



Radiotherapy in the setting of breast reconstruction: types, techniques, and timing

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As the use of breast reconstruction and postmastectomy radiotherapy (PMRT) has increased over the past decade, the typical approach to integrating radiotherapy with breast reconstruction has provoked intense controversy in the management of breast cancer. PMRT can lead to an increased frequency of complications in the reconstructed breast. Conversely, the reconstructed breast can increase the complexity of radiotherapy delivery. How to minimise the frequency of complications without compromising oncological or cosmetic outcomes of the reconstructed breast is an important shared multidisciplinary goal for oncologists and their patients. Several questions remain, however, regarding the type of reconstruction that should be used with PMRT, when reconstruction should be done relative to PMRT and whether radiotherapy treatment should be directed towards the tissue expander or the implant for women who opt for a two-stage expander–implant reconstruction. Following advances in the planning of radiotherapy treatment, new questions about the application of these technologies in the setting of breast reconstruction have arisen. In this Review, we address these questions by reviewing contemporary evidence on the optimal integration of radiotherapy and breast reconstruction in the management of breast cancer.

Introduction

Among the 252 710 women estimated to be diagnosed with invasive breast cancer in the USA in 2017, more than a third of those with early-stage disease will elect mastectomy as their primary surgical method.¹ For these women, reconstruction might be offered as an option by their plastic surgeon. By restoring the breast mound, reconstruction alleviates the psychosocial and physical consequences of undergoing a mastectomy.^{2–4} The popularity of this approach in the USA is illustrated by increasing rates of breast reconstruction in women with early-stage breast cancer undergoing mastectomy, from 15% in 2000 to 32% in 2011, of which the majority largely consists of prosthetic reconstructions.^{5,6} These epidemiological trends run in parallel to increasing rates of bilateral mastectomy during the same time period.⁷ About three-quarters of patients who receive bilateral mastectomies also have breast reconstruction.⁷

In women with locally advanced breast cancer, post-mastectomy radiotherapy (PMRT) was shown to decrease local recurrence and improve survival in patients with node-positive disease.^{8–12} Despite its therapeutic advantages, PMRT increases the risk of complications and often provides poor cosmesis in women with breast reconstructions.^{13–19} Immediate reconstruction could compromise the delivery of PMRT, resulting in increased doses to the heart and lungs.²⁰ Although not entirely resolved, these concerns have been reduced by advances in both plastic surgery and radiotherapy techniques over the past decade, which have facilitated ways to integrate radiotherapy in the setting of breast reconstruction. Minimising complications without compromising oncological outcomes remains a key goal in the treatment of women who undergo reconstruction and receive PMRT.

In this Review, we examine the unique challenges and controversies that arise from integrating PMRT with breast reconstruction. These challenges include questions on the timing of reconstruction (ie, immediate *vs* delayed); the

type of reconstruction performed (implants *vs* autologous); the radiotherapy technique used (conventional *vs* intensity-modulated radiation therapy [IMRT], *vs* proton therapy); the timing of expander-to-implant exchange (ie, before or after radiotherapy); and, the optimal time to perform an exchange or delayed reconstruction following PMRT. A list of commonly used terms is included in the appendix.

Immediate versus delayed (or delayed-immediate) reconstruction with radiotherapy

The timing of reconstruction is always described relative to the time of the mastectomy procedure. Reconstructions can be immediate, delayed, or a hybrid of the two approaches, called delayed–immediate (figure 1). Immediate reconstructions are done at the time of the mastectomy, whereas delayed reconstructions are usually done 6–12 months after the completion of mastectomy and adjuvant therapy.

In patients who require PMRT, there are practical and aesthetic considerations when choosing between immediate and delayed reconstruction. Immediate reconstruction permits the preservation of the breast envelope, and is easier to perform after skin-sparing mastectomy since the goal is to replace the breast volume rather than to replace the missing skin. By contrast, for delayed breast reconstruction after PMRT, a substantial proportion of the skin below the mastectomy incision is often severely fibrotic and needs to be replaced with healthy skin from a donor site to adequately reconstruct the breast contour. In this way, delayed reconstruction not only limits the amount of tissue available for reconstruction but also lengthens the breast scars, making them more difficult to conceal.

Although immediate breast reconstruction is associated with better health-related quality of life than delayed or no reconstruction, some practitioners consider PMRT a relative contraindication to immediate breast reconstruction because of increased complication outcomes.^{4,21–23}

Lancet Oncol 2017; 18: e742–53

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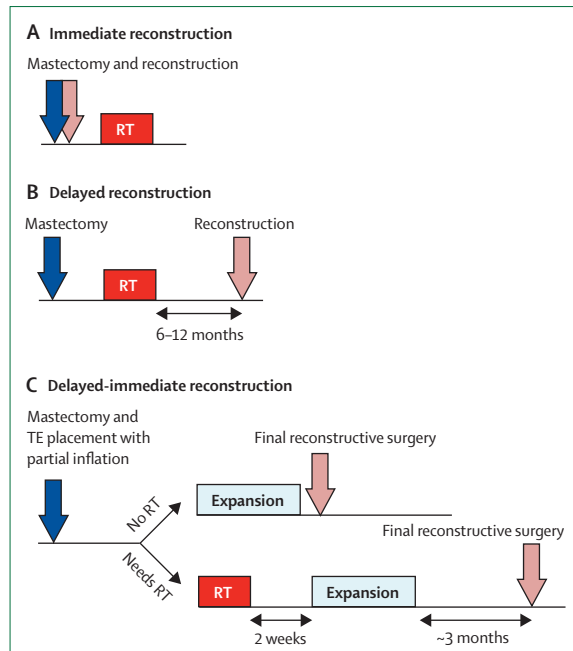


Figure 1: Sequencing of reconstruction processes
RT=radiotherapy, TE=tissue expander.

Nevertheless, a 2017 study²⁴ analysing trends across the studies reported in the US National Cancer Database showed that the use of immediate breast reconstruction increased from 13% to 33% in women receiving PMRT between 2004 and 2013.

One active area of investigation is the use of immediate autologous reconstruction in the setting of PMRT, given the long-term benefits it has on patients' quality of life.²⁵ Practice patterns are highly variable, with some centres routinely irradiating flaps, whereas others avoid this practice and perform flap reconstruction only in the delayed setting. Outcomes following irradiation of flap reconstructions are also variable,²⁶ with some studies showing minimal changes to the irradiated flap, while others report significant incidences of fat necrosis and flap atrophy.

The uncertainties underlying the choice between immediate and delayed reconstruction underscores the importance of the surgical team to preoperatively anticipate the need for PMRT. This dilemma is commonly encountered in women with clinical stage II breast cancer who have been treated with neoadjuvant chemotherapy and in whom lymph node status (the main determinant for requiring PMRT) is either not known or has changed because of response to treatment before mastectomy.

Delayed-immediate reconstruction is a treatment option that was developed in response to this scenario to minimise complications associated with PMRT following flap reconstruction (figure 1). This approach involves placing tissue expanders in all patients at the

time of mastectomy. After interpretation of final pathological changes and determination of the need for PMRT, patients who do not need PMRT will undergo complete reconstruction with an implant or flap, whereas patients who do need PMRT will receive irradiation of the tissue expander followed by definitive reconstruction at a later time.²⁷ This option not only permits the opportunity to avoid radiotherapy to an autologous flap, but also provides an immediate breast mound after mastectomy. Delayed-immediate reconstruction provides a temporising mechanism for the patient, who can now make a final decision about exchanging the expander for either a tissue or implant-based reconstruction at a subsequent time after the completion of radiotherapy.

Implant-based versus autologous breast reconstruction

The primary goal of breast reconstruction is the creation of a symmetrical breast mound. However, this outcome is dependent on the type of reconstructive procedure selected, patient anatomy, the choice between unilateral or bilateral mastectomy, and other surgical factors. Restoration of the breast mound can be done with an implant, autologous tissues, or a combination of an implant and a flap. Several anatomical, patient, and disease-specific factors, such as the size and shape of the breast, availability of tissues around the breast and other donor sites, patient comorbidities, and planned adjuvant therapy, affect the type of reconstruction chosen. This choice must therefore be individualised for each patient. Patient preference is the most important factor in making the final decision, and is essential for achieving long-term patient satisfaction.^{3,28,29} Panel 1 summarises the advantages and disadvantages of implant-based and autologous reconstructions.

Autologous tissue-based reconstruction

Autologous tissue breast reconstruction refers to the use of a patient's own tissues, taken from a different part of the body where there is excess fat and skin to restore the volume (and, in some cases, skin) of the breast after mastectomy. Autologous tissue reconstruction is indicated in women who wish to avoid using implants, who have failed implant reconstruction previously, or who are poor candidates for implant reconstruction—eg, due to their body types or previous breast scar tissue that precludes expansion with a tissue expander and implant insertion. Various donor sites can be used for autologous reconstruction, including the abdomen, infra-umbilical region, back, thigh, or buttocks. Skin, fat, and muscle can be transferred with their original blood supply intact (pedicled flaps) or physically detached and re-attached to vessels at the recipient site (free flaps). The transverse rectus abdominis myocutaneous (TRAM) flap is a pedicled myocutaneous flap that has commonly been described in combination with radiotherapy.³⁰⁻³²

Other common types of autologous reconstructions use the deep inferior epigastric flap (DIEP) or the latissimus dorsi flap.

Autologous reconstructions are considered the gold-standard approach by many plastic surgeons because they are softer, can be individually shaped for the patient, age more naturally with the contralateral breast, and can be used to replace damaged or scarred tissues. Additionally, unlike implants, autologous tissues do not become enveloped in fibrous capsules and can be placed subcutaneously in the anatomical location of the missing breast. Autologous reconstruction also has better perceived aesthetic outcomes from both the physician and the patient compared with implants.^{33–36} In one study²⁵ that used the BREAST-Q evaluation, a patient-reported outcome instrument, to determine patient satisfaction with long-term TRAM flap reconstruction or implants, patient satisfaction with implants reduced over long post-reconstruction surgery time periods, while patient satisfaction with TRAM flap reconstruction remained relatively stable. However, autologous reconstructions can result in donor site morbidity, flap failure (when the flap does not survive), and typically have a longer recovery period than for those who have implants. Complications of autologous reconstruction with PMRT include poor wound healing, fibrosis, fat necrosis, and flap shrinkage, all of which can lead to decreased patient satisfaction and impaired aesthetic outcomes compared with non-irradiated flaps.^{37–40} For example, Crisera and colleagues⁴¹ reported that 13 of 103 women who received immediate autologous breast reconstruction and PMRT had moderate or severe flap distortion. An additional flap or implant was recommended in seven of these patients to correct breast deformity. To reduce the risk of these complications, most plastic surgeons recommend delayed reconstruction when autologous reconstruction is desired and PMRT might be indicated.

Timing of radiotherapy in autologous reconstruction

A historical precedent for avoiding radiotherapy in women who undergo immediate autologous breast reconstruction can be traced back to a 2001 MD Anderson Cancer Center study,³⁰ which showed a significantly higher incidence of fat necrosis, volume loss, and contracture in 32 patients who had immediate breast reconstruction before radiotherapy compared with 70 patients who received PMRT followed by a delayed TRAM procedure. Subsequent reports^{15,26,42} on the effect of radiotherapy on the incidence of complications following autologous tissue reconstruction have been mixed. Berry and colleagues¹⁵ did not find any significant difference between the incidence of complications following autologous tissue reconstruction for patients who did or did not receive radiotherapy. Conversely, another study⁴² reported a higher incidence of overall complications after surgery in patients with irradiated autologous breast reconstructions compared with those who did not receive radiotherapy

Panel 1: Advantages and disadvantages of breast reconstruction

Autologous breast reconstruction

Advantages

- Breast shape can be customised to achieve better symmetry with a contralateral natural breast
- Symmetry less affected by ageing, and weight loss or gain
- Single-stage procedure in most cases

Disadvantages

- Longer operation, hospital stay, and recovery time
- Risk of flap failure
- Scar to the donor site and its potential effects on physical wellbeing

Implant-based breast reconstruction

Advantages

- Shorter operations, hospital stays, and recovery time
- No scars to the donor site

Disadvantages

- Long-term complications, including rupture and capsular contracture
- Usually requires two operations and several tissue expansions

(40% vs 20.2%; $p=0.0023$). However, patients who did receive radiotherapy were reported to have increased wound dehiscence (11% vs 3%; $p=0.049$) compared with those who did not.

More encouraging data from contemporary studies have emerged, providing a stronger rationale for performing immediate reconstruction with autologous tissues. A 2014 systematic review²⁶ of 20 articles showed similar complication rates between patients who had radiotherapy treatment before autologous reconstruction and those who had it after reconstruction. Overall incidence of total flap loss were low (1% in patients who received radiotherapy before reconstruction vs 4% in those who received radiotherapy after reconstruction), with no significant difference in the incidence of fat necrosis, infection, wound healing complications, haematoma, or seroma between groups. A systematic review by Berbers and colleagues⁴³ also concluded that the timing of autologous reconstruction relative to radiotherapy had no significant effect on the total incidence of complications. A meta-analysis⁴⁴ of pooled data from 12 observational studies showed no significant differences in the overall incidence of complications between patients who received immediate and those who received delayed breast reconstruction after PMRT ($p=0.53$). However, women who received delayed reconstruction after PMRT had significantly lower incidence of revisional procedures than those women who received immediate autologous tissue breast reconstruction followed by radiotherapy (odds ratio [OR] 0.15; 95% CI 0.05–0.48; $p=0.001$).

To date, the most compelling data on this topic is from a prospective, multicohort study by the Mastectomy Reconstruction Outcomes Consortium (MROC) involving 11 North American centres and 57 plastic surgeons.⁴⁵ Postoperative complications were reviewed in 175 women who received immediate or delayed autologous reconstruction with PMRT. There was no significant difference in complication rates after 1 year between groups (25.9% in patients receiving immediate autologous reconstruction vs 26.9% in patients receiving delayed autologous reconstruction; $p=0.54$). Although patients with delayed reconstruction reported significantly lower prereconstruction score in the BREAST-Q domains of satisfaction with their breasts, psychosocial wellbeing, and sexual wellbeing than did patients with immediate reconstruction, by 1–2 years after reconstruction both groups reported similar levels of satisfaction in these domains. Collectively, these data suggest that immediate abdominal-based reconstructions tolerate radiotherapy better than previously anticipated with a minimal level of morbidity.

Optimal timing of delayed autologous reconstruction in women receiving PMRT

Several studies^{42,46} have attempted to identify the optimal time for delayed autologous breast reconstruction following PMRT. In a study⁴⁶ of 189 patients who had received delayed abdominal free flap breast reconstructions, Baumann and colleagues reported that patients who had surgery 12 months or more after PMRT showed significantly lower flap loss and repeat operations than did those patients who had surgery within 12 months of PMRT ($p<0.05$). There was no significant difference in partial flap loss, microvascular thrombosis, wound dehiscence, fat necrosis, or infection between the two groups. Conversely, Momoh and colleagues⁴² found no significant difference in the incidence of postoperative complication rates between patients who received reconstruction within 6 months of PMRT and those who underwent reconstruction 6 months after PMRT. Another analysis of these data also showed no difference in the incidence of complications between patients receiving reconstructive surgery within 12 months of PMRT and those receiving surgery 12 months after PMRT. Although these studies did not rigorously define a specific time interval following PMRT after which it is considered safe to perform delayed autologous reconstruction, common sense prevails: the longer one waits for adequate healing of the skin after PMRT, the less likely one is to encounter wound healing complications after surgery.

Implant-based reconstruction

Although delayed autologous reconstruction is the most conservative option for patients who require radiotherapy, not everyone is a candidate or wishes to delay reconstruction until after the completion of radiotherapy treatment. In these patients, implant-based breast reconstruction is a

practical alternative, despite the increase in capsular contracture and reconstructive failure rates associated with radiotherapy to an implant.^{47,48} Implant reconstruction is also a good option for thin patients with few autologous tissue donor sites, athletic patients who do not wish to compromise physical function in other areas of their body as a result of flap harvest, elderly patients, or those with comorbidities, in whom a long surgical procedure is contraindicated.

Implant-based reconstruction can occur either in a single stage or in two stages. Single-stage reconstruction refers to the placement of a permanent implant at the time of mastectomy. However, only a few patients are candidates for single-stage implant reconstruction because of the prerequisite for an adequate quality of mastectomy skin that can withstand direct-to-implant procedure. However, reliable data on the long-term reconstructive and cosmetic outcomes of patients who received PMRT following single-stage implant reconstruction are limited.^{49,50}

Timing of radiotherapy in expander/implant reconstruction

In the setting of PMRT, two-stage expander–implant reconstruction is the most common approach for patients who choose implant reconstruction, and is endorsed by the 2017 National Comprehensive Cancer Network guidelines.⁵¹ During the first part of the two-stage reconstruction, a tissue expander is placed underneath the skin and, usually, the muscles of the chest wall at the time of mastectomy. Postoperatively, the expander is filled incrementally with saline through a metal port during weekly outpatient visits that can continue throughout adjuvant chemotherapy. About 1 month after the completion of chemotherapy, the exchange of the tissue expander for a permanent implant is done as an outpatient procedure.

Ensuring oncological safety of reconstruction in patients with locally advanced breast cancer is a top priority for oncologists and patients alike. The efficacy of this two-stage expander–implant reconstruction process in patients with locally advanced breast cancer who are receiving adjuvant chemotherapy and PMRT has been described^{52,53} by investigators at Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY, USA). Investigators reported 100% locoregional control at 7 years after surgery.⁵² Figure 2 shows two possible sequences of reconstruction events in patients who receive PMRT.⁵⁴ These options are distinguished by the timing of chemotherapy. The first treatment pathway shows the sequence of reconstruction in patients who receive adjuvant chemotherapy (figure 2A), while the second pathway shows the sequence of reconstructive steps in patients who receive neoadjuvant chemotherapy (figure 2B). The median time interval from mastectomy to the beginning of PMRT is 8 months, and the median interval from the end of chemotherapy to PMRT is 8 weeks. Notably, the first sequence is not intended for women who receive neoadjuvant

chemotherapy. The reason behind this restriction is that delaying the initiation of PMRT until after implant exchange is inadvisable in patients who are at high risk of locoregional recurrence because of the risk of large primary tumours or biopsy-proven involvement of lymph nodes. The successful use of these treatment algorithms is highly dependent on multidisciplinary coordination between the breast surgeon, plastic surgeon, medical oncologist, and radiation oncologist, and on direct communication with the patient early on in the treatment course when the need or desire for mastectomy is known and PMRT is anticipated.

The optimal timing of exchange of the expander with the permanent implant relative to radiotherapy is also a subject of heated debate, as evidenced by the increase in studies of two-stage expander–implant reconstruction (table).^{52,54–60} In these eight studies, the proportion of patients with reconstruction failure rates varied substantially from 0% to 40%, depending on whether radiotherapy was delivered to the tissue expander or to the permanent implant. In 2011, Nava and colleagues⁵⁶ reported that 20 (40.0%) of 50 patients had implant failures when radiotherapy was delivered to the issue expander, compared with seven (6.4%) of 109 patients who were treated with radiotherapy to the permanent implant ($p < 0.0001$). Surgeons' assessment of the shape and symmetry of the reconstructed breast showed a higher incidence of good results in patients who received radiotherapy to the permanent implant than those who received radiotherapy to the tissue expander. The incidence of Baker grade IV capsular contracture was the highest in patients receiving tissue expander radiotherapy compared with those who received radiotherapy to the permanent implant (13.3% vs 10.1% vs 0% in the no radiotherapy group; $p = 0.0001$). A subsequent report by Cordeiro and colleagues⁵⁴ also reported a higher proportion of patients with reconstruction failure among patients receiving radiotherapy to the tissue expander compared with those patients receiving radiotherapy to the permanent implant, although this finding was not statistically significant (18.1% vs 12.4%). However, 6-year predicted failure rates were greater for patients receiving tissue expander radiotherapy than for patients receiving radiotherapy to the permanent implant (32% vs 16.4%; $p < 0.01$). An important caveat to this study was that the number of patients with moderate to severe capsular contracture was higher in the permanent implant radiotherapy group than in those who received radiotherapy to the tissue expander, raising the question of whether the reduced incidence of implant failures for those receiving radiotherapy to the permanent implant is worth the higher risk of developing capsular contracture. Other smaller, retrospective datasets have reported no significant differences in the number of complications between the two radiotherapy groups.^{61,62}

Prospective data from a 2016 study⁶⁰ by the MROC group investigating the effect of radiotherapy timing in

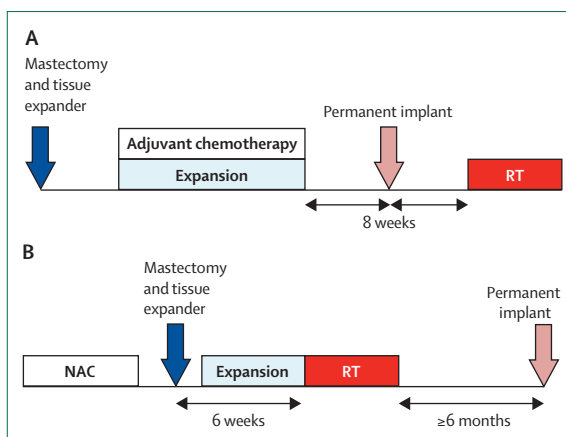


Figure 2: Timing of radiotherapy during two-stage tissue expander-permanent implant reconstruction

(A) Radiotherapy is delivered to the permanent implant. (B) Radiotherapy is delivered to the tissue expander, which is exchanged for a permanent implant more than 6 months after RT. RT=radiotherapy. NAC=neoadjuvant chemotherapy.

	Total number of patients (n)	Median follow-up (months)	Failure rate
Anderson et al (2009)⁵⁵			
Permanent implant	12	48	0.0%
Tissue expander	62	48	4.8%
Nava et al (2011)⁵⁶			
Permanent implant	109	..*	6.4%
Tissue expander	50	..*	40.0%
Ho et al (2012)⁵²			
Permanent implant	151	86	13.3%
Hvilsom et al (2012)⁵⁷			
Permanent implant	49	..*	4.1%
Tissue expander	76	..*	13.1%
Baschnagel et al (2012)⁵⁸			
Permanent implant	4	24	18.0%†
Tissue expander	90	24	..*
Cordeiro et al (2015)⁵⁴			
Permanent implant	210	72	16.4%
Tissue expander	94	72	32.0%
Fowble et al (2015)⁵⁹			
Permanent implant	13	46	7.7%
Tissue expander	86	46	19.8%
Santosa et al (2016)⁶⁰			
Permanent implant	46	14	8.7%
Tissue expander	104	16	11.5%

*Not stated. †Of all patients.

Table: Reconstruction failure rates relative to the timing of radiotherapy treatment in several clinical studies

patients with two-stage expander–implant reconstruction showed no difference in outcomes between those patients who received radiotherapy delivered to the tissue expander and those who received radiotherapy to the permanent implant. In this study, Santosa and

colleagues⁶⁰ reported complications in 150 patients who had two-stage expander/implant reconstruction with PMRT (table). The examined endpoints included major complications, implant loss, and reconstruction failure, defined as removal of the tissue expander or permanent implant without subsequent replacement. All patients were monitored for at least 2 years after reconstruction. The overall proportion of patients with reconstruction failure was 10.7%, with no significant difference between the two groups. Similarly, there was no difference in the proportion of patients who had major complications between the two groups, indicating that timing of radiotherapy was not a significant predictor of complications.

A 2017 meta-analysis⁶³ that analysed data from 899 cases (of whom 489 received radiotherapy to the tissue expander and 410 to the permanent implant) showed that the pooled risk of reconstruction failure was not significantly higher in patients who received radiotherapy to the tissue expander than to those who received radiotherapy to the permanent implant. Notably, the pooled risk of severe capsular contracture was greater for those who received radiotherapy to the permanent implant than in those who received radiotherapy to the tissue expander, which corroborates the data by Cordeiro and colleagues.⁶⁴ This finding seems reasonable since the group who received radiotherapy to the tissue expander might be able to receive capsulotomy at the time of exchange to release scar tissue, minimising the risk of subsequent capsular contracture. Although the incidence of capsular contracture varies substantially from study to study, capsular contracture represents the most crucial long-term risk of implant reconstruction and causes poor cosmesis, pain, and discomfort to the patient. In the absence of persuasive evidence to suggest that one PMRT schedule is better than the other, choosing the option that could reduce capsular contracture is an important consideration when the discussion regarding the risks and benefits of the timing of radiotherapy in expander-implant reconstruction occurs between the patient and her oncologist.

Is there a difference in complications in patients with breast cancer receiving expander-implant reconstruction on the basis of radiotherapy timing? Although the answer might seem obvious after discussing results from the aforementioned studies, the answer is far from clear. High-quality evidence evaluating the type and timing of breast reconstruction in the setting of PMRT remains relatively scarce as most evidence on this question is observational, with only a few randomised clinical trials in this setting. Moreover, variations of published complication rates tend to be secondary to the effects of institutional culture and historical traditions on complication outcomes. Data from some studies have also been difficult to extrapolate either because of non-standardised outcome measures, an absence of information on risk factors associated with surgical complications, small numbers of patients who had

received radiotherapy within each subgroup, and variations in radiotherapy and reconstruction techniques.

Timing of exchange after PMRT in expander-implant reconstruction

For those cases in which radiotherapy is delivered to the tissue expander, the question of when to perform the expander-implant exchange after radiotherapy warrants discussion. Peled and colleagues⁶⁴ compared patients who had an expander-implant exchange within 6 months of PMRT with patients who had the exchange 6 months after PMRT. They found that the proportion of patients with implant failures was higher in patients who had an expander-implant exchange within 6 months, than in those who had the exchange 6 months after PMRT (22.4% vs 7.7%; $p=0.036$). In practice, however, most plastic surgeons will wait at least 6 months following PMRT to carry out the expander-implant exchange to minimise the number of complications, particularly implant failures. Again, common sense prevails and the exact timing of when to perform exchange is probably dictated by how well the skin has healed following PMRT.

Selection of reconstruction types in patients with breast cancer requiring radiotherapy

Few studies have directly compared outcomes of autologous reconstruction with implant reconstruction in patients who have received radiotherapy. A meta-analysis³¹ of four studies that compared these two types of reconstructions reported that autologous reconstruction was associated with less morbidity than implants in the setting of PMRT (OR 0.20; 95% CI 0.11–0.39). These findings were corroborated in 2017 by a large prospective study⁶⁵ on breast reconstruction by the MROC. This study included 2247 women (622 who had radiotherapy, 1625 who did not) who received breast reconstruction at 11 institutions from 2012 to 2015. Investigators found that PMRT was associated with an increased risk of complications at 2 years for patients who had an implant reconstruction (OR 2.64, 95% CI 1.77–3.94; $p<0.001$), while showing that PMRT had similar risks in patients who underwent autologous reconstruction (1.12, 0.66–1.92; $p=0.67$).⁶⁵

Although this MROC study⁶⁵ suggests a higher incidence of complications in irradiated implants than in irradiated flaps, these findings must be viewed in the context of all data on radiotherapy and implant reconstruction that has been collected to date. Several large, single-institution studies of patients treated with PMRT and two-stage expander-implant reconstruction have shown that these patients can successfully complete reconstruction and be satisfied with the results. For example, among 319 patients treated at MSKCC, 91% of patients who received PMRT successfully completed two-stage expander-implant reconstruction (compared with 99% who did not have PMRT).⁶⁶ More than half of patients (53%) who had radiotherapy had acceptable reconstructions, with Baker

grade I or II capsular contracture, 90% of patients with irradiated implants reported being satisfied, of which 94% of patients would choose the same method of reconstruction again.⁶⁶ A practical point to remember during a discussion of the arguments for and against whether to use flap or implant reconstruction is that the use of implants at the initial procedural stage preserves other options, including autologous tissues, for later reconstruction. The converse situation is not true, however, although flap failure necessitating removal of the unviable flap is an uncommon event.

Adjunctive surgical techniques in irradiated breast reconstructions

Surgical techniques can also mitigate the side-effects of radiotherapy in implant-based reconstruction. The current practice is to overexpand the tissue expander by 15–20% to create an ample-sized soft-tissue pocket in anticipation of the development of capsular contracture after radiotherapy. At the time of the exchange procedure, circumferential capsulotomy can be done, which entails incision of the scar tissue lining the pocket around the expander. The purpose of the capsulotomy is to improve contour, particularly lower pole projection.⁵³ Consequently, for women who receive adjuvant chemotherapy with two-stage expander–implant reconstruction and are deciding whether to undergo radiotherapy to the tissue expander or to the permanent implant, the opportunity to receive a capsulotomy at the time of exchange can be an argument for preferring radiotherapy to the tissue expander over radiotherapy to the permanent implant.

Although traditional breast reconstruction ideally calls for complete muscular coverage of the prosthesis, this coverage is not always achievable, particularly in the setting of direct-to-implant reconstruction, nipple-sparing mastectomies, and extensive breast cancer in which the tumour directly invades the pectoralis muscle.⁶⁷ In such cases, plastic surgeons are increasingly using acellular dermal matrices, a derivative of human banked tissue that is composed primarily of collagen but devoid of all natural cellular components such as fibroblasts.⁶⁸ Of the various types of acellular dermal matrices available for clinical use, Alloderm (LifeCell Corporation, Branchburg, NJ, USA) is the most widely used. Acellular dermal matrices serve as a tissue conductive scaffold that is integrated into the native capsule, and revascularised and remodelled over time.⁶⁹ When used as an inferolateral sling, the possible advantages of acellular dermal matrices are reduced pain, improved coverage of the prosthesis, an increased capacity for intraoperative fill, and enhanced inferior pole projection.^{70,71} Among the increasing number of studies on the use of acellular dermal matrices in breast reconstruction, few studies specifically examine the effect of them in the irradiated breast, with only a few studies^{72–77} including irradiated subgroups. Results are conflicting, however, with some

authors reporting excellent cosmetic results and relatively low rates of complications from acellular dermal matrices, both with and without PMRT.^{72,73} Conversely, other studies have suggested an increase in implant infections, seroma, and implant loss, compared with approaches that use total submuscular coverage.^{74,75} Unfortunately, all of these studies are flawed to some extent because of selection bias, non-standard methods of assessing complications, and sparse detail on radiotherapy timing and technique. Despite its widespread use, the purported benefits of acellular dermal matrices in patients who have and have not undergone radiotherapy with breast reconstruction remain largely based on anecdotal evidence and warrant rigorous, prospective study. For similar reasons, the benefits of other adjunctive surgical techniques, such as fat grafting to correct contour deformities after radiotherapy, are unknown.⁷⁸

Development of radiotherapy techniques for reconstructed breasts

Advances in technologies over the past decade have diversified the instruments available for radiotherapy delivery in patients with breast cancer who have undergone reconstruction, reducing the challenges in radiotherapy treatment planning that once seemed insurmountable. Coupled with increasing confidence within the radiation oncology community in treating patients with breast reconstruction, these advances have almost eradicated challenges in radiation treatment planning that once seemed insurmountable in the context of breast reconstruction. This general rule of thumb excludes patients with inflammatory breast cancer, however, in whom immediate reconstruction is generally not recommended given the risk of delaying radiotherapy treatment.

An optimal radiotherapy treatment plan covers the target regions (the reconstruction site, the chest wall, and the regional lymph nodes) with the prescribed radiation dose, while minimising the dose to the adjacent heart and lung. The conventional wisdom was that reconstruction hindered the technical ability to achieve optimal radiotherapy plans.²⁰ This concept has been challenged by more recent studies^{79,80} that have shown the ability to achieve radiotherapy treatment plans via standard field arrangements. Importantly, these studies^{79,80} evaluated the quality of treatment plans on the basis of dose-volume histogram data in patients with breast reconstruction. Most radiation oncologists would agree that the most challenging radiotherapy plans are those designed to include the internal mammary lymph nodes, which lie near the heart. Indeed, a large study⁸⁰ at MSKCC comparing radiotherapy plans in women with reconstructed versus unreconstructed breasts showed that it was not the presence of a reconstruction per se, but the inclusion of the internal mammary lymph nodes, that significantly increased the doses to the heart and

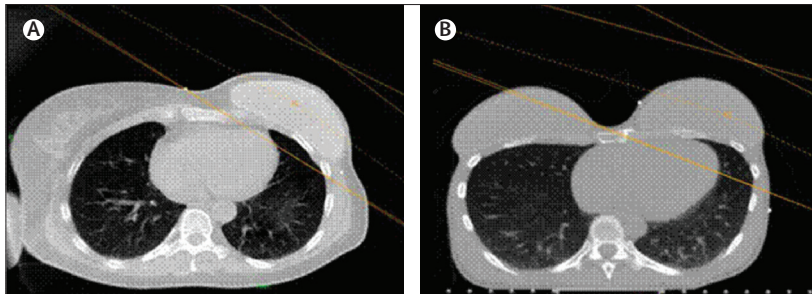


Figure 3: Tangential beam arrangements in unilateral and bilateral implant reconstructions
 (A) In a patient with a unilateral implant, the tangents treat the reconstructed chest wall and nodes. (B) In a patient with bilateral implants, the tangents exit through the contralateral implant and a substantial section of the heart. Reproduced with permission from Ho et al, (2014).⁸⁴

lungs.⁸⁰ These considerations are always counterbalanced by the potential clinical benefits of treatment, extrapolated from studies of patients with breast cancer with one to three positive lymph nodes in whom the inclusion of the internal mammary lymph nodes as part of regional nodal irradiation improved disease-free survival compared with whole-breast radiotherapy alone following breast-conserving surgery.^{81,82}

Between 1998 and 2007, the number of bilateral breast reconstructions increased because of increasing use of contralateral prophylactic mastectomy and the potential advantages of enhanced symmetry afforded by simultaneous reconstruction of both breasts.^{7,66,83} For example, of 1151 patients who had bilateral reconstructions in the MROC study,⁶⁵ 280 (45%) had undergone radiotherapy and 871 (54%) had not. The question of whether bilateral implants hinder radiotherapy planning is frequently raised by oncologists. Precise geometric placement of the tangent beams is particularly crucial to minimise the dose to normal organs and the contralateral side without compromising coverage of the ipsilateral reconstructed chest wall and lymph nodes (figure 3). A study from MSKCC⁸⁴ compared radiotherapy plans of patients with unilateral versus bilateral breast reconstruction. Despite concerns, the authors found that bilateral implants did not diminish the quality of radiotherapy delivery. Common methods to facilitate the clearance of the radiation beams in women with bilateral implants include partly deflating the contralateral tissue expander or taping the contralateral reconstruction away from the treatment field.

Given their larger size relative to a permanent implant, the technical feasibility of irradiating tissue expanders with conventional tangential beam arrangements has often been questioned, particularly in the context of challenging patient anatomies (such as those in which the chest wall and lymph nodes cannot easily be targeted by conventional radiation therapy techniques). There is no consensus among radiation oncologists on whether the deflation of a tissue expander is compulsory before radiotherapy, and common sense typically guides this decision process on a case-by-case basis. Although

removing saline from the ipsilateral tissue expander is a simple manoeuvre, the dosimetric advantages gained from this method are often poor, necessitating more sophisticated radiotherapy solutions. An increasingly common radiotherapy technique in women with breast reconstruction is IMRT or volumetric-modulated arc therapy, which consists of several beams arranged in a non-coplanar way to target the reconstructed chest wall and lymph nodes (figure 4A). Compared with conventional three-dimensional conformal radiotherapy, IMRT and volumetric-modulated arc therapy can customise the prescribed radiation dose to the reconstructed breast and nodes, while keeping high doses away from the lung and heart. Moreover, by reducing the number of so-called hot spots, which are regions of tissue that are receiving higher than the prescribed radiation dose, these techniques can provide a homogeneous dose distribution over targeted regions. A major caveat of IMRT and volumetric-modulated arc therapy is that low doses of radiation are spread throughout the thorax, the long-term effects of which are unknown but nevertheless undesirable. A subtle distinction between volumetric-modulated arc therapy and IMRT is that the radiation beams in the former are arranged as sweeping arcs rather than static beams across the reconstructed breast and lymph nodes, enabling the radiation to be delivered more rapidly than with IMRT. This convenient feature of volumetric-modulated arc therapy enables its combination with deep inspiratory breath-hold techniques, which lead to further reductions in the dose of radiation reaching the heart and lung for patients with breast cancer receiving immediate reconstruction and PMRT, particularly in left-sided treatments.

Proton therapy is another precise method of delivering radiotherapy in women who have had a breast reconstruction (figure 4B and 4C). Because of its lack of an exit dose, the physical properties of protons permit the greatest sparing of surrounding normal tissues from high radiation doses.⁸⁵ Proton therapy is usually reserved for women who will receive radiotherapy to a permanent implant because of concerns over the potential to underdose as a result of the metallic port within a tissue expander. Furthermore, skin doses from proton therapy can be high, raising concerns about the viability of a flap overlying the implant and the potential to enhance the risk for the development of contracture or other complications. Until relevant studies are published, we suggest limiting the use of proton therapy in breast reconstruction only to patients treated in clinical trials so that complications and patient-reported outcomes can be rigorously assessed.

It is likely that these nuances in radiotherapy technique, such as the use of a bolus or boost, radiotherapy modality, fractionation, and nodal target volumes, are all important in determining the final cosmetic outcome in a woman who needs breast reconstruction. The magnitude of each

effect, particularly in the context of variabilities in surgical technique and patient-specific factors, is not well elucidated and leaves many uncertainties in the treatment planning process. More prospective studies are required to objectively measure complication rates in women with breast reconstructions who are receiving uniform radiotherapy treatment. Relatedly, several clinical trials focused on optimising radiotherapy delivery in patients with breast cancer undergoing reconstructions are ongoing or are in development.

A North American phase 2 trial⁸⁶ has reported results of 67 women who received a hypofractionated PMRT regimen of 36.6 Gy in 11 fractions over 11 days to the chest wall and draining lymph nodes, followed by a boost. Among them, 41 (61%) had a breast reconstruction or a tissue expander. Median follow-up was 32 months (range 26.6–35.3). The overall proportion of patients who had an implant removed or an unplanned surgical intervention was 32%, which was similar to historical controls from large single-institution studies. On the basis of these results, a randomised phase 3 trial testing hypofractionation (42.56 Gy in 16 fractions) with standard fractionated postmastectomy radiotherapy in women with immediate breast reconstruction is planned by the Alliance cooperative group (A221505), with a projected trial activation date in late 2017. The primary endpoint of this trial is the reconstruction complication rate, but secondary endpoints will include the rates of lymphoedema, toxic effects including brachial plexopathy, recurrence-free survival, and endpoints for health costs or economics. In the UK, the multicentre Primary Radiotherapy And DIEP flap reconstruction (PRADA) trial (ClinicalTrials.gov, number NCT02771938) is examining the exact timing of pre-operative radiotherapy, with the underlying hypothesis that delivering PMRT before mastectomy and DIEP reconstruction is safe. The primary endpoint of this trial is the rate of open breast wounds at 4 weeks after mastectomy and DIEP flap reconstruction. Secondary outcomes include volume, symmetry and applanation tonometry measurements, and patient satisfaction measured by BREAST-Q.

The need for trials using homogeneous radiotherapy methods in women with breast reconstruction is perhaps best illustrated by a worldwide survey⁸⁷ of radiation oncologists who were treating patients with breast cancer

with breast reconstruction. Delayed-immediate reconstruction was more common in the USA than in other countries. American physicians were more likely than others to treat the reconstructed breasts with either a boost or bolus techniques that increase the dose of radiation delivered to the anterior surface of a reconstructed breast.

Variabilities in radiotherapy delivery have been punctuated by changing indications for PMRT and regional nodal irradiation in women with breast cancer with one to three positive nodes. Guidelines⁸⁸ for the use

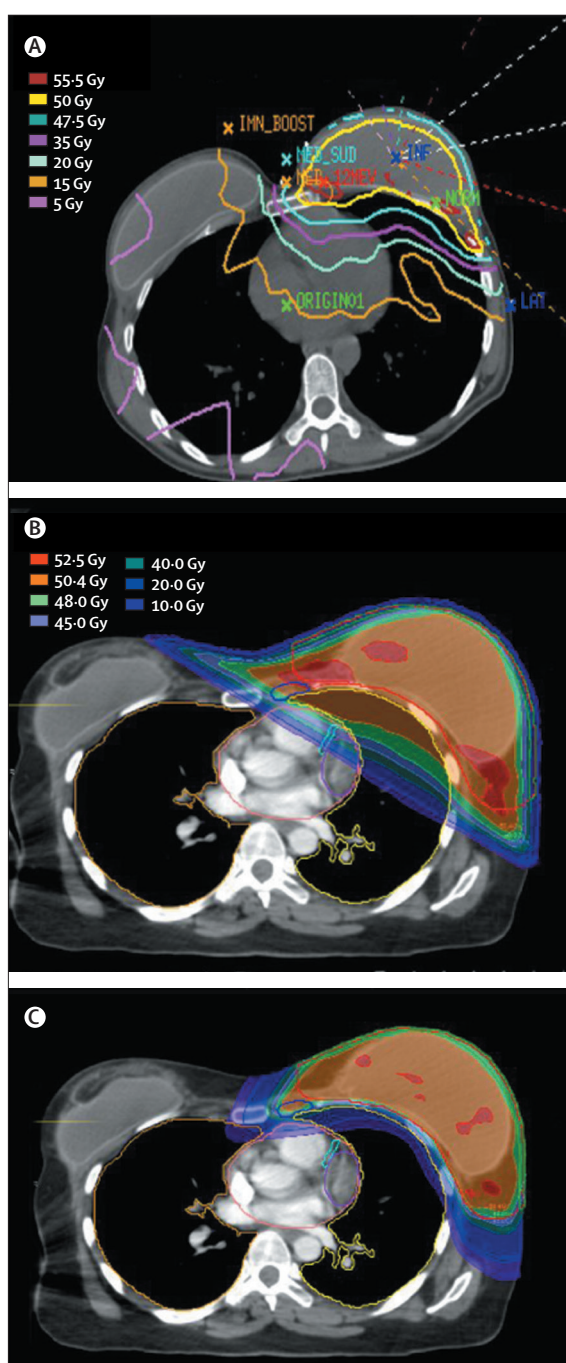


Figure 4: Dose distributions for different radiotherapy techniques used in breast reconstruction

(A) IDL distributions of a patient with bilateral implant reconstruction that was treated with an 8-field IMRT plan. The 50 Gy IDL (yellow) is conformal to the chest wall and internal mammary node and treats a minimal portion of the heart and lung; however, the low dose IDLs, such as the 35 Gy (dark pink) and 5 Gy (light pink), are covering a portion of the thorax. (B) Conventional photon radiotherapy consisting of wide tangential beams is covering the reconstructed chest wall and internal mammary nodes; however, the 100% IDL (orange) includes a section of normal lung and the 48 Gy IDL (green) includes some of the left ventricle and contralateral breast tissue. (C) 50.4 Gy IDLs curve around the reconstructed chest wall and nodal targets in proton therapy, with only the 10 Gy IDL approaching the lung and heart. IDL=isodose line. IMRT=intensity-modulated radiotherapy.

Panel 2: Key points on breast reconstruction relative to radiotherapy treatment

- Radiotherapy can be successfully incorporated into the treatment plan in women who choose immediate reconstruction, regardless of whether an autologous or implant-based approach is used
- Autologous tissues might tolerate postmastectomy radiotherapy better than previously believed, leading to high satisfaction and cosmetic outcome
- Heterogeneity in the delivery of radiotherapy including modality, fractionation, use of bolus, and boost and differences in nodal target volumes could affect reconstruction outcomes
- Implant reconstruction has a higher risk of long-term complications following postmastectomy radiotherapy than autologous reconstruction, but is a practical approach that can preserve the option of delayed autologous reconstruction
- In women who receive two-stage expander-implant reconstruction, evidence does not favour one type of radiotherapy over the other

of PMRT were updated in 2016 by an expert panel that was convened by the American Society of Clinical Oncology, American Society of Therapeutic Radiation Oncology, and Surgical Society of Oncology. The panel acknowledged that, although there is still insufficient evidence to universally recommend PMRT in all women with one to three positive lymph nodes, some biological subgroups could benefit from the treatment. Until these subgroups are accurately identified, however, decisional dilemmas of recommending PMRT in women with breast reconstruction will continue to revolve around the trade-off between clinical benefit and side-effects. In this Review, we summarise the key points surrounding the timing of radiotherapy in the context of breast reconstruction (panel 2).

Conclusion

As more data from trials investigating key issues in breast reconstruction and radiotherapy emerge, new perspectives on the optimal timing of radiotherapy are being welcomed. A wide spectrum of choices regarding reconstruction type and timing remains available to patients with breast cancer who want reconstruction and will require radiotherapy treatment. Many women who are candidates for autologous reconstruction might opt to wait and delay reconstruction to avoid the side-effects of radiotherapy to the reconstruction site altogether. However, for those women who request immediate breast reconstruction, there is emerging evidence that autologous reconstruction can tolerate radiotherapy better than previously believed, with improved quality of life and cosmetic outcomes compared with implants. Results might vary depending on radiotherapy

Search strategy and selection criteria

We searched PubMed using a combination of the terms: "breast reconstruction", "PMRT", "radiation", and "radiation therapy". We searched articles published in English between Jan 1, 1990, and Sept 20, 2017. Articles were also identified through searches of the authors' own files. The final reference list was based on originality and relevance to the broad scope of the review.

techniques, dose or fractionation, and target volumes. Despite their higher incidence of complications, implants remain the predominant form of reconstruction offered to women who receive PMRT and preserve the option of delayed autologous reconstruction. Finally, in women who receive two-stage expander-implant reconstruction, evidence does not favour one schedule of radiotherapy treatment over the other. Regardless of the diversity of reconstruction approaches, each approach should be underpinned by multidisciplinary collaboration and tailored to the patient's oncological and reconstructive goals. Minimising complications and maximising satisfaction in women who will receive PMRT is our unifying, common goal.

Contributors

AYH, ZIH, BJM, and EGW did the scientific literature search, wrote the Review, and interpreted the data. AYH and ZIH produced the figures.

Declaration of interests

We declare no competing interests.

Acknowledgments

BJM has received grants from the National Institutes of Health (R01HL140185, R21CA194882, and T32CA009501); EGW has also received a grant from the NIH (R01CA152192).

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