of this database between January 1999 and December 2013 identified 35 women with inflammatory breast cancer who were treated by neoadjuvant therapy followed by breast-conserving surgery and whole-breast radiotherapy. Twenty of our patients had an axillary lymph node clearance and 14 had sentinel node biopsy. One patient had radiotherapy to the axilla only. All data on these patients were confirmed by reviewing electronic records and patient notes. All patients had full imaging by specialist radiologists and diagnoses were made on histologically on core biopsies by specialist breast pathologists. All patients had investigations to assess the presence of metastatic breast cancer. Patients in the Edinburgh Breast Unit are discussed at a multidisciplinary meeting at diagnosis, following completion of any neoadjuvant therapy and after surgery. Decisions on treatment are taken at this meeting. There was annual follow-up of patients and this included clinical examination and annual bilateral mammography. Survival analyses were by Kaplan–Meier.

Results

Mean age at diagnosis was 60.5 (range 35–89). Median follow-up time was 80 months. There were 20 patients treated with initial chemotherapy (initially anthracycline based and more recently anthracycline and taxanes combined) and 14 patients treated with neoadjuvant endocrine therapy (letrozole 2.5 mg per day). One patient was not treated with systemic therapy prior to surgery. She was 80 years of age when diagnosed in 2002, was considered unfit for chemotherapy and had a small localised cancer directly involving the nipple associated with breast erythema and oedema. Her cancer was ER-rich and treatment was wide excision and axillary surgery and one axillary node was involved. Post-surgery, she received whole breast and regional node radiotherapy combined with tamoxifen. Two years after diagnosis, she developed B cell lymphoma and subsequently died of complications of her haematological disease.

Patients treated with chemotherapy were significantly younger than those treated by endocrine therapy [51.8 vs. 72.5 years, $\Delta = 20.7$ (95 % CI 11.9, 29.5), $p < 0.001$]. HER2 testing was not routine in the early part of this study, so only 19 patients had HER2 testing and 5 patients were found to be HER2-positive and 3 of them received Herceptin. The other two were tested before trastuzumab treatment became available in the UK. Three patients had distant metastases at presentation (M1 stage), and the other 32 had no metastatic disease on staging with bone scan, liver US and CT (Table 1).

In the group of 35 patients having BCT, there were 15 deaths overall with a 5-year actuarial survival rate of 70.3 % (95 % CI 54.8 %, 85.8 %). The median tumour size at diagnosis in the neoadjuvant chemotherapy group was 40 mm and in the neoadjuvant endocrine was 31 mm (Table 2). Five of 20 patients in the neoadjuvant chemotherapy group had no residual cancer at surgery (pathological complete response). The residual tumour size in all patients after neoadjuvant treatment is shown Table 2.

The median survival in the neoadjuvant chemotherapy group was 12.9 years (95 % CI 7.6, 18.1), and 11.8 years in the neoadjuvant endocrine therapy group (95 % CI 1.1, 22.6) ($p = 0.34$).

Fifteen patients were N0 and twenty were N1 at diagnosis. Five-year actuarial rate was 78.9 % (95 % CI 57.6, 100 %) for N0 patients and 63.6 % (95 % CI 42.0, 63.6 %) for N1 patients. This difference was not significant ($p = 0.15$), although numbers were small.

Out of 15 patients who underwent sentinel node biopsy, 4 patients had lymph nodes involved and they underwent subsequent axillary dissection or radiotherapy.

Patients with metastases ($n = 3$) had a significantly worse 5-year survival than those without metastases ($n = 32$) ($p = 0.04$, Fig. 1). Of the 3 patients with distant metastases at presentation (M1), 2 died between 5 and 23 months after diagnosis, and one patient with bone metastases on presentation is still alive 4.84 years after her diagnosis.

In patients without distant metastases (M0), median survival was 11.8 years, compared with 1.9 years in M1 patients. Five-year survival rates were 73.9 % for M0 patients (95 % CI 58.3, 89.5 %) and 33.3 % for M1 disease (95 % CI 0, 86.7 %), respectively.

Table 1 Patient and cancer characteristics

Total number	$N = 35$
Age at diagnosis (years)	Mean 60.5 (35–89); median 59
Age in the neoadjuvant chemotherapy group	Mean 51.3 (29–72); median 52 years
Age in the neoadjuvant endocrine group	Mean 72.7 (48–89); median 77 years
Histological type	
NST	31
Invasive lobular	4
ER-positive (+)	21 (60 %)
HER2-positive (+)	5 (out of 19 assessed)*
Follow-up	Median 80 months (range 20–184)

*16 patients were treated before HER2 testing became routine

Table 2 Comparison of the tumour size in the neoadjuvant chemotherapy and endocrine therapy groups

Neoadjuvant chemotherapy (20 patients)	Neoadjuvant endocrine therapy (14 patients)
Mean tumour size 49 mm (15–100)	Mean tumour size 34 mm (11–78)
Median tumour size 40 mm	Median tumour size 31 mm
pCR in 5 patients (25 %)	pCR in 0 patient (0 %)
Residual tumour size after completion of neoadjuvant treatment	
Median 35 mm (range 12–61)*	Median 11 mm (range 4–44)

*Median size in the 15 with residual disease

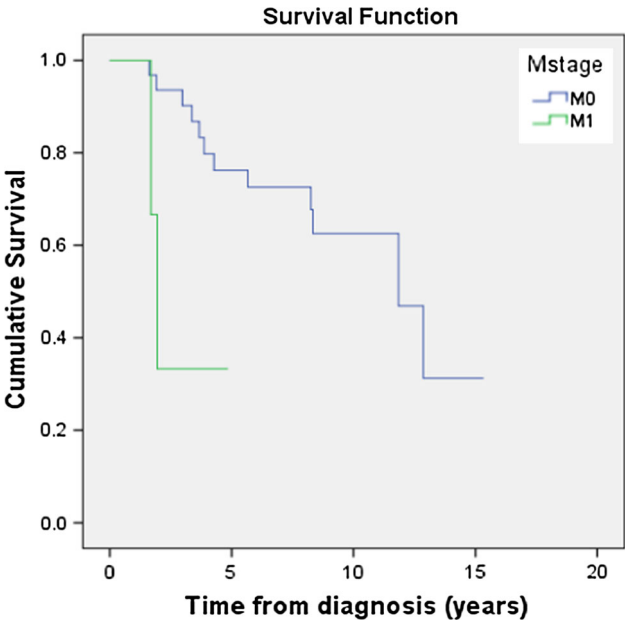

Fig. 1 Overall survival in M0 and M1 stage disease

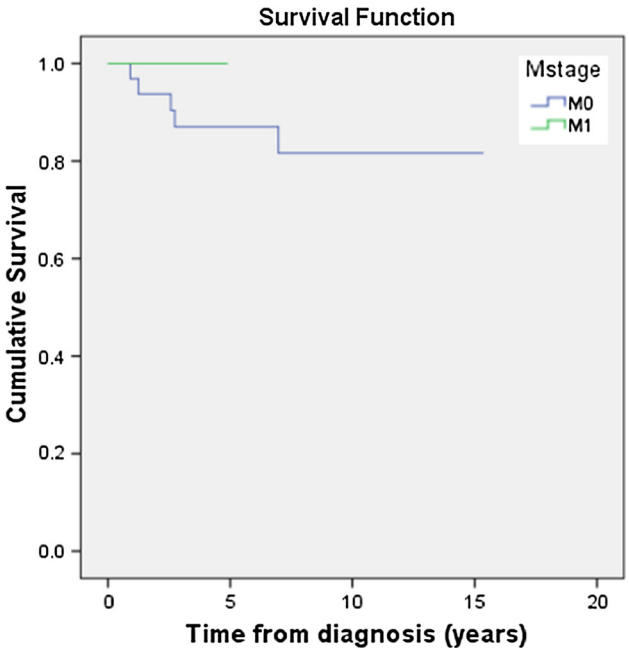

Fig. 2 Local recurrence-free survival related to M stage

Five patients developed locoregional recurrence between 11 and 72 months after initial surgery (median 37 months). Three were in breast only, one patient had both breast and axillary recurrence, and the fifth developed axillary recurrence. The 5-year LR-free survival for all 35 patients was 87.5 % (95 % CI 76.0, 99.0 %)—Fig. 2. No patient with M1 disease developed local recurrence. The 5-year LR-free survival rate for the M0 patients was 86.8 % (95 % CI 74.8, 98.9 %). Local recurrrence did not differ significantly related to nodal status (Fig. 3). The five patients who developed locoregional recurrence are detailed below.

Patient 1 had in breast recurrence 84 months after BCT for inflammatory breast cancer. This cancer was thought likely to be a second breast cancer in the ipsilateral breast.

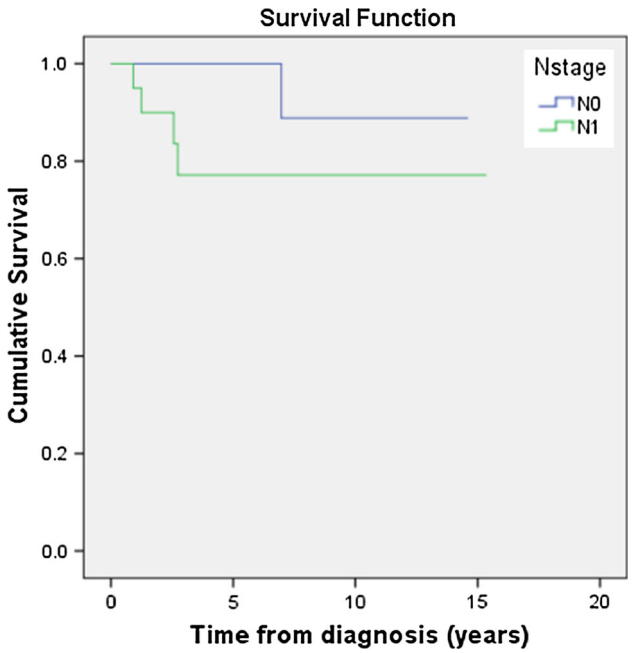

Fig. 3 Local recurrence-free survival related to N stage

This patient had also undergone prior wide local excision for a contralateral breast cancer. On genetic testing, she was found to be BRCA-1 carrier. She was treated with bilateral mastectomy with reconstruction, and is still alive some 21 months after the development of her second breast cancer and 105 months after treatment for inflammatory cancer.

Patient 2 developed recurrence in the breast 15 months after BCT and axillary clearance. Initially, she had neoadjuvant chemotherapy and had 4 positive nodes after neoadjuvant chemotherapy. Within 6 months of developing local recurrence, she developed lung and bone metastases (21 months after initial diagnosis). She died 47 months after initial diagnosis.

Patient 3: 22 months following breast-conserving therapy (BCT), this patient was found to have recurrence in both the treated breast and metastases in the pleura. Her cancer had been bilateral and she had bilateral axillary nodal involvement. She was treated with initial neoadjuvant endocrine therapy; she died 23 months after her initial diagnosis, within 1 month of diagnosis of the breast recurrence and the pleural metastasis.

Patient 4: some 12 months after BCT, this patient had recurrence in the breast and axilla; scans showed she also had metastases in bones and mediastinum. She was initially treated with neoadjuvant chemotherapy, she had 9 out of 9 involved axillary nodes and had adjuvant radiotherapy to the breast, axilla and supraclavicular fossa. She died one month following diagnosis of metastatic disease.

Patient 5 had recurrence in the axilla 31 months after diagnosis. She also had simultaneous nodal metastases in the neck and abdomen. Following neoadjuvant endocrine therapy, she had BCS and a positive sentinel node biopsy and was treated with radiotherapy to the breast and axilla. She died 36 months after her initial diagnosis, 5 months after local and systemic recurrence was identified.

Discussion

As IBC is uncommon, there have been few data from randomised trials to guide treatment, although in the last 2 decades a series of management guidelines have been published [4, 5]. Initially, IBC was treated by mastectomy but this resulted in a high rate of local recurrence with few patients surviving 5 years [6]. The addition of chemotherapy and radiotherapy to mastectomy improved both rates of local control and survival. With neoadjuvant chemotherapy, some patients had a complete pathological response (pathCR) and these women had a much lower rate of developing subsequent distant metastases with a greatly improved overall survival compared to those with residual disease post-chemotherapy [7]. One study found that pathCR was the most important prognostic factor in IBC [8]. In our series, pathCR rates were low. This reflects that there were treated many years ago. One would expect much higher pathCR rates now with the more effective chemotherapy regimens now in use and the improvements in anti-HER2 regimens. Only 3 of 5 patients with HER2-positive breast cancers received trastuzumab in our series because some were diagnosed and treated before trastuzumab became standard of care. Given that negative margins after surgery are associated with better local control and overall survival, mastectomy has been the most commonly used surgical procedure [9, 10]. In many texts, breast-conserving surgery is said to be contraindicated in this condition as is sentinel node biopsy. Only in recent guidelines, it has BCT been considered an option in IBC patients who have an excellent response to neoadjuvant therapy [5].

Although there are few reports of BCT in patients with IBC, the view for many years in Edinburgh has been that in selected patients with localised mass lesions and IBC it is not unreasonable to offer BCT when after neoadjuvant therapy the redness and *peau d'orange* disappears. In these patients, if the cancer is considered excisable by BCS, then this option is discussed with the patient. Over 60 % of the patients in this IBC cohort had ER-rich cancers. Many of these patients were post-menopausal and had other co-morbidities, and so the decision was taken to treat these women with neoadjuvant endocrine therapy (2.5 mg/day) rather than chemotherapy. Responses to neoadjuvant

endocrine therapy in the Edinburgh series were impressive suggesting this is an option for older women with IBC who have ER-rich cancers. Women who had neoadjuvant endocrine therapy were older (mean age = 73 years) compared to those treated with chemotherapy (mean age = 52 years). Their outcomes were not different from patients having neoadjuvant chemotherapy. This suggests that neoadjuvant endocrine therapy is a viable option for older women with ER-rich IBC.

After primary systemic therapy in Edinburgh, a total of 35 had BCT and the outcomes at median follow-up of over 8 years show good rates of local and systemic control that are not different to the rates of control by mastectomy in our practice [11], and this fully justifies our use of BCT. Although there have been other reports of BCT in inflammatory cancer, this is by far the largest series published to date (Table 1). Importantly, in our dataset, there was only a single patient with an isolated in breast "recurrence" and this was actually a second cancer in a treated breast in a BRCA1 mutation carrier. The three other women who developed in breast tumour recurrence did so as part of multiple site metastatic disease. In other words, these women likely developed in breast tumour recurrence as a manifestation of tumour biology not inadequate local treatment. All the women with locoregional and metastatic disease died within a few months of diagnosis of their locoregional recurrence. None of these women had uncontrolled local disease. The other 30 women remained disease-free in the breast until death or latest follow-up. Our data indicate that it is no longer appropriate to state that inflammatory cancer is an absolute contraindication to BCT. It is time to perform a prospective collection of data from many centres, so that if our findings are confirmed then women with IBC who have a good response to systemic therapy can be offered BCT in the knowledge that this is a safe option.

It is also time to consider how best to manage the axilla in patients with IBC. Studies have shown that neoadjuvant chemotherapy can eliminate nodal metastases in IBC but the recommendation in patients with IBC remains axillary dissection. In the current study, patients who were node-negative at diagnosis or who had nodes that resolved after systemic therapy did not have axillary lymph node dissection, but had sentinel node biopsy. There have been no axillary recurrences in the group who were node-negative on sentinel node biopsy. We have now performed sentinel lymph node biopsy in over 20 patients with IBC after primary systemic therapy and out detection rate has been 100 % which is not surprising because sentinel node biopsy has been shown to work in a large series of patients after chemotherapy even if patients are node-positive and then become node-negative after chemotherapy [12]. It may no longer be appropriate to clear the axillary nodes of patients with IBC who are node-negative, as sentinel node biopsy does appear to work in this population. Further studies are clearly warranted.

Compliance with ethical standards

Conflict of Interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Lee BJ, Tannenbaum NE (1924) Inflammatory carcinoma of the breast. Surg Gynecol Obstet 39:580–595
2. Haagensen CD (1956) Diseases of the female breast. Trans N Engl Obstet Gynecol Soc 10:141–156
3. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ (2012) WHO Classification of Tumours of the Breast. WHO IARC, Lyon
4. Dawood S, Merajver SD, Viens P et al (2011) International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 22(3):515–523
5. Rea D, Francis A, Hanby AM et al (2015) Inflammatory breast cancer: time to standardise diagnosis assessment and management, and for the joining of forces to facilitate effective research. Br J Cancer 112(9):1613–1615
6. Kell MR, Morrow M (2005) Surgical aspects of inflammatory breast cancer. Breast Dis 22:67–73
7. Fleming RY, Asmar L, Buzdar AU et al (1997) Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast carcinoma. Ann Surg Oncol 4(6):452–456
8. Harris EE, Schultz D, Bertsch H et al (2003) Ten-year outcome after combined modality therapy for inflammatory breast cancer. Int J Radiat Oncol Biol Phys 55(5):1200–1208
9. Curcio LD, Rupp E, Williams WL et al (1999) Beyond palliative mastectomy in inflammatory breast cancer—a reassessment of margin status. Ann Surg Oncol 6(3):249–254
10. Bristol IJ, Woodward WA, Strom EA et al (2008) Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. Int J Radiat Oncol Biol Phys 72(2):474–484
11. Aziz C (in press)
12. Boughey JC, Suman VJ, Mittendorf EA et al (2013) Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (alliance) clinical trial. JAMA 310(14):1455–1461