Opinion

Post Mastectomy Radiotherapy in Patients with 1-3 Positive Axillary Nodes - A Current Perspective in an Era of Increasing Breast Reconstruction

Sarah Forsyth1, Cindy Mak1, and Sanjay Warrier1,2*
1Chris O’Brien Life House Breast Surgery Department, Australia
2Royal Prince Alfred Academic Institute, Australia

INTRODUCTION

The debate over post mastectomy radiotherapy [PMRT] in patients with 1-3 positive axillary lymph nodes is long standing and despite a recent meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group [EBCTCG] in 2014, the jury is still out [1]. This publication appears to have broadened many breast cancer units indications for radiotherapy, particularly in the post mastectomy setting, which has subsequent effects on our patients undergoing immediate breast reconstruction.

The EBCTCG meta-analysis included 8135 women across 22 randomized trials and aimed to address the still controversial concept of whether PMRT reduces loco regional recurrence [LRR], overall recurrence, and breast cancer mortality in patients with 1-3 positive axillary lymph nodes.

Of the group of women included in the study, 16% [1314] had 1-3 positive axillary nodes and the authors concluded that treatment with PMRT reduced LRR from a rate of 20.3% without radiotherapy to 3.8% with radiotherapy [2p<0.00001]. Overall recurrence and overall breast cancer mortality were also reduced [RR 0.68 and RR 0.80 respectively].

CONSIDERATIONS FOR PMRT

The addition of adjuvant radiotherapy to current systemic therapy regimens

The EBCTCG meta-analysis is one of many papers published in recent years that have perhaps failed to acknowledge the differences in systemic therapy regimens that we currently use compared to those given to patients included in their analysis.

Although the authors were able to identify variations in the systemic therapy regimens the patients received, this was simplified in terms of the possible effects on results and how they extrapolate to current practice. In the 1-3 nodal groups, 62% of women received chemotherapy alone [most commonly methotrexate, cyclophosphamide, and fluorouracil] and 21% of women received Tamoxifen alone. Only 3% of women with estrogen receptor positive disease received both chemotherapy and Tamoxifen, and 14% of women received no systemic therapy at all. However, for the statistical analysis patients were simply categorized as receiving no systemic therapy, or receiving chemotherapy +/- endocrine therapy.

In 2015, Whelan and colleagues published the MA20 trial on the effects of regional nodal irradiation in women with node positive or high risk node negative disease. Although the authors stratified according to type of chemotherapy and if endocrine therapy was given or not given, the patients were recruited between 2000-2007, and only those after 2005 were treated with Rituximab [2]. It is now well known that Trastuzumab significantly reduces loco regional recurrence in HER 2 positive cancers which in turn will effect extrapolation of results reported in such studies [3].

The EORTC trial on internal mammary and medial supraclavicular radiotherapy in early breast cancer was also guilty of this omission. Although 99% of the node positive group and 66% of the node negative group in the trial received systemic therapy, no details were recorded on the type or duration of systemic therapy which again is crucial for outcomes such as LRR and survival in our current treatment paradigms [4].

In 2016, Lai et al., published data on almost 300 patients with early breast cancer and 1-3 positive axillary nodes. These patients were treated with mastectomy and modern systemic therapy regimens but did not receive PMRT. Interestingly, they reported
a 10 year LRR rate of 10% [5], a rate significantly lower than the 17.7% LRR rate reported in a similar cohort of patients in the EBCTCG analysis [1]. These results allow us to question what the LRR rates may have been for the EBCTCG cohort of patients had they received the current standards of systemic therapy, and if PMRT really confers the benefit that is reported in this study.

The advances in treatments and change in practice we have seen since these trials were carried out, which in some cases was up to 50 years ago [note that data collection for the EBCTCG meta-analysis was from 1964-1986] leads us to wonder whether the systemic therapy used was out of date. Current practice now sees the majority of patients being treated with both endocrine and taxane based chemotherapy. It is likely that many of the patients in the EBCTCG analysis were under treated [6]. Furthermore, the chemotherapy regimens used in most of the studies were not in line with current practice and the endocrine therapy was restricted to tamoxifen alone. Aromatase inhibitors are now standard of care in the postmenopausal group and often used in conjunction with zoladex in the premenopausal group.

Molecular and clinic pathological prognostic indicators for recurrence

Another concern with the EBCTCG analysis and other papers published on this topic is the lack of consideration for tumor biology and the effect it has on a patient’s risk of recurrence. It is now common practice to perform basic hormone receptor status and HER-2 status on tumors as this guides our treatment and aids prognostication. Molecular profiling of tumors is a rapidly expanding area of research. Further sub classification of molecular subtypes is likely to aid prognostication and treatment in the near future. We also know that clinic pathological factors such as tumor grade, lymph vascular invasion, and margin status may affect a patient’s risk of recurrence.

During the period of recruitment for the studies included in the EBCTCG analysis, HER-2 status was not always available. Oestrogen receptor status was available, but was not reported. We know that triple negative tumors have higher rates of recurrence [7] and estrogen receptor positive, progesterone receptor positive, and HER-2 negativity are associated with a better prognosis [8]. We also know that treating HER 2 positive women with Trastuzumab lowers LRR irrespective of whether they receive radiotherapy[3] and that modern combined systemic therapy regimens [Trastuzumab and chemotherapy] have better outcomes [9]. All of the above now helps guide the types of adjuvant treatment our patients receive and have significant impact on LRR.

The absence of stratification by biological subtype in the EBCTCG analysis places doubt over the extrapolation of the results to current practice. If the two treatment groups differed in the balance of triple negative and HER 2 positive subtypes, then this could account for significant bias between the treatment groups.

In the above mentioned study by Lai et al., the authors also aimed to identify factors that may increase an individual’s risk of LRR, to help stratify patient treatment in this difficult sub group. They identified three factors that increased the risk of LRR; tumour >3cm, age less than 40 years, and the presence of extensive intra ductal tumour components [5].

Similarly, in 2005 Truong and colleagues published data looking at factors that increase the risk of LRR in the 1-3 node positive groups, as a way of predicting who would benefit from adjuvant radiotherapy. The authors retrospectively reviewed a prospectively collected British Columbia database in patients undergoing mastectomy and axillary clearance, with 1-3 nodes involved. The factors identified as increasing the risk of LRR (>20%) were triple negative disease, age less than 45 years, a medial tumour location, and greater than 25% of node involvement[10]. The findings of this study demonstrate that a tailored approach to the node positive group warrants further investigation.

Although the MA20 study reported improvements in disease free survival and distant disease-free survival in those treated with whole breast irradiation and regional nodal irradiation, again there was not adequate consideration of tumour biology within the groups. A subgroup analysis of ER and PR positive tumour subtypes was performed, however triple negative tumour subtypes and Her-2 status was not considered [2]. These two groups are of more concern when it comes recurrence so this unknown is significant [7,8].

The EORTC study also failed to consider biological subtypes. The groups were stratified according to tumour location, stage, and menopausal status, but the biology of the different tumours was not addressed. Again this leads us to question the reported small but significant reduction that was seen in disease free survival and distant disease free survival in women treated with whole breast radiotherapy and regional nodal radiotherapy [4].

The Korean Radiation Oncology Group [KROG 14-23] has made a valuable contribution to the pool of literature on this subgroup of patients with 1-3 positive axillary nodes. The authors retrospectively analysed 1382 women who underwent mastectomy for T1/T2 cancers with 1-3 positive axillary nodes. All patients included in the study received modern systemic therapy treatment without radiotherapy, with the aim of identifying risk factors that contributed to recurrence, and ultimately those that may benefit from PMRT. Interestingly, the 10 year LRR rate was 10.5% without radiotherapy, which is significantly lower than that reported in the EBCTCG trial [20.3%]. There could be multiple reasons for this discrepancy but of particular importance is that the cohort in the Korean study received systemic therapy in line with current treatment paradigms, however as previously discussed, many of the patients that made up the EBCTCG meta-analysis received outdated systemic therapy [11].

In addition to the low rate of LRR in this study, the following factors were identified as in creasing the risk of LRR; age less than 35 years, T2 stage, high tumour grade, close resection margin and triple negative biological subtype. The authors concluded that patients with four or more of these risk factors could benefit from PMRT, and those with three risk factors warrant discussion.
These findings challenge those of the EBCTCG meta-analysis and highlight the benefits of modern systemic therapy regimens, in addition to supporting a tailored approach to the administration of PMRT in this subtype of patients with 1-3 positive axillary nodes [11].

Current recommendations for PMRT

Although the EBCTCG meta-analysis gives us an update on the longer term results previously published, it does not end the debate on how we should treat women with 1-3 positive axillary nodes following mastectomy. This question requires further trials with superior designs to include patients treated with current systemic therapy regimens and consideration of molecular subtype and clinic pathological features. We eagerly await the results of the SUPREMO trial, the first randomized study on women with intermediate risk breast cancer, comparing overall survival in those receiving chest wall irradiation versus those who do not [12]. Hopefully these results will help characterize who will benefit from PMRT.

Until such time we suggest that PMRT in the 1-3 nodal group should still remain a discussion among treating physicians, with careful consideration of individual prognostic factors including patient age, tumour location, tumour stage and grade, resection margin status and biological tumour subtypes.

The impact of PMRT on breast reconstruction

The next question that warrants discussion is what impact the EBCTCG publication has had on radiotherapy rates and subsequent reconstruction outcomes. Many breast cancer units have broadened their indications for radiotherapy since the publication of these results. This has occurred in conjunction with advances in both mastectomy [skin and nipple sparing mastectomy] and reconstructive techniques.

Reconstruction in the setting of radiotherapy is a challenge that breast surgeons need to consider seriously. It is a balance between the best oncological and cosmetic outcomes for our patients. Recent publications reassure us that the use of implant based reconstruction is oncologically safe. Kronowitz and colleagues reported on LRR rates in the PMRT setting, in those undergoing implant based reconstruction versus those who did not. At 40 months there were no local recurrences in the irradiated group and no difference in recurrence free survival between the groups [13].

The effect of radiotherapy on cosmetic outcomes and subsequent psychosocial effects for our patients is difficult to manage. The current available literature reports increases in overall complication rates, capsular contracture, wound infections, reoperation and implant removal, in those who undergo reconstruction followed by PMRT [14-18].

In addition to this we need to consider what type of reconstruction is most appropriate for our patient. Currently many believe that autologous reconstruction has better outcomes than implant based reconstruction in the PMRT setting [19]. However there have been recent advances in implant based reconstruction that may close this gap in the future [20]. In either setting, the increases in rates of PMRT in recent years come with a larger complication profile and poorer aesthetic outcomes.

Complications of PMRT and immediate breast reconstruction

In 2010, Berry and colleagues reported a series of over 1000 patients undergoing both implant based and autologous reconstruction. They noted a major complication rate of 24.4% in those who underwent implant based reconstruction but did not receive radiotherapy versus 45.4% in those who did. In addition, just under 30% of patients who received PMRT required removal of their implant and 10.3% of this group eventually required autologous based reconstruction. The authors concluded that radiotherapy was the greatest risk factor for major complications in implant based reconstruction, in addition to raised BMI and increasing age. In contrast to this, in the autologous based reconstruction group there was no difference in major complication rates between the patients who received PMRT versus those who did not [14].

Ho and Sbitany showed similar disappointing results in the PMRT setting. Not only did Ho et al., report a 4 times increased risk of complications in those undergoing implant reconstruction followed by PMRT, they also reported significantly higher rates of capsular contracture [15]. Sbitany's group reported increased rates of infection and implant removal in those undergoing PMRT [16].

In a prospective multicenter study of 141 mastectomies and two-stage reconstructions with PMRT, Gross et al., found concerning rates of capsular contracture. At 37 months, 67% of patients had Baker I/II capsular contracture and 32.5% had Baker III/IV contracture. 22% of patients had complete reconstruction failure. This study also offered additional information on other predictors of reconstruction failure with the highest associations being higher grade of tumour, smoking, and a node positive axilla [17].

Rates of reoperation in irradiated reconstructed breasts appear to be higher than those not irradiated. Cordeiro reported on outcomes of PMRT in over 2000 implant based reconstructions. In the group that underwent PMRT implants required removal in 9.1% of cases versus 0.5% of cases in those who did not undergo radiotherapy. The authors further observed a 17.5% implant loss rate at 12 years in the PMRT group, compared to 2% in the non irradiated group [18].

In another series of 151 patients undergoing implant based reconstruction and PMRT, at 7 years 17.1% of implants required replacement and 13.3% required removal. The most common reasons for re operation were infection, implant extrusion and malposition [15].

Cardiopulmonary effects secondary to PMRT

In addition to the cosmetic complications of radiotherapy in breast cancer, there is also the added concern of cardiopulmonary toxicity. This has been widely demonstrated in the literature.
[21-25], most extensively in a meta-analysis carried out by Cheng and colleagues examining the long term cardiac risk after radiotherapy in women with breast cancer [26].

This analysis concluded that there is an increased risk of coronary heart disease and cardiac mortality in women undergoing radiotherapy for breast cancer when compared to those not treated with radiotherapy. In addition, the risk is increased with treatment of the left breast when compared to the right [26]. This finding was supported by Sardar et al., in another robust review, concluding that cardiovascular mortality is significantly higher in women treated with radiotherapy for left sided breast cancer when compared to right sided disease [23].

Furthermore, the dose effect of radiotherapy for breast cancer on ischaemic heart disease was studied in a large Danish and Swedish population. Increased rates of ischaemic events were reported in these women, with a linear increase in adverse events seen with increasing doses of radiation [22].

A systematic review of the published cardiac doses in breast cancer irradiation between 2003 and 2013, demonstrated that the dose to the heart is increased in the setting of left sided breast cancer and internal mammary node treatment [25]. Ohri et al., also reported increased radiation exposure to the heart and lungs in the treatment of internal mammary nodes [24].

Effective techniques such as deep inspiratory breath holds to reduce doses to the heart and lungs have been identified however [25,27-30], which has yielded positive results in multiple trials including that carried out by Jethwa et al. This group recently investigated the timing and dose effects of PMRT in the setting of immediate breast reconstruction. The authors reported that immediate breast reconstruction did not delay PMRT, nor did it confer an increased dose to the heart or lungs [deep inspiratory breath hold techniques were used in the administration of radiotherapy for this study]. In addition, target coverage was not compromised by reconstruction [27].

These findings were supported in two recently published systematic reviews by Smyth et al., and Latty et al., both of which examined the effects of deep inspiratory breath holding techniques on reducing cardiac exposure in breast cancer irradiation [29,30].

Although the above discussed studies demonstrate the effectiveness of these techniques on reducing cardiac toxicity, until the protocols used in these studies are widespread across all breast cancer centres, cardiopulmonary toxicity in PMRT should remain a valid concern for the treating physician.

Radiotherapy before or after reconstruction?

The timing of radiotherapy relative to reconstruction is increasingly less clear. Traditionally, we perform two-stage surgery and reconstruction after radiotherapy treatment is completed. One option would be to consider radiotherapy prior to mastectomy in patients who are candidates for autologous reconstruction.

A meta-analysis published by Barry & Kell reported on the optimum sequencing of breast reconstruction in the setting of PMRT. This study included 1100 patients across 11 studies and reported overall morbidity rates four times higher in those undergoing PMRT compared to those who did not. The authors also considered autologous versus implant based reconstruction outcomes, and found that the risk of complications in autologous reconstruction was one fifth of those undergoing implant based reconstruction. Interestingly, delaying PMRT until after reconstruction did not have any effect on outcomes in this patient group [31].

Radiotherapy and skin/nipple sparing mastectomy

Since the early 90’s when Toth and Lappert first described skin and nipple sparing mastectomies, we have increasingly offered this technique to our patients to improve cosmetic outcomes, conferring subsequent psychosocial benefits [32]. The effects of radiotherapy on reconstruction following these procedures are important to consider.

Burdge et al., published a series on the effects of radiotherapy in over 1000 cases of nipple or skin sparing mastectomies and implant based reconstruction. They reported radiation induced complication rates of 38% in the nipple sparing mastectomy group and 30.8% in the skin sparing group. The rate of wound infection and tissue necrosis was 16.7% and capsular contracture occurred in 10% of cases [33].

Spear and colleagues had similar results in patients undergoing nipple sparing mastectomy and implant based reconstruction followed by radiotherapy. They reported implant loss rates of around 10% and a total complication rate of 33%. They also reported poorer outcomes in those women undergoing PMRT compared to those who had had radiotherapy prior to surgery in autologous reconstruction [34].

Although it is possible to perform these less aggressive mastectomy techniques in the setting of implant based reconstruction and PMRT, the complication rates appear to be higher and this needs to be communicated with the patient prior to their surgery.

CONCLUSION

This is by no means a review of the extensive pool of literature published on this controversial topic; rather an insight into the authors’ view on the recent EBCTCG meta-analysis in relation to other relevant studies. In addition, the authors consider the possible consequences these results may have on women undergoing breast reconstruction.

When considering all of the above mentioned issues, we as breast surgeons should be aware of the risks that PMRT may have on breast reconstruction. When one combines this risk profile with the broader indications for PMRT that have come about since the publication of the EBCTCG meta-analysis, this has the possibility to impact on complication rates and patient satisfaction.

As such, the administration of PMRT in the setting of low nodal burden should be individualized and patients who may benefit from this treatment regimen should be carefully selected.
REFERENCES


