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Report

Patterns of local and distant disease relapse in patients with breast cancer treated with primary chemotherapy: do patients with a complete pathological response differ from those with residual tumour in the breast?

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Summary

This study aimed to evaluate patterns of local and distant disease recurrence in patients having primary chemotherapy and compared patterns of relapse in patients with a complete pathological response with those who had residual breast disease. This is an observational study using a sequential series of patients treated with primary chemotherapy. They were followed up for a minimum of 5 years. All data was collected prospectively. Three hundred forty-one consecutive patients with breast cancer were treated with up to eight cycles of doxorubicin-based chemotherapy. Clinical and pathological response rates were evaluated and patients were followed up for disease recurrence (local and distant) and overall survival. Fifty-two patients (16.5%) had a complete pathological response to chemotherapy. Distant disease recurrence occurred in nine patients (17.3%) but no local recurrence was observed. In patients not having a complete pathological response, 86 patients (32.6%) subsequently developed metastases. Local recurrence of disease occurred in 12 (4.5%). There was a statistically significant difference in overall survival between patients whose tumours had a complete pathological response compared with patients who had residual disease in the breast following chemotherapy (88% versus 70% at 5 years, $p = 0.036$). Following primary chemotherapy, about 84% of patients had residual disease in the breast. Surgery is necessary to ensure complete removal of residual tumour and excellent rates of local control are achievable. A complete pathological response is associated with fewer local and distant recurrences as well as improved survival although there are no differences in time to development of metastatic relapse.

Introduction

Primary chemotherapy was initially used in the treatment of patients with locally advanced breast cancers [1,2]. More recently, primary (sometimes termed neoadjuvant) chemotherapy has been used in the treatment of patients with smaller tumours that would have been considered previously to be 'operable' at the patients' initial presentation [3,4]. The aims of primary chemotherapy have been to reduce the size of the primary tumour in the breast, so as to facilitate breast conservation surgery, and also to abolish or reduce the micro-metastatic disease burden, with the intention of prolonging the patients overall survival. Randomised trials have examined the effects of primary chemotherapy when compared with adjuvant chemotherapy in an attempt to determine if there were any differences in terms of survival [5–10]. Whilst these studies have not confirmed a clear benefit in terms of survival, breast conservation is facilitated [5–10].

Clinical response rates (complete and partial) occur in up to 75% or more of patients [1–10]. These clinical responses do not reflect pathological responses within the breast itself because in up to 85% of patients there is histological evidence of residual tumour within the breast. A complete pathological response, however, does identify those patients who will have a better survival [4,10]. Furthermore, improvements in pathological response rates have occurred with the use of novel chemotherapeutic agents, such as the taxanes, and up to 34% of patients can then have a complete pathological response [11]. In addition, those patients receiving the taxane, docetaxel, also may have a survival advantage over those who receive an anthracycline-based regimen [12].

A key question that has arisen, as a result of the development and application of primary chemotherapy to patients with breast cancer, concerns the appropriate treatment of the residual tumour in the breast itself following completion of chemotherapy. In particular, this is

an important question in those patients who have had a complete clinical response of the primary tumour. The NSABP-B18 study of primary chemotherapy [10] demonstrated that approximately 14% of patients had an ipsilateral tumour recurrence as the first site of disease relapse. However, this was only 5% in those patients who had a complete clinical response to chemotherapy. It was also observed that if the patients' tumour was initially large enough to require mastectomy, but breast conservation was subsequently achieved by giving primary chemotherapy, then there was almost double the risk of local recurrence of disease [10]. Other studies have similarly reported that locoregional recurrence rates were 14% overall with 10% experiencing a local recurrence after breast conservation therapy [13]. Moreover, if patients who have a complete clinical response, after chemotherapy, do not undergo surgery then locoregional recurrences in up to 21% of patients may occur [14]. In an attempt to identify patients at most risk of local recurrence a previous study indicated that local relapses occurred in up to 6% of patients if they had surgery to the breast and post-operative radiotherapy [15]. Furthermore, we have reported previously that the risk of local recurrence in an earlier series of these patients was increased in patients having a poor clinical response, or axillary lymph node involvement, following completion of chemotherapy [15].

Despite having a complete histological response within the breast itself, up to 20% of these patients will experience metastatic distant disease relapse at a later stage [10,11]. It seems likely, therefore, that there is clonal heterogeneity in tumour cells, with the tumour in these metastatic sites having a different chemotherapeutic sensitivity when compared to those in the primary tumour in the breast itself. Alternatively, there may be a different availability and biodistribution of chemotherapeutic agent to cells in the metastatic sites when compared with the primary tumour.

This study has examined a consecutive series of patients who have undergone primary chemotherapy in the Aberdeen Breast Unit and has examined patient outcome. In particular, the patterns of recurrence (local and distant) in patients having a complete pathological response have been compared with that of those patients who have had residual disease in the breast following completion of their primary chemotherapy course.

Patients and methods

Patients

A consecutive series of 341 women with invasive breast cancer presented to the Aberdeen Breast Unit between 1993 and 1999 and received primary chemotherapy for large and locally advanced breast cancers (defined as T2 greater than 3 cm, T3, T4 or N2 tumours with any T stage of primary tumour). Data regarding these patients were collected prospectively and we have previously reported local recurrence in 171 of these patients [15]. The tumours of all patients were subjected to triple assessment, including clinical examination, radiological assessment (mammography and ultrasonography) and fine needle aspiration cytology. Invasive cancer was thereafter histologically confirmed with needle core biopsy, or open surgical biopsy if required. The absence of detectable metastatic disease was confirmed by patients having a full blood count, urea and electrolytes, liver function tests, chest X-ray and isotope bone scan. If the liver function tests showed any abnormality then an ultrasound scan of the liver was performed.

Primary chemotherapy

The standard chemotherapeutic regimen used in these patients was cyclophosphamide (1000 mg/m^2), doxorubicin (50 mg/m^2), vincristine (1.2 mg/m^2) and prednisolone (40 mg/day orally for 5 days) (CVAP), given as 6–8 cycles at 3-week intervals, with dose reductions as per our standard protocols [11]. In addition, 98 of the 341 (28.7%) patients received four cycles of docetaxel (100 mg/m^2), at 3-week intervals, instead of a further four cycles of CVAP, as part of a randomised trial of primary chemotherapy [11]. Patients were assessed by clinical examination to determine clinical responses to chemotherapy according to standard UICC criteria and defined as either having a complete response, partial response, stasis of disease, or progression of disease [16]. Written informed consent was obtained from all patients taking part in this study [11], which was granted approval by the Grampian Research Ethics Committee.

Surgery

After receiving primary chemotherapy, 336 of the 341 (98.5%) patients then proceeded to surgery. This comprised either breast conserving surgery or mastectomy. Mastectomy was performed if the residual tumour size was greater than 3 cm, or if the patient wished to undergo a mastectomy irrespective of residual tumour size. Axillary surgery was performed, with either an axillary node sample or clearance being undertaken at the discretion of the consultant surgeon. If after breast conservation surgery the resection margins were positive for tumour, then a further wide local excision or completion mastectomy was performed to ensure the margins were clear of tumour. Reconstructive surgery, for cosmetic reasons, was not undertaken in this group of patients, but latissimus dorsi flap reconstruction was performed, if required, for tissue cover following removal of large residual tumour masses.

Adjuvant therapy

All patients who underwent breast conservation surgery had radiotherapy given to the breast, according to our

standard protocols. Patients with positive axillary nodes after node sample had radiotherapy to their axillae. This comprised 4250 (plus 750 boost) cGy to the breast after conservation and 4500 cGy to the lymphatic basins (axilla and supraclavicular nodes). Patients with large residual primary tumours, close to the pectoral fascia, after mastectomy also received radiotherapy to their chest wall. Oestrogen receptor (ER) status was recorded in 234 patients. Of these, 108 (46.2%) patients were ER-negative and did not receive tamoxifen, whilst 126 (53.8%) patients were ER-positive and received tamoxifen. The remaining 107 (31.4%) patients (ER status not recorded) received tamoxifen for 5 years, as per the policy in the Aberdeen Breast Unit at these times.

Statistical analyses

All statistical analyses were undertaken using SPSS for Windows (v10). The value of a range of possible patient and tumour related factors in predicting complete pathological response and local recurrence were assessed with a binary logistic regression model using a stepwise entry of each factor. Patients were categorised as having either a complete or incomplete pathological response, and as having either developed a local recurrence or not. In patients with a complete pathological response, a multivariate analysis was performed on possible factors, which may predict patients survival. This was conducted using a Cox's regression model analysing overall survival. A p value of less than 0.05 was considered to be of statistical significance in analyses unless indicated otherwise.

Results

Patients and tumour staging

The median age of the patients was 52 years, with a range 28–77 years, and the median follow up was for 61 months (ranging from 1 to 140 months). The TNM staging (6th edition) of these patients is shown in Table 1. The tumour sizes ranged from 1 to 9 cm in diameter but the median tumour size was 5 cm.

Clinical responses to primary chemotherapy

Clinical response was recorded in 324 (95.0%) patients. Two hundred and thirty four patients (72.2%) had a clinical response (complete and partial) but 88 (27.2%) patients had a complete clinical response to chemotherapy. A further 74 (22.8%) patients had stasis of disease, and 16 (5.0%) patients had progression of disease during primary chemotherapy.

Surgery

Surgery was performed in 336 (98.5%) patients. The remaining five patients did not proceed to surgery because either they had died or the disease had progressed and surgical intervention was not deemed appropriate for the patient at that stage. Mastectomy was undertaken in 218 (64.9%) patients and breast conservation surgery was undertaken in 118 (35.1%) of the total number of patients who underwent surgery. It was noted that 25% of those patients with tumours, which were considered to be unsuitable for breast conserving surgery at initial presentation, because of their size, were able subsequently to have breast conservation surgery following completion of primary chemotherapy.

Histological responses to chemotherapy

Experienced breast pathologists (IDM and SP) undertook a careful and thorough histological examination of the resected breast tissue. Three hundred and sixteen of the patients had their tumour response assessed. This revealed that there was no evidence of residual tumour in 52 (16.5%) of patient's tumours. The remainder of patients, numbering 264 (83.5%) in total, had residual invasive cancer that was identified histologically.

Increasing tumour grade (prior to commencement of chemotherapy) and a better clinical response to chemotherapy were independent predictors of a complete pathological response (Table 2). None of the other factors examined achieved statistical significance in this respect. Axillary node status was recorded in 311 patients. Of this group, 133 (42.8%) patients had residual tumour in the axillary lymph nodes detected histologically. Furthermore, in the 52 patients who had experienced a complete pathological response in the breast, only one had detectable tumour in the axillary nodes. A total of 48 patients (15.4%) had more than four nodes involved with tumour following completion of chemotherapy.

Local recurrence of disease

Local recurrence of disease in the breast or chest wall was recorded at any time point including after onset of distant metastasis. Local recurrence of disease occurred in 12 (3.6%) of the 336 patients who had undergone surgery. No local recurrences occurred in any of the 52 patients who had a complete pathological response, following completion of primary chemotherapy. When the local recurrences were examined in relationship to initial tumour grade, there were two recurrences in those patients with grade 1 tumours, three in those with grade 2 tumours, and seven in patients with grade 3 tumours.

Table 1. TMN staging of the patients' breast cancers prior to commencing primary chemotherapy

	N_0	N_1	N_2
T_2	95	13	2
T_3	105	40	11
T_4	28	23	24

Table 2. Evaluation of factors which may have indicated those patients experiencing a complete pathological response to primary chemotherapy (Binary logistic regression model)

Variable	β	SE	Exp (β)	95% CI for exp (β)	p value
Age	0.010	0.022	1.010	0.668–1.053	0.647
Tumour size	0.003	0.016	1.003	0.972–1.035	0.863
Tumour grade	0.732	0.354	2.079	1.038–4.164	0.039
Nodal stage (clinical)	−0.387	0.434	0.679	0.290–1.592	0.373
Clinical response to chemotherapy	1.734	0.411	5.665	2.538–12.673	0.0001
ER status	−0.023	0.301	0.978	0.542–1.7648	0.940

Abbreviations: ER = oestrogen receptor; β = regression coefficient; SE = standard error; CI = confidence interval.

In relation to clinical response during chemotherapy, four recurrences occurred in patients who had experienced disease progression, five in those with static disease, one in a patient who had experienced a partial response, and two patients experiencing a complete response. All resection margins for the removed tumours were clear on histological examination, either after the original surgery or, if necessary, after a further wider excision of margins or mastectomy. Only a worsening clinical response to chemotherapy indicated those patients most likely to have a local recurrence (Table 3).

Distant recurrence of disease

Distant metastatic relapse occurred in a total of 95 (27.9%) of the 341 patients, and this presented at intervals ranging from 3 to 119 months after completion of primary chemotherapy. Sites of recurrence were in bone (61 patients), liver (15 patients), lung (12 patients) and brain (7 patients). Of the 52 patients in whose primary breast cancer there had been a complete pathological response, 9 (17.3%) experienced subsequent distant metastasis (6 bone, 2 liver and 1 with brain metastases). Median time to the presentation of metastatic disease was 26 months. However, in the 264 patients with an incomplete pathological response to primary chemotherapy, 86 (32.6%) patients subsequently developed metastatic disease (55 bone, 13 liver, 12 lung, 6 brain). Median time to the appearance and detection of metastatic disease in this group of patients was comparable, being 29 months from completion of primary chemotherapy.

Comparing patients who had experienced a complete pathological response in their tumour with those who had not, in terms of risk of metastatic disease, there was a statistically significant difference at the 6% level. The patients with a complete pathological response had less disease relapses ($p = 0.06$). However, there was no difference in median time to presentation of metastatic disease.

In terms of type of breast surgery undertaken, 53 (24.3%) of the 218 patients, who underwent mastectomy, had distant metastasis. In 118 patients undergoing breast conservation surgery, 42 (35.6%) patients had metastasis. There were no statistically significant differences between these groups.

Survival

When considering all 341 patients together there was an 88% 2-year survival rate and a 78% 5-year survival rate, as calculated by Kaplan–Meier analysis (Figure 1). In patients with a complete clinical response to chemotherapy their 5-year survival was 90%, in those with a partial clinical response 77%, and in patients with stasis 72%.

Table 3. Evaluation of factors which may have indicated those patients experiencing a local recurrence of disease following completion of primary chemotherapy (Binary logistic regression model)

Variable	β	SE	Exp (β)	95% CI for exp (β)	p value
Age	0.0379	0.039	1.039	0.963–1.120	0.32
Tumour size	−0.022	0.021	0.979	0.939–1.019	0.29
Tumour grade	−0.994	0.777	0.370	0.081–1.697	0.20
Clinical response	1.421	0.549	4.143	1.412–12.196	0.009
Pathological response	−0.107	0.404	0.898	0.407–1.985	0.79
Surgery[a]	0.225	0.249	0.799	0.490–1.302	0.36
ER status	0.229	0.629	1.257	0.366–4.313	0.71
Node status[b]	1.162	0.859	3.195	0.594–17.197	0.17

Abbreviations: ER = oestrogen receptor; β = regression coefficient; SE = standard error; CI = confidence interval.
[a] Mastectomy or breast conservation surgery.
[b] Assessed pathologically.

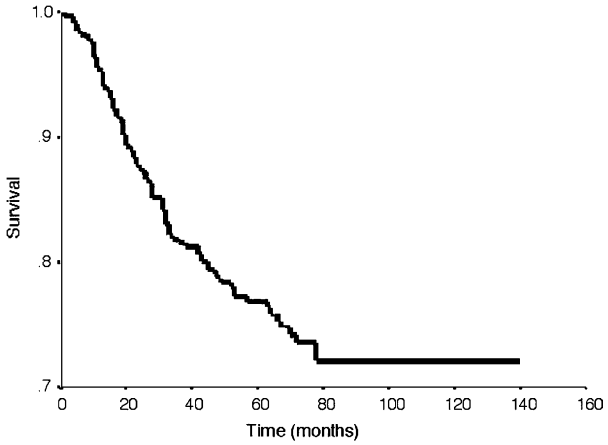

Figure 1. Overall survival of all patients.

In those with disease progression during chemotherapy the 5-year survival was only 12% (log rank = 71.38, $p < 0.01$) (Figure 2).

In terms of pathological response, the 5-year survival of those with a complete pathological response was 88%. In contrast, in patients who had residual disease in the breast following primary chemotherapy (an incomplete response), there was a significant reduction in overall survival with 70% being alive at 5 years (log rank = 4.40, $p = 0.036$) (Figure 3). A multivariate analysis was carried out on patients who had undergone a complete pathological response to determine if there were any factors, which may have allowed a prediction of a better survival in this group of patients (Table 4). The results indicated that there were no other factors that indicated a better survival. A complete pathological response, therefore, was the key indicator of a better overall survival.

Discussion

Following primary chemotherapy, which is given to patients with locally advanced breast cancer, excellent clinical response rates and reduction in tumour sizes can be achieved as documented in our study and by others [1–10,12]. Despite the complete clinical response rate of 27.2%, the overall pathological complete response rate

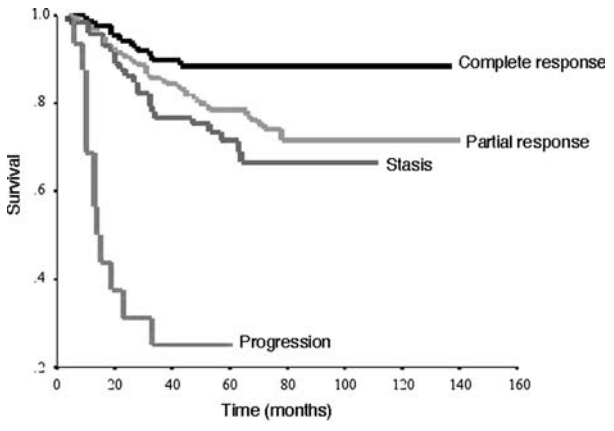

Figure 2. Patients' clinical response in relation to overall survival.

was only 16.5%. Almost 84% of patients will have histologically detectable residual tumour within the breast. Although more recent studies have shown that pathological complete response rates can be significantly increased, by using docetaxel in combination with an anthracycline as primary chemotherapy [11,12,17], two-thirds of patients will still have residual tumour following completion of primary chemotherapy.

At the present time, it is not possible to identify the patients who have a complete pathological response following primary chemotherapy. There are no imaging methods currently proven to detect residual disease with certainty and core biopsies to detect residual disease would be open to sampling error. Surgery, therefore, is necessary for all patients to ensure a complete removal of any residual tumour. Eltahir et al. [4] have shown previously that clinical examination and imaging (breast ultrasonography and mammography) are unreliable indicators of residual disease, therefore, decisions regarding surgery cannot be made using these modalities of assessment.

A recent study of patients receiving primary chemotherapy had audited the outcomes of 453 patients in terms of local recurrence of disease [14]. Although 136 patients had a complete clinical response after completion of primary chemotherapy, only 67 of these underwent surgery to the breast. The remaining 69 patients had radiotherapy to the breast, in an attempt to obtain local disease control, and did not undergo any surgery to the breast. However, 21% of patients not having surgery had a local recurrence in comparison with a 10% local recurrence rate at 5 years in patients who did undergo surgery [14]. The authors commented that this did not achieve statistical significance ($p = 0.09$) but clearly there was an important trend. Nevertheless, if patients who experienced a local recurrence of disease were treated appropriately, then there did not appear to be any detrimental effect on survival [14]. This lack of effect on overall survival is consistent with previous studies, with long term follow ups, which have indicated that local recurrence of disease does not adversely affect eventual patient outcome [18, 19]. In a smaller study of 62 patients with large and locally advanced breast cancer, Cance et al. [13] reported a local recurrence rate of 14% with 79% of patients undergoing breast conservation therapy. However, all patients in this study did undergo surgery to remove residual disease after completion of primary chemotherapy.

In our study, we also adopted the policy of operating on all patients once primary chemotherapy had been completed, and examined the resected breast tissue histologically. Our local recurrence rate, using this protocol, was 3.1% and there was no local recurrence of disease in any of the patients who had experienced a complete pathological response. Our data also indicated that patients were more likely to experience local relapse of disease if they had grade 3 tumours, or if the disease had stasis or progression of disease, during primary chemotherapy. Although a binary logistic regression

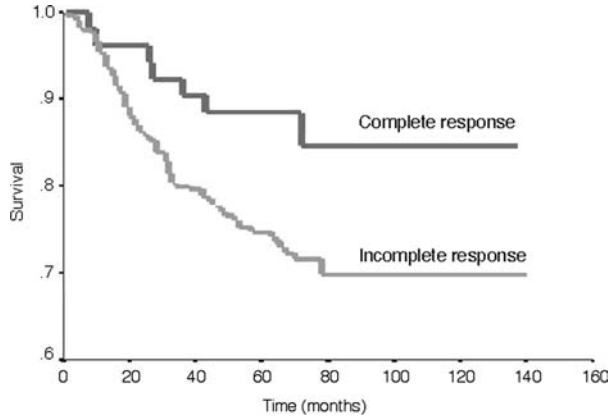

Figure 3. Pathological response of the breast tumours to primary chemotherapy in relation to overall survival.

analysis was carried out to identify factors predicting local recurrence, the small numbers of patients experiencing local recurrence were small making interpretation of this analysis difficult.

On the basis of this study, and previous data, it seems appropriate, therefore, that all patients should undergo surgery once primary chemotherapy has been completed. However, whilst other assessment modalities, such as ultrasound examination [14,20], magnetic resonance mammography [20,21] and positron emission tomography [22], may indicate which patients are most likely to have no residual tumour, following completion of primary chemotherapy, well designed clinical trials are required to confirm this.

It is important to note, that although we can identify patients with a complete pathological response in the breast histologically, these patients have not necessarily experienced a complete pathological response in possible metastatic sites elsewhere in the body. This is indicated by the subsequent development of overt metastatic disease in some patients. In our study, 52 patients had a complete pathological response to chemotherapy, but 17% of this group still experienced a subsequent overt metastatic disease relapse. The sites of metastatic relapse, which are documented in our study, are comparable to patients who have not undergone primary chemotherapy. However, less than 1% of our patients had metastatic relapse demonstrable in the central nervous system. This suggests that the central nervous system is not a sanctuary site for micrometastatic breast cancer cells. Therefore, prophylactic cranial irradiation would not appear to have the potential for benefit in patients with breast cancer receiving primary chemotherapy. This is in contrast to the possible benefits in patients with other tumour types, such as small cell lung cancer, where there may be benefits with a reduction in metastatic relapse within the brain [23].

We also compared the patients who experienced a complete pathological response in the breast with those who had undergone an incomplete pathological response in the breast and had detectable residual disease in the breast. Of this latter group of patients, 30% subsequently developed distant metastatic disease. The pattern of disease relapse, in terms of sites of the tumours, was similar to those patients who had experienced a complete response. Only one patient who had a complete response in the breast had evidence of histologically detectable metastatic disease in the axillary nodes (removed as an axillary sampling procedure).

Previous studies have demonstrated that a complete pathological response does confer a survival advantage in such patients when comparing them with those patients who have experienced an incomplete pathological response [4,10,24]. In view of subsequent metastatic relapse, it has been suggested that there must be some degree of heterogeneity in the ability of metastatic tumour cells to resist chemotherapeutic agents when compared with cells within the primary cancer site in the breast. However, further studies will be required to determine if this is correct.

We have attempted to predict patients likely to respond well (complete pathological response) to chemotherapy. Although other studies have shown that oestrogen receptor status is a predictive factor for response to chemotherapy [25,26] this has not reached significance in this study. This may be due to relatively small numbers of patients with recorded ER status and complete pathological response for any differences to demonstrate a statistically significant difference.

Table 4. Evaluation of factors which in patients with a complete pathological response may have allowed a prediction of overall survival to be made (Cox regression model)

Variable	β	SE	Exp (β)	95% CI for exp (β)	p value
Age	−0.065	0.061	0.937	0.831–1.057	0.293
Tumour size	−0.0003	0.032	1.000	0.939–1.064	0.991
Tumour grade	−0.203	0.841	0.816	0.157–4.241	0.809
Clinical response	−1.473	0.859	0.229	0.042–1.235	0.086
Surgery[a]	−0.359	0.422	0.698	0.305–1.596	0.395
Node status[b]	−0.275	1.245	0.759	0.066–9.719	0.825
ER status	0.946	0.595	2.574	0.066–8.261	0.112

Abbreviations: ER = oestrogen receptor; β = regression coefficient; SE = standard error; CI = confidence interval.
[a] Mastectomy or breast conservation surgery.
[b] Assessed pathologically.

In previous randomised studies of primary versus adjuvant chemotherapy, primary chemotherapy has resulted in an increased rate of breast conservation and this has been an increase in the region of approximately 10% of patients [8–10]. In our series of patients, the analysis also suggested that there was an increased likelihood of breast conservation surgery with primary chemotherapy. Interestingly, of those patients who did undergo breast conservation surgery, one quarter of them had been judged as unsuitable for conservation prior to the commencement of primary chemotherapy because of the large size of their primary breast cancer.

In summary, therefore, a complete pathological response in the breast to primary chemotherapy will be followed by a metastatic relapse in 17% of patients. However, patterns of relapse are comparable to those occurring in patients who have had an incomplete pathological response in the breast. In addition, the central nervous system does not appear to be a sanctuary site for malignant cells in patients receiving primary chemotherapy, therefore, all patients undergoing primary chemotherapy for breast cancer should subsequently undergo breast surgery to ensure the complete removal of any residual tumour.

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