Irish Journal of Medical Science (1971 -) (2019) 188:75–83
https://doi.org/10.1007/s11845-018-1846-6

ORIGINAL ARTICLE

Neoadjuvant chemoradiation and breast reconstruction: the potential for improved outcomes in the treatment of breast cancer

Niamh O' Halloran[1] · Terri McVeigh[1] · Joseph Martin[2] · Maccon Keane[3] · Aoife Lowery[1] · Michael Kerin[1]

Received: 27 February 2018 / Accepted: 8 June 2018 / Published online: 14 June 2018

Abstract

Background Immediate breast reconstruction (IBR) improves psychosocial and quality of life outcomes. Post-mastectomy radiation therapy is indicated for patients with a high risk of locoregional recurrence including locally advanced tumours (≥ 5 cm) or greater than or equal to four axillary nodes positive for breast cancer and can be a relative contraindication to IBR. Administration of radiation therapy pre-operatively, analogous to neoadjuvant chemotherapy, may reduce time to completion of treatment and facilitate better access to IBR.

Methods This is a prospective pilot study in a tertiary referral breast cancer unit, comparing surgical, pathological response and oncological outcomes and time to completion of therapy for a prospective group of patients who received neoadjuvant radiotherapy with a cohort of age- and stage-matched patients requiring post-mastectomy (± reconstruction) radiation between 2010 and 2016.

Results Sixteen patients with locally advanced breast cancer underwent neoadjuvant radiation and were age- and stage-matched to 32 patients who received post-mastectomy radiation therapy (PMRT) between 2010 and 2016. Neoadjuvant radiotherapy resulted in shorter time between diagnosis and treatment completion (245.6 ± 44.2 days in the neoadjuvant group, 291.2 ± 36.7 days in the adjuvant group, $p = 0.001$). A higher proportion of patients undergoing neoadjuvant chemoradiation therapy underwent breast reconstruction (14/16 patients in the neoadjuvant group, 15/32 patients in the adjuvant group, $p = 0.007$) without an increase in complication rate ($p = 0.117$). There was a trend towards improved pathological complete response and survival in the neoadjuvant group.

Conclusion This pilot study confirms that neoadjuvant chemoradiation is a feasible way of delivering breast cancer treatment and may facilitate improved access to IBR.

Keywords Breast cancer · Breast reconstruction · Mastectomy · Neoadjuvant chemoradiation · Neoadjuvant radiotherapy

Introduction

The treatment of breast cancer has changed dramatically over recent decades and currently involves a diverse multidisciplinary team of surgeons, medical oncologists and radiation oncologists [1]. Each of these specialties continues to evolve, resulting in more effective treatments and improved outcomes for breast cancer patients [2–6]. The delivery of chemotherapy in the neoadjuvant setting in the treatment of breast cancer is becoming more common and is frequently delivered with the aim of reducing tumour burden to facilitate breast-conserving surgery (BCS) [7]. However, mastectomy is still a required component of surgical treatment in this group of patients in the case of chemoresistant or multifocal tumours [8]. For patients undergoing mastectomy, breast reconstruction has become the standard of care and is known to improve psychosocial and quality of life outcomes [9]. According the NICE guidelines, all patients undergoing mastectomy should be counselled about immediate breast reconstruction options [10].

Post-mastectomy radiation therapy (PMRT) is central to breast cancer treatment protocols in women with a high risk

✉ Niamh O' Halloran
niamhoh91@gmail.com

[1] Discipline of Surgery, Lambe Institute, NUI Galway, Galway, Ireland

[2] Department of Radiation Oncology, Galway University Hospital, Galway, Ireland

[3] Department of Medical Oncology, Galway University Hospital, Galway, Ireland

of disease recurrence. Indications for this include tumour size ≥ 5 cm, greater than or equal to four positive axillary lymph nodes, the presence of lymphovascular invasion and higher histological grade tumours [11]. Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has suggested that women with one to three positive axillary nodes may also benefit from radiotherapy, thus potentially expanding the indications for radiotherapy in the treatment of locally advanced breast cancer (LABC) [12]. Although it is an effective means of reducing local disease recurrence and improving systemic outcomes [13, 14], radiotherapy can be associated with negative sequelae, particularly in the case of immediate breast reconstruction. Several studies have demonstrated the increased risk of severe capsular contracture in patients who have been treated with radiotherapy post-implant-based reconstruction [15–19]. Short-term complications are more common in implant-based reconstructions in the setting of PMRT including infection (13.5 vs. 5.8%), mastectomy flap necrosis (10.5 vs. 5%) and reoperation secondary to complication (37.0 vs. 16.6%). PMRT is associated with an implant reconstruction failure rate of 16.8% [20]. Subsequently, PMRT has become a relative contraindication to immediate implant-based breast reconstruction. Autologous breast reconstruction appears to be more suitable for patients requiring PMRT; however, radiation still has deleterious effects on aesthetic outcomes [21, 22]. The timing of delivery of post-mastectomy radiotherapy is also crucial to the cosmetic outcome of breast reconstruction. Berbers et al. carried out a systematic review of breast reconstruction before and after PMRT, which evaluated complication rates and cosmetic outcomes of implant and autologous breast reconstruction in relation to timing of radiotherapy delivery post mastectomy. They recommended that replacement of tissue expanders with definitive implants should be carried out before radiotherapy, and autologous reconstruction should be carried out post PMRT to avoid radiation-induced fibrosis and impaired cosmesis [23].The ASCO guidelines do not offer a recommendation on radiotherapy and PMRT secondary to a paucity of evidence [24]. However, IBR should be integrated into patient's management even if radiotherapy is indicated.

Neoadjuvant radiotherapy is the standard of care in certain tumours (e.g. oesophageal, rectal) and is delivered sequentially with neoadjuvant chemotherapy as a "radiosensitiser" [25]. This mechanism is hypothesised to result from enhancement of the radiation damage secondary to the incorporation of chemotherapeutics into the cellular DNA. Inhibition of cellular repair mechanisms also enhances the radiation effects. The combination of neoadjuvant chemotherapy and radiotherapy improves pathological response and decreases rates of distant metastases, as seen in oesophageal and rectal tumours [14, 26]. Controversy exists as to the appropriate time interval between completion of neoadjuvant treatment and surgical resection of the tumour. The ideal interval between neoadjuvant treatment and surgery allows maximal tumour regression while not resulting in greater post-operative complications, thus resulting in optimal long-term oncological, functional and aesthetic outcomes [27]. One meta-analysis reported higher rates of pathological complete response and tumour downstaging in rectal tumours with longer intervals; however, there is limited evidence for timing of resection post-neoadjuvant treatment and further studies are required [28].

A clear survival advantage has been shown in those patients in receipt of neoadjuvant therapy who achieve a pathological complete response (pCR) [2]. A higher rate of pathological complete response has been demonstrated in breast cancer patients treated with neoadjuvant chemoradiation [29]. However, there have been very few studies investigating this novel treatment sequence. Zinzindohoué et al. analysed the pathological complete response rate in those patients treated with neoadjuvant chemoradiation. They reported a rate of 36% which was higher than that published in other studies. However, they also demonstrated that pathological response was also dependent on tumour characteristics such as size, histology, molecular subtype and Ki67 [29]. In addition to pathological response, neoadjuvant radiotherapy in the treatment of breast cancer has also been associated with several other advantages. Grinsell et al. reported on 29 patients who were treated with neoadjuvant chemoradiation therapy and concluded that the challenges associated with operating in a recently irradiated surgical field were outweighed by a shorter treatment period and superior cosmetic results. They also claim that neoadjuvant chemoradiation has at least equivalent oncological safety to standard treatment with adjuvant radiotherapy [30]. Pazos et al., in a study of 22 patients, concluded that delivery of radiotherapy in the neoadjuvant setting simplified the reconstructive pathway, making breast reconstruction more accessible in locally advanced breast cancer [31]. Evidence that delaying delivery of radiotherapy more than 6 months from the start of chemotherapy has detrimental effects on survival also suggests that early radiation therapy is essential [32]. Delivery of radiotherapy in the neoadjuvant setting may also overcome the major side effects of PMRT on breast reconstruction cosmetic outcomes [1], by sparing exposure of the newly reconstructed breast to radiation. We hypothesise that the integration of neoadjuvant radiotherapy into the breast cancer treatment protocol will result in shorter treatment completion times along with making immediate breast reconstruction more accessible to greater numbers of mastectomy patients.

Our aim was to conduct a pilot study to investigate the effect of administration of radiotherapy in the neoadjuvant setting by comparing the uptake of IBR, time to completion of therapy, pathological response rates and outcomes including post-operative complications.

Methods

This ethically approved, prospective pilot study was undertaken in a tertiary referral specialist breast unit. Between 2010 and 2016, 16 patients with locally advanced breast cancer were selected to receive radiotherapy in the neoadjuvant setting prior to mastectomy. The selection criteria for this included a histological confirmation of invasive breast cancer with a tumour size of greater than 5 cm or a tumour requiring mastectomy (multifocal tumour/tumour to breast size ratio, failed trial of BCS), or histologically confirmed nodal involvement. Patients with metastatic disease, a personal history of another solid organ cancer or contraindications to radiotherapy were excluded.

A historic group of age- and stage-matched patients managed using the traditional treatment sequence of neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy was selected for comparative analysis (Fig. 1). These patients are a consecutive cohort of breast cancer patients treated at this institution during the same time period. Each patient in the neoadjuvant radiotherapy group was age- and stage-matched to two patients in the adjuvant radiotherapy group.

Chemotherapeutic regimes were defined by the treating medical oncologist based on the biologic and hormonal features of each individual tumour.

Post-mastectomy and neoadjuvant radiotherapy consisted of a dosing schedule of 50.4 Gy at 6/15 MV in 25–28 fractions delivered over 5 weeks to the chest wall or intact breast. Supraclavicular radiotherapy was administered in 25 patients, consisting of a dosing schedule of 50.4 Gy at 6 MV photons delivered in 25–28 fractions over 5 weeks. The dosing schedule did not differ for those patients whose breast was still intact at the time of radiotherapy administration.

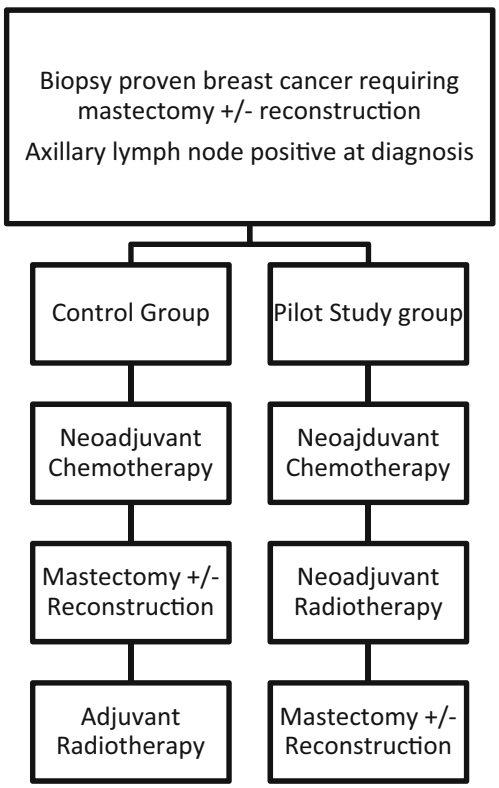


Fig. 1 Study design

All patients undergoing mastectomy were counselled about breast reconstruction options in the outpatient setting, and both implant and autologous reconstruction techniques were performed based on breast size and shape, surgeon's decision and patient preferences. All reconstruction procedures were performed by oncoplastic or plastic surgeons in the same tertiary referral centre.

Pathological response to neoadjuvant treatment and rate of recurrence were analysed for both groups, along with survival. Pathological response was measured by the Chevallier classification, which is defined as follows:

Grade 1: Complete pathological response macroscopically and microscopically
Grade 2: Presence of in situ carcinoma only in the breast, without invasive tumour and tumour cells in the lymph nodes
Grade 3: Presence of invasive carcinoma with stromal alterations, such as sclerosis or fibrosis
Grade 4: No or few modifications of the tumoral appearance

Breast reconstruction procedure details and post-op complications were analysed. Completion of therapy was defined as date of mastectomy with or without reconstruction or date of delayed reconstruction for the neoadjuvant radiotherapy treatment group and as date of completion of adjuvant radiotherapy for the adjuvant radiotherapy treatment group.

Data was analysed using SPSS, version 23. Chi-square test and independent *t*-test were used for variable analysis. p values < 0.05 were considered statistically significant.

Results

Sixteen patients with locally advanced breast cancer were treated with neoadjuvant radiotherapy for the treatment of breast cancer in this study. Each of them was age- and stage-matched to 32 patients who underwent PMRT. The demographic and clinicopathologic details for these patients are outlined in Table 1. The mean age was 49.9 ± 11.1 years, and the mean follow-up was 39.8 months (median 36.6 months).

The neoadjuvant radiotherapy cohort can be subdivided into two groups according to the indication for mastectomy in this study: those patients who underwent primary mastectomy due to tumour multifocality/large tumour size ($n = 9$ patients) and another group of patients who underwent primary

Table 1 Patient clinicopathologic details

Patient characteristics	Adjuvant radiotherapy	Neoadjuvant radiotherapy	*p* value
Age at diagnosis	51.31 ± 12.14	47.0 ± 8.2	0.064 (independent *t*-test)
Mastectomy specimen weight (g)	889.28 ± 635.8	592.13 ± 425.03	0.246 (independent *t*-test)
Tumour histology			
• Invasive ductal CA	28	11	0.191 (chi-square test)
• Invasive lobular CA	3	4	
• Invasive ductal and lobular CA	0	1	
• Predominant in situ component	2	0	
Radiological T size			
• T1	0	0	0.656 (chi-square test)
• T2	4	4	
• T3	10	10	
• T4	2	2	
Nodal status			
• N1	21	14	0.428 (chi-square test)
• N2	6	2	
• N3	0	0	
Grade			
• Grade 1	2	0	0.498 (chi-square test)
• Grade 2	20	12	
• Grade 3	10	4	
Molecular subtype			
• Luminal A	15	12	0.175 (chi-square test)
• Luminal B	6	0	
• Her 2	7	3	
• Triple negative	4	1	

BCS with positive resection margins in whom mastectomy was required as secondary surgery ($n = 7$ patients). There was no significant difference in the age profile of the two groups.

Twenty-eight patients underwent skin-sparing mastectomy (13 in the neoadjuvant radiotherapy group, 15 in the adjuvant radiotherapy group, $p = 0.023$), with 12 patients undergoing nipple-sparing mastectomy (6 in each of the neoadjuvant and adjuvant radiotherapy groups, $p = 0.176$). A higher proportion of patients in the neoadjuvant radiotherapy group ($n = 14/16$) underwent post mastectomy breast reconstruction compared to the adjuvant radiotherapy group ($n = 15/32$) ($p = 0.007$, chi-square test). The majority of these were immediate breast reconstruction with two delayed reconstructions in the adjuvant group and one delayed procedure in the neoadjuvant group. The timing of radiotherapy did not affect the type of reconstruction carried out ($p = 0.135$, chi-square test). A range of autologous and implant-based reconstructive procedures were performed including deep inferior epigastric perforator flap ($n = 4$), extended latissimus dorsi flap ($n = 8$), latissimus dorsi flap with implant ($n = 9$), tissue expander ($n = 3$), direct to implant ($n = 2$) and implant with acellular dermal matrices (ADM) ($n = 3$) (Table 3).

There was no difference in the rate of post-operative complications between the neoadjuvant (five complications) and adjuvant radiotherapy (four complications) groups ($p = 0.117$) (Tables 2 and 3). There were three wound infections in the neoadjuvant group: one requiring oral antibiotics, one requiring removal of implant and ADM (Strattice™ Reconstructive Tissue Matrix) and one requiring debridement and washout of the autologous reconstruction site. There was also one event of wound breakdown in an implant-based reconstruction and one post-op respiratory tract infection in the neoadjuvant group. Complications in the adjuvant radiotherapy group consisted of two seromas requiring drainage, a haematoma requiring evacuation and a subcutaneous parasternal fluid collection. Tumour factors such as clinical tumour stage (T stage) ($p = 0.253$, chi-square test) or nodal status ($p = 0.206$, chi-square test) had no effect on rates of complication. No type of reconstruction was identified as a risk factor for post-op complications ($p = 0.667$). Breast size did not affect complication rates ($p = 0.472$).

The treatment response results are outlined in Tables 2 and 5. Six patients in each of the neoadjuvant and adjuvant groups achieved a pathological complete response, and one patient in each group exhibited no response to neoadjuvant treatment (p

Table 2 Response to neoadjuvant treatment and recurrence

	Adjuvant radiotherapy	Neoadjuvant radiotherapy	*p* value
Pathological complete response (Chevallier classification)			
• Grade 1	6	6	0.335 (chi-square test)
• Grade 2	16	4	
• Grade 3	7	4	
• Grade 4	1	1	
Recurrence			
• Recurrence/metastases	6	0	0.064

= 0.335, chi-square test). Both tumours that did not respond to treatment were of Luminal A subtype. All hormone-negative Her2-overexpressing tumours and triple-negative tumours in the neoadjuvant group had a > 50% response rate to neoadjuvant treatment (Tables 4 and 5). Six patients in the adjuvant group had a recurrence (five distant and one local), whereas there were no episodes of disease recurrence or metastasis in the neoadjuvant radiotherapy group.

The time from diagnosis to completion of treatment was significantly shorter for patients treated with neoadjuvant radiotherapy (Table 4) ($p = 0.001$). In the neoadjuvant radiotherapy group, there was a mean of 48.7 ± 15.3 days between completion of neoadjuvant radiotherapy and mastectomy. In the adjuvant group, there was an interval of 78.5 ± 17.3 days between surgery and commencement of adjuvant radiotherapy treatment. There was no difference in the interval between surgery and commencement of adjuvant radiotherapy between those patients undergoing mastectomy alone (74.5 ± 15.3 days) or mastectomy and reconstruction (84.0 ± 19.4 days) ($p = 0.246$, independent *t*-test). There was no significant difference in length of hospital stay post-op ($p = 0.364$) or length of outpatient follow-up ($p = 0.451$).

There was a trend towards improved survival in the neoadjuvant radiotherapy treatment group compared to the adjuvant radiotherapy treatment group; however, this did not reach statistical significance in our limited pilot study population ($p = 0.243$) (Fig. 2).

Table 3 Breast reconstruction

	Adjuvant radiotherapy	Neoadjuvant radiotherapy	*p* value
Breast reconstruction			
• Mastectomy alone	17	2	0.007 (chi-square test)
• Mastectomy and reconstruction	15	14	
Immediate V delayed reconstruction			
• Immediate	13	13	0.584 (chi-square test)
• Delayed	2	1	
Reconstruction type			
• LD	6	2	0.135 (chi-square test)
• LD + implant	2	7	
• Tissue expander	2	1	
• Implant only	0	2	
• Implant + ADM	2	1	
• DIEP	3	1	
Post-op complications	4 • 2 seroma (Clavien-Dindo grade IIIa) • 1 haematoma (Clavien-Dindo grade IIIb) • 1 parasternal fluid collection (Clavien-Dindo grade IIIa)	5 • 3 wound infection (Clavien-Dindo grades II and IIIb) • 1 wound breakdown (Clavien-Dindo grade IIIb) • 1 respiratory tract infection (Clavien-Dindo grade II)	0.117 (chi-square test)

Table 4 Treatment time

	Neoadjuvant radiotherapy	Adjuvant radiotherapy	*p* value
Diagnosis to completion (days)	245.63 ± 44.16	291.15 ± 38.69	0.001 (independent *t*-test)
Length of stay	8.38 ± 3.6	6.8 ± 2.4	0.364 (independent *t*-test)
Length of follow-up	41.9 months	35.6 months	0.451 (chi-square test)
Completion of neoadjuvant radiotherapy to mastectomy (days)	48.7 ± 15.3 days	n/a	
Completion of mastectomy to starting adjuvant radiotherapy (days)	n/a	78.47 ± 17.3 days	

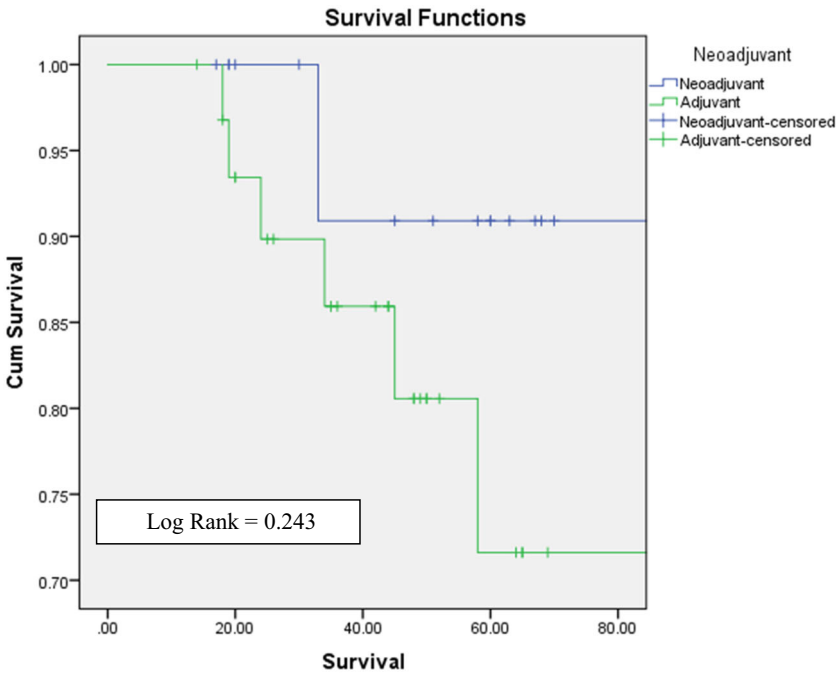
Discussion

The principle finding of this study is that neoadjuvant chemo-radiation allows for a shorter treatment completion time with the possibility of greater access to breast reconstruction without any major increase in complications or any obvious short-term increase in local recurrence. A higher proportion of the neoadjuvant radiotherapy group underwent post-mastectomy breast reconstruction in our study. The delivery of radiotherapy in the neoadjuvant setting also resulted in a shorter time between diagnosis and completion of treatment. This neoadjuvant radiotherapy protocol is an alternative to the concept of delayed breast reconstruction [33], and avoidance of radiating a newly reconstructed breast offers potential protection against fibrosis and capsule formation. The delivery of radiotherapy in the neoadjuvant setting allows for completion of a skin-sparing mastectomy and immediate reconstruction, after the removal of irradiated, less-viable tissue which may cause problems (e.g. skin necrosis) in the post-operative period, resulting in superior cosmetic outcomes by avoiding contracture and exposure of a prosthesis [29]. Two advantages of neoadjuvant radiotherapy with regard to cosmetic outcomes are as follows: (a) skin-sparing mastectomy and IBR can be carried out on women with locally advanced cancer, who may not have been surgical candidates prior to treatment, and (b) as surgery is the completion step of cancer therapy in this protocol, mastectomy and reconstruction do not interfere with chemo- or radiotherapy [33]. Neoadjuvant radiotherapy has the potential to allow IBR to be carried out in women with large, node-positive breast cancers who should not be denied the psychological and physical benefits of breast reconstruction. Receipt of neoadjuvant radiotherapy did not influence choice of reconstruction procedure carried out in our study. There are reports of several types of reconstruction being used in combination with neoadjuvant radiotherapy in the literature: latissimus dorsi (LD) flap [29], LD with implant [33], transverse rectus abdominis muscle (TRAM) flaps [34] and implant reconstruction [8]. LD flaps appear to be most widely studied in this regard and have been proven to be a reliable and robust method of breast reconstruction. Monrigal et al. reported a higher rate of reconstruction failure in TRAM flaps and implant reconstructions than LD flaps [8].

Table 5 Pathological response by subtype

	Complete response	> 50% response	< 50% response	No response	*p* value
Neoadjuvant radiotherapy					
Luminal A	3	3	4	1	0.675
Luminal B	0	0	0	0	
Her 2	2	1	0	0	
Triple negative	1	0	0	0	
Adjuvant radiotherapy					
Luminal A	1	8	5	1	0.313
Luminal B	1	3	1	0	
Her 2	4	3	0	0	
Triple negative	0	2	1	0	

Fig. 2 Survival



Neoadjuvant systemic therapy in the treatment of breast cancer has become increasingly common in recent years for the treatment of large or locally advanced breast tumours and offers the advantages of downsizing tumours to allow for BCS and to ascertain the efficacy of treatment through measurement of the pathological response [35]. Neoadjuvant and adjuvant systemic therapies appear to be equivalent in terms of survival, disease progression and recurrence outcomes [36]. However, a clear survival advantage has been demonstrated in those patients treated with neoadjuvant therapy who achieve a pCR, especially in the case of patients with more aggressive disease subtypes, such as triple-negative breast cancer [2]. The trend towards improved pathological response in our study suggests that there is the possibility of a better prognosis for breast cancer patients treated with neoadjuvant radiotherapy. A study by Zinzindohoué et al. demonstrated a pCR rate of 36% in breast cancer patients undergoing neoadjuvant chemoradiation, a rate that is higher than previously reported with traditional PMRT [29, 37, 38]. Breast cancer tumour subtype also influences the rate of pCR to neoadjuvant treatment. This has been widely studied in relation to neoadjuvant chemotherapy, with hormone-negative tumours exhibiting better pCR rates than hormone receptor-positive tumours [2, 39–41]. We had similar findings in this study.

In our patient population, there were no incidences of local or distant recurrence in the neoadjuvant radiation group compared to six in the adjuvant group. Though this did not reach statistical significance, it does suggest that there is some benefit to be gained from the addition of radiotherapy to the neoadjuvant treatment protocol. Monrigal et al. demonstrated that neoadjuvant chemoradiation was not inferior to the traditional adjuvant delivery of radiotherapy in terms of disease free and overall survival [8]. Roth et al. showed that neoadjuvant chemoradiation resulted in a pCR rate of 29.2% and a better disease-free survival and overall survival, particularly in patients with T2 tumours [42].

The timing of surgery after completion of neoadjuvant chemotherapy and radiotherapy is paramount for the prevention of post-operative complications. It is known that surgery within 2 weeks of chemotherapy can have detrimental effects on outcomes, whereas wounds from surgery carried out several weeks after chemotherapy heal with superior tensile strength [1]. It is generally accepted that 4–6 weeks is the optimum time to operate post-mastectomy radiotherapy, when skin desquamation has settled [28]. Therefore, the 48-day interval between completion of radiotherapy and mastectomy in our study is acceptable. The paucity of evidence for timing of tumour resection post neoadjuvant treatment is not limited to breast cancer surgery and requires well-designed RCTs to guide future treatment guidelines [28].

Overall, neoadjuvant chemoradiation is a feasible way of delivering breast cancer treatment as it results in a shorter treatment time with improved access to breast reconstruction, without increasing complication rates and without any short-term increase in locoregional recurrence.

Conclusion

Neoadjuvant chemoradiation followed by mastectomy and reconstruction is a potential treatment sequence in the delivery of breast cancer treatment with the benefits of shorter

treatment times. The results from this pilot study are encouraging; however, further study in the form of randomised controlled trials and long-term follow-up are required.

Clinical practice points

Currently, the common treatment sequence in breast cancer therapy is neoadjuvant chemotherapy, followed by surgical resection of the tumour and then radiotherapy in the adjuvant setting. Exposure of the reconstructed breast to radiation is known to increase complication rates and results in inferior cosmetic outcomes. As such, an indication for adjuvant radiotherapy is a relative contraindication to immediate breast reconstruction. The delivery of radiotherapy in the neoadjuvant is the standard of care in several tumours, such as rectal and oesophageal cancers. Recently, there has been increased research into neoadjuvant radiotherapy in the setting of breast cancer treatment. Some studies have demonstrated improved rates of pathological complete response to neoadjuvant treatment and improved aesthetic outcomes. This study has found that the delivery of radiotherapy in the neoadjuvant setting for the treatment of breast cancer also results in a significantly shorter time to completion of treatment with a greater number of mastectomy patients undergoing breast reconstruction. In addition, there is no significant increase in the rate of post-op complications. Sequential neoadjuvant chemoradiation followed by tumour resection is a feasible method of treating breast cancer and may become the standard treatment sequence in the future, resulting in greater rates of pathological complete response, shorter treatment time, greater access to immediate breast reconstruction for more patients and improved cosmetic outcomes. However, more randomised controlled trials investigating this treatment sequence are required in addition to long-term data on recurrence, survival and cosmetic outcomes.

Acknowledgements The authors would like to acknowledge Mr. Alan Hussey for his contribution of clinical images to this manuscript.

Funding This research was funded by the Breast Cancer Research (CHY9997). This organisation had no role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval 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.

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