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Primary chemotherapy in breast cancer: *The beginning of the end or the end of the beginning for the surgical oncologist?*

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For the last 2000 years surgery has been the primary treatment for patients with breast cancer. During this period, surgical procedures for breast cancer became more extensive and culminated in the radical mastectomy as described by Halstead. Such extensive surgery was fuelled, and perpetuated, by the widespread acceptance of the Halsteadian concept of tumour biology and tumour spread. As a result of this, radical mastectomy dominated surgical practice for breast cancer for almost 100 years [1]. However, with advances in our understanding of tumour biology, these Halsteadian concepts were challenged. As a result, novel, and less extensive, approaches to the surgical treatment of breast cancer were initiated and evaluated in a scientific manner.

Of particular importance were randomised controlled trials of breast conserving surgery, which were compared with mastectomy in a very careful manner. These trials demonstrated that the more limited surgical procedures resulted in as good a local control of disease, and the same overall survival, when compared with more extensive surgical procedures. Also, the importance of micrometastatic disease and the impact of adjuvant therapies, which are given after surgical resection of the primary tumour, and their impact on survival have become clearer and well recognised [2].

In tracing the development of primary chemotherapy in the management of patients with breast cancer, there are an important group of patients who were first identified over 50 years ago and in whom surgery, either radical or conservation surgery is not appropriate. These are patients with locally advanced breast cancer (defined as tumour greater than 5 cm (T3), fixation of the tumour to skin and/or chest wall (T4), skin oedema (peau d'orange), skin ulceration, satellite nodules and/or infiltration, large (>2.5 cm) or fixed/matted axillary lymph nodes (N2), supraclavicular lymphadenopathy, and/or arm oedema). If they are treated by mastectomy, more than 50% with experience local disease recurrence and very few will survival 5 years or longer [3].

An alternative approach to the treatment of these patients was necessary and one such approach was the use of primary (neoadjuvant) chemotherapy and/or radiotherapy given prior to surgery. This approach was supported by the evidence from studies in animal experimental tumour models, which had indicated that primary chemotherapy might be beneficial in terms of modulating of tumour growth and improving survival if given prior to surgery [4,5]. Therefore, with these pre-clinical studies in mind, De Lana and colleagues reported the effect of treatment with primary chemotherapy in patients with breast cancer who had stage III disease. Vincristine and doxorubicin were given to these patients as primary chemotherapy with the intention of down-staging the disease in the breast prior to subsequent loco-regional treatment [6]. The results were encouraging and substantial numbers of patients responded well, with the primary tumour in the breast being significantly reduced in size. Following on from this and other clinical studies of patients with locally advanced breast cancer, primary chemotherapy was given to patients with breast cancers that were smaller and had been previously considered to be suitable for surgery as the initial treatment.

In many studies, clinical response rates of 75%, (complete and partial) were obtained, with up to 30% of patients

having a complete clinical response and in whom there was no residual tumour detectable in the breast by clinical examination. Subsequently, many investigators have reported similar findings when using primary chemotherapy. Clinical response rates have usually ranged from 51% to 93% [7,8]. Complete clinical responses occur in approximately 20% of patients although in some series, often using complex and prolonged chemotherapeutic regimens, response rates (complete and partial) have been as high as 90% [9]. More recent studies have demonstrated that even higher clinical response rates can be obtained by using newer chemotherapeutic agents. For example, a combination of a taxane (docetaxel) and doxorubin can result in a clinical response rate of up to 95% and as many as two thirds of patients have a complete clinical response [10–12].

In patients who have had a complete clinical response to chemotherapy, is surgery still necessary? The answer to this question is certainly yes at the present time. It is important to remember that whilst clinical responses are excellent, with substantial numbers of patients having no detectable tumour either clinically and/or as identified by imaging (mammography, ultrasonography, magnetic resonance mammography), the pathological responses are substantially less than the clinical ones.

When pathological response rates have been reported, complete histological responses, where there is no residual tumour in the breast, have been reported to occur from 3% to less than 20% of all patients [8,13]. Even with the use of new and more potent chemotherapeutic agents such as the taxanes, complete pathological responses can be increased to 34%. This still means that at least two thirds of patients will have residual tumour in the breast following completion of primary chemotherapy [10–12]. It seems inappropriate, therefore, not to proceed to surgery, with the intention of removing any residual tumour, which is likely to be present in the breast.

Perhaps the necessity for this is not surprising if we consider parallels in the management of testicular tumours. Here, in this situation responses to chemotherapy, even in patients with widespread metastatic disease, can be dramatic with elimination of distant disease and excellent long term survival. However, even when treating patients with widespread metastatic disease primarily with chemotherapy (before any surgery to the site of the primary tumour in the testis), orchidectomy is usually performed after completion of chemotherapy. This is because in up to 12% of these patients there may be residual invasive malignant cells, and also, patients may have in-situ malignancy in the testis, with the consequent risk of disease relapse or further development of another primary tumour [14].

An important development in treating patients with primary chemotherapy (for any type of malignancy) would be to be able to identify those patients with residual tumour following completion of chemotherapy. At the present time this is not possible, but imaging techniques such as magnetic resonance mammography and positron emission tomography may offer this possibility and thus surgery may be avoided in selected patients. The presence of residual tumour within the breast has a prognostic significance for the patient in terms of overall survival. In the NSABP-B18 trial of primary chemotherapy, patients in whom the tumour had undergone a complete pathological response had a significantly better survival than those who had residual tumour remaining in the breast [15].

On the basis of the majority of patients having residual tumour there is still a need for surgery in order to minimise the risk of future local recurrence of disease in patients who have received primary chemotherapy for breast cancer. However, having made this decision as to the requirement for surgery, how extensive should it be? The accepted criteria for undertaking breast conservation surgery in patients not receiving primary chemotherapy are well know and understood. But just how appropriate and applicable are they to patients who have undergone primary chemotherapy?

Recently, McIntosh et al [16] reported a series of 173 women with large and locally advanced breast cancers who had been treated with primary chemotherapy. Standard criteria that are normally used in patients with primary operable breast cancer were applied to patients undergoing breast conservation surgery following completion of primary chemotherapy. The patients in this series had in a local recurrence rate of only 2% if they underwent breast conservation and, 7% if they had undergone mastectomy (median follow up was 62 months). In patients who experienced local recurrence of disease there was a significant reduction in overall survival when compared with those who did not (27 months versus 62 months) [16].

Whether the local recurrence of disease was a predictor of a poor prognosis or was the cause of metastatic disease remains unclear. An important study, which allows further insight, is the NSABP-B18 trial [15]. In this study, 1523 women were randomised to receive either primary chemotherapy or surgery with adjuvant chemotherapy. In patients whose tumours were considered initially to be too large to be suitable for conservation surgery, but in whom conservation surgery was actually undertaken following completion of primary chemotherapy, there was an increased risk of local disease recurrence. The risk of local recurrence was 16% when compared with just 10% in those patients who proceeded to breast conservation

surgery as had been originally planned. In an updated analysis of NSABP-B18, this difference was explained in part by differences in patients' age and their initial clinical tumour size prior to commencing chemotherapy, but there is still a concern as to the adequacy and role of breast conservation surgery in these patients [17].

This is an important issue that requires further consideration. When a tumour responds to chemotherapy, with a consequent reduction in its tumour size and a replacement of the tumour cells by scar tissue, does the tumour reduce size in a uniform symmetrical way? Alternatively, does it reduce in size in an irregular, asymmetrical way with the potential for residual tumour cells to be left in the breast tissue away from the main tumour mass? If it is the latter, which occurs, there are important implications for the significance and appropriateness of what "clear margins" really means when treating patients who have undergone primary chemotherapy with breast conserving surgery.

In the potential for, and application of the use of primary chemotherapy in the management of the common solid cancers, its use in the treatment of patients and the lessons learned are being applied to the management of patients with other solid cancers. For example, the use of primary chemotherapy, prior to undertaking surgery, is well described in patients with advanced gastric and oesophageal cancers [18,19], soft tissue sarcomas [20], ovarian cancers [21] and non-small cell lung cancers [22].

It is clear from these, and other studies, that the use of primary chemotherapy will result in a down-staging of the primary tumour with a subsequent increase in surgical tumour resection rates. Significant numbers of patients can then proceed to surgical resection of the tumour in which this would not have been possible prior to the administration of primary chemotherapy. Furthermore, in terms of overall survival, there does appear to be evidence accumulating that this is increased when compared to patients not receiving primary chemotherapy but proceeding directly to surgery if this was technically feasible [19–21,23].

However, it is interesting to note that whilst clinical responses in terms of decreasing tumour size are good, the same problems that are present in the management of patients with breast cancer also apply to patients with other cancer types. The pathological responses to primary chemotherapy are significantly less than the clinical responses. Moreover, the majority of patients treated with primary chemotherapy will have residual tumour as assessed histologically [18–22]. As for those patients treated for breast cancer, in these patients with different tumour types, subsequent surgical resection of probable residual tumour is still necessary. Once there is a technique for accurately identifying those patients who do not have any tumour remaining following completion of primary chemotherapy then again there is the possibility of selected patients not requiring what are often major surgical procedures with significant morbidity and mortality.

As we are embarking into the third millennium, surgery is still a key modality in the multidisciplinary management of patients with breast cancer who receive primary chemotherapy. Nevertheless, the potential for avoidance of surgery, at least in selected patients in whom there is no residual tumour remaining is real and tangible, – if they can be identified accurately. In other areas of breast cancer treatment and management such as in situ cancer, breast reconstruction, then the role of surgery is clear – at least for the present time. Perhaps improvements in health education, elimination/reduction of risk factors predisposing to breast cancer, developments in our understanding of nutrient-gene interactions central to carcinogenesis, and the possibility of chemoprevention, may obviate the need for surgery. Whilst we may be witnessing the end of the beginning for the breast surgical oncologist, at the present time surgery still has a prime position in the management of patients with breast cancer.

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