4. TOXICITY FROM RADIATION IN BREAST CANCER

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Breast cancer is probably among the most common diagnoses found on daily patient treatment lists in the majority of Radiation Oncology departments. This makes understanding what type of toxicity to expect from radiation for breast cancer and its management of prime importance, since it affects significant numbers of patients daily. Radiation for breast cancer is predominantly to the intact breast for early stage disease with post-mastectomy radiation comprising a smaller proportion of radiation delivered for this diagnosis. The acute toxicity that develops as well as the type of late sequelae that can occur in each of these treatment scenarios is similar. During intact breast or chest-wall radiation, the organs commonly at risk for radiation injuries that manifest as acute and late toxicity include skin, chest wall, lung, and heart. When regional nodal irradiation is added, the shoulder, brachial plexus, and axillary lymphatics are also at risk for potential injury.

In general, radiation for breast cancer post-lumpectomy and post-mastectomy is very well tolerated by most patients and does not significantly impair their daily activities. Acute side effects of treatment are generally common in occurrence, self-limiting, and resolve within 4–6 weeks after the treatment is completed. Skin reactions and the constitutional symptom of fatigue dominate the early toxicity profile. Late toxicity or permanent sequelae can be divided into two groups: the more common effects on the appearance of the breast such as persistent breast edema, hyperpigmentation, and fibrosis and those that are very uncommon but can have significant health consequences as a result of permanent injury to other organs such as brachial plexopathy, radiation pneumonitis, cardiac morbidity, or secondary malignancy.

A. ACUTE REACTIONS

A1. Skin

Skin reaction is the most common side effect during breast cancer radiation. Over 90% of women who receive radiation for breast cancer will as a result develop some skin changes during their course of treatment.[1]

Skin is divided into two main sections: the outermost layers or epidermis and the deeper layers or dermis. Acute radiation changes in the skin primarily reflect injury to the epidermis.[2,3] The epidermis is composed of several layers. The stratum corneum is the outer most layer, which is made up of flattened dead cells and comprises approximately 25% of the total epidermal thickness. Beneath the stratum corneum is a thin layer called the stratum granulosum, which is a transitional layer between the non-viable stratum corneum above and the viable layers below. The viable layers include the stratum spinosum, which contains mostly post-mitotic cells. The deepest layer, where the majority of the cell division occurs, is the basal cell layer. The basal cell layer is the primary target for radiation injury that results in the clinically visible acute radiation skin reactions.

Approximately half the cells produced in the basal layer undergo the process of terminal transition.[2] From the basal layer, post-mitotic cells enter the more superficial viable layer stratum spinosum, then into the transitional region or the stratum granulosum. In this layer, the cells become flattened, lose the nucleus and other organelles, and ultimately become mature, keratinized, or cornified cells of the stratum corneum. From the stratum corneum, cells detach and desquamate, but are continually replaced by cells produced in the basal layer that undergo terminal transition. The entire epidermis turns over on average in about 30 days.

The thickness of the dermis varies from 1 to 3 mm and contains blood vessels, nerves, hair follicles, and various glands. The dermis is subdivided into two layers: the superficial papillary layer and the deeper reticular dermis. The papillary layer is highly vascularized. The reticular dermis has the characteristic bundles of collagen fibers that give the skin its biomechanical properties.[2,3]

Radiation-induced changes in the skin are characterized by several phases. A transient early erythema can be seen within a few hours after radiation and subsides after 24–48 hours.[2] This is believed to be an inflammatory response, i.e., histamine-like substances are released that cause dermal edema and skin erythema from the permeability and dilatation of capillaries. The main erythematous reaction occurs 3–6 weeks after the radiation begins and reflects a varying severity of loss of epidermal basal cells. It has been shown that the fields treated with 2 Gy daily fractionation do not show changes in the basal cell density until total doses of 20–25 Gy are delivered.[3] The reddening of the skin is thought to represent a secondary inflammatory reaction or hyperemia.[2,3] With higher radiation doses, there is a marked reduction in the number of mitotic cells and an increase in degenerate cells. If cells are not being reproduced at the same rate in the basal cell layer and the normal migration of cells to the stratum corneum continues, the epidermis becomes denuded in the time equivalent to its natural turnover, or approximately 30 days. When sufficient numbers of clonogenic cells in the basal layer persist

to sustain repopulation, atypical thickening of the stratum corneum may be seen and the patient will experience dry flaking skin in the treated area, or dry desquamation. This is typically seen at doses ≥45 Gy. If new cell proliferation is inadequate, moist desquamation with exposed dermis and oozing of serum occurs. The repopulation of the basal layer of the epidermis after irradiation is predominantly from the surviving clonogenic cells within the irradiated area. This is typical of moist desquamation that occurs between the does of 45 and 50 Gy with 2 Gy fractionation. Total skin doses of ≥60 Gy are associated with moist desquamation that does not heal as well.[2,3] When an area of irradiated skin is completely denuded of clonogenic epithelial cells, the healing of moist desquamation must occur totally as a result of the division and migration of viable cells from the skin around the irradiated area. When large areas of skin are irradiated to high doses such that the reproductive cells in the basal layer are depleted, cell migration from the edges of the field can be ineffective. In such situations, secondary ulceration involving the loss of dermal tissue can occur as a result of infection or trauma.

If radiation continues at a time when moist desquamation is evident, then further injury may lead to dermal and subcutaneous necrosis. Necrosis has been characterized by the damage of blood vessels in the dermis and is evidenced by the loss of endothelial cells and reduction in dermal blood flow prior to the onset of necrosis.

The radiation doses utilized for breast cancer treatment are typically 45–50.4 Gy with 1.8–2.0 Gy fractionations to larger fields for the intact breast, chest wall, or nodal sites. Cumulative doses of 60–66 Gy may be given to smaller boost volumes of the lumpectomy site or chest wall. With this standard dosing, breast radiation will result in 80–90% of patients developing some skin erythema and dry desquamation; in 30–50% of patients, the erythema is more severe and is associated with skin tenderness; in 5–10% of patients, patchy moist desquamation confined mostly to skin folds can be seen; and in <5% of patients, confluent moist desquamation occurs.[1]

An understanding of what to expect for a typical acute skin reaction from standard breast cancer radiation is important so that a foundation exists for evaluating products and techniques that hope to prevent or treat these symptoms. A useful prospective study was done that carefully documented the skin reactions each week of 126 breast cancer patients receiving breast radiation after lumpectomy and axillary node dissection.[1] In this study, the whole breast received 45 Gy in daily fractions of 1.8 Gy with a 20 Gy electron boost delivered by 1 field daily with 2 Gy fractions. Patients were treated 5 days/week. A modified Radiation Therapy Oncology Group (RTOG) scoring system for acute skin reactions was used, which made patchy moist desquamation limited to skin fold scored as 2.5 instead of 2 (Table 1). The irradiated breast was divided into eight sections for observation: sternum, axilla, UOQ, UIQ, LOQ, LIQ, nipple, and inframammary fold. In addition to the skin observations, a VAS pain score and written description of topical agents used was recorded as well. The range of skin reactions recorded in the nine regions of the breast is shown in Table 2. This demonstrated that during weeks 1–2, skin reactions are uncommon. During week 3, almost 50% of the patients had developed mild erythema and for up to 12% more severe erythema was seen. By week 4, about 80% of the patients demonstrated skin changes with 20% of these being more severe. The emergence of patchy moist desquamation in skin folds was also

Table 1. RTOG acute toxicity scoring for skin[4]

Toxicity score	0	1	2	3	4
Description	No change over baseline	Follicular, faint or dull erythema, dry desquamation, epilation, decreased sweating	Tender or bright erythema, patchy moist desquamation,* moderate edema	Confluent moist desquamation, other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis

*Confined to skin folds.

Table 2. Acute skin toxicity (range) in 126 breast cancer patients during a course of breast radiation after lumpectomy.[1] Patients (%) demonstrating modified RTOG toxicity score

	Score					
Week	0	1	2	2.5	3	4
1	98–100*	0–1	0–1	0	0	0
2	94–98	0–5	0–1	0	0	0
3	33–46	40–48	4–18	0	0	0
4	16–22	49–65	4–18	0	0	0
5	4–8	52–67	24–40	1–8	0–2	0
6	6–16	38–63	6–33	2–10	0–2	0
7	8–28	41–57	6–38	0–10	0–2	0

*All percentages estimated from bar graph.

Table 3. Worse observed skin toxicity with best supportive care during a course of breast radiation following lumpectomy. Patients (%) with RTOG SCORE

Study	*N*	0	1	2	3	4
Porock[1,*]	126	8	63	31	2	0
Fischer[17]	89	7	58	32	3	0

*Weeks 5 and 6.

seen in week 4. The frequency of reactions was at its worse during weeks 5–6. Patchy moist desquamation occurred in four sites: sternum, axilla, UOQ, and inframammary fold during the radiation course, and confluent moist desquamation occurred only in the axilla. This description of the acute skin reaction for breast radiation is confirmed when one looks at the best supportive care arm of the RTOG 97-13 study (Table 3) and finds very similar percentages of acute toxicity scores.

The pain scores associated with the acute skin reactions in the Podrock study are listed in Table 4. From this it is seen that, overall, the vast majority of patients did not develop significant pain associated with their course of breast radiation. The highest frequency of pain scores >0 occurred during week 6. At that time, 17% of patients developed pain: 9.6% scored their pain as 1–3 or mild, 6.3% scored it at 4–6 or moderate, and 0.9% had

Table 4. Distribution of 126 breast cancer patients according to VAS pain scores during a course of breast radiation following lumpectomy[1]

	Pain VAS (%)								
Week	0	1	2	3	4	5	6	8	9
1	99.2	0.8							
2	98.4	0.8	0.8						
3	96.8		2.4	0.8					
4	92.8	0.8	0.8	1.6	3.2			0.8	
5	87.3	1.6	2.4	3.2	1.6	2.4	0.8	0.8	
6*	83.2	2.7	6.0	0.9	1.8	1.8	2.7		0.9
7†	88.6		4.4	0.9	1.8	1.8	2.7		

*$N = 115$.
†$N = 114$.
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severe pain scored at 9. By week 7, this fell to 12% scoring >0 on the pain scale and 6 was the highest pain level scored.

Multiple factors in this population were found to be associated with more severe acute skin reactions. These included mean patient weight, breast size ≥D-cup, lymphocele aspiration, and being a current smoker.[1]

The use of topical agents was also recorded in this study. The percent of patients using a topical agent by week was 0%, week 1; 11%, week 2; 37%, week 3; 53%, week 4; 56%, week 5; 57%, week 6; and 39%, week 6. The choice of cream in this study was based on the nurse's assessment. These experiences lead them to recommend light moisturizers in the early phase of treatment, with a switch to thicker oil-based products for the peak of the reaction if necessary.

There have been numerous studies evaluating the benefit of applying a topical agent to the skin during the course of breast radiation (Table 5). Although studies examining various topical agents appeared shortly after x-ray therapy emerged a century ago,[5] this discussion will focus on studies primarily in breast cancer patients published since 1990. The intention of most of these studies has been prevention of, instead of treatment for, acute radiation skin toxicity.

A Canadian study evaluated the impact of not washing versus washing the skin on the acute skin reactions for 100 breast cancer patients.[6] The washing patients had significantly lower worst RTOG acute toxicity scores ($P < 0.04$), and less frequently developed moist desquamation (14% vs. 33%, $P < 0.03$). No significant difference between arms for the occurrence of dry desquamation was seen—74% no washing and 56% washing arm. On univariate analysis, washing, chemotherapy, concomitant chemotherapy schedule, weight >165 lb, and dosimetric hotspot were all predictors ofworse acute skin toxicity. On multivariate analysis, concomitant chemotherapy schedule, weight >165 lb, and dosimetric hotspot remained the strongest predictors of increased skin toxicity. Non-washing was weakly associated ($P = 0.06$).

Another study from Norway evaluated no cream versus the use of Bepanthen® cream during radiotherapy in 86 patients with each patient serving as their own control.[7]

Table 5. Prospective trials in breast cancer patients evaluating topical agents for reduction of acute radiation skin reaction

Topical agents	*N*	Author	Study design	Toxicity scoring	Results	*P*
Washing versus no washing	100	Roy[6]	Randomized	RTOG	Washing: less skin reaction less moist desquamation	0.03
Bepanthen versus placebo	86	Lokkevik[7]	Randomized double blind	Institution*	Less desquamation	
Hyalurenic acid versus placebo†	130	Ligouri[10]	Randomized	Institution	Reduced skin toxicity wks 3–7	<0.001
Chamomile cream versus almond oil	50	Maiche[8]	Pt own control	Institution	No significant difference in maximal toxicity score	NS
Sucralfate cream versus placebo	50	Maiche[9]	Pt own control, physician blinded	Institution	Reduced grade II toxicity with faster recovery time	0.05
Aloe vera versus placebo	194	Williams[11]	Randomized double blind	Modified RTOG	No difference maximal radiation reaction or weekly scores	NS
Aloe vera versus observation	106	Williams[11]	Randomized double blind	Modified RTOG	No difference maximal radiation reaction or weekly scores	NS
					No difference erythema, moist desquamation	<0.001
Aloe vera versus aqueous cream	208	Heggie[12]	Randomized double blind	Institution	Aloe vera: more dry desquamation, more pain	0.003
Aloe vera versus soap	77	Olsen[13]	Randomized	RTOG	Aloe vera may delay onset skin reactions	NS
MMF‡ (steroid) versus emollient cream	49	Bostrom[14]	Randomized double blind	Institution	MMF: < maximal erythema	0.011
					< burning	0.069
					< itching	0.087
0.1% Methyl prednisone versus 0.5% dexpanthenol versus control	36	Schmuth[15]	Randomized double blind	Institution	Reduced mean toxicity severity with steroids	<0.005
0.2% Hydrocortisone versus placebo†	21	Potera[16]	Pt own control	Institution	No significant difference	NS
Biafine versus best supportive care	172	Fisher[17]	Randomized	RTOG	No difference in maximal skin toxicity	NS
Biafine versus Lipiderm versus control	74	Fenig[19]	Randomized	RTOG	No difference in maximal skin toxicity	NS
Biafine	60	Szumacher[18]	Prospective single arm	RTOG	Less severe toxicity than expected when giving chemotherapy concomitantly	
Biafine versus Calendula	245	Pommier[20]	Randomized	RTOG	Calendula: < grade 2–3 toxicity	0.001
					< pain	0.003

*Institution developed and used its own toxicity scoring scale.
†Small percentage of breast cancer patients.
‡Mometasone furoate cream (Elocon®).

Bepanthen®, or dexpanthenol cream, had been used extensively at the reporting institution for acute skin reactions. Eighty percent of the patients were breast cancer patients and the rest were laryngeal cancer patients. Each patient applied the Bepanthen® cream twice-daily beginning with the first day of treatment to half the field and none to the other half. The evaluators were kept blinded. Three patients discontinued the Bepanthen® cream because of "untoward or allergic" reactions. There was a statistically significant reduction in desquamation with the use of the cream. With further analysis, this effect on desquamation was mainly for "low-grade lesions." The authors concluded that there was no overall significant effect of the ointment. Chamomile cream and almond ointment have also been studied in breast cancer patients in a similar fashion using the patient as her own control. Neither agent had a significant overall effect, but the almond ointment did reduce grade II toxicity.[8]

An interesting study reported a significant reduction in high-grade skin toxicity with the use of hyaluronic acid 0.2% cream (Ialugen®) compared to placebo in a population of predominantly head and neck cancer patients.[10] A double-blind randomized trial was performed in 134 patients (68% had head and neck cancer, 22% breast cancer, and 10% pelvic cancer) with the agents applied twice daily (1–2 hours after treatment and evening) for 10 weeks. No concomitant medications were allowed. The hyaluronic acid group had significantly delayed onset of skin reactions, overall less severity in toxicity, and faster resolution of reactions than the placebo group.

Aloe vera has been used by various institutions for radiation-induced skin toxicity.[11–13] Aloe vera is an extract derived from the tropical cactus genus, Aloe. It is available over the counter in a variety of preparations and used generally for other types of dermatitis such as sunburn. The North Central Cancer Treatment Group (NCCTG) and the Mayo Clinic collaboratively conducted a randomized, prospective trial evaluating aloe vera gel as a prophylactic agent for acute skin toxicity in breast cancer patients receiving either intact breast or chest-wall irradiation.[11] Two separate studies were conducted: the first was randomized in a double-blinded manner to aloe vera gel or a placebo gel, and then 108 women were randomly assigned aloe vera gel or observation. Gel application was BID and began within the first 3 days of RT and continued for 2 weeks afterward. The study allowed treatment with other topical agents once a skin reaction was demonstrated. Patients with marked erythema and pruritus were to use 1% hydrocortisone cream. An acute toxicity scoring system, somewhat similar to the one established by RTOG (Table 1) was used; however, only dry desquamation was scored as grade 2 and any moist desquamation was scored as grade 3. No significant differences were found between the two arms in either of the study leading the authors to conclude that aloe vera was unable to decrease radiation-induced dermatitis. No mention was made of the agents used for the "treatment" of dermatitis during the study and no analysis was performed to evaluate if this may have confounded the study's results. The scores of health care providers and patients were examined and revealed that they were highly correlated. It is notable that 36% of the time, patients judged their dermatitis to be more severe than did their health care provider, and for only 7% did patients judge their dermatitis as less severe than the physician ($P < 0.0001$).

Another randomized trial found some benefit from aloe vera gel in reducing erythema associated with radiation but inferior to an aqueous cream for relief of dry desquamation and pain.[12] In this study, 225 patients after lumpectomy for early stage cancer were randomized in a double-blinded fashion to use aqueous cream or 98% aloe vera gel on their skin during breast radiation. The aloe vera or aqueous cream was applied three times daily beginning with RT and continued for 2 weeks post-treatment. This study found that the cumulative probability for pain (26% vs. 16%, $P = 0.03$) and dry desquamation (70% vs. 41%, $P \leq 0.001$) was greater in the aloe vera arm compared to aqueous cream. The cumulative probability for pruritus was also higher in the aloe vera arm but did not reach statistical significance. However, statistical significance was obtained for increased >grade 2 erythema in the aqueous cream arm ($P = 0.06$). Subjects in either arm with a bra cup ≥ size D were significantly more likely to experience severe erythema when compared to smaller breast sizes.

Finally, a third study compared aloe vera gel plus mild soap to mild soap alone in a randomized blinded manner in a heterogeneous group of cancer patients receiving RT.[13] This study reported that for patients who had not shown skin reactions by 27 Gy, those patients using aloe vera had a significant delay in the onset of skin reactions ($P = 0.013$). This led the authors to speculate that aloe vera is protective for radiation dermatitis in some people.

Topical steroids have also been commonly used for the management of acute radiation skin reactions for breast cancer patients.[14–16] A small double-blind randomized study from Sweden compared mometasone furoate MMF (Elocon®) with an emollient cream in 50 breast cancer patients.[14] The agents were applied once daily, 3 times a week until 24 Gy, and then once daily until 3 weeks post-treatment. Patients using the steroid cream had statistically lower maximal erythema scores, $P = 0.011$. Less itching and burning symptoms were reported with the MMF, but it did not reach statistical significance and there was no difference in VAS pain scores between the two agents.

Another smaller double-blind randomized trial compared 0.1% methylprednisolone (Advantan®) to 0.5% dexpanthenol (Bepanthen®) in 31 breast cancer patients receiving breast radiation after lumpectomy.[15] Using a 15-point scoring system, there were fewer patients with scores ≥4 in the steroid group ($P < 0.05$), and slightly lower mean scores with methylprednisolone treatment. A skin-specific quality-of-life (QOL) tool (Skindex) demonstrated significant reduction in the dimension of embarrassment ($P < 0.05$) and approached significance for the dimensions of fear ($P = 0.06$) and physical discomfort ($P = 0.057$). The authors concluded that the use of corticosteroid reduced the clinical severity of radiation dermatitis and lessened its negative impact on the patients skin-related QOL.

Biafine is a water-based emulsion for dermal wound healing that has been used widely in France for the management of acute radiation skin reactions. Four recent studies have evaluated its efficacy in this role.[17–20] The RTOG conducted a randomized phase III trial comparing Biafine to the best supportive care for preventing or reducing acute skin toxicity in 172 women receiving breast radiation after lumpectomy.[17] There was no statistical difference in maximum toxicity, time to development of ≥grade 2 toxicity, or resolution of toxicity between the two arms. Large-breasted women (D-cup or larger) had a higher frequency of ≥grade 2 toxicity, overall. Biafine use was associated with

statistically less toxicity at 6 weeks post-RT in large-breasted women ($P = 0.002$). Patients with ≥grade 2 toxicity had significantly worse QOL ($P = 0.048$).

A phase II study evaluated Biafine for 60 breast cancer patients receiving concomitant breast radiation with CMF chemotherapy.[18] Eighty-three percent had grade 2 toxicity and 2% grade 3. The authors concluded that this was less than what would probably occur with no topical therapy in this clinical scenario.

A small prospective study from Israel evaluated acute skin toxicity in 74 women receiving breast radiation after lumpectomy randomly assigned to Biafine, Lipiderm, or observation.[19] Lipiderm is a moisturizing cream popular in Israel. Patients could have additional topical therapies for radiation skin reaction if clinically warranted. There was no significant difference between the three arms for the %grades 3–4 reactions or the mean maximal score.

Finally, Biafine was compared to Calendula in 254 breast cancer patients undergoing radiation following lumpectomy or mastectomy in a Phase III randomized study from Lyon, France.[20] Calendula is fabricated from a plant of the marigold family and commercially available in France. It is used for the topical treatment of irritant dermatitis, skin lesions, and superficial burns.[20] The radiation to the intact breast was 52 Gy in 2 Gy fractions with 5 MV accelerator and a 10 Gy boost to the tumor bed with electrons. After mastectomy, the chest wall received 46 Gy with electrons. The ointment was applied at the beginning of RT, twice daily until completion. No other prophylactic agent was allowed, but treatment of > grade 2 toxicity with other topical agents was permitted. Acute skin toxicity was evaluated according to the RTOG scale in four regions: breast or chest wall, inframammary fold when present, axilla, and within the supraclavicular field. There was a lower incidence of grades 2–3 acute skin toxicity with the use of Calendula compared to Biafine, 41% versus 63%, respectively ($P < 0.001$). Grade 3 toxicity was observed in 7% who used Calendula, and in 20% who used Biafine ($P = 0.034$). When these results were examined by treated region, it was found that significant reductions in acute toxicity were primarily in the inframammary fold, axilla, and the supraclavicular field. There were no significant reductions in acute skin toxicity over the breast, chest wall, or internal mammary regions. The mean maximal pain score on the VAS was 1.54 for the Calendula and 2.1 with Biafine ($P = 0.03$). A multivariate analysis of factors associated with radiation-induced skin reactions during breast cancer treatment found that a body mass index ≥ 25 ($P < 0.001$) and type of ointment used ($P < 0.001$) were most predictive. For patients undergoing lumpectomy, chemotherapy prior to RT ($P < 0.001$), BMI ≥ 25 ($P<0.001$), and ointment used ($P = 0.001$) were risk factors for skin toxicity. The authors conclude that Calendula should be proposed as preventative treatment for patients undergoing radiation for breast cancer.

In summary, the multiple studies above that examined primarily prophylaxis of acute skin toxicity by a topical agent demonstrated some reduction in toxicity with hyaluronic acid and Calendula application. Washing the irradiated skin was also associated with less severe skin reactions. In general, topical steroids reduced symptoms, particularly erythema and pruritus. Aqueous cream application reduced the occurrence of dry desquamation in comparison to aloe vera.

At the Medical College of Wisconsin, all the breast cancer patients are put on a light moisturizer (Clean and Moist®) during their first week of treatment to be used

twice daily and continued until 4 weeks post-radiation. If patients cannot tolerate this product, they are instead given Biafine or some other comparable moisturizer. A switch is made to a thicker oil-based product (typically Aquaphor®) as necessary later in the treatment course depending on the severity of reactions that develop. Patients are asked to apply the moisturizer at least 2 hours before each radiation treatment to minimize a potential bolus effect. A steroid cream (e.g. Synalaar, Lidex) is prescribed for those patients who develop significant pruritus and/or a raised bumpy follicular rash associated with their skin erythema. Patients are encouraged to take acetaminophen, ibuprofen, or other over-the-counter non-steroidal pain relievers as directed for breast discomfort. For that small percentage of patients who develop pain >3/10 on the VAS scale that does not respond to the measures above, a narcotic analgesic is prescribed. We have commonly used Ultracet or Tylenol with codeine for this as tolerated. We find the most common need for narcotic type pain medication is to help patients sleep more comfortably at night. It is our observation that patients experience two different types of breast discomfort during radiation. The first type is associated with the skin reaction and is localized to the most severe skin changes. This is the discomfort for which analgesics are most often prescribed. The second type is sharp shooting pains in the breast that patients tend to report in the latter half of treatment that are unrelated to the severity of the skin reaction. Patients refer to these as "zingers," or "electric shock" type pains. These become less frequent following the completion of treatment and resolve over the next several weeks.

On average, >80% of acute skin toxicity during breast radiation is grades 1–2 with moist desquamation confined to the skin fold areas such as the axilla or the inframammary fold. The incidence of grade 3 acute skin toxicity in the studies detailed above (and in Table 5) averaged about 11% (range 0–40%). When moist desquamation does occur, it is recommended that the RT is held or, if possible, the affected area of the skin is blocked out of the field, particularly when radiating for breast conservation. Moist desquamation is associated with an increased risk of late telangiectasia development that can contribute to cosmetic failure.

Very little information exists examining the optimal method for managing radiation-induced moist desquamation. Instead, moist desquamation has been approached with the general principles of wound healing that applies to injuries from other mechanisms. The prevailing philosophy has been that wound healing is more rapid in a moist environment. As a result, hydrocolloid (HC) dressings have been used increasingly for radiation-induced moist desquamation. HC dressings are pliable sheets made of material such as pectin or gelatin with a polyurethane backing. Studies have demonstrated their benefit in a wide range of injuries including pressure sores, leg ulcers, donor sites, and minor burns.[21,22] The HC dressing absorbs wound exudate and forms a gel that keeps the wound surface moist. It has also been shown to be an effective barrier for bacteria. They are best for low to moderate exudate wounds. There are limited data examining their efficacy in radiation-induced moist desquamation. One study compared a Tegaderm type dressing to a conventional dressing (hydrous lanolin gauze) in 16 patients and found shorter overall healing time in patients where the Tegaderm type dressing was used.[23] Other studies have demonstrated that occlusive HC dressings reduced healing

time for management of moist desquamation.[24] An interesting study from Hong Kong randomly assigned 42 patients with mostly head and neck cancers who had developed moist desquamation to a HC dressing or application of gentian violet for management.[25] There was no significant difference in the overall healing time between the two therapies. However, although patients assigned to HC dressings experienced increased discomfort associated with dressing changes, patients were more satisfied with the HC dressings and rated them with a higher mean comfort score ($P = 0.0002$) and a better aesthetic acceptance ($P = 0.007$).

When moist desquamation occurs from breast radiation, our clinic uses HC dressings. The challenge is to get these dressings to conform and stick to areas such as the axillary, inframammary, or supraclavicular folds. Frequently, a secondary dressing such as dry gauze or an ABD is placed over the HC dressing and then gauze mesh tubes (Stockinette) or gauze bandage (kerlex) is fitted around the thorax to keep everything in place. The dressing is removed for treatment. After treatment, the nursing staff gently cleans and débrides as much as possible any necrotic material within the desquamating area with normal saline and reapplies the dressing. Patients change the dressings again at home as necessary depending on the amount of exudate. It has been our experience, as well as others,[1] that patients with tender, dry desquamation are more comfortable with the application of a HC dressing.

Avoidance of moist desquamation is a major goal of the skin care strategy during radiation therapy for breast cancer. In review of the studies above, larger BMI, patient size, and/or breast size, and skin folds were consistent predictors of more severe skin reactions. It is crucial that this be taken into consideration at the time of simulation when the patient's treatment position is set and immobilization established. When establishing the patient's treatment position, techniques should be used to minimize significant inframammary or axillary redundant skin folds where the incidence of moist desquamation is high. This can be a challenge to accomplish for larger and/or ptotic breasts that tend to hang laterally on the chest wall or inferiorly on the abdominal wall. A breast ring and cup have been advocated for this purpose.[26] These are fitted around or over the breast and fastened to keep the breast upright on the chest wall to avoid skin redundancies. These have been shown to have some bolus effect and can worsen acute skin toxicity.[26] Our institution and others have used a prone breast radiation technique in this group of women with larger and/or ptotic breasts.[27,28] Using a 3-dimensional radiation therapy technique, a homogenous dose distribution can be achieved comparable to the supine position in patients with smaller breasts.

Concurrent chemotherapy with breast radiation has also been associated with worse acute skin toxicity in many series.[29–34] Select series are shown in Table 6 demonstrating a higher rate of grade 3 skin toxicity with combined modality therapy. Anthracycline-based chemotherapy in particular has been associated with severe acute skin toxicity when given concomitantly with breast radiation.[31,34] Conflicting results are observed with concomitant CMF and paclitaxel chemotherapy. Caution is advised in delivering chemotherapy together with breast radiation given the potential for worse acute toxicity and no consistent evidence that it offers a benefit in terms of survival and/or local regional recurrence rates over sequential therapy.

Table 6. Acute skin toxicity from concurrent radiation and chemotherapy for breast cancer

Regimen evaluated	Author	Patient population	% Grade 3 toxicity	% Other toxicity	Conclusion
Paclitaxel every 3 weeks	Ellerbroeck[29]	24 BCT s/p AC × 4	0%*	8 pts with treatment break >3.5 days	Well tolerated
Paclitaxel every 3 weeks	Hanna[30]	20 stage II–III 6 6 BCT/14 MRM s/p AC × 4	33%*	20% clinical RT pneumonitis	Approach cautiously
Paclitaxel twice weekly	Formenti[31]	44 stage IIB–III neoadjuvant	7%*	14% post-MRM complications	Well tolerated
Paclitaxel every 3 weeks	Bellon[32]	29 stage III or recurrent	10%*	Bolus associated w/↑ toxicity	Concurrent therapy feasible
Docataxel every 3 weeks		15 Stage III or recurrent	40%*	One case of acute pericarditis	
CMF every 3 weeks	Isaac[33]	220 stage I–III BCT 75% MRM 25%	1.5%*		Acceptable adjuvant regimen
CMF (classic) every 21 days	Fiets[34]	51 (73% BCT)	41%†	4% Clinical pneumonitis	Too toxic
AC every 21 days		61 (56% BCT)	70%†	17% Hospitalization	

*RTOG acute toxicity.
†Common toxicity criteria version 2.
BCT, breast conserving therapy; MRM, modified radical mastectomy; AC, Adriamycin and Cytoxan; CMF, Cytoxan, methotrexate, 5-FU.

A2. Fatigue

During radiation for breast cancer, patients will commonly report that they feel fatigued. Fatigue in breast cancer patients receiving radiation seems to be mild to moderate in intensity and develops in a characteristic pattern. This is illustrated in a small study that reported on 15 women who demonstrated mild fatigue (2–4 on a 10-point scale) during a course of radiation for early stage breast cancer. The intensity of fatigue peaked at the 4th week, plateaued through the 7th week, and then dropped beginning with the 11th week.[35] Similarly, a different study in 30 breast cancer patients receiving radiation reported that fatigue peaked at weeks 4–6 and returned to baseline level 1 month after treatment.[35] Another study examining fatigue with a FACT fatigue subscale demonstrated that 43% of 52 women receiving breast radiation developed significant fatigue (score >37) and in 54% minimal or no fatigue was found. They reported that fatigue increased during the first few weeks of breast radiation, peaked at week 4 and then remained stable until 2 weeks after RT and was beginning to return to the baseline levels by 6 weeks post-treatment.[37]

Although radiation-related fatigue may be mild to moderate and dissipate within several weeks after the treatment is completed, when present, it can have a significant effect on patients' daily functions and overall QOL. This is demonstrated in a study evaluating fatigue with the Fatigue Severity Scale in 35 patients with prostate cancer and 34 with breast cancer, comparing scores prior to treatment and 1 week afterward.[38] Using this tool, 69% of the patients report of subjective fatigue that was relatively modest, and 28% demonstrated an increase in severe fatigue (score of >42) from a baseline of 19%. Measures by the EORTC QOL scale demonstrated significant decreases in role, cognitive, and social functioning as well as global QOL during radiation. In this and the previous study, an important predictor of fatigue level after radiation was the baseline fatigue prior to starting the treatment. A different study evaluated fatigue in 76 breast cancer patients at 6 time points: pre-RT, 2 weeks into treatment course, end of RT, and 3 and 6 months post-RT using Pearson Byars Fatigue Feeling Checklist.[39] This study, in contrast to previous ones, demonstrated fatigue onset in the first week of treatment, stabilizing thereafter, and resolving by the end of RT. Fatigue scores were back to pre-treatment level by the 3 and 6 month follow-up. Subjects in this study had significant alterations in functional activities from the start of radiation until its completion. Alteration in functional activities returned to baseline by 3 months after treatment. This study also evaluated Fatigue Relief Strategies to determine how patients managed their fatigue. Seventeen self-initiated strategies were assessed. The strategy of sit and sleep were consistently the most frequently used strategy and scored as the most effective.

During a course of breast radiation, patients should be guided about self-management of fatigue, that is, prioritizing essential activities and deferring, postponing, or delegating activities that are non-essential. Patients who work full-time are advised that they may need to reduce their work hours during the last 2 weeks of breast radiation and for 2 weeks afterward. A discussion about what type of documentation a patient needs to reduce work hours if necessary may be in order. Treatment of specific causes related to fatigue should be done, e.g., anemia, depression, anxiety, and insomnia.[40] In addition,

convincing clinical evidence has emerged that exercise can be an effective strategy for management of fatigue related to breast cancer treatment.

One such study examined the effect of exercise on fatigue levels by randomizing 46 women aged 35–64 receiving breast radiation after lumpectomy[41] to an exercise program versus usual care during treatment. In the exercise group, 86% reported exercising for at least 30 minutes ≥3 times per week and the usual care tended to decrease their activity level as the treatment progressed. One hundred percent of patients in the study reported fatigue during treatment, but the fatigue scores were lower for the exercise group. Anxiety, depression, and difficulty sleeping were common for both groups; however, greater symptom intensity was found in the usual care group.

On the basis of this, we guide our patients to rest when they feel tired and to be active when they feel good. All the patients are counseled about the benefits of exercise for minimizing fatigue symptoms during treatment. Patients are encouraged to maintain their exercise routines when they feel well and given support if they express interest in beginning the exercise programs during treatment.

B. LATE TOXICITY

B2. Breast Appearance

The main goals of breast conservation therapy in early stage breast cancer are to provide primary tumor control comparable to mastectomy and to preserve an acceptable cosmetic appearance of the breast. An unsatisfactory cosmetic outcome should be considered as a potential late toxicity. The rate of poor or fair cosmetic outcome in most series is 15–20% or less.[42–46,48–50] It has been demonstrated in many studies that surgical factors including the extent or volume of surgical resection[45,46] and scar orientation,[45] have the largest impact on breast appearance and the cosmetic outcome.[42–47] The use of chemotherapy and patient factors such as breast size, older age, and race have also been associated with more frequent cosmetic failures.[42–47] However, several radiation treatment factors are associated with poorer cosmetic outcomes as well. It is important to consider these factors when planning radiation treatment to minimize the late toxicity rate. Table 7 lists the cosmetic outcomes from single institution retrospective studies that have analyzed the impact of radiation techniques on subsequent cosmetic outcome.

Wazer et al. from New England Medical center at Tufts demonstrated an increase in fair/poor cosmetic outcomes with larger chest-wall separations (24 cm mean) and

Table 7. Physician assessed cosmetic results from breast conservation therapy

Institution	*N*	F/U (years)	Excellent (%)	Good (%)	Fair (%)	Poor (%)	Radiation factors associated with poorer cosmesis
Tufts U[46]	234	4.2	41	47	9	3	Heterogeneous RT dose; Boost; use of >2 fields
Harvard/JCRT[44,49]							Breast dose >50 Gy; use of >2 fields; boost dose >18 Gy; implant boost
<1981	504	8.9	58	28	10	4	
1982–1985	655	5.6	73	23	3.5	0.5	
Washington U[45]	458	4.4	38	44	15	4	Use of >2 fields; breast dose >50 Gy; no compensator filters

greater maximal dose inhomogeneity (13% mean) at the central axis.[46] The use of a boost and a supraclavicular and/or axillary field were the other factors associated with a higher proportion of fair/poor cosmetic outcomes. In this study, an electron boost, but not an interstitial implant boost, was associated with the decline in cosmetic outcome. Patients in this study were treated with 6 MV photons, 81 patients with an implant boost, and it is not stated what proportion were treated to >2 fields.

The effect of radiation technique on the cosmetic result was demonstrated by the Joint Center for Radiation Therapy and Harvard Department of Radiation Therapy when it compared cosmetic results in two different cohorts of patients treated between 1970–1981 and 1981–1985.[44] In the earlier cohort, 85% received a 3-field technique, 95% an implant for boost, 33% ≥ 50 Gy breast dose, and 85% >18 Gy boost dose. The institution had previously found that the use of >2 fields, an implant boost, boost dose >18 Gy and a breast dose >50 Gy were associated with poorer cosmetic outcomes.[48,49] Treatment techniques had changed during the latter time interval, such that 55% received a 3-field technique, 47% an implant for boost, 5% ≥50 Gy breast dose, and 42% >18 Gy boost dose. The cosmetic results were significantly better with the techniques used in the latter period (Table 7). When examined, there was no influence of the boost, number of fields treated, and/or the daily dose on cosmetic outcome in the latter cohort.[44]

Washington University[45] similarly found that the percentage of excellent/good cosmetic outcomes decreased with the use of more than 2 fields ($P = 0.034$), and increasing radiation dose to the entire breast ($P = 0.024$). With increasing separations at the central axis, a relative deterioration occurred in excellent/good ratings, especially with the use of lower energy, 4 MV photons. This is inferred to be from the dose inhomogeneity that occurs with the larger chest-wall separation. The effect of dose homogeneity on cosmetic outcome is again demonstrated in this study by a significantly higher frequency of excellent/good cosmetic scores (82%) that occurred with the use of compensating filters compared with no use of compensating filters (59%) ($P = 0.002$). Daily fraction size (1.8 vs. 2.0 Gy), boost versus no boost, and the type of boost did not influence cosmetic outcome in this series.[45] Other studies have confirmed the influence of radiation therapy factors on cosmetic outcomes. For instance, Ryoo et al.[43] reported that the use of a wedge in the breast tangents was a significant factor for obtaining a good cosmetic result.

The cosmetic failure rates reported in all of these studies reflect treating physician observation. Studies that include patient-rated cosmetic evaluations demonstrate fairly good concordance with physician-rated cosmesis and satisfaction with a range of cosmetic outcomes.[45,50]

In an attempt to objectively measure cosmetic outcome, Pezner et al. developed a Breast Retraction Assessment (BRA) that quantified the amount of retraction of the treated breast in comparison to the untreated one by measuring the lateral and vertical displacement of the nipple.[42] On multivariate analysis in order of descending importance, patient age >60, extensive breast resection, patient weight >150 pounds, and upper quadrant primary site were the most significant factors related to breast retraction after BCT. None of the RT parameters studied were associated with breast retraction. Subset analysis related that the volume of the boost had some relation to retraction, but did not reach statistical significance.

Table 8. Cosmetic outcome from EORTC 22881/10882 Boost versus no boost trial[51]

	No boost		Boost	
Score (%)	Post-OP	3-YEAR	Post-OP	3-YEAR
Excellent	37.4	41.7	34.8	32.7
Good	47.3	43.9	45.0	38.2
Fair	13.7	13.1	18.8	25.8
Poor	1.6	1.4, $P = 0.23$	1.4	3.3, $P < 0.001$

The effect of the boost on the cosmetic result was evaluated in a randomized trial, EORTC 22881/10882.[51] In this trial, 5569 stage I and II breast cancer patients who had received lumpectomy, axillary dissection, and breast radiation up to 50 Gy over 25 fractions were randomized between a boost of 16 Gy or no boost if the lumpectomy resection margins were negative. Cosmetic outcome in each arm was assessed by two methods postoperatively and at 3 years: by a 5-physician panel evaluating photographs in a sample of 713 patients (Table 8) and by the percentage BRA relative to a reference length in a sample of 1141 patients.

Postoperatively, there was no significant difference in cosmetic assessment between the two arms, but by 3 years, the patients in the boost arm had a significantly lower rate of excellent/good cosmetic outcome and nearly double the rate of fair outcomes (13% no boost vs. 25.8% boost) ($P = 0.0001$). Very few patients in either arm had a poor result at either time period. By the panel assessment, the boost group had significantly worse median scores for all the items evaluated—appearance of the surgical scar, breast size, breast shape, nipple position, and areola shape. Interestingly, despite the observations of the panel, the difference in the percentage BRA was small, less than 1% between the two arms. Even in the larger sample size, this difference reached only borderline statistical significance ($P = 0.04$).

In contrast, radiation did not have a deleterious effect on cosmetic outcome in a subset of 101 women accrued to the Milan III trial that randomized women with breast cancers $\leq$2 cm in size to quadrantectomy (QUAD) or quadrantectomy plus breast irradiation (QUART).[52,53] Radiation consisted of 50 Gy whole breast dose followed by a "scar" boost of 10 Gy, all delivered with 2 Gy fractionation. This study also evaluated cosmesis with two separate measures: an objective measurement of nipple and breast displacement to assess symmetry; and second, with a subjective rating by physicians and patients. There was not a statistical difference in cosmetic outcome between the QUAD versus QUART by either measure.[53] The absence of a negative effect from radiation in this trial may be as a result of the lower total dose to the boost area of 60 Gy versus 66 Gy in the ETORTC trial.

In summary, there is a whole host of patient and treatment factors that can contribute to cosmetic failure as a late toxicity from breast conservation therapy. However, the radiation factors that influence the cosmetic outcome in most series are the use of a boost, greater than 2 fields (i.e., the addition of a supraclavicular, axillary, or internal mammary field), the total dose, and dose heterogeneity in the breast fields. Newer radiation therapy planning methods such as 3-dimensional conformal therapy or intensity-modulated

radiation therapy can produce more homogeneous dose distributions through the breast. However, CT-based treatment planning for breast cancer is still emerging. In 1999, the Patterns of Care Study demonstrated that a CT was used for radiation treatment planning in only 17% of intact breast cases and 15% of those irradiated post-mastectomy.[54,55]

The efficacy of the boost for improving local control, particularly in certain subsets of patients, has been demonstrated.[56,57] Care should be taken that the boost is delivered using the appropriate techniques to minimize morbidity. Careful image-guided localization of the cavity will help reduce excess breast tissue being taken to higher doses unnecessarily.

B2. Augmented or Reconstructed Breast Appearance

Breast cancer patients who receive radiation to an augmented breast following lumpectomy or a reconstructed breast following mastectomy have a higher risk of cosmetic failure.

Augmentation

Breast augmentation preceding the diagnosis and treatment of a breast cancer can create a clinical conundrum. The appearance of the breasts is, typically, particularly important in this patient group; yet, their risk for cosmetic failure following breast conservation therapy is higher in some studies. Table 9 lists the rate of excellent or good cosmetic results in multiple studies demonstrating a wide range of outcomes.[58–63] Three studies demonstrate acceptable rates of 85–100% excellent/good cosmesis, but in the other 3, only 27–45% of patients achieved this result. Fairly uniform radiation techniques were used among these studies with the augmented breast receiving on average a range of 45–50 Gy with cobalt, 4 or 6 MV photons and subsequent boosts of 10–20 Gy delivered in most cases. The primary cause of cosmetic failure in irradiated augmented breasts is capsular contracture, which has been demonstrated to occur in 57–65% of cases.[59–62] The average time interval for onset of capsular contracture was reported at 22 weeks.[62] Mark et al. reported that the capsular contracture seemed related to the type of the implant (silicone 64% and saline 40%) and was more likely with sub-muscular (64%)

Table 9. Cosmetic outcome following lumpectomy and breast irradiation in women with previous breast augmentation

Institution (author)	N	Mean follow-up (mo.s)	% Excellent/good or % Bakers 1–2* cosmetic outcome
Beaumont (Victor)[56]	8	32	100
Van Nuys (Handel)[59]	26	NA	27*
Memorial SK (Ryu)[66]	3	24	33[†]
Cornell U. (Chu)[64]	7	43	85
USC, UCLA (Mark) [62]	21	22	43
John Wayne Cancer Institute (Guenther)[63]	20	45	85

[†]66% ultimate after one patient had surgical revision for capsular contracture.
NA means not available.

versus sub-glandular (50%) placement.[62] Baker's classification provides an assessment of capsular contracture. Baker I is a soft breast or implant with no deformity, II—the implant has a slightly thickened consistency with slight deformation, III—the implant is firm to hard and moderate deformity of the breast is noted, and IV—the implant is hard and there is severe breast deformity. There is an inherent risk of capsular contracture from breast implants in general unrelated to radiation. The overall incidence of capsular contracture after cosmetic breast augmentation with implants is 12% and is significantly greater for breast reconstruction following mastectomy for cancer treatment (34%) or cancer prophylaxis (30%).[64]

Surgical revision can improve the cosmetic outcome from capsular contracture in an augmented breast in some cases. At Memorial Sloan Kettering, Ryu reported that 2 patients underwent surgical revision with a subsequent excellent result.[60] Eight patients in the Van Nuys experience underwent revision surgeries after capsular contracture. Five patients had a capsulectomy and a new implant placed and 4 (80%) subsequently had an excellent cosmetic outcome.[59]

Reconstruction

An increasing percentage of breast cancer patients who are ineligible for breast conserving therapy or who have more locally advanced breast cancer are seeking reconstruction of the breast following mastectomy.[65] The options for breast reconstruction are tissue expansion with subsequent prosthetic implant placement or autologous tissue reconstruction. Immediate breast reconstruction during the same surgical period as the mastectomy provides the psychological benefit of waking-up post-procedure with a breast mound in place. However, a dilemma has emerged in that there is clinical evidence that breast reconstructions that undergo radiation have a higher risk of cosmetic failure,[58–62,66–71] while even a larger percentage of mastectomy patients may now be considered candidates for treatment since publication of a survival advantage in a subset of women who receive post-mastectomy RT.[72,73]

Table 10 lists the cosmetic outcome from immediate expander/implant breast reconstruction that underwent a course of post-mastectomy irradiation. In three of these studies, there was a low rate of acceptable cosmetic outcome.[58,60,66] The radiation treatment was similar in these studies with the chest wall/reconstructed breast receiving

Table 10. Cosmetic outcome following mastectomy with implant reconstruction and subsequent irradiation for primary or recurrent breast cancer

Institution (author)	*N*	Cancer	Mean follow-up (months)	% Excellent/good cosmetic outcome
Beaumont (Victor) [58]	13	Primary	32	54
Cornell (Chu)[61]	27	Recurrent	30	93
Washington U. (Kuske)[66]	65	68% Primary	48	45
Memorial SK (Ryu)[60]	11	Recurrent	24	56
Memorial SK (Cordeiro)[67]				
RT	68	Primary	34	80
No RT	81	Primary	34	88 (P = ns)

on average of 50 Gy with cobalt, 4 or 6 MV photons, standard fractionation, and an electron boost to the chest wall was used for many. A similar radiation technique was used at MD Anderson Cancer Center for 12 patients, 6 post-mastectomy with implant reconstruction, and 6 cancers arising in a previously augmented breast.[68] Comparable results were noted with no excellent, 33% good, and 42% poor cosmetic outcomes. In two studies,[58,66] the use of bolus application during radiation was associated with a significantly worse cosmetic outcome. At Beaumont Hospital,[58] 87% of patients who were treated without bolus application had a good to excellent result compared to 37% who were treated with bolus application ($P = 0.016$). Similarly, Kuske et al.[66] from Washington University reported that the use of a bolus layer was the only radiotherapy factor found to influence cosmetic results: 81% of patients with no bolus had an excellent/good cosmetic result versus 37% of patients for whom bolus was used during radiation ($P = 0.003$). In this study, the use of bolus also resulted in a higher complication rate (51% vs. 23%, $P = 0.048$). The use of compensators or wedges was associated with a lower complication rate but did not have a significant effect on cosmesis. Eight of 70 reconstructed breasts in this study were treated without a compensator or wedge and all of these patients experienced complications ($P = 0.036$).

Two studies in Table 10 reported a high rate of acceptable cosmetic outcome from irradiation of expander/implant reconstructions.[61,67] Chu et al. from New York Hospital, Cornell University Medical Center, reported a 93% excellent/good and 7% fair/poor cosmetic result in 27 patients with recurrent breast cancer 1 month to 10 years following mastectomy and silicone implant reconstruction.[61] Nine patients in this study received "wide-local field technique" and were not treated to the entire reconstructed breast.

The other study with acceptable cosmetic results was recently reported from Memorial Sloan Kettering and looked at 687 breast cancer patients who underwent immediate tissue expander/implant reconstruction following mastectomy.[67] At this institution, patients underwent mastectomy with placement of the tissue expander. Tissue expansion was continued during chemotherapy; and then 4 weeks following the completion of chemotherapy, the tissue expander was exchanged for the permanent implant. Post-mastectomy radiation began 4 weeks after this exchange. Eleven percent of 81 irradiated implants were subsequently removed versus 6% of 542 non-irradiated cases. The ultimate success rate for implant reconstruction was 90% versus 99% for irradiated and non-irradiated cases, respectively ($P = 0.001$). The 81 irradiated cases were matched to 75 non-irradiated control cases. There was an 80% excellent/good cosmetic result after post-mastectomy radiation that was not statistically different from the 88% noted in the non-irradiated cases.[67] Non-irradiated cases did have a higher rate of very-good/excellent cosmetic result. Overall, 68% of the irradiated patients developed a capsular contracture compared with 40% of those non-irradiated ($P = 0.006$). Irradiated patients were more likely to develop a Baker's grade III contracture (33.3% vs. 9.3%), but there was no significant increase in grade IV or severe contracture. Sixty-seven percent of irradiated patients were satisfied with their reconstructions and 72% stated that they would choose the same form of reconstruction again. The authors concluded that although irradiation increased the incidence of implant complication and contracture, the rates of reconstructive success and patient satisfaction remained high.

The long-term cosmetic consequences of irradiation following an autologous breast reconstruction have been contradictory. Kuske et al. reported that cosmetic results in 8 patients who underwent PMR after immediate transverse rectus abdominis myocutaneous (TRAM) flap reconstruction were good/excellent in 87% despite a 63% complication rate.[66] Similarly, a study by Zimmerman et al. from UCLA, reported 90% patient-rated good/excellent cosmesis in 21 patients who underwent radiation following immediate free TRAM flap breast reconstruction and had a mean follow-up interval of 19 months.[69] Other series have demonstrated worse complication rates from radiation after TRAM flap reconstruction.[71] This inconsistency is illustrated by two reports with similar outcomes but different conclusions. Nineteen patients who received radiation after pedicled TRAM flap reconstruction were compared to 108 patients who underwent radiation prior to a similar reconstruction at Emory University.[70] Thirteen or 68% of the 19 cases irradiated post-TRAM reconstruction had local recurrence of cancer requiring radiation. There was no significant difference in the rate of complication for an irradiated TRAM (31%) versus radiation pre-TRAM (25%) flap reconstruction. There was a 17% complication rate for 572 non-irradiated TRAM flap reconstructions at the institution overall. The authors concluded that the complication rate does not change whether a patient receives radiation before or after her TRAM flap reconstruction, only the nature of the complication changes (fat necrosis instead of fibrosis). A similar retrospective study from MD Anderson Cancer Hospital also compared the complication rate for post-mastectomy radiation after ($n = 32$) and before ($n = 70$) free TRAM flap breast reconstruction.[71] The delayed reconstruction was performed an average of 43 months post-completion of radiation. There was no difference in the rates of early complications (vessel thrombosis, partial flap loss, total flap loss, and mastectomy flap necrosis) between the two groups. There were significantly more late complications (fat necrosis 43.8%, flaps with volume loss 87.5%, and flaps with contracture 75%) in the immediate reconstruction group compared to the group that underwent reconstruction after completion of radiation (fat necrosis 8.6%, flaps with volume loss 0%, and flaps with contracture 0%). Twenty-eight percent of the 32 flaps that were irradiated required additional flap or an external prosthesis to correct the volume loss. On the basis of this experience, the authors concluded that patients who are candidates for free TRAM flap breast reconstruction and need post-mastectomy radiation, reconstruction should be delayed until radiation therapy is complete. Unfortunately, neither of these studies provided physician- or patient-rated cosmetic data or patient satisfaction scores.

An interesting study from the Michigan Breast Reconstruction Outcome Study evaluated factors that influenced complication rates in a prospective cohort of 326 women who underwent breast reconstruction after mastectomy from 1994 to 1998. Twenty-three plastic surgeons from 12 centers in Michigan, Pennsylvania, Louisiana, and Ontario contributed patients to the survey.[74] Sixty-four percent were immediate reconstructions and 24% were expander/implant, 55% were pedicle tram flap, and 21% were free TRAM flap reconstructions. No significant differences were observed across procedure types with regard to patient demographics or comorbidities. Complication data were collected 2 years after reconstruction. Overall, there were no complications in 54.6%, 1 complication in 29.1%, and 2 complications in 16.3%. Twenty-three percent had one

major complication, and 8% had 2–3. Multivariate analysis to assess the effect of reconstruction type and timing while controlling for patient age, body mass index, smoking, chemotherapy, and radiation demonstrated that only immediate reconstruction and body mass index were significantly associated with higher total complication rates. For TRAM flap reconstructions, the major complication rates were 36% in the immediate group and 18% in the delayed group ($P = 0.002$). Trends for higher complication rates were noted with radiation therapy and chemotherapy in separate analyses. Radiation before or after surgery for an expander/implant reconstruction was associated with higher overall complication ($P = 0.08$) and major complication ($P = 0.07$) rates. Chemotherapy was associated with significantly higher major complications in TRAM flap procedures ($P = 0.03$).

B3. Chronic Pain

Breast cancer patients can report pain in the irradiated breast, chest wall, or nodal regions for years after treatment. A survey of 127 breast cancer survivors who were on average 3 years post-treatment was done and revealed that 27% reported chronic pain.[75] The pain was rated mild in severity for 90% of patients. The sites of pain affected were breast 86%, ipsilateral arm 69%, and ipsilateral axilla 81%. Pain in all three sites was reported in 58%. The prevalence of pain was 27% after lumpectomy with RT, and 23% after mastectomy alone. The impact of irradiation on breast pain has been reported from two randomized studies. A companion study to assess breast pain was done at Princess Margaret Hospital during a prospective trial that randomized breast cancer patients older than 50 years to tamoxifen alone or tamoxifen and breast RT after lumpectomy.[76] This study found that radiation did not adversely affect breast pain up to 12 months post-treatment. Another QOL study that accompanied a randomized trial of observation versus breast RT after lumpectomy demonstrated that patients did have increased breast pain during irradiation and up to 2 years post-treatment. At 2 years no difference between the treatment groups could be detected in the rates of skin irritation, breast pain, and being upset by the appearance of the breast.[77]

B4. Fibrosis

Skin thickening or fibrosis of the breast or chest wall can occur after radiation for breast cancer. An analysis was done for complications after BCT in 294 patients treated at MD Anderson Cancer Center from 1990 to 1992.[78] Breast radiation was delivered with standard fractionation to a total prescribed dose of 50 Gy. Fibrosis was noted to develop in 29%, but only 3.7% experienced grade 2 (moderate) and 0.3% grade 3 (impaired ROM) fibrosis.[78] Similar to the findings associated with cosmetic failure, breast fibrosis developed more commonly in patients treated with additional radiation fields (38% vs. 21%, $P = 0.001$) and in patients who received a boost (33% vs. 22%, $P = 0.04$).

The influence of total dose and fraction size on the development of subsequent breast fibrosis is demonstrated by a study from the University of Hamburg that evaluated long-term radiation sequelae using LENT-SOMA criteria[80] in three groups of women who had undergone BCT with a minimum of 6 years follow-up: group 1 received 60 Gy total breast dose with 2.5 Gy fractions (1983–1987, $n = 45$); group 2—55 Gy total dose

with 2.5 Gy fractions (1988–1993, $n = 345$); and group 3—55 Gy total dose in 2 Gy fractions (1993–1995, $n = 200$). Grades 2–3 breast fibrosis developed in 58%, 51%, and 20% of patients in groups 1– 3, respectively.[79]

The effect of hypofractionation and the latency for developing subcutaneous fibrosis was studied by Bentzen et al. from Aarhus, Denmark. Fractionation studies compared two groups of breast cancer patients treated with post-mastectomy irradiation between 1978 and 1982: 163 women treated with a minimum target dose of 36.6 Gy to mid-axilla in 12 fractions of 3.05 Gy delivered twice weekly versus a sample of 66 women treated with a total dose of 40.92 Gy to mid-axilla over 22 fractions of 2.04 Gy delivered 5 fractions per week.[81] This study found that the incidence of fibrosis increased with time during the first 4 years of follow-up. By 3.2 years, 90% of the fibrosis had been expressed. A longer latency was demonstrated for the most severe fibrosis at 4.4 years, in comparison to grade 1 fibrosis which had developed by <2 year. The incidence of moderate to severe fibrosis was nearly double in the hypofractionated, 2 fraction per week schedule, 96% versus 45% in the 5 fraction per week schedule.[81]

Certain patient populations may be at risk for developing exaggerated fibrotic reactions following radiation. Patients with certain collagen vascular diseases (CVDs) may represent such a subset and are discussed later. Breast cancer patients who are heterozygous for the Ataxia Telangiectasia Mutation (ATM) have been reported to have more severe fibrosis following radiation.[82]

B5. Skin Telangiectasia and Atrophy

Telangiectasia or dilatations of the dermal vasculature that lie within a few millimeter of the epidermis can occur following radiation for breast cancer. Several studies examining post-mastectomy radiation have demonstrated that the incidence of telangiectasia is affected by total radiation dose,[84,85,87] larger fraction size,[81,84] and the occurrence of moist desquamation.[85–87]

The Gothenburg fractionation trials conducted during post-mastectomy radiation in Sweden in the 1970s examined the effect of radiation dose, fraction size, and dose-rate on the development of telangiectasia (as a measure of late skin reaction) following radiation with 12–13 MeV electrons.[83,84] These studies used patients as their own control comparing effects on the right versus left irradiated parasternal region. At greater than 5 years of follow-up, the frequency of mild, moderate, and severe telangiectasia was 79%, 49%, and 20%, respectively, for 2.61 Gy delivered daily 5 times per week for 21 fractions (54.81 Gy total dose) versus 100%, 79%, and 30%, respectively, for 5 Gy delivered twice weekly for 9 fractions (45 Gy total dose) ($P < 0.01$).[84] Another study in the Gothenburg series confirmed that the occurrence of telangiectasia were greater for 4 Gy delivered twice per week for 10, 11, and 12 fractions compared to 2 Gy delivered 5 times per week daily for 25, or 30 fractions. Within each fractionation schedule, the incidence of telangiectasia rose significantly with increasing total dose. Another study used four fractions of 7.2 Gy given once-a-week to compare the effect of delivering the dose per fraction over 4 minutes versus 32 minutes.[83] Prolongation of the treatment time resulted in a significant reduction in the incidence of telangiectasia: 85%, 65%, and 23%, respectively, for the minimal, distinct, and severe telangiectasia for the 4 minute

treatment time versus 62%, 32% and 6%, respectively, for the prolonged treatment time of 32 minutes ($P < 0.01$). Bentzen et al. in the Aarhus fractionation studies described above,[81] also reported the effect of fraction size and the latency for development of telangiectasia. Like fibrosis, the incidence of telangiectasia increased over time. It was not until after 4.7 years of follow-up time that 90% of the telangiectasia was expressed. The incidence of moderate to severe telangiectasia was 81% in the 2 fractions per week schedule versus 62% in the 5 fractions per week schedule.

With the incorporation of these concepts into modern radiation practice, the incidence of telangiectasia is less frequent after post-mastectomy radiation. The overall incidence of telangiectasia was 59% at 5 years for 120 post-mastectomy patients whose chest wall was irradiated using 12 or 15 MeV electrons with 50–50.4 Gy over 25–28 fractions, 5 days-a-week. The use of a scar boost for 10–16 Gy with 9 MeV electrons was the only factor found to be predictive for the development of telangiectasia.[85]

The development of telangiectasia after breast conserving therapy is less common but still related to fraction size and total dose. The University of Hamburg study outlined above evaluating fibrosis, demonstrated the effect of dose and fraction size on subsequent development of telangiectasia.[79] Grades 2–3 telangiectasia developed in 29%, 17% and 6%, respectively, for 60 Gy delivered with 2.5 Gy fractionation 4 days-a-week, 55 Gy with 2.5 Gy fractionation 4 days-a-week, and 54 Gy with 2 Gy fractionation given 5 days-a-week with cobalt-60 teletherapy. Pezner et al. reported an overall 18% incidence of telangiectasia by 5–9 months following breast radiation that gradually increased to 30% by the second year of follow-up in 119 patients who underwent BCT and received 50–50.4 Gy at 1.8–2 Gy per fraction. On multivariate analysis, boost, patient age >60, and use of regional nodal fields was predictive for developing telangiectasia.[42] The incidence of telangiectasia was 7% for the no boost group ($n = 72$), compared to 36% for the 47 that were boosted ($P < 0.001$). An even lower rate of telangiectasia was reported in the women evaluated for cosmetic outcome on the Milan III trial where the incidence was 3% in the QUART versus 0% in the QUAD arms.[53]

The development of telangiectasia is also associated with the occurrence and severity of moist desquamation during the acute skin reaction.[86,87] From the Aarhus data, the estimated incidence of severe telangiectasia after 44 Gy in 22 fractions increases from 27% to 49% in patients who developed ≥grade 2 moist desquamation (10–49% of the field) as an early radiation reaction.[86]

Patients who are distressed by the appearance of the telangiectasia can be potentially treated with pulsed dye laser (PDL). PDL is an established treatment for cutaneous telangiectatic disorders and is considered both efficacious and safe.[88] A study of 8 patients with telangiectasia post-mastectomy demonstrated that in 7 who finished PDL treatment, there was 100% vessel clearance occurred in the treated areas.[89] Three patients required three treatments, 3 patients needed two treatments, and 1 patient was treated just once to obtain clearance.

B6. Collagen Vascular Diseases

These are a heterogeneous group of diseases that have been considered as a relative contraindication for breast conserving therapy with radiation because of sporadic reports

of severe acute and late-treatment-related toxicity.[90,91] A study from Yale University specifically examined the incidence of acute and late toxicity after breast radiation for conservative therapy in the setting of CVD.[92] They identified 36 cases of CVD (17 rheumatoid arthritis (RA), 5 systemic or discoid lupus (S or DL), 4 scleroderma (SCD), 4 Raynaud's, 2 Sjögren's, 4 dermatomyositis/polymyositis) among the 1677 patients in their database who had undergone BCT, and matched each case to two control patients of similar age, tumor, and treatment factors. The breast was irradiated to a median dose of 48 Gy followed by a boost to the lumpectomy site to a total median dose of 64 Gy. There was no significant difference in acute toxicity for the CVD group overall compared to the controls. When analyzed by specific CVD, only the SCD subset was associated with an increased risk of acute toxicity. A significantly greater incidence of late toxicity was found between the CVD (17%) and control groups (3%) ($P = 0.0095$). Again, this was limited to the 4 SCD patients when this was analyzed by specific CVD. The late toxicities noted in 3 SCD patients were fibrosis-necrosis, ulceration-necrosis, and cord paralysis-dense fibrosis. The authors concluded that patients with SCD have higher rates of complications after breast irradiation, but that other CVD should not be considered contraindications.

Three other retrospective series have examined the relationship between CVD and radiation-induced complications. Two hundred nine patients with CVD with a variety of malignancies underwent irradiation to a median dose of 45 Gy (13–81 Gy) at Massachusetts General Hospital from 1960 to 1985.[93] Most patients, 131 (60%) had RA and the other 78 had non-RA CVD (28 patients had S or DLE, 17 polymyositis/dermatomyositis, 16 SCD, 8 ankylosing spondylitis, and four mixed connective tissue disorder). The patients in the RA group did not have higher rates of acute or late radiation toxicities. The non-RA CVD did not have higher acute toxicity rates, but had a significantly greater percentage of late complications, 21% versus 6% at 5 years ($P = 0.0002$).

Another series from the University of Iowa studied 61 patients with CVD who had been irradiated for various malignancies to matched-control groups of 61 irradiated patients without CVD.[94] Of the patients with CVD, 39 patients had RA, 13 had S or DLE, 4 had SCD, 4 had dermatomyositis, and 1 had polymyositis. Those with SLE had a non-significant higher rate of acute toxicity as compared to the control group (36% vs. 18%, $P =$ n.s.). Patients with RA had a non-significant increase in late complications when compared to the control group (24% vs. 5%, $P =$ n.s.). Among the late toxicities observed in the RA group were perforated sigmoid colon, small bowel obstruction, soft tissue necrosis, radiation pneumonitis, and fatal constrictive pericarditis. Patients with CVD treated with palliative doses of RT (<40 Gy) had acute and late complication rates equivalent to the controls.

Finally, another recent retrospective study from the University of Louisville compared acute and late toxicity from radiation for various malignancies in 38 patients with documented CVD to 38 matched-control cases.[95] There was not a significantly higher incidence of acute or late toxicity when the two groups were compared. However, the few SCD patients in this study had a higher rate of grade III acute and late complication following irradiation.

Breast cancer patients with CVD should be made aware of the potential for exaggerated acute and late toxicity related to radiation treatment, but should not be considered ineligible for breast conservation with radiation. From three retrospective studies so far, it appears that patients with SCD and other non-RA CVD may be at the highest risk for severe toxicities such that breast radiation in this group should be approached with caution.

B7. Lymphedema, Shoulder Immobility, and Brachial Plexopathy

These three toxicities are discussed together as they are all primarily consequences of supraclavicular and/or axillary irradiation in the treatment of breast cancer.

Lymphedema

Arm edema or lymphedema in breast cancer patients is caused by an interruption of the normal filtration process that occurs between capillaries, interstitial tissue, and lymphatic vessels in the arm. Under normal circumstances, capillary pressures force fluid into the interstitium and reabsorption pressures pull most of the fluid back into the capillary at the venous side. The remainder of the filtered fluid and protein are removed by lymphatic vessels. Without the functioning lymphatic system, protein, cells and non-reabsorbed fluid remain in the interstitial tissue. The stasis of fluid in the subcutaneous tissues of the arm leads to increased weight and girth of the extremity. Patients with arm edema secondary to breast cancer therapy can experience difficulty performing skills at home or work because of functional impairment, psychological distress as a result of the change of body image, and chronic pain, leading to significantly reduced QOL.[96,97,98] The primary treatment factors contributing to arm edema are the extent of axillary node dissection and nodal irradiation. There are multiple other clinical factors that have been associated with an increased subsequent risk of lymphedema, of these, infection[100,101] and obesity[116] are frequently reported.

Until recently, axillary node dissection was a standard part of the surgical management of invasive breast cancer regardless of tumor size or nodal involvement. The incidence of subsequent lymphedema in several studies is shown in Table 11 and averages about 13%. Studies with longer follow-up tend to show a greater incidence of arm edema. Increased rates of lymphedema have been reported with more extensive dissection,[103,104] greater number of nodes removed,[105,107,108] and splitting the pectoralis muscle.[107] Sentinel lymph node biopsy has resulted in significantly less morbidity with estimates of subsequent lymphedema being <1–3%.[110,111]

The addition of supraclavicular and/or axillary radiation following a dissection results in a higher incidence of lymphedema. The incidence of lymphedema following axillary node dissection and nodal irradiation ranges from 9% to 58% in the studies presented in Table 12. Increased rates of lymphedema have been described in association with both the British Columbia and the Danish Breast Cancer Cooperative Group (DBCG) 82B and 82C randomized trials that reported a survival advantage with the addition of chest wall and comprehensive nodal RT following mastectomy and chemotherapy. In the British Columbia trial, symptomatic lymphedema was reported in 9% of those irradiated versus 3% in the non-RT arm.[72] Hojris reported 14% lymphedema from

Table 11. Incidence of arm lymphedema after axillary dissection

Institution (author)	*N*	Measure	Nodal RT (%)	Lymphedema (%)
Johns Hopkins (Lin)[99]	283	Arm circumference >2 cm	6	16
Memorial Sloan Kettering, (Peterek)[100]	263	Arm circumference >2 cm	0	13
Wessex Radiotherapy (Ivens)[102]	126	Arm circumference, water displacement >200 cc	0	10

Table 12. Incidence of arm lymphedema after axillary dissection and nodal irradiation

Institution (author)	Year	*N*	Surgery	Measure	AND (%)	AND + RT (%)
Royal Marsden (Kissen)[104]	1986	200	BCS*35%	Limb volume >200 cc	0†	9.3†
					7.4‡	38.3‡
Odense University (Ryttov)[112]	1988	57	Mastectomy	Arm circumference >2.5 cm	11	46
Umea and Lund University (Segenstrom)[113]	1991	136	Mastectomy	Volume displacement >150 cc	21	58
Netherlands Cancer Inst. (Bijker)[114]	1998	691	Mastectomy	None given	6	28
Aarhus University (Hogris)[109]	2000	84	Mastectomy	Arm circumference/limb volume >200 cc	3	14
MD Anderson Cancer Center (Meric)[78]	2002	294	BCS¶	Arm circumference >3 cm	10	18
Massachusetts General Hosp. (Powell)[115]	2003	727§	BCS¶	Arm circumference "frequently" >2 cm	1.8	8.9

*BCS, breast conserving surgery.
†Axillary sampling.
‡Axillary clearance.
¶All patients received breast irradiation.
§No axillary dissection done in 14% of population.

irradiated versus 3% from non-RT in 84 women who had all been treated on the DCBG 82B and 82C trials at a single institution (Table 12). The extent of dissection prior to nodal irradiation impacts the rate of subsequent edema.[104] For instance, the risk of symptomatic edema in patients treated at JCRT/Harvard was 4% after RT alone without dissection, 6% after level I/II dissection plus axillary radiation versus 36% after a complete AND with axillary RT.[103] The incidence of arm edema following nodal irradiation in an un-dissected axilla ranges from 4% to 8%.[103,104]

Breast irradiation alone after lumpectomy and axillary node dissection seems to have a negligible effect on the incidence of lymphedema. The average incidence of lymphedema in the studies listed in Table 13 is 15%, which is similar to what is reported in the studies in Table 11 with axillary node dissection alone. The randomized trial from

Table 13. Incidence of arm lymphedema following breast conserving surgery, axillary node dissection, and breast irradiation

Institution	*N*	Measure	AND*(%)	Nodal RT (%)	Lymphedema (%)
Memorial Sloan Kettering (Werner) [116]	282	Arm circumference >2.5 cm	100	24	12.1
Northwestern University (Kiel)[105]	183	Arm circumference >2.0 cm	82	0.01	17.5
City of Hope (Pezner)[107]	37	Arm circumference >2.5 cm	86	0	14
Centro per lo Studio e la Prevenzione Onocologica (Herd-Smith)[108]	601	Arm circumference >5% difference	100	0	17.9

*Axillary node dissection.

the Uppsala-Orebro Breast Cancer Study that studied cancer recurrence from lumpectomy alone versus lumpectomy and breast irradiation in 381 women also evaluated arm morbidity.[117] Complete arm circumference data were available from 273 patients (117 in the RT group and 155 in the non-RT group). There was no associated difference between arm edema or any of the other arm symptoms evaluated (pain, numbness, impaired shoulder mobility) with the addition of breast irradiation. The number of nodes dissected was an important determinant of arm morbidity. At 3–12 months following treatment, arm symptoms were reported in 53.6% who had $\geq$10 lymph nodes found in the axillary specimen versus 33.6% who had <10 found. The frequency of arm symptoms reduced with time, such that at 13–36 months, the rate of arm symptoms was 33% and 19.5% for $\geq$10 versus <10 nodes found, respectively.

Radiation technique may influence the risk of lymphedema. Large fraction size and the inadvertent overlapping of fields have been associated with an increased incidence of arm edema.[118] Johansson et al. reported on 150 patients treated with RT in the mid-1960s following radical mastectomy. The patients were divided into three groups based on their fractionation: 4 Gy × 11 fractions delivered over 21 days; 4 Gy × 11 fractions delivered over 15 days; and 3 Gy × 14–15 fractions delivered over 20 days. With a follow-up of >30 years in surviving patients, the incidence of lymphedema was 70% and 69% from the two 4 Gy fractionation schedules versus 25% in the 3 Gy fractionation schedule ($P < 0.0001$). The patients in the 3 Gy fractionation group were treated with much smaller supraclavicular and internal mammary fields that may also have contributed to their lower rates of arm edema.

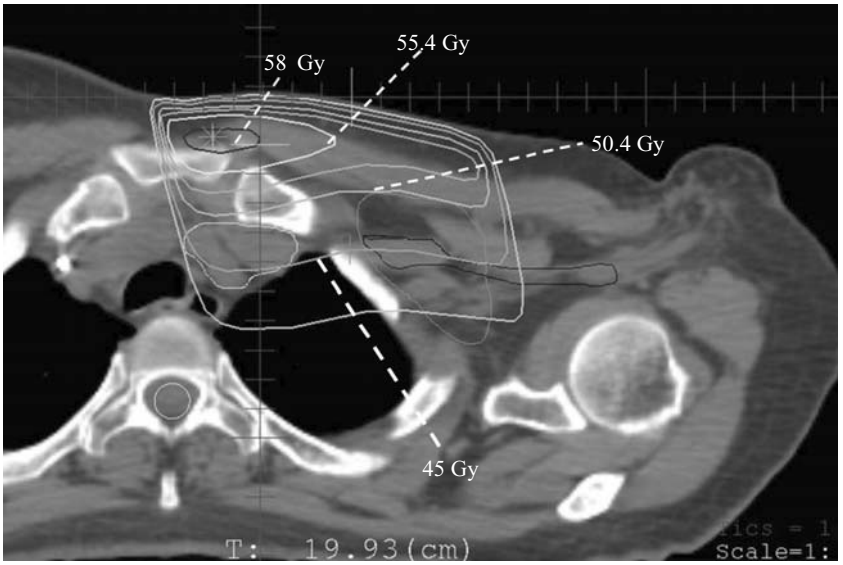
In the 1998–1999 Patterns of Care Study of post-mastectomy irradiation, the fractionation was $\leq$2 Gy in 97%, and 93% were prescribed a total dose between 45 and 50.4 Gy using 6 MV photons.[55] However, only 15% of the patients had CT-based treatment planning. A heterogeneous dose distribution can potentially lead to delivery of an unintentional larger fractions size and over-dosage in an area of the field that contains critical normal tissue. For instance, a 15–20% hot spot in a supraclavicular field dosed to 50.4 Gy over 25 fractions at a depth of 3 cm could lead close to 58–60 Gy being delivered with

2.2–2.3 Gy fractionation (Figure 1a). This is compounded with the use of an additional posterior axillary field that was used in 40% of the patients in the PCS post-mastectomy study.[55] This field was dosed most frequently to mid-axilla in the PCS study using 6 MV photons. When this field is used and dose prescribed at mid-axilla, it is important to watch the cumulative dose at $D = 3$ cm anteriorly, as the fractionation at this site with the combined supraclavicular field and exit from the posterior axillary field can become significantly higher than intended (Figure 1b). Omitting the posterior axillary field has resulted in lower rates of lymphedema in some retrospective studies. There was a 3% rate of lymphedema reported in 82 node-positive patients treated at the University of Michigan with supraclavicular irradiation only after a level I/II axillary dissection.[119]

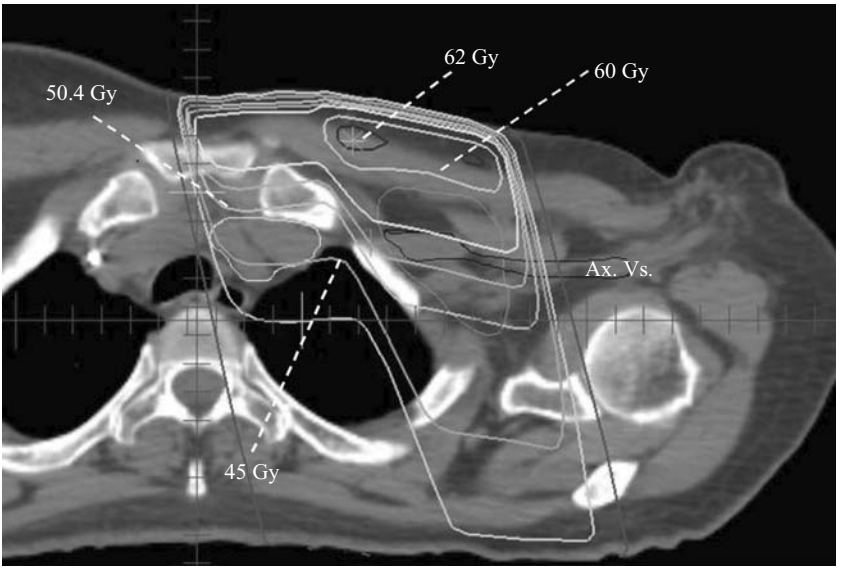
Complete decongestive therapy (CDT) of complex physical therapy has become a commonly recommended therapy for management of lymphedema.[120,121] The goal of CDT is to reduce arm edema to a minimum level, maintain the results, and prevent infections. It has four main components: (1) manual lymph drainage, (2) skin and nail care, (3) compression bandaging and/or garments, and (4) therapeutic exercise. The efficacy of CDT was evaluated in a prospective trial of 20 breast cancer patients after diagnosis of lymphedema. Following CDT, there was a median decrease in girth of 1.5 cm and median volume reduction of 138 cc. During follow-up at 6 and 12 months, there was a mild increase in girth and volume but stabilized at less than 1 cm and 100 cc below study entry.[122] Other studies have demonstrated symptomatic and objective measures of response to CDT.[123]

Hyperbaric oxygen therapy (HBOT) has demonstrated effectiveness when studied for management of radiation associated sequelae of the mandible, bladder, soft tissue, as well as breast.[124] A recent Phase II trial from Royal Marsden Hospital evaluated HBOT in 21 patients with chronic lymphedema following nodal irradiation for breast cancer.[125] Only 3 of 19 patients achieved the primary treatment goal of a $\geq$20% relative reduction in volume. A larger percentage of patients (6/13) had evidence of improved clearance rate of radiotracer uptake on lymphoscintigraphy after HBOT. Twelve of 19 patients reported symptomatic improvement. Given these findings, HBOT deserves further study.

There have been several pharmacological agents studied for treatment of lymphedema. Two randomized trials have evaluated coumarin. An initial study in 31 breast cancer patients with arm edema and 21 patients with leg edema were randomized in a double-blind, crossover design to receive coumarin or placebo for 6 months. Each reported a >20% reduction in volume following coumarin therapy.[127] A second trial randomizing 140 women with arm edema following breast cancer treatment with the same double-blind cross over design failed to demonstrate any benefit from the coumarin and reported a 6% rate of hepatotoxicity.[126] Dafilon, a flavanoid, did not have an overall significant effect when evaluated in a randomized trial in 94 patients.[128] However, in 24 patients with severe edema there was a significant reduction in arm volume. Selenium for treatment of radiation-associated lymphedema has been prospectively studied in 12 breast cancer patients with arm edema and 36 patients with endolaryngeal edema.[129] Sodium selenite at 350 μg/kg for a total daily dose typically of 500 μg daily over 4–6 weeks was used. Ten of the 12 breast cancer patients demonstrated a significant reduction of arm circumference measures. Given this finding, further investigation is warranted.



(a)



(b)

Figure 1. (a) Supraclavicular field. Isodose distribution from a prescription of 50.4 Gy to a depth of 3 cm with 6 MV photons and 1.8 Gy fractions. (b) Supraclavicular field with a posterior axillary boost (PAB). Isodose distribution for 50.4 Gy to a depth of 3 cm with 6 MV photons and 1.8 Gy fractions for the supraclavicular field. PAB dosed 10.6 Gy to mid-plane with 0.38 Gy fractions.

Shoulder Immobility

Impaired shoulder movement is primarily the consequence of axillary treatment. The type of surgical treatment and whether nodal irradiation is used influence the probability of subsequent shoulder consequences.

The cause of impaired shoulder motion following axillary node dissection and radiation is probably multifactorial. Damage to the pectoralis muscle is most likely an important factor for the development of shoulder dysfunction. Analysis of the Aarhus fractionation studies for post-mastectomy irradiation revealed that the occurrence of shoulder impairment post-treatment increased with increasing absorbed dose and the more hypofractionated schedule.[133] This gives credence to fibrosis of the pectoralis muscle and/or other chest-wall musculature as the main pathogenesis for impaired shoulder function post-irradiation. However, injury to ligaments, cartilage, joint capsule, vasculature, peripheral nerves, and lymphatic drainage may all contribute, directly or indirectly.

The impact of surgical procedure on shoulder movement was studied by Sugden et al. in 141 women treated for breast cancer in 1991 and assessed for arm function by a single observer 18 months post-treatment. Ninety-three women were assessed pre-RT and 18 months post, and the remaining 48 were only assessed post-treatment. Shoulder motion was measured for impairment in six movements: abduction, flexion, extension, both supination and/or pronation. The type of operation was the most important factor for the development of shoulder problems. Before RT, the incidence of a reduction in at least one shoulder movement was 78% for mastectomy patients and 43% in the lumpectomy group ($P < 0.01$).[130] Eighteen months post-treatment, the incidence of any reduced shoulder movement was 79% for the mastectomy patients and 35% in the lumpectomy group ($P < 0.01$).[130] Seventy-three percent had reduction in any of the shoulder movements measured following RT versus 35% who did not have axillary RT ($P \leq 0.001$). Patients with persistent shoulder dysfunction before RT had a 60% chance of persistent movement problems afterward, as compared to 24% with normal pre-RT shoulder movement ($P < 0.001$).

Review of Table 14 demonstrates three other studies with higher rates of shoulder impairment following post-mastectomy irradiation.[109,112,114] In these studies, impaired shoulder mobility ranged 2–6.8% following mastectomy alone versus 8–38% after the addition of irradiation. There has been less shoulder impairment reported after lumpectomy, axillary node dissection, and breast irradiation.[78,130,131] Deutsch reported a 1.5% rate of impaired shoulder motion in 232 post-lumpectomy patients and Meric et al. reported that 1.4% had decreased range of motion in 294 breast conservation patients. Arm mobility was among the arm symptoms that were not affected by the addition of breast RT following lumpectomy in the Upsala-Orebros randomized trial of lumpectomy and axillary node dissection ± breast irradiation described above.[117] Similarly, in the NIH randomized trial between MRM versus lumpectomy, node dissection, and irradiation, there was no significant difference in either treatment arm for shoulder range of motion at 1 year follow-up.[132]

Table 14. Incidence of impaired shoulder mobility after irradiation

Institution (author)	*N*	Surgery	Nodal RT (%)	Measure	Surgery (%)	Surgery + RT (%)
Netherlands Cancer Inst. (Bijker)[114]	691	Mastectomy	70	Patient self report	3.4	8* 18.9†
University of Oxford (Sugedn)[130]	39 102	Mastectomy Lumpectomy	35	Measured ROM‡	71¶ 31§	81¶ 59§
Aarhus Univ. Hosp. (Hogris)[109]	84	Mastectomy	100	Measured ROM	2	16
Odense University (Ryttov)[112]	57	Mastectomy	23	Measured ROM	6.8	38

*Axillary sampling.
†Axillary clearance.
‡ Range of Motion.
¶Mastectomy patients.
§Lumpectomy patients.

Brachial Plexopathy

Brachial plexopathy after radiation therapy is uncommon and typically seen only when regional nodal irradiation has been delivered. The clinical syndrome most frequently presents with paresthesias, and is associated with pain and/or weakness in the ipsilateral arm.[134,135] Weakness tends to be slowly progressive. The onset of symptoms can be seen within 6 months of completing radiation. While some studies document that most patients develop symptoms within 3 years,[134] others have demonstrated that the risk is progressive with time.[135,136] The entire brachial plexus is typically involved,[134,135] though some cases have documented involvement of just the upper or lower trunk. The mechanism of radiation-induced brachial plexopathy is not completely understood, but it is suspected that fibrosis of tissue around peripheral nerves occurs with injury to small vessels that leads to ischemia. Pathologic studies have shown loss of myelin, fibrosis and thickening of the neurolemma sheath, and obliteration of the vasonevum.[137]

The incidence of brachial plexopathy in reported series for breast conservation is very low. Pierce et al. from the Harvard group reported 20 (1.2%) of 1624 patients developed brachial plexopathy. The median time to occurrence was 10 months (range 1.5–77 months) and in 17 (85%), the symptoms had completely resolved by 1–2 years. Three women had severe, progressive symptoms for an overall rate of permanent brachial plexopathy of approximately 0.2%.[138] Supraclavicular/axillary radiation, axillary dose, and the use of chemotherapy were significantly associated with the development of brachial plexopathy. The 1117 patients treated with supraclavicular/axillary field developed brachial plexopathy in 1.8%, compared to none in the 507 patients treated to the breast alone ($P < 0.009$). Of those women who received nodal irradiation, higher rates of brachial plexopathy were seen with axillary doses >50 Gy (5.6% vs. 1.3%, $P = 0.004$), and the use chemotherapy (4.5% vs. 0.6%, $P < 0.001$). Other retrospective series of BCT from single institutions confirm that brachial plexopathy is very rare when just breast irradiation is delivered.[78,139,140]

Table 15. Hypofractionated supraclavicular/axillary irradiation and brachial plexopathy

Institution (author)	*N*	F/U (years)	Prescribed total dose (Gy)	Fraction size (Gy)	Fractions/ week	Energy	Brachial plexopathy (%)
Hamburg (Bajrovic)[141]	140	8	60	3.0	4	Co-60	14
Odense (Olsen)[142]	79	8	36.6	3.05	2	8–16 MV	35
Umea (Johansson)[136]	71	12	40	4	5	Co^{60}	63

Brachial plexopathy as a late morbidity from supraclavicular/axillary irradiation has been examined in older post-mastectomy series. In these studies, its incidence is associated with increasing fraction size and total dose (Table 15), similar to what is seen for late fibrosis. In the series from Hamburg University,[141] the 60 Gy in 3 Gy fractions was at a maximum depth of 0.5 cm. It is estimated that the dose to the brachial plexus at a depth of 3 cm was 52 Gy with a 2.6 Gy fraction. The rate of all brachial plexopathy grade 1 was 14% and all the damage was found to be progressive over the observation period, so that the percentage of patients with $\geq$3 plexopathy was 2% after 5 years, 5.5% after 10 years, 11.8% after 15 years, and 19.1% after 19 years, respectively.[141] In the report from Odense University by Olsen et al., patients had been treated according to the DBCG 77 protocol. Of the 35% rate of brachial plexopathy, 19% had mild symptoms of sensory disturbances and/or weakness, and 16% had severe symptoms that disabled her in daily life.[142] A very high rate of plexopathy was seen in the patients treated from 1963 to 1965 at the Umea University Hospital.[136] The prescription dose was 40 Gy in 11 fractions, but only 2 or 3 fields were treated per day so that the dose was given in 16–17 treatments over 3–4 weeks. Overlap occurred between the axillary and supraclavicular fields so that the given dose to the brachial plexus was much higher. A retrospective calculation showed that the dose to the brachial plexus was 54–57 Gy delivered over a complex combination of 1.8 Gy, 3.4 Gy, and 5.2 Gy fractions. The mean time for onset of BP was 4.2 years. There also was a progression of symptoms seen in this study over the entire follow-up period that was as long as 34 years. Of the 17% of women alive at 34 years follow-up, 92% had paralysis on their arm. A 5% rate of vocal cord paralysis that had onset at a mean of 19 years follow-up was also seen in this study. All of these occurred in left-sided lesions indicating recurrent nerve involvement.[136]

Subsequent post-mastectomy studies have demonstrated a lower rate of BP following nodal irradiation. One hundred and twenty-eight women irradiated on the DBCG 82B and 82C post-mastectomy studies were evaluated with thorough neurological exams to detect the presence of any neuropathy. The dose to the supraclavicular and axillary nodes was 50 Gy in 25 fractions on this study. After a median follow-up of 4.1 years, mild BP was noted in 9% and disabling symptoms in 5%. There was a higher incidence of plexopathy following radiation in patients who received chemotherapy ($P = 0.01$) and were younger than 47 years (0.04). Thirty three patients who did not receive radiation had no occurrence of plexopathy. These numbers represented a significant reduction in the incidence of BP when compared to the DBCG 77 trial.[135] Interestingly, Hogris

et al. evaluated 84 patients for the presence of late morbidity that had been treated at his institution on the DBCG 82B and 82C trials. Paresthesias and weakness of the arm were more common in the irradiated patients than in the non-irradiated patients. Subjective complaints of paresthesia and weakness occurred in 7% and 28%, respectively, of the irradiated patients, and in none and 19%, respectively, of the non-irradiated patients. Objective examination revealed that 21% had paresthesias and 14% weakness in the irradiated group, and 7% and 2%, respectively, in the non-irradiated group. No patient had more than mild, grade I weakness measured.[109]

During the planning for supraclavicular or axillary nodal irradiation at our institution, the axillary vessels are contoured as a structure within the axilla to be a surrogate for the brachial plexus. It is our policy to not match over this structure to minimize the potential for inadvertent overlaps. The area of the contoured vessels is monitored to ensure that there are no dosimetric hotspots in or around the structure that would give an unintentional higher dose (Figure 1b).

B8. Cardiac Morbidity

Radiation of the breast or chest wall for left-sided breast cancers can inadvertently deliver significant doses to the heart. Radiation injury to the heart is seen most frequently in the pericardium. The parietal pericardium develops variable degrees of fibrosis that replaces the outer adipose tissue.[143] Although pericardial fibrosis can progress to constriction, this is uncommon and adhesions between the pericardium and epicardium are rarely seen. Accumulation of pericardial fluid is more commonly seen in this scenario. The occurrence of pericarditis associated with the radiation for breast conserving therapy is extremely uncommon. Pierce et al. reported 3 (0.4%) of 831 left-sided breast cancer patients developed chest pain requiring inpatient evaluation at 2, 2, and 11 months post-treatment.[138] Two of these patients had clinical syndromes consistent with pericarditis, and the third had evidence of a minor myocardial infraction. Other single institution series have reported no occurrence of pericarditis[139] or incidences $<1\%$.[140]

Pathologically, the myocardium is involved less frequently than the pericardium, but tends to develop a more serious lesion.[143] It is characterized by patches of diffuse fibrosis affecting usually the anterior wall of the left ventricle and, less frequently, the right ventricle. Myocardial fibrosis is thought to be a result of injury to endothelial cells of the myocardial capillaries. Lesions to the coronary arteries are also presumed to be as a result of endothelial cell injury. Injury to the intimal cells is followed by eventual replacement of the damaged intima by myofibroblasts, deposition of platelets, and all the other events that occur usually in atherosclerosis.

Radiation for left-sided breast cancer has been associated with increased morbidity and mortality from ischemic heart disease.[144–147] Older radiation therapy techniques, particularly those used for the initial post-mastectomy irradiation trials, included a significant portion of the heart. An initial meta-analysis of eight randomized post-mastectomy radiation trials that began before 1975 demonstrated that for long-term breast cancer survivors, patients who had received irradiation had higher subsequent mortality rates at 10–15 years follow-up.[144] A subsequent analysis was done that examined cause-specific

mortality, included more post-mastectomy trials, and had longer follow-up revealing that there was not a significant difference in mortality after 10 years in those patients treated with irradiation. In fact, there was a trend for improved survival for those who were irradiated post-mastectomy. This modest survival benefit was offset by excess cardiac mortality in irradiated patients.[145] Most of the trials included in these initial overviews used radiation techniques with either orthovoltage or Co-60 that are now considered obsolete methods. These techniques compared to current ones with megavoltage radiation have been shown to deliver higher radiation doses to a larger percentage of the heart.

Cardiac mortality and the radiation treatment technique associated with it have been studied extensively in the Stockholm trial.[146–148] This trial included 960 breast cancer patients enrolled during 1971–1976 who were randomly allocated to preoperative RT, postoperative RT, or to mastectomy alone. There was no decrease in overall survival associated with radiation on this trial. Instead, there was a benefit with radiation (pre- and post-RT vs. surgical controls) during the entire follow-up period that was of borderline significance ($P = 0.09$). Each of the treatment techniques used in the trial were modeled with CT planning in four current breast cancer patients. The consistently largest irradiated heart volume was observed with left-sided tangential ^{60}CO fields. On the basis of this analysis, the different radiation techniques used on the trial were classified into three groups of low, intermediate, and high cardiac dose–volumes. When the records of the 960 patients in the Stockholm trial were linked with a Swedish registry of death certificates, mortality due to ischemic heart disease was significantly higher in the "high" dose–volume subgroup when compared to surgical control. In the low or intermediate dose–volume subgroups, the mortality due to ischemic heart disease was similar to surgical controls.[146] An update of this analysis in 1998 with 20 year median follow-up estimated a relative risk of myocardial infarction of 1.3 (95% CI 0.7–2.6) and cardiac mortality of 2.0 (95% CI 1.0–3.9, $P = 0.04$) in the high volume group only. No excess cardiac risk was observed in the lower dose–volume groups.[147]

This same group evaluated the proportion of heart volumes that was included in the 50% isodose (at least 25 Gy) from the dose–volume histogram (DVH) of 100 consecutive left-sided breast cancer patients irradiated following lumpectomy during 1994–1995 and compared it to the estimated heart volumes of patients treated on the Stockholm trial. The mean irradiated heart volume that received at least 25 Gy in the 1994–1995 cohort was 5.7% for the whole group and 11.9% in those with the highest volume.[148] The highest heart-volume group comprised 6% of the population. In comparison, the mean irradiated heart volume included in the 50% isodose for patients in the Stockholm Trial was 25%. This study demonstrates that the majority of left-sided breast cancer patients undergoing breast irradiation following lumpectomy do not receive irradiation to substantial heart volumes when modern radiation techniques are used.

A population-based study from Ontario, Canada, of patients receiving post-lumpectomy breast radiation during 1982–1987 demonstrated that 2% of women with left-sided RT had a fatal MI compared to 1% of women who had right-sided RT.[149] No data about radiation technique were available. Two other population-based studies,

one from Sweden for patients treated during 1970–1985, and the other from SEER for patients treated in the US in 1973–1992, have reported a relationship between left-sided breast cancer treatment and subsequent late cardiac events and mortality.[150,151] In addition, the meta-analysis of 40 randomized trials of RT involving 20,000 breast cancer patients by the Early Breast Cancer Trialists Collaborative Group demonstrated that the addition of RT resulted in a reduction in breast cancer mortality, but was nearly offset by increased non-cancer mortality, particularly vascular.[152]

Three series from single institutions have not shown an increase in myocardial infarction (MI)[154] or cardiac-related mortality[153,155] after 9–12 years follow-up, respectively, in women radiated with more modern techniques as part of BCT.

Furthermore, no increase in morbidity or mortality from ischemic heart disease occurred in those patients receiving radiation compared to the non-radiation group in the DCBG 82B and 82C PMR trials that included 3083 women and have a median follow-up >10 years.[156] This is particularly important as all radiated patients enrolled in these trials received regional nodal treatment including the internal mammary chain. This underlies the importance of careful radiation treatment planning in order to minimize the amount of heart within the fields for left-sided breast cancer.

Multiple techniques have been described to reduce the amount of irradiated heart-volume during breast cancer treatment. These include adding a "heart block,"[157,158] 3-dimensional conformal therapy,[157] intensity-modulated radiation therapy,[157,158] and respiratory gating.[159,160] At our institution, the heart volume is contoured for all left-sided breast cancer with CT treatment planning using the definition of heart used by Geynes et al.[148] Our defined dose constraints are that the percent heart volume within the 50% isodose is kept ≦8% for breast only irradiation and ≦10% for when regional nodal irradiation is added. In some cases, we have used prone breast irradiation to reduce the amount of heart-volume irradiated for left-sided cancers.

B9. Radiation Pneumonitis

Symptomatic radiation pneumonitis is uncommon when only the breast is irradiated following breast conserving therapy. It typically onsets 2–3 months after completing treatment with a clinical syndrome of cough, fever, shortness of breath, and radiologic changes confined to the radiation therapy field.[161] Symptoms can persist for several weeks and in general are self-limiting. Pulmonary fibrosis typically follows in the effected portion of the lung.

Lingos et al. reported a 1% incidence of radiation pneumonitis in 1624 patients treated during 1968–1985 for breast conserving therapy. The incidence increased to 3% when nodal irradiation was added and 8.8% when nodal irradiation and chemotherapy was delivered.[162] Even higher incidences of radiation pneumonitis have been reported following regional nodal radiation depending on the treatment technique with and without chemotherapy.[163–165]

The incidence of pneumonitis based on irradiated lung volumes from different radiation therapy techniques used to treat breast cancer patients has been studied by Lind et al.[167] On the basis of the report of Graham et al., ≧20 Gy (V_{20}) was chosen as the

ipsilateral lung tolerance level to document. The average irradiated ipsilateral lung volumes at ≧20 Gy (V_{20}) in 84 patients was: breast treatment only, 7%; breast + regional RT (without internal mammary nodes), 20%; breast + regional RT (with internal mammary nodes), 30%; post-mastectomy local regional RT (with internal mammary nodes), 35%. A positive correlation was found between the incidence of pulmonary complications and increasing ipsilateral lung volumes receiving >20 Gy ($P = 0.001$). The incidence of moderate symptomatic post-treatment pneumonitis (requiring steroid treatment) for the respective lung volumes was 0.5%, 7.5%, 11%, and 11.5%.

The dose constraints for lung at our institution are as follows. For breast irradiation alone, ≤10% of the ipsilateral lung should receive ≧20 Gy. For breast and/or chest wall and regional nodal irradiation ≤25% of the ipsilateral lung should receive ≧20 Gy.

B10. Secondary Malignancy

The overall survival of early stage breast cancer is good so that there are increasing numbers of long-term breast cancer survivors that need to be followed for the occurrence of secondary malignancies.

It is well established that patients treated for one breast cancer have a higher risk of subsequent contralateral breast cancer (CBC).[168–172] The risk for CBC averages between 1.1% and 1.5% per year. On the basis of the evidence from both randomized trials and population-based studies, it does not appear that breast radiation to one breast increases this risk for subsequent CBC. In the randomized trials evaluating breast conserving therapy, the rate of subsequent CBC was similar in either the mastectomy or radiation treatment arms. The Milan I trial that randomized 701 breast cancer patients to either radical mastectomy or quadrantectomy and radiation demonstrated 28 CBC in the mastectomy arm and 22 in the radiation group at up to 19 years follow-up.[170] Ten-year follow-up of the NCI randomized trial demonstrated 10 CBC in the 116 mastectomy patients and 7 in the 121 who underwent lumpectomy and radiation.[169] At 15-year follow-up of the Institut Gustave, Roussy, 13 CBC occurred in the 91 patients treated with mastectomy and 10 in the 88 patients who had radiation following tumorectomy.[168]

Multiple population-based studies have evaluated whether the incidence of CBC could be linked to radiotherapy for the first breast cancer. A study from the Connecticut Tumor Registry of 41,109 breast cancer patients treated between 1935 and 1982 revealed 655 CBC that were matched with 1189 controls did not demonstrate an overall increase in CBC after radiation treatment.[171] A non-significant trend for increase in CBC was seen in a subset of 45 women who were <45 years old at diagnosis and who were 10 years post-radiation treatments. A population-based study from Denmark looking at 529 breast cancer patients with CBC and 529 matched controls did not demonstrate an increased risk of CBC after radiation for a first breast cancer.[172] A 4.2% incidence of CBC was documented for 134,501 breast cancer cases treated between 1973 and 1996 in the SEER database.[173] In this study, a cox proportional hazards regression model demonstrated that radiation treatment for the first cancer was associated with an increased risk of CBC after 5 years of follow-up (RR = 1.14, 95% CI 1.03–1.26, $P = 0.001$). This study was limited by the unavailability of confounding information, such as tamoxifen use, that could affect the incidence of CBC. In conclusion, there has been

no consistent evidence that the use of radiation for one breast cancer causes a second CBC. However, adherence to radiation techniques that reduce the contralateral breast dose is advised, especially in younger patients.

There is increasingly compelling evidence that breast cancer patients are at higher risk of subsequently developing lung cancer following radiation; especially for those who smoke. Data from SEER were used to assess the subsequent risk of lung cancer in breast cancer patients that were irradiated. A total of 122 lung cancers developed in 13,750 women who received radiation and 473 in the 41,196 who were not radiated (0.88% vs. 0.11%).[174] This risk was confined to the ipsilateral lung. A population-based study from the Danish Cancer Registry has also demonstrated a slightly elevated lung cancer risk after 10 years in radiated breast cancer patients.[176] A study from the Connecticut Tumor Registry with an analysis for smoking history demonstrated that the increased risk of subsequent lung cancer in the ipsilateral lung following radiation for breast cancer was much greater for smokers than non-smokers.[175] The relative risk for a subsequent ipsilateral lung cancer was 6.7 (95% CI 0.6–79.4) for non-smokers and 76.6 (95% CI 8.1–724) in smokers. No information was available in this study regarding radiation technique, volume of lung radiated, or extent of smoking history. This relationship between radiation for breast cancer, smoking, and secondary lung cancers was further evaluated in a study from MD Anderson Cancer Center using 280 lung cancer cases with a prior diagnosis of breast cancer matched to a group of 300 randomly selected breast cancer cases who did not develop lung cancer.[177] Smoking increased the odds of lung carcinoma in breast cancer patients who were not irradiated (OR 6.0, 95% CI 3.6–10.1). Irradiation did not increase the odds for developing lung cancer in non-smokers (OR 0.5, 95% CI 0.3–1.1). The odds ratio for both smoking and irradiation was 9.0 (95% CI 5.1–15.9). The volume of lung-irradiated during breast cancer treatment may be an important determinant for risk of secondary lung cancer. This was demonstrated in a study from the NSABP that found an increased risk of subsequent ipsilateral lung cancer in patients who underwent chest wall and regional nodal irradiation following mastectomy but non-breast irradiation alone after lumpectomy.[178] In summary, breast cancer patients who smoke should be strongly encouraged to quit. We find in our clinic that breast cancer patients are very receptive to and successful with smoking cessation interventions. The amount of lung irradiated in all patients should be minimized, but particular attention should be paid to smokers with low-risk breast cancer.

Second primary sarcomas occur in or near the treatment field in approximately 0.1–0.2% of patients at 10 years. At the Institut Gustave, Roussy, France, 6919 patients treated for breast cancer, 11 developed secondary soft tissue sarcoma at a mean latency time of 9.5 years.[179] Similarly, 19 soft tissue sarcomas were noted in a population of 13,490 women treated for breast cancer in Sweden between 1960 and 1980.[180] A higher incidence of angiosarcoma, in particular, was demonstrated after irradiation for breast cancer in 194,798 cases in the SEER database.[181] A total of 20 cases developed in 48,975 irradiated patients versus 7 in the 146,303 non-irradiated cohort. This emphasizes the importance of long-term follow-up for breast cancer patients who have been irradiated so that early diagnosis and intervention of this rare complication can be done.

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