The Role of Radiotherapy in Breast Cancer Management

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Abbreviations

CHF	Congestive heart failure
CT	Computed tomography
DCIS	Ductal carcinoma in situ
DIBH	Deep inspiration breath-hold
EORTC	European Organization for Research and Treatment of Cancer
IMNs	Internal mammary nodes
IMRT	Intensity-modulated radiation therapy
LINAC	Linear accelerator
MLC	Multileaf collimator
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
NSABP	National Surgical Adjuvant Breast and Bowel Project
PET	Positron-emission tomography
US	Ultrasound

17.1 Introduction to Radiation Oncology

At the end of the nineteenth century (1895), Wilhelm Roentgen announced the discovery of "a new kind of ray" that allows the "photography of the invisible." The biologic and therapeutic effects of the newly discovered X-rays were soon recognized, particularly because of the dermatitis and epilation they caused. In the early 1896, a few weeks after the public announcement of Roentgen's discovery, among the first therapeutic uses, Emil Grubbe in Chicago irradiated a patient with recurrent carcinoma of the breast and Herman Gocht in Hamburg Germany, irradiated a patient with locally advanced inoperable breast cancer and another patient with recurrent breast cancer in the axilla [1]. Despite the technical limitations of the early equipment, tumor shrinkage and at times complete elimination of the tumor were noticed. However, the full potential of radiation therapy could not be achieved in those early days because of the limited knowledge regarding fractionation, treatment techniques and uncertainties in how to calculate the tissue dose so as to deliver safe and effective doses of radiation.

17.1.1 Physics of Radiation Therapy

The X-rays and gamma rays are part of the spectrum of electromagnetic radiation that also includes radio waves, infrared, visible, and ultra violet light. They are thought of as small packets of energy called photons. The X-rays reaching

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I. Jatoi and A. Rody (eds.), *Management of Breast Diseases*, DOI 10.1007/978-3-319-46356-8_17

the tissue deposit their energy and because the energy is quite high, it causes ejection of orbital electrons from the atoms, resulting in ionization, hence the term ionizing radiation. Once the energy is deposited, many interactions occur, resulting in the generation of more free electrons and free radicals. Because the human body is made mostly of water, the energy absorption leads to a chain reaction, resulting in the formation of multiple, reactive free radical intermediates. Any of the cell constituents such as proteins, lipids, RNA, and DNA can be damaged. Apoptosis, signal transduction, and lipid peroxidation are all altered as a result of direct or indirect effects of radiation; however, DNA double-strand breaks seem to be the most critical damage that if unrepaired or incorrectly repaired will result in cell death.

The radiation dose is measured in terms of the amount of energy absorbed per unit mass. Presently, the measurement unit is gray (1 Gy is equal to 1 J/kg). The past measurement unit was the Rad, and 100 Rads = 1 Gy. The beam energy determines its medical usefulness. The clinically useful energy ranges of the electromagnetic radiation are superficial radiation 10–125 keV, orthovoltage 125–400 keV, and supervoltage, over 1000 keV (>1 meV). As the beam energy increases, it can penetrate deeper and more uniformly into tissue, and the skin sparing increases. The reason for skin sparing is that the electrons that are created from the interaction between photons and the tissue travel some time before they interact with tissue molecule and deposit the maximum dose. In the superficial and orthovoltage ranges, because of the lower energies, most of the dose is deposited at or very close to the skin (i.e., with significant skin dose), a significant dose is absorbed in bones, and useful beam energy cannot reach tissues at more than a couple of centimeters deep, resulting in marked dose inhomogeneity in the tissue. The great advantage of the supervoltage/megavoltage photons is that as the energy increases, the penetration of the X-ray increases, absorption into bone is not higher than the surrounding tissue and skin sparing increases. Therefore, maximum dose does not occur on the skin but at depth in the tissue, and more homogeneity can be achieved in the targeted volume.

The era of modern radiation therapy started approximately 50–60 years ago when supervoltage machines became widely available because of advances in technology resulting from atomic energy research, the development of the radar, and advances in computing. The availability of high-energy beam revolutionized the field of radiation oncology. Initially, the cobalt machine, a by-product of atomic research, and subsequently the linear accelerator (LINAC) generating beams with the energy ranging from 4 to 24 meV became available; currently, LINACs are mostly in use. A photograph of a LINAC is shown in Fig. 17.1. In the LINAC, electrons are accelerated to very high speeds. The high-speed electrons are guided to strike a tungsten target to produce the X-rays.

For certain clinical circumstances, the electron beam is preferred. Electrons differ in the way they deposit energy in the tissue. With electrons, the maximum dose is reached close to the skin surface with minimum skin sparing; however, there is a marked fall in radiation dose at certain depth in the tissue. This depth can be carefully chosen depending on the energy of the electron beam. Electron beams are mostly used for therapy of superficial tumors or to supplement (boost) photon therapy.

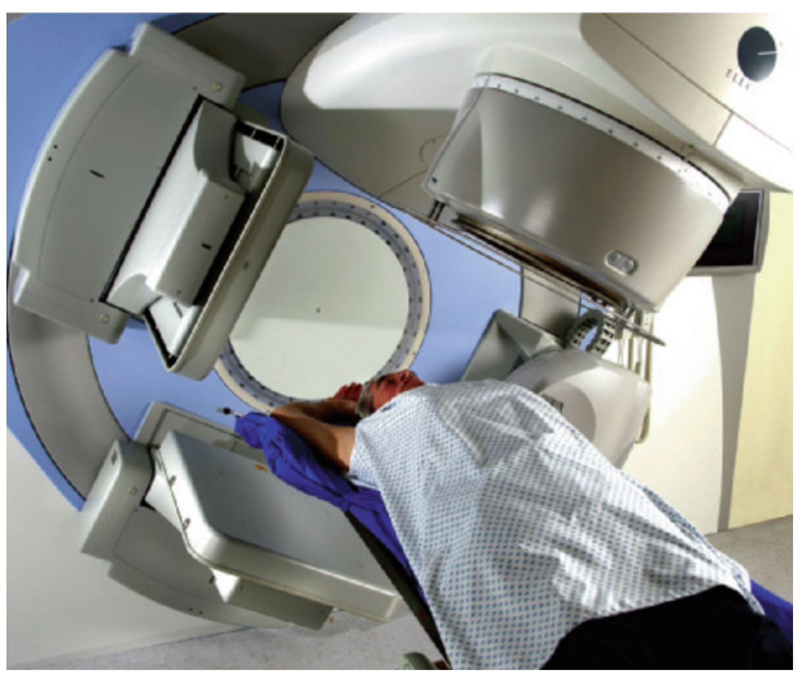

Fig. 17.1 A linear accelerator (LINAC) used for radiation therapy treatments (*photograph* courtesy of Elekta)

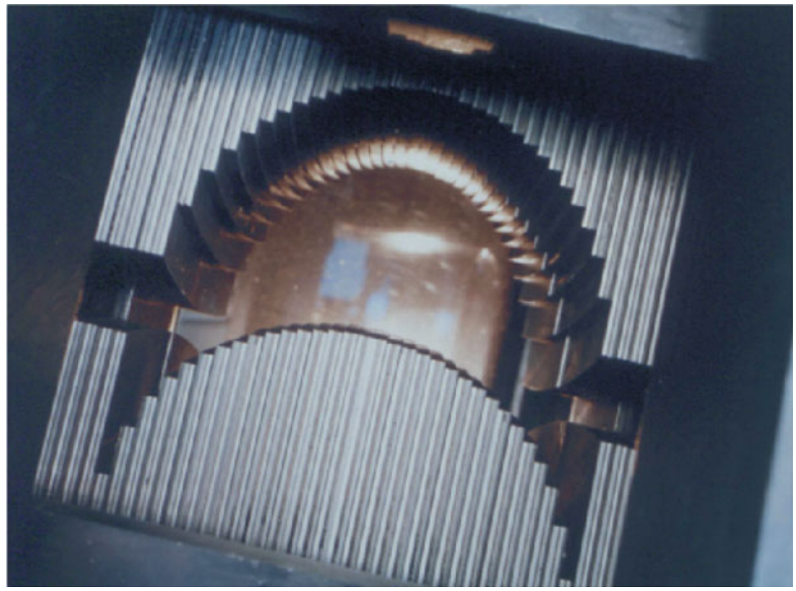

Fig. 17.2 The multileaf collimator (MLC) used to shape the treatment beam (*photograph* courtesy of Elekta)

Protons are heavy-charged particles generated in cyclotrons. Due to relatively large mass and charge protons have a limited range, little lateral scatter and small exit dose. Protons are well suited for pediatric brain tumors and tumors in close proximity to the spinal cord. There is no established use for protons in breast cancer.

To conform to the tumor shape and anatomy, the radiotherapy beam is tailored to each individual patient by using beam modifiers placed in the path of the beam. They may include such devices as collimators, tissue compensators, individually constructed blocks, or, more recently, the multileaf collimator (MLC). An image of a MLC is shown in Fig. 17.2. From the early days of manual computing when dose was calculated in a single point in the treated volume, recent computing advances led us to calculate dose in 3D in the tumor and surrounding tissue and account for differences in tissue density (i.e., lung, bone) as well as modify the dose inside the target area by "dose painting" or intensity-modulated radiation therapy (IMRT). We are now able to deliver more accurate radiation treatments and tailor treatments to individual patient anatomy with increased efficacy and less morbidity. When dose can be delivered more accurately to the tumor and more normal surrounding tissue can be spared, dose intensification can be attempted to achieve higher cure rates without increased complications. Uniform dose distribution and reduced dose in the surrounding tissue result in decreased acute and long-term side effects. Exclusion of as much normal tissue as possible from the path of the radiation beam is always of great importance, since many patients are also receiving chemotherapy that may result in higher probability of late complications.

17.1.2 Radiation, Surgery, and Chemotherapy

Radiation therapy is a local-regional curative modality that can be used either alone or in combination with surgery and chemotherapy. The rationale for combining surgery and radiation is because their patterns of failure are different. Radiation is less effective and failures occur more at the center of the tumor where there is the largest volume of tumor cells, some necrotic and in hypoxic conditions. Radiation is most effective at the margins where the tissue is well vascularized and the volume of tumor cells is the lowest. The extent of the surgery on the other hand is usually limited by the normal structures in the proximity of the tumor. The bulk of the tumor can be usually excised, but to remove all microscopic disease, at times, the surgery may need to be too extensive. Hence, the failures of surgery are usually at the margins of excision and that is where radiation is the most effective. To increase its therapeutic effectiveness, the radiation can also be combined with chemotherapeutic and biologic agents. Because these modalities have different mechanisms of cell kill and can interfere with different phases of the cell cycle, the combined effects may be additive, synergistic, or the systemic agents may act as sensitizer to the effects of radiation; however, it also increases the probability of side effects.

17.1.3 Technical Aspects of Radiation Planning and Delivery

Radiation therapy is an integral part of the management of all stages of breast cancer. Prior to embarking on radiation treatments, careful treatment planning is necessary. This includes decisions regarding patient positioning and immobilization. Both are essential for accuracy of therapy to ensure day to day reproducibility, and patient comfort. The treatment planning is done with the aid of a simulator, which is a machine with identical geometrical characteristics as the treatment machine; however, instead of high-energy treatment rays it generates diagnostic X-rays to image the target (i.e., the irradiated volume). More recently, computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), and positron-emission tomography (PET) have been incorporated into the simulator, allowing even more accurate target identification in the actual treatment position. After the target and normal structures have been delineated in 3D, alternative treatment plans are generated and optimized. The plan that gives the best coverage of the target with minimal dose to the surrounding tissue and minimal inhomogeneities is chosen. The dose and homogeneity in the target are of great importance. Cold and hot spots have to be minimized because cold spots in the target will leave cancer undertreated, thus a source of disease recurrence, while hot spots may increase the risk of complications. The treatment planning is a team effort between the physician, physicist, dosimetrist, and technologist. It is an interactive process that usually goes through multiple iterations until the optimal plan is reached.

In the treatment of nonmetastatic breast cancer, the radiation is aimed at the breast/chest wall, and depending on the clinical situation, also at the regional lymphatics such as the supraclavicular, axillary, and internal mammary lymph nodes. The treatment goal is eradication of tumor with minimal side effects. The CT scanner can be used to delineate the targeted area and the critical structures to which dose should be limited. The beam arrangement that traverses the least amount of normal critical organs is chosen. In the treatment of the intact breast or chest wall, medial and lateral tangential beams are used (Fig. 17.3). Tangential beams allow the encompassing of the breast tissue while including limited amounts of lung or heart. Using 3D or IMRT treatment planning software, the dose distribution is calculated for the entire breast volume. Beam modifiers are incorporated to minimize the volume of tissue receiving higher or lower than the prescribed dose and minimize the dose to the

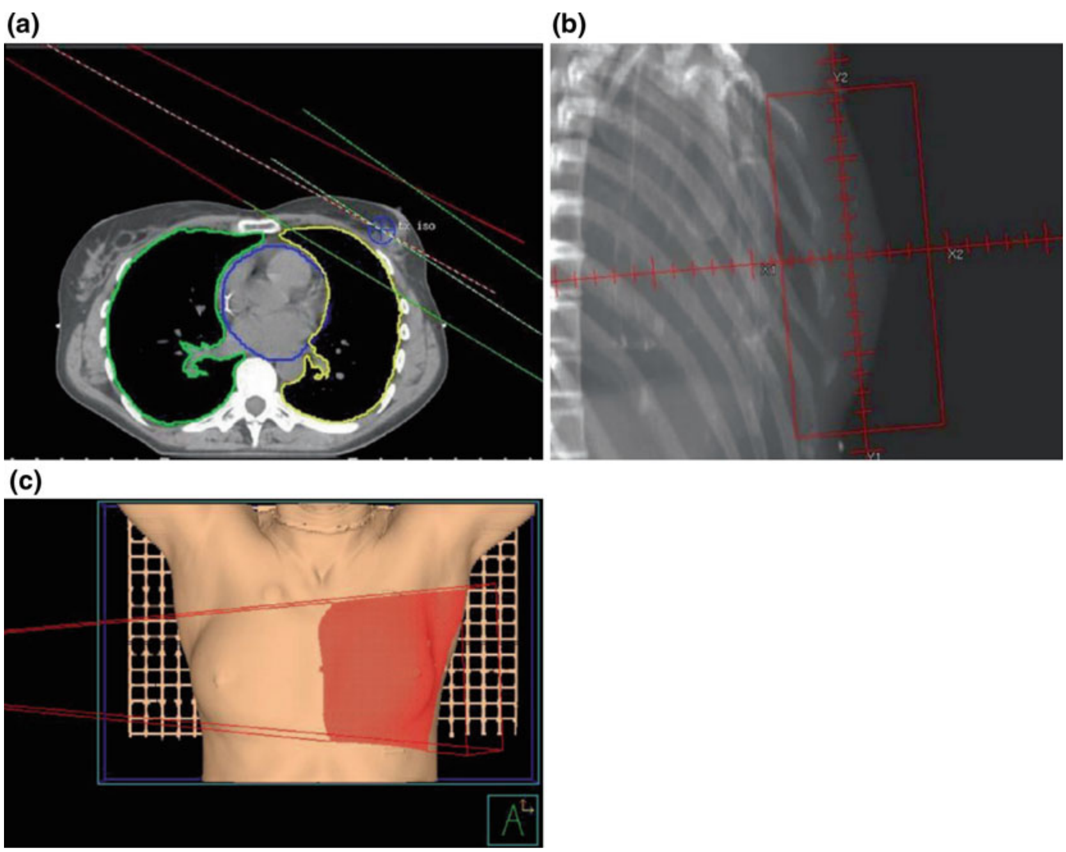

Fig. 17.3 Tangential beam arrangement for the treatment of the intact breast or chest wall. **a** An axial view showing the medial and lateral tangential beams covering the breast tissue. **b** The view from the beam direction, “beams eye view.” Note the small amount of lung or heart in the treated volume. **c** The projection of the tangential beams on the patient’s skin. These views were obtained from computer tomography (CT)-based simulation workstation

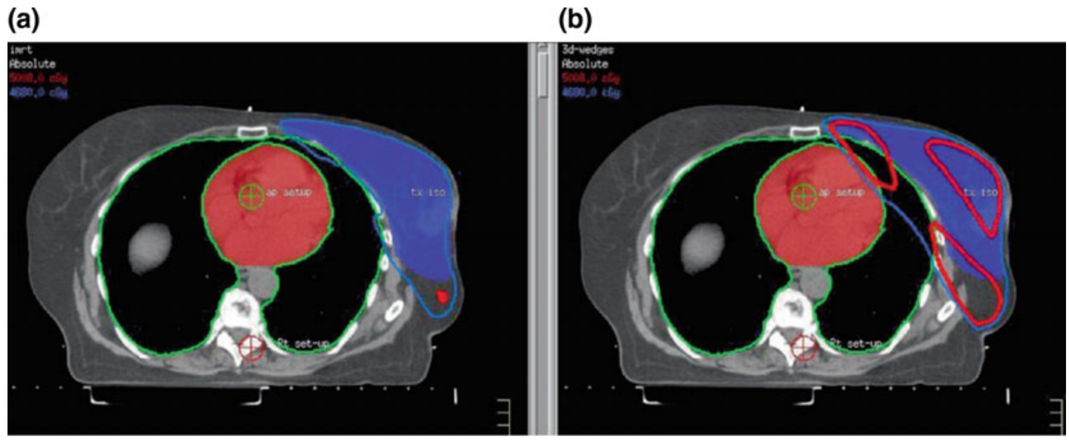

Fig. 17.4 Dose distribution in the breast using intensity-modulated radiation therapy (IMRT) planning (**a**) and 3D treatment planning (**b**). Note the elimination of "hot spots" in the IMRT plan

skin surface while ensuring that the glandular tissue several millimeters under the skin is not undertreated. IMRT allows the generation of a more homogenous plan, thus resulting in less acute side effects such as moist desquamation, pain, and breast lymphedema [2, 3]. Figure 17.4 demonstrates the more homogeneous dose achieved with IMRT, eliminating the "hot spots."

In many situations, IMRT also affords better conforming of the dose around the breast tissue, thus decreasing the dose to heart, lung, contralateral breast, and axilla, as well as less scatter dose [4]. More recently, development of the deep inspiration breath-hold (DIBH) technique has been shown to reduce incidental cardiac irradiation. Deep inspiration enables anatomical displacement of the heart medially, inferiorly, and posteriorly (i.e., away from the chest wall) resulting in decreased incidental cardiac irradiation. To treat the supraclavicular or axillary nodes and limit the dose to the spinal cord, a field shown in Fig. 17.5 is used. This field is usually an anterior/posterior field slightly angled to exclude the upper thoracic and lower cervical spinal cord. Various techniques are used to perfectly match all the fields so as to prevent an overlap or a gap between them. Depending on the clinical situation, radiation treatments are given daily for 5 1/2–6 1/2 weeks. In standard fractionation schedule, 1.8 or 2.0 Gy fractions are being used. Fractionation is necessary to keep the normal tissue complications to a minimum while achieving maximum tumor control. Several hypofractionated schedules using 15 fractions of 2.66–3.20 Gy in 3–5 weeks have been tested in randomized trials [5, 6]. In the selected patients, results show equivalence for local control and cosmesis to the schedule of 2.0 Gy in 5 weeks.

Proton therapy is currently being studied as an alternative potential strategy to achieve an optimized dose distribution [7]. At present time, protons are not being generally used in the treatment of breast cancer.

17.1.4 Adverse Effects of Radiation to the Breast

Treatments are usually well tolerated. Acute side effects may include fatigue, breast edema, skin erythema, hyperpigmentation, and at times desquamation mostly limited to the inframammary fold and axilla. Acute skin changes usually should resolve 1–2 weeks posttreatment. Higher treatment fraction sizes may result in more breast edema and fibrosis, thus jeopardizing the cosmetic outcome. The cosmesis posttreatment is usually good to excellent in a large majority of patients. However, there are no good objective quantitative criteria to evaluate the cosmetic outcome. Posttherapy, there is a gradual improvement in the appearance of the breast, hyperpigmentation resolves, skin color returns to normal, and breast edema resolves. The return to normal color and texture happens in a large majority of patients [8], but in some, it may take 2 or even up to 3 years.

With modern megavoltage therapy and treatment planning, the long-term side effects are limited. They depend on the radiation dose, fraction size, the energy of the beam, and the volume of radiated tissue. Most of the side effects can be limited with appropriate treatment planning.

Symptomatic pneumonitis is exceedingly rare, occurring in less than 1 % of patients, particularly in those treated only with tangential fields and not receiving chemotherapy. The risk is 3–5 % if chemotherapy is given and if the supraclavicular nodes need to be treated. It has been noted that if chemotherapy and radiation are given sequentially instead of concomitantly, the risk is lower. A study by Lingos et al. showed that the risk of radiation pneumonitis was 1 % if chemotherapy and radiation were given sequentially and could be as high as 9 % if the treatments were concurrent [9]. The risk also depends on the type, dose, and scheduling of the chemotherapeutic agents. The risk is further reduced by using 3D or IMRT treatment planning techniques. Those

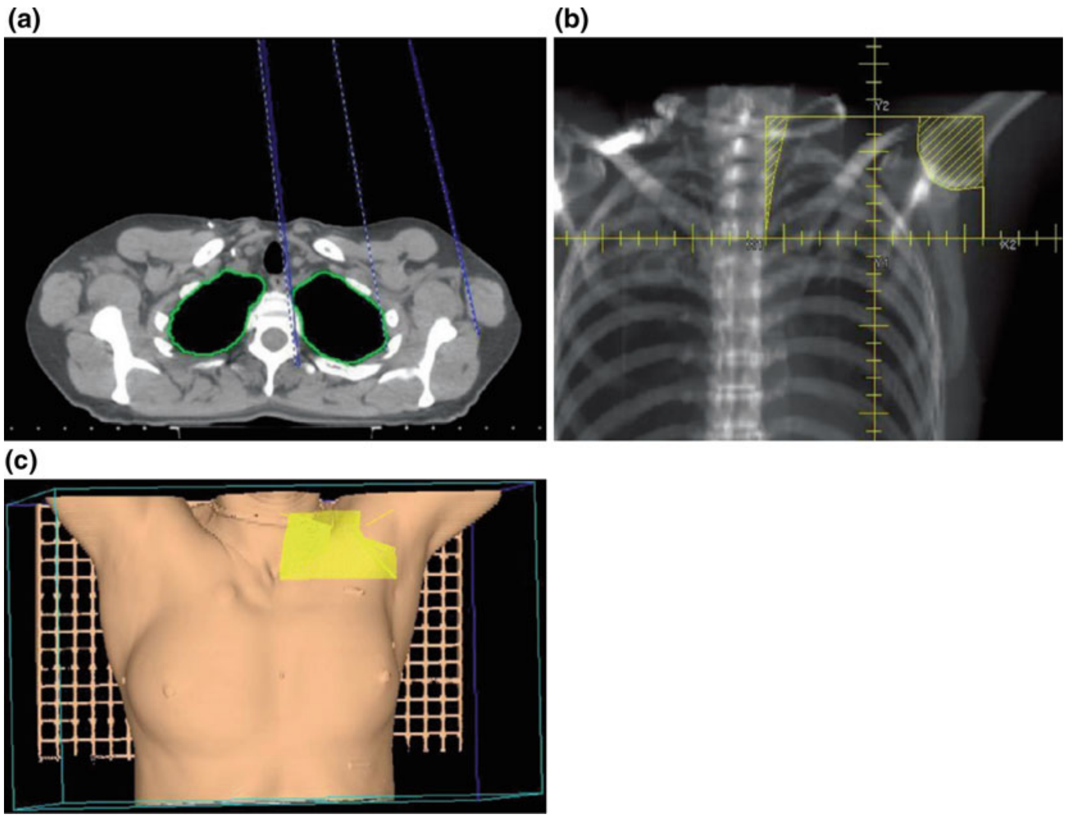

Fig. 17.5 The beam arrangement for the supraclavicular and axillary apex area. **a** An axial view. Note how the beam is directed to avoid the spinal cord. **b** The view from the beam angle also showing the blocking of the spinal cord and humeral head. **c** The beam as it projects on the patient skin

patients in whom symptomatic pneumonitis develops, it is usually mild and reversible either spontaneously or after a short course of steroids. Damage to the brachial plexus may develop in less than 1 % of the women treated with the currently used doses and fraction sizes. Larger fraction size may result in an increased risk of brachial plexopathy. There is a small risk of rib fractures, and soft tissue necrosis is exceedingly rare. In more than 2000 patients treated at the University of Chicago Center [8], no rib fractures or soft tissue necrosis were noted. Radiation may cause damage to the heart. The effects are dependent on the radiation technique used. The early trials of postmastectomy radiation have shown an increase in cardiac deaths in the long-term survivors [10]. However, in those days, an anteroposterior photon beam was used to treat the internal mammary nodes (IMNs), resulting in full-dose radiation to a large segment of the heart [11]. More recent reports show less risk of cardiac disease [12, 13]. The effects on the heart may include pericarditis [14], acceleration of coronary artery disease, cardiomyopathy, congestive heart failure (CHF), valvular heart disease, pericardial disease, and conduction block [15–19]. Although subclinical abnormalities may occur soon after irradiation such as microvascular injury and accelerated atherosclerosis, the resulting symptoms may not be apparent until decades later. With the currently used CT-based 3D and IMRT treatment planning techniques, excessive dose to a large part of the heart can be avoided. Moreover, utilizing the DIBH technique can further reduce incidental cardiac irradiation [20–22]. Many of the active and currently used chemotherapeutic agents (Adriamycin, Taxol) may also have deleterious effects on the heart. Except in rare occasions, the radiation and these chemotherapeutic agents are not given concurrently. No significantly increased risk of heart-related complication has been noted using sequential chemotherapy and radiation treatments. However, the long-term combined effects of cardiotoxic chemotherapeutic agents and radiation are not yet completely known because the newer drugs have not been used that long. Cardiac disease may become evident 10 to even 20 years posttherapy. Thus, longer follow-up will be needed before firm conclusions are reached. There has been substantial increase in the use of trastuzumab in the treatment of breast cancer. There are no data showing increased cardiac toxicity when combining radiation and trastuzumab, but longer follow-up will be necessary for more definitive data. In the interim, particular attention should be given to the treatment planning of left-sided breast cancer after cardiotoxic chemotherapy, even more so if the IMNs need to be treated.

Lymphedema may develop following axillary dissection and can be exacerbated with radiation. Although not life-threatening, it can significantly impact on quality of life. The risk of lymphedema depends on the extent of axillary node dissection and the extent of the radiation to the axilla. With a complete axillary dissection, including all three levels of axillary nodes and radiation therapy, the risk of lymphedema may be more than 40 %. However, if the surgery is only limited to level I and II dissections and the axilla is not radiated, some lymphedema may develop in up to 30 % of women, but the risk of significant lymphedema is only 3–5 %. The lymphedema is significantly less if surgery to the axial is limited to a sentinel node biopsy [23]. When compared to axillary lymph node dissection, axillary radiation following a positive sentinel lymph node biopsy results in reduced risk of lymphedema (11 % vs. 23 % at 5 years) [24]. The risk can be reduced by preventing trauma or infections to the arm on the dissected side. The condition can be chronic. It can be stabilized with physical therapy and manual lymphatic decompression but at times is difficult to eliminate. Early physical therapy and manual lymphatic decompression are very important and may reverse early stages of lymphedema.

There is a small risk of second malignancies in the long-term breast cancer survivors treated with radiation [25]. In general, for a woman with breast cancer, the risk of contralateral breast cancer is approximately 0.5–1 % per year, of which 3 % or less could be attributed to previous radiation [26, 27]. In the study by Boice et al., most of the risk was seen among women radiated before age 45. After age 45, there was little, if any, risk of radiation-induced secondary breast cancers. This has been further confirmed in a case control study in a cohort of more than 56,000 mostly perimenopausal and postmenopausal women. The dose to the contralateral breast was calculated to be 2.51 Gy, and the overall risk of contralateral breast cancer was not increased in patients receiving radiation therapy. The secondary tumors were evenly distributed in various quadrants of the breast, also arguing against radiation-related contralateral breast cancer [28]. In patients, treated at the University of Chicago, with mastectomy between 1927 and 1987, there was no increase in contralateral breast cancer in women who also received chest wall radiation [29].

Other treatment-related malignancies include lung cancer, sarcoma, and leukemia. The risk of treatment-related lung cancer is small. Studies from the Connecticut Tumor registry of patients treated between 1945 and 1981 show that in 10-year survivors, approximately nine cases of radiotherapy-induced lung cancer per year would be expected to occur among 10,000 treated women [30]. The risk is significantly increased with smoking [31]. The reported cumulative risk of sarcoma in the radiation field is 0.2 % at 10 years [32]. The risk of leukemia is minimal with radiation only; however, in combination with alkylating agents, the risk may be higher [33]. There are conflicting reports regarding the risk of esophageal cancer [34, 35]. Possibly, the increased risk in some studies is related to radiation techniques that used an anterior/posterior field to treat the IMN. In general, in most contemporary plans, the esophagus is excluded from the path of the beam. Many published studies tend to report the risk of second malignancies as the relative risks. It is important to realize when reading and evaluating the clinical literature that from the patients' and physicians' perspective, the concept of relative risk is not very informative because the relative risk of an event with radiation may be very high compared to no radiation, but if the absolute risk is very low, it has no management or practical clinical value. Thus, absolute numbers or percentages of the risk are much more relevant and informative.

17.2 Radiation Therapy in the Early-Stage Breast Cancer

17.2.1 Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS), noninvasive ductal carcinoma, or intraductal carcinoma refers to proliferation of malignant cells confined within the basement membrane. DCIS, a premalignant condition, if untreated, is likely to progress to invasive breast cancer [36, 37]. Management of DCIS remains one the most controversial aspects of breast cancer treatment. It is a disease of the mammographic era with a significant increase in the incidence rate in the last decade. The nonpalpable DCIS, which comprises the majority of currently diagnosed disease, was almost unknown 25–30 years ago. In 2015, more than 60,000 women were diagnosed with DCIS [38]. The natural history is long, and although the incidence has been increasing in recent years, there are few studies of the alternative treatment options that have sufficient power and length of follow-up to have definite answers. The treatment options include simple mastectomy, or local excision, with or without radiation. Several factors are important in the management decision of a patient with DCIS. Any evidence that the disease is or could be extensive such as diffuse, suspicious, or indeterminate microcalcifications or multicentricity, as well as a mammogram, which is difficult to follow, or if there is uncertainty that the patient can comply with a program of routine mammograms for follow-up are contraindications for breast-conserving surgery. Status of the margin following local excision and the histologic subtype are important when making treatment decisions, and as always, patient wishes and comorbidities need be considered. If negative margins of excision cannot be obtained, breast conservation attempts have to be abandoned. Among histologic subtypes, high-grade nuclei and comedo necrosis appear to be more aggressive variants and seem to have a higher risk of recurrence or progression to invasive breast cancer. However, it is not clear if the risk of recurrence is higher with comedo DCIS, or just that the recurrences appear sooner and if the follow-up were long enough, the recurrence rate would be the same in patients with comedo or noncomedo histology.

Mastectomy was traditionally the standard of therapy for DCIS. The recurrence rates following mastectomy were 1 % or less and the cancer-related mortality 2 % [39]. However, after the documented success with breast-conserving therapy in infiltrating ductal carcinoma, it became increasingly difficult in the daily practice to recommend mastectomy to women with DCIS. Paradoxically, women who were adhering to a strict regimen of screening and were detected as having DCIS could be “rewarded” with mastectomy, while if they just would have waited a few years for the disease to progress to invasion, they could have breast-sparing surgery. There are no randomized trials that compare mastectomy to breast-conserving therapy; however, a decision analysis of trade-offs shows that there may only be a 1–2 % difference in the actuarial survival rates at 10 and 20 years if the initial therapy is breast-conserving surgery and radiation compared to mastectomy [40]. The small difference is most likely because at least half of the recurrences after breast conservation are DCIS and among the other half that are invasive, most are detected at an early stage. As in many other clinical dilemmas in breast cancer management, the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators significantly contributed to the changes in practice and redefined the standard of care in DCIS. NSABP-17 is a large, prospective randomized trial of 818 women that shows, with a median follow-up of 8 years, that radiation therapy following breast-conserving surgery reduces both the invasive and noninvasive ipsilateral breast cancer recurrences and the particular impact was on the reduction of invasive breast cancer recurrences. The incidence of noninvasive cancer was reduced from 13 to 9 %, and invasive breast cancer from 13 to 4 % [41]. All patients benefited from radiation irrespective of tumor size or pathologic characteristics. No features could be identified that would allow selection of patients in whom radiation could be eliminated [42, 43]. With a longer follow-up time, the combined data from NSABP-17 and NSABP-24 confirm the significant decrease in invasive breast cancer recurrence and improved survival [44]. A separate analysis of the effects of radiation on DCIS in the earlier NSABP-06 trial also showed a reduction in local failure with radiation [45]. A randomized trial performed by the European Organization for Research and Treatment of Cancer (EORTC) breast cancer cooperative group confirmed the NSABP-17 finding [46]. With radiation, the local recurrences at 10 years decreased from 26 to 15 %. In multivariate analysis, the addition of radiation, the architecture, grade of DCIS and margins status were independent predictors of recurrence. It is clear that negative margins are important for local control; however, controversy exists regarding the definition of adequate negative margins. Both the width of margins and the radiation dose influence local control. Boost radiotherapy has been shown to significantly decrease the risk of relapse in young women [47]. Excellent local control was also achieved when boost was given even when margins were defined as DCIS not touching the ink [48]. Although with longer follow-up and more information from the combined prospective and retrospective studies, the data may change, with the current information available in patients who are candidates for breast conservation, the local recurrence after excision alone is 20–30 %, and this can be reduced with radiation to approximately 10–15 %. To further improve the outcome, NSABP performed a study in which all patients who were candidates for breast conservation were treated with local excision followed by radiation and randomized to tamoxifen or placebo. This study, NSABP-24, enrolled more than 1800 women [49]. Tamoxifen therapy resulted in 32 % decrease in recurrences compared to radiation only without tamoxifen.

In several retrospective studies, attempts were also made to determine the patients in whom radiation can be eliminated. Silverstein et al. devised a scoring system combining the size of the DCIS, margins, grade, and necrosis [50]. This scoring was subsequently modified showing that margins alone are predictive of local recurrence [51]. Using the information regarding pathologic margins, the authors attempted to develop criteria when DCIS can be satisfactorily treated by local excision, when radiation therapy should be added, and when mastectomy is required. However, because the number of events in relation to the number of patients was low, the differences were not statistically significant and firm conclusions could not be reached [52]. They showed that in the low-risk patients when margins of excision are more than 1 cm, the 12-year local recurrence rate is 13.9 % compared to 2.5 % if postexcision radiation is given [53]. The widths of the margins can significantly compromise cosmesis. In breast conservation surgery, the surgical margins’ width is in close inverse correlation with cosmesis. When performing the surgical excision, the surgeon is carefully balancing an oncologic surgery to achieve adequate margins and cosmesis because wide margins and removal of large amount of tissue may significantly impact on cosmesis. It is also important to recognize that because of the pathologic characteristics of DCIS, it is frequently difficult to determine the exact size of the DCIS and many pathologists are reluctant to do so. Thus, since many times the pathologic size is unavailable or cannot be accurately ascertained, some studies report DCIS size in millimeters, others in number of slides with DCIS, while others by using its mammographic size. This heterogeneity makes the comparison of local recurrence rates between studies difficult. A prospective study reported by Wong et al. attempted to select patients with DCIS in whom radiation following conservative surgery can be eliminated [54]. They included grade 1 and 2 DCIS, ≤2.5 cm, excised with more than 1-cm margins. The rate of local recurrence was 2.4 % per year, corresponding to a 5-year recurrence rate of 12 %. The study closed early because the number of recurrences met the predetermined stopping rules. This study demonstrated that it is very difficult to select patients in whom radiation can be omitted. RTOG 9804 demonstrated that even in good-risk DCIS where the local recurrence rate is low addition of RT further decreases the risk of recurrence [55]. Some small, incidental DCIS and small, low-grade DCIS excised with wide margins (>1 cm) can be followed after the local excision without radiation [56]. DCIS size, margins, histology, mammographic presentation, age, comorbidities, life expectancy, and patient preference are all factors in decision making regarding the optimal management of each individual patient.

17.2.2 Invasive Breast Cancer

17.2.2.1 Breast Conservation

In 1990, the National Institutes of Health (NIH) convened a Consensus Conference to address the issue of breast-conserving therapy in stage I and II breast cancer [57]. The participants concluded that breast-conserving therapy is equivalent and possibly better than mastectomy. The summary statement is presented in Fig. 17.6. The conclusions were based on six randomized trials that all showed equal survival in patients treated with breast-conserving therapy compared to those undergoing mastectomies. With additional follow-up and update, the results have been further

NIH Consensus Conference (1990)
Early-Stage Breast Cancer (38)

Breast conservation therapy is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is *preferable* because it provides *survival equivalent* to the total mastectomy and axillary dissection while preserving the breast.

Fig. 17.6 The National Institutes of Health (NIH) consensus conference statement

confirmed and they are holding [58–63] (Table 17.1). Breast-conserving therapy with radiation may be even associated with better survival than mastectomy [64]. Breast-conserving therapy means local excision of the bulk of the tumor followed by moderate doses of radiation to eradicate residual foci of tumor cells in the remaining breast. Despite the NIH Consensus Conference conclusions, it seems that the acceptance of breast-conserving therapy is far from uniform and greatly varies by geographical areas [65, 66]. Overall, breast conservation rates vary from 60 to 70 %. There are significant barriers for utilization of breast-conserving therapy [67–70]. Medical contraindications and patient choice do not seem to be the major factors in the under utilization of breast-conserving surgery [71]. More than 80 % of the women, independent of age or race, if given the option, will opt for breast conservation.

The role of the radiation is to decrease the risk of local failure in the breast, but it also contributes to survival [34, 72–75]. It accomplishes what mastectomy would have done, i.e., treatment to the entire breast. Treatments are usually delivered to the whole breast and are followed with an additional radiation, “boost” to the lumpectomy site. Careful pathologic studies of mastectomy specimens have shown that microscopic residual disease is present away from the primary (index) tumor; however, the highest burden is in the same quadrant less than 4 cm from the primary tumor [76]. Extrapolation from early radiation therapy studies established the appropriate dose to eradicate microscopic foci of disease in the range of 45–50 Gy. This is the dose usually given to the entire breast. The higher burden of microscopic disease around the primary site is encompassed in the “boost” volume. Reported local control rates in the randomized trials and retrospective studies vary from 70 to 97 % [8, 61, 77]. Many factors have been suggested as having an impact on local control rates. Some have been confirmed in multiple studies while some were shown not to be of importance when longer follow-up and more data became available. Higher radiation doses to the lumpectomy site that are achieved by using a “boost” have been shown to improve the local control rates [78]. Most local recurrences following mastectomy occur in the first 3–5 years post-surgery; however, postbreast-conserving therapy recurrences have been documented to occur up to 20 years. Up to 5–8 years from diagnosis, most of the recurrences are in the same quadrant as the primary. Subsequently, the proportion changes in favor of tumor “elsewhere” in the breast [79]. These are most likely second primaries.

The determination whether a patient is candidate for breast-conserving surgery and radiation is a multidisciplinary effort in which close communication between the surgeon, the mammographer, the pathologist, the medical oncologist, and the radiation oncologist is necessary. Contraindications for breast-conserving surgery [80, 81] include:

Table 17.1 Overall survival (%) in six randomized trials of breast-conserving treatment compared to mastectomy

Stage I and II breast cancer		
Treatment (References)	Mastectomy (%)	BCT (%)
NSABP B-06 [61]	47	46
NCI [62]	58	54
Milan [58]	59	58
IGR (Paris) [63]	65	73
EORTC [59]	73	71
DBCCG [60]	82	79

Follow-up of 6–20 years
BCT breast conservation therapy; *DBCCG* Danish Breast Cancer Cooperative Group; *EORTC* European Organization for Research and Treatment of Cancer; *IGR* Institute Goustave Roussy; *NCI* National Cancer Institute; *NSABP* National Surgical Adjuvant Breast and Bowel Project

1. Multicentric disease, i.e., disease in separate quadrants of the breast.
2. Diffuse malignant appearing, or indeterminate microcalcifications.
3. Prior radiation treatments to doses that combined with the planned dose will exceed tissue tolerance. This may happen in women who have received radiation at younger age for lymphoma, particularly Hodgkin's disease.
4. Inability to obtain negative surgical margins following attempts for breast-conserving surgery. Negative excision margins appear to be the most important factor impacting on local control. If the margins are positive, the risk of local recurrence is increased [8, 82, 83]. Focally positive margins can be controlled with radiation, but more extensively involved margins are usually an indication for reexcision. However, data are also emerging, demonstrating that by increasing the boost dose, the local recurrences are similar to the local recurrences in women with negative margins of excision [8, 83].
5. Pregnancy is a contraindication for breast-conserving therapy because of the concerns on the effects of radiation on the fetus. Sometimes, surgery can be done during the third trimester and followed with radiation after delivery. This latter is to be done only after careful consideration because chances for cure ought not to be compromised for cosmetic reasons.

Relative contraindications for breast conservation include:

1. Tumor size: size of the tumor as compared to the breast size may pose some challenge from the cosmetic outcome perspective. Majority of the randomized trials of breast-conserving therapy included women whose tumors were ≤4 cm. But, the tumor size is mainly a consideration as it relates to the cosmetic outcome. Breast conservation should only be attempted if an acceptable cosmetic outcome can be achieved. If the tissue deficit because of the size of the tumor is large in relation to the breast size, then it is preferable to perform a mastectomy followed by breast reconstruction. The ratio between tumor size and patient's breast size determines the advisability of breast-conserving therapy.
2. Tumor location: tumor location in the vicinity of the nipple may require excision of the nippleareola complex. This may result in less than optimal cosmesis but does not impact on outcome. Many women will opt for breast preservation even if the nipple is removed because it still leaves behind most of the breast tissue and native skin.
3. Breast size: there are some technical difficulties in the radiation treatment of women with large breasts, but if adequate immobilization can be devised and adequate dose homogeneity can be achieved, breast conservation is preferable to a mastectomy that would result in major asymmetry.
4. History of collagen vascular disease: individuals with history of collagen vascular disease, particularly lupus or scleroderma, are reported to be at significantly increased risk of complications, particularly soft tissue and bone necrosis, most likely because of compromised microvasculature. Other criteria such as patient age, family history, and positive axillary lymph nodes are not contraindications for breast-conserving therapy.

Although breast cancer appears to be more aggressive in very young women, there is no clear evidence that if the currently used criteria for breast-conserving therapy are followed, breast conservation should be denied to young women. Very young women aged 35 or less may have more aggressive disease and they are at higher risk of both distant and local recurrences. Some have been advocating mastectomy for these women; however, to date, there has been no documented benefit in survival to mastectomy. At the other end of the age spectrum, although the perception may be that cancer is less aggressive and that older women are not as interested in breast preservation, the studies do not support this contention. Several reports have in fact shown that survival and disease-free survival from breast cancer are lower in older women [84–86]. There are also no indications that elderly women have significantly more problems tolerating radiation compared to younger women.

A challenging question is whether mutations in the two genes that predispose to breast cancer, BRCA1 and BRCA2, are a contraindication for radiation and thus breast-conserving treatment. Hypothesis yet to be proven is whether radiation to the remaining breast tissue, or scatter radiation to the contralateral breast increases the risk of a second breast cancer, or conversely, radiation is more effective in patients with known mutations because the normal function of the genes is DNA repair and the mutations could prevent the tumor cells escape from the effects of radiation. If unable to repair the damaged DNA, the effects of controlling the tumor with radiation may be enhanced. In a case control study of women treated with breast-conserving surgery and radiation, early results showed that following radiation, there is no increased risk of events in the ipsilateral breast in patients with known BRCA mutations compared to those with no mutations [87]. A subsequent update with additional follow-up shows that BRCA1/2 mutations are independent predictors of local recurrence. In women with BRCA1/2 mutations who also underwent oophorectomy, the local recurrence rate following breast-conserving surgery and radiation was 8 % compared to 10 % in women with sporadic breast cancer [88]. Interestingly, the 10-year risk of contralateral breast cancer in the BRCA1/2 carriers was 16 % despite the oophorectomy. In a different study, when patients with local recurrence following radiation were matched with a group without local recurrence, mutations were found to be more common in patients with recurrences and they occurred primarily in younger women, in different quadrants than the index tumor, and occurred late, most likely representing new primaries [89]. There is currently no evidence that women with mutations in BRCA1 or BRCA2 or with a family history of breast cancer have worst survival rates if offered breast-conserving therapy, including radiation [90, 91], particularly if they also undergo oophorectomy and receive adjuvant systemic therapy [88].

Several studies have attempted to define a subpopulation of patients who may not need radiation (Table 17.2). They vary in length of follow-up, inclusion criteria, and details of therapy. In studies from Sweden and from Canada, the investigators tried to determine whether in patients with small tumors, radiation could be omitted. Thus, they limited their studies to patients with ≤2-cm node-negative tumors [92, 93]. These trials showed a significant decrease in local failures when radiation was given but no significant difference in survival. Nevertheless, there was a trend toward overall survival benefit in the group receiving radiation [93, 95]. None of the trials were powered with sufficient number of patients to detect <10 % benefits in survival. In a prospective single institution study, attempts were made to select the most favorable patients with lowest risk of recurrence and enroll them in a study of only breast-conserving surgery without radiation [94]. The criteria for inclusion were tumor size ≤2 cm, negative axillary nodes, absence of lymphatic invasion, absence of extensive intraductal component, at least 1-cm margin of normal breast tissue around the tumor, and the breast easy to follow mammographically. The median tumor size was 6 mm. Even in this very favorable group, the failure rate was 24 % at 7 years. The trial was closed prematurely because the observed failure rate exceeded the expected rate predetermined by the trial stopping rules. This study highlights the difficulty in selecting the patients in whom radiation treatments can be eliminated.

Chemotherapy or tamoxifen may contribute to local control but by themselves are not sufficient. For example, in the NSABP-06 trial, the local failure in patients undergoing only local excision without radiation was approximately 32 %. In those who underwent local excision and also received chemotherapy, it was close to 40 %, demonstrating that chemotherapy did not decrease the local failure rates. However, in the comparable group who after local excision were receiving both chemotherapy and radiation, the cumulative risk at 12 years was only 5 % [95], while in those receiving radiation only, the local failure rates were 12 %. This demonstrates that radiation decreases the local recurrence rates and is further decreased when also combined with chemotherapy. Other studies have also confirmed better local control rates with the addition of chemotherapy to radiation [96, 97]. Even the very high doses of chemotherapy alone that were given as part of bone marrow transplant programs were not sufficient for local control [98].

To increase the feasibility of breast-conserving therapy, neoadjuvant chemotherapy has been attempted with satisfactory results. Some women who would not be candidates for breast conservation because of tumor size may become candidates for breast conservation if they first receive chemotherapy and the tumor shrinks, without impacting on their survival [99].

Table 17.2 Local recurrence (%) following local excision compared with local excision and radiation in stage I breast cancer

	Excision	Excision and radiation	Follow-up (years)
Liljergen et al. [92]	24	8	10
Clark et al. [93]	35	11	8
Lim et al. [94]	23	N/A	7

N/A not applicable

Many women who undergo breast-conserving therapy are also receiving adjuvant chemotherapy, and in these women, the sequencing of chemotherapy and radiation needs to be decided. One prospective randomized trial and several retrospective studies had somewhat conflicting results. Some studies show that giving chemotherapy first before radiation increases the risk of local failure, while others show that giving chemotherapy first does not significantly increase local failure rates and it may result in better distant disease-free survival and overall survival [100–102]. If local excision with negative margins is achieved and the patient is a candidate for breast conservation, it is unlikely that her survival will be impacted by delay in radiation because of initial chemotherapy, particularly with the shorter dose dense chemotherapy regimens. Thus, in general, women complete their chemotherapy before proceeding with the radiation treatments. In some instances, concomitant chemotherapy and radiation therapy have been given. However, this may increase the risk of side effects and jeopardize the cosmetic outcome without demonstrated benefit in outcome.

Depending on the clinical situation, radiation is delivered to the draining lymphatics that include axilla, supraclavicular nodes, and IMNs. Radiation to the draining lymphatics improves distal disease-free survival and decreases the locoregional recurrence rate [103, 104]. Axillary radiation is indicated if the axilla has not been dissected, if a limited dissection or SNB was done and it includes positive nodes, or if gross disease was found, particularly in the apex of the axilla close to the axillary vein. Communication between the surgeon and the radiation oncologist regarding the findings at surgery is of great importance. The undissected axillary apex nodes and supraclavicular nodal areas are treated if the axilla has been dissected and positive nodes were found. Attempts should be made in this situation to eliminate the dissected portion of the axilla from the path of the beam. With the advent of CT-based 3D treatment planning and IMRT, the treatment to the draining lymphatics can be individually tailored to the anatomy and the extent of the disease. Treatment to the IMN is given mostly if the primary lesion is medially or centrally located and the axillary lymph nodes are positive with metastatic breast cancer. CT-based 3D treatment planning and, in selected patients, IMRT planning are of advantage, particularly for left-sided lesions where further care needs to be undertaken to minimize the amount of treated heart. Treatment with DIBH can be used to further reduce the radiation due to the heart. Treatment with DIBH significantly increases the treatment complexity. Emphasis needs to be given to ensure the reproductively of the patient positions during the treatment. Treatment of the regional lymphatics in addition to the tangential fields also adds technical complexity to the treatments. If multiple beam angles are needed, overlap or underdose should be avoided. Use of IMRT in these situations may eliminate the need to match fields.

Good disease control in the axilla with minimum morbidity can be obtained from radiation to axilla without dissection [105] when the axilla is clinically negative. Thus, axillary dissection is indicated if the results would change the planned therapy. In patients who undergo sentinel node biopsy if the sentinel node has no disease, radiation to the axilla is omitted. If 1–2 nodes are positive, complete dissection or radiation to the axilla are likely to be of equivalent efficacy [24, 105–107].

Close follow-up after breast conservation is essential to detect local recurrences, new primaries, and contralateral disease. In general, true local recurrences occur earlier while disease in other quadrants develops later, i.e., 5 years or longer after therapy. Although institutional policies for mammographic follow-up vary, a reasonable policy would be routine yearly mammograms.

Postmastectomy Radiation

Postmastectomy, the risk of local recurrence varies depending on the number of positive nodes in the axilla, size of the tumor, length of follow-up, and how the local recurrences are being scored. As number of nodes with metastatic disease in the axilla increases, the risk of chest wall recurrences increases. In fact, the number of positive axillary lymph nodes has more impact on the rate of chest wall recurrence than the size of the tumor. The length of follow-up and how the recurrences are being scored are also important. Frequently, if a patient develops metastatic disease, there is a tendency to overlook a local recurrence. Most local-regional recurrences occur in the first 3–5 years following mastectomy, but disease may recur even 10–15 years postmastectomy [108, 109]. Thus, long-term follow-up is important in evaluating the risk of recurrences [110]. Local recurrences impact on survival and also have a significant impact on the quality of life. Chest wall recurrences may ulcerate and become malodorous and painful. Radiation can significantly decrease the risk of local recurrences postmastectomy. The benefit is proportional to the risk. Once clinically manifested, the likelihood of controlling a recurrence is only 50–60 %. There is some disagreement regarding who should be receiving postmastectomy irradiation. Most are in agreement when it comes to patients with four or more positive nodes in the axilla or a tumor more than 5 cm in size. But, the dilemma starts with a woman for example with 3.5–4 cm tumor and three positive nodes, particularly if she is young? Do we have sufficient information to counsel these younger women when the potential life expectancy is 20–30 years? Data on sufficient cohorts of women with the various combinations of tumor size, number of positive axillary lymph nodes, and long enough follow-up are difficult to come by, particularly for those who also receive chemotherapy. Recht et al. reviewed the local failure rates in patients treated with mastectomy and chemotherapy without radiation in the various Eastern Cooperative Group

Table 17.3 Percent cumulative incidence of LRF (10 years) following mastectomy and chemotherapy

Node positive	Size (cm)					
	≤1	1.1–2	2.1–3	3.1–4	4.1–5	≥5
1	3	11	12	10	6	27
2	8	14	12	20	14	31
3	20	18	11	8	14	36
4	19	17	22	26	37	33
5–6	22	23	27	25	22	47
7–9	12	33	30	32	32	41
≥10	39	30	31	36	35	31

LRF local regional failure
Source Reprinted with permission. ©1999 American Society of Clinical Oncology. All rights reserved. Recht et al. [111]

trials [111]. Their results are shown in Table 17.3. Arriagada et al. reported the cumulative rates of chest wall failure in patients not receiving chemotherapy to be up to 30–35 % in women with four or more positive nodes, and 25–30 % if one to three nodes are positive [112].

The impact of chest wall radiation on survival had been controversial because the natural history of breast cancer is long, the techniques of radiation are continuously improving, allowing better coverage of the target with less morbidity, and because currently in majority of the women, chemotherapy is also given. older meta-analyses and reports from pre-3D treatment era showed that radiation decreases breast cancer deaths, but in some studies, an increase in the risk of cardiovascular disease was noted [10, 113, 114]. Very few of the studies included in these meta-analyses used 3D radiation therapy planning or gave chemotherapy. The capability currently exists to design CT-guided plans tailored to individual's anatomy. When treatments are designed with CT-guided planning, the exact target location can be determined and the volume of lung and heart in the treatment field minimized, thus decreasing the risk of long-term side effects. Image-guided radiation techniques and respiratory gating have the potential to further decrease the long-term sequelae or radiation.

Two contemporary randomized studies from Denmark and Canada in which women were treated with chemotherapy show better disease-free and overall survival in patients who also received radiation therapy to the chest wall and draining nodes in addition to systemic therapy (Table 17.4) [110, 115–117]. The benefit from radiation therapy on survival was in fact equivalent to the benefit women achieved from chemotherapy [118]. These studies reignited the discussions regarding the benefits of postmastectomy radiation particularly, the benefits in women with one to three positive nodes. The question posed was could the finding be extrapolated to the practice in the USA, since in some women in the Danish Breast Cancer Cooperative Group trial, the median number of lymph nodes dissected was only seven. Some argued that usually in the USA, the axillary node dissections are more extensive. The investigators reanalyzed their data separately for women with one to three positive nodes and also in those with ten or more nodes dissected. They confirmed the significant benefit in survival in women with one to three positive nodes and also in those who had the more extensive axillary dissection [117]. A second criticism of the Danish and Canadian trials was that the chemotherapy used was cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). This regimen is much less frequently used. Contemporary regimens are more dose intense and the question has been raised whether the benefits of radiation therapy are maintained with more intense regimens. There are no randomized trials to answer this question. However, an elegant analysis done by Ragaz et al. shows that at all chemotherapy dose intensity level, radiation therapy significantly decreases the risk of recurrence [110]. Radiation therapy to decrease the local recurrences was needed even following the very high doses of chemotherapy used in bone marrow transplant studies [98]. These results were further confirmed in the most recent update of the Early Breast Cancer Trialists Collaborative Group [34, 75] showing that for every four local recurrences prevented one breast cancer death can be avoided

Table 17.4 Impact of postmastectomy radiation therapy on overall survival in patients also receiving systemic therapy

Overall survival (%)				
	Follow-up (year)	CMF and radiation	CMF	*p* value
Overgaard et al. [115]	18	39	29	0.015
Ragaz et al. [110]	20	52 TAM and radiation	43 TAM	0.02
Overgaard et al. [116]	10	45	36	0.03

CMF cytoxan, methotrexate, 5 fluorouracil; *TAM* tamoxifen

[34, 74]. A trial in the USA was initiated to answer specifically the question of the benefit of postmastectomy radiation in women with one to three positive nodes. However, the trial had to be closed due to low accrual rates. Since in both the Canadian and Danish trials, and in the trials included in the meta-analysis from EBCTCG [75], women were also treated to their IMN, this question also has received renewed interest. Radiation therapy to the IMN may benefit all the women but particularly those with medial or central lesion in whom multiple axillary nodes are positive. Inclusion of the IMN, in left-side breast cancer, will undoubtedly increase the volume of heart treated, and depending on the technique used may possibly increase the dose to the esophagus. Thus, if the IMNs are to be included, treatments should be done with CT-based planning so that the IMN can be localized and the volume of lung, heart, and esophagus minimized. Two recently published randomized trials addressing nodal irradiation [103, 104] did not specifically address the question of IMN irradiation. The only contemporary randomized trial available demonstrates no benefit in OS to IMN irradiation [119].

The management of locoregional breast cancer recurrences depends on the prior therapy. Disease that recurs after breast-conserving surgery and radiation therapy is usually treated with mastectomy. There have been attempts in patients in whom a very early recurrence is found to only perform an excision with satisfactory results. However, the number of patients treated in this manner is low and the follow-up is too short to realize the full impact of this management strategy [120]. A full course of radiation for the second time is difficult to deliver because of the risk of long-term complications. The breast may become fibrotic and cosmetically unappealing. However, recently some data have been emerging regarding the feasibility of retreatment, particularly if there has been a long interval since prior therapy and if only partial breast treatment is done. If feasible, a recurrence that occurs postmastectomy should be excised with negative margins. Radiation, particularly if not previously given, will decrease the risk of further recurrences. The radiation fields need to encompass the chest wall and regional lymphatics, not only the area of recurrence, because it seems that if only a small radiation field is used, recurrences may appear just outside the irradiated area [121].

Radiation and Breast Reconstruction

Many women who undergo mastectomy also opt for breast reconstruction. The techniques of reconstructive surgery have been changing. There is a significant decrease in the use of silicone or saline implants in favor of autologous tissue with pedicle or microanastomosis. The reconstructed, vascularized tissue is of great advantage in minimizing the risk of complications from radiation. The reported risk of complications in patients undergoing reconstruction and radiation varies anywhere from 18 to 51 %. In the more recent publications, the risk of complications is at the lower end of range, probably because of improvement in the techniques of both surgery and radiation. The optimal sequencing of radiation and reconstructive surgery is not well established; thus, multiple factors need to be considered, and because a general consensus is lacking, good communication between all the members of the oncologic team is essential. The issue under consideration is the operation in a previously irradiated field if the reconstruction is being done following radiation. The concerns are less with the techniques that are using autologous vascularized tissues. On the other hand, if the reconstruction is done immediately after mastectomy and this is followed with the radiation, there are concerns regarding the cosmesis, firming, and fat necrosis after radiating the reconstruction, and the possible obscuring of a recurrence. However, there are data showing that the great majority of the recurrences are not obscured by the myocutaneous flap [122]. In general, good to excellent cosmesis is being achieved in the majority of the women who have radiation to the reconstructed breast. If there are no other contraindications, breast cancer occurring in an augmented breast can be treated with breast conservation. There may be some complications such as scaring or fat necrosis, but the risk seems to be low [123] and the cosmetic outcome very good; thus, the augmentation does not need to be removed prior to the radiation. In the minority of patients in whom complications will later develop, the reconstruction may have to be revised or removed. This treatment strategy would leave the majority of women with the breast augmentation spared.

17.3 Locally Advanced Breast Cancer

Locally advanced and inflammatory breast cancers, stage III disease, pose a major management challenge. Because of the very high risk of local and distant failure, no single modality is satisfactory in controlling the disease; thus, all three treatment modalities, i.e., chemotherapy, radiation therapy, and surgery, need to be incorporated in a management plan. Since this disease presentation is not very common and because its definition encompasses a spectrum of diseases from large primary tumors with some skin edema, or small, limited skin ulceration to huge necrotic masses or global inflammatory changes, large randomized trials to define the standard of care are lacking. If the patient is a candidate for mastectomy, surgery may be performed upfront followed by adjuvant systemic therapy and radiation. Radiation alone as the local treatment modality in patients with large tumors is suboptimal. Control of the disease can only be obtained, at most in 50 % of the patients and large doses are needed, which may result in long-term sequelae, including fibrosis and tissue necrosis [124]. However, postmastectomy radiation is very effective in reducing the local failure rates. The microscopic residual disease can be well controlled with 50–60 Gy and failure rates would decrease from 30–40 to 10–15 %. Because the risk of metastatic disease is very high, there is general consensus for the need for systemic therapy despite the fact that several small randomized trials failed to demonstrate benefit for chemotherapy, probably because the patient numbers were low and the disease is very heterogeneous. Retrospective studies show significant benefits compared to historical controls [125, 126].

Despite the general consensus that there is need for aggressive control of both local and distant disease, there are some controversies regarding the sequencing of the various therapies and the need for both radiation and surgery for local control. In most situations, even if the patients are technically operable, neoadjuvant chemotherapy is given first. Response rates to neoadjuvant chemotherapy are usually good, and complete clinical response can be achieved in up to 30 % of the patients. Patients with the best response have also the best chances for survival. If a good response to chemotherapy is obtained, then mastectomy is undertaken followed with additional chemotherapy and radiation. Comprehensive radiation fields are used to include the chest wall and draining lymphatics tailored to the anatomy and clinical situation. If there is no response to initial chemotherapy, a switch to radiation or different chemotherapy regimen is needed. Although not clearly established, retrospective reviews indicate that the local control is better if both surgery and radiation are given than with either modality alone [127].

Inflammatory breast cancer has a very high risk of metastatic disease and also very high risk of local failure if surgery alone is performed. Because of the involvement of dermal lymphatics, the disease is much more extensive than can be clinically appreciated; therefore, even if negative margins can be obtained, the disease soon recurs. Historically, because of its systemic nature, the 5-year survival rates were at most 10 %. However, with the combination of chemotherapy, surgery, and radiation, the 5-year survival rates are approaching 30–50 % [126, 128, 129]. The sequencing of treatments depends on response to therapy. Neoadjuvant chemotherapy is initiated as soon as possible and response assessed after each cycle. If good response is obtained, surgery is being performed followed with additional chemotherapy and radiation to the chest wall and draining lymphatics. If, however, response to chemotherapy is poor, radiation is added in order to bring the patient to a stage of operability. Because of the competing risks of both local and distant disease, concomitant chemotherapy and radiation protocols have been attempted with promising preliminary results [130–132]. The challenge is to concomitantly give sufficient chemotherapy to be therapeutically effective for metastatic disease as well as sufficient dose of radiation to control local disease, all this without severe complications. Currently, targeting inflammatory mediators and associated signaling pathways is studied to develop new treatment strategies. For instance, a Notch inhibitor RO4929097 has shown to down-regulate the expression of inflammatory cytokines IL-6 and IL-8 and reduce self-renewal properties of inflammatory breast cancer stem cells [133].

17.4 Radiation as Palliation

Radiation treatments are frequently an integral component of the palliative management plan for advanced and metastatic disease. Painful, weeping, malodorous chest wall recurrences can be controlled with radiation, thus significantly contributing to quality of life and the ability to resume normal lifestyle. The symptomatic effects of brain, bone, spinal cord, brachial plexus, choroidal, and liver metastases can be palliated with radiation and the effects can be durable for the lifetime of the patient. Single brain metastases or few metastases in the same proximity can be treated with stereotactic radiosurgery, significantly improving the outcome, particularly if the disease at the primary site is controlled, or there is no evidence of disease elsewhere. When the goal is palliation, decisions regarding dose, fractionation, and length of therapy are determined based on the life expectancy and quality of life considerations. It is important to always keep in mind that the goals are palliation; thus, the side effects should be kept to a minimum and the treatment course kept as short as possible.

The role of locoregional therapy in the patient with metastatic diseases is being studied in an ongoing randomized trial. Retrospective studies have shown better prognosis if optimal locoregional therapy is given [134, 135].

17.5 Summary

Radiation therapy is an integral part of the management of breast cancer in all stages of the disease from DCIS to metastatic disease. Treatments should be tailored to each patient's clinical situation and anatomy to obtain the best disease control with minimum side effects. The new and developing technologies such as 3D treatment planning, IMRT, and image-guided techniques provide us with the tools to accomplish this goal.

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