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Consequences of Radiotherapy for Breast Reconstruction

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1. Introduction

What is the problem? The late effects of radiotherapy, which manifest from six months onwards, can have long-lasting and generally progressive and irreversible effects on normal tissues. In this chapter we will discuss the clinical effects of radiotherapy on breast reconstruction, but many of the aspects will also be relevant for other areas of reconstructive surgery for cancer. A literature review has been performed to determine the clinical impact of radiotherapy on breast reconstruction following mastectomy for breast cancer. The evidence base for clinical decision-making regarding the best scheduling of treatments and reconstruction technique will be examined. To explain the long term effects of radiotherapy on normal tissues, the underlying biological processes that radiation induces will be discussed, on the basis of our pre-clinical and translational research in this area. In particular, the effects on blood vessels and lymph vessels, inflammation and fibrosis will be highlighted, as these are relevant to reconstructive surgery following radiotherapy. Biological intervention strategies for future research to minimize the negative effects of radiotherapy on normal tissues will be described.

2. Impact of radiotherapy on clinical outcome in reconstructive surgery

In this section we describe the results of a literature search performed through Medline and by following up on studies listed in the reference section of published papers. This is therefore not a complete review on all available studies on the subject. However, we have tried to focus on the current knowledge pertaining to the indications for breast reconstruction and radiotherapy in breast cancer patients following mastectomy, and the issues involved when the two treatments are combined.

2.1 For which patients is radiotherapy and breast reconstruction an issue?

Despite of the fact that many breast cancer treatment guidelines state that reconstruction should be discussed with patients before undergoing mastectomy (for example the early breast cancer treatment guidance: UK National Institute for Clinical Excellence NICE guidelines 2009; Dutch national guidelines 2011), often only a minority of mastectomy patients undergo the procedure. From our own experience, we know that in the

Netherlands, about 25% of patients treated in a specialized cancer centre undergo a breast reconstruction, whereas this figure is below 10% in patients treated in general hospitals. In Denmark, Hvilsom et al. (2011a) investigated the socioeconomic factors that influence the likelihood of undergoing an immediate or delayed breast reconstruction after mastectomy. Overall, 14% of patients had undergone a reconstruction. They found that the offer of breast reconstruction was unequally distributed, and living in an area where the hospital has a plastic surgery department significantly increased the odds of undergoing a reconstruction. In younger patients up to 45 years of age, educational level had no influence on the chances of reconstruction, but at older ages the longer the education, the higher the chances of reconstruction. Alderman et al. (2008) have assessed the impact of discussion of breast reconstruction with patients by their surgeon on the decision-making process for their cancer in 1844 respondents in the USA, and found a similar pattern to that seen in Europe. Only 33% of patients had discussed the possibility of reconstruction with their general surgeon. Most patients were aware of breast reconstruction, but choose not to undergo the procedure. Many patients had limited knowledge of the procedure and a negative perception of what it entailed. This was related to ethnic background and educational level. Also, the uptake of delayed reconstruction is often low due to lack of information regarding the procedure and concerns about safety (Alderman et al. 2011).

2.2 Indications for breast reconstruction

Studies have suggested that breast reconstruction following mastectomy can have a positive effect on well-being and revalidation, although this has not been demonstrated in all studies, and most are small, single institution retrospective assessments that are therefore liable to bias. For example, Rowland et al. (2000) reported that women with a breast reconstruction had a higher rate of dissatisfaction with their sexual functioning compared to women after breast conserving therapy or mastectomy without reconstruction. Harcourt et al. (2003) performed a prospective multicentre study with 103 women to assess women's decision making for or against reconstruction. Their results showed that women report improved psychological distress functioning in the year following their breast cancer surgery, whether this was mastectomy alone, or with immediate or a delayed reconstruction. However, they also reported that women were conscious of an altered body image at one year post-operatively irrespective of whether they had a reconstruction or not. They concluded that breast reconstruction does not necessarily confer psychological benefits compared to mastectomy alone. In contrast, Al-Ghazal et al. (2000a) retrospectively assessed psychological morbidity and satisfaction of cosmetic outcome in patients who had been treated with breast conserving therapy, mastectomy or mastectomy with reconstruction. Although the greatest morbidity was observed in the mastectomy group, this was less in the reconstruction group, with the best results for the breast conservation group.

There is also some evidence from retrospective studies that a direct or immediate reconstruction is preferable to a secondary or delayed reconstruction (Al-Ghazal et al. 2000b; Fernandez-Delgado et al. 2008). Metcalfe et al. (2011) performed a prospective study in 190 women with questionnaires pre-operatively and at one year of follow-up. Women who were undergoing delayed breast reconstruction had significantly higher levels of body stigma, body concerns, and transparency than women who were undergoing mastectomy alone (i.e. without a reconstruction), or a mastectomy with an immediate reconstruction. Of these

women, 158 (83.2%) completed the one year follow-up. There were, however, no significant differences in any of the psychosocial functioning scores between the three groups.

In a Cochrane database systematic review of immediate versus delayed reconstruction, D'Souza et al. (2011) identified only one randomized clinical trial on the subject, with 64 women, carried out from 1978-1980, i.e. more than 30 years ago (Dean et al. 1983). This study had methodological flaws and a high risk of bias. They concluded that there was some evidence that immediate reconstruction reduced the psychiatric morbidity at three months postoperative compared to delayed or no reconstruction.

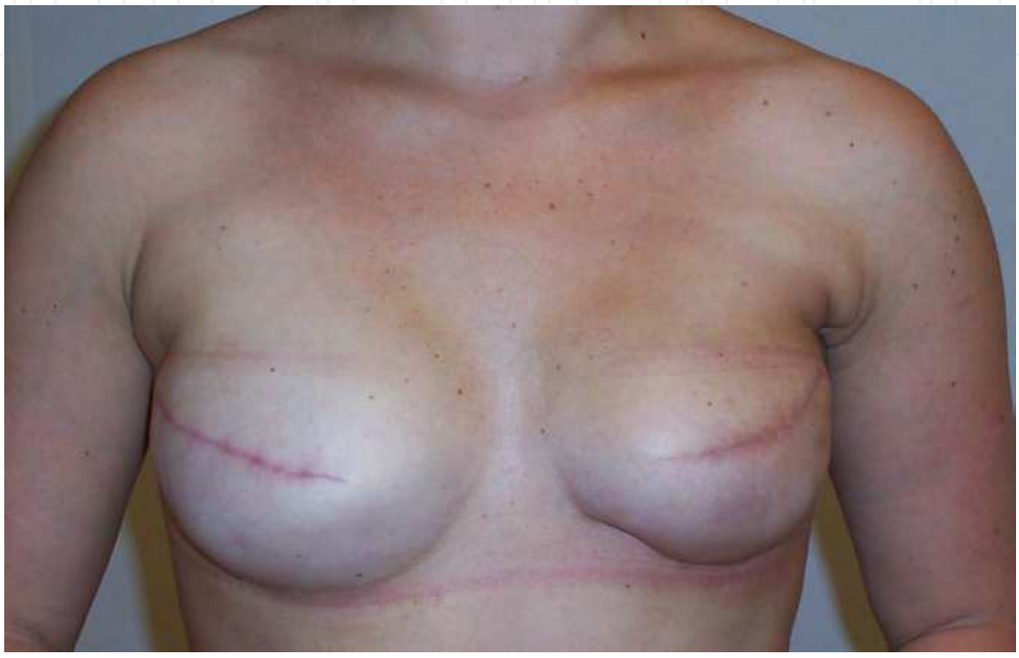


Fig. 1. Bilateral skin sparing mastectomy and immediate breast reconstruction; left sided irradiation post reconstruction showing retraction of the reconstruction compared to the unirradiated right side.

2.3 Oncological safety of breast reconstruction

There are concerns that patients may have a potentially higher risk of local recurrence after a skin-sparing mastectomy compared to a modified radical mastectomy. In one retrospective study of 133 cases with a median follow-up of at least five years, the local recurrence rate was higher in the subcutaneous mastectomy group, but the survival was not significantly different (Horiguchi et al. 2001). In contrast, Carlson et al. (2001) reported that immediate reconstruction with an implant had a higher local control rate than reconstruction with autologous tissue. However, these results were not confirmed in other studies. Nedumpara et al. (2011) reported on a series of 691 consecutive patients undergoing mastectomy, of whom 136 (20%) underwent immediate breast reconstruction (either with latissimus dorsi flap or subpectoral implant). The median follow-up was 55 months. For the whole group or within prognostic categories, they found no differences in local recurrence, distant metastases or survival between the group treated with mastectomy alone and the group with direct reconstruction. Lanitis et al. (2010) performed a meta-analysis of nine

observational studies in which skin-sparing mastectomy was compared to non skin-sparing mastectomy. The local recurrence rate was reported in seven of these trials (including a total of 3436 patients) but there was no difference between the two types of mastectomy for this end-point. There is no evidence that the detection of recurrences or that the recurrence rate is affected by breast reconstruction (Gerber et al. 2009; Slavin & Goldwyn 1988). The indications for post mastectomy radiotherapy, or other adjuvant therapy, are therefore not influenced by whether a patient has had reconstructive surgery or not.

In conclusion, there is some evidence that an immediate breast reconstruction is to be preferred to a delayed reconstruction, and that this is safe from an oncologic perspective. However, most guidelines caution the use of immediate breast reconstruction if radiotherapy is scheduled, or if there is a high chance of an indication for radiotherapy, for reasons discussed below (breast cancer treatment guidance: UK NICE guidelines 2009; Dutch national guidelines 2011). Unfortunately, the radiotherapy indication is not always certain pre-operatively.

2.4 Indications for post-mastectomy radiotherapy

Post-mastectomy radiotherapy reduces the local recurrence rate and improves survival (Clarke et al. 2005; Kyndi et al. 2009; Overgaard et al. 2007; Ragaz et al. 2005). It is offered to high risk patients (stage III and IV) and to patients with intermediate risk (stage II) in selected cases, but practice varies widely (Marks et al. 2008). The role of post-mastectomy radiotherapy to the chest wall area in this group is the subject of an ongoing international clinical trial (Russell et al. 2009a) and translational research (Cheng et al. 2006a; Cheng et al. 2006b). For the patient group with intermediate stage disease there is often uncertainty pre-operatively whether radiotherapy will be indicated. Often the pathological nodal status is an important determinant, and this is only certain after histological examination of the operation specimen has been performed (Vinh-Hung et al. 2009). This makes decision making regarding performing an immediate reconstruction difficult. From published reports of clinical studies, it is clear that radiotherapy has a negative effect on the results of reconstructive surgery, and is a risk factor for a worse cosmetic result, as discussed below.

2.5 Implant based versus autologous reconstruction and radiotherapy

When reviewing the literature regarding radiation effects on breast reconstructions, it is important to bear in mind the limitations of the studies reported, especially the reporting of complications. Many studies are inconsistent in the definitions of complications or adverse outcomes, details on follow-up duration, and risk factors (Potter et al. 2011). In particular, the follow-up duration is relevant for radiotherapy effects, as these are progressive at later time points (Turesson 1989). A selection of the larger published studies is discussed below.

Some authors report very poor outcomes for breast reconstruction after radiotherapy. Jhaveri et al. (2008) have retrospectively assessed complications and cosmetic outcome of implant-based versus autologous immediate reconstruction in 92 patients who subsequently underwent radiotherapy. The median follow-up was 38 months. The rate of severe complications (IV antibiotics, surgical intervention, removal or replacement of the reconstruction) was 33.3% in the implant group versus 0% in the autologous group, a highly significant difference. An acceptable cosmetic outcome was obtained in 51% of the patients in the implant group.

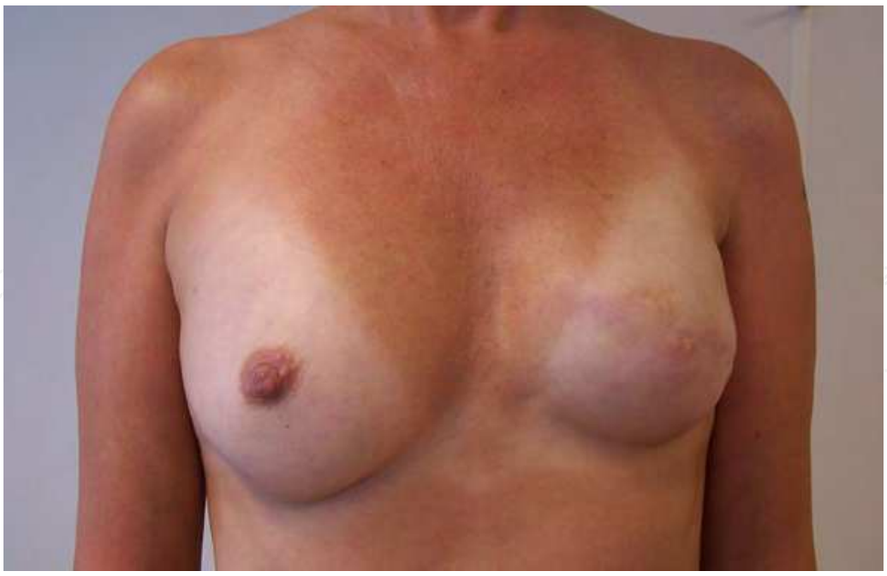


Fig. 2. Left-sideds skin sparing mastectomy and direct reconstruction with implant followed by irradiation. Right breast untreated.

Chawla et al. (2002) reported on a series of 48 patients who were treated with radiotherapy and reconstruction. The two year complication rate was much higher in the implant reconstruction group (53%) compared to the TRAM (transverse rectus abdominis musculocutaneous) reconstruction group (12%). No other factors were predictive.

Kronowitz & Robb (2009) have performed an extensive literature review of radiation therapy and breast reconstruction. For immediate reconstruction with an implant, they concluded that radiotherapy is associated with a 40% complication rate and capsular contracture and 15% extrusion rate of the implant. Also reconstructions with autologous tissue were found to have an increased rate of fibrosis and contracture if radiation is delivered to the reconstruction site after the reconstruction (figures 1-4).

Hvilsom et al. (2011b) have reported on the results of implant-based reconstruction for breast cancer from a prospective database registry of plastic surgery between 1999 and 2006. The study concerned the risks of capsular contracture and re-operation for 717 patients undergoing one-stage or two-stage delayed breast reconstructions with implants, but without autologous tissue. They found that radiotherapy was associated with a significantly increased risk of capsular contracture. The adjusted hazard ratio for capsular contracture with a one-stage procedure (performed with expandable implants) was 3.3 (95% confidence interval: 0.9 - 12.4) with a ten year risk of 20.5% in the radiotherapy group versus 7.0% in the unirradiated group. With a two-stage procedure (with temporary expanders followed by a scheduled second implant exchange) the adjusted hazard ratio was even higher at 7.2 % (95% confidence interval: 2.4 – 21.4), with ten year risks of 17.1% versus 8.2%. Not surprisingly, patients who received radiotherapy were also more likely to have nodal metastases and chemotherapy compared to patients without radiotherapy. There was a non-significant increase in re-operation rate in the irradiated patients. The majority of severe capsular contractures and re-operations occurred in the first two years, regardless of whether radiotherapy was given or not. This is somewhat intriguing, considering the continuing long-term development of fibrosis following radiotherapy, as discussed later in this chapter.

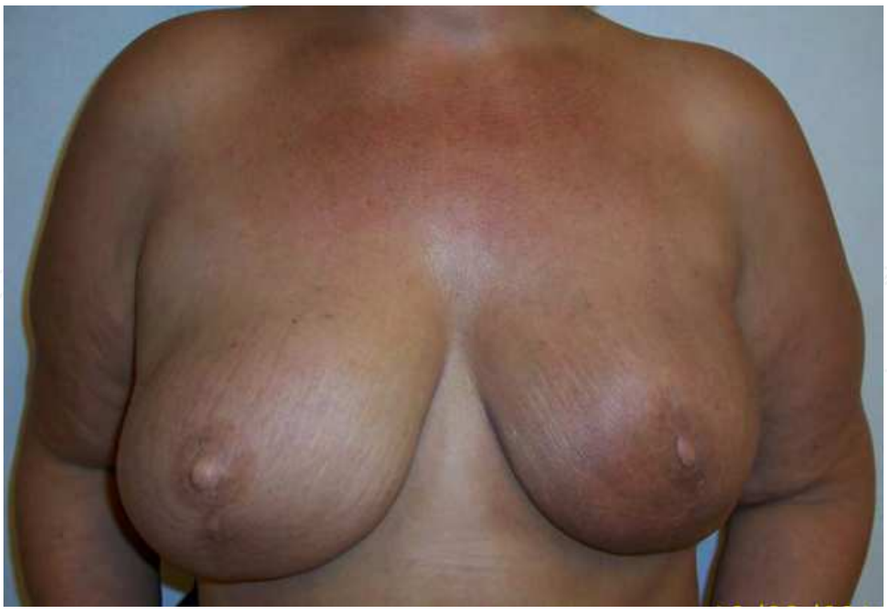


Fig. 3. Bilateral DIEP reconstruction, followed by radiotherapy to the left side. Note the volume loss on the left side (after 3 years follow-up). There was also some fat necrosis in both DIEP flaps, more extensive on the left side.

In contrast, other authors report generally satisfactory results for patients undergoing breast reconstruction and radiotherapy. Cordeiro et al. (2004) reported on a retrospective study of immediate breast reconstruction with a tissue expander and a permanent implant before starting post-operative radiotherapy. Sixty-eight of 687 patients received radiotherapy, with a mean follow-up of 34 months and they were compared to 75 unirradiated patients. Although 68% of the irradiated patients developed capsular contracture, compared to 40% in the unirradiated group, 80% of the irradiated group had acceptable (good to excellent) aesthetic results, compared to 88% of the unirradiated group, a non-significant difference. Patient satisfaction with the reconstruction was 67% in the irradiated group compared to 88% in the unirradiated group. They concluded that implant reconstruction should be considered for patients undergoing postoperative radiotherapy, especially those who may not be candidates for autologous reconstruction. Behranwala et al. (2006) assessed capsular contracture, cosmesis and symmetry at four years after implant-based reconstruction in 114 patients of whom 44 were also treated with radiotherapy. The incidence of capsule formation was 39% in the irradiated group compared to only 14% in the unirradiated group. Capsular contraction was associated with worse scores for symmetry, photographic assessments, and pain. They concluded however that although the chances of capsular contraction were three times higher in the radiotherapy group, 60% of patients do not get capsule formation four years after radiotherapy, and so this should be considered a viable option for breast reconstruction in selected cases.

Krueger et al. (2001) compared the complication risk and failure rate of implant/expander reconstruction in nineteen patients with radiotherapy with those of 62 patients without radiotherapy. With a median follow-up of 31 months, complications occurred in thirteen of the irradiated patients (68%) compared to 19 of the unirradiated patients (31%). Reconstruction failure was experienced by twelve patients in the whole group (15%) and

was significantly related to experiencing a complication and to radiotherapy. Interestingly, they also performed a satisfaction study amongst the patients in the study with a seven point questionnaire and a five point Likert scale. Sixty-six patients completed the survey. A lower percentage of patients (10%) reported satisfaction with the result if they experienced a reconstruction failure compared to 23% of patients expressing satisfaction if the reconstruction was successful. Tamoxifen use was associated with a decreased esthetic satisfaction, but rather unexpectedly radiotherapy was not. Although this was a relatively small study, the results suggest that if patients have a successful reconstruction with an implant technique, radiotherapy does not adversely affect their satisfaction, if they are well informed about the possible disadvantages.

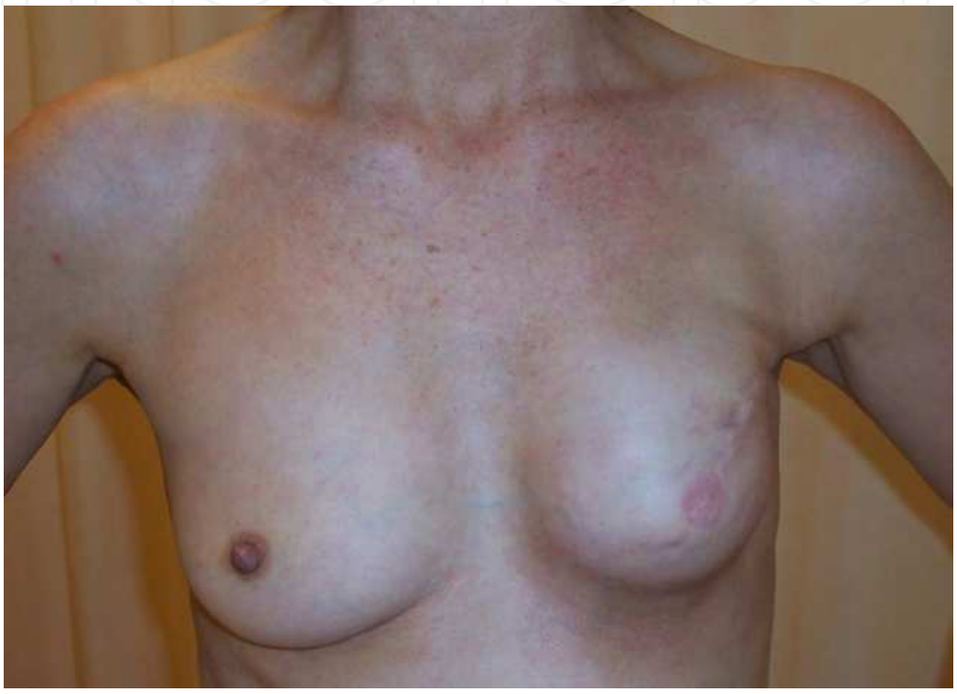


Fig. 4. Skin–sparing mastectomy with implant followed by chest wall irradiation on the left side.

Hussien et al. (2004) performed a retrospective audit over a time period in which the use of adjuvant post-mastectomy radiotherapy increased. They noted an increased tendency to the use of autologous tissue reconstruction in the more recently treated cohort, ascribed to better preoperative prediction of which patients have a radiotherapy indication postoperatively. Autologous tissue reconstruction seems to produce better results in patients who require radiation (figures 5 and 6). In one series there was an increased complication rate and slightly poorer but acceptable cosmetic outcome if radiotherapy was given prior to the reconstruction (Kroll et al. 1994). However, in other series, minimal disadvantage was seen for radiotherapy in the results of autologous reconstructions whether they were with a free-flap or pedicled technique (Slavin & Goldwyn 1988; Williams et al. 1995). Williams et al. (1995) reported on 108 patients who underwent TRAM reconstruction after radiotherapy. With this technique both the recipient bed and the vascular pedicle is included in the radiation field. They compared the irradiated patients to 572 patients who had not been irradiated. Overall there were comparable

complication rates; fat necrosis (17% versus 10%) was the only outcome that was significantly worse result after irradiation (figure 3). Obesity was also associated with higher rates of fat necrosis. Another series (Soong et al. 2004) also reported good tolerance of post-mastectomy radiotherapy after autologous reconstruction, without any flap necrosis or flap loss, with 85% of the patients rating the cosmesis as good to excellent.

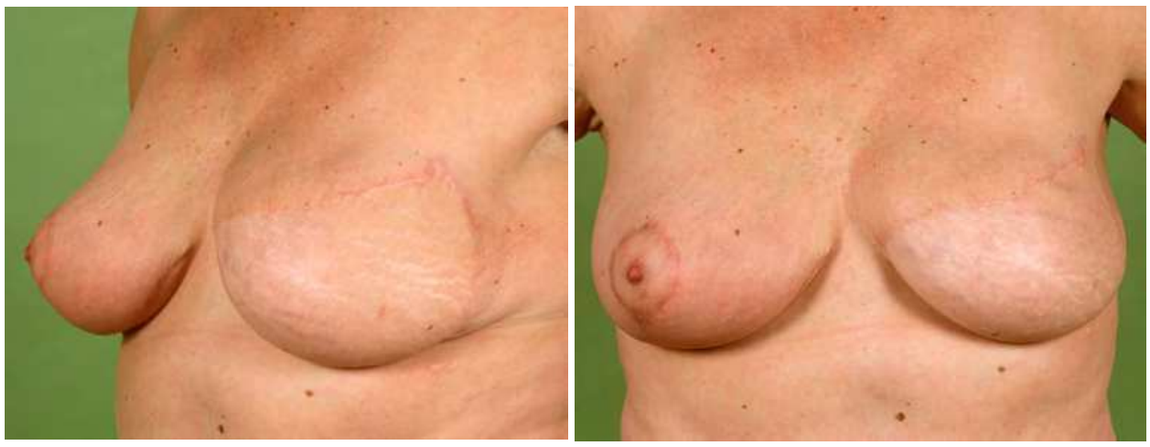


Fig. 5. Results of deep inferior epigastric perforator (DIEP) free-flap reconstruction after chest wall radiotherapy to the left side. On the right side a reduction mammoplasty has been performed.

2.6 Sequencing of reconstruction and radiotherapy

Whether the timing of radiotherapy delivery before or after implant reconstruction influences the complication rate has been investigated by Javaid et al. (2006) who performed a systematic review of published studies including at least 20 patients. There were no randomized trials on the topic identified. Four studies directly compared the results of reconstruction performed before or after radiotherapy, and two of these reported worse outcomes associated with post-reconstruction radiotherapy. Anderson et al. (2009) could not find significant differences in complication rate for patients irradiated after permanent implant reconstruction compared to patients irradiated with a temporary tissue expander, followed by insertion of the permanent implant. For both groups the complication rate was low. There was a slight increase in expander loss compared to permanent implant loss, and slightly better cosmetic outcome in the expander group (excellent /good in 90% versus 80% in the permanent implant group), but both comparisons were non-significant. The same group also reported low complication rates for radiotherapy after reconstruction, whether this was with implant or autologous techniques. The five year major complication rate, defined as requiring corrective surgery or loss of the reconstruction, was 0% in the TRAM group, compared to 5% in the implant group. The sequencing of radiotherapy and reconstruction was not a significant factor influencing the complication rate, nor was the type of reconstruction or other patient-related factors. The only factor that influenced the complication rate was the use of customized bolus material for the radiotherapy treatment. However, due to the long-term effects of radiation on tissue, in particular on connective tissue and microvasculature, it is unlikely that the timing of the radiotherapy in relation to the reconstructive surgery will have much impact on the fibrosis risk or implant loss, as discussed later on in this chapter. For patients undergoing

reconstruction with a flap technique, there is some evidence that the results are impaired if radiation is given following the reconstruction due to fibrosis and contracture of the tissue. Thus, waiting until after radiotherapy has been completed before performing a flap-based reconstruction would have a logical preference. This is despite the fact that patients therefore have to undergo a delayed reconstruction (figures 3, 5 and 6).

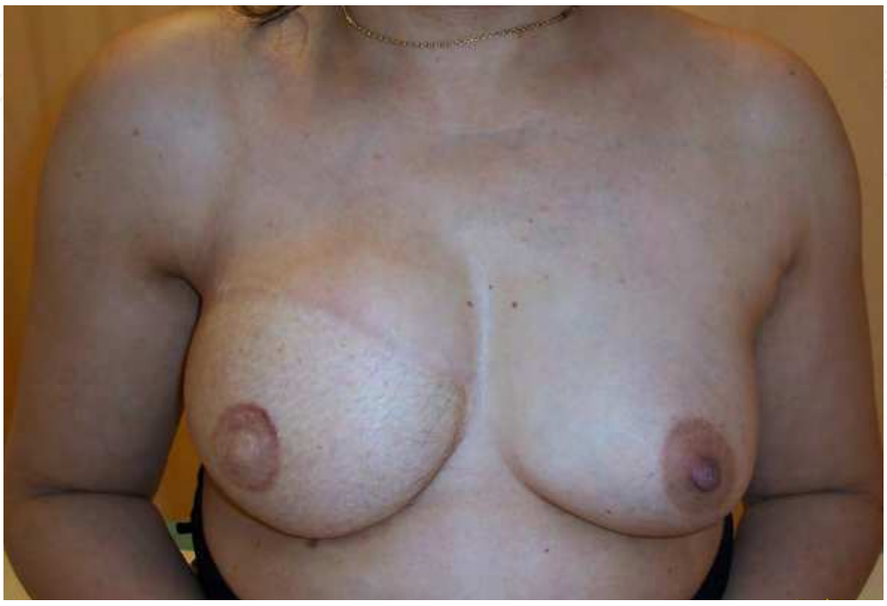


Fig. 6. DIEP free-flap reconstruction on the right side following radiotherapy to the right chest wall.

Performing a free flap-based reconstruction in a previously irradiated area may help improve perfusion and lymphatic drainage (Chang & Kim 2010) (figure 7). Tran et al. (2001) assessed two cohorts of patients after TRAM flap reconstruction performed over a ten year period. Early and late complications were compared. There was no difference in the early complication rate, but there was a great increase in the late complication rate in the immediate reconstruction group compared to the delayed reconstruction group (87% versus 9%). Twenty-eight percent of the immediate reconstruction group required additional surgery to correct for distortion due to flap shrinkage. In contrast, Zimmerman et al. (1998) assessed the results of immediate TRAM flap reconstruction followed by radiation therapy in 21 patients. Most patients thought that there was no effect on cosmetic outcome from the radiotherapy, and a few patients even thought that it was improved due to the radiation. Williams et al. (1997) compared the results of radiation given before or after TRAM flap reconstruction. They concluded that the timing of the radiotherapy did not influence the rate of complications, only the type of complication: fibrosis if radiation was given after the reconstruction, and fat necrosis if radiation was given beforehand. Gill et al. (2004) have presented the ten-year retrospective results of 758 DIEP (deep inferior epigastric perforator) flap breast reconstructions. In their analysis of risk factors for complications, post-reconstruction radiotherapy had the highest odds ratio of 5.40 (CI 2.95-9.92) and level of significance, the only other significant factors were current smoking (odds ratio = 2.24) and hypertension (odds ratio = 1.60). Pre-reconstruction radiotherapy and other factors consisting of age over 60 years, chemotherapy, diabetes mellitus, obesity, abdominal scar and two venous anastomoses were

not associated with an increased odds ratio for complications. The specific complications associated with post reconstruction radiotherapy were fat necrosis and partial flap loss.

2.7 Strategies to avoid problems when radiotherapy and breast reconstruction are combined

To reduce the risk of complications after breast reconstruction when there is also an indication for radiotherapy the following strategy can be applied. First, a good prediction is needed of which patients require radiotherapy. This cannot be defined with certainty in some patients with intermediate risk breast cancer. Better determination of which patients with intermediate risk breast cancer will benefit from radiotherapy is currently the subject of an international, randomized clinical trial (Russell et al. 2009a). There is some evidence that patients who require radiation have fewer complications if reconstruction is performed with autologous tissue after radiotherapy rather than with an implant alone, and if the radiotherapy is completed before the reconstruction (Woerdeman et al. 2004, 2006) (figures 5-8). Also, careful attention to radiotherapy technique can help to improve the dose distribution and cause less side effects (Anderson et al. 2004). Furthermore, breast reconstruction performed after radiotherapy can also help to reduce radiotherapy side effects such as lymph oedema (Chang & Kim 2010) (figure 7).

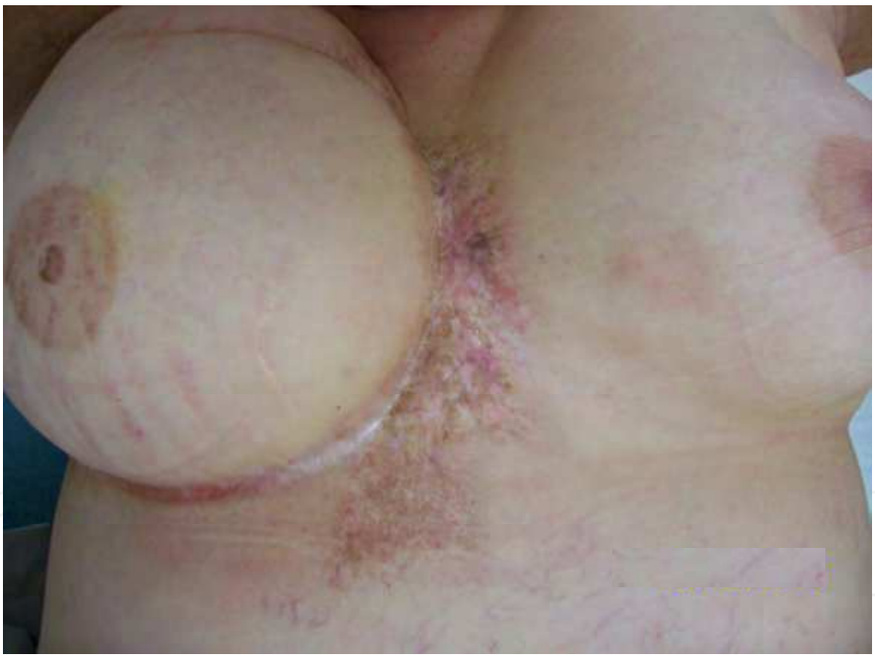


Fig. 7. DIEP reconstruction after radiotherapy. Note the extensive telangiectasia and fibrosis in the radiation field to the internal mammary chain nodes.

3. Late biological effects of radiation on normal tissues

Radiotherapy can affect normal tissues at very long time intervals after the initial treatment. This can cause increased morbidity and mortality, especially cardiovascular morbidity and secondary tumour induction, also in breast cancer patients (Darby et al. 2005; Giordano et al. 2005; Patt et al. 2005; Roychouduri et al. 2007). However, these serious effects occur in only a

small proportion of patients. There are also less serious effects of radiotherapy that affect a greater proportion of patients and include tissue changes such as fibrosis, oedema and microvascular changes, which can negatively impact on (plastic) surgery and reconstruction, as discussed above. To explain the sometimes very long latency - spanning months to decades - of the normal tissue effects of radiotherapy one has to diverge from the paradigm that radiation only affects cells at the level of DNA damage at the time of radiation. There is increasing evidence for long-term changes in the micro-environment and cell-cell interactions in irradiated tissues. Biological responses to irradiation evolve and amplify, mostly in a non-linear fashion, altering cell differentiation and senescence, and inducing cytokine signals that affect unirradiated cells or generate a state of chronic genomic instability. The sum of these events, occurring in different organs and tissues, is highly modulated by genotype, and predicates the health risks. The non-mutagenic effects of radiation on stroma and tissues contributes significantly to the late clinical consequences of radiotherapy, long after the patient has been cured of the original cancer for which they were treated. This includes fibrosis and late vascular damage, but also contributes to the development of radiation-induced cancer (Barcellos-Hoff 2010). These late changes due to radiotherapy are subject to wide inter-individual variation, depending on genetic differences, but also other treatments and co-morbidities (Safwat et al. 2002). Some of the individual components of late normal tissue effects of radiotherapy relevant for the plastic surgeon are discussed below.

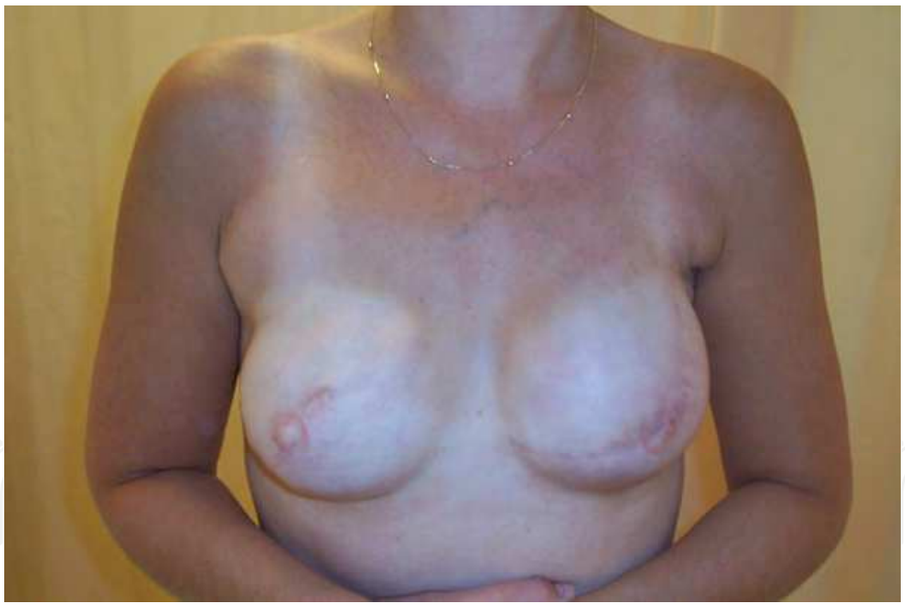


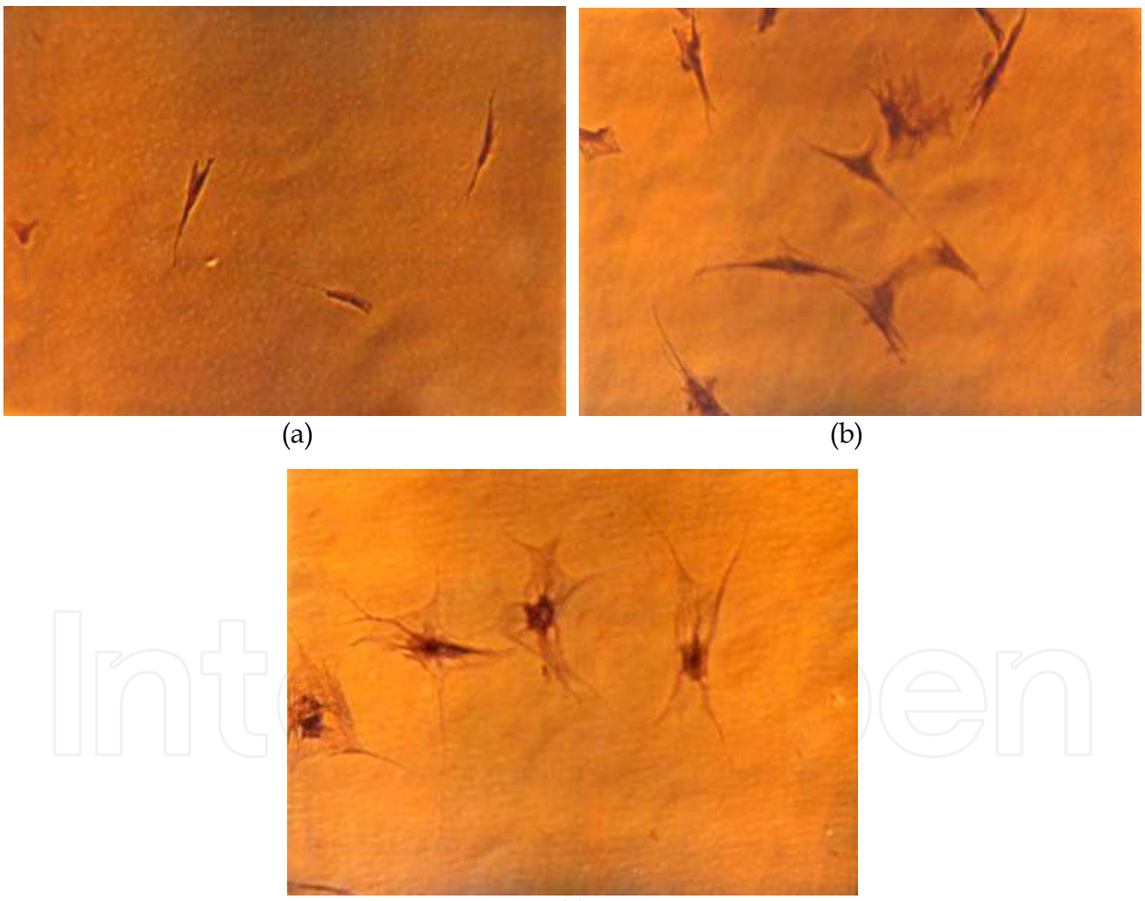
Fig. 8. Skin sparing mastectomy with implant on the right and reconstruction with implant and thoracodorsalis pedicled lap after radiotherapy on the left. No radiotherapy given on the right side.

3.1 Radiation-induced fibrosis

The fibroblast is the main target cell responsible for the fibrotic response after radiation exposure. Fibroblasts which survive the cell killing effects of radiation, undergo an accelerated ripening and differentiation. The differentiated fibroblasts are post-mitotic and

thus unable to divide (Herskind et al. 1998a; Akudugu et al. 2006, 78:17-26); Herskind et al. 2000; Russell et al. 2000) (figure 9). This has consequences for wound healing after surgical procedures, as active fibroblast differentiation is required for successful wound healing (Akudugu et al. 2006).

Mature, post-mitotic fibroblasts have large nuclei and cytoplasmic compartments, and are capable of producing large amounts of collagen fibers. The increase in collagen production shows a dose response relationship in that the higher the radiation dose, the more collagen production is observed (Lara et al. 1996). *Ex-vivo* studies of primary fibroblast cultures have shown that there is a wide inter-patient variation in the response of fibroblasts to irradiation; both in the intrinsic cellular radiosensitivity (cell killing) as in the degree of induction of terminal differentiation (Herskind et al. 1998a; Herskind et al. 2000; Johansen et al. 1994; Lara et al. 1996).



(a) (b)

(c)

a) Unirradiated: 30 - 50 divisions possible *in vitro*.
b) After *in vitro* irradiation: 2-3 divisions possible.
c) Two weeks after 2 Gy *in vitro* irradiation: post-mitotic differentiation.

Fig. 9. Fibroblasts derived from unirradiated skin of breast cancer patients in primary tissue culture.

This is also reflected by clinical observation: for a standard radiation dose there is a large variation in the degree of fibrosis development observed between different patients after radiation treatment for breast cancer, both after breast conserving treatment and after mastectomy (Bentzen et al. 1989; Bentzen et al. 1993; Borger et al. 1994; Collette et al. 2008) (figure 10). This inter-individual difference remains even after all known technical and clinical factors which can affect fibrosis development are taken into account (Borger 1994). However, it has not as yet proved feasible to predict the degree of fibrosis developing in individual patients on the basis of biological parameters such as intrinsic fibroblast radiosensitivity or radiation-induced fibroblast differentiation *in vitro* (Russell et al. 1998, 2000, 2002, Peacock et al. 2000).

Radiation causes a massive increase in the production, activation, and signaling of the cytokine transforming growth factor-beta (TGF-β) (Rube et al. 2000). The effects of TGF-β on fibroblasts have been studied *in vitro* and *in vivo* (Illsley et al. 2000*)*. It is postulated that these differences in radiation response may be at least in part due to genetic variations in genes regulating TGF-β production or signaling. For example, specific Single Nucleotide Polymorphisms (SNPs) have been associated with increased risk of radiation induced-fibrosis in some studies, although this has not been confirmed in larger series (Andreassen et al. 2005; Andreassen & Alsner 2009). Interfering with TGF-β signalling reduces the degree of radiation-induced fibrosis *in mice* (Scharpfenecker et al. 2009) and may be a therapeutic intervention in the future which could be applied to radiation-induced fibrosis, but this research is as yet in a very preliminary stage.

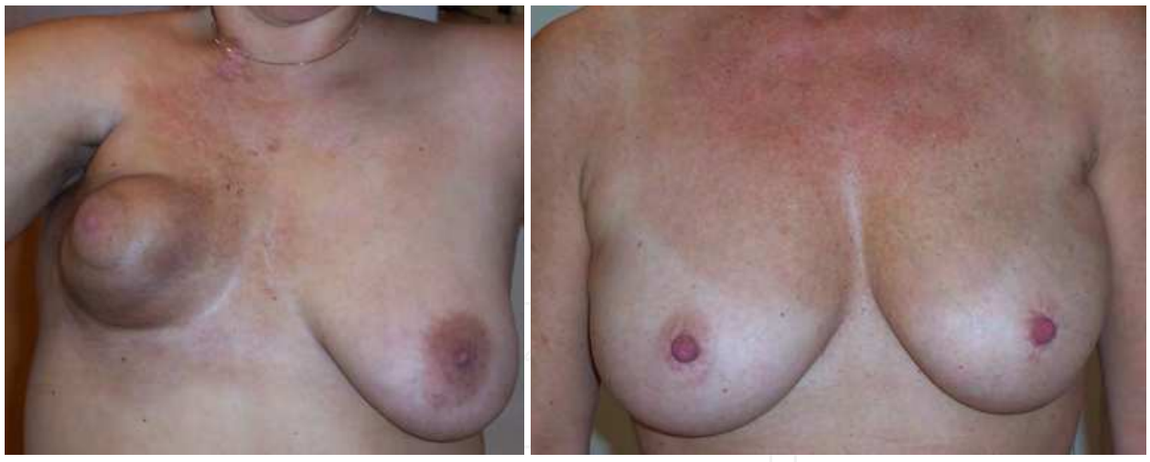
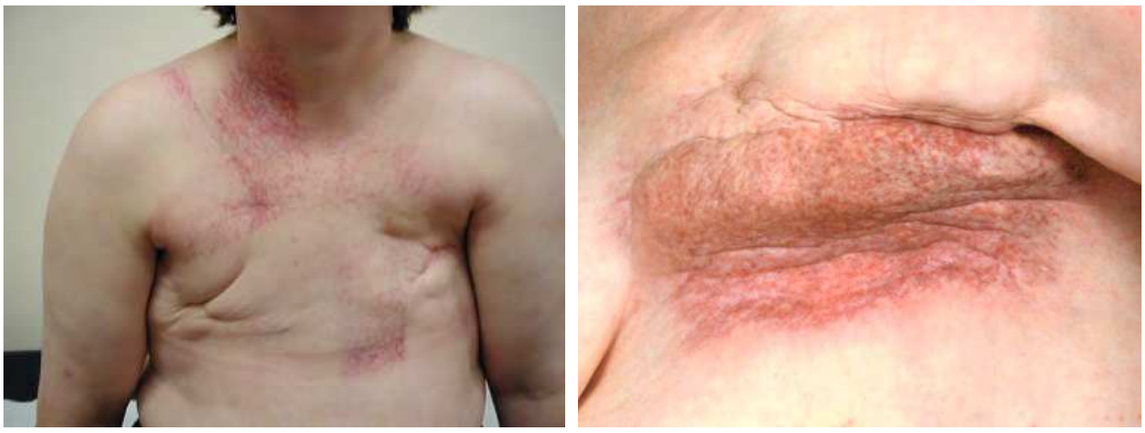


Fig. 10. Clinically there is wide variation in the degrees of fibrosis development, here after breast conserving therapy. Left: Extreme fibrosis 2 years following treatment; right clinically no fibrosis ten years after treatment of the left breast.

The variation between patients in the fibrotic response to radiation also impacts on the results of breast reconstruction, especially in the degree of capsule contracture with implant-based reconstructions. The biological differences between patients in the degree of fibrosis development after irradiation can explain why there are such wide estimates for the rate of clinically relevant capsule contracture seen with implant-based reconstructions reported in the literature, as discussed in section 2.

3.2 Radiation-induced microvascular damage

Vascular injury is a major cause of late radiation morbidity developing slowly and progressively over many years. Vascular lesions manifest in microvessels as telangiectasia which are characterised as dilated, tortuous and thin-walled blood vessels. Telangiectasia develop in skin, mucous membranes and also internal organs. In skin, telangiectasia appear after radiotherapy for breast cancer in 80% of the patients, but only become clinically apparent after several months to years following the radiation treatment with a mean latency of 4.7 years, and with a considerable inter-patient variation in the rate of onset and extent. For all patients, the levels increase with increasing follow-up time (Tucker et al. 1992; Turesson 1989; Turesson 1990). Skin telangiectasia may be dismissed as only having cosmetic consequences; yet they are a cause of dissatisfaction, especially if located in the décolleté, or neck (figure 11).



Left: telangiectasia of the skin following irradiation to the periclavicular area.
Right: telangiectaia following chest wall irradiation. Note also the increase in fibrosis.

Fig. 11. Clinical appearance of microvascular damage in the skin.

Further, radiation-induced damage in the skin may contribute to graft failure after free-flap reconstructive surgery because of impaired perfusion of the tissue. Also, telangiectatic lymph vessels cause lymph oedema and affect quality of life. Perturbations of the lymphatic network after irradiation are illustrated by the finding of altered lymph drainage patterns on sentinel node procedure performed for breast cancer that develops secondary to irradiation for Hodgkin's lymphoma up to decades earlier (van der Ploeg et al. 2009) (figure 12).

As with the development of fibrosis, TGF-β signalling (in concert with other growth factors) also plays an important role in the development of telangiectasia and the recovery of the microvasculature following radiation (Herskind et al. 1998b; Kruse et al. 2009). The importance of properly regulated TGF-β signaling in sustaining normal homeostasis of the microvasculature is illustrated by patients with the syndrome hereditary hemorrhagic telangiectasia (HHT). HHT patients have a mutation in either the TGF-β receptor called Activin receptor–like kinase-1 (ALK-1) or the accessory receptor endoglin (Jacobson 2000). HHT patients develop telangiectasia of the skin, or internal organs probably precipitated by trauma. This can lead to severe blood loss from mucous membranes, for example from nose bleeds. However, recovery of endothelial cell damage after irradiation is different to that

after other types of trauma, because of the sustained increase in TGF-β levels in the irradiated tissue over many months and years following irradiation (Ehrhart et al. 1997).

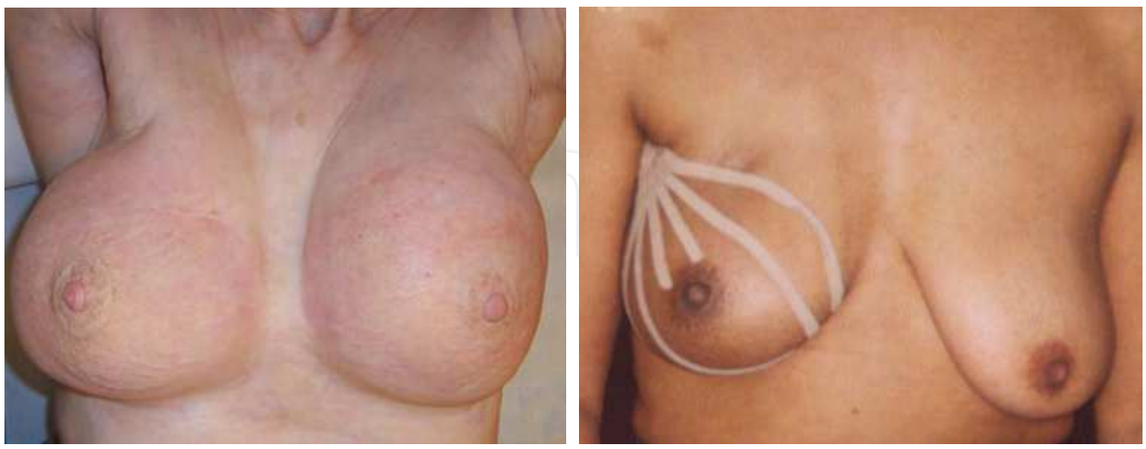


Fig. 12. Left: lympho-vascular damage causing chronic lymph oedema of the breasts after bilateral irradiation; right: kinesiotaping for lymphoedema of the right breast after breast conserving therapy.

Preclinical studies in the mouse kidney (chosen as a model as it is rich in microvessels) have shown that ALK-1 and endoglin are upregulated after irradiation (Scharpfenecker et al. 2009). This is accompanied by increased telangiectasia formation and fibrosis development. Accordingly, in skin punch biopsies taken from irradiated breast cancer patients, an increase in endoglin RNA was observed in the irradiated skin with macroscopically visible telangiectasia compared to non-irradiated skin from a contralateral site (unpublished data). Paradoxically, reduced receptor levels in heterozygous mice (that serve as a model for the human HHT syndrome) seem to protect from development of late normal tissue damage, as fibrosis and telangiectasia development are delayed in these mice after kidney irradiation. The mechanism of how the two TGF-β receptors modulate repair after irradiation is not clear, but our data suggest that they regulate the expression of vascular endothelial growth factor (VEGF), which is crucial for endothelial cell survival and repair.

In pre-clinical murine models, we have observed that the development of telangiectasia (after a lag period of several months following the radiation treatment) is associated with an inflammatory cell infiltrate, composed predominantly of macrophages.

Macrophages may contribute to the development of normal tissue damage, especially fibrosis, but also to vascular damage, by producing excessive amounts of cytokines and pro-fibrotic factors thereby preventing proper repair of the damaged tissue. Studies in our pre-clinical murine system suggest that both endoglin and ALK-1 regulate the secretion of some of these pro-inflammatory / pro-fibrotic factors, thereby modulating tissue repair (Scharpfenecker et al. 2011).

In another study performed by our group, biopsies from irradiated and unirradiated skin taken from cancer patients undergoing plastic surgical reconstructions were analysed by immunohistochemistry. The number of lymphatic vessels was increased in 67% of the

irradiated biopsies (unpublished data, figure 13). Irradiated biopsies also contained significantly more macrophages than the respective non-irradiated controls (unpublished data, figure 14). Seventy-five percent of the patients with increased lymphatic score also displayed an increase in macrophage numbers.

Inhibition of the release of mononuclear cells from the bone marrow is a strategy currently under investigation to prevent tumour re-growth following radiation, through inhibition of vasculogenesis (Ahn & Brown, 2009). We are currently conducting a clinical trial to investigate whether biphosphonate administration in breast cancer patients can reduce telangiectasia formation in the skin. Biphosphonates are frequently indicated in breast cancer patients to treat both osteoporosis resulting van endocrine therapy, and also for patients with osseous metastases to reduce the risk of fractures. They are also being investigated in trials as adjuvant treatment to improve the disease free survival. Biphosphonates are powerful inhibitors of metalloproteinase-9 (MMP-9), an enzyme that promotes the release of mononuclear cells from the bone marrow. In this way, biphosphonates might modulate monocyte infiltration into the irradiated tissue, thereby reducing late toxicity.

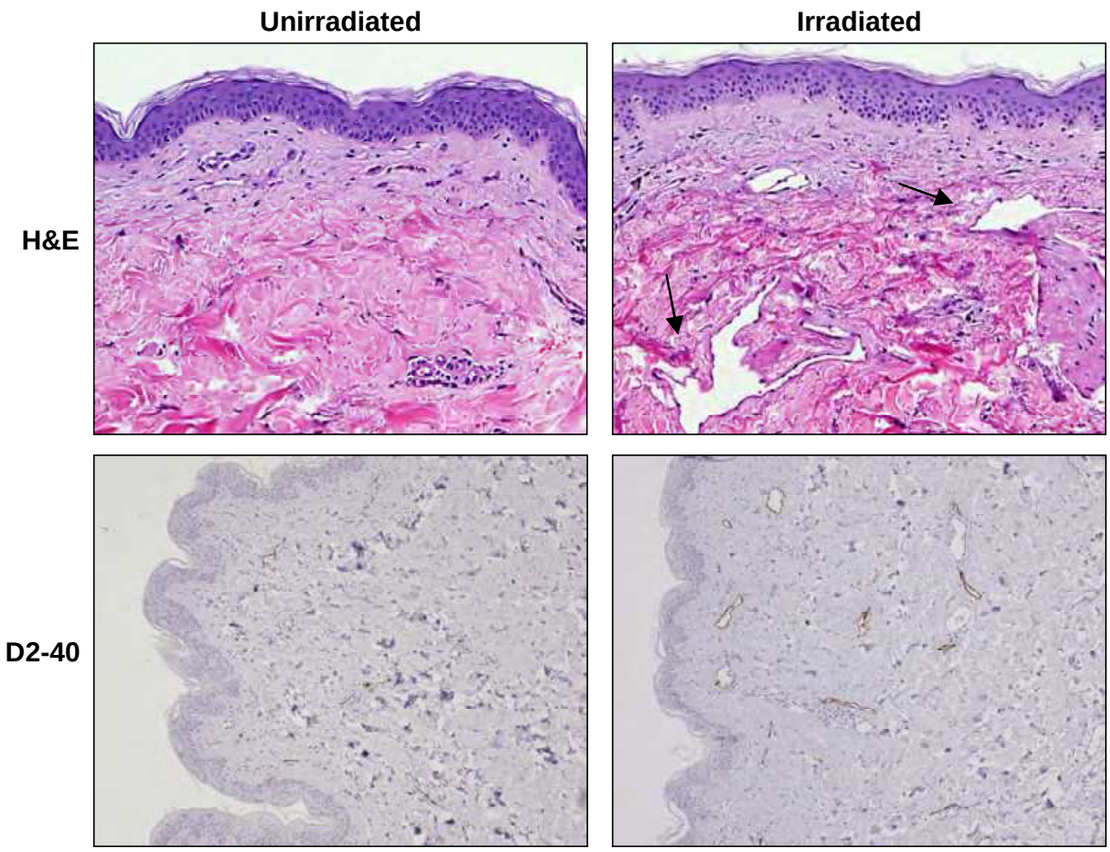


Fig. 13. Increase in the number and diameter of lymphatic vessels following irradiation. Upper panels: haematoxylin and eosin staining of histological sections of skin. Arrows show telangiectatic lymph vessels. Lower panels: brown D2-40 staining for lymphatic vessels.

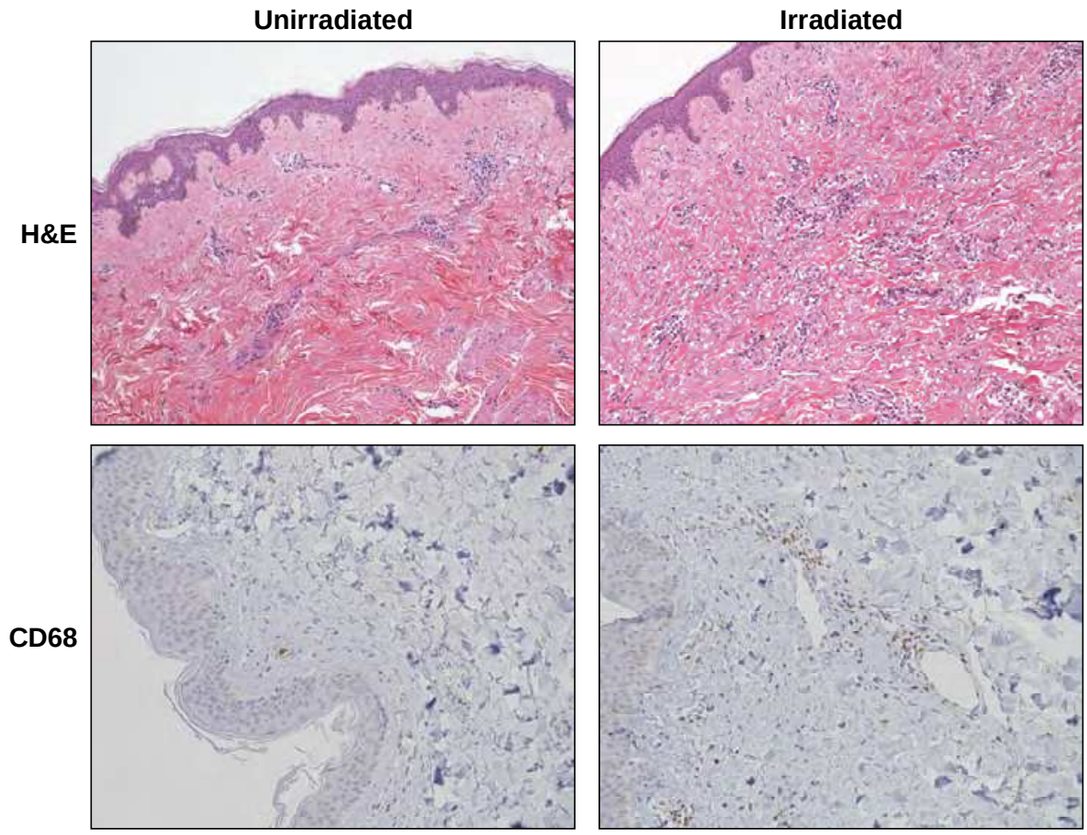


Fig. 14. Increase in macrophage infiltration in irradiated skin compared to non-irradiated skin. H&E: haematoxylin and Eosin; CD 68: immunohistochemical marker for macrophages (brown stain).

3.3 Changes to muscular arteries following radiation and atherosclerosis

Clinical studies have demonstrated and increased risk of atherosclerosis in the radiation field. For example in patients treated for head and neck cancer, there is an increased risk of ischemic stroke, and in patients receiving mediastinal irradiation an increase in coronary vascular disease and myocardial infarction (Aleman et al. 2003; Dorresteijn et al. 2002; Dorresteijn et al. 2005; Hooning et al. 2007). In a study performed on irradiated muscular arteries and control vessels in breast cancer patients and head and neck cancer patients undergoing free-flap reconstructive surgery, we observed an increase in the intima media thickness (IMT) in the irradiated vessels compared to the unirradiated vessels in the breast cancer patients. In the head and neck cancer patients we observed an increase in the glycoprotein content of media the irradiated vessels compared to the unirradiated control vessels (Russell et al. 2009b, figure 15). Although there was a significant increase in the IMT of the internal mammary arteries that had previously been irradiated, the absolute thickness was still very limited. This is compatible with the finding that the internal mammary arteries are rather resistant to developing atherosclerosis, (indeed they are the vessels of choice for coronary artery grafting), and to our knowledge, no reports of graft failure in breast reconstruction have been ascribed to atherosclerosis in the internal mammary artery.

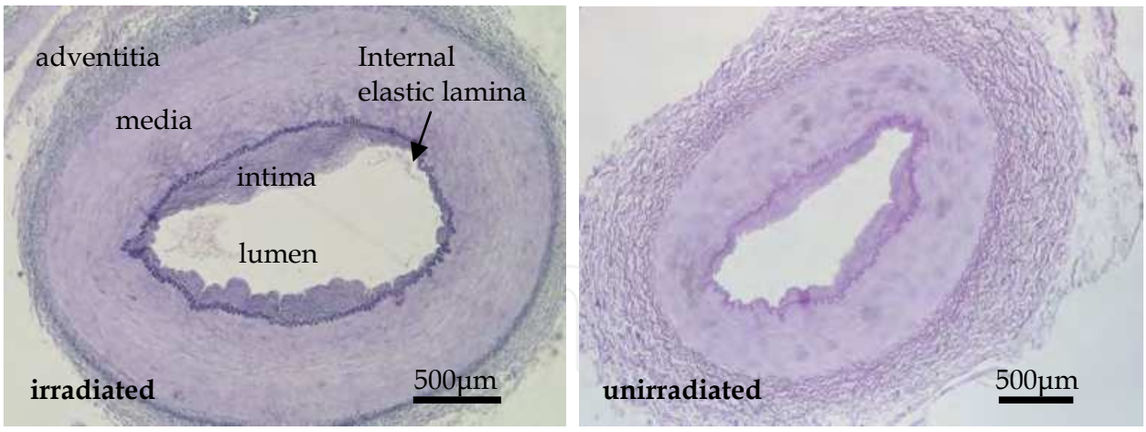


Fig. 15. Histological cross section of the irradiated facial artery of a patient with head and neck cancer undergoing free-flap reconstruction (left panel) showing increased intima thickness, compared to the radial artery of the same patient used as the donor vessel.

In animal models, radiation-induced atherosclerosis displays a more inflammatory and thrombosis-prone plaque phenotype compared to age or cholesterol-induced lesions. In addition, radiation-induced atherosclerosis is resistant to pharmacological interventions that reduce age-related atherosclerosis such as aspirin or statins (Stewart et al. 2006; Hoving et al. 2008, 2010 & 2011, manuscript submitted). There has been a report of atherosclerosis in donor vessels of free flaps precluding the use of the flap, but this was in a patient with head and neck cancer and not after radiation to the artery (de Bree et al. 2004).

3.4 Atrophy of skin and subcutaneous tissues following irradiation

Radiotherapy can also cause atrophy of tissues, which usually manifests over several years. This is due to cellular loss (mitotic death) caused directly by the irradiation, but also secondary to poor perfusion related to the vascular damage. Atrophy due to mitotic cells death manifests at a rate which is dependent on the normal cell turnover in an organ or tissue. In tissues with a slow natural turnover such as connective tissue, it may be months or years before a cell goes into mitosis after radiotherapy, only then does the DNA damage cause mitotic failure. Some cell types, such as fibroblasts can survive for decennia in a tissue after radiation (Peacock & Yarnold, personal communication) and remain metabolically active, for example in collagen production. However, a longer time points there is an increased chance that the cells will eventually go into apoptosis or a failed mitosis and die, causing atrophy of the tissue or organ, with functional or structural loss as a result. Thinning of the dermis layer of the skin after radiotherapy is well documented (Rezvani et al. 2000).

Atrophy of skin can cause thinning and discolouration over implants used for breast reconstruction (figures 16 and 17). Volume loss of breast tissue is commonly seen after breast conserving therapy, and can be attributed to a combination of atrophy, fibrotic contracture and fat necrosis (figure 18). If tissue atrophy becomes even more pronounced, then even necrotic tissue breakdown can occur, but this is luckily a quite rare and late event after radiotherapy. Extra stress on tissues due to a surgical intervention, anaemia or diabetes can precipitate the development of necrosis.

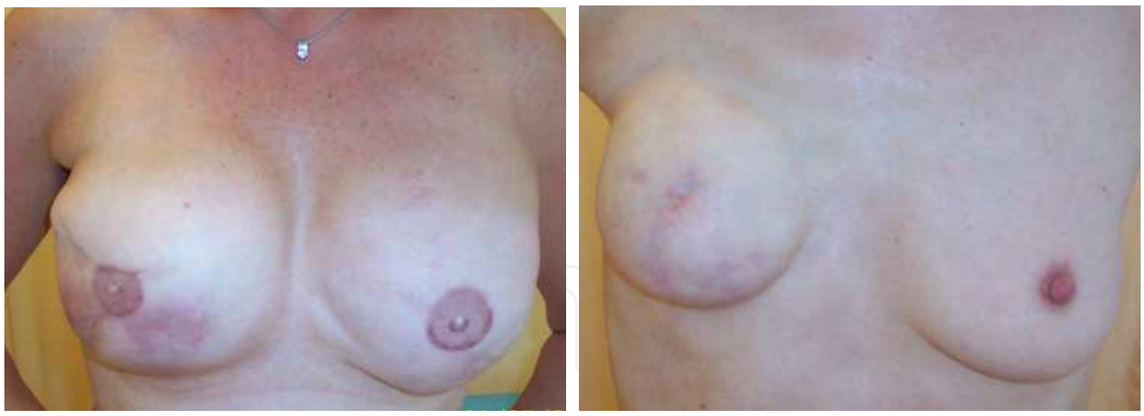


Fig. 16. Clinical manifestation of atrophy after radiotherapy: in both patients there is the appearance of atrophy of skin overlying an implant after irradiation to the right side.

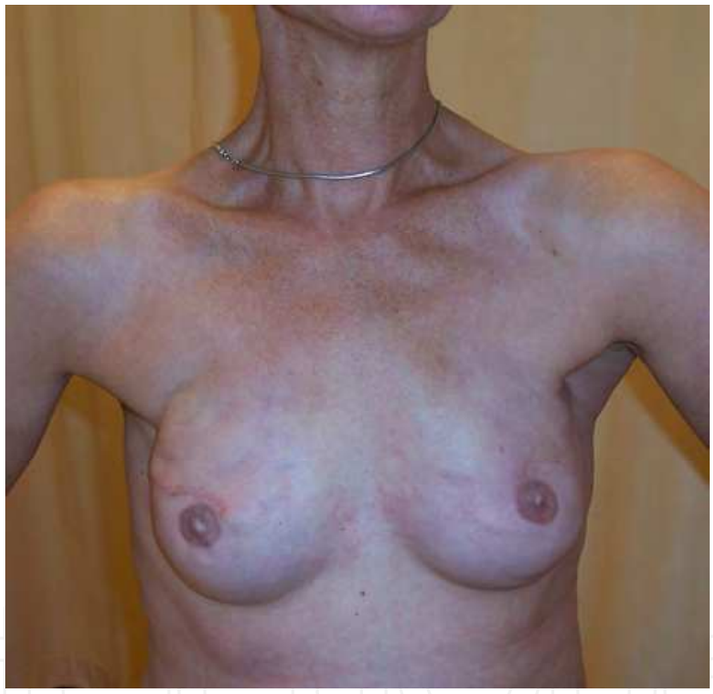


Fig. 17. Bilateral skin-sparing mastectomy 25 years after mantle field irradiation for Hodgkin lymphoma (radiation–induced breast cancer). Note muscle atrophy in neck and chest wall area.

4. Conclusions

Breast reconstruction and radiotherapy are two treatment modalities commonly employed to combat the health consequences of breast cancer; on one hand reducing the esthetic and psychological impact, and on the other hand reducing the risk of local recurrence and increasing survival. From our literature review, it is clear that clinicians have limited high level evidence on which to base clinical decisions regarding the optimal type and timing of reconstruction and radiotherapy. For this chapter, we have limited our review to the effects

of radiotherapy on breast reconstruction. Aspects such as the impact of breast reconstruction on radiotherapy delivery, or the use of plastic surgical techniques to restore the contour of the breast after breast conserving therapy have not been considered. Due to the large variation in the quality of the studies published, and the use of non-standardized end-points and follow-up duration, the results should be interpreted with caution. Although general conclusions can be drawn, for example that radiotherapy increases the risk of fibrosis, it is unwise to quote an exact percentage when advising individual patients on the optimal treatment strategy. Not only are the results influenced by individual clinical and surgical factors, but there is a very wide variation in the rate and extent of the development of late radiotherapy effects, both between patients and even within individual patients depending on follow-up duration, radiation technique and scheduling, and other treatments, medication and co-morbidity. This is one of the reasons why series of treatment outcome reported in the literature can seem to have contradictory conclusions. It has not as yet proven possible to predict, on a biological basis, which patients are more predisposed to develop more extreme radiation-induced late effects than others.

We have examined the underlying radiobiological causes of the clinical manifestations of late radiation-induced changes in normal tissues. The most relevant effects for breast reconstruction are the increased development of fibrosis and the micro-vascular and micro-lymphovascular abnormalities, which in turn lead to secondary effects such as micro-thrombi, tissue hypoxia and necrosis. In the current context, fat necrosis is the most common problem. Necrosis of other tissue types solely due to radiotherapy is usually a very late event occurring several decades after the radiation exposure. The increased risk of atherosclerosis in muscular arteries following radiotherapy is not a clinical problem in the breast cancer population in as far as the effects on reconstructive surgery are concerned, although for other cancer patient groups, such as those with head and neck cancer, radiation accelerated atherosclerosis can impact reconstructive surgery, also because of the predisposition to vascular pathology due to other risk factors such as male sex and smoking in these patients.

Research by our group and others has shown that the late biological effects of radiation on connective tissue and vessels and other cells is not determined solely at the time of radiation exposure, but can be modulated by factors months or even years later. Late effects in normal tissues after irradiation are due to a gradual process of tissue modulation and repair and mis-repair that can result in pathological states such as fibrosis and telangiectasia. Cytokines such as TGF-β, VEGF, MMP-9 can all vary in levels and interactions over time, and this might be influenced by genetic variation between patients. Also, we have evidence that inflammatory cell infiltration in the irradiated area contributes to both the fibrotic response and telangiectasia formation.

For future research, it is exactly this continuing process of tissue changes following radiation that open up opportunities for therapeutic interventions. Modulating cytokines or inflammatory cell activity to reduce the development of fibrosis or micro-vascular damage, at time points long after the patient has been cured of the cancer for which she received the radiation is an attractive strategy. This is currently under investigation in early clinical trials, both by our group and others. By improving the therapeutic ratio of radiotherapy (increased cure but less side effects), the quality of skin and subcutaneous tissues should improve and

aid plastic surgeons in achieving the optimal restorative results for their patients with breast cancer and other types of cancer.

5. Acknowledgements

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Selected Topics in Plastic Reconstructive Surgery

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Plastic Surgery is a fast evolving surgical specialty. Although best known for cosmetic procedures, plastic surgery also involves reconstructive and aesthetic procedures, which very often overlap, aiming to restore functionality and normal appearance of organs damaged due to trauma, neoplasm, ageing tissue or iatrogenesis. First reconstructive procedures were described more than 3000 years ago by Indian surgeons that reconstructed nasal deformities caused by nose amputation as a form of punishment. Nowadays, many ancient procedures are still used like the Indian forehead flap for nasal reconstruction, but as with all fields of medicine, the advances in technology and research have dramatically affected reconstructive surgery.

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