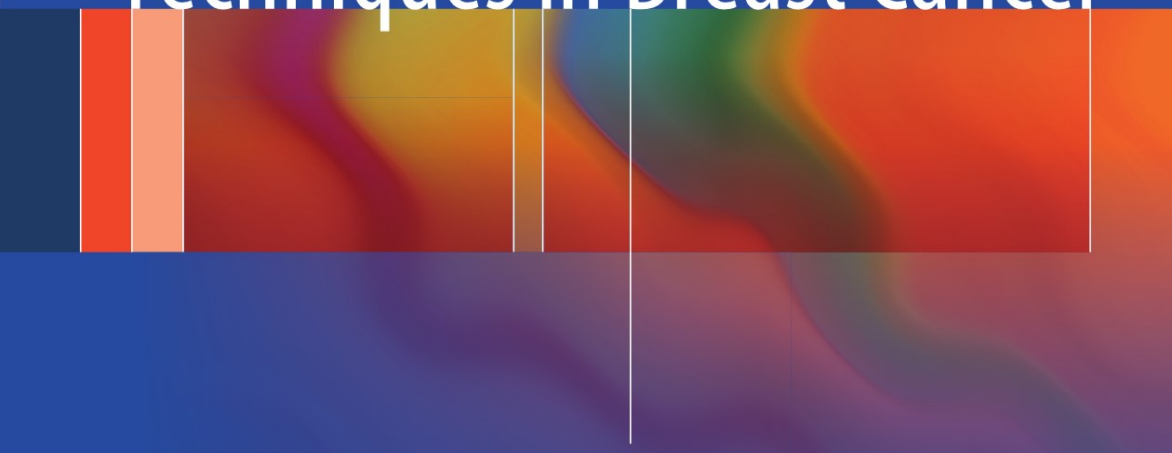
Principles and Practice of Modern Radiotherapy Techniques in Breast Cancer



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Dedicated to the memory of Professor Ibtisam Lale Atahan, M.D. (1945–2007)

Preface

Breast cancer is the most common malignancy among the female population. With the advances in systemic therapies and modern radiotherapy techniques, hopefully, breast cancer patients can have a long life expectancy. Therefore, it is crucial that radiation therapy should be carried out with minimum complications and with the utmost efficiency. The goal of this book is to provide a radiotherapy textbook, supported by practical information and current theoretical knowledge, which will contribute to the planning and implementing of modern radiotherapy techniques in breast cancer.

The primary challenge confronted during the determination of target volumes and organs at risk in the course of modern breast cancer radiotherapy is the identification of anatomic structures. Classic radiological atlases are designed at a neutral position of the body; however, computerized tomography simulation scans of patients with breast cancer, prior to radiotherapy planning, are obtained as the arms are held in various positions. Therefore, the positions of anatomic structures are quite different as compared with their neutral position, and this may result in significant contouring errors. Furthermore, the delineation of critical organs such as the heart, the main vessels of the heart, the esophagus, the brachial plexus, and the lung is crucial during the implementation of modern radiotherapy techniques in breast cancer. We believe that an atlas of breast cancer radiotherapy, demonstrating the delineation of both target and critical structures, in actual treatment position, will be very useful for our daily practical applications. Furthermore, the text is supported with up-to-date theoretical knowledge in all aspects of breast cancer, including epidemiology, molecular and biological basis, and integration of systemic therapies with radiotherapy in order to aid radiation oncologists during all steps of breast cancer radiotherapy.

We believe *Principles and Practice of Modern Radiotherapy Techniques in Breast Cancer* will assist residents, fellows, and clinicians in the radiation oncology field in learning and practicing breast cancer radiotherapy. The information presented in this book will be refined as radiotherapy techniques and clinical research advance.

Izmir, Turkey, 2012 — Ayfer Haydaroglu
Ankara, Turkey, 2012 — Gokhan Ozyigit

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Contents

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Part I
General Information

Chapter 1
Epidemiology and Etiology of Breast Cancer

Gul Kitapcioglu

1.1 Introduction

Breast cancer is the most common cause of cancer death among women worldwide, and breast cancer is by far the most frequent cancer among women, with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). It is now the most common cancer both in developed and developing regions with approximately 690,000 new cases estimated for each region (population ratio 1:4). Incidence rates vary from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe, and are higher (greater than 80 per 100,000) in the developed regions of the world (except Japan) and lower (less than 40 per 100,000) in most of the developing countries [1].

The range of mortality rates is much less in (high-incidence) developed regions (approximately 6–19 per 100,000) because of the more favorable survival of breast cancer. As a result, breast cancer ranks as the fifth cause of death from all cancers (458,000 deaths), but it is still the most frequent cause of cancer deaths in women in both developing (269,000 deaths, 12.7% of total) and developed regions, where the estimated 189,000 deaths is almost equal to the estimated number of deaths from lung cancer (188,000 deaths) [1]. Incidence rates are relatively higher in more developed countries, whereas rates are lower but increasing in less developed countries [2]. According to the standardized incidence rates of breast cancer in countries such as France and Belgium, Denmark and the Netherlands, and the United States, as well as in the developed countries of Western Europe, it is the most common cancer in women in developed countries (109.19/100.000; 101.12/100.000; 99.74/100.000; 98.46/100.000; respectively) [1, 3, 4].

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Higher breast cancer incidence rates detected in developed countries can be attributed to a variety of reasons, such as higher standards of living, early menarche age, late age of pregnancy and birthing, fewer pregnancies, and also easy accessibility to the use of techniques such as mammography, early diagnosis opportunities, and adequate data recording systems. Breast cancer rates fell over the last 10 years worldwide, and this downward trend, seen especially in developing countries, may be linked to the reduction of the use of hormone replacement therapy (HRT) during menopause [2, 5].

1.2 Breast Cancer Risk Factors

1.2.1 Reproductive Factors

Environment, genes, and lifestyle seem to cooperate in increasing or decreasing the probability of development of female breast cancer [6], and this complicated causal relationship can lead to more difficulties in the prevention of the disease. The World Health Organization declared in an August 2005 report that estrogen is carcinogenic in women, and that estrogen exposure is associated with lifelong risk of breast cancer. Studies have also displayed the relationship between endogenous hormone levels and breast cancer [7].

Where the lifetime exposure to endogenous sex hormones is concerned, life stages of women have come to the fore. Younger age at menarche, older age at menopause, late age at first full-term pregnancy, and number of pregnancies have been the subject of various research studies investigating the relationship between the risk of breast cancer and hormones. As a result, it has been proved that women below the age of 12 years at onset of menarche have a higher risk of breast cancer as a result of a longer period of estrogen exposure at the breast epithelium. It seems the same causal mechanism is valid for the older ages of the menopause. For late age onset of menopause, each 1-year delay can result in a 3% increase in the risk of breast cancer [8].

Multiple full-term pregnancies and early age of pregnancy decrease the risk of breast cancers and can be considered as protective situations. Women who experience pregnancy when they are younger than age 20 years carry approximately half of the risk of women whose first pregnancy was older than age 30 years. The mechanism can be linked to early maturation of breast tissue in accordance with pregnancy, with breast-feeding showing a similar protective effect [9–11]. The effects of the reproductive factors are related to the effects of progesterone and estrogen receptors. The relative risk of the reproductive factors is shown in Table 1.1.

Table 1.1 Relative risks and risk factors of breast cancer

Relative risk	Reproductive factors	Cause
	Older age at menopause (>65 yr)	Long-term exposure to endogenous estrogen
>4	Postmenopause breast density	
2.1–4.0	Increased bone density	
1.1–2.0	Older age at first full-term pregnancy (>30 yr)	Oophorectomy at younger than age 40 yr is preventative
	Younger age at menarche (<12 yr)	
	Older age of menopause (>55 yr)	
	Not breast feeding	
	Incomplete pregnancies	
	Oral contraceptives (long term)	Exogenous hormone exposure
	Hormone replacement therapy (>5 yr)	
	Obesity (postmenopausal)	

1.2.2 Obesity

Obesity has been associated with a twofold increase in the risk of breast cancer in postmenopausal women, whereas it has been correlated with a reduced incidence of breast cancer among premenopausal women [12].

Endogenous estrogen in postmenopausal women is primarily found in adipose tissue, secondary to the aromatization of adrenal androgens, with a higher risk of developing breast cancers. A study found that women who gained 55 pounds or more after the age of 18 years had an approximately 55% greater risk of breast cancer compared with those who maintained their weight. A gain of 22 pounds or more after menopause was associated with an 82% greater risk of breast cancer, whereas losing at least 22 pounds after menopause and maintaining weight were associated with a trend toward decreased breast cancer risk [13].

1.2.3 Diet

The observation that breast cancer rates are much higher in the countries with high-fat diets than underdeveloped countries and Japan, where fat intake is recognized as being much lower, it has been suggested that high-fat diets might increase the risk of breast cancer. However, it was reported in a pooled analysis of seven prospective studies no association was found between fat intake and breast cancer risk among adult women living in more developed countries [14, 15]. These results do not entirely exclude any significant effect of fat on breast cancer, while there would be a considerable error in measurement of fat intake by dietary questionnaires [2].

Excessive fat intake can increase breast cancer risk by increasing the endogenous estrogen levels. Further studies are required to confirm the effect of diet on breast cancer.

1.2.4 Oral Contraceptive Use

Key et al. reported that the overall effect of oral contraceptive use on the risk of breast cancer among young premenopausal women is low because the small increase in relative risk is acting on a very low background risk. In older premenopausal women, oral contraceptives can be a less favorable choice because of the absolute risk of breast cancer, as well as other health hazards which increase rapidly at ages from 40–50 years [2]. Additionally, in their randomized controlled trial, Rossouw et al. pointed out that after an average follow-up of approximately 5 years, combined oral contraceptive therapy (estrogen plus progesterone) has a 26% higher risk then therapy using only estrogen, and also reported a 15% increase for estrogen plus progestin use for less than 5 years, with a 53% increase for use for more than 5 years [16].

1.2.5 Hormone Replacement Therapy

The Million Women Study, a cohort study of all quarter of British women between the ages of 50–64 years, was set up especially to investigate the relation between various patterns of HRT use and breast cancer incidence and mortality. It was reported in the study that the use of HRT at that time was associated with an increased risk of incidence and fatal breast cancer; the effect was found to be substantially greater for estrogen-progesterone combinations compared with other types of HRT (relative risks [RR] have been reported; for combined treatment of estrogen-progesterone, RR = 2.00; for estrogen, RR = 1.30; and for Tibolon, RR = 1.45) [17]. Similar findings were reported by Magnusson et al., who found that users of hormonal therapy for menopause are considered at higher risk of breast cancer compared with women who have never used these therapies [18].

The results from the Million Women Study reported that minimal or no overall increase was detected in RR of breast cancer in past users of HRT.

1.2.6 Smoking

In many cohort studies conducted in recent years, it has been suggested that smoking increases the risk of breast cancer, especially among women who smoked cigarettes for a long period of time or who started smoking at a young age [19, 20]. Additionally, in a larger prospective cohort study by Luo et al., such associations have been further confirmed in postmenopausal women [21].

Additionally, Luo et al. also reported that they observed a significantly increased risk of breast cancer associated with the amount and duration of smoking among nonobese women. The mechanism behind this relation can mainly be attributed to the carcinogenic effects of tobacco smoking on breast tissue [22].

1.2.7 Alcohol

Smith-Warner et al. reported that alcohol consumption was associated with a linear increase in breast cancer incidence in women [23]. In a similar study, Chen et al. reported that low levels of alcohol consumption were associated with a small increase in breast cancer risk, with the most consistent measure being cumulative alcohol intake throughout the adult life. Alcohol intake both at earlier and later ages of adult life was independently associated with breast cancer risk [24].

1.2.8 Heredity

Various aspects of genetic transition of cancer can be monitored. Historically, French surgeon Paul Broca had identified a large number of breast cancer host families in 1860 [25]. Since then, researchers have confirmed Broca's insight. Presently, it has been proved that 5–10% of all breast cancers were a result of mutations in the genes at high risk, such as *BRCA1* and *BRCA2* (familial risks of breast cancer) [26].

Patients having these mutations and indicating the inheritance of Mendel (i.e., dominant, recessive, X-linked) defined a hereditary breast cancer. When the family history is suggestive of a hereditary predisposition, but the number or distribution of the cancers is not definitive, then families are described as having familial cancer [27]. Specific genetic alterations have been identified for many of the established hereditary breast cancer syndromes that are responsible for 10% of all breast cancer cases. Hereditary breast-ovarian cancer (HBOC) syndrome is an inherited tendency to develop breast, ovarian, and other cancers. Although most cancers are not inherited, approximately 5% of those with breast cancer and approximately 10% of women with ovarian cancer also possess HBOC. Approximately 80–90% of cases of hereditary breast and ovarian cancers are caused by mutations in the *BRCA1* and *BRCA2* genes [28]. A study reviewing 22 trials reported that the average cumulative risks among *BRCA1*-mutation carriers at age 70 years were determined as 65% for breast cancer and 39% for ovarian cancer. The corresponding estimates for *BRCA2* were 45% and 11%, respectively [29, 30].

Typically, the *BRCA1* mutation carriers increase rapidly, as well as high-grade, estrogen receptor negative breast tumors in premenauposal women. Foulkes et al. also reported that *BRCA1* serves as a breast stem cell regulator [31].

Further studies have revealed that women with mutations in either the *BRCA1* or *BRCA2* gene have a predicted lifetime risk of breast cancer between 37% and 85%, and a lifetime risk of ovarian cancer between 15% and 40% [27, 32, 33].

The p53 tumor suppressor protein can prevent carcinogenesis. In breast cancers, p53 is mutated in almost 30% of cases, with a higher frequency in some tumor subtypes. Tumor p53 mutation is reported to be a factor for good prognosis in some studies, while in others it is a factor for poor prognosis [34]. In breast cancers, the

p53 inactivation was 20–30%. The presence of mutations on p53 can demonstrate tumor transition from in situ to invasive carcinoma as a marker. Li-Fraumeni syndrome (LFS) is a classic cancer predisposition disorder that is commonly associated with germ-line mutations of the *p53* tumor suppressor gene. Germ-line mutations in *p53* predispose to LFS, including childhood sarcomas and brain tumors, as well as early-onset breast cancer [35, 36]. The risk of breast cancer is 50–60% by age 45 years [34] and those in pentaerythritol tetranitrate are responsible for Cowden disease, in which breast cancer is a major feature and the risk of breast cancer is 25–50% [27, 33].

1.3 Molecular Epidemiology of the Breast Cancer

Breast cancers, which have different clinical properties, pathologic features, morphology, grade, and hormone receptors, are very different biological and clinically heterogeneous groups of diseases. Breast cancer is classified jointly by estrogen receptor (ER) and progesterone receptor (PR) status in human epidermal growth factor receptor-2 (Her-2). Her-positive tumors are observed in 60–70% under the age of 35 years and in 80% over the age of 60 years [1], which also shows the heterogeneous etiology. In all age groups, rates of Her-2 positive and Her-2 negative are quite similar. Risk factors for breast cancer include obesity, lifestyle factors, reproductive factors, as well as some environmental and postmenopausal obesity lifestyle factors. ER and/or PR may indicate a tight relationship [37, 38]; although no relationship between genetics and ER/PR receptor status was seen [39]. Mavaddat et al. reported that they could not find any association between ER-positive and ER-negative receptors, but under the age of 50 years, the ER-negative disease rate is high in relations and family [40].

Gene expression profiling in tumor tissues with polymerase chain reaction suggests that breast cancers may be divided into subtypes consisting of two ER-positive types (luminal A and luminal B) and three ER-negative types (Her-2), expressing basal-like, and unclassified "normal-like", with distinctive clinical outcomes [41, 42]. Yang et al. [43, 44] and Gaudet et al. [43, 44] reported that they observed significant differences in terms of tumor subtypes for the distribution of age at menarche, age at first full-term birth, and body mass index (BMI) among premenopausal women. Basal-like tumors were related to the youngest age at menarche and highest BMI among premenopausal women, whereas luminal A tumors were associated with the oldest mean age at first full-term birth.

The Carolina Breast Cancer Study also investigated the risk factors that could cause such differences. They reported that a number of risk factors depending on the subtype of tumor were also observed, and the effects were opposed of each other. More importantly, having more than one child, the age of the completed first pregnancy was found to be a protective factor for luminal A, in turn these factors are found as predisposing to basal-like cancers [45]. Millikan et al. reported other well-known risk factors showing a different behavior according to the subgroups.

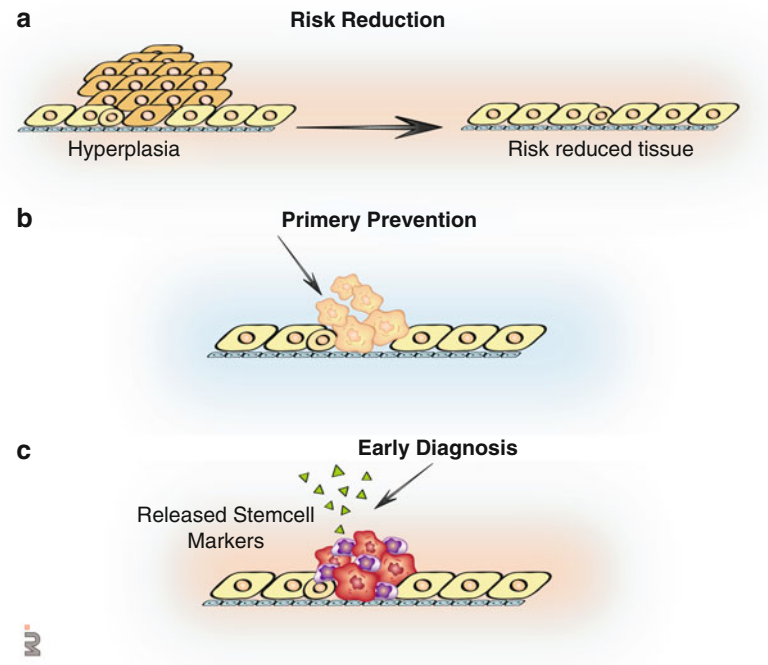

Fig. 1.1 Breast cancer prevention steps

For example, a measure of obesity with high waist-to-hip ratio also increases susceptibility to ER-negative and ER-positive cancers. Younger menarche age, Multiparity, the age at first full-term pregnancy (younger age), increased waist-to-hip ratio are considered as factors increasing the risk of triple-negative breast cancer. However, the number of births and the age at first birth showed no difference between the triple-negative group and the other groups [46].

Cancer stem cell hypothesis shows that breast stem cell populations targeting strategies for prevention and treatment of breast cancer are very efficient, and are shown in Figure 1.1.

1.4 Conclusion

Breast cancer should be regarded as one of the most important cancers affecting women in the future, therefore, there is a need for prevention. There would be great benefit of education programs aimed at promoting breastfeeding, at the reduction of abdominal obesity, promoting a healthy lifestyle and healthy nutrition, especially in preventing bad progressive types of breast cancer progression.

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Chapter 2
Staging of Breast Cancer

Zeynep Ozsaran and Senem Demirci Alanyalı

2.1 Introduction

Five decades ago, Denoix et al. proposed classification system (tumor node metastasis [TNM]) based on the dissemination of cancer according to the features of the primary tumor (localization, size, and extension to the surrounding structures), regional lymph nodes, and the presence of metastases. Currently, the TNM system which was formulated by Union International Cancer Centre (UICC) and the American Joint Committee on Cancer (AJCC) is being used for every cancer site [1].

The most important function of staging is to anatomically group patients to determine the treatment algorithm and prognosis. Accurate staging carries substantial importance to compare the treatment results among the studies [2].

In 1960, the UICC published the TNM staging system adapted for breast cancer. Revisions to the staging system were updated in 1962 and the seventh edition was published in 2009 [3]. The differences between the sixth and the seventh edition of the staging system are:

- T1mic changed to T1mi to indicate microscopic disease.
- Clarification of wording of "not clinically detected" and "clinically detected" internal mammary nodes.
- Subdivision of Stage I into IA and IB (IB includes T0-T1 with nodal micrometastases).
- New cM0(i+) category defined for the presence of either disseminated tumor cells detectable in bone marrow or circulating tumor cells or found incidentally in other tissues if not exceeding 0.2 mm.
- The category of "yc" or "yp" was introduced to distinguish stage after preoperative, or "neoadjuvant" systemic therapy and surgery.

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2.2 Rules for Classification

2.2.1 Clinical Staging

Clinical staging includes physical examination, with careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supraclavicular, and cervical), imaging, and pathologic examination of the breast or other tissues as appropriate to establish the diagnosis of breast carcinoma. Imaging and clinical findings obtained after a patient has been treated with neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy are not considered elements of initial clinical staging. If recorded in the medical record, these should be denoted using the modifier prefix "yc."

2.2.2 Pathologic Staging

Pathologic staging includes all data used for clinical staging, in addition to data from surgical exploration and resection as well as pathologic examination (gross and microscopic) of the primary carcinoma, regional lymph nodes, and metastatic sites, including not less than excision of the primary carcinoma with no macroscopic tumor in any margin of resection by pathologic examination. If surgery occurs after the patient has received neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy, the prefix "yp" should be used with the TNM classification [2].

2.3 American Joint Committee on Cancer Staging of Breast Cancer

2.3.1 Primary Tumor

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner should use the major headings (T1, T2, and T3). If other measurement, such as mammographic or pathologic, is used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

- *Tx* Primary tumor cannot be assessed
- *T0* No evidence of primary tumor
- *Tis* Carcinoma in situ

- *Tis* (*DCIS*) Ductal carcinoma in situ
- *Tis* (*LCIS*) Lobular carcinoma in situ
- *Tis* (*Paget's*) Paget's disease of the nipple with no tumor
- *T1* Tumor 2 cm or less in greatest dimension

  $T1_{mic}$ Microinvasion 0.1 cm or less in greatest dimension
  T1a Tumor greater than 0.1 cm but not more than 1 cm in greatest dimension
  T1b Tumor greater than 0.5 cm but not more than 1 cm in greatest dimension
  T1c Tumor greater than 1 cm but not more than 2 cm in greatest dimension

- *T2* Tumor greater than 2 cm but not more than 5 cm in greatest dimension
- *T3* Tumor greater than 5 cm in greatest dimension
- *T4* Tumor any size with direct extension to chest wall or skin, only as described below
  Note: Invasion of the dermis alone does not qualify as T4

  T4a Extension to chest wall, not including pectoralis muscle
  T4b Edema (including peau d'orange or ulceration of the skin of the breast or satellite skin nodules confined to the same breast)
  T4c Both (T4a and T4b)
  T4d Inflammatory carcinoma.

2.3.2 Regional Lymph Nodes

Definitions for classifying the regional lymph nodes (N) are different for clinical and for pathologic classification.

2.3.2.1 Clinical Lymph Node Classification (cN)

- *Nx* Regional lymph nodes cannot be assessed (e.g., previously removed)
- *N0* No regional lymph node metastases
- *N1* Metastases to movable ipsilateral level I,II axillary lymph nodes
- *N2* Metastases to ipsilateral level I,II axillary lymph nodes fixed or matted, or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases

  N2a Metastases in ipsilateral level I,II axillary lymph nodes fixed to one another (matted) or to other structures
  N2b Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastases

- *N3* Metastases to ipsilateral infraclavicular (level III) axillary lymph node(s) with or without level I,II axillary lymph node(s) involvement, or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident

level I,II axillary lymph node metastases, or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a Metastases in ipsilateral infraclavicular lymph node(s)
N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c Metastases in ipsilateral supraclavicular lymph node(s).
*Note: "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

2.3.2.2 Pathologic Classification (pN)

- *pNx* Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
- *pN0* No regional lymph node metastases histologically

Note: Isolated tumor cell clusters (ITC) are defined as single tumor cells or small cell clusters not or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated usually detected only by immunohistochemistry (IHC) or molecular methods but which may be verified on hematoxylin and eosin stains. ITCs do not usually show evidence of malignant activity (e.g., proliferation or stromal reaction)

pN0 (*i*−) No regional lymph node metastases histologically, negative IHC
pN0 (*i*+) Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0 (*mol*−) No regional lymph node metastasis histologically, negative molecular findings (reverse transcriptase polymerase chain reaction [RT-PCR])
pN0 (*mol*+) Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC

– *pN1* Micrometastases or metastases in one to three axillary lymph nodes, and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected*

  pN1mi Micrometastases (greater than 0.2 mm, and/or more than 200 cells, but none greater than 2.0 mm)
  pN1a Metastases in one to three axillary lymph nodes, at least one metastasis greater than 2.0 mm
  pN1b Metastases in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*
  pN1c Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

– *pN2* Metastases in four to nine axillary lymph nodes, or in clinically detected** internal mammary lymph nodes in the absence of axillary lymph node metastases

  pN2a Metastases in four to nine axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
  pN2b Metastases in clinically detected** internal mammary lymph nodes in the absence of axillary lymph node metastasis

– *pN3* Metastases in 10 or more axillary lymph nodes, or in infraclavicular (level III) lymph nodes, or clinically detected** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I,II axillary lymph nodes, or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected** or in ipsilateral supraclavicular lymph nodes

  pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastases to the infraclavicular (level III axillary lymph) nodes
  pN3b Metastases in clinically detected** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes, or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**
  pN3c Metastases in ipsilateral supraclavicular lymph nodes.

*"Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.
**"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Table 2.1 AJCC 7th Edition Staging for Breast Cancer

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0-T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

2.3.3 Distant Metastasis (M)

- *M0* No clinical or radiographic evidence of distant metastases
- *cM0*(*i*+) No clinical or radiographic evidence of distant metastases, but deposits of moleculary or microscopically detected tumor cells detected in circulating blood, bone marrow, or other nonregional nodal tissues, that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
- *M1* Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proved larger than 0.2 mm.

2.3.4 Staging

The staging grouping is summarized in Table 2.1.

* T1 includes T1mi.

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

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Chapter 3
Molecular Classification

Ayfer Haydaroglu

3.1 Introduction

In the research studies conducted for the analysis and classification of breast tumors, DNA microassays and gene expression patterns are primarily used. Breast tumors are divided into different groups with these methods. Gene expression-based classifications are known to have important effects on survival and prognosis. Breast cancer is a heterogeneous disease comprised of different histologic subtypes. This heterogeneity results in different clinical presentations and carries different underlying molecular markers. Determining the classification of the tumor based on genomic as well as phenotypic variability will provide important information about the course of the disease and facilitate determining the most relevant therapy model. In this chapter, molecular and genetic factors determining the classification of breast cancer, genomic structure of breast cancer, genetic tests, as well as the role of the developmental hierarchy of the breast epithelial cells and breast cancer stem cells (CSC) on classification will be discussed.

3.2 Advances in Genomic Research

Breast cancer is a heterogeneous disease comprised of different histologic subtypes. This heterogeneity results in different clinical presentations and carries different underlying molecular markers [1]. Genomic heterogeneities of tumors are thought to be clarified by using the DNA microarray technology, which emerged in the scientific world with the Human Genome Project [2]. Molecular portraits of human breast tumors were first revealed in 2000 by a research group at Stanford University, who used fluorescently labeled cDNA [3]. In gene expression analysis, two different

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types of epithelial cells are found: luminal epithelial cells lining the inside of the ductus, and basal cells lining the outer surface. The gene cluster related with the basal epithelial cells was keratin 5, keratin 7, integrin-β4 and laminin. The luminal gene cluster included estrogen receptor (ER), GATA binding protein 3, X-box binding protein 1, and hepatocyte nuclear factor-3-α. This study is considered highly significant in terms of indicating concomitance of the genotypic diversity and phenotypic diversity for breast cancers. In the study, among 8,012 human genes represented by cDNA microarrays, 496 were identified as having "intrinsic" properties that can distinguish different tumors from each other [3]. In another study conducted by the same group of researchers in 2001, breast cancer was screened for p53 mutation, and 30 of 63 tumors were found to have p53 mutations. Regarding the distribution of p53 mutations; luminal A subtype contained 13%, human epidermal growth factor receptor-2 (Her-2)-positive group contained 71%, and basal-like group contained 82 [4]. Furthermore, the prognostic value of the new molecular taxonomy was evaluated in the study and it was concluded that basal-like and Her-2-positive groups displayed the worst survival rates, whereas luminal B and C groups had worse survival rates compared with the luminal A group, which was observed to have the best survival rates [4]. In 2007, the same group identified a new molecular subtype of breast cancer named "claudin-low." In that subtype, gene expressions of claudins 3, 4, 7 and E-cadherin, which are known as tight-junction proteins, were detected at rather low levels [5]. Low level of cell-to-cell adhesion proteins might suggest the likelihood of early tumor dissemination. In a 2009 experiment conducted using $CD44^+/CD24^-$/low cells, a new genomic signature named "tumor-initiating cell" was defined, which showed similarity to the genomic structure of the claudin-low tumors. In these studies, the claudin-low group was considered to have more stem cell-like features, contrary to the very few epithelial cell markers [6–8]. The claudin-low group was determined to have $CD44^+/CD24^-$/low and CD49f + EpCAm−/low antigenic profile, which was characterized as breast CSC and "tumor initiating cell." In the studies performed by immunofluorescence technique, both mesenchymal and also epithelial cell features have been observed in those cells [7, 8].

Currently, information about human genome and genomes of many other species has been accessed, the number of genes in the genome and size of the genome have been specified, and gene functions, as well as molecular definitions regarding normal and pathologic conditions, have been identified. However, there is still much to be learned. Research studies on breast cancer are continuously ongoing and different genetic secrets are revealed consistently. Certain genetic tests that are specific for classification of breast cancer and determining recurrences have been developed and are widely used.

3.2.1 Gene Expression Profiling Tests

Gene expression profiling tests can be used to determine genetic profile, i.e., immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and quantitative

cDNA analysis (cDNA microarray). IHC and FISH are semiquantitative tests and can detect estrogen receptor (ER) and Her-2 status at a low cost. However, qRT-PCR and cDNA are highly expensive and complicated quantitative analysis methods that require qRT-PCR and cDNA fresh-frozen tissue examination [9].

3.2.2 Gene Analysis Tests

More than 10 gene analysis tests that can apply paraffin block specimens and fresh-frozen tumor specimens have been used [10]. The main tests for gene analysis listed below.

3.2.2.1 Prediction Analysis of Microarray 50 Method Test

Breast cancer was grouped into four main subtypes as luminal A, luminal B, Her-2-enriched, and basal-like with the prediction analysis of microarray method (PAM50), which can predict 50 genes [11, 12]. In the literature, it was reported that the PAM50 test can group node-negative breast cancer cases as high, medium, and low, and predict response to neoadjuvant therapy. With PAM50, the luminal A group was less responsive to adjuvant chemotherapy, whereas tumors with a high score were responsive. However, Her-2 positivity detected using PAM50 was not compatible with IHC/FISH results, which might make diagnostic use of PAM50 disputable [13].

3.2.2.2 70-Gene Test (MammaPrint)

The 70-gene test was developed with specimens prepared from available frozen tissues of T1-T2 N0 invasive breast cancer patients who had participated in a study conducted by Veer et al. in 2002. Among the genes of the patients who developed distant metastasis within 5 years, 70 genes were determined and used as a "MammaPrint prognostic score" [14]. In further validation tests, Vijver et al. examined 205 patients and found metastasis-free survival rates (for at least 5 years) of 95% in patients with good prognostic scores, but 60% in patients with poor prognostic scores [15]. This test can determine the likelihood of developing distant metastasis within 5–10 years after diagnosis using molecular technology. Despite the prognostic values of the DNA-based test methods, difficulties in using fresh-frozen samples are considered the main constraint of the test.

3.2.2.3 21-Gene Analysis (Oncotype DX™)

The 21-gene breast cancer analysis can predict the risk of distant metastasis in 10 years and response to adjuvant chemotherapy in women with hormone receptor–positive, lymph node–negative breast cancer. In 2001, the recurrence score (RS) method was developed with a reverse PCR method in paraffin blocks. Sixteen cancer-related (i.e., proliferation, invasion, Her-2, and ER pathways related genes) and five additional genes, a total of 21 genes can be evaluated using the test. RS reflects 10-year distant recurrence rate. Patients are interpreted as low-risk (RS, <18), medium-risk (RS, 18–30) and high-risk (RS, ≥ 31) groups. Accordingly, for the patients who had used tamoxifen for 5 years, 10-year distant metastasis was less than 12% in the low-risk group, 12–21% in the medium-risk group, and 21–33% in the high-risk group [16].

3.2.2.4 Genomic Grade Index (MapQuantDX Assay)

The genomic grade index (GGI) is based on the evaluation of 97 genes that are related in ER-positive cases with cell proliferation [17], but its performance is limited in ER-positive patients.

3.2.2.5 Theros Breast Cancer Index

The Theros breast cancer index index is confirmed in ER homeobox positive and node negative patients treated with adjuvant tamoxifen [18]. The high ratio of *homeobox 13* gene vs. *interleukin-17B* gene (H/I) is predictive of a decrease in disease-free survival and overall survival rates. The H/I test can identify messenger RNA in paraffin sections of cancer tissues. Of many gene analyzing tests, only certain tests such as Oncotype Dx, Mammaprint, Theros, and Mapquant (GGI) can be used as commercial kits [19].

3.3 The Role of Developmental Hierarchy of Breast Epithelial Cells and Breast Cancer Stem Cells in Classification

3.3.1 Breast Stem Cells in the Development of Breast

Breast stem cells (BSC) maintain a normal development process of breast, which is a very dynamic gland and is continuously modified structurally because of hormones throughout life. BSC are also responsible for tissue regeneration and repair procedures in the breast [20]. BSC can activate in response to certain environmental stimuli such as hormones, and ensure the required alterations in

the breast with symmetric and asymmetric division. Estrogen increases BSC through paracrine FGF/FGFR/Tbx3 signaling pathway. Tamoxifen, an inhibitor of this signaling pathway, is used as an anti-estrogen to prevent mammosphere formation [21].

On the other hand, hormonal signals during gestation stimulate BSC and lead to asymmetric division of stem cells. BSC initiate the alterations to ensure onset of proliferation of milk-producing cells and prepare the breasts for lactation [22]. Numerous transcription regulators have been shown to control different aspects of breast development. Wnt, Notch, and Hedgehog signaling pathways are the conserved ones among many different types of adult stem cells, but inhibition in the control of these pathways is related with oncogenesis and plays a central role in carcinogenesis [23].

BSC can be differentiated from luminal epithelial cells with the level of CD24 expression. Although cells expressing the highest level of CD49f have been shown to be enriched in terms of breast repopulation capacity, it has also been proved that myoepithelial cells and stem cells could not be differentiated easily as a result of common cell surface phenotypic profile and gene expression profile. The similarities between stem cells and myoepithelial cells partly reflect the common basal positions [24].

3.3.2 The Role of Breast Stem Cells in Carcinogenesis

Mature stem cells maintain their functions through paracrine and endocrine signals from the microenvironment, neural stimuli, and the resulting metabolic products. Different stimulus may result in mutations and carcinogenesis. In the developmental hierarchy of breast epithelial cells, multipotent early progenitor cells develop from BSC, and they give rise to myoepithelial and luminal epithelial progenitor cells. Differentiated myoepithelial cells develop from myoepithelial progenitor cells, whereas differentiated alveolar and luminal cells develop from luminal progenitor cells. These developments occur as a result of asymmetric and restrictive cell divisions that appear with the stimuli related to the requirements. Molecular and genetic carcinogenesis mechanisms at any stage of developmental hierarchy reveal different types of cancers (Fig. 3.1). Tumors that have originated from the mutations of normal stem cells possess heterogeneous structure and a significant metastatic potential. Tumors that have originated from mutations of progenitor cells demonstrate relatively homogenous structure and less metastatic properties. Cancers which were initiated from dedifferentiation of adult cells, such as luminal cells, are well-differentiated and exhibit a relatively good prognosis [25]. Recent studies have demonstrated that adult BSC play a significant role in breast cancer [26]. Adult stem cells, which can survive for a longer period of time, are more prone to accumulate genetic mutations. On the other hand, a limited number of progenitor cells function as targets for oncogenesis. Each subtype has a distinct natural history and response to treatment.

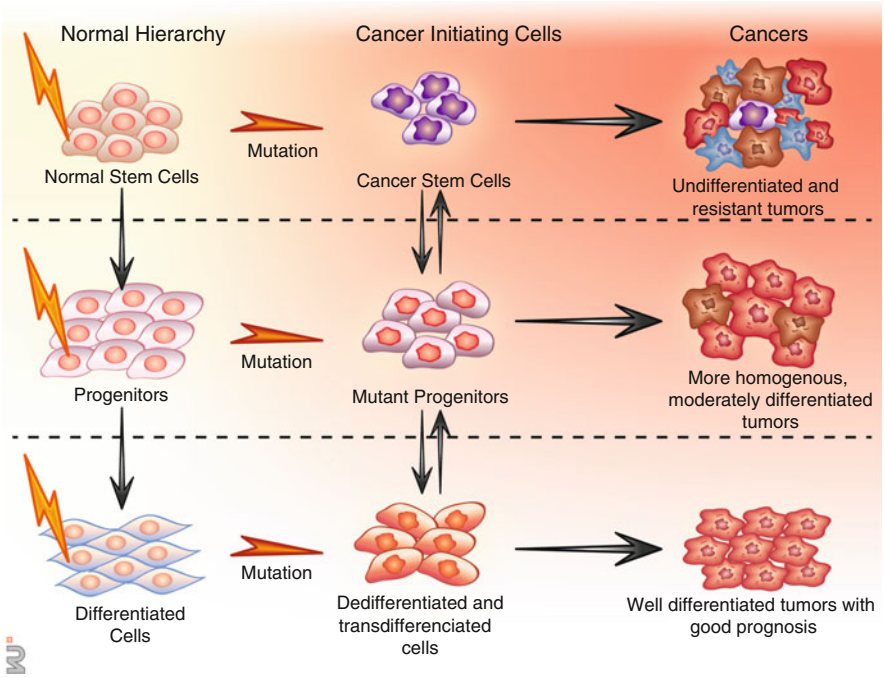

Fig. 3.1 In the normal stem cell (NSC) hierarchy, normal progenitor cells develop from NSC, and they give rise to differentiated mature cells. Different factors related with microenvironment may lead to mutations and cancer-initiating cells

Based on the clonal evolution model, which is about how tumors develop and grow by unlimited cell divisions, different model approaches have been described; the stochastic model (coincidental), the hierarchical model, and the mixed cancer model [38, 39]. The stochastic model (classical tumor model) suggests that all the cells of a neoplasm possess equipotential to develop cancer and any single cell of tumor origin can develop new tumors with characteristics similar to the original tumor. According to the hierarchical model (CSC model), only the CSCs have tumorigenic capacity, while the remaining portion of the tumor is assumed to consist of cells having no ability to form new tumors [38]. The mixed cancer model is suggested as a combination of these two models [39]. Mutations can transform differentiated normal, progenitor, or stem cells to cancer-initiating cells. CSCs can accumulate additional mutations which can undergo clonal selection and lead to different CSC clones (genetic divergence). Predominant clones determine the subtype of the breast cancer. Ultimately, based on the genetic and molecular structure, triple-negative breast cancer, Her-2-gene amplified, or luminal subtypes of breast cancers have been identified (Fig. 3.2).

Breast cancer is the first solid malignancy for which CSCs have been identified and isolated. In breast cancer, exploring the stem-like tumor cells may explain the dilemma regarding difficulties to eliminate cancer and show how novel therapeutic pathways can be targeted [26]. Targeting these minority cells because of their

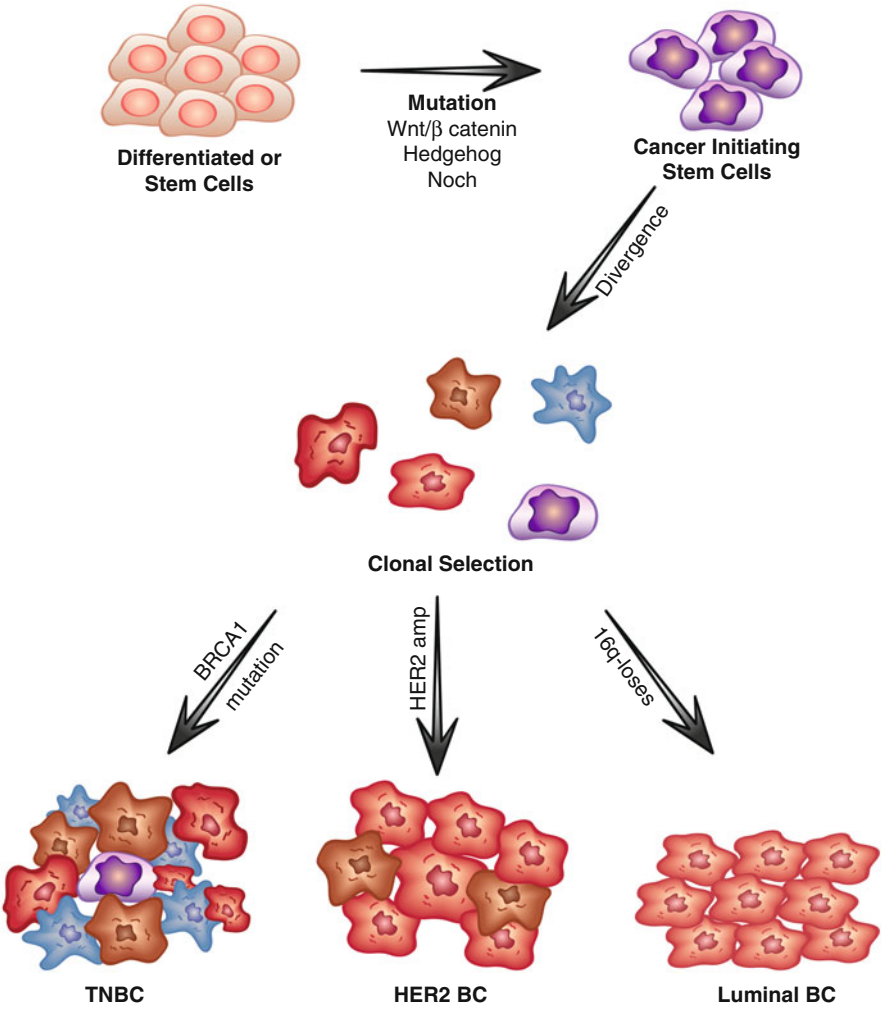

Fig. 3.2 Breast cancer subtypes according to the mixed cancer model. *TN* triple negative; *BC* breast cancer; *Her-2* human epidermal growth factor receptor. Breast cancer stem cells (CSC)

metastasis capacity and their engagement in a majority of deaths resulting from breast cancers has opened new areas in the treatment of breast cancer [27].

Many studies investigating the breast CSC and specifying cell surface markers are available. However, consensus could not be reached on phenotypic properties [1]. In light of the recent experimental studies, full consensus could not be reached on the universal marker which can differentiate breast CSC from other breast cells and isolate them, or on the combination of various markers, because breast cancer is a heterogeneous group of neoplasm, consisting of different histologic subtypes. Heterogeneity is associated with different clinical outcomes and of the underlying different molecular markers [1].

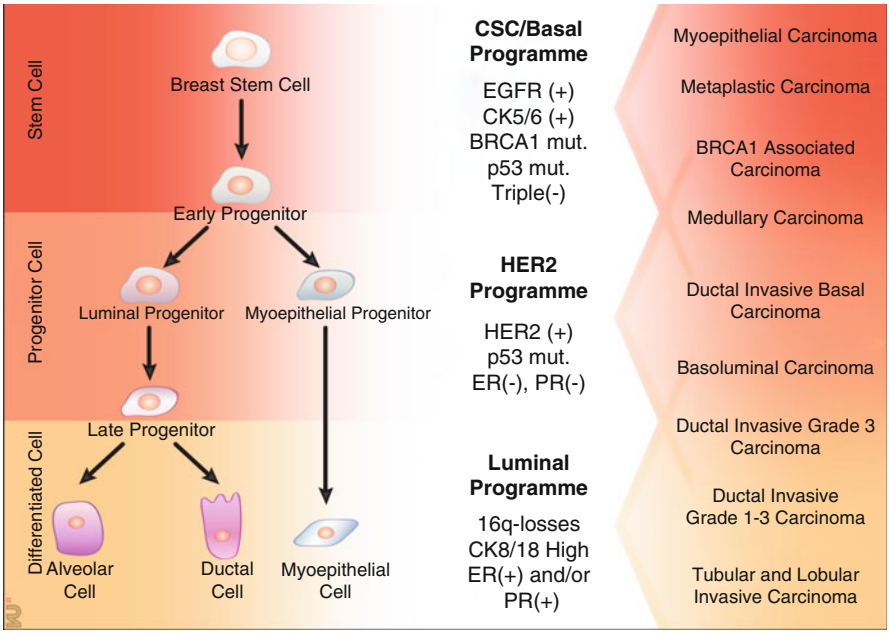

Fig. 3.3 Developmental hierarchy of epithelial breast cells and the specifications of the carcinogenesis program caused by the cancer-initiating cells originated from this hierarchy. Reflection of the molecular and genetical taxonomy of CSC/basal, Her-2, and luminal programs to histopathologic types of cancers identified by immunohistochemistry

The stage of the cells, which occur as a result of mutations throughout breast development hierarchy and initiate breast cancer, is highly important in terms of classification (Fig. 3.3). When a mutagenic change in the CSC/basal program leads to carcinogenesis, then having significant stem cell properties and a lack of epithelial changes are remarkable in that tumor. In addition to epidermal growth factor receptor (EGFR) and CK 5/6 positivity, BRCA1 and p53 mutations are also frequently seen, triple-negative breast cancer develops. IHC, myoepithelial carcinoma, metaplastic carcinoma, cancers associated with BRCA 1 mutations, and medullary carcinomas are seen. In Her-2-enriched subtype breast cancers developed from progenitors at the stage when Her-2 amplification begins, Her-2-positive, ER- and progesterone (PR)-negative cancers with significant p53 mutations can develop, IHC displays grade 3 invasive ductal carcinomas, basoluminal carcinomas, basal-like invasive ductal carcinomas, and medullary carcinomas. In mutagenic carcinogenesis developed in the luminal program and cancers developed secondary to luminal dedifferentiation have been determined to cause progression of luminal type breast cancers, genetically evident with loss of 16q, increase in CK 8/18, ER positivity and/or PR positivity. IHC shows grades 1–3 invasive ductal carcinomas, tubular, and lobular carcinomas [40].

The stage at which breast cancer-initiating cells develop in the development hierarchy is important for classification. Triple-negative breast cancer develops at the stage that stem cell properties are retained, and epithelial changes are not

yet detected, Her-2-enriched breast cancers develop at the stage that Her-2 amplification has not yet initiated, and breast cancers with luminal properties develop at the stage just after luminal differentiation (Fig. 3.3).

DNA microarray and gene expression studies have identified five different breast cancer subtypes and the normal breast-like type [28]. According to molecular taxonomy, breast cancers can be subdivided into luminal A or B, Her-2-enriched, triple-negative breast cancer basal-like, claudin-low, and normal breast-like subtypes. Differences in mutation profiles as well as cancer-initiating cells are recognized to cause differences in subtypes [27] (Table 3.1).

The luminal A subtype is defined as ER- and/or PR-positive, Her-2-negative and low Ki-67. In the epithelial development hierarchy of breast, luminal A subtype cancers develop after highly differentiated luminal-like properties are acquired [32]. CK8/18 is high grade in luminal A, but variable in luminal B. The luminal A subtype contains GATA binding protein 3, X-box binding protein 1, and hepatocyte nuclear factor-3-α of the ER-α gene, high expression of genes such as trefoil factor 3 and LIV-1. This is the most common type of low-grade tumor, with low recurrence risk, and generally good prognosis, and is common in the postmenopausal white population [29]. Response to anti-hormonal therapy is good, although low to chemotherapy.

In the St. Gallen consensus, cut-off for Ki67 was considered as 14% in order to identify breast cancer as luminal A subtype [30]. The cut-off value was defined by receiver operating characteristic curve developed as a result of patient data [2]. Cheang et al. distinguished luminal A tumors from luminal B tumors with a sensitivity of 72% and a specificity of 77% [31]. Distinguishing luminal A and B tumors is valuable for clinicians in determining chemotherapy options. Therefore, based on the data of their study, Ki-67 has gained more importance in many centers in distinguishing hormone receptor-positive Her-2-negative luminal tumors.

3.3.2.1 Luminal B Subtype

The luminal B subtype is shown to have luminal properties of ER- and/or PR-positive, either Her-2-positive or -negative, and high Ki-67 index. The expression level of ER-related genes occurs more in luminal A, whereas more proliferative genes are expressed in luminal B. The expression of ER linked genes is moderate in the luminal B group. Luminal B is distinguished from luminal A with the Ki-67 index higher than 14%, when Her-2 is negative. Cellular and nuclear stages are variable. Response to chemotherapy and anti-hormonal therapy is also variable, while Her-2-positive tumors are responsive to anti-Her-2 therapy [32]. In a study conducted with lymph node-negative and clinically low-risk group of patients, 10-year relapse-free survival rates and breast cancer specific survival rates of the hormone receptor positive but Ki67 $<14\%$ group, hormone receptor positive but Ki-67 ≥ 14, and also hormone receptor positive and Her-2-positive groups were reported as 78%, 67%, 64% and 92%, 79%, 78%, respectively [31].

Table 3.1 Molecular classification of breast cancer luminal A subtype

	Luminal A	Luminal B	Her-2-positive	basal-like	Claudin-low	Normal-like
ER and/or PR	(+) High ER expression	(+) Moderate ER expression	(−)	(−)	(−)	(−)
Her-2	–	−/+ Her-2	(+)	(−)	(−)	(−)
Speciality	Low Ki-67 <14%, p53 mutation 13 %, GATA-3, XBP1, FOXA1, CK8/18 high	High Ki-67 >14%, p53 mutation 40 %, MKI67, CCNB1 and MYBL2 gene expressions	Her-2 and Her-3 (+), p53 mutation 71 %, GRB7 (+)	p53 Mutation 80%, BRCA mutation frequently, CK5/6 (+), EGFR (+), cytokine gene family	Claudin 3,4,7 low, E-Cadherin low, CD44+/CD24-/low CD49f + EpCAm-/low, stem cell-like, epithelial mesenchymal transition genes expression	Adipose tissue markers, lipoprotein, lipase, p53 mutation 33%
% in the breast cancers	30	20	15–20	10–25	5–7	7

ER estrogen receptor, *PR* progesterone receptor, *EGFR* epidermal growth factor receptor, *Her-2* human epidermal growth factor receptor-2

3.3.2.2 Her-2-Positive Subtype

The Her-2-positive subtype is defined as ER and PR negative and Her-2 positive. Most of them are high grade, with high values of Ki-67. Lymph node involvement is generally present at diagnosis. It is responsive to chemotherapy and Her-2 therapy [32]. Tumor initiation corresponds to late progenitor stage in which luminal properties have not yet developed. Clinically, 15–20% of breast tumors are Her-2-positive tumors, but 30–40 % of them are ER positive and the majority is ER negative.

3.3.2.3 Her-2-Enriched Subtype

The Her-2-enriched subtype is expressed by a small subgroup of triple-negative breast cancer. Some of these tumors are clinically triple negative, despite having the signatures of Her-2-enriched subtypes. Her-2-enriched tumors are both ER and PR negative [28]. Her-2-positive tumors do not belong to the triple negative group, which is important with regard to therapy modeling. The important outstanding question is whether the Her-2-enriched group of the triple-negative group will respond to Her-2-targeted therapy or not [28].

3.3.2.4 Basal-Like Subtype

The basal-like subtype consists of ER, PR, Her-2 negative, and known as triple negative. It is CK 5/6 positive. This subtype is mostly EGFR positive. EGFR and CK 5/6 markers increase specificity in identification of basal-like tumors [33]. They are high-grade tumors with significantly high Ki-67 index values. They are more common in premenopausal women and respond well to chemotherapy. Basal-like subtypes are very heterogeneous, and consist of 10–25% of all breast tumors, and 50–75% of the triple-negative subtype, depending on the demographic characteristics of the population [28]. Clinically, they are among the most aggressive tumors with a high recurrence risk and poor prognosis. These tumors are highly proliferative, and the average value of the proliferative index is rather higher [34]. Luminal progenitor cells reside in the developmental hierarchy, and have similar properties to those of the basal-like tumors. *BRCA-1* mutation occurs as a consequence of the luminal progenitor/basal-like phenotype, and blocks developmental hierarchy at this stage by inhibiting differentiation subsequent to a loss of BRCA for any reason [28], and it can accompany the BRCA1 mutation.

3.3.2.5 Claudin-Low Subtype

The claudin-Low subtype consists of 5–7% of all breast cancers and is the most primitive tumor subtype, displaying BSC-like features [28]. They are typically triple

negative, and begin to develop before any differentiation occurs in the cellular hierarchy, and exhibit stem cell properties. Treatment response is generally very low, and tumor residue are highly detected during the posttreatment period [27]. The claudin-low subtype of receptor-negative cancers can express luminal genes such as cell-cell adhesion genes and GATA-3 potential target genes, at tight junctions [35]. Gene expressions of many genes such as claudin 3, 4, and 7 are rather low. Claudin-low tumors can lack junction-associated proteins, such as E-Cadherin.

The claudin-low subtype is also characterized with expression of the endothelial and lymphocytic markers and mesenchymal features. Metaplastic breast cancers, which largely represent the chemoresistant subtype of basal-like group, have been reported to have a distinct molecular profile similar to the claudin-low subtype and enriched with epithelial mesenchymal transition signature genes [36]. It is interesting that expression profiles of metaplastic tumors and claudin-low tumors share common features with the breast CSCs containing CD44 + CD24/low phenotype [37].

3.4 Conclusion

Through the marathon initiated with the Human Genome Project, information regarding human genome and genomes of other various species have been accessed, number of genes have been determined, genome sizes have been identified, information about functions of these genes, and molecular identification of normal and pathological states have been performed.

Access to the genetic information in biologic systems and in a living cell, knowledge of cancer and stem cell biology, and furthermore, application of the knowledge about structure and function of biologic molecules into practice have enlightened molecular structure of cancer, which is an important health problem today, and facilitated advanced diagnosis and treatment efforts. In the past 10 years, advances in molecular oncology have moved us toward the “genomic” era. Vast improvements during the genomic era unveiled molecular and genetic questions, prognostic and predictive factors are better understood, and therapy regimens are guided according to the molecular classification. Advances in molecular oncology proceed with a dizzying speed. We believe molecular studies will continue to fully support tumor-specific therapy regimens in the coming years.

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Chapter 4
Prognostic and Predictive Factors

Senem Demirci Alanyalı

4.1 Introduction

There is an increasing recognition that breast cancer can be heterogeneous and composed of a variety of subgroups with different prognosis. Identification of favorable and unfavorable groups helps clinicians to individualize and tailor the treatment for each patient. In order to complete risk stratification, patient and tumor characteristics were being used as prognostic and predictive factors. By definition, the prognostic factor is a measurable variable that correlates with the natural history of the disease. In contrast, a predictive factor is one that is associated with response to a given therapy. Some factors, such as estrogen receptor (ER)/progesterone receptor (PR) status and human epidermal growth factor receptor-2 (Her-2)/neu gene amplification and/or overexpression, are both prognostic and predictive [1]. This chapter focuses on the widely used major prognostic and predictive factors related to patient and tumor characteristics for breast cancer-specific outcomes.

In 1999, prognostic factors had been categorized into three groups by the College of American Pathologists [2].

Category I: Proved prognostic importance and useful in clinical patient management (tumor node metastasis [TNM] staging information, micrometastasis, histologic grade, histologic type, mitotic count, and hormonal receptor status).

Category II: Extensively studied factors but their importance remains to be validated in clinical studies (Her-2/neu, proliferation markers, lymphatic and vascular channel invasion, and p53).

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Category III: All other factors not sufficiently studied (DNA ploidy analysis, microvessel density, epidermal growth factor receptor, transforming growth factor-α, bcl-2, pS2, and cathepsin D).

4.2 Prognostic Factors

4.2.1 Tumor Size

Tumor size, which is the essential part of TNM staging, was shown as a prognostic factor especially for node negative patients. Researchers from the University of Chicago reported on the natural history of 826 lymph node (LN)-negative patients with a median of 13.5 years of follow-up for survivors after mastectomy, and indicated tumor size as the strongest predictor of outcome and time to relapse on multivariate analysis. Patients with tumors smaller than 2 cm had a 20-year disease-free survival (DFS) rate of 79% and a median time to recurrence of 48 months as compared with patients with tumors larger than 2 cm, who had a survival rate of 64% ($p < 0.001$) and a median time to recurrence of 37 months ($p = 0.01$) [3]. Similarly, in Saint Gallen consensus guideline tumors greater than or equal to 2 cm were in the low-risk group, whereas tumors larger than 2 cm were in the intermediate-risk group [4].

Carter et al. analyzed survival rates of approximately 25,000 breast cancer patients from SEER (Surveillance, Epidemiology, and End Results) data and concluded that tumor size and LN status were found to act as independent but additive prognostic indicators. As tumor size increased, survival decreased regardless of LN status; and as LN involvement increased, survival status also decreased regardless of tumor size [5]. Moreover, another SEER analysis had modeled the effect of tumor size on mortality in 83,686 early-onset breast cancer patients. Gompertzian expression provided a good fit for the effect of tumor size (in millimeters) on mortality, irrespective of nodal status. Quantitatively, for tumor size between 3 and 50 mm, the increase of crude cumulative death rate (number of observed deaths divided by the number of patients at risk) increased with size from 10 to 25% for N0 and from 20 to 40% for N (+) patients [6].

The influence of tumor size does not clearly define for local recurrence as it does for survival of patients treated with breast conservation therapy (BCT). Previous studies showed no difference in breast recurrence rates among patients with T1 and T2 disease [7]. Several other factors such as adjuvant radiotherapy (RT) dose, and boost dose may diminish the effect of tumor size on local recurrence rates. However, for patients who had undergone mastectomy, tumor size larger than 3 cm was shown as a risk factor for local regional recurrence (LRR) [8–10].

4.2.2 Lymph Node Status

The presence of axillary LN metastases is still the strongest prognostic factor for DFS and overall survival (OS). Ten-year survival rates were reported with approximately 65–80% for node-negative and 25–43% for node-positive patients in the published studies [11].

TNM utilizes the number of LN metastases (N1: 1–3 [+], N2: 4–9 [+], and N3 ≥ 10 [+]) for nodal staging [12]. The number of metastatic LN has a significant impact on survival rates as follows: 5-year survival rate was 82.8% for node negative, 73% for 1–3 node positive, 45.7% for 4–12 node positive and 28.4% for more than or equal to 13 node-positive patients [13, 14].

Recently, the concept of lymph node ratio (LNR) was introduced. Atahan et al. reviewed the prognostic role of LNR (number of involved LNs divided by the number of LNs dissected) in lymph node-positive patients and mentioned that LNR can be even more important than the absolute number of involved nodes for LRR and survival [15].

Furthermore, there was an increasing role of sentinel lymph node (SLN) biopsy during the last two decades with the advances of surgical oncology. Currently, clinicians are experiencing the concept of isolated tumor cells and micrometastasis. By definition, isolated tumor cells ([p] N 0 [i +]) are defined as single tumor cells or small cell clusters not greater than 0.2 mm and micrometastasis ([p] N 1 [mi]) is LN metastases greater than 0.2 mm and/or greater than 200 cells but none greater than 2.0 mm. (p) N 0 (i) (+) accepted as (p) N 0 and has similar prognosis with (p) N 0 [12]. A recent study from The Netherlands compared the outcomes of 1,411 T1-T2 breast cancer patients with N0, N1mic, N1a and N1b disease and the authors stated that distant metastases rate, DFS, and OS were comparable with (p)N(0) and (p)N (1mi) and were significantly worse for (p)N(1a) and (p)N(≥1b) patients, and mentioned that survival was not associated with the presence of micrometastases [16]. However, the largest SLN study evaluated 2,000 patients with isolated tumor cells or micrometastases, and reported that isolated tumor cells and micrometastases are associated with increased risk of disease events of about 1.5 compared with node-negative disease they recommended considering the use of adjuvant systemic therapy in those patients [17]. Therefore, the results are conflicting and larger data accumulation is required to better understand the prognostic role of (p) N 0 (i) (+) and (p) N (1mi) for disease-specific outcomes.

4.2.3 Histopathologic Subtype

Several studies showed that tubular, mucinous, papillary, and medullary subtypes had a more favorable prognosis and metaplastic, undifferentiated, and micropapillary subtypes had worse prognosis than invasive ductal carcinoma and invasive lobular

carcinoma [18–20]. With the multicentric nature of invasive lobular carcinoma arose the concern of having higher local recurrence rates than in invasive ductal carcinoma. However, studies have compared patients with invasive ductal carcinoma and with invasive lobular carcinoma for disease-specific outcomes and demonstrated that local failure and OS rates were similar for both [21, 22].

4.2.4 Tumor Grade

Multiple grading systems have been utilized by pathologists over the years (Scarff-Bloom-Richardson, Elston and Ellis) and these grading systems evaluate the tubule formation, nuclear pleomorphism, and mitotic count. Overall grade is composed of points from these three variables and tumors are graded as grade 1, 2, or 3. Grade 1 (well-differentiated) tumors have better survival than grade 2 (moderately differentiated) and grade 3 (poorly differentiated) tumors [23]. Warwick et al. analyzed the prognostic factors by the function of time in their 20-year follow-up study and concluded that value of tumor grade, LN status, and tumor size at the time of diagnosis have a lasting influence on subsequent survival, albeit attenuated in later years [24].

4.2.5 Lymphovascular Invasion

Lymphovascular invasion (LVI) of the tumor is the presence of tumor cells in the peritumoral region and has been demonstrated as a poor prognostic factor in many studies [25, 26]. Truong et al. analyzed 763 breast cancer patients treated with postmastectomy RT, and found that LVI was present in approximately one third of patients. LVI was significantly associated with LRR (relative risk [RR] = 2.32; 95% CI; range, 1.26–4.27; $p = 0.007$), distance relapse (RR = 1.53; 95% CI; range, 1.00–2.35; $p = 0.05$), and OS (RR = 1.46; 95% CI; range, 1.04–2.07; $p = 0.03$) [27].

Lee et al. analyzed 2,760 node-negative breast cancer patients between 1974 and 2000 and divided patients into two groups: 990 into the no adjuvant therapy series; and 1,765 into the selective adjuvant therapy series. Overall, survival was associated on multivariate analysis with LVI in both patient series [28]. Similarly, investigators from India showed the 5-year local control rate in absence of LVI was 93.5% in contrast to 76.5% ($p = 0.0098$) when LVI was present in node-negative premenopausal women not receiving adjuvant systemic therapy. The OS rate was 91% in the absence of LVI in contrast to 74% in presence of LVI ($p = 0.02$). On multivariate analysis, LVI was the independent prognostic factor affecting the DFS ($p = 0.001$; 95 % CI; range, 1.46–4.96) [29].

4.2.6 Extensive Intraductal Component

Extensive intraductal carcinoma (EIC) is defined when greater than or equal to 25% of the tumor is intraductal carcinoma and intraductal carcinoma is seen outside (adjacent to) of the infiltrating tumor border. Researchers had reported 5-year breast recurrence rate as less than 10% for EIC (−) patients, which reaches 30% in EIC (+) patients and EIC was found as a poor prognostic factor for recurrence [30, 31].

The role of EIC as a prognostic factor for local recurrence is closely related to the margin status and its presence becomes important for patients with a positive margin. The 5-year incidence rate of recurrence for patients with greater than a focally positive margin without EIC was 19%, whereas its was 42% for EIC-positive patients [32].

4.2.7 Race

Although breast cancers in African American women are clinically and biologically more aggressive, whether these more aggressive clinicopathologic features translate into higher LRR after BCT remains an incompletely answered question. Differences in disease presentation, treatment outcome, and toxicities in African American women with early-stage breast cancer treated with BCT were analyzed by Vicini et al. [33]. The authors stated that African American women present with larger and more aggressive breast tumors and, as a result, more frequently received adjuvant chemotherapy and LN irradiation. They observed no statistically significant difference in LRR in African American patients compared with their Caucasian counterparts [33]. Newman et al. reviewed studies reporting treatment choices and response rates in African American women with breast carcinoma and they concluded that African American women with breast carcinoma potentially may respond as well to appropriate local and systemic therapy as white women with breast carcinoma [34]. Regarding survival, Simon et al. reviewed 10,502 women and stated that white women had better survival rates than African American women during the first 4 years of diagnosis [35]. Similar results were also found by Pierce et al. showing higher rates of the regional-only failure in African American women as compared with white women (9% vs. 1% [$p = 0.002$] respectively), worse 5-year OS rate (82% vs. 91 % [$p = 0.01$]; respectively), and DFS rates (64% vs. 83% respectively [$p = 0.0002$]) [36].

4.2.8 Age

Young age with various cutoff levels (e.g., 30, 35, 40, and 50 years) was demonstrated as one of the most important prognostic factors by many investigators for local recurrence in patients treated with BCT [37, 38]. Fowble et al. analyzed

980 women with stages I to II breast cancer and reported that women younger than 35 years had a 53% 8-year relapse-free survival rate, compared with 67% for women 36–50 years, and 74% for women older than 50 years [38]. Mirza et al. analyzed 1,083 stages I to II breast cancer patients treated with BCT and confirmed that patients younger than 50 years had almost four times higher risk of LRR [39]. Nevertheless, current aggressive adjuvant treatment seems to diminish the poor prognostic value of young age [40].

The data regarding the influence of age on survival are conflicting. Younger patients generally presented with larger disease, ER (−), PR (−), higher grade tumors, and positive lymph nodes [41, 42]. SEER analysis that included 200,000 breast cancer patients revealed that those under the age of 40 years were 39% more likely to die when compared with those 40 years or older (hazard ratio = 1.39; 95 % CI; range, 1.34–1.45) [43].

Arriagada et al. reported on the prognostic factors of 2,410 breast cancer patients over a follow-up period of longer than 25 years, and studied the prognostic factors by the function of time after diagnosis. The authors indicated that four factors were related strongly to the risk of death in the first 5 years: tumor size, histologic grade, the number of involved axillary lymph nodes, and age at diagnosis. After 10–15 years of follow-up, only age at diagnosis was related to the risk of death [44].

4.2.9 Surgical Margin

The definition of negative surgical margin was inconsistent in the literature. The National Surgical Adjuvant Breast and Bowel Project (NSABP) defines negative margin as no tumor cells seen on the inked margin regardless of the distance, other researchers define negative margin as 1 or 2 mm beyond the invasive cancer [32, 45, 46].

The impact of surgical margin on local recurrence for patients treated with BCT was evaluated by researchers and data from many institutions suggest that recurrence rates are lower when margins are negative rather than positive. In the literature, the LRR ranged between 2–12% for negative margin and 2–33% for positive margin [11].

Nonetheless, several other studies failed to show margin status as an independent risk factor for recurrence, probably as a result of the complex interaction between local recurrence and RT dose, boost dose, administration of chemotherapy, hormonal therapy, patient age, the presence of EIC, and follow-up duration [46–48].

4.2.10 Proliferative Indices

The proliferation rate of tumor cells can be evaluated by the fraction of cells in S-phase, thymidine labeling index (TLI), mitotic index (MI), proliferating cell nuclear antigen (PCNA), and Ki-67. A recent comprehensive systematic review

Table 4.1 Surrogate definitions of intrinsic subtypes of breast cancer (modified from the Saint Gallen 2011 consensus; with permission)

Subtype	ER PR	Her 2	Ki 67
Luminal A	ER and/or PR positive	Negative	Low (<14%)
Luminal B			
Luminal B (Her-2 [−])	ER and/or PR positive	Negative	High
Luminal B (Her-2 [+])	ER and/or PR positive	Positive	Any
Her-2	ER and PR absent	Positive	
Basal-like (triple negative)	ER and PR absent	Negative	

and meta-analysis was published which included 85 studies in 32,825 early-onset breast cancer patients and the authors concluded that Ki-67, MI, PCNA, and LI are associated with worse survival outcomes [49]. In the Saint Gallen 2011 Consensus, Ki-67 was accepted as a marker to distinguish luminal A and luminal B (Her-2 [−]) and this grouping helps clinicians to decide the form of systemic therapy [50].

4.2.11 Molecular Prognostic Factors

During their evolution, breast cancer cells differentiate into five subtypes: normal, luminal A, luminal B, Her-2-enriched, and basal (Table 4.1) [50]. ER, PR, and Her-2 status were being used as surrogate markers to identify the molecular subtypes although genetic analysis is more precise. Researchers classified breast cancer according to surrogate markers and validated the prognostic impact of subtypes on survival with a large number of patients [51, 52].

Subtype profiling helps to identify the group of patients with an increased risk of distant metastases and who may need aggressive systemic therapy, as well as the favorable group of patients who can be treated successfully with endocrine manipulation only. However, its influence on locoregional control is not widely studied. Nguyen et al. studied 793 patients with invasive breast cancer and who received BCT; they approximated molecular subtypes by surrogate markers. With a median follow-up of 70 months, the overall 5-year cumulative incidence of local recurrence was 1.8% for luminal A, 1.5% for luminal B, 8.4% for Her-2, and 7.1% for basal subtypes. On multivariate analysis with luminal A as baseline, Her-2 and basal subtypes were associated with increased local recurrence, where luminal B and basal subtypes were associated with increased distant metastases [53].

4.2.12 BRCA1-2 Mutations

Breast cancer patients with *BRCA1-2* mutations have an increased risk of late recurrences and contralateral breast cancer as compared with their sporadic

counterparts [54, 55]. Moreover, breast cancer patients with *BRCA1-2* mutations diagnosed at younger ages had mostly triple (−) tumors and poor prognosis. Pierce et al. conducted a large study including 160 breast cancer patients with *BRCA1-2* mutations and compared them with 445 sporadic breast cancer patients. They demonstrated no significant difference in breast recurrence between the two groups, however, a subset analysis showed higher rates of local relapse in those carriers who had no prophylactic oophorectomy [56].

4.3 Predictive Factors

4.3.1 Estrogen and Progesterone Hormonal Receptors

ER and PR positivity (>10%) have a prognostic and predictive value in breast cancer. Patients with the expression of both ER and PR benefit from hormonal therapy (tamoxifen or aromatase inhibitor) and have good prognosis. Among the ER (+) tumors, 50–60% respond to hormonal therapy; whereas in ER (−) tumors, only 10% respond to hormonal therapy. Use of 5-year tamoxifen in the ER (+) group decreases annual odds of recurrence by 39% and annual odds of death by 31% [57].

Prospective studies assessing early stage postmenopausal breast cancer patients treated with initial tamoxifen and sequential anastrozole or exemestane showed OS benefit compared with tamoxifen only [58, 59]. The MA-17 trial also demonstrated a survival advantage with extended letrozole in node-positive breast cancer patients [60].

4.3.2 Her-2

Approximately 20% of breast cancer patients had Her-2 overexpression (3[+] by immunohistochemistry/an amplified Her-2 gene copy number by fluorescence in situ hybridization). Amplification of Her-2 is correlated with higher tumor grade, negative ER, PR status, and is also associated with worse prognosis and nonetheless, can predict the response to trastuzumab. The updated results of the HERA trial showed DFS advantage in Her-2-positive patients treated with trastuzumab for 1 year [61]. Her-2 expression is also a predictive factor for response to anthracyclines and taxanes as compared with cyclophosphamide, methotrexate, and fluorouracil (CMF) [62].

Table 4.2 Saint Gallen risk grouping (2007)

Risk category	
Low risk	Node negative AND all of the following features pT ≤2 cm, AND Grade 1, AND Absence of extensive peritumoral vascular invasion, AND ER and/or PR expressed, AND Her-2/neu gene neither overexpressed nor amplified, AND Age ≥35 years
Intermediate risk	Node negative AND at least one of the following features pT >2 cm, OR Grade 2–3, OR Presence of extensive peritumoral vascular invasion, OR ER and/or PR absent, OR Her-2/neu gene overexpressed or amplified, OR Age <35 years Node positive (1–3 involved nodes) AND ER and/or PR expressed, AND Her-2/neu gene neither overexpressed nor amplified
High Risk	Node positive (1–3 involved nodes) AND ER and/or PR absent, OR Her-2/neu gene overexpressed or amplified Node positive (four or more involved nodes)

4.4 Estimation of Risk of Recurrence, Death, and Benefit From Systemic Treatment

4.4.1 Genetic Profiling

With the advances in DNA microarray technologies, gene expression signatures of tumors are now available for clinicians to determine prognosis and to predict the benefit of the systemic treatment. Paraffin-embedded or fresh tumor tissues are required for gene profiling. The most commonly used tests are Oncotype DX® (Genomic Health, Inc.) and MammaPrint® (Agendia BV). Oncotype DX assesses 21 genes to predict the risk of recurrence in ER (+) and N (−) or p N1 mic, ER/PR (+), Her-2 (−) tumors that are smaller than 0.5 cm [63]. These tests are mainly aimed at identifying patients who will benefit from hormonal therapy or chemotherapy.

4.5 Risk Grouping

In 1998, the Saint Gallen consensus defined three risk groups (minimal/low, intermediate, and high) for LN (−) patients based on ER/PR status, tumor grade, and age and T size [64]. In 2007, they added Her-2 and nodal status to the risk grouping system and defined low-, intermediate-, and high-risk patients (Table 4.2) [4]. Finally, in

2011, they mentioned the importance of intrinsic subtypes and provided their recommendation for the treatment modality for these specific subtypes (Table 4.2) [50]. Endocrine therapy alone was recommended for luminal A; endocrine ± cytotoxic therapy for luminal B (Her-2 [−]); cytotoxics + anti-Her-2 + endocrine therapy for luminal B (Her-2 [+]); cytotoxics + anti-Her-2 for Her-2-positive and cytotoxics for triple-negative patients. The panel also defined histologic subtypes as endocrine responsive (cribriform, tubular, and mucinous) and as endocrine nonresponsive (apocrine, medullary, adenoid cystic carcinomas, and metaplastic) for considering endocrine therapy or cytotoxics.

Adjuvant online is a Web-based tool for adjuvant treatment decision making in breast cancer patients [65]. Age, comorbidity, ER status, tumor grade, tumor size, and number of positive nodes are taken into account to predict the benefit of hormonal therapy, chemotherapy or both for mortality and relapse rates.

4.6 Conclusion

As mentioned throughout the text, breast cancer is a heterogeneous disease and treatment modalities significantly vary among patients. Because there is a complex interaction between the patient, tumor, and treatment-related prognostic and predictive factors, clinicians need to consider these as a whole and follow the consensus statements and guidelines, and consult for genetic profiling in need for the decision of individualized treatment for the patient.

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Chapter 5
Mechanisms of Resistance to Radiation

Serra Kamer and Beste Melek Atasoy

5.1 Introduction

Radiotherapy is a very effective treatment for achieving local tumor control in breast cancer. However, intrinsic tumor cell radioresistance is a significant clinical problem that limits the results of the treatment. Chemotherapeutics that could specifically sensitize tumors to radiation would greatly increase the ability to deliver higher doses while limiting radiation damage to surrounding normal tissue, but efforts to develop clinically useful tumor radiosensitizers have had limited success.

Tumor recurrence resulting radioresistance is still one of the major problems in radiation treatment for breast cancer. Unfortunately, there are no tests routinely applicable to identify the level of radioresistance, and its mechanism requires further investigation. Yet, validated markers are necessary not only to improve the prediction of tumor response to radiotherapy, but also to identify the tumor resistance in order for patients to be spared radiotherapy and its associated toxicity. In this chapter we summarize the evidence for possible molecular targets currently being improved by pharmaceutical strategies with a combination of radiotherapy in order to overcome tumor radioresistance in breast cancer.

Different factors have been identified as influencing radiation resistance of cells (Fig. 5.1). These factors and pathways have been studied and can be broadly divided into:

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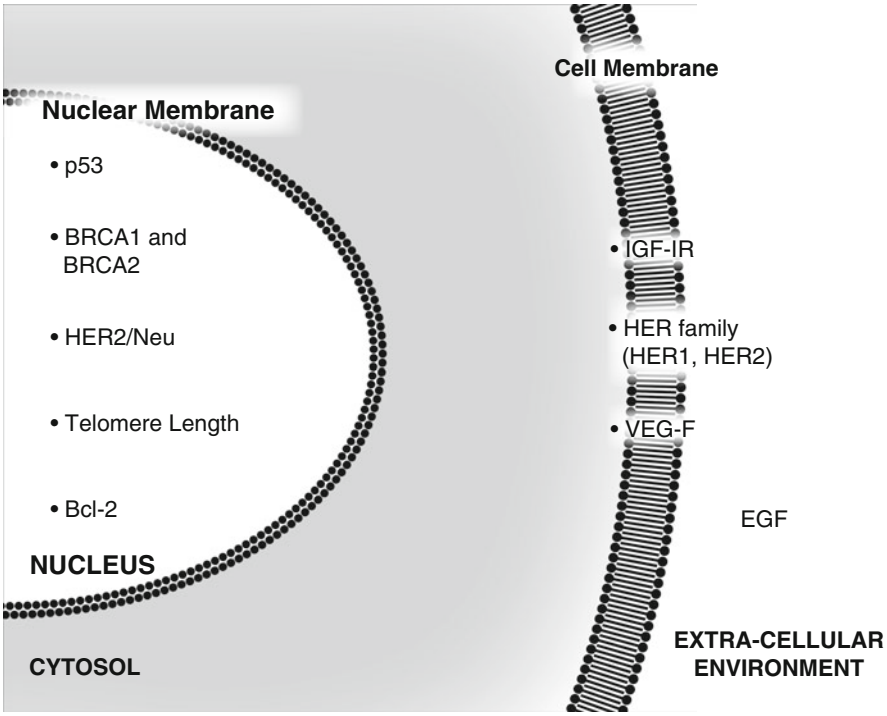

Fig. 5.1 Factors influencing radioresistance of cells

1. Cellular response and DNA repair capacity
2. Growth factors
3. Gene related factors
4. Breast cancer stem cells

5.2 Cellular Response and DNA Repair

When high energy x-rays interact with molecules of an organism they cause ionization and a release of electrons which cause secondary damage from oxygen-related molecules to DNA and other tissues [1]. Ionizing radiation is thought to kill tumor cells by inducing lesions in DNA, that unless faithfully and rapidly repaired, interfere with subsequent mitotic divisions causing mitotic catastrophe and permanent cessation of cell division. The result of the damage can be either single-strand breaks (SSB) or double-strand breaks (DSBs) within DNA [2]. It is known that double-strand DNA breaks are difficult to repair, or nonrepairable DNA lesions are recognized by DNA damage cell cycle checkpoints that lead to repair pathways [2]. DSBs, on the other hand, do contribute to the lethal effects of ionizing radiation

because they are repaired rather slowly and can lead to chromosome aberrations when incorrectly rejoined DNA repair takes place as part of one of five main biochemical pathways [3, 4]. These pathways include: nucleotide excision repair, mismatch repair (MMR), base excision repair, nonhomologous end joining (NHEJ), and homologous recombination. Some of these pathways are thought to be important for the repair of radiation damage and some are not. For example, the MMR pathway is not thought to be an important pathway for radiation-induced lesions, while the NHEJ pathway is critical to radiation resistance. Although there are multiple proteins involved in NHEJ, the DNA dependent protein kinase catalytic subunit, DNA-PKcs, is a key enzyme. In response to DSBs, DNA-PKcs is activated by phosphorylation and together with its regulatory subunits, KU70 and KU80, stabilizes the break. This complex, together with additional proteins, namely Mre11, Rad50, Nbs1, XRCC4, and DNA ligase IV completes rejoining of the broken ends of DNA. Ataxia telangiectasia mutated is another important repair protein that participates in governing of the cell cycle checkpoints in response to DNA damage [2, 5, 6]. Because DNA repair pathways remove radiation-induced DNA lesions and protect cells from lethality, the pathways represent potential therapeutic targets to radiosensitize tumors [5–7].

Together, the DNA repair pathways protect against both cell killing and mutagenesis. Thus, individuals with heritable DNA repair defects often display hypersensitivity to radiation toxicity, increased risk of cancer, or both. The evidence that DNA repair can protect against radiation-induced cell killing is very strong, and comes from the biochemical and genetic level from a wide variety of cellular, animal, and human studies. This overwhelming evidence of the radioprotective effect of cellular DNA repair suggests that DNA repair proteins may be excellent druggable targets for radiosensitizing tumor cells [6, 7].

In addition to DNA repair, reoxygenation, reassortment, and repopulation are also thought to contribute to the effectiveness fractionated radiotherapy [1].

5.3 Growth Factor Receptors and Signaling Pathways in Radiation Resistance

There are growth factor receptors such as epidermal growth factor receptors (EGFR), insulin-like growth factor receptor (IGFR), and vascular endothelial growth factor (VEGF) receptor located in cell membrane. As in other human malignancies, growth factor-altered radiosensitivity may help to understand and improve the radiation response mechanisms in breast cancer. The activation of these receptors triggers intracellular signaling pathways. The cascades are ending in nuclei with their effect on cell progression, promoting the proliferation and inhibition of apoptosis. Therefore, the pathways may be a potential target for enhancing the response to radiotherapy in patients with breast cancer. Liang et al. showed that phosphatidylinositol 3-kinase (PI-3K)/Akt activity contributed to the resistance of human breast cancer cells to ionizing radiation [8]. The authors found that the inhibition of the PI-3K/Akt pathway sensitized human breast cancer cells to radiotherapy.

EGFR: Epidermal growth factor (also called Her-) family has been widely investigated in human malignancies. The correlation of EGFR over expression and radiation resistance in breast cancer has been reported previously [8, 9]. Particularly, Her-2 inhibitors can modify the cellular responses to ionizing radiation inducing apoptosis, cell cycle arrest, and modifying DNA repair, and can represent one of the most appropriate targets for breast cancer therapy. Zhou et al. tested a dual EGFR/Her-2 inhibitor, GW572016, on the proliferation and radiation response of either EGFR or Her-2 endogenously overexpressed human breast cancer cell lines [10]. They showed the radiosensitizing effect only after EGFR inhibition but were unable to show Her-2 inhibition due to lack of inhibition of intracellular signaling pathway of PI-3K/Akt. In another study, Sambade et al. worked on a dual EGFR/Her-2 kinase inhibitor, lapatinib, for its radiosensitizing effect on EGFR or Her-2 expressed breast cancer xenografts. They administered lapatinib combining with fractionated radiotherapy and observed growth impairment with an enhancement ratio average of 2.75 [11]. Moreover, durable tumor control in the Her-2 expressed cells was more effective with the combination treatment than either lapatinib or radiotherapy alone. The possible mechanism is the inhibition of downstream signaling to PI-3K/Akt signaling pathway.

IGFR: Turner et al. reported a correlation between high levels of IGFR and increased tumor recurrence following lumpectomy and radiation therapy [12]. Moreover, in estrogen receptor positive breast tumors, IGFR1 levels are found as elevated and this has been linked with increased radioresistance and tumor recurrence [12, 13]. Iwamoto et al. worked on mannose 6-phosphate (M6P)/IGFR2 that is a negative regulator of cell growth [14]. They reported a dose-dependent rapid expression of M6P/IGFR2 following ionizing radiation exposure in estrogen receptor positive MCF7 human breast cancer cells. Authors concluded that posttranscriptional dysregulation of M6P/IGFR2 is a contributing mechanism in breast cancer development and breast cancer response to therapy.

VEGF: VEGF is an important mediator of angiogenesis and it is up-regulated under hypoxic conditions [15]. Linderholm et al. analyzed VEGF content in 302 node-negative breast cancer patients treated with only locoregional radiotherapy and they reported VEGF status as a significant predictor of relapse-free and overall survival in early breast cancer patients who had early stage or estrogen receptor positive tumors [16]. Labidi et al. reported VEGFR inhibitor (Bevacizumab) administration in brain metastases in combination with paclitaxel in their four cases [17]. Patients received bevacizumab 10 mg/kg on days 1 and 15. They observed significant antitumor activity with one complete response and three partial responses in the brain metastases.

5.4 Gene-Related Radiation Resistance

BRCA1 and BRCA2: Inherited mutations in *BRCA1* or *BRCA2* genes are responsible for less than 5% of breast cancers. BRCA mutant cells cannot repair radiation-induced DNA damages, particularly DSBs, properly [18]. Hence, chromosomal

abnormalities occur in the incompletely repaired DNA and lead to cell death by triggering the apoptosis in tumors. However, Baeyens et al. suggested that mutations in *BRCA1* or *BRCA2* genes do not play a main role in chromosomal radiosensitivity even though they are both involved in DNA repair/signaling processes [19]. Similarly, Nieuwenhuis et al. experimented on fibroblasts and lymphocytes taken from heterozygotic BRCA individuals with different mutations [20]. There was no major inability to repair radiation-induced DNA breaks observed in cells from carriers of mutations in one allele of the *BRCA1* or *BRCA2* genes. Hence, despite *BRCA1* or *BRCA2* mutation, carriers have an increased sensitivity to ionizing radiation and may not have an excess risk for normal tissue reactions after radiotherapy. Hence, in one allele BRCA1/BRCA2-mutated patients, there may not an increased sensitivity to ionizing radiation and may not have an excess risk for normal tissue reactions after radiotherapy.

On the other hand, Coleman argued that the chromosomal radiosensitivity led by *BRCA1* and BRCA2 mutations might increase susceptibility to carcinogenic effects in normal cells [21]. In low doses i.e., for diagnostic purposes *BRCA1* and *BRCA2* mutation carriers might have an increased risk of breast cancer. Ernestos et al. reported that BRCA1 and BRCA2 mutation carriers had a significantly higher number of mean chromatid breaks per cell and a higher maximum number of breaks as compared with their matched controls [22]. They found that healthy carriers and carriers with a cancer history were more radiosensitive than the control group.

p53: *p53* mutations are the most common genetic alterations in human primary breast carcinoma and are associated with worse prognosis and with chemotherapy resistance and radioresistance. The inability to trigger *p53* dependent apoptosis may be a possible way to explain the mechanism of *p53* mutations in terms of radioresistance. Marchetti et al. analyzed *p53* gene status as a prognostic value in 13 patients with high-risk breast cancer with 10 or more involved axillary nodes. They found an increase rate of relapse among the *p53* mutant group and concluded that *p53* mutations may help identify the subsets of breast cancer patients among risk groups and prognosis [23].

Mayer et al. studied lymphocytes both from breast cancer patients with strong acute radiation toxicity and from normal reacting patients [24]. They identified 153 genes that were significantly altered by a fold change of more than 50% by irradiation. They also identified 67 radiation-induced genes involved in p53 signaling, cell cycle control, and apoptosis capable of differentiating between severe radiosensitive and normal reacting patients.

5.5 Telomeres

The stability of chromosomes during the cell cycle is maintained by telomeres in the eukaryotic chromosomes. Altered telomere maintenance is detected in some diseases (i.e., ataxia telangiectasia), Nijmegen breakage syndrome, and Fanconi's anemia. Patients suffering from these diseases are clinically more sensitive to radiation. Therefore, the possibility of telomere maintenance as a potential genetic

marker of radiosensitivity in breast cancer is questioned. Slijepcevic et al. argued that the lymphocyte telomere length may be a predictor for breast cancer susceptibility and severity of acute reactions to radiotherapy [25]. Zhong et al. reported a significant negative correlation of telomere length and radiosensitivity in breast cancer cell lines [26]. However, Iwasaki et al. did not find any correlation between lymphocyte telomere length and acute skin reactions following radiotherapy in in vitro samples of breast cancer patients [27]. Barwell et al. investigated the mean terminal restriction fragment (TRF) lengths in white blood cells for correlation with chromosome radiosensitivity and apoptotic response as a marker for breast cancer susceptibility [28]. The authors found a positive correlation between age-adjusted apoptotic responses and mean TRF in newly diagnosed untreated breast cancer patients. However, they did not detect a significant difference in TRF lengths between breast cancer patients and unaffected controls.

5.6 Breast Cancer Stem Cells and Radioresistance

The definition of cancer stem cell resistance is that recurrence after radiotherapy is associated with the survival of these cells. This concept is a hot topic in the field of cancer research with several studies reporting the importance of stem cells after conventional radiotherapy [29, 30].

The $CD44^{+}/CD24^{-/low}$ stem cells are relatively resistant to ionizing radiation [31–33]. In vivo studies show that side populations, which initiated tumors, are more resistant to ionizing radiation than the nonside population [34]. In addition to these findings, some studies reported increase of cancer stem cells during the course of fractionated radiation [31]. Currently, with the results of in vivo studies, it is believed that breast cancer stem cells are the reason for some breast cancer recurrences after radiotherapy [35]. The detailed pathways related to the radioresistance of cancer stem cells have not been fully elucidated [35]. Different theories have been trying to explain of the mechanism related with resistance to therapies (Fig. 5.2) including:

1) repair of DSB in DNA
2) G2 arrest in cell cycle
3) down regulation of senence pathway
4) decrease of cell death

Most of the preclinical data show that cancer stem cells are more radioresistant compared with tumor cells [31–33]. Ongoing studies are focusing on this hot topic. In vitro studies are trying to explain mechanistic insights to radioresistance of cancer stem cells. DSBs and reactive oxygen species levels are lower in $CD44^{-}/CD24^{-}$ mammospheres compared with adherent and monolayer cultures following ionizing radiation [31]. In vitro experiments are reported [36] a reduced level of reactive oxygen species and a reduced number of DSBs and more active single DNA strand break repair pathways in breast cancer stem cells. Investigators

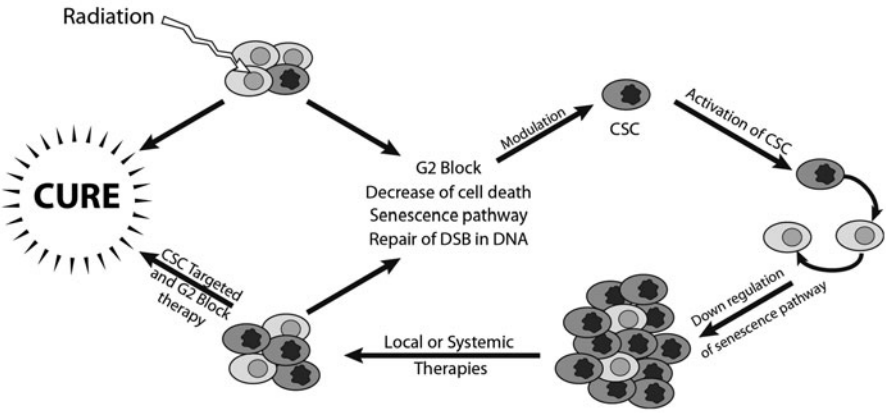

Fig. 5.2 Theroies related with radioresistance of breast cancer stem cells

conclude that down regulation of senence pathway has the major role in resistance of breast cancer stem cells [36]. Furthermore, breast cancer stem cells were resistant to radiation-induced apoptosis and were arrested in the G2 phase of the cell cycle [37]. Cancer stem cell use may be extended to the G2 phase as a mechanism for more DNA damage.

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Chapter 6
Interaction of Chemotherapy, Radiotherapy, and Timing

Bilge Gursel and Ayfer Haydaroglu

6.1 Introduction

New methods that have been developed to regulate and modify the biological response of tumors and of normal tissues to radiation to achieve maximum benefit with minimum harm to the adjacent normal tissues should be considered be among the most significant developments in radiotherapy (RT) in recent years. These methods include different fractionation schemes, the application of chemical and biological agents, and effective therapies targeted toward molecular pathway-signal transduction mechanisms. Among these treatment strategies, the most widely used method in clinical practice is the combination of chemotherapy (CT) with RT. Since the development of CT and RT, many studies have been published regarding adjuvant treatment of breast cancer, which remains a controversial issue. However, despite advances and innovations in breast cancer treatment, there is still no consensus on the optimal treatment approach, mainly because breast cancer is a heterogeneous group of diseases with a wide spectrum of biological behaviors. In this section, the molecular biological mechanisms of the interaction between RT and CT in breast cancer, as well as the optimal timing of RT and CT, will be discussed in light of relevant randomized trials.

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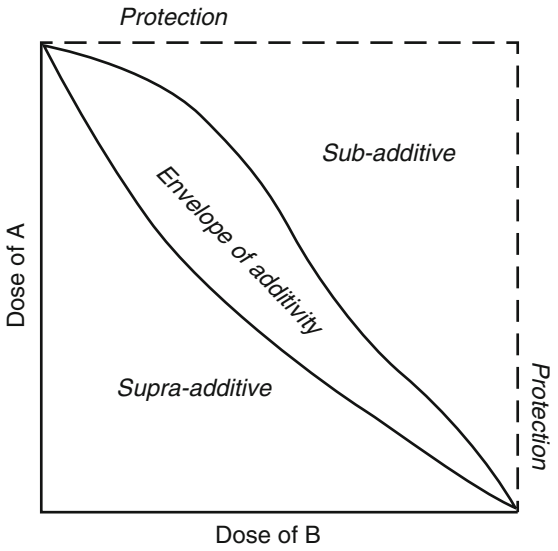

Fig. 1 An isobologram for two agents which does response curves are nonlinear. In the middle there is the envelope of additivity, in the left supra-additive, and in the right sub-addititve regoins. (Modified from ref 1 with permission. Copyright 1979 by Elsevier Science Inc.)

6.2 Biological Basis of the Interaction Between Treatment Methods in Breast Cancer

When using RT and CT together, it is very important to consider the interactions between the two modalities and to what extent their effects and side effects can increase. For this purpose, some basic concepts will be discussed briefly. In light of the information obtained from experimental studies, the effects of the combination of the two treatment modalities on cell death have been described using the concepts of "additivity," "supra-additivity" (synergism), and "subadditivity" [1]. To put it simply, if the effect of RT is given a value of three and the effect of CT is given a value of two, then an additive effect would be equal to five, whereas a synergistic effect would be equal to six, and a subadditive effect would be equal to four. However, cell death induced with chemotherapeutic agents and RT is dose dependent and nonlinear, so the effects of the combination can be defined using an isobologram curve. With an isobologram curve, the analysis is performed according to the localization of the effect, whether at the envelope of additivity or on its left side (supra-additive) or right side (subadditive) (Fig. 6.1).

6.3 Interaction Mechanisms of the Two Modalities

6.3.1 Spatial Cooperation

The application of a combination of RT and CT is used in the treatment of illnesses in different anatomic regions. For example, in breast cancer, surgery and postoperative RT target local and regional control of the disease, while CT controls systemic disease [2].

6.3.2 Independent Cell Death and Shared Toxicity

CT and RT are often used sequentially but not concomitantly. To distribute potential toxicity across the two models, the sum of the cell death rates of each of these models is preferably used. Lower rates of toxicity are observed because of the use of two treatment modalities, compared with the higher rates of using either one of the two models alone [1].

6.3.3 Cellular and Molecular Interactions

The effects and side effects of concurrent application of CT and RT are generally more significant compared with the effects of sequential application precisely because of this mechanism of interaction [1].

6.3.4 Increased Level of Chromosomal/DNA Damage and Repair

DNA is the target of both CT and RT. CT increases the number of double-strand breaks in DNA caused by RT and prevents the repair of these breaks. Agents that affect the metabolism of nucleosides and nucleotides can inhibit the repair of radiation-induced DNA damage, and are recognized as the most potent radiosensitizing agents, including fluoropyrimidines, thymidine analogs, gemcitabine, and hydroxyurea [3].

6.3.5 Cell Synchronization and Selective Effect

RT is lethal mostly in the G2/M phase. Taxanes arrest cells in the G2/M phase [4]. The agents 5-fluorouracil, methotrexate, and doxorubicin are selectively effective in the S phase and kill cells in the RT-resistant phase [3].

6.3.6 Increased Apoptosis

Both RT and CT can lead cells to apoptosis. In a study by Milas et al., when gemcitabine was applied together with RT, additive, but not synergistic, effects on apoptosis were observed [5].

6.3.7 Reoxygenation

In various studies, hypoxic cells were shown to be 2.5–3 times more resistant to radiation than normal cells [6]. CT agents can shrink tumors and thereby facilitate the oxygenation of non-oxygenated tissues. Paclitaxel, administered a few hours before RT, was shown to result in more oxygenated and more radiosensitive tissues [7].

6.3.8 Inhibition of Cell Proliferation

Aiming to inhibit repopulation, which is induced in the period between two RT fractions, might be an example of this interaction [3].

6.4 Clinical Outcomes of RT and CT Applications in Breast Cancer

6.4.1 The First Combined Chemotherapy Regimens and Radiotherapy

CMF (cyclophosphamide, methotrexate, and fluorouracil), which was among the first-used combined CT regimens, did not overlap with RT and had a fairly well-tolerated adverse effect profile; therefore, it was used in concurrent application trials. Bellon et al. applied CMF therapy concurrently with reduced-dose RT and reported excellent tumor control and low levels of late toxicity at a median of 94 months of follow-up [8]. In a randomized, phase III study by Arcangeli et al., concurrent chemoradiotherapy and sequential application of CT and RT (RT after CMF) was compared in cases that had undergone breast-conserving surgery. Five-year disease-free survival, metastasis-free survival, local recurrence-free survival, and overall survival rates of the 206 patients did not show significant differences between the two groups [9]. Moreover, no differences were detected in terms of toxicity, and eventually, concurrent CMF chemoradiotherapy was reported to be safe. Additionally, it was also reported that in patients with negative surgical margins, up to 7 months of postponement of RT is safe. In the ARCOSEIN trial, concurrent and

sequential chemoradiotherapy protocols were compared in early breast cancer [10]. As the combined CT protocol, mitoxantrone, fluorouracil, and cyclophosphamide were used, and 5-year disease-free survival, local regional recurrence-free survival, metastasis-free survival, and overall survival rates were compared, but no differences were detected among the groups. However, in the subgroup analysis of the node-positive group, 5-year local and regional recurrence-free survival was found to be significantly better in the concurrent chemoradiotherapy group (97% vs. 91%, $p = 0.02$). In that study, with regard to acute adverse effects, esophagitis (115 patients vs. 89 patients, $p = 0.04$) and anemia (111 patients vs. 81 patients, $p = 0.02$) were observed more often in the concurrent chemoradiotherapy group. Regarding late-term adverse effects, subcutaneous fibrosis, telangiectasia, skin pigmentation changes, and breast atrophy rates were again found to be higher in the concurrent arm of the study, and the difference was considered statistically significant [11]. A limitation of this research is that mitoxantrone has not been used in adjuvant treatment of breast cancer since 2006. In Trial VI of the International Breast Cancer Study Group, node-positive breast cancer patients who had undergone breast-conserving surgery were given RT following three or six cycles of a CMF regimen, and local control was not affected [12].

6.4.2 Anthracycline-Based Regimens and Radiotherapy

In a study conducted by Bull et al. in 1978, CMF and cyclophosphamide, doxorubicin, and fluorouracil (CAF) regimens were compared, and response to therapy with CMF was observed in 62% of cases, while response to CAF occurred in 82% of patients. In contrast, hematologic and gastrointestinal toxicity rates were reported as higher in the CAF regimen, although they were within acceptable ranges [13]. Following this study, which attracted great interest for doxorubicin, new studies were further designed to answer questions about sequential and concurrent use of doxorubicin and RT. In addition to the efficiency advantage, the adverse effect profile of four cycles of a combined regimen of doxorubicin and cyclophosphamide (AC) was found to be more effective, except that this regimen was associated with the development of amenorrhea. Alopecia was detected in 40% of patients treated with the CMF regimen, while the rate was almost 100% with doxorubicin [14]. The incidences of nausea and vomiting were higher than with CMF [15]. In left breast cancer cases receiving doxorubicin 450 mg/m^2, Shapiro et al. reported the incidence of cardiac events in those cases irradiated with deep tangential or hockey-stick methods as 3.6%, compared with 0.9% in nonradiated cases [16]. Fiets et al. compared the tolerability of RT applied concurrently with AC and with CMF therapy models, and they reported a higher incidence of grade 2 or worse skin reactions (70% vs. 47%, $p = 0.05$) and esophagitis (36% vs. 18%, $p = 0.06$) in the AC arm, compared with the CMF arm [17]. Therefore, RT and anthracycline are preferably applied as sequential regimens. Whether RT or CT should be applied first in this sequence was investigated in the "upfront-outback"

study by the Joint Center for Radiation Therapy (JCRT). A total of 244 early breast cancer cases that had undergone breast-conserving surgery were randomized to receive 12 cycles of cyclophosphamide, doxorubicin, methotrexate, fluorouracil, and prednisone treatments, either before or after RT. Recht et al. reported at a median of 58 months, and Bellon et al. reported 135-month follow-up results [18, 19]. In the early results, distant metastasis at 5 years was detected in 36% of the therapy arm started with RT, while the rate was 25% in the arm started with CT ($p = 0.05$); therefore, starting with CT in patients with systemic metastasis risks was recommended [18]. In the late-term results of the same trial, the two treatment arms did not display any statistically significant differences with regard to survival and mortality rates [19]. Furthermore, neutropenic fever (17% vs. 7%) and infectious pneumonia (5% vs. 1%), which require hospitalization, were observed more in the treatment arm started with RT [18]. In a retrospective study, RT application after the third of a total of six cycles of a CT (CMF or FAC) regimen was investigated, and worse results with regard to disease-free survival ($p = 0.001$), systemic disease-free survival ($p = 0.003$), and cancer-specific survival ($p = 0.01$) were obtained with this sandwich regimen compared with sequential applications with either RT or CT administered first [20]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 study compared AC and CMF regimens for postmastectomy patients, and no significant differences were found in terms of local control between the groups. AC therapy lasted an average of 63 days, while CMF therapy lasted for 154 days [21]. In a review of three studies on chemoradiotherapy, it was concluded that if RT could be applied within 7 months after surgery, then CT before RT could be safely administered, and local recurrence and overall survival rates did not change [22].

6.4.3 Taxane-Based Regimens and Radiotherapy

The taxanes are a more recently developed group of chemotherapeutic agents, which include paclitaxel and docetaxel, that trigger cell death in the G2-M phase. This effect is interesting in terms of its interaction with RT, while the lethal effect of ionizing radiation is higher in this phase [4]. Cells with p53 mutations were found to be more sensitive to the cytotoxic effects of paclitaxel [23–25]. The first study of the use of adjuvant taxane in breast cancer was conducted as part of the Cancer and Acute Leukemia Group (CALGB) 9344 study. In cases of node-positive breast cancer, 4 AC, followed by a paclitaxel regimen, was found to decrease recurrence rates by 22%, while mortality rates decreased by 26% [26]. In a meta-analysis of 13 chemoradiotherapy trials to investigate the outcomes with the addition of taxane to anthracycline-based CT, increased disease-free survival (5-year risk reduction of 5%) and overall survival (5-year risk reduction of 3%) rates were reported [27]. In concurrent application of taxanes and doxorubicin, the overall survival advantage that had been detected with sequential application disappeared [27]. Skinner et al. applied neoadjuvant paclitaxel 60 mg/m^2 weekly concomitantly with RT in patients

with local advanced breast cancer [28]. Because of the occurrence of unexpected severe skin toxicity in the first two patients, the dose was reduced to 30 mg/m^2 twice a week, and the total RT dose was reduced from 50 to 45 Gy as required. An objective clinical response rate of 89% was achieved. The surgical complication rate was recorded to be as high as 41%, although it was limited with regard to acute toxicity due to chemoradiotherapy. With regard to adjuvant taxane-based CT and concomitant RT applications, Bellon et al. reported more frequent grade 3 skin toxicity when RT was given with docetaxel, compared with paclitaxel [29]. Ellerbroek et al. and Hanna et al. noted increased rates of skin and cosmetic problems when RT and taxane regimens were applied concomitantly [30, 31]. In addition, concomitant application of paclitaxel with RT was reported to increase the risk of pneumonia to as high as 15–30% [31–33]. Therefore, in the treatment of breast cancer, sequential application of RT and taxane regimens is currently preferred. Four cycles of AC, followed by four cycles of paclitaxel application, were detected to prevent the recurrence rate by 17% with acceptable toxicity effects, and this regimen has now become the standard treatment for high-risk node-positive patients [26, 34, 35]. Based on the CALGB 9344 trial, Bellon and Harris [36] and Sartor et al. [37] emphasized that sufficient data have been obtained to reach a consensus on sequential application of CT and RT regimens. The same year, in the St. Gallen consensus, the order of CT and RT in sequential application was determined, except for some special circumstances. If either breast-conserving surgery or mastectomy has been performed, then the ensuing adjuvant therapy should begin with a CT regimen, followed by RT. For special reasons, if concomitant application is preferred, then a CMF regimen is favored. Concomitant anthracycline or taxane-based regimens with RT are not recommended because they may increase symptomatic radiation injury, particularly to the heart and lungs. In the St. Gallen consensus, the panelists could not reach consensus regarding how to approach and sequence RT and CT applications in cases that need to be given CT long term [38]. The consequent St. Gallen consensuses did not contribute additionally to answering questions regarding the sequencing and interaction of RT and CT in the adjuvant treatment of breast cancer [39]. In the National Comprehensive Cancer Network guidelines, the recommendation for the adjuvant treatment of breast cancer is to apply RT after CT when there is an indication [40].

6.5 Special Issues and Current Applications

6.5.1 Neoadjuvant Chemotherapy Regimens and Radiotherapy

The NSABP B-18 and the European Organization for Research and Treatment of Cancer (EORTC) 10902 trials were conducted to investigate neoadjuvant CT, and both trials reported no differences in terms of survival and distant metastasis between adjuvant CT and neoadjuvant CT, while better breast-conserving surgery

rates were reported with neoadjuvant therapy [41–43]. In the M.D. Anderson Cancer Center study, which examined RT after a neoadjuvant approach, the addition of RT to therapy for patients with locally advanced breast cancer who were given neoadjuvant CT followed by mastectomy, was shown to have independent positive effects on cause-specific survival, particularly in stage III breast cancers ($p < 0.0001$) [44]. When neoadjuvant CT is applied in locally advanced or unresectable breast cancer cases, CT is recommended to be completed before surgery, and RT should be initiated just after surgery without any delay [45].

6.5.2 Surgical Margin and Adjuvant Radiotherapy

The status of the surgical margin is the most important prognostic factor in terms of local recurrence risk [46]. In the EORTC 22881/10882 trial, 5-year local recurrence rates were determined in three patient groups with inked margin distances that were negative (2 mm or more of tumor-free margin), close (less than 2 mm of tumor-free margin), and positive, respectively, as 5%, 7%, and 16% ($p = 0.03$). According to Morrow, both for in situ and invasive tumors, the recurrence risk is recognized to be higher with tumors reaching the inked margins, and despite the tumors not reaching the margins, the data on whether a wider margin reduces local recurrence are conflicting [47]. There is also strong evidence that the elapsed time between surgery and RT is another determining factor [48]. In the ARCOSEIN trial, conducted with cases having close surgical margins or with unknown cases, the local failure observed when CT was initiated before RT was reported as significantly higher than with the reverse application (20% vs. 8%) [10]. Subgroup analysis of the late-term results of the JCRT study reported a local recurrence rate of 32% in cases with close surgical margins when treatment was started with CT, but the rate was 4% when treatment was started with RT [19].

6.5.3 Accelerated Partial Breast Irradiation and Interaction With Chemotherapy

In partial breast irradiation, particularly when applied in the form of brachytherapy, RT is generally completed before CT; therefore, data on the sequence of RT and CT and also data on their interaction are not clear to date. Haffty et al. reported better cosmetic results with MammoSite if CT was initiated 3 weeks after RT. The incidence of the "recall phenomenon" was 9.4%; however, the incidence increased to 29% when CT was initiated within 1 week after MammoSite ($p = 0.06$) [49]. In the TARGIT B trial, if CT was indicated, then CT was applied between brachytherapy and external RT applications, with the result that such a sandwich application is considered safe and efficient at a median of 60.5 months, although efficiency and tolerability data continue to be generated [50].

6.5.4 *No Axillary Dissection in 1–3 Positive Axilla*

With regard to the sequencing of CT and RT applications and their interactions, no addition to the conclusion of the St. Gallen consensus of 2005 had been made in the St. Gallen 2011 consensus. However, some consensus decisions with regard to surgery and RT may affect the sequence of RT and CT treatment modalities. In the late 1800s, Halsted emphasized the importance of complete surgical resection in the treatment of breast cancers. However, the recent St. Gallen consensus of 2011, with regard to the terms of the data from ACOSOC-011, accepted the new approach of tangential irradiation without axillary dissection following partial resection in patients with 1–2 positive axillary sentinel lymph nodes [39, 51, 52]. In this group of patients, in finalizing the local treatment of breast cancers, the issue of sequencing may soon come into question.

6.6 Conclusion

In the treatment of breast cancer, the importance of surgery, RT, and systemic therapies cannot be denied. However, the application, dosing, and timing of each of these treatment modalities indicate significant changes in a dynamic process. Understanding and correctly interpreting the effects of the changes of each treatment model on the other models is very important. According to the data obtained from different studies conducted before 2005, in the context of the adjuvant treatment of breast cancer, application of RT within 7 months following surgery is recognized safe for local control, and additionally, effective CT is recommended to be completed during this period of time. Concomitant protocols can be tried in high-risk patients. However, the risk of experiencing adverse effects may increase significantly with the concomitant use of anthracyclines or taxanes with RT. Together with the necessary notifications and precautions, concomitant therapy applications may be used in this patient group; still, further studies on new treatment options should be carried out. New data are eagerly anticipated from ongoing studies on the interactions between accelerated partial breast irradiation and CT and between chest wall irradiation without dissection and CT in patients with 1–2 positive lymph nodes.

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Chapter 7
Interactions of Radiotherapy With Hormonotherapy

Muge Akmansu

The various forms of adjuvant therapy in breast cancer including postoperative irradiation and chemotherapy or hormonal therapy decrease the mortality rate among the affected population. Adjuvant radiotherapy is a standard form of treatment after breast-conserving surgery and certain mastectomized patients. Periodically, some patients can suffer from long-term toxicity such as radiation pneumonitis or radiation fibrosis of the lung. In very rare situations after breast radiotherapy, bilateral lymphocytic alveolitis of the lung (BAL) can occur. BAL is an accepted allergic reaction of the lung and this form has different etiologic and pathologic factors apart from radiation pneumonitis and radiation fibrosis. BAL is a bilateral reaction of the lung but it occurs after unilateral thoracic apex irradiation resulting from radiotherapy in breast carcinoma patients [1]. In one study, patients with pneumonitis at the time of BAL had significantly higher ($p < 0.05$) alveolar CD4 subset cells ($24.8 \pm 10.2\%$) than asymptomatic patients ($15.2 \pm 8.9\%$). Maximal reductions in total lung capacity($p < 0.01$) and residual volume ($p < 0.05$) occurred 60 days after irradiation. The early lymphocytic alveolitis which can occur in breast cancer patients after unilateral irradiation is always bilateral and does not predict subsequent development of radiologic evidence of pneumonitis [1, 2]. This situation is different than radiation pneumonitis and fibrosis. True radiation pneumonitis and fibrosis resulting from radiotherapy in breast carcinoma patients is of different incidence. The incidence changes because of reasons such as usage of particular drugs and radiation therapy techniques, as well as other causes. Nonetheless, radiotherapy of the breast can cause long-term effects such as radiation pneumonitis and fibrosis on lung, or skin reactions such as dermatitis or fibrosis. The incidence of lung injury resulting from radiation in breast cancer patients varies between 4.5% and 63% [3]. Some radiation pneumonitis and fibrosis are silent. However, when imaging modalities are used, side effects can be seen. Because the irradiated lung volume is very small,

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most of these side effects do not change patient activities of daily living or lung capabilities.

In most patients, adjuvant radiotherapy and hormonotherapy are the two approaches that need to be taken after breast-conserving surgery. However, optimal sequencing of antiestrogen therapy and whole-breast or chest wall and peripheral radiotherapy has not been established. Early studies were done on use of tamoxifen. In a prospective study on radiotherapy treatment using Co-60, it was seen that when tamoxifen is used concurrently with radiotherapy, increase in pulmonary fibrosis is statistically significant [4]. In the same study, advanced age and postmenopausal status predisposed to pulmonary fibrosis. The median time for the development of pulmonary fibrosis was 8 months.

In an animal study, effects of tamoxifen on radiation-induced pulmonary fibrosis in rats were evaluated. There were three groups in that study [5]. In the first group, tamoxifen was started after the completion of irradiation. In the second group tamoxifen is used concurrently with radiation. In the third group, rats had thoracic irradiation only, they did not receive tamoxifen. The animals were sacrificed 16 weeks after the completion of treatment in all three groups. The fractional incidence values of pulmonary fibrosis are 3%, 10%, and 36% in the areas of RT only, sequential treatment, and concurrent treatment, respectively ($p < 0.005$). The conclusion of the study showed that concomitant use of tamoxifen appears to increase radiation-induced pulmonary fibrosis and it seems more convenient to delay tamoxifen until the completion of irradiation [5].

A recent study, however, found no association between concurrent tamoxifen and increased side effects of whole-breast irradiation [6]. In that study, Harris et al. concluded that with a median follow-up of 10 years, the local recurrence rates, disease-free survival, and overall survival were 3% vs. 7%, 85% vs. 76%, and 81% vs. 86% respectively [6].

In different study it was suggested that tamoxifen can arrest cancer cells in the radioresistant G1 phase of the cell cycle, but the data from preclinical experiments were not conclusive [7]. In a retrospective series there was no statistically significant difference in local control or survival usage of tamoxifen and radiotherapy between sequential and concomitant treatment [8].

At TATA Memorial Hospital (India), a phase III randomized study was initiated. It was an open study that was sponsored by the Indian Council of Medical Research to answer the questions of CONcurrent vs. SEquential Tamoxifen and radiotherapy (CONSET), (NCT00896155). Inclusion criteria were patients with large operable lesions with locally advanced breast cancer undergoing modified radical mastectomy that requires adjuvant postoperative radiotherapy. All patients were randomized into two groups. Both groups receive tamoxifen for a period of 5 years. The primary endpoint of this study is lung fibrosis and the secondary endpoints are locoregional and distant failure. The Indian Council of Medical Research aims to accrue 260 patients over 3 years. Since the trial started accrual in December 2008, 95 patients have been included into this trial to date. This phase III randomized controlled trial will provide the final answers to questions of appropriate sequencing of tamoxifen and radiotherapy in breast cancer [9]. With improving overall survival rates in breast cancer, there is emerging focus on the quality of life after adjuvant treatment.

In a phase II randomized trial, concurrent or sequential adjuvant letrozole and radiotherapy effects are evaluated for cosmetic after conservative surgery for early-stage breast cancer (CO-HO-RT). In this study, the randomized trial was undertaken in two centers in France and one center in Switzerland between January 12, 2005 and February 21, 2007. The study was registered with Clinical Trials at clinicaltrial.gov (number NCT 00208273). One hundred fifty early-stage postmenopausal women were included in the study. Seventy-five of the patients are undergoing concurrent radiotherapy and letrozole and the other 75 patients are undergoing sequential radiotherapy and letrozole. Whole breast was irradiated to a total dose of 50 Gy in 25 fractions over 5 weeks. In the case of supraclavicular and mammaria interna lymphatics irradiation, the dose was 44–50 Gy. Letrozol was administered orally once per day at a dose of 2.5 mg for 5 years. Letrozol was begun before 3 weeks of radiotherapy in the concurrent group and it was started after 3 weeks of radiotherapy in the sequential group. The primary endpoint was the occurrence of acute and late radiation-induced grade 2 or higher toxic effects of the skin and lung fibrosis. During radiotherapy and within the first 12 weeks after radiotherapy, 31 patients in the concurrent group and 31 patients in the sequential group had grade 2 or worse skin toxicity. Four patients in the concurrent group and six patients in sequential group had grade 3 skin dermatitis during radiation therapy and after at the end of the 26 months after radiotherapy late skin effects were evaluated. Two patients in each group had grade 2 or worse subcutaneous fibrosis resulting from radiotherapy [10].

In this study all patients who had grade 2 or worse subcutaneous fibrosis had a radiation-induced lymphocyte apoptosis value of 16% or less, irrespective of the sequence with letrozole. Lung toxicity was assessed by clinical examination, computed tomography (CT) scan, and pulmonary function test at baseline and at 6, 12, 18, and 24 months. After 24 months, only yearly clinical assessments and CT scans were done, up to month 120. An independent committee of radiologists compared changes in lung CT scans from baseline. Cosmetic assessment included clinical examination by two independent physicians at two different times for scanning adverse events with cosmetic (CTC) scale, photographs, and two quality of life questionnaires from the European Organization for Research and Treatment of Cancer. Additionally, no lung fibrosis or other lung toxicities were detected during the study using CT at month 24. Disease-free survival at 2 years was 97% (95% CI; range, 89.2–99.3) in both groups. All of the patients in the study were administered the EORTC-QLQ-C30 and QLQ23 quality of life test (functional and symptom scales). Quality of life at 24 months did not differ significantly in the two groups. Compared with baseline, only pain and dyspnea were significantly increased in the sequential group. Mean score for pain was 17.6 vs. 29.3 ($p = 0.02$); and the mean score for dyspnea was 11.9 vs. 20.5, ($p = 0.04$).

In the view of these study results, clinicians can safely deliver letrozole and radiation therapy concurrently although there is some doubt about the potential long-term toxic cardiac effects on concurrent usage. However, until the present there were no unfavorable data.

There was yet a different study that compared radiation toxicity in patients treated with concurrent or sequential anastrozole and whole-breast irradiation [8]. The study was retrospective and consisted of 249 postmenopausal women with

breast cancer with consecutive estrogen receptor or progesterone receptor (+). In 66 women, either concurrent tamoxifen was given with radiation or the sequence of hormonal therapy was not known, and those women were excluded from the analysis. A total of 57 patients received concurrent anastrozole and radiotherapy, and adjuvant hormone suppression therapy (anastrozole or other aromatase inhibitors or tamoxifen) was administered after completion of breast irradiation in 126 patients. The frequency of acute grade 2 dermatitis was 24.6% in the concurrent group vs. 20.6% in the sequential group ($p = 0.55$). Grade 3 dermatitis (8.8% vs. 7.1%; $p = 0.77$) and treatment interruptions because of skin reactions (14.0% vs. 11.2% $p = 0.69$) were not different between groups, and clinically detectable breast fibrosis was not different either. In the study, average whole-breast doses were 5,036 cGy in the concurrent group, and 50.4 Gy in the sequential group. Follow-up lung toxicity for each group was not reported. Mean follow-up was 28 months for the concurrent group and 30.8 months for the sequential group. The crude locoregional recurrence rate was 1.8% for the concurrent group vs. 4.0% for the sequential treatment group. There were some limitations to the study. First, patient ages were statistically different for each group. Second, in the concurrent anastrozole group, women were more likely to have received cytotoxic chemotherapy, which may have increased frequency and severity of radiation dermatitis. Third, in the sequential group, various hormone suppressive agents were used. However, there were no significant unfavorable data for the concurrent group.

In view of this literature, we can conclude that aromatase inhibitors and radiation therapy can be used concomitantly. However, when administering tamoxifen and radiation therapy concomitantly, while at the same time the radiation treatment fields are covering the peripheral lymphatic (especially supraclavicular fossa) region, extra attention should be paid to the skin and lung.

However, as stated by the AROME Group, a definitive answer on whether concurrent use improves outcomes can only be given following a randomized trial using both hormone therapy drug categories [11].

In patients with breast conservation, cosmesis is the end result in a range of factors that fall under the broad topics of surgery, radiation therapy, chemotherapy, and hormonal treatment. All of these modalities, and timing of these treatments, can play a role in compromising cosmetic results.

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Part II
Therapeutic Results of Radiotherapy in Breast Cancer

Chapter 8
Ductal Carcinoma In Situ

Nuran Senel Bese and Ayfer Ay

8.1 Introduction

Ductal carcinoma in situ (DCIS) represents a spectrum of abnormal cells confined to the breast and is a risk factor for invasive cancer development. The incidence has increased dramatically in recent years as a result of widespread use of screening mammography. Given the lack of clarity and the incomplete data regarding the natural history, prognostic factors, and biology of DCIS, important therapeutic questions remain unanswered. Currently, patient age, size of the lesion, nuclear grade, comedonecrosis, and the margin width are accepted as the major parameters for treatment decision. In this chapter, treatment approach for patients with DCIS and the role of radiotherapy will be discussed.

8.2 Treatment of Ductal Carcinoma In Situ

For a woman with newly diagnosed DCIS, the options for local treatment of the breast are surgical excision (lumpectomy) plus radiation treatment, lumpectomy alone without radiation treatment, or mastectomy. At the era of radical mastectomy, the cure rates are approaching 98% [1]. A meta-analysis of 21 studies including 1,574 patients with DCIS treated with mastectomy demonstrated a local recurrence rate of only 1.4% [2]. There are no prospective randomized trials comparing

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Table 8.1 Van Nuys Prognostic Index for ductal carcinoma in situ

Score	1	2	3
Size	≤15 mm	16–40 mm	≥41 mm
Margin	≥10 mm	1–9 mm	<1 mm
Pathologic classification	Non-high-grade lesion without comedonecrosis	Non-high-grade lesion with comedonecrosis	All high-grade lesions, with or without necrosis
Age (yrs)	>60	40–60	<40

Silverstein [4]

mastectomy with breast-conserving surgery (BCS) and radiation therapy in patients diagnosed with DCIS. As the long-term follow-up data from early invasive breast cancer comparing mastectomy and excision followed by radiation has matured, investigators became more confident that BCS was a reasonable treatment option for women with invasive breast cancer. It seemed logical to offer BCS to women with a lesser stage of disease, and this ultimately advanced as a standard option or DCIS without ever being tested in a phase III randomized trial.

However, there are still indications for mastectomy and these are established as multicentric disease, diffuse malignant-appearing microcalcifications on mammography, large lesions, and persistent positive margins after BCS, prior radiation therapy to the breast, the need for radiation therapy during pregnancy, or patient preference for mastectomy. Radiation therapy is not generally indicated in patients with DCIS who have undergone a mastectomy because of historically low recurrence rates.

For the majority of patients, BCS remains the standard method but major questions related to DCIS treatment are to define the subgroup of patients who would not need postoperative radiation treatment after adequate excision of the disease. Silverstein and colleagues developed the Van Nuys Prognostic Index (VPNI) in 1995 to predict the risk of local recurrence following BCS using different clinical and pathologic features [3]. In a retrospective study of 333 patients, three factors were used in the initial analysis: tumor size, margin width, and pathologic classification. Each predictor was assigned a score of 1 (favorable) to 3 (unfavorable), with the sum of these three factors used to calculate a cumulative score. Patients were grouped into three categories on the basis of their cumulative scores. In an update to their analysis, age was added to the VPNI scoring system (Table 8.1). In the data compiled by Silverstein et al., no statistical difference was shown in 12-year local recurrence-free survival rates in patients with a low risk of VNPI score (4–6), with or without radiotherapy after local excision indicated that patients with favorable risk factors could be followed with lumpectomy only [4]. However, it should be noted that this was not a prospective randomized trial with methodologic shortcomings, and the scoring system was not independently validated.

On the other hand, three important prospective randomized clinical trials demonstrated that all subsets of patients benefited from radiation therapy in terms of decreased local recurrence. The National Surgical Adjuvant Breast and Bowel

Project (NSABP) B-17 study [5] randomized 813 women with DCIS to BCS alone or BCS followed by whole-breast radiation therapy to a total dose of 50 Gy in 25 fractions. At a median follow-up of 12 years, local recurrence rates were significantly higher for the group of patients who did not receive irradiation after BCS (31.7% vs. 15.7%). The percentage of invasive and noninvasive recurrences was high in the BCS only group. Of note, no significant difference was observed in overall survival between the two groups. In the central pathology review of the NSABP B-17 trial, microcalcifications extending beyond a maximum dimension of greater than 1 cm and moderately marked comedonecrosis associated with increased local recurrence, but radiotherapy lowered the incidence of local recurrence among all subgroups regardless of the baseline risk. The European Organization for Research and Treatment of Cancer (EORTC) 10853 trial [6] randomized 1,010 women with DCIS who underwent BCS and no further treatment or BCS followed by whole-breast radiation therapy to a total dose of 50 Gy in 25 fractions. With a median follow-up of 10.5 years, the EORTC 10853 trial also showed that radiotherapy decreased the risk of local recurrence compared with BCS alone (15% vs. 26%). Again, there was no significant difference in overall survival between radiotherapy and no further treatment groups. In the central pathology review of the EORTC 10853 trial, radiotherapy also lowered the incidence of local recurrence among all subgroups regardless of the baseline risk. Finally, the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) conducted a trial [7] that randomized women using a 2×2 factorial design to BCS or BCS followed by radiation therapy to a total dose of 50 Gy in 25 fractions. The study also investigated the role of tamoxifen in decreasing the risk of ipsilateral and contralateral disease. The trial included four arms: BCS alone, BCS and radiation therapy, BCS and tamoxifen, and BCS with radiation therapy and tamoxifen. With a medium follow-up of 12.7 years, local recurrence was significantly higher in the BCS group without radiotherapy (22% vs. 7%).

One meta-analyses and one systemic review also evaluated the role of radiotherapy after BCS [8, 9]. In the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of 3,729 eligible women were randomized after lumpectomy to receive radiotherapy vs. not to receive radiotherapy [8]. The 10-year rate of ipsilateral local failure (invasive carcinoma plus DCIS) was decreased by 15.2% with the addition of irradiation. Adding radiation treatment after lumpectomy reduced 10-year rate of invasive local failure by 8.4%. There were no differences in the 10-year rates of overall survival, mortality without recurrence, or cardiac mortality. Systematic review of the Cochrane database also found four prospective trials and showed that radiotherapy decreased the rate of local recurrences by 50% without any difference in overall survival. No significant toxicity that could be attributed to radiotherapy was found [9].

In order to define a subgroup of patients who will not need radiotherapy after BCS, some prospective phase II randomized trials were established including patients with very good prognosis. In a prospective single-arm study in which 158 patients were treated with wide excision alone, the 5-year rate of local

recurrence was 12% [10]. In the study a minimum negative margin of 1 cm or no tumor on reexcision required, mammographic extent of the disease should be less than or equal to 2.5 cm with low histopathologic grade. As this rate of local recurrence exceeded the predetermined stopping threshold for local recurrence, the study was closed early because of accrual. The Eastern Cooperative Oncology Group (ECOG) also designed a nonrandomized registration study (ECOG E5194) with the intent of identifying prospectively favorable patients with DCIS for treatment using local excision alone. The two arms of the study were (1) low-or intermediate-grade DCIS, 2.5 cm in size or smaller; or (2) high-grade DCIS 1 cm in size or smaller. A minimum margin width of 3 mm was required. The median age was 60 years. At a median follow-up of 6.2 years for the 565 patients with low or intermediate grade, the 5-year rate of ipsilateral local recurrence was 6.1% and the 7-year rate was 10.5%. At a median follow-up of 6.7 years for the 105 patients with high-grade DCIS, the 5-year rate of local recurrence was 15.3% and the 7-year rate was 18%. These results suggest that patients with high-grade DCIS are not suitable for treatment with excision alone without radiotherapy. For patients with low- or intermediate-grade DCIS, additional follow-up is needed [11]. In a recent retrospective study, DCIS patients who met the enrollment criteria of ECOG E5194 treated with lumpectomy and adjuvant whole-breast radiotherapy with a total boost dose of 64 Gy to the tumor bed were analyzed. With an average follow-up time of 6.9 years, the 5- and 7-year ipsilateral breast recurrence rates for the low-grade group were 1.5% and 4.4%, respectively, and ipsilateral breast recurrence rates for the high-grade group were 2% and 2%, respectively, for the same periods [12]. Additionally, the ipsilateral recurrence rates of 194 DCIS patients who met the enrollment criteria of ECOG E5194 in the Accelerated Partial Breast Irradiation (APBI) registry trial were analyzed. With a median follow-up of 51.5 months, the 5-year rate of ipsilateral breast recurrences was 2% for the low-grade group and 3% for the high-grade group treated with APBI [13].

Biological markers as steroid receptors, proliferation markers, cell cycle and apoptotic markers, angiogenesis-related proteins, epidermal growth factor receptors, extracellular matrix-related proteins, and COX-2 were analyzed in a comprehensive review of 6,252 patients, and none of the novel and key breast cancer biological markers were found to be associated with increased risk of recurrence for patients with DCIS [14].

Currently, prospective and retrospective studies have demonstrated excellent long-term outcomes after breast conservation treatment with radiation. It is not possible to define the subgroup of patients who would not require radiation therapy according the results of prospective randomized trials, meta-analyses, or biological factors. However, in retrospective analyses and in prospective trials, a number of risk factors were identified for the increased risk of ipsilateral breast recurrences such as palpable mass, age younger than 60 years, larger tumor size, higher tumor grade, or involved or close surgical margins [15]. If the physician considers that the risk of recurrence is very low, this can be discussed with the patient and omission of irradiation is considered after BCS.

8.3 Radiation Therapy to Whole Breast After Breast-Conserving Surgery in Patients With DCIS

The most common fractionation used in patients with DCIS is 50 Gy at 2 Gy per fraction; the fractionation scheme was used in the NSABP B-17, EORTC, and UKCCCR studies [5–7]. Radiation therapy should be given to the whole breast using tangential fields that maximize coverage of the breast and tumor bed while minimizing exposure of ipsilateral lung and heart. In recent years, there has been a strong interest in delivering a higher dose per fraction, resulting in fewer fractions hypofractionation in patients with early invasive breast cancer. The role of hypofractionation in patients with DCIS has not been studied extensively. APBI is also used in patients with early invasive breast cancer as part of a clinical trial or for selective patients in daily clinical practice. However, APBI has not been recommended for patients with pure DCIS [16]. A boost dose to the tumor bed is commonly given to patients with early invasive breast cancer following whole-breast irradiation. Randomized trials have shown a small but statistically significant benefit in local control for patients with invasive breast cancer [17]. Limited data are available on the benefit of a boost for patients with DCIS. A radiation boost is generally given at the discretion of the treating physician and can be based on additional risk factors. The role of a 16 Gy boost dose has been investigated in open prospective clinical trials [18, 19].

8.4 The Role of Adjuvant Systemic Treatment in DCIS

Adjuvant endocrine therapy, which has been demonstrated to provide benefit in estrogen receptor (ER)- and progesterone receptor-positive invasive carcinoma, may have a role in the adjuvant treatment of DCIS. There have been two major randomized prospective trials, NSABP B-24 [20] and the UK/ANZ trials [7] which address the use of tamoxifen, a selective ER modulator. In the NSABP B-24 study, patients in both arms of the study received BCS plus radiotherapy to 50 Gy. They were then randomized to 5 years of 20 tamoxifen 10 mg PO bid ($n = 902$) or placebo ($n = 902$). The study demonstrated a benefit to adjuvant tamoxifen in preventing invasive carcinoma of the ipsilateral breast; a benefit that appears to be confined to ER + patients. However, patients with positive and indeterminate surgical margins were included in the study. Therefore, the question arises if adequate locoregional treatment can influence the value of systemic treatment in preventing an invasive recurrence [20]. The UK/ANZ trial was conducted using a 2×2 factorial design to evaluate both adjuvant tamoxifen and, independently, adjuvant radiotherapy as mentioned above. After a median follow-up of 12.7 years, it was shown that tamoxifen reduced the incidence of all new breast events, reducing recurrent ipsilateral DCIS and contralateral tumors but having no effect on ipsilateral invasive disease. The study confirmed the long-term beneficial effect

of tamoxifen in reducing local and contralateral new breast events for women with DCIS treated by complete local excision. The long-term results of this study support the utilization of tamoxifen in DCIS [17]. However, the decision should be made according to the risk benefit analyses, receptor status, and the risk of developing contralateral disease [21]. The role of aromatase inhibitors in patients with DCIS is still under investigation.

8.5 Conclusion

DCIS is a noninvasive tumor with the potential to transform into invasive breast carcinoma. Treatment options are targeted at decreasing the risk of local recurrence of both invasive and noninvasive forms. BCS followed by radiation therapy has been shown to have long-term local control and is currently considered the standard of care. Mastectomy can be an alternative treatment modality for DCIS patients who are not suitable for BCS. There was no clinical or pathologic subgroup of patients identified who did not benefit from radiation therapy according to clinical trials and biological markers. Although there is no high level of recommendation, omission of irradiation can be considered for patients with a very low risk of recurrence, at the discretion of treating physician and the patient.

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Chapter 9
Early Stage Breast Cancer

Maktav Dincer

9.1 Introduction

In the multimodality treatment of breast cancer, adjuvant radiotherapy has an important role in achieving excellent local control and increasing survival. It has been easier to confirm the role of radiotherapy for local control [1, 2]; whereas it took decades to show that adjuvant radiotherapy also increased the survival rates [3, 4]. In this chapter, trials and meta-analysis of postoperative adjuvant radiotherapy for invasive early-stage breast cancer in the both settings of breast conservation therapy (BCT) and after mastectomy (postmastectomy radiotherapy [PMRT]) will be summarized; local control vs. survival issues will be discussed. Discussions related to cases of in situ ductal carcinoma, techniques of radiotherapy, side effects and complications, and management of locally advanced breast cancer can be found elsewhere.

9.2 Breast-Conserving Surgery and Radiotherapy

Randomized trials started by the end of the 1970s were intended to show the noninferiority of BCT (local excision of the tumor plus breast radiotherapy) to more radical local treatments (mastectomy ± postoperative radiotherapy) [5–9]. The follow-up of patients in the trials has exceeded 20 years, and survival of the patients in the BCT group vs. the mastectomy group is still equivalent, and the local control rates are similar. The National Surgical Adjuvant Breast Project (NSABP) group conducted the NSABP B-06 trial on 1,851 patients with stages I or II with breast cancer smaller than 4 cm that were locally excised with negative margins [10].

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Randomization was conducted in three arms, total mastectomy vs. lumpectomy alone vs. lumpectomy plus 50 Gy whole breast radiotherapy. Node-positive patients received 5-fluorouracil based adjuvant chemotherapy. At 20-year follow-up, overall survival (OS), disease-free survival (DFS), and distant metastases free survival (DMFS) were not significantly different among the three arms. Addition of breast radiotherapy to breast-conserving surgery reduced the local recurrence rate from 39% to 14%. The Milan group conducted a similar randomized trial (Milan I) in 701 patients with stage I breast cancer [6, 11]. Randomization was conducted in two arms, radical mastectomy vs. quadrantectomy plus 60 Gy breast radiotherapy. Node-positive patients received CMF (cyclopospamide, metothrexate, fluorouracil) combination chemotherapy. At 20-year follow-up, OS (59% and 58 %) and cause-specific survival (76% and 74%) rates were almost identical, whereas local recurrence after radical mastectomy was 2.3%, but 8.8% after BCT. The European Organization for Research and Treatment of Cancer (EORTC) conducted the 10801 trial on 902 patients with stages I or II breast cancer [12]. Patients were randomized and the study was conducted in two arms, modified radical mastectomy vs. lumpectomy plus breast radiotherapy (whole breast 50 Gy plus a boost). It should be noted that patients with positive margins after lumpectomy were admitted to the trial and radiotherapy dose was boosted in them. After 10 years of follow-up, OS (66% and 65%) was identical in both arms. However, local recurrence after mastectomy was 12%, but 20% after BCT. Although long-term follow-up shows somewhat increased local recurrence rates in the early pioneer studies, the overall survival rates were almost identical between mastectomy and breast conservation groups. Higher local failure rates in the BCT arms can be related to patient selection criteria flaws, inaccurate pathology assessments, and poorer mammographic and radiotherapeutic techniques. With the advent of better preoperative assessment, surgical margin determination, and treatment techniques, the benchmark today for local failure after BCT is approximately 2% [13]. In the EBCTCG meta-analysis published in 2000, seven trials randomizing for mastectomy or breast-conserving surgery plus whole breast radiotherapy were analyzed [2]. In the total of 3,100 women randomized, at 10 years, local failure and OS rates for mastectomy vs. BCT groups, respectively, were reported as 6.2% vs. 5.9% and 71.5% vs. 71.1%. This meta-analysis confirms that breast-conserving surgery plus postoperative radiotherapy is an alternative and well-documented safe treatment for early breast cancer.

Because BCT was confirmed as a standard management, the next the role of radiotherapy in BCT was questioned in randomized trials. The NSABP B-06 trial consisted of two arms of breast conservation: lumpectomy alone and lumpectomy plus radiotherapy [5, 10]. In the node-positive patients treated with lumpectomy and chemotherapy (but no radiotherapy), at 12 years the local failure rate was 41%; in patients without axillary metastases that were managed with lumpectomy alone, local failure was reported as 32% [5]. The breast recurrence rate for patients who also received radiotherapy was 5% (in node-positive patients who also received chemotherapy) and 12% (in node-negative patients). The Milan III trial was conducted from 1987 through 1989, and 601 patients were randomized with tumors smaller than 2.5 cm to quadrantectomy vs. quadrantectomy plus whole breast

radiotherapy [11]. Premenopausal women received CMF adjuvant chemotherapy and all hormone receptor-positive patients and all postmenopausal patients received tamoxifen. At 7-year follow-up, patients who underwent quadrantectomy alone experienced 9% local recurrence and quadrantectomy plus radiotherapy patients experienced 0% in-breast recurrence [11]. With long-term follow-up, the addition of radiotherapy reduced local failure rates from 24% to 6% [11, 14]. However, OS survival was not different between the two arms. A study in Uppsala-Orebro randomized patients with stage I tumors from 1981 through 1988 to quadrantectomy vs. quadrantectomy plus whole breast 50 Gy radiotherapy [15, 16]. Included were low-risk patients who didn't receive any systemic therapy. At 10-year follow-up, radiotherapy reduced the local failure rates from 14% to 4%; OS and DFS rates were similar. Two other lumpectomy alone vs. lumpectomy plus whole breast 50 Gy randomized trials also deserve mentioning. The Ontario Clinical Oncology Group randomized 837 patients and found that at 5 years, radiotherapy reduced local failures from 30% to 8% [17]. In a Scottish trial, radiotherapy reduced local failures from 25% to 6% in 585 stage I or stage II patients [18]. By the mid 1990s, the standard for BCT was wide local excision (with axillary surgical staging) plus whole breast radiotherapy. However, some retrospective, unplanned, subgroup analyses showed that in patients with low-risk characteristics (postmenopausal, T1N0, hormonal receptor positive, low grade, etc.) the in-breast recurrence rates were low enough and acceptable without postoperative radiotherapy [19]. This observation and the hypothesis of local excision alone in selected low-risk patients initiated a new series of prospective trials.

In Boston, the Joint Center for Radiation Therapy group selected a presumably low recurrence risk group of patients and entered them into a prospective registry trial after lumpectomy and no radiation and no systemic therapy [20]. Entry criteria for the trial were: single focus of T1 tumor, invasive ductal/tubular/colloidal carcinoma (no lobular carcinoma, etc.), no extensive intraductal component, no lymphovascular space invasion, no axillary metastases, and tumor-free surgical margins more than 1 cm histopathologically. The study was planned for 90 patients, but accrual was stopped at 87 cases when a higher than expected rate of recurrence was noticed. Among the patients entered, median tumor diameter was 0.9 cm and median patient age was 67 years. For a highly selected group of patients, in-breast local failure rate at 5 years was 16%; annual breast cancer recurrence rate was 3.6%. Four of the 87 patients developed distant metastases within 56 months. It was concluded that even in highly selected patients, lumpectomy only (without radiotherapy and without systemic therapy) was not an acceptable management strategy. Following this experience, randomized trials of breast-conserving surgery with systemic hormonal treatment (tamoxifen) with or without whole-breast radiotherapy were conducted to evaluate the role of adjuvant radiotherapy in selected low-risk patients under hormonal management. In a Canadian trial, 769 patients older than age 50 years with T1/T2N0 tumors and estrogen receptor (ER)-positive disease were randomized after lumpectomy to tamoxifen plus radiotherapy vs. tamoxifen alone [21]. At 8 years, the addition of radiotherapy reduced the local failure rate from 12% to 4% ($p<0.05$). DFS was improved from 76% to 82% with the addition

of radiotherapy ($p < 0.05$); however, OS and cause-specific survival rates were not different. A similar design trial was conducted in North America by the Cancer and Leukemia Group−B (9343/INT trial) [22]. In that trial, 636 older patients (older than age 70 years) and smaller tumors (TI) again with ER-positive disease were randomized after lumpectomy to tamoxifen plus radiotherapy vs. tamoxifen alone. At 8 years, the addition of radiotherapy reduced the local failure rate from 7% to 1% ($p < 0.05$). However, OS and cause (breast cancer)-specific survival rates were not different. Based on these data, some groups are prepared to offer the option of no postlumpectomy radiotherapy and follow-up with only hormonal management in elderly patients with small, low-risk tumors, when the surgical margins are safely free of tumor. This is an option especially for patients older than 70 years and with comorbidities. The NSABP B-21 trial randomized 1,009 patients with T1N0 and ER-positive disease, to three arms after lumpectomy: radiotherapy and tamoxifen vs. radiotherapy and placebo vs. tamoxifen alone [23]. At 8 years, the addition of radiotherapy reduced local failure rates from 16.5% (tamoxifen alone) to 2.8% (radiotherapy plus tamoxifen); the radiotherapy alone arm had a local failure rate of 9.3%. Again, no difference in OS or DMFS was detected. A combination of radiotherapy plus tamoxifen achieved the best local control rate after breast-conserving surgery. Other than in selected elderly patients with comorbidities and tumor-free margins, postoperative adjuvant breast radiotherapy is a major component of BCT. In some cases only the tumor site irradiation in very short courses (single fraction to 10 fractions in 5 days [accelerated partial breast irradiation]) whether is a safe method as conventional whole-breast irradiation for 5–7 weeks will be discussed elsewhere.

Conventional postoperative breast irradiation is a two-phase treatment: whole-breast radiotherapy for 5 weeks plus a tumor bed boost dose for 1–1.5 weeks. The boost dose is recommended in patients with tumor-free margins (current BCT acceptance criteria) and in patients of all age groups [24]. A randomized boost study was conducted in Lyon, France on 1,024 patients [25]. In stage I and stage II cases after local excision with tumor-free margins and axillary dissection, all patients received whole-breast radiotherapy of 50 Gy over 5 weeks; they were then randomized to 10 Gy electron boost vs. no further radiotherapy. At 5 years, the addition of a boost dose reduced the local failure rate from 4.5% to 3.6% ($p = 0.04$). The largest boost vs. no-boost trial was conducted by the EORTC [26]. A total of 5,319 stage I and stage patients after local excision and axillary dissection received the standard 50/2 Gy per fraction whole-breast irradiation; they were then randomized to 16/2 Gy boost (additional tumor bed radiotherapy dose) vs. no further radiotherapy. At 5 years the actuarial local recurrence rates were 7.3% for breast only vs. 4.3% for breast and boost radiotherapy groups, respectively ($p < 0.001$). Although the relative advantage with boost was similar for all age groups of patients younger than 40, 41–50, 51–60, and older than 60 years, absolute gains in breast controls were most prominent in patients younger than 40 years [24, 26]. In the youngest age group, 16 Gy electron boost reduced local failures from 19.5% to 10.2% at 5 years, with some compromise with the cosmetic outcome. A boost dose can be applied through three techniques: photon fields, en face

electron field, and interstitial brachytherapy. According to the EORTC 22881 trial results, cosmetic outcome is similar with the three techniques [27]. Because of its ease in planning and delivery, the electron boost technique is preferred by many whenever it yields a homogenous dose delivery. Whether a boost dose of 10 Gy is acceptable instead of 16 Gy in patients with tumor-free margins and preferable for a better cosmetic outcome is at the discretion of the treating radiation oncologist. Also, whether a higher boost dose (like 26 Gy) will yield better local control rates in very young patients is the subject of an ongoing randomized trial ("young boost trial"). The current BCT concept does not allow patients with more than limited focal margin involvement (in the rare instances) to be admitted for adjuvant radiotherapy [19]. Patients with margin involvement problems usually require reexcision before beginning radiotherapy. In the rare cases of focal (limited) margin involvement in deep (pectoralis fascia) or anterior (subcutaneous) margins, patients are accepted for radiotherapy when reexcision is not technically feasible.

A tumor-free or negative margin is defined in many different ways by leading institutions or authors. For example, NSABP defines a negative margin as no tumor cells touching the inked margin. Usually, in North America a tumor-free margin of 2 mm beyond invasive cancer is considered negative. In Europe, a somewhat larger margin, closer to like 5–10 mm, is desired to define as negative. Positive margin status has been reported as the most important factor associated with local relapse [19]. In the report by DiBiase et al., patients with negative margins had no local recurrence at 10-year follow-up, but with close margins had a 14% local recurrence, and with positive margins had a 33% local recurrence rate despite large boost doses supplemented to the tumor bed [28]. These findings are confirmed by other institutional results. In another study, at 12-year follow-up, a local relapse rate of 30% in patients with positive margins, compared with 24% with close margins, and with 9% in patients with negative margins [29]. Also, the amount (volume) of carcinoma near the final margin had an impact on the rate of local failure.

9.3 In-Breast Recurrence vs. Mortality

Vinh-Hung and Verschraegen reported a pooled analysis for risks of ipsilateral breast tumor recurrence (IBTR) and mortality in patients treated with breast-conserving surgery with or without radiotherapy [30]. The objective of the study was to investigate whether radiotherapy or its omission after breast-conserving surgery has measurable consequences on local tumor growth and patient survival. They conducted a pooled analysis of 15 randomized trials published in the literature with a total of 9,422 patients treated with radiotherapy vs. no radiotherapy after breast-conserving surgery. They studied the IBTR and patient death from any cause. The relative risk of IBTR after breast-conserving surgery, comparing patients treated with no radiotherapy or radiotherapy, was 3. The relative risk of mortality was 1.086, which corresponded to an estimated 8.6% relative excess mortality if radiotherapy was omitted. They concluded that omission of radiotherapy is associated with a large

increase in risk of IBTR and with a small increase in the risk of patient mortality. In a similar analysis, Whelan et al. reported that IBTR after lumpectomy was predictive of subsequent mortality, based on their findings from a randomized trial [17]. The purpose of the study was to determine whether IBTR postlumpectomy was independently predictive of distant relapse and mortality in women with node-negative breast cancer. They conducted a randomized trial between 1984 and 1989 in which 837 patients with node-negative disease who had undergone lumpectomy and axillary dissection were randomized to either postoperative breast radiation or no further treatment. The endpoints of the recent proportional hazards regression analysis were mortality and distant relapse using the fixed covariates, treatment, age, tumor size, ER status, and nuclear grade. At a median follow-up of 66 months, the cumulative rate of IBTR at 5 years was significantly greater for the no radiotherapy group compared to the radiation group; 30 % vs. 8 %, respectively, ($p < 0.0001$). In addition, IBTR predicted increased mortality (relative risk $= 2.28, p = 0.0006$), with a similar result being observed for distant relapse. The authors concluded that local breast recurrence following lumpectomy was associated with an increased risk of distant relapse and death. In 2005, the EBCTCG reported on a meta-analysis where 7,300 women were treated with breast-conserving surgery in trials randomizing patients to radiotherapy vs. no radiotherapy [4]. The reduction in local recurrence with radiotherapy was significantly high in every separate trial. The recurrence rate comparing those allocated radiotherapy with those not allocated radiotherapy corresponded to a proportional reduction of 70%. Considering all ten trials together, the 5-year risk of local recurrence was 7% among those allocated radiotherapy and 26% among those not allocated radiotherapy, corresponding to an absolute reduction of 19% in local recurrence risk. The proportional risk reduction for breast cancer mortality was much lower than for local recurrence, and none of the trial-specific breast cancer mortality results were clearly significant on their own. However, collectively, there was a significant impact on breast cancer mortality indicating a reduction of about 15% in the annual breast cancer mortality rate. The 15-year risk of death from breast cancer was 30.5% among those allocated breast-conserving surgery plus postoperative breast radiotherapy and 35.9% among those allocated breast-conserving surgery alone; this corresponds to an absolute reduction in mortality of 5.4% ($2p = 0.0002$). In an updated meta-analysis, the EBCTCG reported the effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death, along with the absolute magnitude of the reductions according to various prognostic and other patient characteristics [31]. In that meta-analysis, individual patient data for 10,801 women in 17 randomized trials of radiotherapy vs. no radiotherapy after breast-conserving surgery were undertaken to study whether radiotherapy reduces recurrence and breast death more so for some subgroups of patients than for others. Overall, radiotherapy reduced the 10-year risk of any (i.e., locoregional or distant) first recurrence from 35.0% to 19.3% (absolute reduction, 15.7%; $2p < 0.00001$) and reduced the 15-year risk of breast cancer death from 25.2% to 21.4 % (absolute reduction, 3.8 %; $2p = 0.00005$). Of the 10,801 patients analyzed, a vast majority (8,337) were pathologically confirmed node-negative (pN0) cases. In women with pN0 disease, the absolute recurrence reduction varied according to age, grade,

ER status, tamoxifen use, and extent of surgery, and these characteristics were used to predict large (≥20%), intermediate (10–19%), or lower (<10%) absolute reductions in 10-year recurrence risk. Absolute reductions in 15-year risk of breast cancer death in these three prediction categories were 7.8%, 1.1%, and 0.1%, respectively. In the few women with node-positive disease ($n = 1{,}050$), radiotherapy reduced the 10-year recurrence risk from 63.7% to 42.5% (absolute reduction, 21.2%; $2p < 0.00001$) and the 15-year risk of breast death from 51.3 to 42.8 % (absolute risk reduction, 8.5%; $2p = 0.01$). Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10. In summary, breast radiotherapy halved the rate at which the disease recurs and reduced the breast cancer death rate by a sixth (similar to the rate in their previous report [4]) after breast-conserving surgery. The absolute benefits from radiotherapy varied substantially according to the characteristics of the patient that predicted recurrence. This finding was interpreted as "the results may enable both doctors and patients to have a better idea of the benefit that is likely to be gained from radiotherapy on a patient-by-patient basis; thus, it is likely that as a result of this paper, some women will be given radiotherapy who would not otherwise have had it; it is also likely that some women will not be irradiated who would otherwise have been." Accordingly, the finding will be reflected in the future treatment protocols. The results suggest that killing microscopic tumor foci with radiotherapy in the conserved breast reduces the potential for both local recurrence and distant metastasis. In addition, it was reported that radiotherapy did not increase the 15-year risk for death from causes other than breast cancer. The study confirmed the current consensus that there is no group of patients from whom radiotherapy can be omitted after breast-conserving surgery, though the absolute benefit in low-risk older patients treated with tamoxifen after breast-conserving surgery (without radiotherapy) was very small. However, it should be stressed that patients older than 70 years were underrepresented in the meta-analysis; therefore, the applicability of these data to this low-risk subgroup of women (with events per women-year without radiotherapy of about 2%) is limited. The older group, when experiencing comorbidities, also has the competing risk of non-breast cancer mortality. On the other hand, it was shown that radiotherapy greatly improved 10-year recurrence risk even in young women with high-grade ER-positive tumor even if they were taking tamoxifen.

9.4 Cosmetic Results

The Harvard group defined a simple scale, by global assessment of the appearance of the breast, with four points (excellent, good, fair, poor) to evaluate the cosmetic outcome of women treated with BCT [32]. They reviewed the records of 593 patients. At median follow-up of 76 months, the breast appearance (i.e., cosmetic results) was generally excellent or good. The percentages of excellent, good, fair, and poor results at 3 years were 65%, 25%, 7%, and 3%, respectively. Patients not

receiving adjuvant chemotherapy were more likely than those receiving chemotherapy to have excellent scores at 5 years (71% vs. 40%). Tumor size also influenced cosmetic outcome: 73% of patients with T1 tumors vs. 55% with T2 tumors had excellent scores at 5 years. Results were found to be stable over time, with only 5% deteriorating to a lower score after 5 years. They concluded that the cosmetic results achieved with breast-conserving surgery and postoperative breast radiotherapy are good to excellent in about 90% of patients and that these results remain stable for at least 7 years. The outcome of cosmetic results in the EORTC randomized trial of boost vs. no boost was published [33]. In the trial, women with negative surgical margins were randomized to a boost of 16 Gy to the tumor bed or no further treatment after whole-breast irradiation. Patients with microscopically incomplete excision were randomized to receive a boost of 10 or 25 Gy. Boosting techniques included external beam radiation or interstitial implant. Cosmetic results at 3 years were assessed in 364 women with boost and 367 without boost. The position of the nipple in the treated breast was measured by contrasting to the contralateral nipple. Excellent to good results were obtained in 71% of cases in the boost group and 86% of cases in the no boost group. Factors associated with worse cosmetic result were inferior tumor location, large excision volume, postoperative wound complications, and application of a boost dose.

9.5 Breast Conservation in Hereditary Breast Cancer

Hereditary breast cancer represents 5–10% of all breast cancer patients and a larger proportion of patients with early-onset disease [34]. Most hereditary breast cancers are associated with germ-line *BRCA1* and *BRCA2* mutations and these genes were identified and sequenced in 1994 and 1995 [35, 36]. It has been said that: Given the relatively recent identification of these tumor suppressor genes, the available literature with respect to outcomes related to radiation therapy (in terms of increased radiosensitivity or lack of local control) has limitations with small patient numbers, short follow-up periods, and lack of prospective trials.

A study from the Memorial Hospital, Memorial Sloan Kettering Cancer Center (MSKCC) comparing outcomes between mutation carrier and noncarrier Jewish Ashkenazi women treated with BCT found nonsignificant increased rates of IBTR in mutation carriers, 22% vs. 6.9%, respectively, at 10 years ($p = 0.25$) [37]. However, age was the only factor that independently predicted for IBTR, with patients younger than 50 years having a 2.5-fold relative risk of recurrence. But the mutation status was the only factor significant for contralateral breast events (3.5-fold relative risk of event). A multi-institutional analysis of 160 mutation carriers from 11 institutions in the USA, Canada, and Israel was performed with results compared with outcomes in 445 cases with sporadic breast cancer [38]. At 10 years, there was no significant difference in rates of IBTR, with 12% for carriers and 9% for controls ($p = 0.19$). In a multivariate analysis, lack of chemotherapy use and young age were independent predictors of IBTR; *BRCA1* and *BRCA2* status was

not. Results of analysis of contralateral breast events were significantly higher for *BRCA1* and *BRCA2* carriers at 10 years than for controls, with 26% for carriers and 3% for sporadic controls ($p < 0.0001$). Oophorectomy was associated with a reduction of IBTR. Tamoxifen was associated with a reduction in contralateral breast cancer risk. Haffty et al., also observed increased rates of IBTR and contralateral breast events in BRCA carriers in the absence of oophorectomy and tamoxifen [39]. In another study of 655 carriers treated with either breast conservation or mastectomy it was demonstrated that the use of chemotherapy significantly reduced the rate of IBTR (in conserved breasts) and no differences were observed in OS despite differences in local control between the two surgical modalities [40]. Locoregional management of breast cancer in *BRCA1* and *BRCA2* mutation carriers can be summarized as follows [40, 41]: Published results suggest an increased risk of IBTR in BRCA carrier patients treated with BCT, but no evidence of decreased OS rates in women selecting BCT compared with mastectomy. Data also suggest risk reductions in breast events with chemotherapy and hormonal management in women treated conservatively. Randomized comparisons of BCT vs. mastectomy will never be conducted in these patients given the rarity of the condition and the personal decision-making processes in such cases. It has also been shown that there is no increased toxicity with radiotherapy in *BRCA1* and *BRCA2* carriers [41, 42]; therefore, radiotherapy should not be withheld when indicated in the management of *BRCA1* and *BRCA2* carriers because of toxicity concerns.

9.6 Postmastectomy Radiotherapy

When the results of two (Danish and British Columbia) modern era randomized studies of PMRT were published in the same journal and the same issue in 1997, and showed significant overall survival advantage in addition to locoregional control gain with irradiating chest wall and lymphatics, it resulted in great popularity for indicating PMRT in every case that was found to have axillary metastases or a tumor larger than 5 cm [43, 44]. OS gain of 9–10% with PMRT was accepted with great enthusiasm by the Radiation Oncology Society. Until the publication of those results, PMRT was indicated with hesitation because it was not clear whether the adjuvant modality had mortal side effects (mainly cardiac), while increasing locoregional control, and therefore the net benefit was not known. In fact, the overview published in 1987 showed that patients in the PMRT arm of the randomized studies had higher mortality rates because of cardiac diseases [1]. At that time, after the publication of the overview, many cooperative groups disregarded PMRT in their research protocols of mastectomized breast cancer patients, even in locally advanced cases.

Following the publication of the Danish and British Columbia trials, more current meta-analyses of PMRT trials were published [3, 4, 45, 46]. The current research confirmed that PMRT can increase survival. One of the largest overviews

of PMRT was published by the EBCTCG in 2005 to analyze PMRT benefits in randomized trials [4]. In that report, in the total of 9,933 women randomized, those who had axillary involvement had a locoregional recurrence of 29% without PMRT, whereas only 8% had locoregional recurrence with the addition of PMRT, at 15 years. Breast cancer mortality was decreased by an absolute 5% as a result of this local control gain. However, in cases without axillary metastasis, at 15 years locoregional recurrence was 8% without PMRT, and 3% with adjuvant PMRT; this small benefit was not reflected in OS. Van de Steene et al., reanalyzed the trials that were included in the EBCTCG overview by stratifying the trials according to certain objective parameters [46]. They reported that adjuvant PMRT significantly increased survival in the following cohorts of patients: newer studies conducted after 1980 ($P = 0.05$), larger studies that included more than 600 patients ($p = 0.03$), studies that used standard fractions of radiotherapy as 200–275 cGy/day ($p = 0.02$), studies that were conducted in patients with better prognosis (cure rates of above 50% according to stage) ($p = 0.03$). It was shown that modern and standard irradiation techniques were likely to result in survival gains in PMRT; in the subgroup that gained the most benefit, mortality was reduced by 20%. Whelan et al. chose 18 trials that randomized patients to PMRT after systemic treatment [3], with a total of 6,367 patients in their meta-analysis. Women treated with mastectomy and systemic therapy had 17% decrease in risk of mortality with the addition of PMRT ($p = 0.04$). In one other meta-analysis, the quality of radiotherapy technique was investigated as a factor to impact survival gains with PMRT [45]. The researchers chose the optimal technique of irradiation as 2 Gy/fraction/dose, 40–60 Gy total dose, and both chest wall and peripheral lymphatics irradiation as a comprehensive application. In the group labeled as irradiated with optimal technique, PMRT reduced locoregional recurrence by 80%, and significantly increased breast cancer survival. However, in the group irradiated with suboptimal doses, recurrences were reduced by 70%, and in the group irradiated with suboptimal treatment fields, recurrences were reduced by 64%; in both of the last two groups a survival advantage could be shown with PMRT.

The topic that is still debated currently in terms of PMRT is in which subgroups of patients to indicate the treatment. It is totally accepted by the oncology society that in patients with mastectomy who have a tumor smaller than 5 cm, no axillary involvement and negative surgical margin, PMRT is not indicated. According to the consensus statements [47, 48] and guidelines [49–52], PMRT is indicated in patients with moderate (about 10%) or high (more than 20%) recurrence rates; that is, if more than four lymph nodes are involved with metastasis, or staged as T3N+, T4, or have surgical margin involvement. This generalization does not include patients staged as T1/T2 and only one to three lymph nodes found to be involved after mastectomy and axillary clearance. However, there are reports that claim PMRT increases locoregional control and even survival in patients with even single lymph node metastases [53, 54]. PMRT in patients with one to three lymph nodes in early stage patients is the most controversial adjuvant radiotherapy indication in breast cancer.

The Danish Breast Cancer Group (DBCG) randomized premenopausal patients (82b trial) after mastectomy and systemic chemotherapy (CMF), and postmenopausal patients (82c trial) after mastectomy and adjuvant tamoxifen indication to PMRT vs. no PMRT [43, 55]. In both trials, PMRT significantly improved local control and survival. Those two trials have been criticized for suboptimal surgical techniques (few lymph nodes dissected to call it a dissection or clearance, but sampling), and suboptimal systemic treatments (not classic CMF administration, and only 2 years of tamoxifen prescription). It was proposed that PMRT improved results because of the suboptimal techniques of the other two treatment modalities (therefore, compensated in a way). The DBCG have conducted a reanalysis regarding these criticisms of their patients in whom more than eight lymph nodes were dissected [53]. That was an unplanned subgroup analysis of 1,152 patients chosen from 3,083 cases randomized in the 82b and the 82c trials. They reported even better local control and survival gains in the subgroup of patients with one to three positive nodes that received PMRT and were followed for over 15 years. However, local control and survival rates in the group with more than four involved nodes not receiving PMRT were so low (when compared to other institutions' results) that again suboptimal surgical and medical oncology management is suspected. The DBCG report can be regarded as hypothesis generating. The EORTC group also retrospectively analyzed their subgroup of patients with one to three lymph nodes to be involved after mastectomy [54]. They also reported that PMRT improves local control and survival at most in patients with one to three positive nodes involved. Researchers also indicated that their findings should be used as an initiative to start a new randomized PMRT trial in the low-moderate risk patients.

In 2005, the EBCTCG published their updated results of all PMRT randomized trials [4]. There were 25 trials and 9,933 cases that were treated by mastectomy and axillary surgery and then randomized for radiotherapy. PMRT advantage at 15 years was reported as follows: isolated locoregional recurrence rates in the node-positive group were reduced from 29% to 8% and breast cancer mortality reduced from 60% to 55%. In node-negative group locoregional recurrence rate was very low (8%) without radiotherapy, radiotherapy reduced it to 3%, but this small gain was not reflected as a survival advantage. According to EBCTCG data, PMRT, reduced locoregional recurrences by 11.6% absolute value in one to three positive-node patients, and by 14.8% absolute value in more than four positive-node patients (again, implying a benefit for PMRT in all node-positive cases). It was proposed that for every four locoregional recurrences prevented at 10 years with PMRT, one breast cancer death is prevented at 15 years. Some groups claim that one third of the patients analyzed in the EBCTCG report are from the two criticized trials of the DBCG and Canada, and that the two trials have very high rates of local and regional recurrences in the absence of PMRT; however, in other groups' experiences, locoregional recurrence rates are not that high, especially in the one to three node-positive patients. In the DBCG report, at 15 years one to three node-positive patients had locoregional recurrence rates of 27% and 4%, without PMRT and with PMRT, respectively [53]. The Eastern Cooperative Oncology Group, M.D. Anderson Cancer Center, International Breast Cancer Study Group, and NSABP

reported the rates of locoregional recurrence in one to three node-positive patients treated with mastectomy and no PMRT as 9%, 11%, 10%, and 7%, respectively [56–60]. A modern-era randomized PMRT study (SUPREMO) in patients with low-to-moderate risk factors (one to three axillary nodal positivity) has concluded accrual and the results are soon to be published.

9.7 Radiotherapy Fields

PMRT currently consists of chest wall irradiation plus peripheral lymph node region irradiation and the approach is called "comprehensive radiotherapy." There is consensus that when PMRT is indicated, chest wall should be included in all patients, as this is the site of recurrence in more than half of the cases diagnosed with locoregional failure [19]. However, there is controversy regarding inclusion of peripheral lymphatic areas to PMRT fields.

Two recent randomized studies from the EORTC (22922/10925) and the National Cancer Institute of Canada (NCIC) (MA.20) have completed accrual and are awaiting results. In the EORTC 22922/10925 trial more than 4,000 stages I to III patients after breast-conserving surgery were randomized to breast irradiation vs. breast plus internal mammary chain (IMC) and supraclavicular (SCV) node irradiation [61]. Node-negative patients were included if the tumor was medially or centrally presented; all node-positive patients were eligible for inclusion. More than 1800 early-stage patients after surgery were randomized to breast irradiation vs. breast plus İMC and SCV nodes irradiation in the NCIC MA.20 trial. The trial also accrued high-risk node-negative and node-positive cases. It is interesting that most of the node-positive patients had only one to three involved ganglions. In a preliminary report it was presented that the addition of regional nodal irradiation, even in patients with one to three lymph nodes involved, significantly decreased regional recurrences, increased DFS, decreased distant metastases rates, and showed a trend toward improved survival [62].

It is not customary to include lower levels (I and II) of the axillary fossa with the PMRT fields if surgical clearance is believed to be done optimally. In a surgically treated axilla, recurrence rates are very low, and there are no data that show the advantage of adjuvant radiation of these levels postoperatively. Also, high rates of arm edema after axillary dissection plus axillary irradiation makes the justification of this regional radiotherapy difficult [63, 64]. IMC node irradiation is left to the discretion of the treating radiation oncologist, awaiting the results of the two recent randomized trials stated above. SCV fossa is irradiated when there are more than four lymph nodes involved, as the recurrence rate is above 15% when not treated [65]. Controversy continues regarding patients with one to three involved nodes for the irradiation of the SCV fossa, awaiting the mature results of the MA.20 trial. Further discussions of elective regional nodal irradiation in patients with early-stage breast cancer, and design of regional nodal irradiation fields in patients with positive sentinel nodes but without axillary dissection can be found elsewhere [65, 66].

9.8 Conclusion

Postoperative adjuvant radiotherapy is a very important treatment modality after breast-conserving surgery and after mastectomy. It has been numerously shown that postoperative radiotherapy significantly improves locoregional control, DFS, breast cancer cause-specific survival, and most importantly, overall survival. Some indications of postoperative radiotherapy (PMRT in one to three positive-node patients, IMC and SCV node irradiation in low-risk patients, postoperative breast radiotherapy in elderly and low-risk cases), currently need further evidence. Some questions related to the techniques of the modern era (field design in sentinel node-positive patients without axillary dissection) will need further clarification and consensus guidelines. However, ongoing and closed to accrual randomized trials awaiting results will hopefully answer most of these questions in the near future.

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Chapter 10
Locally Advanced Breast Cancer

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10.1 Introduction

Locally advanced disease requires multimodality therapy that includes surgery, radiotherapy, and chemotherapy. Radiotherapy plays an important role in the management of locally advanced breast cancer. Postoperative radiotherapy significantly reduces the risk of locoregional failure and improves disease-free survival (DFS). Three important randomized clinical trials have shown a significant benefit in local control, DFS, and overall survival (OS) with the addition of radiation therapy for patients with stages II and III breast cancer. In addition to these data, the Early Breast Cancer Trialists' Collaborative Group meta-analysis concluded that one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided. In conclusion, radiation therapy has an important role and all guidelines recommend radiotherapy as a standard treatment in the management of locally advanced disease.

Locally advanced breast cancer has several clinical presentations, from large primary tumor with or without extensive regional lymph node metastases to inflammatory breast cancer (stage IIB (T3N0M0)—IIIA-IIIC disease) [1].

Locally advanced disease requires multimodality therapy. A multimodality treatment approach is usually required for achieving optimal control of local, regional, and distant disease. Combined modality treatments include surgery, chemotherapy, and radiation. In addition, hormone receptor-positive disease should be treated with hormonal therapy, and human epidermal growth factor receptor-2/neu-positive disease should be treated with trastuzumab. Combined modality therapy has significantly improved the prognosis for patients with advanced breast cancer [2].

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The combined modality treatment for any given patients should be individualized over a wide range of clinical presentations, ranging from surgery followed by adjuvant chemotherapy, to neoadjuvant chemotherapy followed by surgery. In all cases, the application of radiation therapy is tailored to the extent of disease at initial presentation.

Postoperative chest wall and regional lymph node adjuvant radiation therapy has traditionally been given to selected patients considered at high risk for locoregional failure following mastectomy. Factors associated with a high rate of local recurrence after mastectomy include having a large (T3) primary tumor, at least four positive axillary lymph nodes, extracapsular nodal extension, and very close or positive surgical margins [3].

Three randomized clinical trials have shown that DFS and OS benefit from the addition of chest wall and regional lymph node irradiation in women with positive axillary lymph nodes after mastectomy and axillary lymph node dissection [4–7].

The first trial was performed by the Danish Breast Cancer Cooperative Group (DBCG). They randomized 1,708 premenopausal women (DBCG 82 b trial) with either positive axillary nodes, a tumor size of more than 5 cm, or invasion of the cancer to skin or the pectoralis fascia [4]. After modified radical mastectomy and a level I axillary lymph node dissection, all patients received nine cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy regimen. About one half of all patients were randomly assigned to receive radiation therapy. The radiation field included the chest wall, supra- and infraclavicular nodes, axillary nodes, and internal mammary nodes. The dose of radiation for most patients was 50 Gy given over 5 weeks. DFS was 48% in the radiotherapy plus CMF group, and 34% in the CMF alone group at 10 years. Also, OS was 54% in the radiotherapy and CMF group, compared with 45% in the CMF alone group. Radiotherapy reduced the risk of local recurrence by about 80% and the risk of death by about 30%. The study showed that radiotherapy after mastectomy significantly improved DFS and OS, irrespective of tumor size, the number of positive nodes, or the histopathologic grade. The same group performed a study (DBCG 82 c trial) in 1,300 postmenopausal high-risk breast cancer patients treated with tamoxifen alone or with postoperative radiotherapy to the chest wall, and regional lymph nodes showed that radiation therapy reduced the risk of local recurrence from 35% to 8% and improved DFS from 24% to 36% and OS from 36% to 45% [5]. Because many patients had relatively few lymph nodes removed in the DBCG 82 b and c trials, these studies were pooled and reanalyzed to include only the 1,152 node-positive patients with eight or more nodes removed [6]. Radiotherapy reduced the 15-year locoregional failure rate from 51% to 10% and improved the 15-year survival from 12% to 21% in four or more node-positive patients.

The third trial was conducted by the British Columbia Cancer Agency and included 318 premenopausal women with at least one positive axillary node [7]. After a modified radical mastectomy with level I and level II axillary node dissection and adjuvant CMF chemotherapy, patients were assigned to receive no further chemotherapy or radiation therapy. The radiation fields were similar to that of the Danish trial. But the dose of radiation was about 25% lower, 37.5 Gy given in

16 fractions. DFS was 48% in the radiation group compared with 30% in the CMF alone group at 20 years. Also, OS was 47% in the radiation group compared with 37% in the CMF alone group. Approximately one third of systemic breast cancer events and breast cancer deaths were reduced by radiation therapy. The impact of radiation was compared for the subgroups of patients with one to three positive lymph nodes and those with four or more positive lymph nodes. The benefits for radiotherapy were seen in patients with one to three positive nodes and in those with four or more positive nodes.

The Early Breast Cancer Trialists' Collaborative Group published a meta-analysis based on data from 8,500 women with mastectomy, axillary clearance, and node-positive disease and enrolled in randomized trials of radiotherapy [8]. In their update, the 5-year local recurrence risk was reduced using radiotherapy from 23% to 6% (reduction, 17%), 15-year breast cancer mortality risk was reduced from 60.1% to 54.7% (reduction, 5.4%), and an overall mortality was reduced from 64.2% to 59.8% (reduction, 4.4%). In subgroup analyses, the 5-year local recurrence rate was reduced by 12% for women with one to three positive lymph nodes and by 14% for women with four or more positive lymph nodes. The authors concluded that in the hypothetical absence of other causes of death, about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided.

Locally advanced breast cancer is currently treated with preoperative chemotherapy prior to mastectomy as the initial therapeutic approach in most cases. However, information on the efficacy of postmastectomy radiation therapy is limited. There are two retrospective analyses that have provided evidence for benefit of radiation therapy for this group of patients [9, 10].

The University of Texas M. D. Anderson Cancer Center retrospectively compared 542 patients treated with neoadjuvant chemotherapy, mastectomy, and radiation therapy with the outcomes of a control group of 134 patients who were treated with neoadjuvant chemotherapy and mastectomy without radiation [9]. The 10-year locoregional recurrence rates were significantly lower for irradiated patients at 11% compared with 22%. Patients who presented with clinical stage III or IV disease but subsequently achieved a complete pathologic response to neoadjuvant chemotherapy also had a significantly high rate of locoregional recurrence that was reduced with radiation therapy. At 10 years, the locoregional recurrence rate was reduced from 33% to 3%. Radiation therapy improved cause-specific survival in patients with stage IIIB disease, clinical T4 tumors, and four or more positive nodes. The authors concluded that radiation therapy should be considered for these patients regardless of their response to neoadjuvant chemotherapy. In 2007, the same institution reported their updated data that included 226 patients who achieved a pathologic complete response to neoadjuvant chemotherapy [10]. The 10-year local recurrence rate for patients with stage III disease was significantly reduced with radiotherapy from 33% to 7%. Also, the use of radiation therapy was associated with an improvement in disease-specific survival and OS.

10.2 Conclusion

Randomized trials and meta-analyses have demonstrated that radiation therapy plays an important role in the treatment of locally advanced breast cancer. All guidelines recommend radiation as a standard treatment in the management of locally advanced disease [11–14].

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Chapter 11
Metastatic Breast Cancer

Zeynep Ozsaran and Senem Demirci Alanyalı

11.1 Introduction

The role of radiotherapy (RT) for metastatic breast cancer is broken down into three settings: the first and most common is palliative radiotherapy, the second is stereotactic RT for oligometastases, and the third is the irradiation of the breast for locoregional control. The goal of treatment is to prolong survival, to lengthen the time to progression, to provide relief for disease-related symptoms, and to improve the quality of life of the metastatic patient. Nevertheless, treatment modalities with minimal toxicity are preferred for each patient on an individual basis. A multidisciplinary team including a medical oncologist, a radiation oncologist, a breast surgeon, and a psychiatrist is necessary for guiding optimal treatment.

11.2 Bone Metastases

Bone metastases generally advance to regions such as the vertebrae, pelvis, cranium, and proximal parts of the diaphysis possibly due to the high blood flow in these regions (Fig. 11.1).

Standard diagnostic procedures include plain radiographs and bone scintigraphy, while further evaluation includes computed tomography (CT) and magnetic resonance imaging (MRI). Treatment decision making is the responsibility of the multidisciplinary team based on the risk of fracture; presence of nerve/cord compression; the size, number, location, and nature of the metastases; and life expectancy of the patient (see Fig. 11.2 for treatment algorithm).

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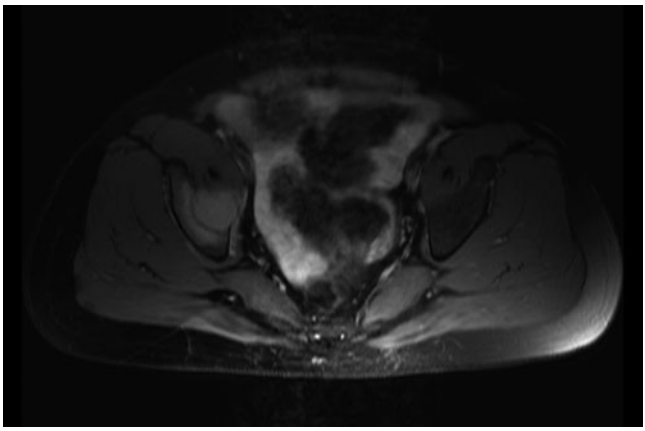

Fig. 11.1 Bone metastases in right acetabulum and soft tissue extension

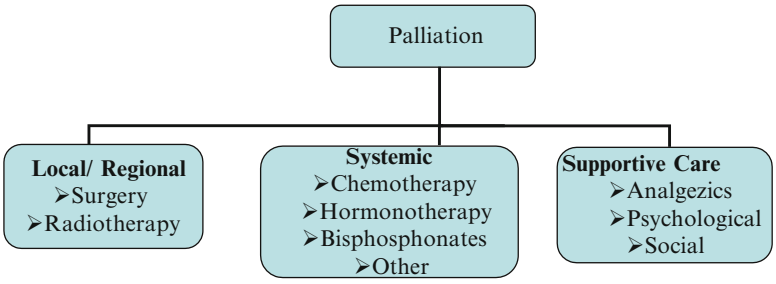

Fig. 11.2 Palliative treatment algorithm for bone metastases

RT is the preferred treatment option for palliation because of its fast and long-standing relief of symptoms with minimal toxicity. For patients with metastatic breast cancer, the most common indication of RT is for bone metastases. Goals of palliative RT are to palliate pain, improve function, and to decrease the risk of fracture and compression [1–4].

By administration of RT to the tumor-bearing metastatic bone, the following physiologic processes continuously occur: Initially, degeneration and necrosis followed by collagen proliferation; increase blood flow and osteoblastic activity and finally bone trabeculation and mineralization begin. Recalcification occurs within 3–4 weeks, and remodulation after 6 months. After administering RT, palliation of pain that had been caused by the secreted humoral factors following RT occurs (i.e., prostaglandin, shrinkage of the tumor, and reduced periostal tension). Palliation of pain can be achieved for 65% of patients and recalcification of the involved bone could be seen on radiographs a few months after RT.

A recent review article indicated that partial palliation of pain may be achieved in 58% of patients and complete palliation of pain in 23% [5]. Several randomized trials had compared various dose and fractionation models for palliative RT (i.e., 10 × 2 Gy, 10 × 3 Gy, 5 × 4 Gy, 1 × 8 Gy) but there is no stated consensus

regarding the optimal dose and fractionation model. Previously, our group published a randomized trial comparing three different dose-fractionation models (10 × 3 Gy, 5 × 4 Gy, 1 × 8 Gy) in 109 differently located bone metastases. In regard to palliation rate, duration, and need for analgesics, 10 × 3 Gy was found to be superior over 1 × 8 Gy (respectively; $p = 0.014$, $p = 0.031$, and $p < 0.001$). In our analysis we concluded that for patients with solitary metastases, having greater than 1 year of life expectancy and a long-term interval between initial diagnosis and the onset of metastases, administration of higher doses with more fractionations would be preferred. For patients with multiple metastases with short life expectancy and for centers with high patient load, single-fraction models should be considered. Moreover, in order to preserve the bone marrow of patients who are planning to undergo chemotherapy, care should be taken to avoid unnecessary bone marrow irradiation [6].

The Radiation Therapy Oncology Group (RTOG) 97-14 randomized trial evaluated two different fractionation models (1 × 8 vs. 10 × 3 Gy) for breast and prostate cancer patients with bone metastases, and did not demonstrate any difference regarding pain palliation and the need for narcotic analgesics. However, acute side effects were found to be higher in the 10 × 3 Gy arm of the study and the reirradiation rate was found to be higher in the 1 × 8 Gy arm of the study [4].

Spinal cord compression is an oncologic emergency and early treatment is required. Neurologic condition and sensorial and motor impairment levels of the patient should be evaluated. Decision for RT and the dose fractionation model should be considered according to the localization, size, and number (single or multiple) of metastases, the presence of other metastases, performance status, and life expectancy of the patient. Randomized trials have evaluated 10 × 3, 5 × 5, 5 × 3, 5 × 4, and 1 × 8 Gy and found no difference regarding pain palliation and the use of narcotic analgesics. However, as a result of long-term palliation and less need for retreatment, long-term models are preferred for patients with a long life expectancy [3–5].

The American Society for Therapeutic Radiology and Oncology (ASTRO) guideline evaluated the results of 25 randomized clinical trials, 20 prospective single-arm trials, and four meta-analysis/systemic reviews. According to the comparison of randomized trials using 10 × 3, 6 × 4, 5 × 4, and 1 × 8 Gy, fractionated RT courses have been associated with an 8% repeat treatment rate vs. 20% after a single fractionation. No difference was observed between these fractionation schemas for late term side effects. Task Force strongly suggested that stereotactic body radiation therapy (SBRT) should be used in available clinical trials and SBRT should not be the primary treatment of vertebral bone lesions causing spinal cord compression. Additionally they stated that SBRT might be feasible, effective, and safe for the repeat treatment of spinal lesions. The task force suggested inclusion criteria for SBRT for spinal bone metastases as follows: Spinal or paraspinal metastases detected using MRI, no more than two consecutive or three noncontiguous spine segments involved, age 18 years or older, Karnofsky Performance Status (KPS) greater than or equal to 40–50, medically inoperable (or patient refused surgery), histologic proof of malignancy, biopsy of spine lesion if first suspected metastasis, oligometastatic or bone only metastatic disease, and any

of the following: previous external beam radiation therapy (EBRT) less than 45 Gy total dose, failure of previous surgery at that spinal level, and presence of gross residual disease after surgery [7].

The choice of surgical decompression for the spinal cord compression should be made by an interdisciplinary team while considering the performance status, primary tumor site, extent and distribution of metastases, and expected survival rate, and longer fractionation models (i.e., 10 × 3 Gy) was suggested for spinal cord compression. The guideline favors surgical decompression for spinal cord compression in patients 65 years or younger, KPS greater than or equal to 70, projected survival of more than 3 months, slow progression of neurologic symptoms, maintained ambulation, nonambulatory status for less than 48 h, solitary site of tumor progression, absence of visceral or brain metastases, spinal instability, relatively radioresistant tumor types such as melanoma, site of origin suggesting relatively indolent course (such as prostate, breast, and kidney), and for patients where EBRT had previously failed. The task force mentioned that bisphosphonates do not obviate the need for EBRT for painful sites of metastases and might, in fact act effectively when combined with EBRT [7].

Bisphosphonates prevent osteoclastic bone resorption and are an essential part of the treatment of bone metastases. After administration, they bind to the bone minerals around the osteoclasts and inhibit osteoclast maturation and induce apoptosis both in osteoclast and tumor cells, and also inhibit osteoclast migration to the bone resorption area, decrease cytokine production, and inhibit invasion and adhesion of tumor cells to the bone matrix. Published series have demonstrated that the use of bisphosphonates decreases pain and the need for analgesics, prolongs the time interval for the development of new bone metastases, and improves the quality of life of the patient. The current treatment algorithm for use of bisphosphonates is to initiate their use during the first occurrence of bone metastases continue through progression [8]. The National Comprehensive Cancer Network guideline recommends the use of bisphosphonates in metastatic bone disease and its use is connected to fewer skeletal-related events, fewer pathologic fractures, and less need for radiation therapy and surgery to treat bone pain [9].

The combination of bisphosphonates with RT was evaluated in a retrospective study including 372 patients treated with RT alone and RT + bisphosphonates (with three different fractionation models; 10 × 3 Gy, 5 × 4 Gy, 1 × 8 Gy). For the whole group, 79.8% of patients had greater than 50% palliation and no difference was seen between different dose fractionation models or with the addition of bisphosphonates for palliation rates [10].

American Society of Clinical Oncology (ASCO) guidelines on the use of bisphosphonates in breast cancer originally published in 2000, and updated in 2003 and 2011. According to the ASCO guidelines, initiation of bisphosphonates is recommended for bone metastases detected on bone scintigraphy, CT, or MRI and no consensus was stated for bone metastases detected only on bone scintigraphy but not with other imaging techniques. For patients with nonskeletal metastases, bisphosphonates might have an impact for pain control but were not recommended for other than clinical trial [11].

11.3 Brain Metastases

Brain metastastes are observed less frequently than bone, lung, and liver metastases. Depending on the location of the metastatic lesion, the symptoms (i.e., headache, nausea and vomiting, paresis, plegia, epilepsy, syncope, and mental status alterations) might impair the quality of life of the patient, and therefore brain metastases are considered an oncologic emergency (see Fig. 11.3).

Treatment decision making for brain metastases is based on tumor localization, size, and number; the presence of other metastatic sites; performance status of the patient; and the time interval between primary diagnosis and the onset of metastases (Fig. 11.3). The initial approach to treatment is to decrease the intracranial pressure with steroids within the first 48 h and to alleviate neurologic symptoms. Dexamethasone is the preferred steroid agent with use of doses of 16 mg/day. However, the long-term use of steroids can cause side effects such as gastrointestinal bleeding, perforation, hyperglycemia, pancreatitis, vision impairment, and increased rate of infection and therefore, RT is the preferred treatment option for long-term palliation of brain metastases [4, 8, 10, 11].

Surgical excision can significantly improve survival of selected patients with brain metastases, providing a median survival of 10–12 months, and a 5-year overall survival rate of 12%. Patchell et al. evaluated 48 patients with single brain metastases and randomized patients into two groups; group 1 was treated with 36 Gy (12 × 3 Gy) to whole brain and group 2 was treated with surgical excision followed by the same RT fractionation. Local recurrence was seen in 52% of patients in the RT only group and 20% in the surgery + RT group ($p < 0.05$) and time to recurrence was 5 months vs. 14 months, respectively, in RT only and surgery + RT group ($p = 0.02$). Patients treated with surgery + RT maintained KPS of greater or equal to 70% much longer than the patients treated with radiation alone (median, 38 weeks vs. 8 weeks; $p < 0.005$). Median length of survival was 15 weeks vs. 40 weeks, respectively, in RT only and surgery + RT group ($p < 0.01$). The authors emphasized the role of surgery in solitary brain metastases due to the lower recurrence rates, improved survival, and quality of life [12].

However, the decision for surgical resection should be evaluated individually and restricted to patients with suitable localization for surgery, controlled primary disease, and patients without meningeal metastases. Resection of the largest lesion in multiple brain metastases may provide symptomatic relief but is not a standard procedure. For patients with solitary metastases but who are unsuitable for surgery, and for patients with multiple metastases, optimal treatment is whole brain RT. RT improves survival, provides a palliation rate of 60–90%, improves KPS by 10–20%, and improves severe neurologic symptoms in two thirds of patients. Commonly used dose-fractionation models are 5 × 4, 10 × 3, and 10 × 2 Gy and no difference was detected regarding palliation and survival rates among these models.

Graham et al. conducted a trial that included 113 patients with brain metastases with no or stable extracranial tumors and randomized patients into two study arms; in the first arm included patients who were treated with 20 × 2 Gy and the second arm included patients who were treated with 5 × 4 Gy. No survival difference was

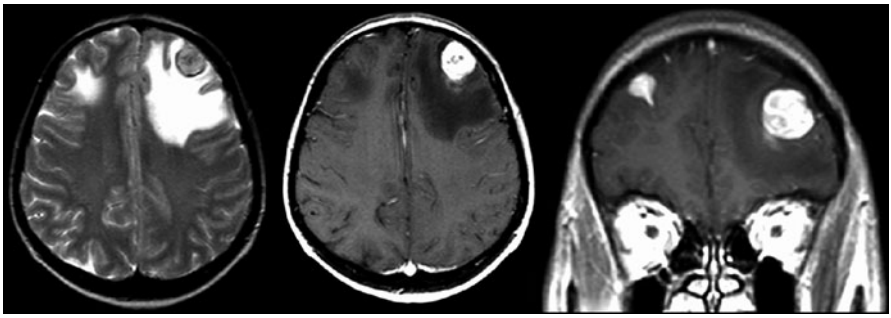

Fig. 11.3 Brain metastases

seen among the two arms but the rate of intracranial progression was 44% in the long fractionated arm and 64% in the short fractionated arm ($p < 0.05$) and the rates for surgery and/or reirradiation were 4% in arm one and 21% in arm two ($p < 0.05$). The authors concluded that 40 Gy provides better intracranial control in patients with a long life expectancy and a good prognosis [13].

During the last decade stereotactic radiosurgery (SRS) has been accepted as an alternative to surgery for solitary metastases or oligometastases. SRS also increases the dose to the metastatic region.

Linskey et al. published a systematic review and evidence-based clinical practice guideline and aimed to answer the question of whether patients with newly-diagnosed metastatic brain tumors should undergo SRS compared with other treatment modalities. The authors reviewed studies of patients treated with RT + SRS with tumors smaller than 3 cm, midline shift less than 1 cm, and KPS greater than 70%. They concluded that single-dose SRS along with whole brain radiation therapy (WBRT) improves survival of patients with solitary metastases who have KPS greater than or equal to 70 (level 1 evidence); single-dose SRS along with WBRT is superior in terms of local control and maintaining functional status when compared with WBRT alone for patients with 1–4 metastatic brain tumors who have KPS greater than or equal to 70 (level 2 evidence); single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2–3 metastatic brain tumors (level 3 evidence). The review compared surgical resection plus WBRT vs. SRS plus WBRT and no survival difference was noted (level 2 evidence). Single-dose SRS and WBRT alone were compared and single-dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of survival (level 3 evidence) [14].

11.4 Palliation of Patients With Oligometastases

A group of patients with metastatic breast cancer with biologically less-aggressive and slow-growing tumors have longer survival rates compared to other metastatic breast cancer patients. In the published literature, 5-year survival rates and cure

rates of patients with oligometastases and good performance status are approximately 5–10% and 2–5%, respectively. Progression of metastatic disease in breast cancer is significantly different from other types of cancers; breast cancer patients with limited metastases are being treated with surgery and/or radiotherapy with curative intent in addition to systemic chemotherapy [14, 15]. Aggressive local treatment may improve disease-free and overall survival rates with a chance of cure [15]. Local treatment approaches for oligometastatic patients include resection, radiofrequency ablation, RT, and particularly SRS with its noninvasive advantage and better treatment tolerance.

Parallel to the advances of technology radiotherapy discipline is evolving and radiosurgery is an option for both cranial and extracranial metastases. Milano et al. had defined oligometastases as less than five metastases and demonstrated that the stereotactic RT improves survival rates in this group of patients (liver, lung, bone, thoracic, and abdominal lymph nodes) [15].

11.5 Breast/Chest Wall RT for Metastatic Patients

RT of the breast/chest wall can be applied to patients who are metastatic at diagnosis. Studies have showed that 3.5–10% of the patients diagnosed at the metastatic stage and surgery for the primary tumor of the breast may improve patient survival rates [16, 17]. Studies are being conducted to better understand the efficacy of RT of the breast and peripheral lymphatics for patients with metastatic disease at diagnosis. Scodan et al. analyzed 598 patients with metastatic breast cancer and showed that local RT decreases the death rate by 30% as a result of decreasing tumor burden and risk of tumor dissemination and by increasing the effectiveness of chemotherapy [16]. However, well-designed randomized studies are required in this area.

11.6 Conclusion

In metastatic breast cancer patients RT can be utilized effectively for the palliation of the metastases and for breast/chest wall irradiation in selected patients.

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Part III
Radiotherapy Atlas in Breast Cancer

Chapter 12
The Organs at Risk and Radiation Tolerance Doses

Senem Demirci Alanyalı, Naim Ceylan, and Ayfer Haydaroglu

12.1 Introduction

During the last two decades, early diagnosis and better treatment options have improved the survival rates of breast cancer patients [1]. Radiotherapy (RT) is an essential component of the treatment of patients with early and locally advanced disease and has been shown to reduce local recurrence risk by approximately 20% and breast cancer mortality risk by 5% [2]. However, RT-induced toxicities may manifest from months to decades after treatment and may be related to severe morbidity and mortality. Older RT techniques are particularly associated with an excess risk of non-breast cancer mortality, which was mainly from heart disease [2]. The goal of modern RT techniques is to improve the therapeutic ratio by increasing tumor control and decreasing toxicity.

Breast tissue/chest wall and regional lymphatics have close proximity to vital organs such as the lung, heart, and coronary arteries. Moreover, consideration should be given to the contralateral breast, contralateral lung, brachial plexus, esophagus, thyroid, and spinal cord as well. The optimal delineation of organs at risk (OAR) carries substantial importance due to its influence on treatment planning evaluation. Inadequate delineation of OAR results in the misinterpretation of dose volume histograms (DVH) [3]. Therefore, differences in contouring are clinically and dosimetrically significant and a consensus is highly desirable.

The aim of this chapter is to provide delineation algorithms for OAR and dose-volume constraints for RT planning of breast cancer. Dose-volume constraints derived mainly from Emami estimates, major Radiation Therapy Oncology Group (RTOG) protocols, and the recent Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) reviews [4–9].

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12.2 Lung

12.2.1 Contouring

To our knowledge, no guideline or atlas is available for contouring. A level of −500 and a window of 1,500 Hounsfield units (HU) to contour lung parenchyma, and a level of 50 and a window of 350 HU to contour the mediastinum was recommended. Computed tomography (CT) should start at or above the mandible and extend several centimeter below the inframammary fold (including the entire lung). A CT scan thickness of less than or equal to 0.5 cm should be utilized. All inflated lung and small vessels (<1 cm or vessels beyond the hilar region) should be contoured and the trachea/bronchus, proximal bronchial tree, and descending aorta should be excluded. Autocontouring capabilities of modern treatment planning systems are being used for this purpose [10]. However, clinicians should review and edit the automated contours for missing or overcontoured areas. The delineation of lungs is shown in Fig. 12.1.

Both lungs should be contoured separately as ipsilateral and contralateral lung and evaluated in DVH. For breast cancer patients, dose-volume constraints of the ipsilateral lung is the major concern in contrast to the total lung dose-volume for other intrathoracic malignancies (i.e., lung, lymphoma) [6].

12.2.2 Dose-Volume Constraints and Toxicity

Radiographic abnormalities are seen in approximately 27–40% of breast cancer patients treated with RT; the frequency of clinically significant pneumonitis is less than 10%. Acute radiation pneumonitis (ARP) occurs 8–16 weeks following RT and consists of dyspnea, nonproductive cough, pleuritic chest pain, fever, rales, and radiographic changes such as pneumonia. ARP responds well to steroids, and the risk of ARP is associated with RT dose, fractionation, irradiated lung volume/lung region, presence with concurrent chemotherapy (taxanes) or hormonal therapy, older age (>60 y), and patient-related factors such as history of lung disease, poor pulmonary function test, history of smoking, and genetic susceptibility for toxicity [11]. Subclinical lung damage includes decrease in pulmonary function tests and radiologic changes and generally does not cause any clinical symptoms [12]. RT-induced late lung toxicity manifests many months after RT, is detectable on radiographs, and often clinically asymptomatic.

Emami et al. gathered data from two-dimensional (2D) planning and defined the dose constraints of the lung. TD5/5 (tolerance dose of complication rate of 5% within 5 years of RT) of the whole lung is 17.5 Gy, 2/3 of the lung is 30 Gy and 1/3 of the lung is 45 Gy [4]. With conventional 2D treatment planning to limit the lung within 3 cm or less of the chest wall was accepted and routinely is used in the clinics [11].

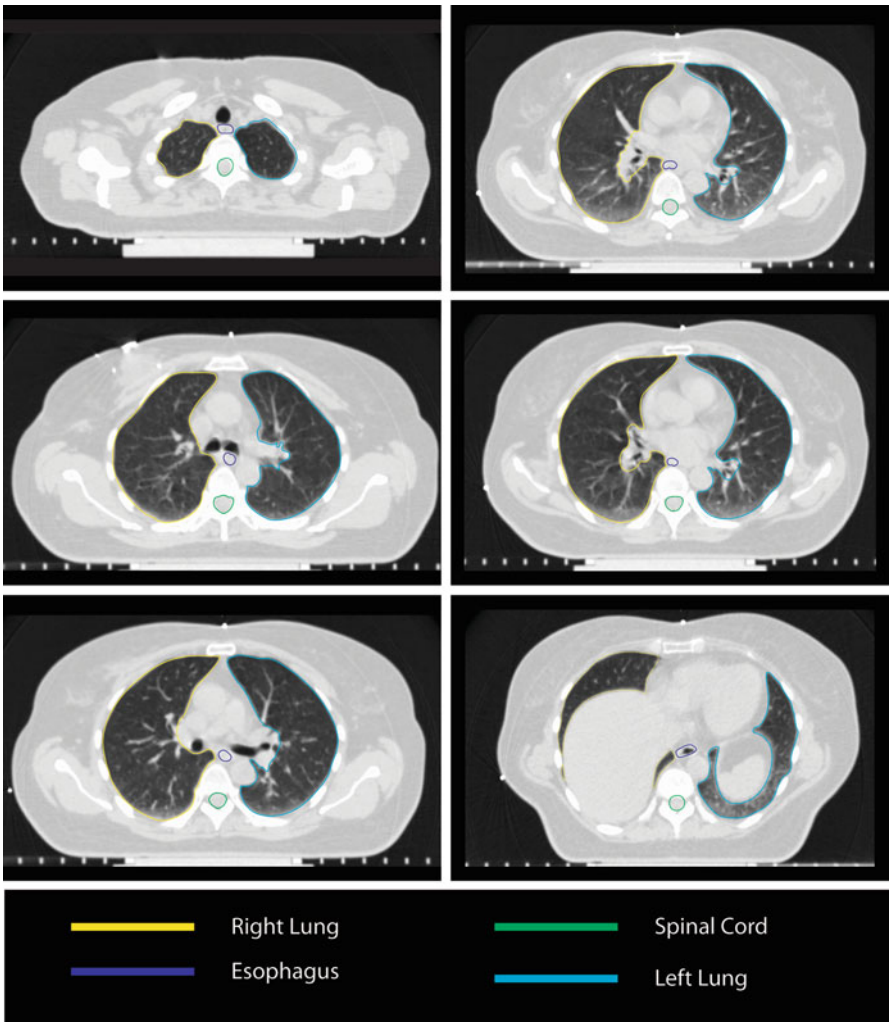


Fig. 12.1 The delineation of both lungs as organs at risk

With three-dimensional (3D) planning we are now able to evaluate dose and volume. Dosimetric predictors of RT-induced lung injury are mean lung dose (MLD) and percentage of the total lung volume treated to a minimum of x dose (such as V5, V13, V20, V30, and V40) and parameters derived from intrathoracic malignancies (lung tumors and lymphomas). Marks et al. reported V20 $\leq$ 30% is associated with a symptomatic pneumonitis risk of <20%, and as the MLD increases from 7 to 27 Gy, the risk of symptomatic pneumonitis increases from 5% to 40% [6]. Graham et al. reported the rate of clinically significant pneumonitis as 0% for V20 $<$ 22% and the risk increased to 36% for V20 $>$ 40% [13]. Data from the Princess Margaret Hospital suggest minimal risk of grade 2 radiation pneumonitis (RP) with a V20 $<$ 36% and MLD $<$ 14 Gy. The risk of RP was <20%

for V20 $\leq$ 30% [14]. Therefore, limiting MLD $\leq$ 20–23 Gy and V20 $\leq$ 30–35% was recommended to keep the RP risk at less than 20% for intrathoracic malignancies.

However, dose distribution (higher doses to small lung volume) and DVH parameters (ipsilateral and contralateral lung vs. total lung) of breast cancer are different from those of lung cancer. For patients with breast cancer, the rate of symptomatic pneumonitis is approximately 1–2% after whole-breast RT without nodal RT [11].

Published studies have showed that the rate of symptomatic pneumonitis appears to be less than 4% if the V20 is kept to less than 7%, and may be somewhat higher (up to 7–16%) when the V20 increases toward approximately 30% [15–21].

The RTOG 1005 breast cancer study protocol suggests keeping the ipsilateral lung V20 $\leq$ 15%, V10 $\leq$ 35% and V5 $\leq$ 50% for patients treated with tangents only. The V5 of the contralateral lung should be less than 10–15% [5]. The dose-volume constraints can vary according to the addition of regional nodal irradiation and no clear consensus for those was stated [22]. The University of Michigan reported on their dosimetric study on four different intensity modulated radiotherapy (IMRT) techniques for comprehensive locoregional irradiation (breast, supraclavicular, infraclavicular, internal mammary lymph nodes). Dose-volume constraints were defined as left lung V20 $<$ 33% [23]. Similarly, Lind et al. investigated the relation of ipsilateral V20 constraint and RP and aimed to keep V20 $<$ 30% in their patient population treated with locoregional RT and found that V13 is correlated with radiologic RP and might be a promising dose constraint for the future studies [24].

Dose-volume constraints of the ipsilateral lung are presented in Table 12.1.

12.3 Heart

12.3.1 Contouring

Feng et al. developed and validated a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. The atlas was developed by a cardiologist, cardiac radiologist, and radiation oncologist. The whole heart, along with the substructures, including the chambers, great vessels, cardiac valves, conduction system, and major coronary vessels were delineated. For optimal visualization of most structures on CT images, investigators recommended a level of 50 and a window of 500 Hounsfield units (HU) and for viewing cardiac vessels, a level of 50 and a window of 150 HU [25]. The delineation of the heart is shown in Fig. 12.2.

12.3.1.1 Pericardium

To predict the rate of pericarditis, Martel et al. recommended contouring the pericardium volume. The “pericardium volume” was defined as a “rind” within

Table 12.1 Summary of dose-volume constraints used in protocols and published studies

	Ipsilateral lung	Heart	Esophagus	Contralateral breast	Brachial plexus
RTOG protocols	RTOG 1005[a] [5]	RTOG 1005[a] [5]	RTOG 0623 [5]	RTOG 1005[a] [5]	RTOG 0619 [5]
		Left-sided BC	RTOG 0617 [5]		
	Ideal	Ideal	Mean dose 34 Gy, 60 Gy to 10 cm	Ideal	Maximum dose 66 Gy
	V20 $\leq$ 15%	V20 $\leq$ 5%		D max $\leq$ 3 Gy	V60 $<$ 5%
	V10 $\leq$ 35%	V10 $\leq$ 30%		Acceptable	RTOG 0522 [5]
	V5 $\leq$ 50%	Mean dose $\leq$ 400 cGy		D max $\leq$ 3.3 Gy	Max dose 60 Gy
	Acceptable	Acceptable			
	V20 $\leq$ 20%	V25 $\leq$ 5%			
	V10 $\leq$ 40%	V10 $\leq$ 35%			
	V5 $\leq$ 55%	Mean dose $\leq$ 500 cGy			
Pittsburg Cancer Inst.[a] [47]	V20 $<$ 20%	V30 $<$ 20% (left BC)	NS	NS	NS
University of Michigan[a] [48]	V20 $\leq$ 33%	V15 $\leq$ 1%	NS	V10 $\leq$ 1%	NS
French Society of Radiation Oncology [35]	V20 $<$ 15 % V30 $<$ 10%	<35 Gy	Max 40 Gy (15 cm)	NS	<55 Gy
VCU[b] [43]	V5 $\leq$ 30%	V5 $\leq$ 50%	V30 $\leq$ 0	V 2.5 $\leq$ 0	NS
	V20 $\leq$ 10%	V10 $\leq$ 30%			
	V0 $\leq$ 50%	V20 $\leq$ 10%			
		V30 $\leq$ 3%			
British Columbia[b] [49]	Max dose 40 Gy	Max dose 40 Gy	NS	Max dose 10 Gy	NS
	V10 $<$ 60%,	V10 $<$ 60%			

BC breast cancer; *VCU* Virginia Commonwealth University; *NS* not stated.
[a]breast tangents only.
[b]breast tangents+regional nodes.

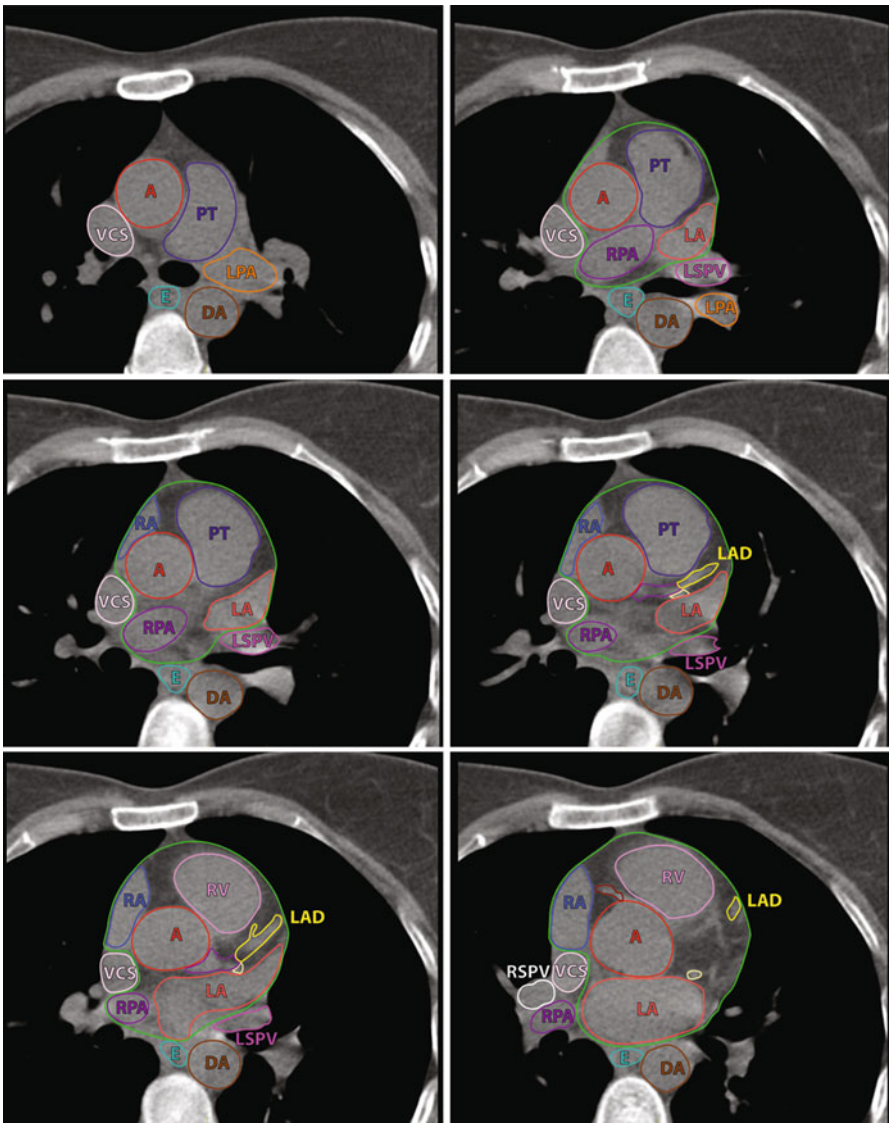


Fig. 12.2a (continued)

the previously contoured heart volumes. The manually contoured heart volumes served as the outer border, and the inner border was automatically contoured 1 cm within these same contours using the planning system [26].

12.3.1.2 Whole Heart

The superior border is located inferior to the left pulmonary artery and continues to the diaphragm inferiorly. Because cardiac vessels locate in the fatty tissue within the pericardium, they should be included in the contours.

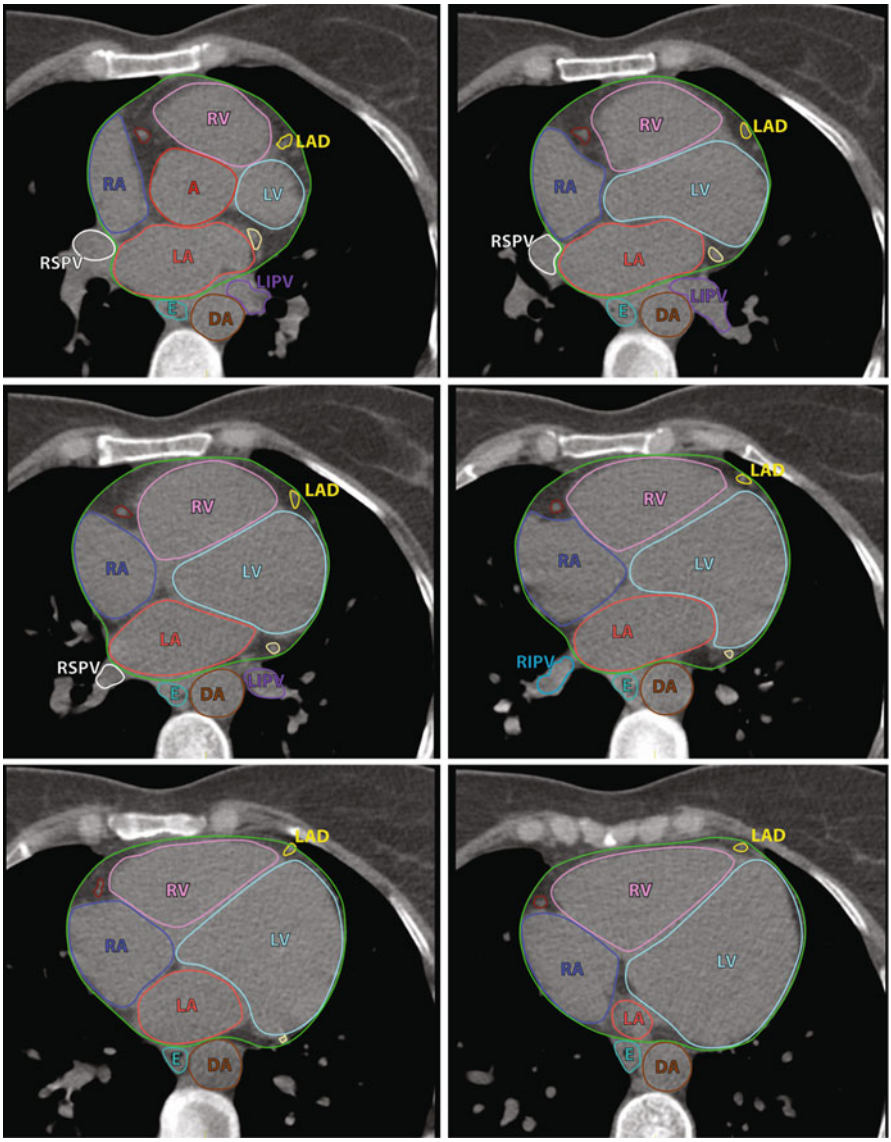


Fig. 12.2b (continued)

12.3.1.3 Chambers

The left atrium is observed as the most superior chamber of the heart on axial CT and begins just inferior to the left pulmonary artery and is located to the left and posterior to the pulmonary trunk. The left ventricle is located anterior to and to the left of the left atrium. The right atrium starts to the right of the aortic root superiorly. The right ventricle lies beneath the sternum and connects to the pulmonary trunk.

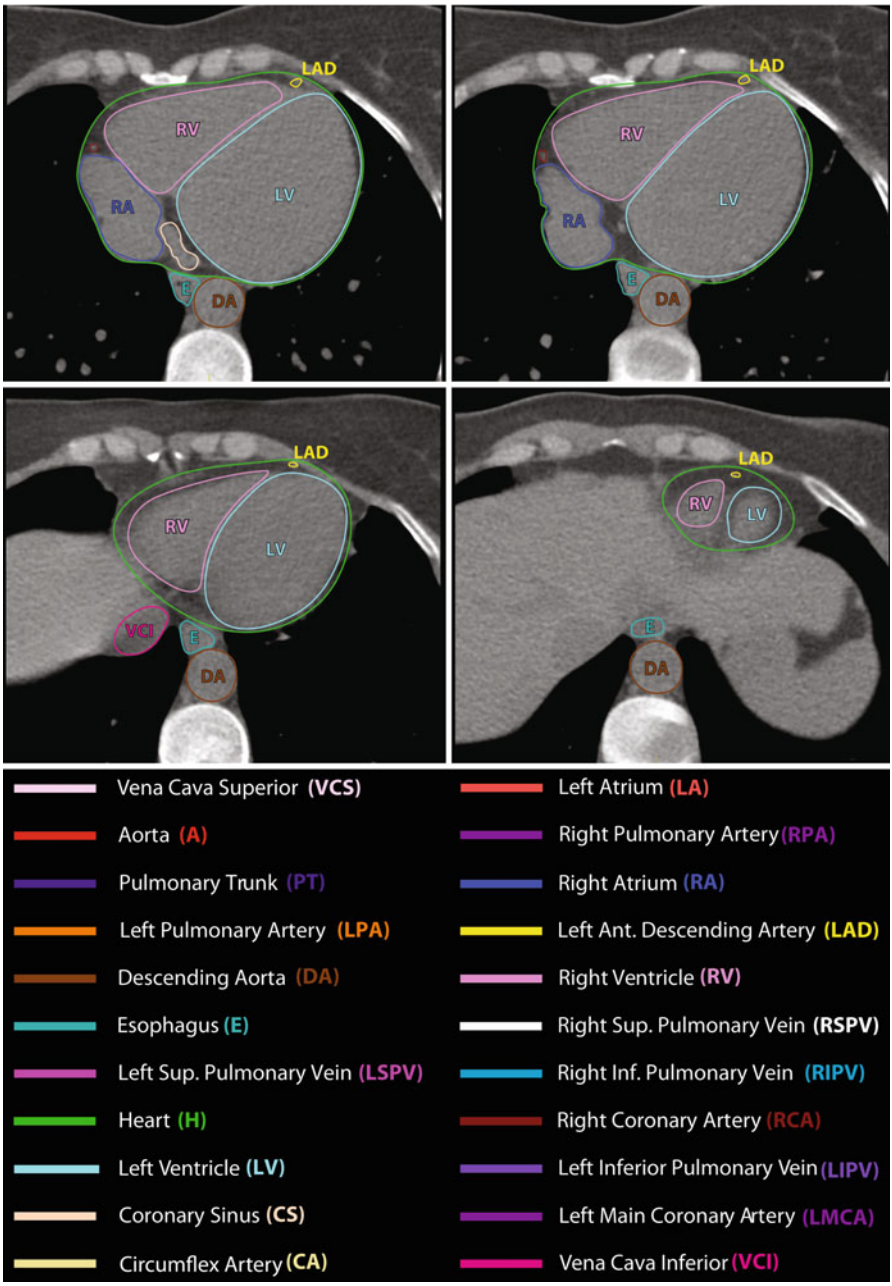


Fig. 12.2c (**a**–**c**) The delineation of the heart as an organ at risk

12.3.1.4 Vessels

The left main artery originates from the left side of the ascending aorta, inferior to the right pulmonary artery. The left anterior descending artery (LAD) originates from the left coronary artery and runs through the interventricular groove between the right and left ventricles (contouring adjustment of the level to 50, window to 150 was recommended).

The left circumflex artery originates from the left coronary artery and runs between the left atrium and ventricle. The right coronary artery originates from the right side of the ascending aorta.

12.3.1.5 Valves

The aortic valve is placed within the ascending aorta and leaflets create a "Y" shape on a contrast scan. The pulmonic valve is found within the pulmonary trunk and leaflets create a "X" shape on a contrast scan. The tricuspid valve is located between the right atrium and ventricle and the mitral valve is located between the left atrium and ventricle, and both are difficult to observe and delineate.

12.3.2 Dose-Volume Constraints and Toxicity

RT-induced heart injury may manifest as acute or late toxicity. Pericarditis is an acute injury often transient but may be chronic. Late injury includes congestive heart failure, ischemia, coronary artery disease, and myocardial infarction. Late toxicity manifests from months to decades after RT and can cause cardiac morbidity or mortality [27].

For centers using 2D planning, Emami et al. estimated the heart tolerance doses as follows: TD5/5 of the whole heart is 40 Gy; 2/3 volume of the heart is 45 Gy, and 1/3 volume of the heart is 60 Gy [4]. RTOG protocols have defined heart dose-volume constraint for left-sided breast cancer as V20 $\leq$ 5%, V10 $\leq$ 3%, and mean dose of $\leq$400 cGy. Dose-volume constraints of the heart for the right-sided breast cancer were defined to keep V20 = 0 and V10 $\leq$ 10% is ideal, but V25 = 0 and V10 $\leq$ 15% is acceptable as well [5]. A recently published QUANTEC review reported that the risk of pericarditis is <15% if V30 < 46% with the mean dose of <26 Gy. For breast cancer patients, normal tissue complication probability estimates predicted that V25 < 10% is associated with <1% cardiac mortality approximately 15 years after RT [7]. Dose-volume constraints of the heart are presented in Table 12.1.

There have recently been an increasing number of dosimetric studies comparing the dose to the left anterior descending coronary artery and left ventricle with sophisticated techniques such as intensity modulated radiotherapy (IMRT) and

tomotherapy. Plan comparisons were done by the mean, median, and maximum doses and V5, V10, V15, and V20, but no clear dose-volume threshold was defined. The University of Michigan defined the dose-volume constraint of LAD as maximum dose <15 Gy and mean dose <5 Gy [23].

12.3.3 Cardiac Pacemakers and Implantable Cardioverter Defibrillator

Pacemakers are electrical devices that can stimulate atria, ventricles, or both in order to regulate the natural rhythm of the heart. Implantable cardioverter defibrillators (ICDs) can actively shock the heart back into normal rhythm in the event of a dangerous arrhythmia. A recent review by Hudson et al. evaluated the effect of RT on the latest generation of pacemakers and ICDs. The authors emphasized the steps before and during treatment of patients with pacemakers and ICDs [28].

Before RT planning, it is essential to learn the radiation tolerance data from the manufacturer of the device and to consult the cardiologist to understand the pacemaker/ICD dependency of the patient. Conformal RT planning is encouraged and it is recommended to keep the pacemaker/ICD dose as low as possible. The maximum pacemaker dose should be kept to <2 Gy or device relocation should be considered. At no point should the cumulative dose exceed 5 Gy. The ICD maximum dose should be <1 Gy, or device relocation should be considered. It is advisable to avoid using portal imaging, gating, and breath control systems which produce electromagnetic interference. Cardiac monitoring using electrocardiography (ECG), cardiopulmonary resuscitation devices, and a hospital defibrillator with external pacemaker capability should be maintained during treatment. Thermoluminescence dosimetry needs to be performed on the first day to check dose received by the pacemaker.

For pacemaker/ICD-dependent patients, ECG is essential during every treatment session and device checks are advised after every session. In the case of bradycardia, staff should be prepared to use external pacing [28].

12.4 Brachial Plexus

12.4.1 Contouring

Brachial plexus originates from the spinal nerves exiting the spinal canal through neural foramina from the C4-C5 (C5 nerve roots) to the T1-T2 (T1 nerve roots). Contouring of brachial plexus was defined in head and neck contouring guidelines, however, due to the positioning differences of breast cancer patients, the atlas was summarized and modified by Kong et al. [10, 29].

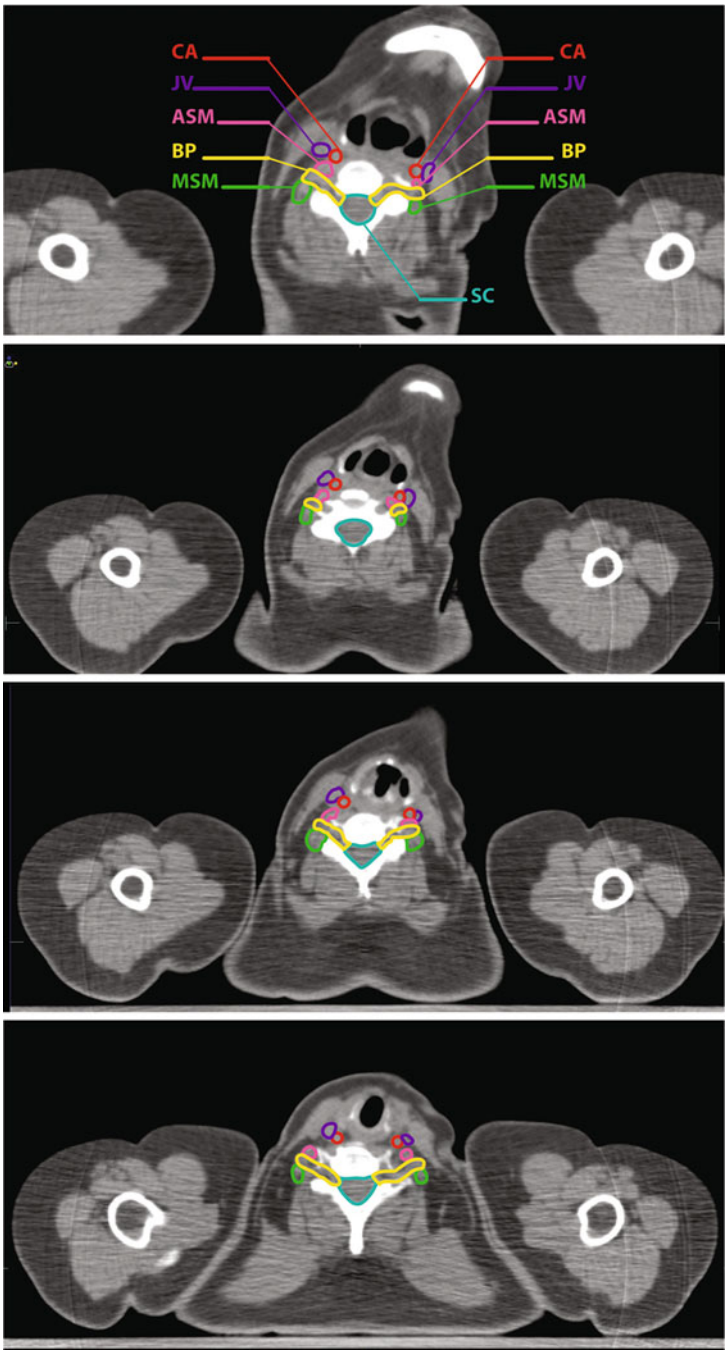
The authors recommended the following steps for contouring brachial plexus for patients with arms above the head: The key steps of contouring brachial plexus are to identify scalene muscles, subclavian- axillary arteries and veins, and cervical-thoracic vertebrae. The authors recommended locating the neural foramina at the C4-C5 and T1-T2 levels to first identify the C5 and T1 roots, then to locate the subclavian and axillary neurovascular bundle to identify the lateral aspect of the brachial plexus inferiorly. The anterior and middle scalene muscles from the C5 vertebral level to their respective insertions on the first rib need to then be located. Contouring of the brachial plexus begins at the neural foramina at the C4-C5 level and moves caudally to the region from the lateral aspect of the spinal canal laterally to the small space between the anterior and middle scalene muscles. At levels at which no neural foramina are present, contouring the space or soft tissue between the anterior and middle scalene muscles is recommended. Continue to contour the space between the anterior and middle scalene muscles; eventually, the middle scalene muscle will terminate in the region of the subclavian neurovascular bundle. Contour the brachial plexus structures inferiorly until the region of the subclavian vascular bundle is identified, the second rib should serve as the medial limit.

Administering intravenous contrast or MRI fusion may help to contour the brachial plexus. However, the delineation of the brachial plexus in breast cancer patients might be difficult for two reasons; first, it may be hard to distinguish the vessels and scalene muscles on CT images without using contrast, and second, the neutral anatomy alters as a result of axillary lymph node dissection and head position which is generally turned to the opposite direction. The delineation of brachial plexus is shown in Fig. 12.3.

12.4.2 Dose-Volume Constraints and Toxicity

RT-induced brachial plexopathy (RIBP) results from direct neurotoxic effects of irradiation and/or secondary effects on vessels. Time to onset of RIBP widely varies, and symptoms can arise months to many years after radiotherapy with a median time of 10 months. Symptoms include shoulder and arm pain and/or weakness and atrophy of the muscles of the hand. In mild cases, symptoms may resolve within 12 months. In severe cases, sensory and motor loss progress gradually, eventually rendering the arm useless. The incidence of severe RIBP ranges from 1% to 5% in women receiving radiotherapy following mastectomy, but less severe RIBP may be present in an additional 9% of patients [30–32]. The incidence increases with higher doses of radiotherapy (>50 Gy), and when chemotherapy is also given [33, 34].

Emami tolerance dose estimates were 60 Gy for the whole, 61 Gy for two thirds, and 62 Gy for one third of the brachial plexus [4]. RTOG protocols recommend keeping the BP dose <60–66 Gy for patients treated with concomitant radiochemotherapy with conventional fractionation. These protocols consist of patients with lung and head and neck cancer where higher doses of RT were utilized as compared



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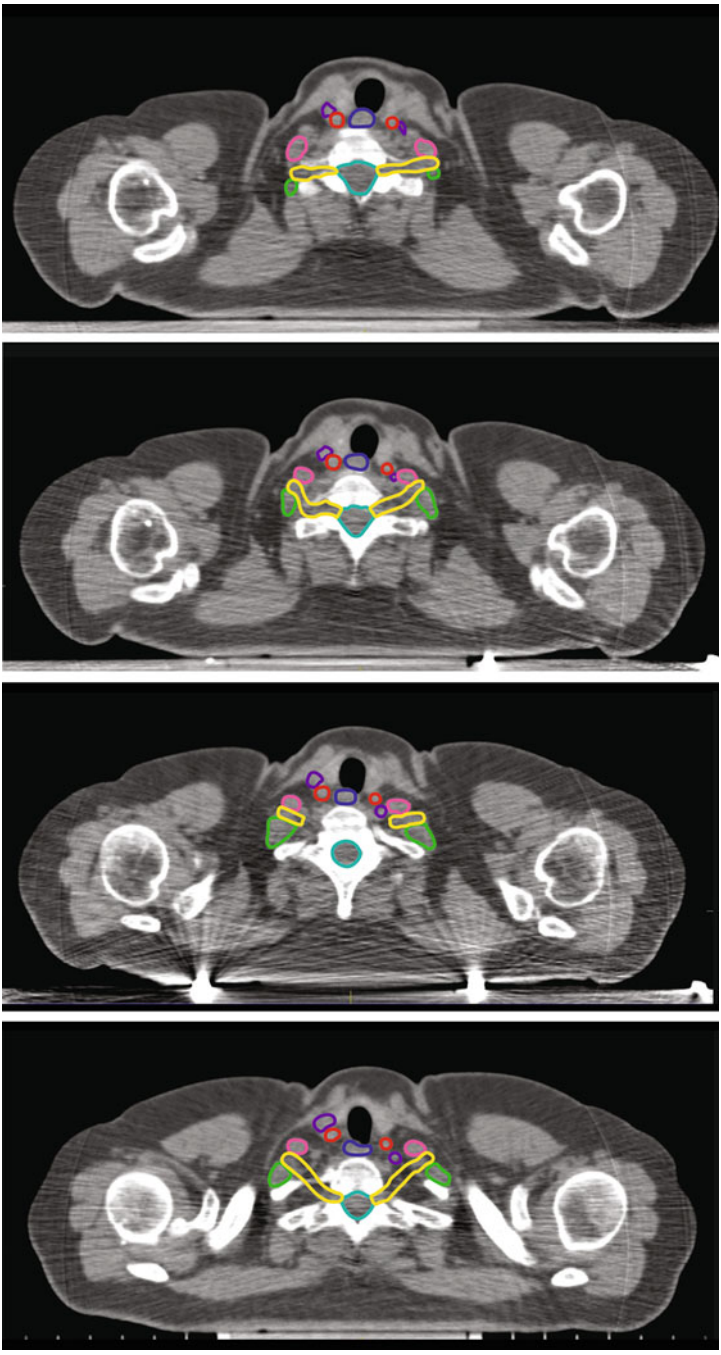

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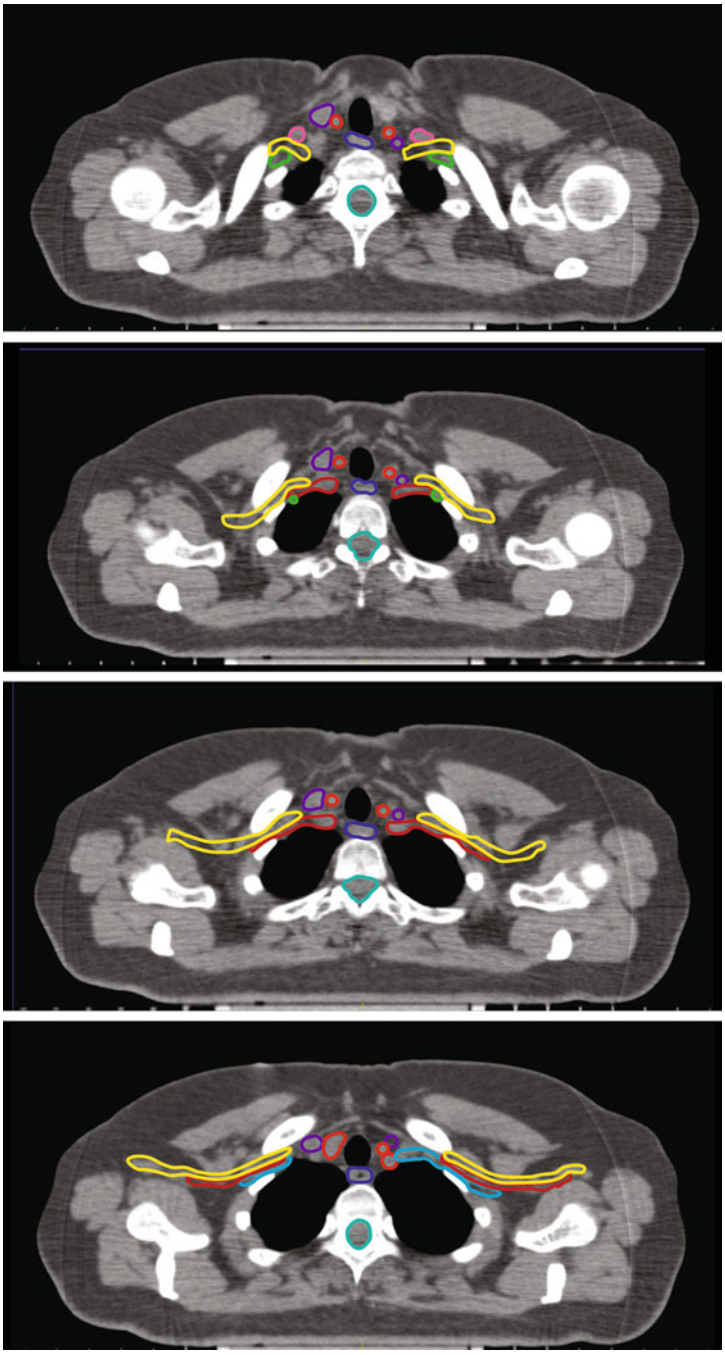

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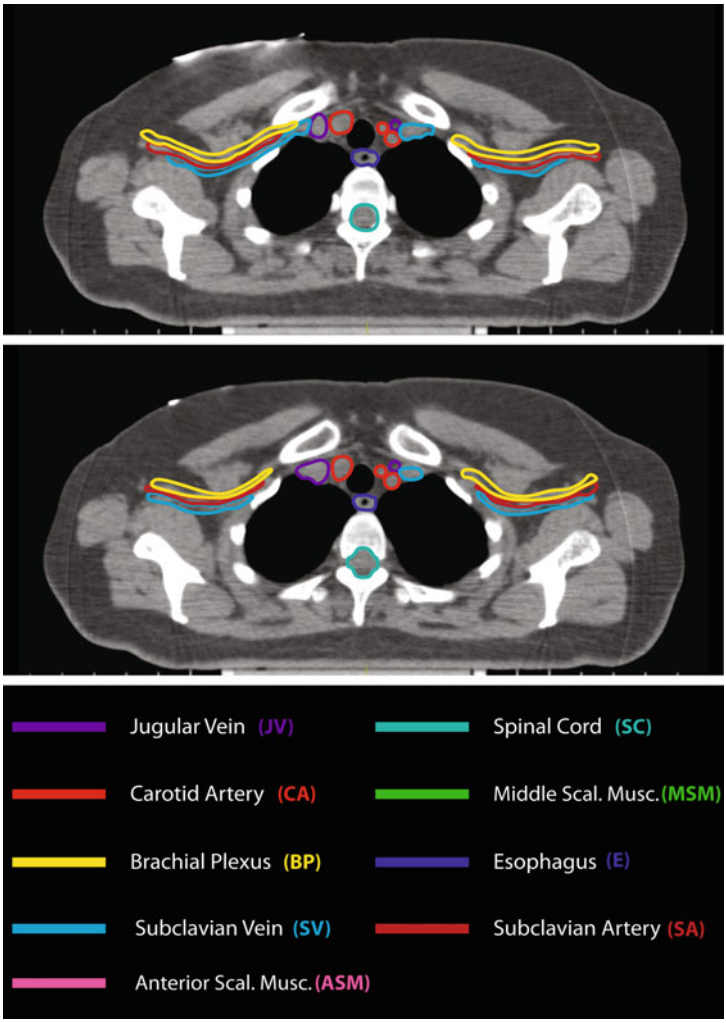

Fig. 12.3 (continued)

with breast cancer [5]. Furthermore, French Society of Radiation Oncology recommends keeping the BP dose below 55 Gy [35] (see Table 12.1).

12.5 Contralateral Breast

12.5.1 Contouring

Contralateral breast should be contoured as an organ at risk as suggested by the RTOG guideline [5].

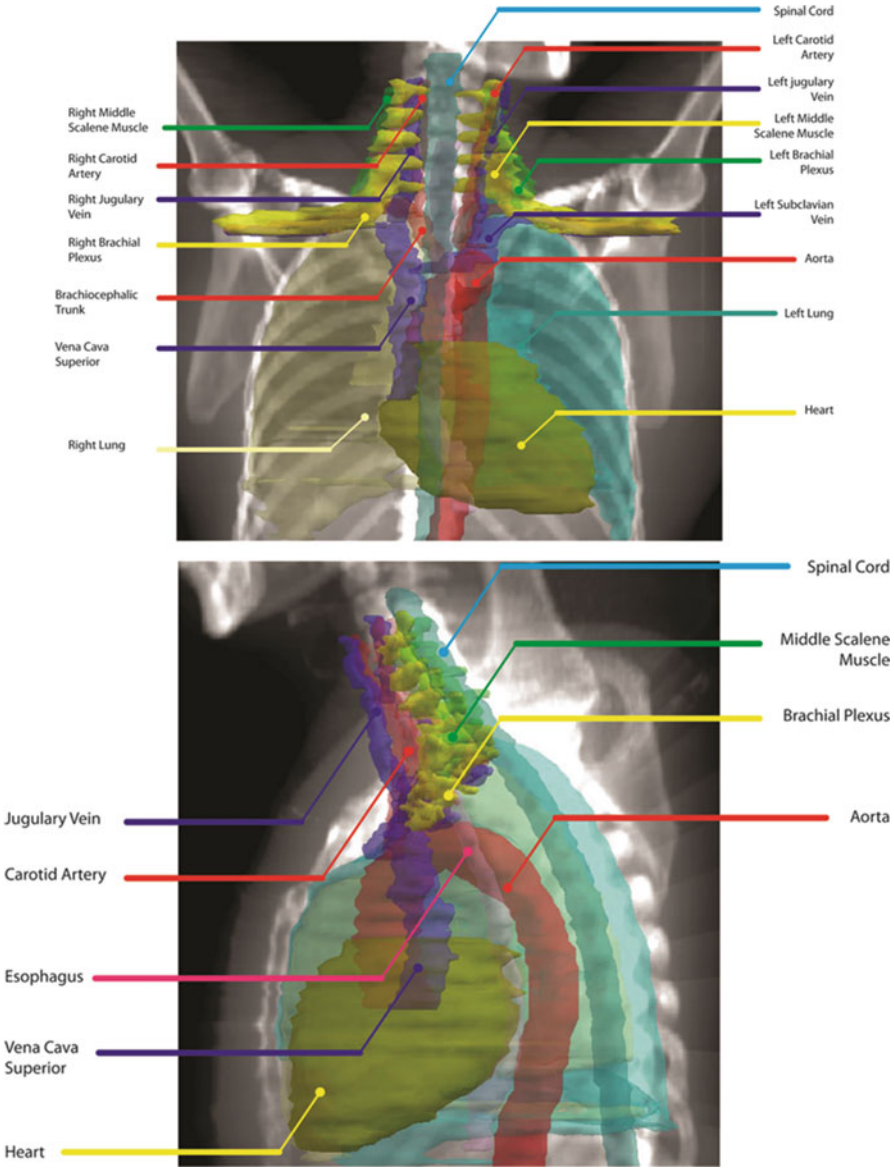

Fig. 12.3 (**a–f**) The delineation of the brachial plexus as an organ at risk

12.5.2 Dose-Volume Constraints and Toxicity

Several studies have indicated that there has been an increased risk of contralateral breast cancer, particularly in young women treated with RT [36, 37]. The dose to the contralateral breast is because of the medial tangent beam and the result of a collimator scatter, leakage, scatter from blocks and wedges, etc. Dosimetry studies have reported lower contralateral breast doses with IMRT as a result of not using the wedges [38]. The RTOG breast study protocol recommends keeping the D max of the contralateral breast <3–3.3 Gy [5]. Investigators had minimized the D max to <3.9 Gy and mean dose of ≤0.3 Gy for patients treated with multifield IMRT (9-field technique) [23].

12.6 Esophagus

12.6.1 Contouring

In their published review, Kong et al. recommended contouring the esophagus with mediastinal windowing. Esophagus contouring should begin from the level of the cricoid cartilage and continue through every CT slice until the gastroesophageal junction ends at the stomach (Fig. 12.1). The use of oral contrast is not recommended [10].

12.6.2 Dose-Volume Constraints and Toxicity

Acute toxicity is caused by the damage of the mucosal layer and causes dysphagia, odynophagia, and dysmotility. Late toxicities include stricture, fibrosis, ulceration, fistula, and perforation [11]. The esophagus is a dose-limiting organ for RT planning of intrathoracic malignancies. Emami et al. defined the tolerance dose of the esophagus for the endpoint of stricture and perforation to limit the dose to the whole esophagus to 55 Gy, two thirds of the esophagus to 58 Gy, and one third of the esophagus to 60 Gy [4]. QUANTEC reviews reported that the risk of developing grade 3 and higher esophagitis was less than 20% if the mean esophagus dose is less than 34 Gy, and dose-volume parameters of V35 < 50%, V50 < 40%, and V70<20% are also associated with the risk of esophagitis [8].

However, small portion of the esophagus of the breast cancer patient is in the supraclavicular field, and with the selection of an appropriate gantry angle, it is possible to exclude most parts of the esophagus from the supraclavicular field. Special attention is required particularly for patients treated using multifield IMRT and with non-coplanar fields. See Table 12.1 for a summary of dose-volume constraints.

12.7 Spinal Cord

12.7.1 Contouring

The spinal cord can be contoured according to the bony limits of the spinal canal. Cranially, contouring begins at the same level of the esophagus to the bottom of L2 or where it ends. Ongoing RTOG studies define spinal cord contouring as 10 cm above from the superior extent and 10 cm below from the inferior extent of the PTV (planning target volume) [10]. However, it is not applicable for breast cancer patients due to the localization and spinal cord contouring begins from the most upper slice with including medulla spinalis through the last slice of CT (Fig. 12.1).

12.7.2 Dose-Volume Constraints and Toxicity

RT-associated spinal cord injury may be transient or irreversible. The most common syndrome is transient myelopathy known as "Lhermitte's sign" with onset 2–4 months after irradiation. Chronic progressive myelopathy is rare and initial symptoms such as paresthesias and sensory changes begin 9–15 months following RT and progress. Risk of myelopathy is associated with higher fraction size, shorter overall treatment time, and irradiation of long lengths of the cord (>10 cm) [11]. Emami et al. defined the tolerance dose of the spinal cord based on the irradiated length of the cord as follows: 47 Gy to 20 cm, 50 Gy to 10 cm, and 50 Gy to 5 cm [4]. In RTOG protocols, the maximum dose to the spinal cord is limited to 45–50 Gy [5]. QUANTEC reviews mentioned that the risk of myelopathy increased from 0.2% if the maximum dose is 50 Gy, to 50% when the maximum dose is 69 Gy [9].

For breast cancer patients treated with supraclavicular field, the length of the cord is relatively short but consideration is given to shield the spinal cord by adjusting the medial border of the supraclavicular field and implementing customized blocks.

12.8 Thyroid Gland

12.8.1 Contouring

The thyroid gland is located in the anterior neck and consists of two lateral lobes connected anteriorly with isthmus. The thyroid lobes extend to the level of the middle of the thyroid cartilage superiorly, and extend to the level of the sixth tracheal ring inferiorly. Laterally, the thyroid lies just medial to the common carotid arteries. The most posterior aspects of the lateral lobes may touch the esophagus and the anterior surface of the thyroid is just deep to the strap muscles of the neck [39].

12.8.2 Dose-Volume Constraints and Toxicity

Hypothyroidism or hyperthyroidism may occur following RT. The risk of both is increased in the first 3–5 years following RT and the risk of thyroid nodules increased at more or equal to 10 years after RT [40]. The 5–8 year rate of hypothyroidism was reported as 48% and 67%, respectively, for head and neck cancer patients treated with RT and chemotherapy. Median time-to-development of hypothyroidism was 1.4 years [41]. Emami et al. estimated the TD5/5 of the whole thyroid as 45 Gy [4]. Johansen et al. analyzed the dose distribution in the thyroid gland and concluded that tissue with radiation doses less than 30 Gy is available for sufficient thyroxin production [42]. Dogan et al. limited the thyroid dose to V50 $<$ 20% in breast cancer patients treated with breast and regional lymph nodes with multifield IMRT [43]. In breast cancer patients treated with supraclavicular field at least half of the thyroid is out of the field. The other half in the field might be protected with the customized blocks.

12.9 Skin

12.9.1 Contouring

For patients treated with breast-conserving therapy (BCT: lumpectomy and RT), cosmetic outcome carries substantial importance. For patients treated with BCT where skin is not at risk, the selection of adequate beam energy, careful contouring, and plan evaluation (reviewing the D max and hot spot regions) may help to spare skin (4–5 mm thickness is appropriate to include the epidermis, dermis, and hypodermis) in order to reduce acute and late toxicity and subsequently maintain cosmesis [44].

12.9.2 Dose-Volume Constraints and Toxicity

Acute skin toxicity includes erythema, hyperpigmentation, and skin desquamation. Late toxicities include skin fibrosis, telengiectasis, contracture, and even necrosis [11]. Sophisticated RT techniques were shown to reduce the acute skin toxicity [44–46]. Emami et al. estimated tolerance doses of skin (TD5/5) as 50 Gy for 100 cm^2, 60 Gy to 30 cm^2, and 70 Gy to 10 cm^2 [4].

12.10 Conclusion

Published data on toxicity are widely based on patients treated with conventional fractionation and toxicity results of other fractionation regimens (hypofractionation/accelerated partial breast RT) are accumulating. It is important for

clinicians to utilize the above-mentioned dose-volume constraints to predict acute and late toxicities for breast cancer patients with a long life expectancy.

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Chapter 13
Chest Wall and Regional Lymphatics

Gokhan Ozyigit, Melis Gultekin, and Ferah Yildiz

13.1 Introduction

The female breast rests above the anterior thoracic wall superficial to the pectoralis major muscle [1]. The breast tissue usually extends from the midline to near the midaxillary line and cranial-caudally from the second or third anterior rib to the inframammary fold (sixth or seventh anterior rib), depending on the size (Fig. 13.1) [2]. The largest volume of tissue located in the upper-outer quadrant of the breast extending into the region of the low axilla is known as the axillary tail of Spence (Fig. 13.1). This anatomic region is a common site for primary breast carcinomas.

The breast communicates with the serratus anterior muscle and the upper portion of the abdominal oblique muscle in addition to the pectoralis major muscle. The breast is apportioned into four quadrants: Upper inner, upper outer, lower inner, and lower outer.

The breast is composed of mammary gland, fat, connective tissue, blood vessels, nerves, and lymphatics (Fig. 13.2) [1]. The mammary gland is embryologically derived from the ectoderm and has two fascial layers [3]. The superficial fascia lies deep to the dermis and the deep fascia surrounds the fascia of the pectoralis major muscle [4]. Anteriorly breast tissue communicates with the skin via Cooper's ligament, and posteriorly it is separated from the pectoralis major muscle by the retromammary bursa (Fig. 13.2). The retromammary bursa contains loose areolar tissue and the suspensory Cooper's ligaments, which are fibrous bands of connective tissue that are important for movement of the breast [4]. These supporting structures can lead to dimpling of the skin clinically associated with breast tumors [2].

Breast tissue is composed of epithelial parenchymal elements and the stroma. The stroma is rich in vascular supply and lymphatic network. The breast

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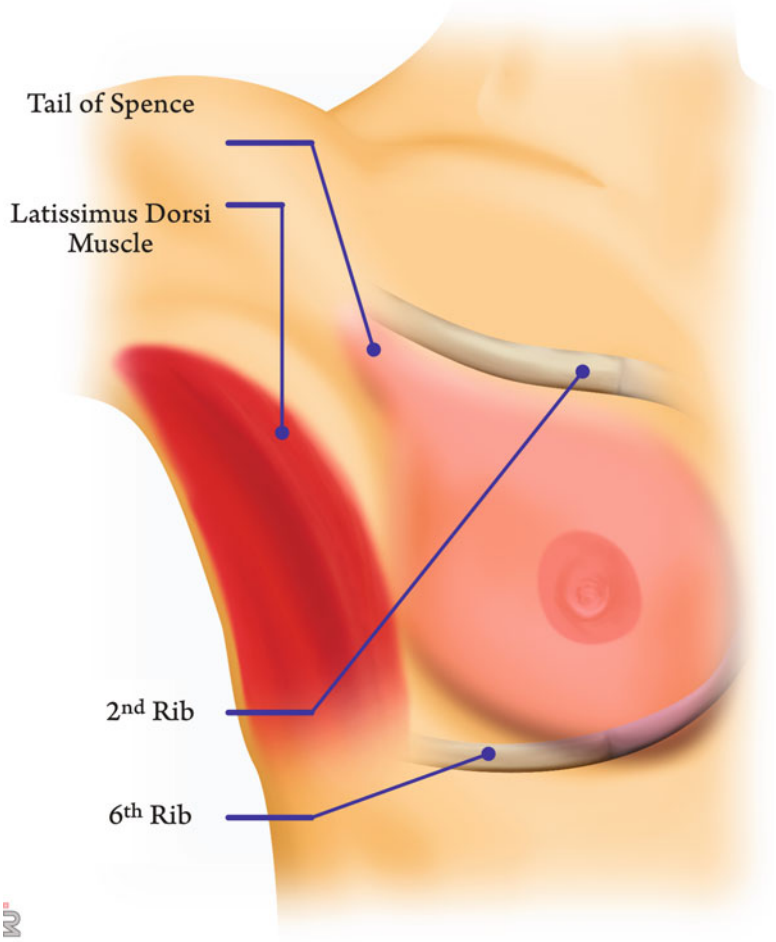


Fig. 13.1 The boundaries of the breast

parenchyma contains 15–20 lobes (Fig. 13.3). The lobes of the breast are divided further into lobules, which range from 20 to 40 in number. The function of the lobules is to produce and secrete milk, and the function of the ducts is to transport lactation products to the nipple. The nipple is composed of smooth muscular and elastic tissue, which is situated at the fourth intercostal space and surrounded by the areola. The lobules are composed of branched tubuloalveolar glands. All lobes flow out into main lactiferous ducts. The lactiferous ducts expand through a lactiferous sinus underneath the areola and then reach through a narrowed orifice onto the nipple. The nipple and the areola contain sebaceous and apocrine glands. The glands are embedded in subcutaneous connective tissue, which reaches between the lobes and the lobules as septa. The interlobular space has rich adipose tissue. In contrast, intralobular space has rich connective tissue. The terminal ductal

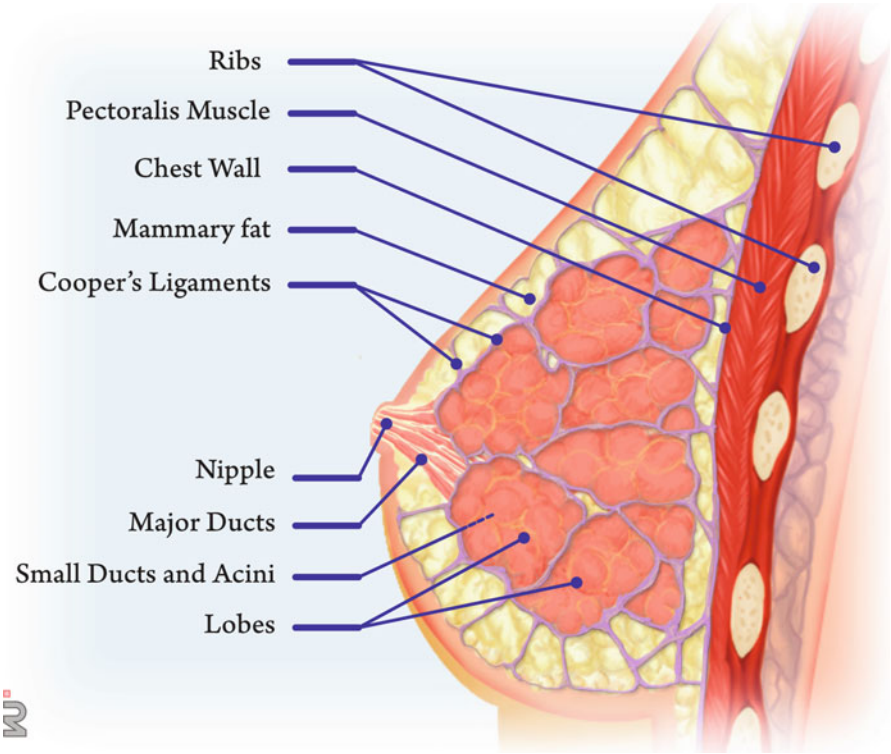


Fig. 13.2 Breast tissue communicates with the skin anteriorly via Cooper's ligament and posteriorly it is separated from the pectoralis major muscle by the retromammary bursa

lobular unit is the location of most breast carcinomas, which consists of the ductal system and the lobules.

The breast receives major blood supply from the internal mammary and lateral thoracic arteries. The anterior perforating branches of the internal mammary artery cover almost 60% of the breast, primarily the medial and central parts. The internal mammary artery and vein beginning in the supraclavicular fossa and then goes down from the first through the sixth anterior interspaces [5]. The remaining contributions to the breast are the subscapular and thoracodorsal arteries; the lateral branches of the third, fourth, and fifth intercostal arteries; and the pectoral branch of the thoracoacromial artery (Fig. 13.4).

13.2 Regional Lymphatics of Breast

The lymphatic drainage of the breast was first described by Sappey, who performed the first gross anatomic mappings of the lymphatic system by injecting mercury into the lymphatic vessels of human cadavers in 1874 [6]. As an open-ended

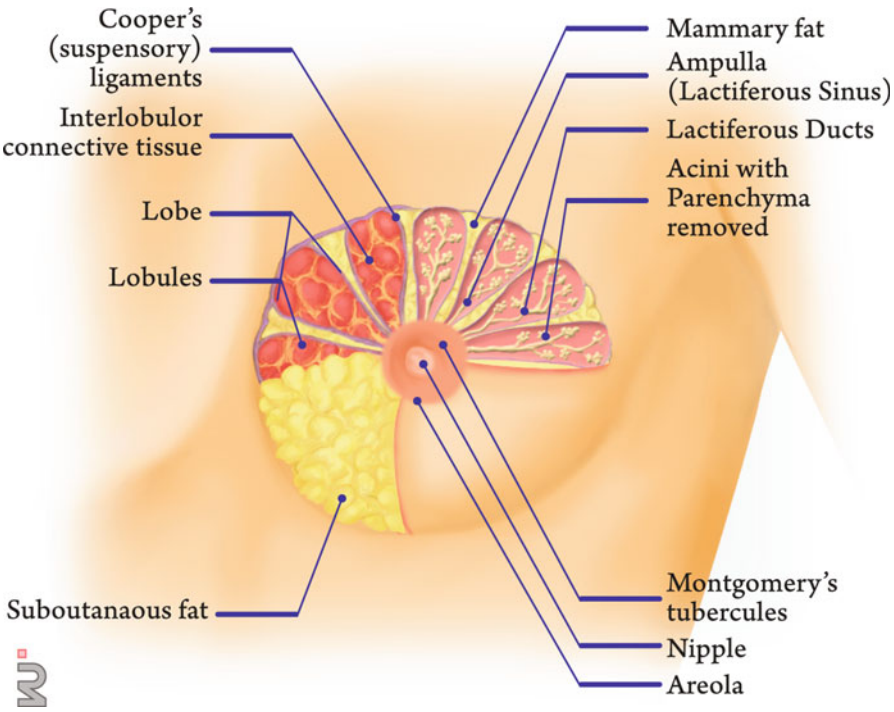


Fig. 13.3 The breast tissue is composed of the epithelial parenchymal elements and the stroma. The stroma is rich in vascular supply and lymphatic network. The breast parenchyma contains 15–20 lobes, and the lobes of the breast are divided further into lobules, which range from 20 to 40 in number

lymphatic drainage system, lymphatic capillaries come up from the secretory lobules [7]. Lymph is consequently carried to collecting vessels. The vessels go with the lactiferous ducts to the areolar region. Sappey differentiated a superficial group of lymphatics existing in the skin above the breast (subcutaneous lymphatics) and a deep group draining the mammary gland itself (intramammarian lymphatics) [6]. There is a rich lymphatic network between the intramammarian lymphatics and the superficial cutaneous lymphatic system in the breast and these lymphatic groups drains into the axillary and internal mammary lymph nodes (IMN). The route of the mammary gland lymphatics is from the skin, nipple, lactiferous tubules, and surrounding parenchyma drain into the subareolar lymphatic plexus, which divides into medial and lateral trunks [6]. The medial trunk receives lymph from the inferior breast, and the lateral trunk receives lymph from the superior breast. These two trunks drain into the lower axillary lymph nodes. However, Turner-Warwick demonstrated that most lymph from the breast drains directly into the axillary lymph nodes that bypassed the subareolar plexus [8]. He also expressed that collectors surpassing directly from the posterior surface of the breast go through the pectoralis major muscle and deep fascia, which then routes through the intercostal

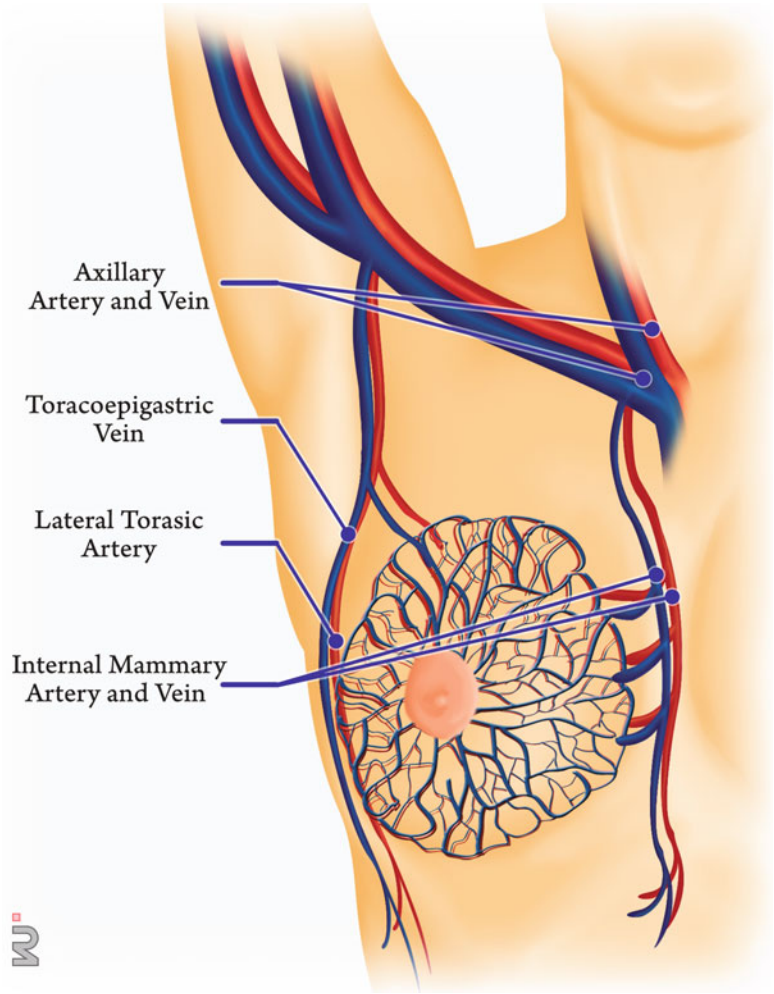


Fig. 13.4 The major blood supply to the breast is from the internal mammary and lateral thoracic arteries

spaces before passing medially to reach the IMN. It was noted that all quadrants of the breast drain directly into the axilla itself or either the internal mammary or posterior intercostal nodes [9].

The latest anatomic studies have additionally confirmed that breast lymphatic drainage, as a model, contains superficial, deep, and perforating systems with respect to the association with the deep fascia [10]. The authors stated that the superficial system drains into the axilla, generally to a lymph node just behind the pectoralis minor muscle. The deep system drains to the axilla and also interacts with the perforating system which drains into the IMNs. Suami et al. reported that the perforating system and the superficial system do not have any relationship [10].

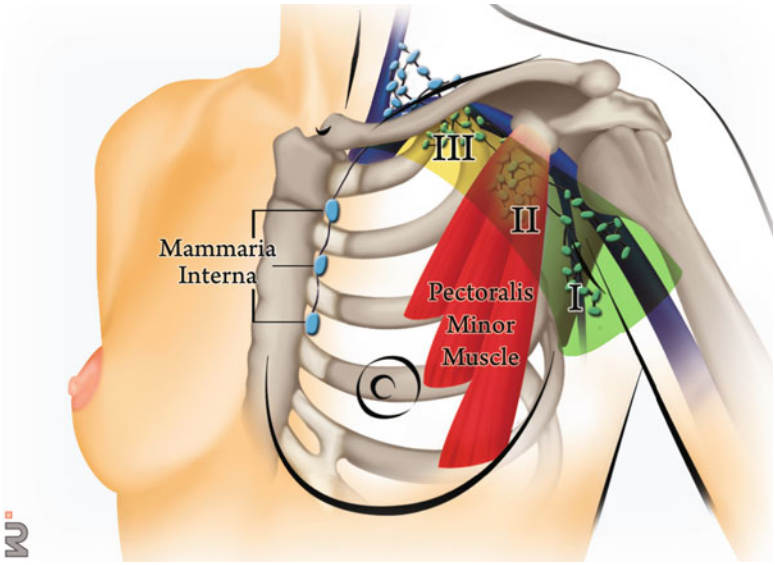


Fig. 13.5 The pectoralis minor muscle, which connects at the coracoid process, divides the axilla into three continuous anatomic levels: level I (proximal), which is inferior and lateral to the muscle; level II (middle), which is posterior to the muscle; and level III (distal), which is superior and medial to the muscle. The internal mammary lymphatics situated between the first intercostal space and the sixth intercostal space and are in the anterior interspaces along the margins of the sternum which are 3–4 cm lateral to midline

Collectively, lymphoscintigraphy and cadaveric studies have shown that drainage patterns from any quadrant of the breast can occur, with the principal lymphatic drainage of the breast being into the axillary lymph nodes. The axillary lymph nodes can be subdivided into six major groups: the axillary vein group (lateral group), external mammary group, scapular group, central group, subclavicular group, and interpectoral group (Rotter nodes located between the pectoralis major and minor muscles) [4]. The axillary nodes drain into lymphatics that route through the axillary and contiguous subclavian vein. From there, the lymphatics may flow off primarily into the jugulosubclavian confluence or primarily go beyond the jugular and bronchomediastinal lymphatics [11]. The ipsilateral axillary lymph nodes contain more than 75% of the lymph of the breast [9]. The pectoralis minor muscle that inserts at the coracoid process divides the axilla anatomically into three continuous levels: level I (proximal), which is inferior and lateral to the muscle; level II (middle), which is posterior to the muscle; and level III (distal), which is superior and medial to the muscle and is also known as the infraclavicular region (Fig. 13.5). Level II nodes also include the interpectoral nodes of Rotter, and level III nodes are continuous with the supraclavicular lymph nodes medially and anteriorly. The tumor may spread to the supraclavicular lymph nodes passing through the axillary lymph nodes. When lymph are blocked in the lymphatic trunks or the internal jugular–subclavian venous confluence, retrograde spread can occur

in the lateral supraclavicular nodes and further extend posteriorly or in a cephalic direction. It is difficult to inspect the supraclavicular nodes at greatest risk if positioned at the back of the sternocleidomastoid muscle (SCM). On the contrary, it would be easier to detect when the supraclavicular nodes more laterally located. The breast parenchyma may infrequently flow off directly into the supraclavicular lymph nodes. In addition to the frequently described lymph nodes, other less common drainage routes have been found. Retrosternal lymphatic drainage to the contralateral internal mammary chain takes place sporadically. Subcutaneous drainage to the contralateral axilla does not likely occur except when the ipsilateral drainage is damaged by lymphatic obstruction as a result of tumor growth, previous surgery, or irradiation [12]. Drainage in a retrograde direction to the liver can also be observed through the internal mammary chain when normal lymph flow is blocked [13]. It is also observed among a small number of patients that the posterior intercostal lymph nodes get lymph from the breast [8]. Caplan also reported drainage to the anterior intercostal nodes [14]. Internal mammary nodes and interpectoral nodes that are produced by retromammarian lymphatics are described by anatomic studies regarding the arrangement of the breast lymphatics [13, 14]. These lymphatics result from the breast lobules, continue on the surface of the pectoral fascia, and progress with penetrating blood vessels through the pectoral and intercostal muscles.

The internal mammary lymphatics are situated between the first intercostal space and the sixth intercostal space and are situated in the anterior interspaces along the margins of the sternum, which are 3–4 cm lateral to midline (Fig. 13.5). Injection studies with vital dyes have demonstrated that the IMNs receive their lymph from deep lymphatics [8, 13, 15]. These lymphatics arise from the breast lobules, leave the posterior surface of the breast, and pass through the pectoral and intercostals muscles to drain into the IMN. The nodes are small (2–5 mm in diameter) and can be determined on treatment planning computed tomography (CT) scan; they are located either medial or lateral to the internal mammary artery and vein [16–18]. Carcinomas arising in the medial, central, or lower quadrant of the breast tend to drain more frequently into the IMN, in addition to the axilla. Autopsy studies and extended radical mastectomy series have demonstrated that IMN metastases are most commonly observed in the first three intercostal spaces with fewer lymph nodes identified in the fourth and fifth interspaces (87–98% vs. 2–13%) [19–22].

The degree of axillary nodal involvement by the tumor is the single most important prognostic factor in breast carcinoma. In general, axillary lymphatic involvement is more common in levels I and II than in levels I and III or level III alone. Surgical approaches to the axilla routinely include only levels I and II lymph node dissection. In a study of 1,446 patients with breast carcinoma, Veronesi et al. demonstrated that the incidence of skip metastases is quite rare. With negative level I lymph nodes, only 1.2% of patients had level II involvement, whereas 40% of patients with positive level I lymph nodes also had metastatic higher level nodes [23].

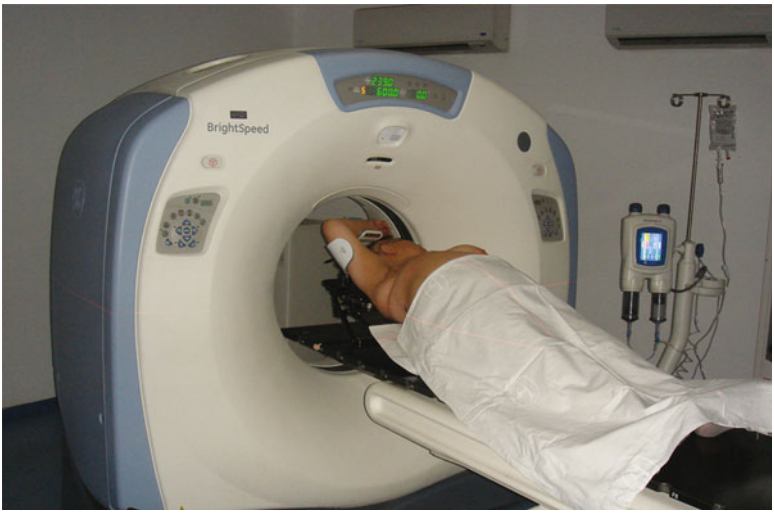


Fig. 13.6 Planning CT is used to more precisely delineate target volumes in a treatment position. Most patients are scanned in the supine position, with the breast tilt boards and their ipsilateral arm abducted (90–120°) and externally rotated (Courtesy of Hacettepe University)

13.3 Target Volume Delineation

In current practice, individualized CT-based treatment planning is used as a standard for the delineation of the target volume and the organs at risk volume in patients with breast carcinoma. Radiation oncologists get the opportunity of defining the target volumes on CT after the advent of the three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT). An understanding of the distribution and probability of involvement of the specific nodal groups is critical for target volume delineation. Locoregional treatment with 3D-CRT and IMRT requires accurate target and normal tissue delineation. Therefore, anatomic boundaries of the clinical target volumes that are easily visible on CT slices must be identified. The planning CT scan is used in order to more precisely delineate target volumes in a treatment position. Most patients are scanned in the supine position, with the breast tilt boards and their ipsilateral arm abducted (90–120°) and externally rotated. Patient positioning is shown in Fig. 13.6.

Patients undergo noncontrast CT simulations. Three radiopaque pellet markers are placed at the anterior midline and at right and left lateral points on the skin to define the isocenter (Fig. 13.7). Radiopaque wires are placed on the surgical scar. The CT scan is acquired in 5-mm slices from the sixth cervical vertebra to the upper abdominal region. The chest wall CTV and regional nodal CTV are then contoured separately on the CT slices according to Radiation Therapy Oncology Group recommendations. Targeted areas of interest and critical organs such as the great vessels, heart, contralateral breast, bilateral lungs, spinal cord, brachial plexus, thyroid, and esophagus should be contoured very carefully in each slice.

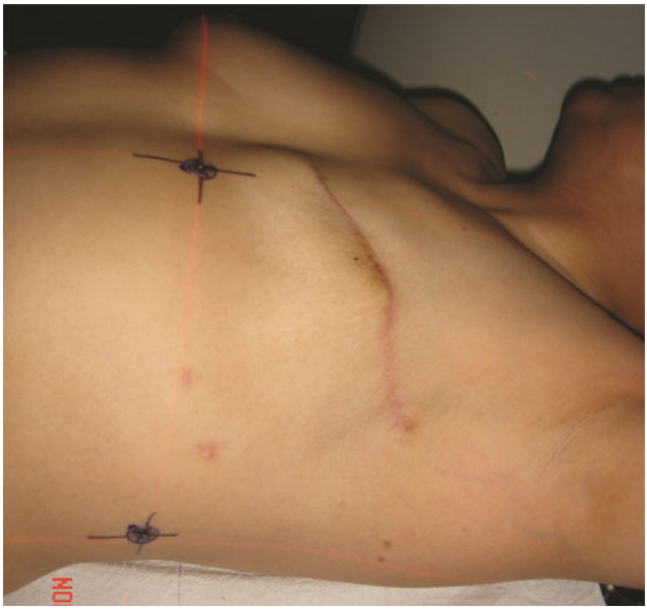


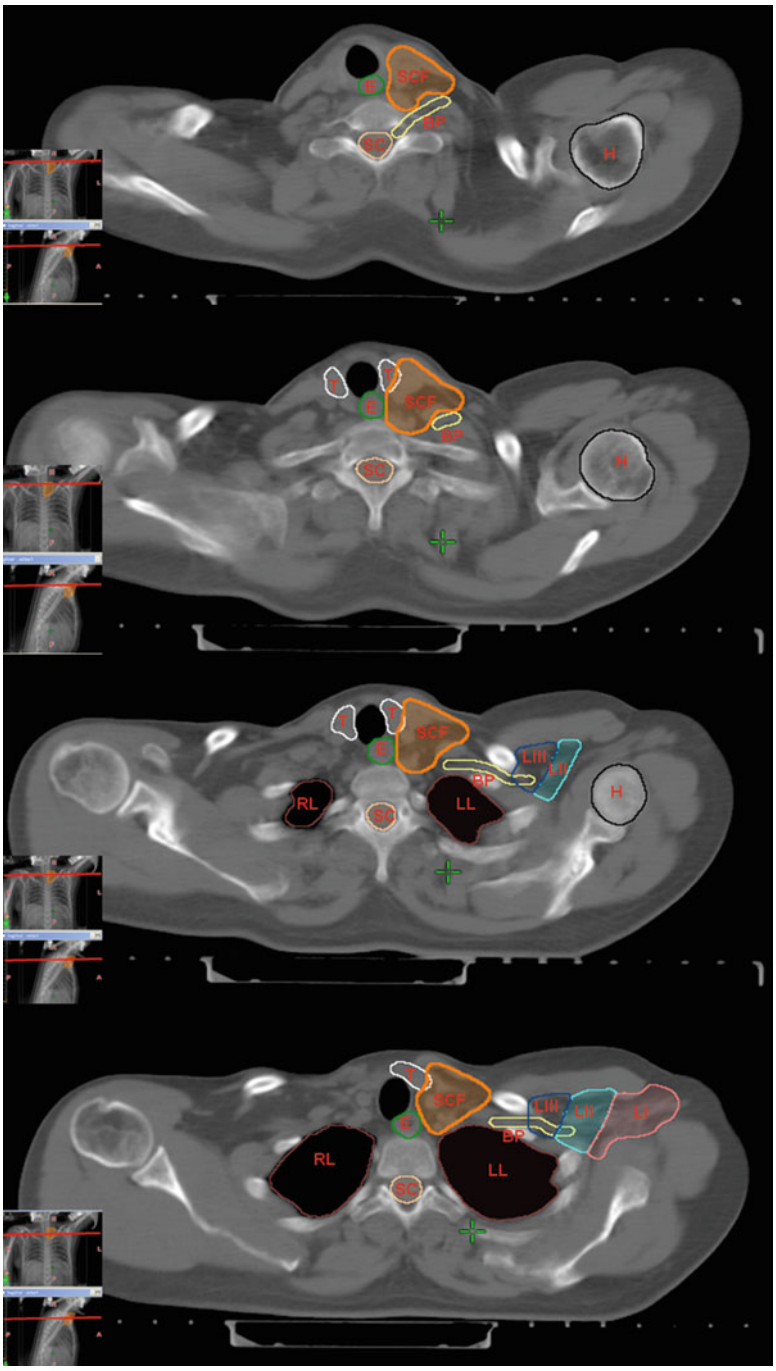
Fig. 13.7 Radiopaque pellet markers are placed at the anterior midline and at right and left lateral points on the skin to define the isocenter during CT simulation

The target volume delineation for a postmastectomy patient is shown in Fig. 13.8.

13.3.1 Chest Wall

Adjuvant radiation therapy plays a significant role in the locoregional treatment of breast carcinoma [24–27]. The reason for postmastectomy radiotherapy is to improve the overall survival rate and to decrease the recurrence rates of cancer in the chest wall, skin, mastectomy scar, and the regional nodes, in addition to the axillary, supraclavicular, and internal mammary nodes. It is crucial to select the appropriate patients for postmastectomy irradiation and the patients must be carefully reviewed to notice the potential for morbidity of therapy.

The current recommendation for postmastectomy radiotherapy is to treat patients with four or more positive axillary lymph nodes, T3, or T4 tumors and invasion of the pectoral muscle or the surgical margins that have a high risk of local recurrence [28–30]. Lymphovascular space invasion, positive surgical margin, involvement of the skin or nipple, gross multicentric disease, and gross extracapsular spread are the other relative indications. The guidelines of the American Society of Clinical Oncology note that the chest wall, including the supraclavicular region, should be irradiated. However, for patients with axillary



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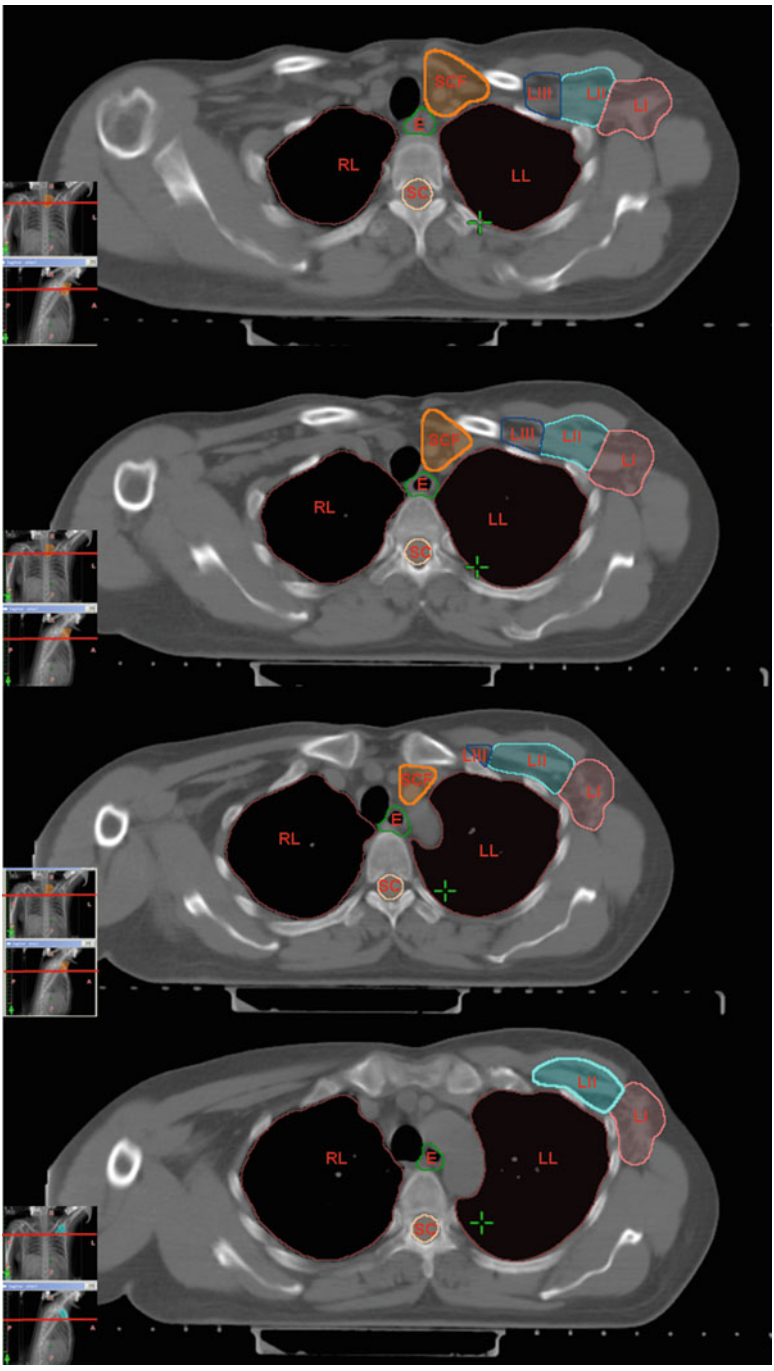

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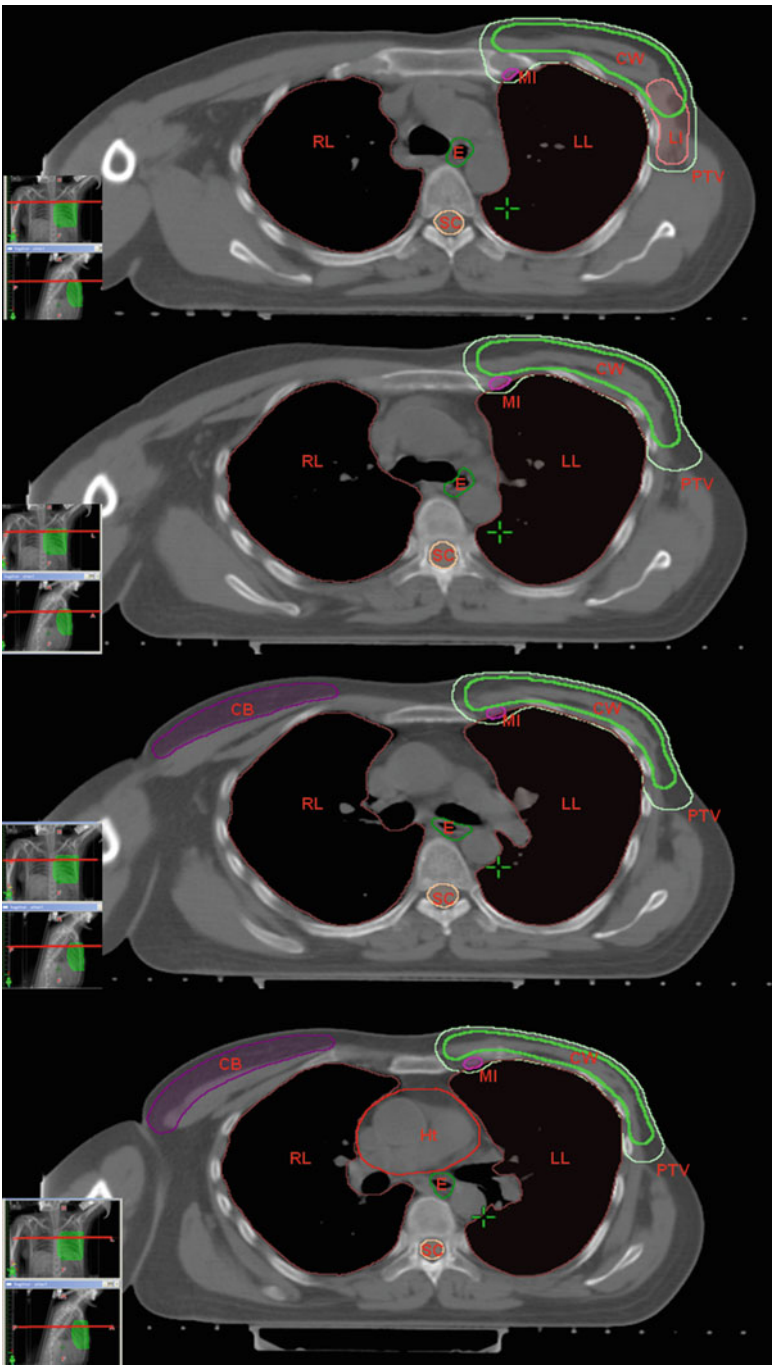

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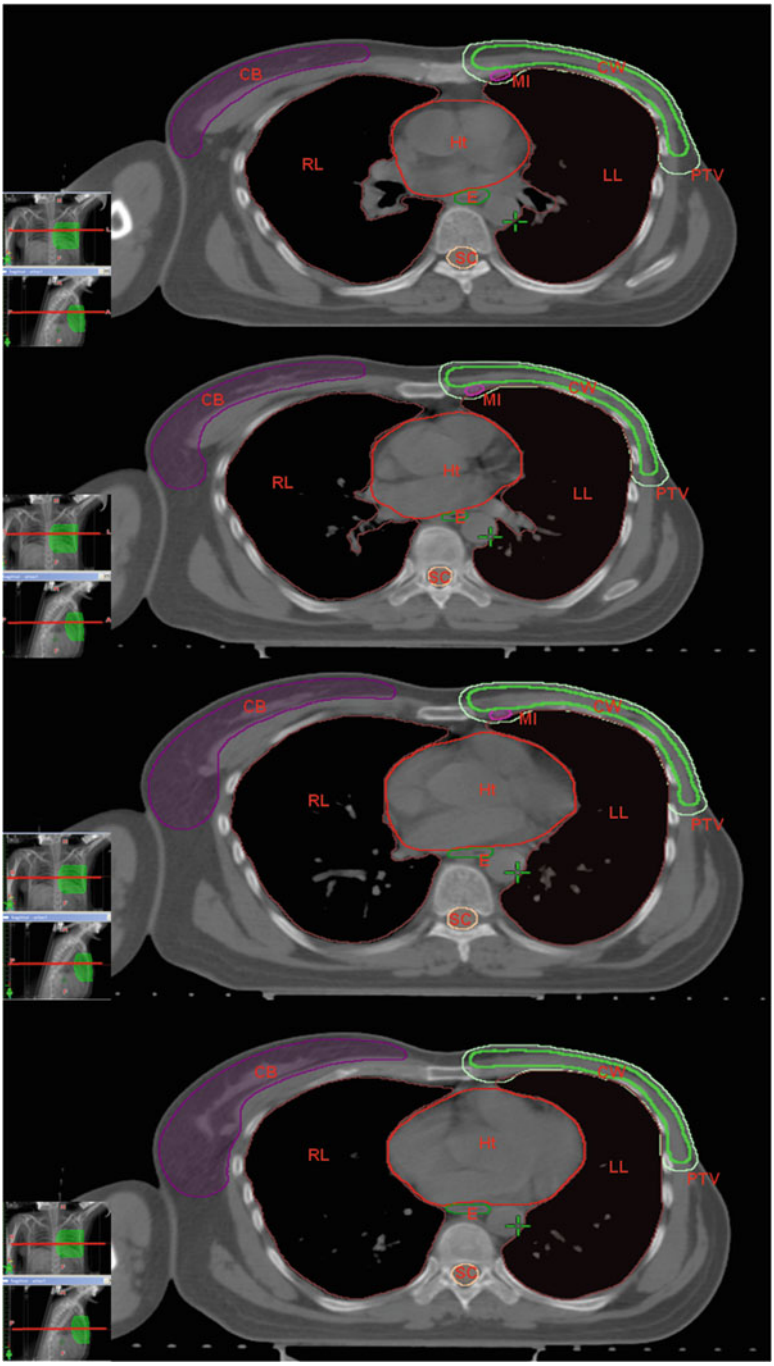

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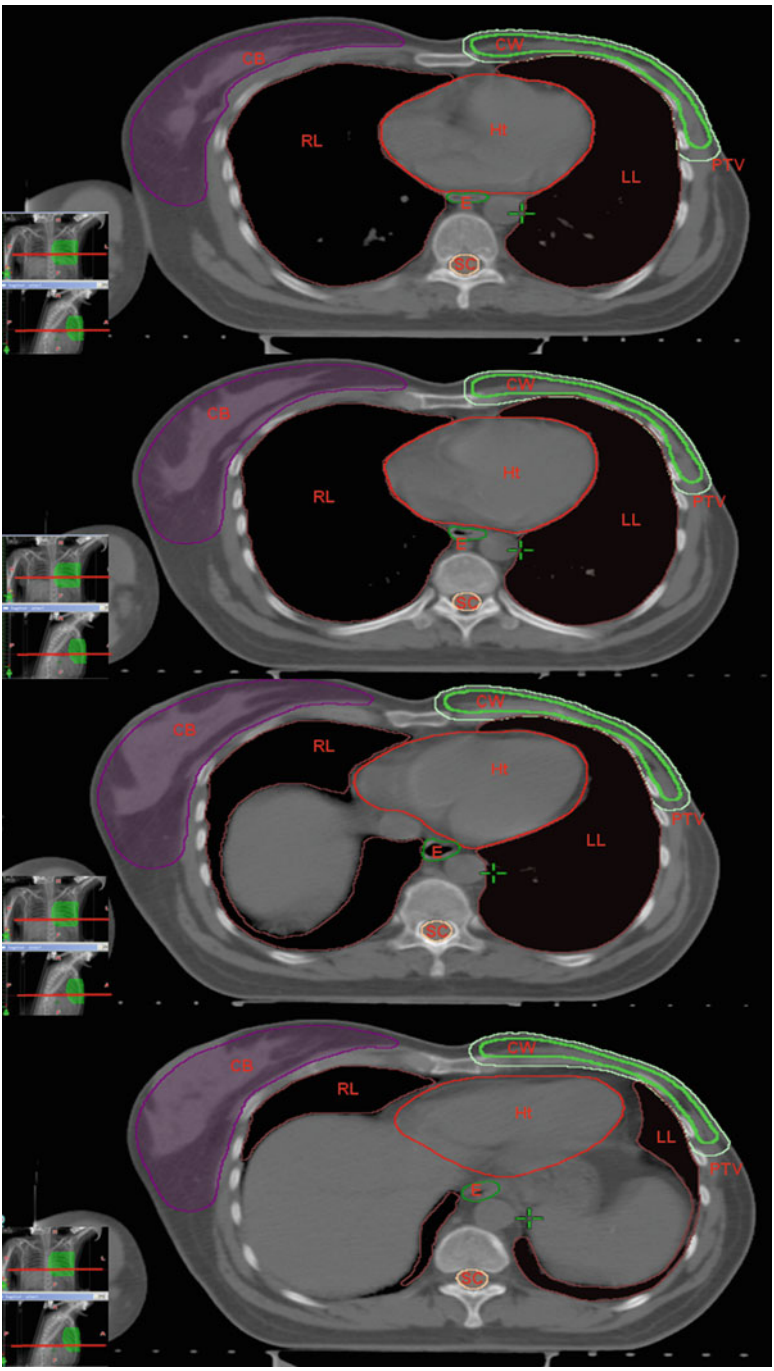

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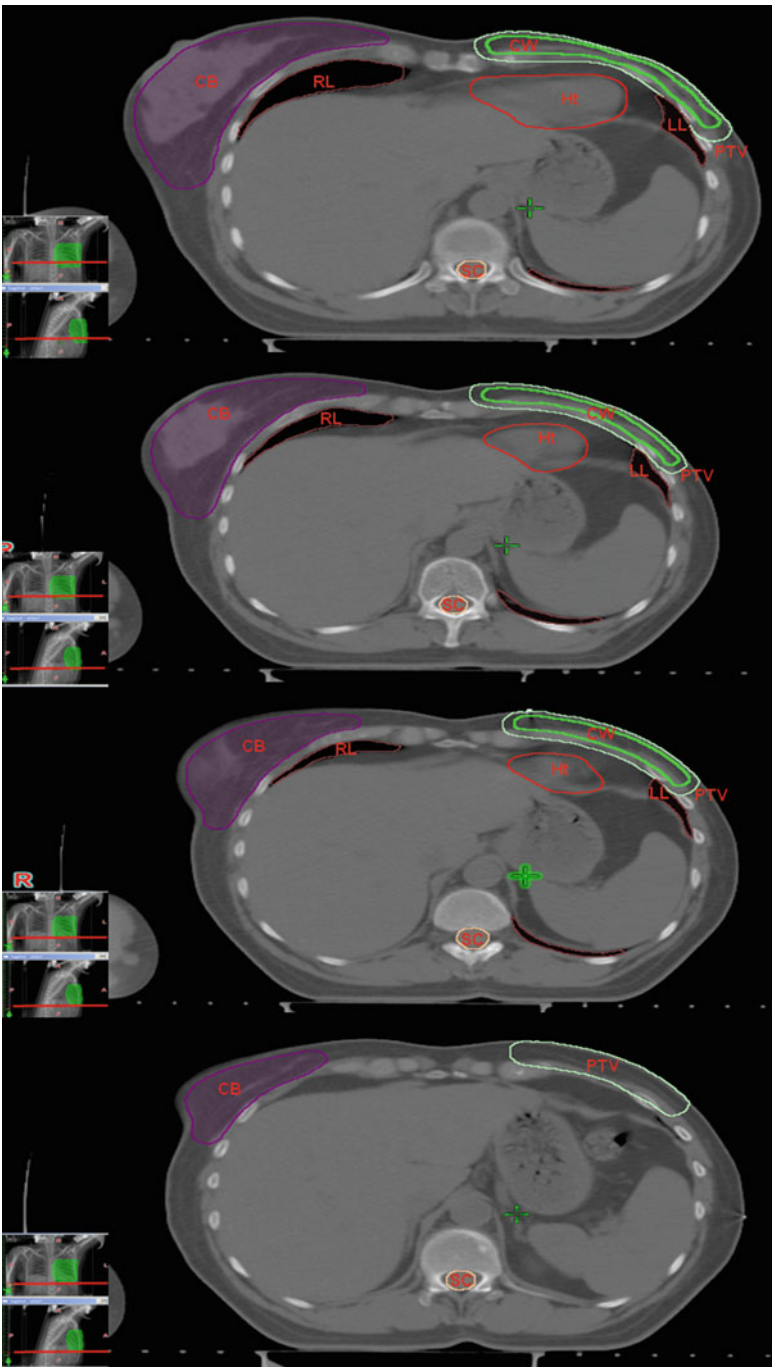

Fig. 13.8 Target delineation for postmastectomy patient. *PTV* planning target volume for chest wall (*light yellow*); *CW* clinical target volume for chest wall (*green*); *SCF* supraclavicular fossa lymhatics (*orange*); *LI* level I axillary lymphatics (*pink*); *LII* level II axillary lymphatics

Table 13.1 Chest wall anatomic boundaries

Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Caudal border of the clavicle head	Clinical reference and loss of CT apparent contralateral breast	Skin	Rib-pleural interface (includes pectoralis muscles, chest wall muscles, ribs)	Clinical reference and mid axillary line typically, excludes latissimus dorsi muscle	Sternal rib junction

lymph node dissection, full axillary radiotherapy should not be performed routinely [28]. In case of undissected axillary apex and supraclavicular fossa, it is recommended to include the chest wall and draining lymphatics in the treatment volume.

The entire ipsilateral chest wall that would be typically considered at risk for recurrence in a patient with mastectomy is included in the irradiated volume. Target volume should cover the surgical scar; nevertheless, extreme ends of the surgical scar may be excluded medially or laterally in the target volume in order to decrease dose to acceptable heart and lung limits. The superior limit of chest wall CTV is defined by the caudal border of the clavicle head. The inferior border is defined according to the contralateral breast tissue. The lateral border is meant to estimate the lateral border of the previous breast, typically to the mid axillary line. CTV should cover the area up to the lateral edge of the pectoralis muscles except for the latissimus dorsi muscle. The chest wall CTV typically should not the cross sternal rib junction. To compensate for the dose calculation uncertainties in the buildup region, the anterior margin of the CTV should be parallel to, but still 3 mm inside, the skin. Posteriorly, chest wall CTV is considered to extend to the rib-pleural interface, including the pectoralis muscles, chest wall muscles, and ribs (Table 13.1).

13.3.2 Regional Nodes

Regional lymph node metastasis is an important prognostic factor for locoregional recurrence and overall survival in patients with breast carcinoma. It is correlated with tumor size, grade, and location within the breast. Depending on tumor size, the risk of axillary lymph node involvement varies between 5% (for T1G1 tumors) to

Fig. 13.8 (continued) (*turquoise*); *LIII* level III axillary lymphatics (*dark blue*); *MI* mammaria interna lymphatics (*magenta*); *E* esophagus (*dark green*); *H* humerus (*black*); *SC* spinal cord (*yellow*); *LL* left lung; *RR* right lung; *Ht* heart (*red*); *T* thyroid gland (*white*); *BP* brachial plexus (*dark yellow*); *CB* contralateral breast (*dark magenta*)

50% (for T3 tumors) [31]. Supraclavicular lymph node metastasis increases with the number of axillary lymph node metastasis. The risk of IMN metastasis for upper outer tumors and lower inner tumors varies between 3% and 65%, respectively, in patients with early-stage breast carcinoma [32].

The irradiation of the lymph nodes has shown a decrease for the risk of nodal recurrence [17, 33]. Nodal volumes contoured for targeting will depend on the specific clinical case. If the adequately dissected axilla is negative and there is no extracapsular extension, axillary radiotherapy may not be indicated. On the other hand, if the patient has had an inadequate axillary dissection, or there is evidence of extracapsular extension, the full axillary region should be treated.

13.3.2.1 Supraclavicular Lymph Nodes

The supraclavicular lymph nodes (anatomically called the inferior deep cervical lymph nodes) are mostly split into two sections: the medial supraclavicular lymph nodes and the lateral supraclavicular lymph nodes which are involved with less frequency [19, 34]. The first lymph nodes contain the inferior jugular nodal chain and the medial section of the transverse cervical nodal chain covering sentinel lymph nodes which are the most inferior-located lymph nodes of this chain [19, 34–36]. The second lymph nodes include the lateral part of the transverse cervical nodal chain [19, 35]. According to Robbins' classification of lymph nodes of the neck, the medial and lateral supraclavicular lymph nodes are defined as level IV and level Vb lymph nodes, respectively [37].

With great success of obtaining regional failure rates of only 0.0–1.5% for the first failure, for patients at high risk, microscopic residual disease of the supraclavicular and infraclavicular regions have usually been cured using radiation therapy [38, 39].

Medially, the supraclavicular region extends to the lateral edge of the trachea, excluding the thyroid gland and cricoid cartilage superiorly. Anteriorly, it is bound by the SCM. The posterolateral border of the field is at the anterior and medial borders of the anterior scalene muscle, while the posteromedial border extends medially to the carotid artery and internal jugular vein. The inferior border is defined at the level of the junction of the brachiocephalic and axillary veins or caudal edge of the clavicle head. The superior aspect of the chest wall field border is roughly accepted as being at the supraclavicular caudal border. Laterally, it extends from the lateral edge of the SCM muscle to the junction of the first rib and clavicle (Table 13.2).

13.3.2.2 Axillary Lymph Nodes

Based on the SEER (Surveillance, Epidemiology and End Results) database, Du et al. found that there is a significant increase in breast cancer mortality by a factor of 1.76 in patients with no treatment applied to the axilla. It is clearly defined

Table 13.2 Supraclavicular anatomic boundaries

Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Caudal to the cricoid cartilage	Junction of brachiocephalic axillary veins/ caudal edge clavicle head	Sternocleidomastoid (SCM) muscle	Anterior aspect of the scalene muscle	Cranial: lateral edge of SCM muscle caudal: junction first rib-clavicle	Excludes thyroid and trachea

that no difference on results have been observed for surgery alone, radiotherapy alone, or both combined [40]. Separate from axillary involvement, Strom et al. verified the risk of a local recurrence in the low-mid axilla as only 3% in actuality at 10 years after surgery alone [41].

Level I

The superior border is defined by the cross lateral edge of the axillary vessels of the pectoralis minor muscle and by the inferior edge by pectoralis major muscle where it inserts into the ribs. The anterior surface of pectoralis major muscle and latissimus dorsi muscle defines the anterior border of level I and the anterior surface of the subscapularis muscle describes the posterior surface. The boundary is limited laterally by the medial border of the latissimus dorsi muscle and medially by the lateral border of pectoralis minor muscle (Table 13.3).

Level II

Axillary vessels cross medial edge of the pectoralis minor muscle defines the superior end of level II and the inferior end is bordered by the axillary vessels cross lateral edge of the pectoralis minor muscle. The anterior border is accepted as the anterior surface pectoralis minor muscle and posterior is defined by the ribs and intercostals muscles. The boundary reaches laterally to the lateral border of pectoralis minor muscle and extends medially to the medial border of pectoralis minor muscle.

Even though some authors indicate differing views about the percentage of patients with metastases at the interpectoral nodes, the positive interpectoral nodes at the time of surgery are found in almost 14% of patients with operable breast cancer [42–44]. Routine interpectoral lymph node dissection does not apply during axillary lymph node dissection. In patients at high risk, inadequate treatment of this region has been associated with decreased survival [45], therefore, interpectoral lymph nodes may be included in level II borders [46] (Table 13.4).

Table 13.3 Level I axillary anatomic boundaries

Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Axillary vessels cross lateral edge of pectoralis minor muscle	Pectoralis major muscle insert into ribs	Plane defined by: anterior surface of pectoralis major muscle and latissimus dorsi muscle	Anterior surface of subscapularis muscle	Medial border of latissimus dorsi muscle	Lateral border of pectoralis minor muscle

Table 13.4 Level II axillary anatomic boundaries

Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Axillary vessels cross medial edge of pectoralis minor muscle	Axillary vessels cross lateral edge of pectoralis minor muscle	Anterior surface pectoralis minor muscle	Ribs and intercostal muscles	Lateral border of pectoralis minor muscle	Medial border of pectoralis minor muscle

Level III

Level III of the axilla is also called the "axillary apex." The superior border is defined at the level of the insertion of the pectoralis minor muscle into the coracoid process. The inferior border is where the axillary vessels cross the medial edge of the pectoralis minor muscle. Level III of the axilla extends laterally to the medial border of the pectoralis minor muscle and medially to the thoracic inlet. The anterior extent for level III is considered to be the deep surface of the pectoralis major muscle and the posterior extent was is by the ribs and intercostal muscles (Table 13.5).

13.3.2.3 Internal Mammarian Lymph Nodes

Because of uncommon clinical failures and applying adjuvant therapy to the majority of patients at risk, the treatment of IMNs is controversial [17, 47]. Some authors have reported that almost 20% of patients with clinically operable breast cancer have metastases to the IMNs affecting long-term survival [48, 49]. However, it is difficult to treat IMNs because their exact location is usually unknown, and normal tissue is normally irradiated with the radiation fields which cover them [50, 51]. On the other hand, irradiation of the lung and heart is an important problem after IMN irradiation. Two meta-analyses of randomized trials of postmastectomy radiotherapy, of which most included IMC irradiation, demonstrated that there was a significant increase in non-breast cancer mortality in women who had undergone

Table 13.5 Level III axillary anatomic boundaries

Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Pectoralis minor muscle insert on cricoid	Axillary vessels cross medial edge of pectoralis minor muscle	Posterior surface pectoralis major muscle	Ribs and intercostal muscles	Medial border of pectoralis minor muscle	Thoracic inlet

radiotherapy [25, 48, 52]. Therefore, an accurate definition of IMNs is mandatory for decreasing the early and late complications of radiotherapy related to target volume delineation. IMNs could be missed in the majority of patients using conventional radiotherapy planning. IMNs are usually not visible and thus internal mammary vessels which are closely applied to the nodes can be used to locate the exact location of the nodes and to help delineate the target volume. IMNs are located within the anterior intercostal spaces and it is clinically accepted that the nodes in the upper three intercostal spaces are the most significant [1, 16]. It is easy to define the position of the vessels using CT without contrast and recommend delineation of the IMNs from the superior aspect of the medial first rib to the cranial aspect of the fourth rib. Several guidelines for the defining the margin around the internal mammary vessels and the amount of covered intercostal spaces in IMNs are available in the literature [36, 50, 53–55]. It is suggested that the margin should be around 5 mm laterally and medially of the internal mammary vessels [46, 53, 54].

13.4 Conclusion

The best possible selection and delineation of target volumes and organs at risk is essential for the implementation of 3D-CRT and IMRT allowing better optimization of dose homogeneity. The advantage of modern radiotherapy techniques is that with the use of CT treatment planning, the most suitable plan can be determined so that radiotherapy complications are avoided or minimized. Several guidelines have been released during the past few years regarding the selection and the delineation of the chest wall and regional lymphatics. Less treatment variations patients and more multi-institutional clinical trials or retrospective studies can be obtained if the guidelines are applied to daily practice of radiation oncology.

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Chapter 14
Breast and Tumor Bed

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14.1 Introduction

Radiotherapy (RT) following breast-conserving surgery is effective in improving local control and long-term survival. An additional boost to the tumor bed is also important to further decrease local recurrence after whole-breast irradiation. Precise delineation of RT target volumes and normal organs is critical for conformal RT. In this chapter, target volumes are defined and delineations of these volumes are also described according to the Radiation Therapy Oncology Group (RTOG) breast cancer atlas. Delineations are also shown in the treatment planning computed tomography (CT) scans from two patients who had undergone prior breast-conserving surgery.

RT is a standard treatment option for early-stage breast cancer patients as an adjuvant therapy [1]. RT following breast-conserving surgery is effective in improving local control and long-term survival [1]. Precise delineation of RT target volumes and normal organs is critical for conformal RT because treatment planning and delivery stems from these delineations.

Seventy to eighty percent of local recurrences occur in the tumor bed resulting from the residual tumor cells after surgery, thus the boost RT to the surgical bed in conservative treatment is recommended as the studies support the benefits [2–4]. An application of a 10 or 16 Gy radiation boost to the tumor bed in addition to 50 Gy to the whole breast was found to increase local control [2–4]. The European Organisation for Research and Treatment of Cancer boost trial showed that an additional boost field of 16 Gy on the excision site was shown to increase local control, but reduced cosmetic outcome [2]. Accurate definition of the target boost volume is therefore essential. More accurate definition of the target volume can reduce unnecessary irradiation of breast glandular tissue complication rates [2].

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Gross tumor volume (GTV) is defined by the International Commission on Radiation Units and Measurements as the gross demonstrable extent and location of a malignant growth [5]. As the macroscopic tumor is removed during breast-conserving surgery with a variable margin of tissue leaving a cavity, there is no GTV. Usually, the cavity walls are also named as the tumor bed and clips inserted around them during surgery. Residual whole-breast tissue is a clinical target volume (CTV) for adjuvant RT. Accurate target positioning is crucial for delivery of precise dose to the whole breast. As a result of compensate respiration, intra- and interfractional variations in the breast, and patient's position and setup uncertainties, planning target volume (PTV) margins are added to CTV. A CTV-PTV margin of 1 cm is mostly used for a standard breast target volume. If there are clips in the tumor bed, these margins can be arranged to cover the tumor bed adequately.

With the continuous improvement of RT technologies, customized planning and treatment can be geared toward each patient such that, planned CT prior to RT is typical for each patient. Glandular breast tissue, heart, and both lungs are delineated with use of axial CT slices. Sagittally and coronally reconstructed images are used for verification. Muscles, ribs, overlying skin, and excision scars are not treatment targets for RT. Exact delineation of the breast and tumor bed is required for each patient that underwent breast-conserving surgery. Excision cavity volumes are delineated based on the surgical clips and the seroma or hematoma or other surgical changes seen on CT scans [6–8]. The CTV for tumor boost is defined as a 1.5-cm expansion of the tumor bed, trimmed off of the skin, chest wall, and pectoral muscle. The PTV is specified as a 5-mm circumferential expansion of the CTV.

Boost target volume includes postoperative seroma, it is frequently assumed that it does not change significantly during RT. However, studies have demonstrated 36–50% seroma reduction prior to RT and 22–62% during RT [8–16]. As a result of seroma reduction, the volume of RT boost defined at the commencement of RT may cause the breast to be radiated unnecessarily, increasing risk of fibrosis and additional cosmetic worsening [17–19]. Studies have shown that changes in boost volume during RT resulting from seroma shrinkage are significant in relation to clinical interobserver variations [11, 20, 21]. It is suboptimal to use seroma cavity delineation for target positioning in high-risk patients that receive chemotherapy between surgery and RT [22]. Because of contraction of the cavity, a smaller volume is defined during RT [22]. This might have a negative effect on the local control in the future. To reduce these issues and to define the precise target, CT may be implemented a few times, but there is no consensus on this topic.

There are significant variations in defining target volumes for breast RT [8–16, 20–24]. Many studies in the literature report that even at the same clinic, the target volume definition process may vary. Target volume delineation studies are presented in many publications providing detailed recommendations and training. As such, Hurkmans et al. observed that CTV based on CT delineated by multiple observers varied by 17. 5% [10]. Landis et al. reported large variations in delineating the lumpectomy cavity among specialized radiation oncologists [23]. Struikmans et al. showed that two volumes delineated by different observers overlapped on an average of 87% or 56% for breast or boost volumes, respectively

[24]. Recently, the RTOG conducted a study and concluded that there are differences in target and normal organ delineation for breast RT among institutions and observers that appear to be clinically and dosimetrically significant [25].

As a result, there is a need for systematic consensus on target volume definition and standardization for breast radiation using modern RT technology. For that matter, the RTOG established a breast cancer atlas for RT [26].

14.2 According to the consensus, breast clinical target volume mainly:

1) Considers referenced clinical breast at time of CT
2) Includes the apparent CT glandular breast tissue
3) Incorporates consensus definitions of anatomic borders:
   a) Cranially clinical reference and second rib insertion
   b) Caudally clinical reference and loss of CT apparent breast
   c) Anterior Skin
   d) Posterior excludes pectoralis muscles, chest wall muscles, ribs
   e) Laterally clinical reference and midaxillary line typically, excludes latissimus dorsi muscle
   f) Medially sternal-rib junction
4) Includes the lumpectomy CTV
5) Lumpectomy GTV: includes seroma and surgical clips when present.

14.3 The CT Plans of Two Sample Patients Present the Definition of Breast and Tumor Boost

14.3.1 Case I: Intact Postlumpectomy Breast (Fig. 14.1)

- Stage I (T1c, N0, M0) left breast cancer
- Surgery: lumpectomy and axillary node dissection
- Radiation: breast
- Six surgical clips placed at lumpectomy site
- External markers placed at time of CT:
  - Markers at AP and lateral setup points
  - Four wire markers for clinical estimate of cranial, caudal, medial, and lateral extent of anticipated tangents
  - Wire extending from 9- to 3-o'clock position around the inframammary fold
  - Wire over the lumpectomy scar.

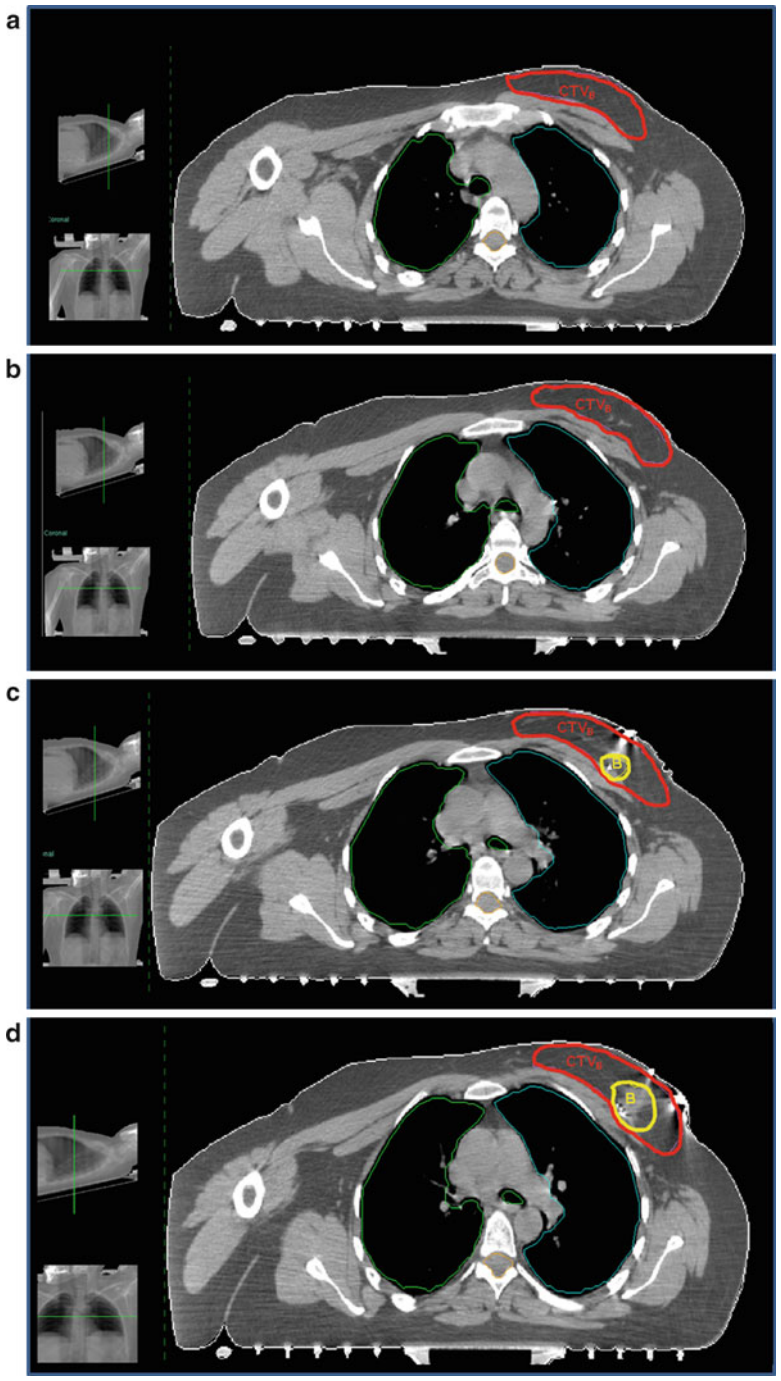

Fig. 1 (continued)

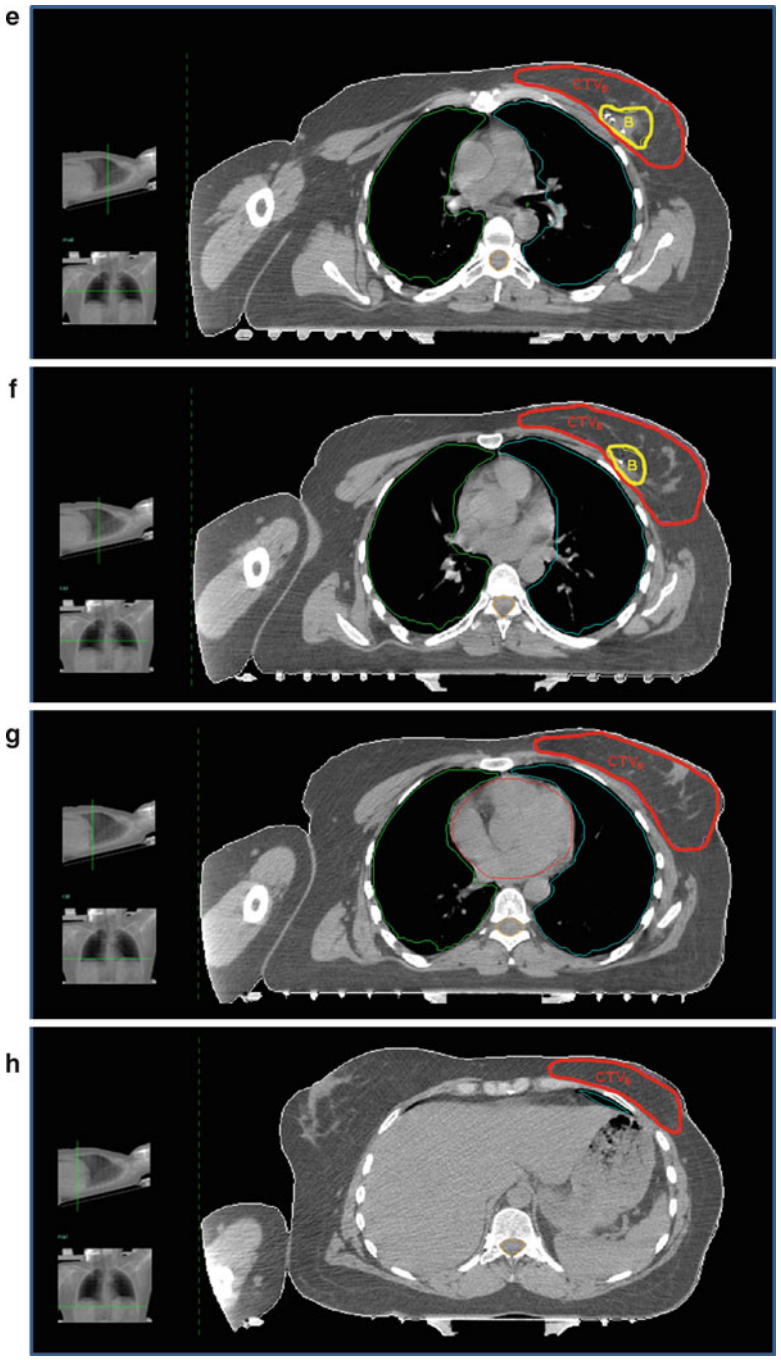

Fig. 14.1 Contouring of clinical target volumes (CTVs) in a female patient with left-sided breast cancer. CTV_B = CTV for intact breast (*red*), B = tumor bed for boost CTV (*yellow*)

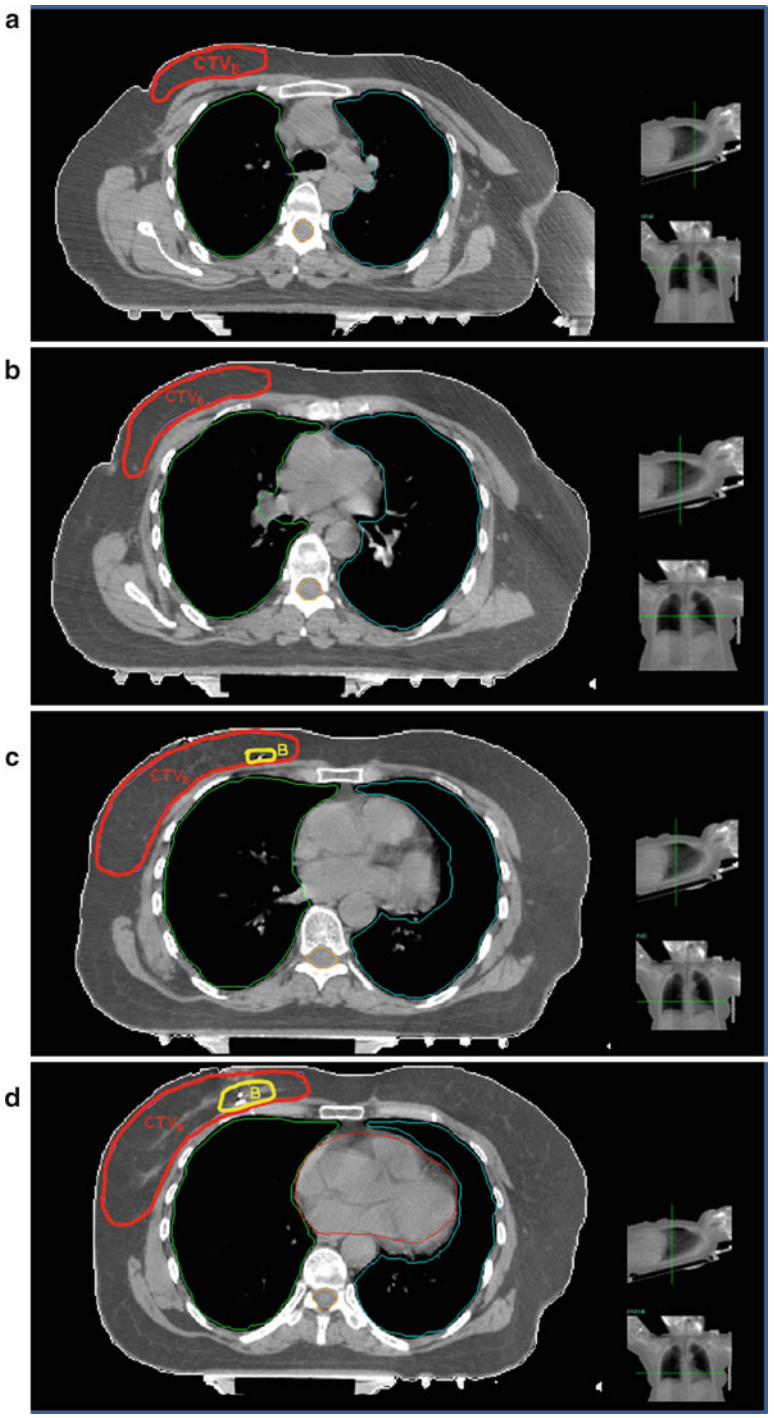

Fig. 2 (continued)

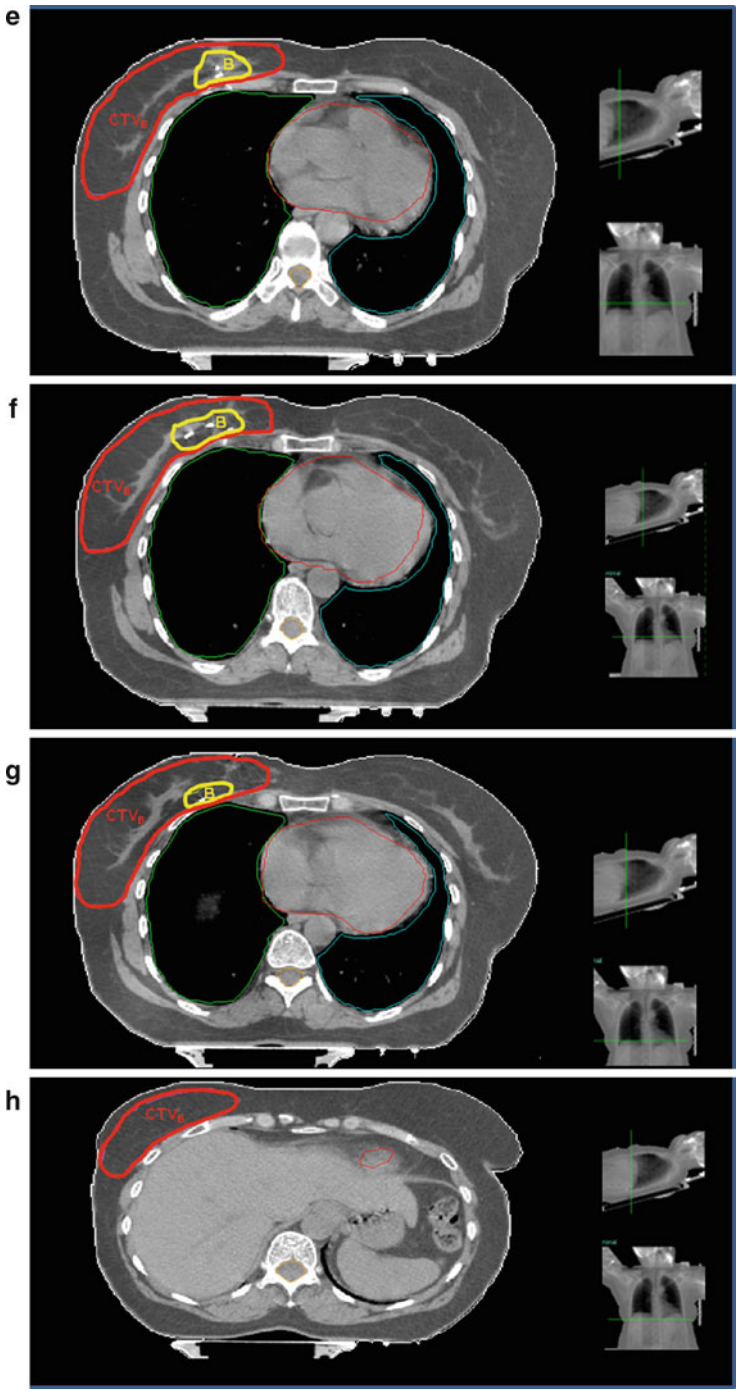

Fig. 14.2 Contouring of clinical target volumes (CTVs) in a female patient with right-sided breast cancer. CTV_B = CTV for intact breast (*red*), B = tumor bed for boost CTV (*yellow*)

14.3.2 Case II: Intact Post Lumpectomy Breast (Fig. 14.2)

- Stage I (T1a, N0, M0) right breast cancer
- Surgery: lumpectomy and axillary node dissection
- Radiation: breast
- Six surgical clips placed at lumpectomy site
- External markers placed at time of CT:
  - Markers at AP and lateral setup points
  - Four wire markers for clinical estimate of cranial, caudal, medial, and lateral extent of anticipated tangents
  - Wire extending from the 9- to 3-o'clock position around the inframammary fold
  - Wire over the lumpectomy scar.

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Part IV
Modern Radiotherapy Tecniques in Breast Cancer

Chapter 15
Simulation and Patient Fixation Methods

Sibel Kahraman Cetintas, Lutfi Ozkan, Sema Gozcu, and Ali Altay

15.1 Introduction

Radiotherapy (RT) for breast cancer patients, the appropriate indications and use of modern methods has been confirmed positive contributions that disease, disease-specific and overall survival in meta-analysis [1, 2]. The aim of RT is homogeneous distribution of the dose required for tumor control (±5%) at the target volume while protecting healthy tissue [3]. RT techniques can be difficult and vary depending on the anatomic structure of the region to be irradiated (breast, chest wall, or regional lymphatic) that target volumes could be in different depths and geometries [3–5]. Over time, with technologic advances and increasing experience in clinical practice, different simulation and treatment techniques have been developed [6–17]. Beginning in the 1950s, use of megavoltage treatment equipment in modern RT processes has reached a new point, with the use of magnetic resonance imaging, positron emission tomography, and computed tomography (CT) for treatment planning and in determining the target volumes. In a realistic virtual environment, a large number of techniques can be reviewed and an optimal technique can be formed using modern planning computers. Intensity modulated radiotherapy is becoming increasingly popular for critical organ volumes and dose reductions better than for target volume can be achieved [18, 19].

15.2 Technical Problems in Breast Cancer Radiation Therapy

The main purposes of breast cancer RT are preventing hot and cold regions of dose between the adjacent areas, creation of adequate dose distribution at the peripheral lymphatic; minimizing irradiation of lung, heart, and organs at risk; maximum

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protection of the mediastinal tissues; cosmetically acceptable results; and providing applicable and easily repeatable setup conditions [20–23]. RT doses and fields should be planned according to patient, clinical, radiologic, and pathologic examination data. Patients with arm opening problems should be referred to physical therapy programs to prepare for simulation. Physical therapy in the early period prevents arm opening limitation [24].

15.3 Simulation and Fixation

Patients undergoing RT treatment as a result of clinical evaluation must be informed about the treatment procedures and expectations of treatment implementation. Following that, the patient can been be sought for a physical barrier that limits the patient in treatment position. The most common problem with axillary dissection and sleeve opening the cases, patients with limited movement of the arm opening is prepared by the methods of physical therapy and rehabilitation. In addition, breast and body structure problems (such as kyphosis, scoliosis, pectus deformity) that can effect immobilization should be identified and the appropriate technical solutions developed for them.

One of the most important tasks complete before the simulation is to prepare the immobilization devices that could provide a repeatable treatment position. The psychology of the patient, comfort, position repeatability, and beam entry points should be considered in the preparation of the immobilization tool [14, 17, 25–27]. Based on practices in different facilities over the years, achieving immobilization of the equipment is commercially produced and widely used. The most well known of these are the inclined plane, breast board, Board-Wing Butterfly Board, Vac-fix bag-Vacuum Cradle Bed, and alpha cradle, and all have advantages and disadvantages [9, 12, 14, 25–27].

15.3.1 Breast Board

The apparatus included an inclined plane, and the arm support is a combined system consisting of fasteners should be prepared as follows;

- Patient placed in supine position and a hip fixer placed.
- Board is angled as sternum parallel to the floor.
- The treated arm is in higher position as much as possible.
- Position data entered into the patient treatment chart.

The breast board is the most common and preferred board because of its easy preparation and repeatability, the apparatus does not require immobilization for each patient, and it is less costly (Fig. 15.1). The disadvantages are patient set-up differences and limited tilt angles.

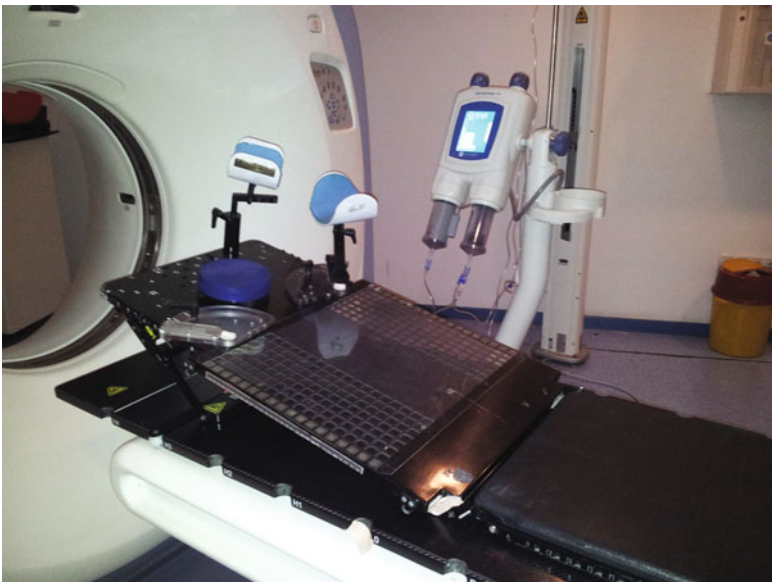

Fig. 15.1 A breast board

15.3.2 Alpha Cradle

This is a chemical mixture obtained from the foam and is based on of taking the form of the body, used for fixing the corpus and extremities of the body. Prepare as follows;

In the treatment position, sternum and arms are parallel to the floor and arms are over the head, patient is on a prepared plastic cover over the foam.

- Foam solutions are mixed in a container.
- The mixture is poured into a plastic bag and the bag is closed.
- As the foam is enlarging it provides that the foam is taking the shape of the body.

The advantages are that it is unique to the patient, reduces errors by providing stabilization, and easy set-up. However, it cannot adapt to the body of the patient during loss or gain of weight, or if the patient has any differences in the body shape. The system is expensive and is only meant for single use. Also, the solution used for preparation of the system is a highly toxic chemical, so a protective mask needs to be worn during application.

15.3.3 Vacuum Bed

The vacuum bed consists of microspheres and is based on a system that takes the form of the body by vacuuming the air in it, and it is used for fixing the corpus and extremities of the body (Fig. 15.2). It is prepared as follows:

Fig. 15.2 A vacuum bed

– In the treatment position, sternum and arms are parallel to the floor and arms are over the head, patient is on a plastic bed filled with microspheres.
– By vacuuming the bed any shape can be taken.

Its advantages are that it is unique to the patient, reduces errors by providing stabilization, and has an easy set-up. It is ideal compare with the alpha cradle because it is reusable and has no chemical exposure. However, it has the disadvantage of losing vacuum during the treatment period and deforms. It is important to sustain the vacuum stability during the entire treatment period.

The patient should be given a reproducible position that will not change during the forthcoming treatment period. Age, menopause, anxiety, breathing, weight gain, breast or chest wall structure of the volume, and the number and length of RT time plays a role in immobilization. With routine use of CT planning, the stability of the simulation position became more important [14–19].

15.3.4 Breast Fixation

In breast RT, in addition to the stability of the patient, the stability of irradiated breast is also important. This issue is also important for pendulous breasts, and strapping of the breast into position with tapes, thermoplastic mask, and premoulded plastic breast cups can be used for stabilization. For the construction of the thermoplastic mask, water temperature must be 77°C for 2.5 min, to form 2–5, and 10 min waiting for it to finish. For fixing the big breast volumes, cable-stayed silicon bra, silicone cup hanger Kosmas, and nipple rings are available. Sometimes the patient is used to secure with the special large vacuum bed. Particularly with larger breasts, the fixing apparatus can lead to an increase in acute skin reactions under the breast and the tail of the breast [27].

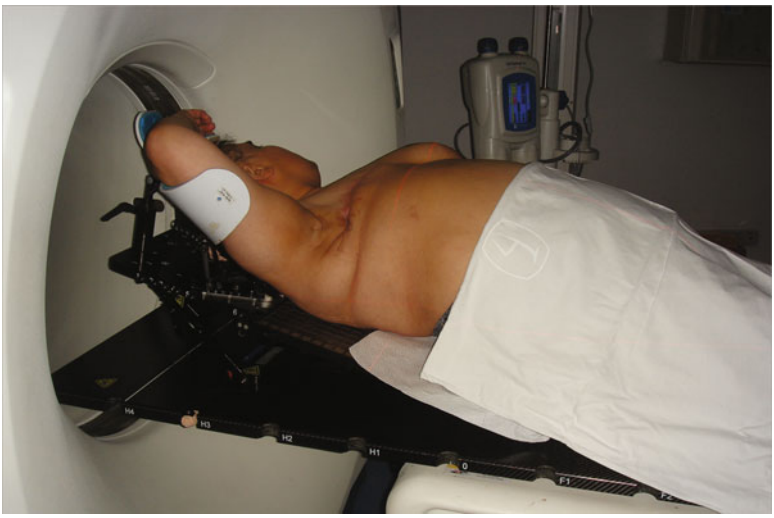

Fig. 15.3 The supine position on a breast board during CT simulation (Courtesy of Hacettepe University)

15.4 Simulation Techniques

The main function of the simulator is to demonstrate target volumes while preventing the normal tissues from being exposed to extra radiation that are in the area of radiation treatment. The simulation process should be explained to the patient in detail. The patient should be told not to move and maintain their position afterward. In breast RT, the supine position is mostly used; sometimes the prone position for very large pendulous breasts is used as well as the side (lateral decubitus) position [23, 25–30].

15.4.1 Supine Position

The patient is set supine, in the middle of the plane, midsternal line is parallel to the table in the angled specific immobilization system (Fig. 15.3). The patient is positioned flat on her back (fully supine) on a stable or breast tilt board—lift up position. The angle that is used to eliminate patient slope of the sternum at the inclined plane can be adjusted according to the clinic requirements. Very steep angles can increase the dose of the lung in the supraclavicular area. The collimator and the table are retained to the zero-degree position. The face and the head of the patient are turned slightly upward and the arm is placed perpendicular to the body. If the peripheral lymphatic will not be irradiated, arm can be placed under the head. Arm stability minimizes the risk of setup errors [14, 17, 26]. To remove the other

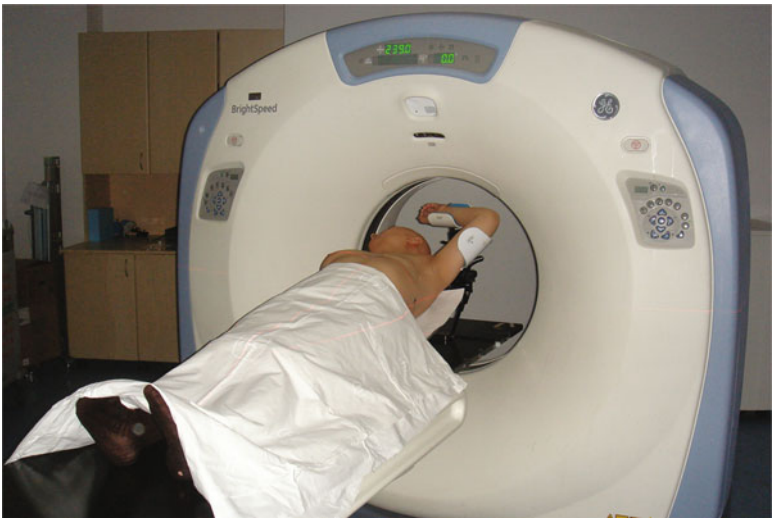

Fig. 15.4 CT simulation of a patient with breast cancer (Courtesy of Hacettepe University)

breast from the radiation area, the other arm is placed below the elbow or hand held in a curl back position. The extension of both arms above the head expands and elevates the chest wall, lifting it away from the underlying heart. For use of CT-based treatment planning, the choice of arm position enables the woman to pass through the CT (Fig. 15.4). Legs must be straight and contiguous. Use of a hip stabilizer allows fixing of the position. Incision and drainage areas are marked with thin radiopaque wire. Position information of patient set-up should be noted on the treatment chart and the computer system.

The supine position is the most commonly used method which and has been proven to be effective. The position is very useful for repeatable set-up to combine irradiation of the breast and the lymphatics [23, 25, 26].

15.4.2 Prone Position

To achieve a homogeneous dose distribution in large breasts, and in order to move the lungs from the area, prone techniques can be chosen [23, 27–29]. The advantages are a more homogeneous dose distribution, fewer hot spots, a lower dose to the lungs and the normal tissue, ease of set-up in planning. The the disadvantages are not be able to cover the whole chest wall, need of separate set-up for breast and lymphatic irradiation, and discomfort to the patient. Griem et al. reported that for the planning the prone position, the inner tangential wedge usage requirement reduction, inhomogenity, the lung dose reduction in for the V10 and V20 [28]. Algan et al. reported that, in the prone position, tumors in the posterior localization GTV will not be covered in more then 73% of patients [29].

15.4.3 Lateral Decubitus Position

In large breasts, to protect the normal tissue and to provide a better isodose, side-lying positions can also be used. A lateral decubitus position that flattens the breast stroke can be treated with the standard field borders [30]. In experienced centers, while the heart and the lung doses decrease, the position applicability must be even easier. Situations that require peripheral lymphatic irradiation is an application which is the difficulty of providing the same setup.

If there is a problem with arm opening in cases of bilateral breast radiation therapy, a patient-specific (both arms up) position and fixing can be applied. Simulation and field properties as of the patient and the center's own experience may change.

15.5 Conclusion

To achieve the potential benefits of breast irradiation, it is critically important to position the target volume accurately in relation to the RT treatment beams. Doses of hot and cold regions of the junction regions of space should be considered in breast cancer treatment planning. For the doses to critical organs in the irradiated region, and dose distributions in the target area of treatment for the determination of position, take advantage of the CT slices and use advanced treatment planning systems will provide a great benefit. With the development of new treatment techniques, conformal coverage to the target volumes and protection of organs at risk are improving.

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Chapter 16
Three-Dimensional Planning Techniques

Murat Koylu, Nezahat Olacak, and Ayfer Haydaroglu

16.1 Introduction

Breast cancer is the leading type of cancer found in women. Radiotherapy is commonly administered in this type of cancer, as well as surgery, chemotherapy, and hormone therapy. Conventionally, two-dimensional (2D) wedge compensators have been used for many years; however, in parallel with the advancement of medical technologies, they have been upgraded and replaced by more advanced three-dimensional conformal radiotherapy (3D-CRT) technique. Particularly with the use of computed tomography (CT) in radiotherapy treatment simulation and planning, tumor location can be determined more confidently, and highly homogenous and conformal radiation dose distributions can be obtained. Thus, unintended high radiation doses can be reduced in the critical structures such as the skin, lung, and HEART, so that early and late adverse effects are ensured to be decreased. Planning and implementation of the 3D-CRT have improved over the course of time through developments concerning medical technology and expert-level experience. Through developing different techniques, improved patient comfort, accurate applicability, and further reduction in the adverse effects are ensured [1].

Based on the methods and tools used in the implementation phase, CRT can be categorized under three main headings. They are simple conformal radiotherapy, which consists of radiation fields distinctively identified by direct radiography and limited CT data; 3D-CRT, which is composed of 3D data of tumor volume defined on CT images in accordance with International Commission on Radiation Units and Measurements (ICRU) 50 and 62; and advanced 3D-CRT, a more complex technique which is also known as intensity modulated radiotherapy [2, 3].

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16.2 3D-CRT

3D-CRT is the type of radiation therapy that would ensure not only precisely shaped treatment fields involving only the target tissue, but also realistic isodose distributions by using 3D image data. In 3D-CRT, a more homogeneous and higher radiation dose is delivered to the precisely defined target, while dose to nearby nontarget normal tissue volumes is reduced. Implementation of 3D-CRT requires CT data of patients, treatment planning software, and treatment verification systems as well as realization of a series of stages such as image acquisition, target and critical structure definition, treatment planning, evaluation of the treatment plan, data transfer, and treatment start [2, 4].

16.3 Rationale for 3D-CRT in Breast Cancer

In breast cancers, 3D-CRT starts with immobilization of the patient at the time of treatment position. Three radiopaque markers, one in the front and two at the sides, are placed at the presumptive central section of the area including the target and critical structures, and this point is regarded as the origin. CT images of the target region are taken mostly at the required cross-sectional thickness, and the outer contour of each section is marked and denoted to the treatment planning computer [4, 5].

Definition of the structure volume is an indispensable requirement for a significant 3D-CRT and accurate dose estimation. The target and critical structure volumes for 3D-CRT are defined according to ICRU Reports 50 and 62. The gross target volume (GTV) refers to the palpable or visible structure. However, this definition is not used for breast cancer. The GTV and the presumptive subclinical tissue volume having microscopic disease are known as the clinical target volume (CTV). Arrangement of beams to ensure precise radiation of CTV, with some added margins, leads to the geometric concept of the planning target volume (PTV). Thus, precise clinical radiation volume could be achieved and false-irradiation risks resulting from errors regarding tissue, tumor, and patient movements, as well as arrangement and planning of radiation beams would be minimized. Radiation-sensitive normal critical structures near the target are of great importance with regard to exceeding and also regulating the tolerance doses of radiation [2, 4–7].

Data obtained from CT of the target, structures at risk, and skin contours of the patient, as well as electron density information used for calculating dose irregularities caused by human tissue differences constitute a basis for 3D-CRT treatment planning. The intention in this process is to deliver high-dose irradiation to the target, while ensuring relevant dose distribution to protect organs at risk. The treatment planning process generally consists of several steps. First, the irradiation technique is determined either as a constant source-to-skin distance (SSD) or as source-to-axis distance (SAD) for beams. The number of beams,

mechanical data of these beams (gantry, collimator, SSD), and shaping of the target volume by multileaf collimator or special blocks are determined by virtual simulation through digitally reconstructed radiographs (DRRs). Isodose distribution can be achieved by correcting tissue inhomogeneities determined by CT data. Compensators, "wedge" filters, and bolus-like accessory tools compensate high- and low-dose areas and deliver a total dose directly to the target and realize homogenous dose distribution. Steps to be taken until reaching optimal treatment parameters are generally called treatment plan optimization [2, 5].

Evaluation of a 3D-CRT treatment plan consists of two parts. The first step is determining the radiation conformity index (RCI) and the dose homogeneity index (DHI). RCI describes how the delivered dose is spread within the target tissue and organs at risk. It is the indicator of the extent to which the delivered dose is involved in the target [6]. RCI calculated with the following formula:

$$\mathrm{RCI} = (\mathrm{TV_{ref}}/\mathrm{TV}) \times (\mathrm{TV_{ref}}/\mathrm{V_{ref}})$$

$\mathrm{TV_{ref}}$ describes the target volume covered by the reference isodose, TV is the target volume, and $\mathrm{V_{ref}}$ is the volume covered by the reference isodose. RCI ranges between 0–1, and the closer the RCI is to 1, the higher the dose conformity.

DHI describes the uniformity of the dose within the target volume [8]. DHI calculated with the following formula:

$$\mathrm{DHI} = (\mathrm{D_2} - \mathrm{D_{98}})/(\mathrm{D_{pres}}) \times 100$$

$\mathrm{D_{98}}$ describes the dose for 98% of the target volume, $\mathrm{D_2}$ is the dose received by 2% of the target volume, and $\mathrm{P_{pres}}$ is the prescribed dose. For an acceptable treatment plan, DHI should be smaller than 15 and the lower it is, the more homogeneous the dose distribution [8].

The second step is evaluating dose-volume histogram (DVH). DVHs are graphic formats showing dose distribution with volume in target and organs at risk. Sufficient dose delivered to the target tissue or how much damage occurred in the organs at risk can be determined using a DVH.

Transferring data for the approved treatment plan electronically through a network reduces potential errors. Data transfer includes parameters such as gantry of each beam, collimator, field size, SSD, SAD, table and multi leaf collimator positions, and the treatment duration [2].

Successful implementation of treatment refers to the success of the whole process. The purpose of verifying the treatment plan is to ensure the correct treatment alignment by adjusting the isocenter of beams identified with the treatment planning computer on the three-axis treatment instrument. The most commonly used radiologic verification techniques for 3D-CRT are conventional and electronic portal imaging techniques. In two techniques, front and side DRR outputs relating the isocenter of the beams and information defining the anatomy, which have been identified on the treatment planning computer, are used. In conventional portal imaging, front and side radiographic films taken with the

x-ray source are compared with DRR images so that correct patient positioning is ensured. The use of an electronic portal imaging device technique is gradually becoming widespread. Front and side DRRs digitally transferred from the planning computer are compared with electronic images taken with the treatment instrument; accordingly, the correct patient position is verified before the treatment [4].

16.4 3D-CRT Techniques in Breast Cancers

To achieve patient comfort and more accurate treatment of breast cancers, many techniques have been developed over the course of time. Depending on the position of the patient, the number of isocenters used, and the treatment method, these techniques are distinguished with the parameters of supine or prone positioning, use of single isocenter or multiple isocenters and isocentric or fixed SSD irradiation.

16.4.1 Whole-Breast Irradiation Techniques

16.4.1.1 Single Isocentric 3D-Conformal Whole-Breast Irradiation Technique

The single isocentric 3D-CRT technique is one of the radiotherapy techniques used for breast-conserving purposes. The patient is immobilized in the CT device with the arms over the head. Radiopaque catheters and markers are used to locate palpable breasts, scars, and skin marks, and marked on the patient. CT images are taken from the midcervical level to the midabdominal level at intervals of 2–5 mm, and are subsequently transferred to the planning computer [9, 10].

Breast PTV is generated by adding margins of 10 mm in the craniocaudal direction and 5 mm in other directions to the breast CTV including glandular breast tissue. The boost CTV is generated by adding a 3D margin of 10 mm around the lumpectomy cavity, while the boost PTV is generated by adding an additional margin of 5 mm. Organs at risk such as the heart, lungs, and contralateral breast are also marked at the computer tomography(CT) sections [10].

Two opposing tangential photon beams of 4–6 MV are used for irradiation of breast PTV. Isocenter of these beams is determined at the midpoint of breast PTV. At the central section, with the images obtained by using markers located on the skin and DRR, gantry angles are determined to ensure maximal protection of the heart, lungs, and contralateral breast. The fields are structured by means of breast PTV and multileaf collimator, while ensuring the edges adjacent to the lung are overlapped. Dose delivery and wedge filters provide dose homogeneity and at least

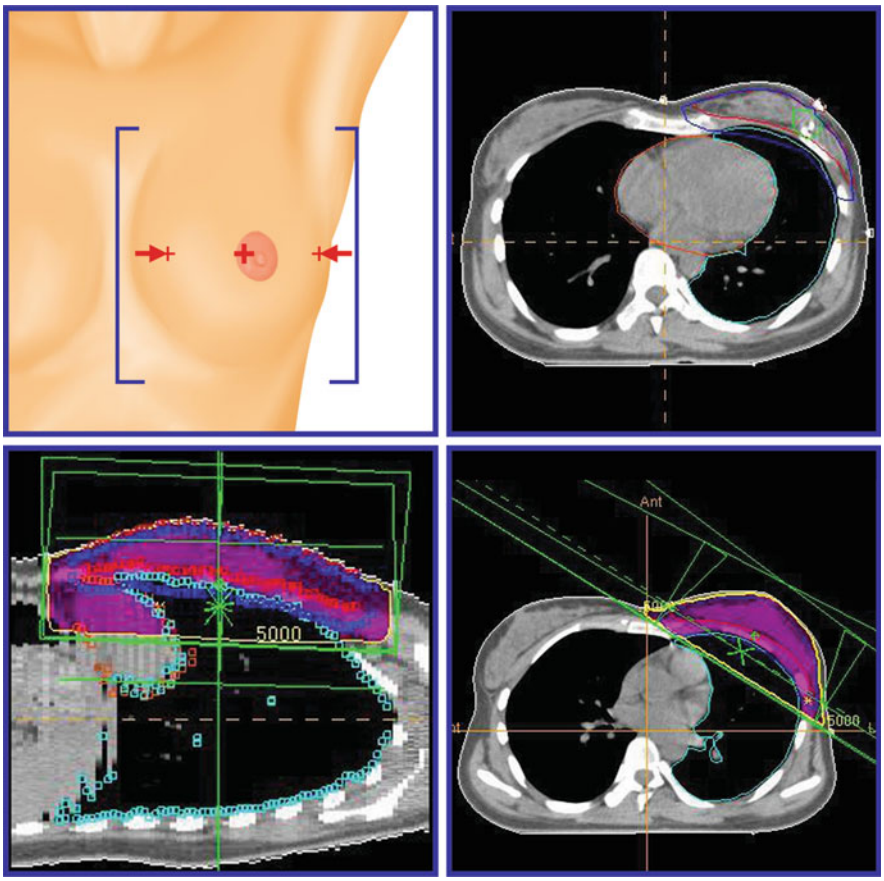

Fig. 16.1 Single isocentric 3D-conformal whole breast ırradiation technique

95% of the target dose delivery to PTV (Fig. 16.1). The treatment plan is completed by an additional 16 Gy boost PTV delivery to the tumor bed with electron or photon beams [10].

16.4.1.2 Single Isocentric Half-Beam 3D-Conformal Whole-Breast Irradiation Technique

In early-stage breast cancers, whole-breast irradiation following conserving surgery is performed as an alternative to mastectomy. In this treatment approach, the single isocentric half-beam whole-breast irradiation technique is used and opposing tangential photon fields of daily 2 Gy for 25 days totally 50 Gy to the whole breast, and subsequently, daily 2 Gy to the tumor bed totally 10–16 Gy are delivered [11–14].

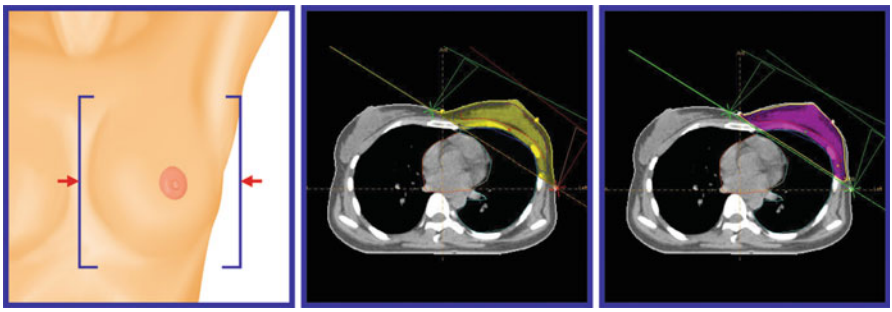

Fig. 16.2 Single isocentric half-beam 3D-conformal whole breast irradiation technique

In this technique, the patient is immobilized in the supine position with the arms over the head. Contours of the palpable breast are designated with radiopaque markers. The markers are placed in the midsternal and midaxillary planes at the central section, and CT images are obtained from the neck to the diaphragm, encompassing the entire lung, at intervals of 2–5 mm, and are transferred to the planning computer. Organs at risk such as the lungs, heart, and contralateral breast are plotted, with breast CTV and tumor bed CTV are marked on the CT scans [6].

In this technique, half beams of photons having 6 MV energy and 100 cm SAD are used. Thus, unnecessary irradiation to the lungs is prevented by overlapping of the central beam axes without any divergence at the edges of treatment fields adjacent to the lungs. The midsternum point marked at the central section is distinguished as the central axis border of the medial tangent field. By using the DRR images, gantry angle is determined for a way to include the least volumes of the lungs, heart, and contralateral breast within the treatment field. Field borders are determined by adding 2 cm to the breast CTV. The central axis border of the lateral tangent field just opposing to the medial tangent field is the midaxillary plane marked at the central section. Homogeneous dose distribution is assured in both tangential fields by using wedge filters and by adjusting dose delivery. The dose is normalized to two thirds of the perpendicular distance from the posterior margin of tangential fields to the skin surface at a central section. Ninety-five percent PTV is assured to receive a minimum of 95% of the prescribed dose (Fig. 16.2). Treatment is subsequently completed by delivering 10–16 Gy to the tumor bed, either as photons or electrons [10, 12].

16.4.1.3 Prone-Position Irradiation Techniques

The prone-position irradiation technique is not widely used because it requires special immobilization tools and may be troublesome for some patients. However, breasts treated with this technique hang down away from the chest wall, and therefore, volume of the lungs and heart located in the treatment area is highly minimized. Additionally, target tissue movements due to breathing are also minimized. On the other hand, this technique reduces radiation-induced toxicities

and gives better cosmetic results. Yet, implementation of this technique requires a specially designed prone breast pad with holes to allow breasts to hang down, and is produced from carbon fiber, a material with weak stopping power against radiation. Prone-position irradiation techniques can be examined in two main groups as whole-breast irradiation and partial breast irradiation techniques [15–18].

Prone 3D-Conformal Whole-Breast Irradiation Technique

For large- and pendulous-breasted patients treated undergoing breast-conserving radiotherapy, prone whole-breast irradiation enables reduction of radiation-induced toxicities. The prone breast pad is placed on the CT table and the patient is positioned in the prone position on the pad, with the ipsilateral arm placed over the head, and the breast to be treated is hung from the hole of the prone breast bed. Five markers, three at the back and at the sides, representing the ISOCENTER, are adhered to the skin of the patient at the transverse plane. Two other markers are placed at the middle and lateral breast sides. From the mandible to diaphragm, CT scans are obtained at 2–5 mm intervals, and transferred to the planning computer. The skin, both lungs, heart, and target tissues are marked at transverse sections [17, 19].

The midpoint of PTV is chosen as the isocenter. Using DRR images, opposed tangential fields are created, and the upper margin is determined just below the clavicle head while the lower margin is specified at 2 cm below the inframammary fold. At reference transverse cross-sections, the dorsal border of the beams is the line connecting the sternal skin marker to the point located in the front of the latissimus dorsi muscle at the side chest wall. Homogeneous dose distribution can be obtained by using the wedge filters and 6 MV photon beams (Fig. 16.3). The PTV is assured to receive at least 95% of the target dose. With this technique, a total of 50 Gy given in 25 days with daily doses of 2 Gy fractions is delivered to the PTV [18, 20].

Prone 3D-Conformal Accelerated Partial Breast Irradiation Technique

After breast-conserving surgery, 3D-accelerated partial breast irradiation treatment in the prone position is performed with an increased fraction dose delivered in a shorter period of time, moreover, the volume of irradiated normal tissue is even less. The patient is positioned in the prone position on the special pad in the CT device, hanging the breast to be irradiated down, away from the chest wall. Three markers that represent the ISOCENTER are placed on the skin of the patient, two at the sides and one at the back. From the mandible to the diaphragm, CT images are obtained at intervals of 2–5 mm and transferred to the planning computer [16].

After the surgery, the cavity is plotted as the CTV. PTV is defined by adding 1.5 cm margin to CTV. Volumes of ipsilateral lung and heart are plotted on the CT scans. The midpoint of PTV is chosen as the isocenter. Opposed small tangential

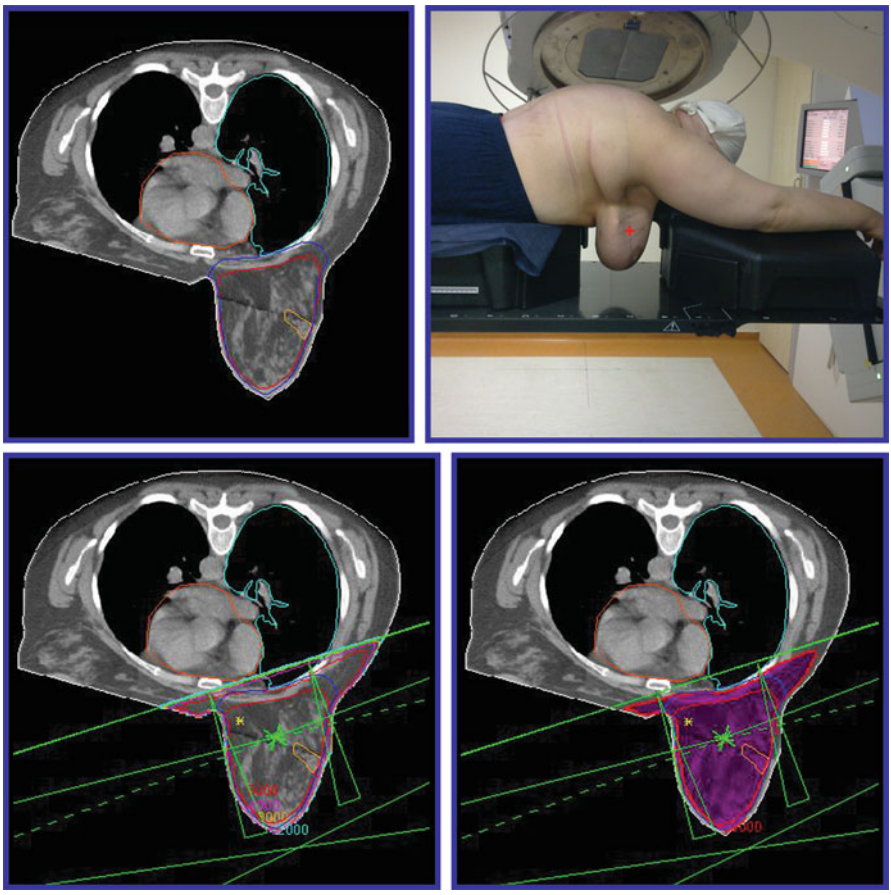

Fig. 16.3 Prone 3D-conformal whole-breast irradiation technique

fields are created through multileaf collimators (Fig. 16.4). Homogeneous dose distribution is obtained by using the wedge filters. Ninety-five percent of the target dose is assured to cover the whole PTV [16].

16.4.1.4 Peripheral Lymphatic Irradiation Techniques

When the supraclavicular lymphatic field is irradiated exclusively, the anterior field with an angle of 10–20° is used to protect the spinal cord and the esophagus. Borders of the irradiation field are limited by the upper limit of the tangential fields at the bottom, the midpoint of humeral head laterally, and the beginning edge of the vertebrae as the midline. Supraclavicular and infraclavicular lymphatics are also included in the field. For slim patients, when axillary radiation is required in the supraclavicular lymphatic field, only the single anterior field can be irradiated.

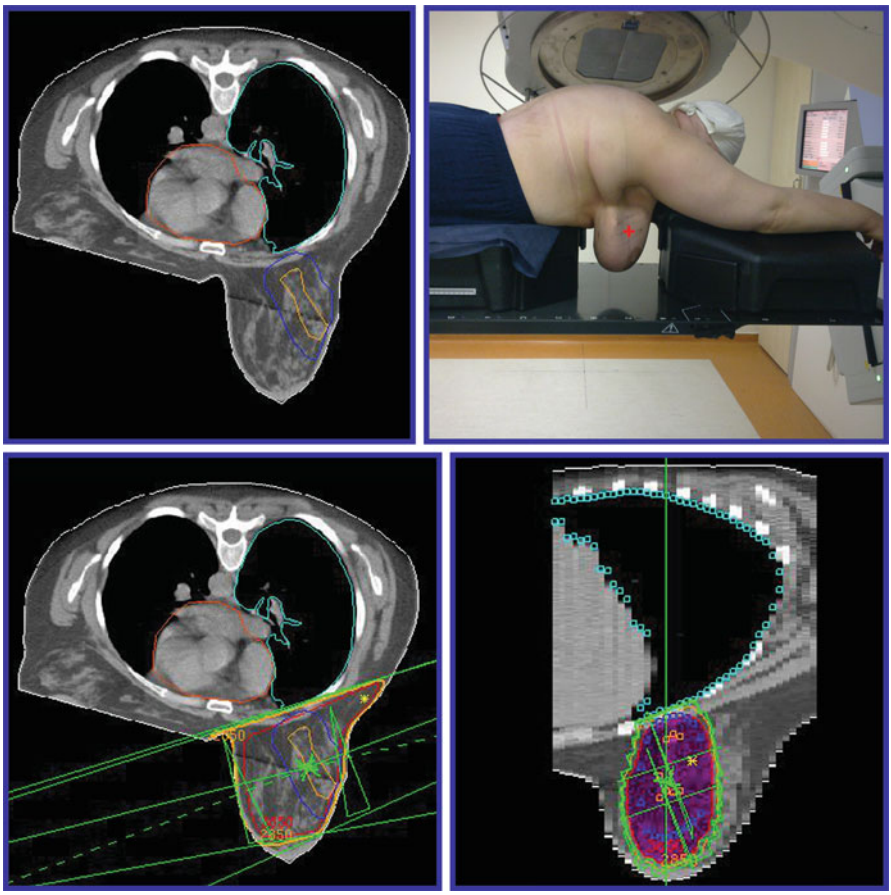

Fig. 16.4 Prone 3D-conformal accelerated partial breast irradiation technique

However, depths of the settlement area of the axilla and supraclavicular lymphatic fields are different, so the missing dose can be supplemented with an extra dose from the back side. The axilla (level 3 and level 2) are included in the supraclavicular lymphatic field. Irradiation of mammary internal lymphatics is included only for the medial and central quadrant tumors that are greater than 3 cm. Internal mammary lymphatics are irradiated with different techniques during chest wall and mammary irradiation.

16.5 Single Isocentric 3D-Conformal Irradiation Technique

Anterior and posterior supraclavicular axillary irradiation is required if there is supraclavicular and axillary lymph node involvement risk during radiotherapy administration for breast cancer. Overlapping of the upper limit of the tangential

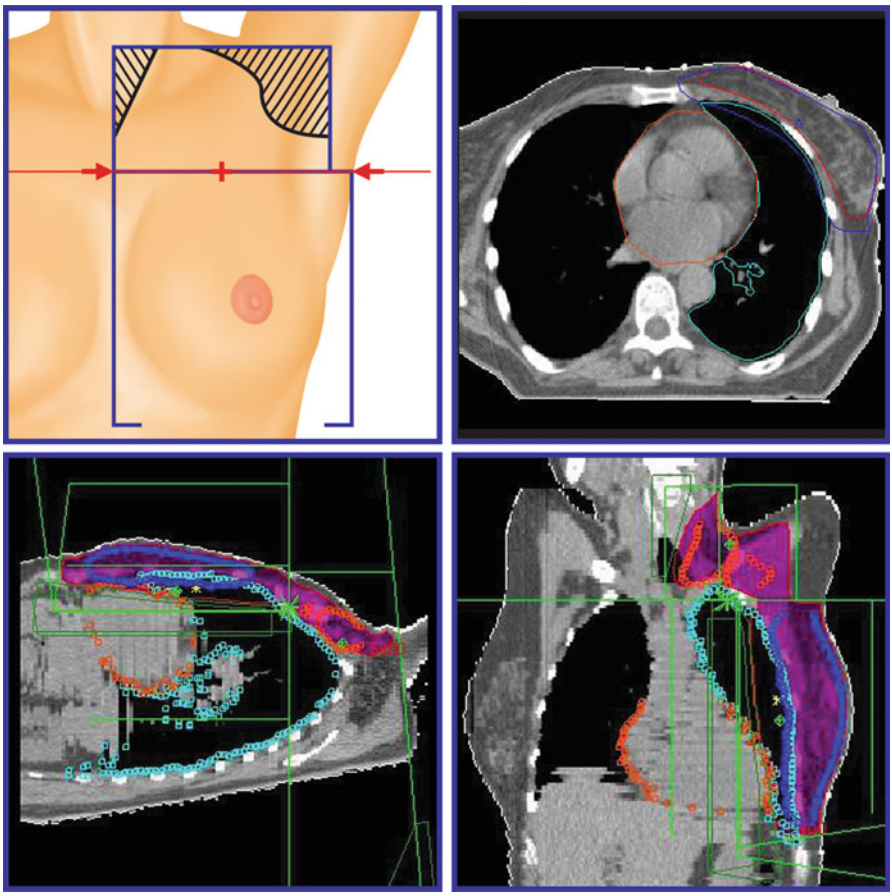

Fig. 16.5 Single ısocentric three-field 3D-conformal irradiation technique

fields and the supraclavicular area causes a problem. Single isocentric 3D/4D- CRT techniques have been developed to overcome this problem.

One single isocenter is used for the three-photon field which is used for cases having only supraclavicular lymph node involvement. This isocenter is identified on the axis conjoining the supraclavicular and tangential fields, at a depth passing through lower edge of the supraclavicular and thoracic wall. All the fields are formed by asymmetric collimation. At the tangential fields, the gantry angle is determined in a way to cover breast tissue within the clinical margin specified with radiopaque wires, while involving minimal lung tissue in the treatment field. Wedge filters are used to provide dose homogeneity in these fields, whereas table and collimator angles are not. Shielding is essential due to the lack of the collimator angle, because lung and heart tissue volumes included in these fields are higher than usual. The gantry angle is zero, while table and collimator angles are not used in the supraclavicular fields (Fig. 16.5). Shielding is performed for the humeral head, larynx and cord in this area [21].

When axillary lymph node involvement is an issue, posterior axillary irradiation is required in addition to the anterior supraclavicular area. In such a case, the single isocenter point is identified for two tangential, anterior supraclavicular and posterior axillary photon fields. In order to set up the posterior axillary field, the anterior supraclavicular field is copied to the gantry 180° by using the same isocenter. Borders of the axillary field can be defined with the clavicle medial superiorly, including 1–1.5 cm of the lung tissue to the rib level inferiorly, crossing the humeral head lateral superiorly, and joining the medial inferior margin in a way to remain in the anterior axillary field.

Two different dose normalization points are used in the three-field technique. The first is defined for tangential fields, and is roughly 3 cm distance from the isocenter toward foot and on the thoracic wall. The other is defined for supraclavicular fields, and is 3 cm distance toward head, at a 3 cm depth. In the four-field technique, additionally, the dose delivery from the axillary field is normalized to the midline depth. Supraclavicular and tangential fields are given a total of 50 Gy, in 2 Gy daily fractions for 25 days, however, total dose delivery is completed by 50–56 Gy for the axillary field [21, 22].

16.6 Multi-Isocentric 3D-Conformal Irradiation Technique

As a result of their depth difference, axillary and supra lymph node involvement in breast cancers requires anterior supra and posterior axillary treatment dose delivery. The anterior supra axillary field crosses over the humeral head medially at the midsternal line. By positioning a 10–15° gantry angle to the beam, the esophagus, spinal cord, and larynx can be shielded. The posterior axillary field, the clavicle at the medial superior, margin including 1–1.5 cm of the lung tissue to the rib level at the inferior, while crossing over with the humeral head at lateral superior side, and conjoins with medial inferior margin without exceeding beyond to the anterior axillary field. The center of the fields defined for the anterior supraclavicular field and the posterior axillary field are determined as the isocenter (SSD at 100 cm).

Tangential fields are adjusted for gantry angle in order to provide full coverage to the clinical margins of the breast defined with radiopaque wires and to ensure minimal lung volume is included in the treatment area. For the tangential photon fields with SSD at 100 cm, table and collimator angles are adjusted accordingly so that margins that overlap with superior fields become parallel. Wedge filters are used to ensure homogeneous dose distribution (Fig. 16.6).

The dose normalization point for the tangential fields is defined on the thoracic wall at the central section of the field. The dose normalization point for the anterior supraclavicular field is defined at 3 cm depth of field central axis of field. The axillary dose received from the anterior supraclavicular area is calculated and the missing axillary dose is completed from the posterior field by normalizing to the midline

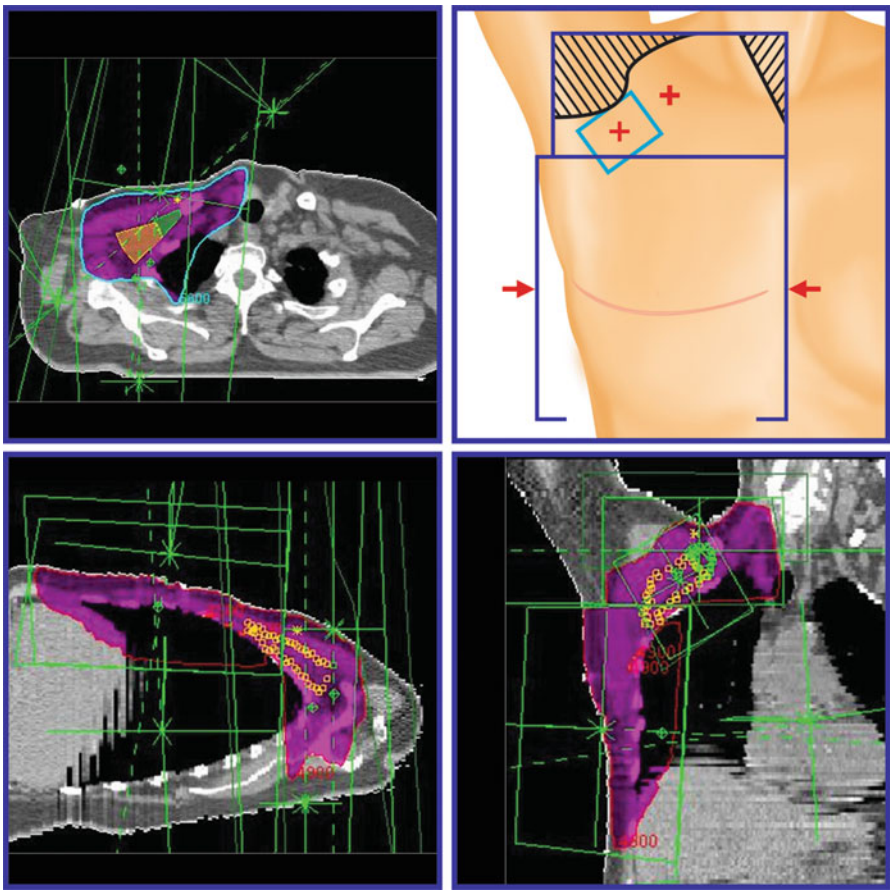

Fig. 16.6 Multi-isocentric 3D-conformal irradiation technique

depth at the central section. A dose of 50 Gy is delivered from the tangential and anterior fields, while 50–56 Gy is delivered from the supraclavicular field.

16.7 Irradiation Techniques for Breast Cancers Involving Internal Mammary Nodules

The necessity for incorporating the internal mammary nodes (IMN) into target fields for treatment has been widely discussed for many years, and when compared with treatment performed by standard tangential fields, it was detected as causing an increase in the volume of the ipsilateral lung and heart. Significant increase in cardiac diseases has been detected in the patients irradiated in this way, while poor cosmetic results are obtained as a result of the overlapping treatment fields. Thus, different treatment techniques have been developed over time in order

to reduce the total irradiation dose delivered to the organs at risk (i.e., heart and lungs), to improve poor cosmetic results, and to obtain a more homogeneous dose distribution [23].

Chest wall CTV, including anterior surface of the ribs, and IMN CTV are marked at CT sections, while 5 mm distance is added to each CTV in 3D to obtain PTVs. In addition, organs at risk such as the heart, both lungs, and contralateral breast are also marked [24].

The supraclavicular field is bordered so that the midpoint of the inferior edge is considered as the isocenter and adjusted with the gantry angle to exclude the cervical spinal cord and the esophagus from the treatment field. The upper border of the tangential fields inferiorly, mid to the humeral head laterally, and the starting points of vertebrae as the midline configure the area. Supraclavicular node PTV is delivered, total of 50 Gy dose in 2 Gy fractions for 25 days. Certain clinics deliver 75% of dose from the anterior photon field, with the remaining 25% from the posterior photon field to the supraclavicular nodes [23–25].

Some techniques do not display significant changes with regard to the CT scanning phase, marking the critical organs and target structures, and supraclavicular field planning. A distinguishing feature for novel systems is irradiating chest wall or breast PTV and IMN PTV by using various beams. In all of the techniques, a total 50 Gy dose, in 2 Gy fractions for 25 days, is delivered to the breast or chest wall PTV and the IMN PTV [26].

16.7.1 Four-Field Technique

In this technique, supraclavicular photon beams, the medial and lateral tangential photon beams, and the internal mammary anterior electron beams are used. One single isocenter is used for photon beams. This isocenter is identified in the middle of the inferior border of the supraclavicular photon beam passing through the inferior edge of the clavicular head under the skin. Collimator rotation of the tangential photon beams are avoided with a lung block in a way to allow isocentric setup. The majority of the chest wall is irradiated with tangential photon fields (Fig. 16.7).

The medial part of the chest wall PTV and the whole IMN PTV are excluded from tangential photon beams. By using anterior electron beams, the medial part of the chest wall and IMN PTV are irradiated. In this way, the dose to the heart, lung, and contralateral breast is further reduced. The isocenter of the internal mammary area is different from the isocenter of the photons. The right border of the electron is 3 cm away from the midline, and the left border is overlapped by the medial tangential field in a way to ensure the least and optimal coverage of PTV. The overlap should not be greater than 5 mm, and 5–10° gantry angle should be adjusted. The width of the electron field is approximately 6 cm, while its upper limit is the same with the medial tangential field. The entire dose of IMN PTV is covered by anterior electron beams [27, 28].

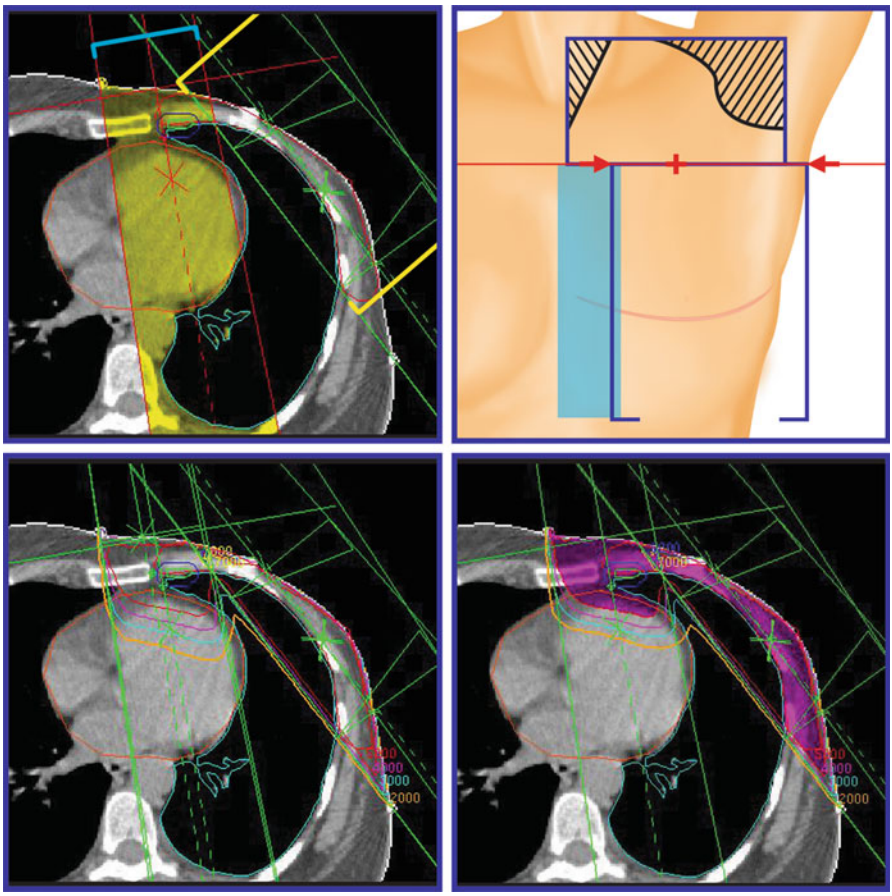

Fig. 16.7 Four-field technique for IMN radiotherapy

16.7.2 Five-Field Technique

The distinction in this technique is that the dose to deliver to IMN is the combination of both electron and photon beams. Supraclavicular, tangential photon fields are generated with the same method used in the four-field technique. Through the medial and lateral tangential fields generated with the isocentric technique, the large part of the chest wall PTV is irradiated. In addition to the "four-field technique," 6 MV photon beams are added to the electron field to irradiate medial chest wall PTV and IMN PTV. The photon beam can be generated in two different ways. In the first, isocenter, gantry angle, and field borders are used that are identical with the electron field. Then, very high doses can occur in the overlapping section with the medial tangential field. In the second, supraclavicular photon beams and medial and lateral tangential photon beams are generated from the identical isocenter.

IMN photon beams are adjusted with gantry angle to assure overlapping with tangential fields without any divergence on the skin. In these circumstances, the dose delivered to the contralateral breast may increase (Fig. 16.8). Sixty percent of the dose to the IMN PTV and medial chest wall is provided by electron beams and 40% of the dose by photon beams [27, 29].

16.7.3 Divided Electron Field Technique

Supraclavicular photon fields and tangential photon fields are created from the identical single isocenter by using the same method of "four-field technique." For irradiation of the medial segment of the breast or chest wall PTV and IMN PTV outside of the tangential photon fields, electron beams are used. As is known, the 1–3 intercostal part of IMN carries a higher risk. Accordingly, the field to be irradiated with electron beams is irradiated by using a combination of two electron beams. High-energy electron beams are delivered to the upper region having higher risk, while lower energy electron beams are used for the less risky lower region (Fig. 16.9).

Both electron beams are adjusted by 15–20° angles in order to overlap with the tangential fields to avoid very low or very high dose occurrence. The dose that the heart and lungs receive has been minimized with this technique [30].

16.7.4 Wide Tangential Field Technique

In this technique, three photon beams are used including the supraclavicular, wide medial, and lateral tangential fields. The isocenter is determined to be just in the middle of the bottom edge of the supraclavicular photon beam passing through the clavicular head under the skin. Collimator rotation is prevented by using wide lung blocks while generating tangential fields and overlapping with the lower side of the supraclavicular field is assured without divergence. Using DRR images, the gantry angle is adjusted to ensure maximal protection of the heart and ipsilateral lung and maximal 25% of the total dose delivery to the contralateral breast. By adjusting medial and lateral tangential fields with a few degrees of angle, the medial-posterior borders are made parallel.

Required blocks are performed in a way to include minimal heart volume in the treatment field and ensure optimal coverage for the target. Wedge filters and radiation loadings are used to obtain homogeneous dose distribution (Fig. 16.10). With this technique, the photon-electron beam dose problems resulting overlapping are highly eliminated [31].

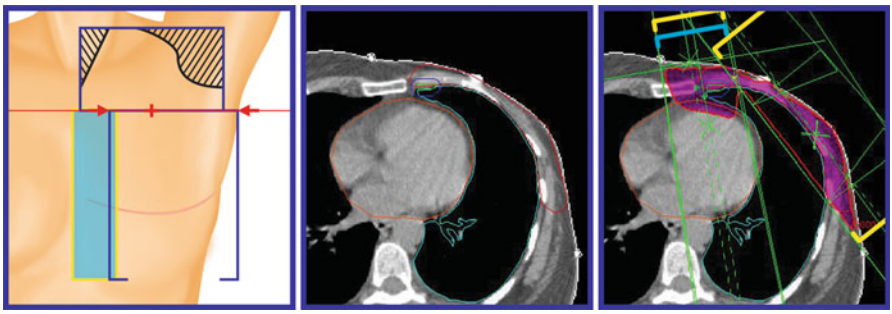

Fig. 16.8 Five-field technique for IMN radiotherapy

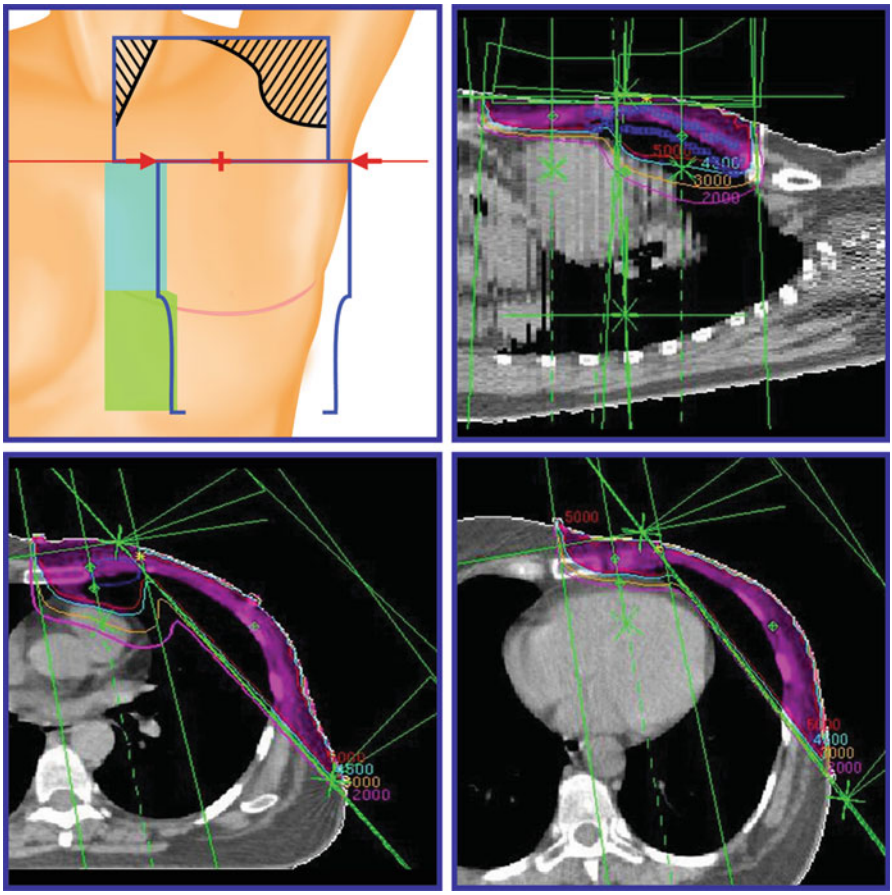

Fig. 16.9 Divided electron field technique for IMN radiotherapy

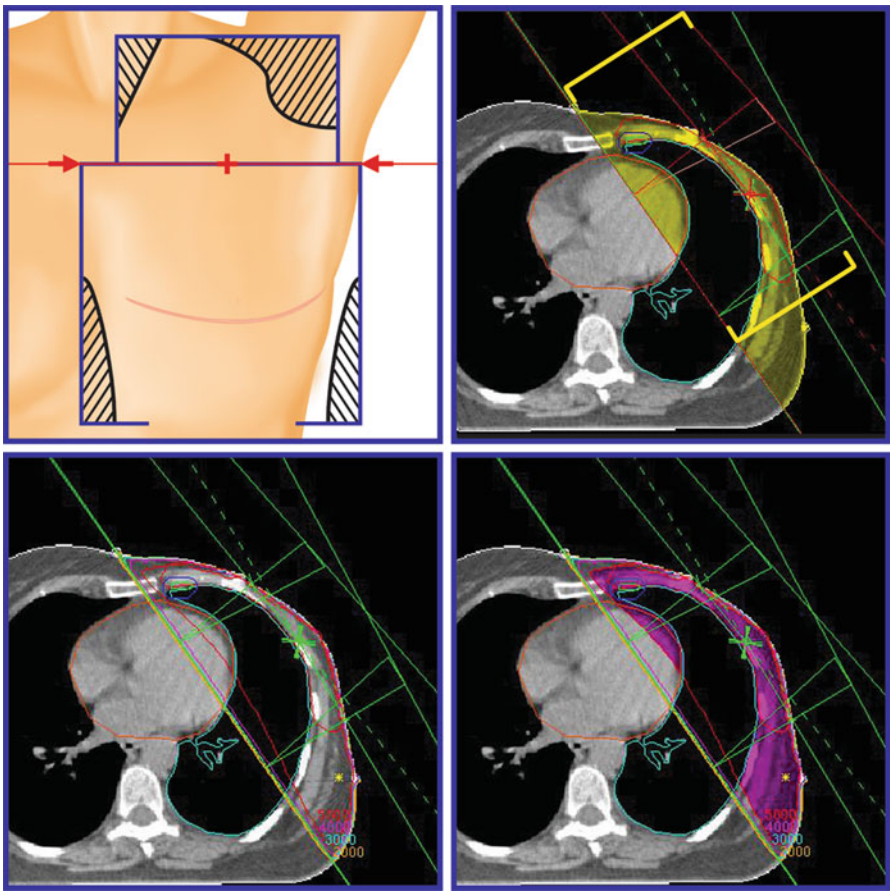

Fig. 16.10 Wide tangential field technique for IMN radiotherapy

16.7.5 Mixed Technique

In this technique, a total of five beams are used, three tangential photon beams, one electron beam, and one supraclavicular beam. The isocenter of tangential and supraclavicular photon beams is determined at the middle of the bottom edge of the supraclavicular photon beam passing through the clavicular head under the skin. Standard tangential photon fields are created by adding 1.5–2 cm margins to palpable breast tissue in a way to cover breast or chest wall PTV. The border of the field is 3 cm to the midline (using DRR images); the gantry angle is adjusted to ensure maximum 3 cm lung volume is included in the treatment field. A wide internal tangential field including both breast and chest wall PTV and IMN PTV is adjusted with gantry angle in a way to minimize the dose received by the heart, lungs, and contralateral breast.

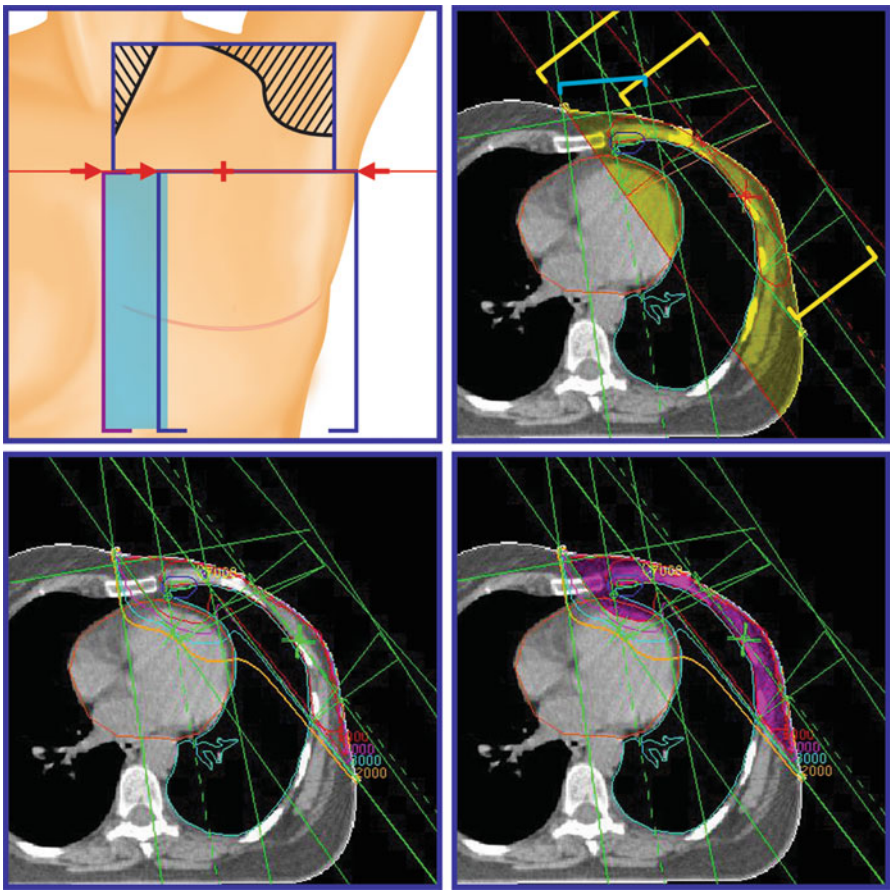

Fig. 16.11 Mixed technique for IMN radiotherapy

Through addition of SSD 100 cm frontal electron beams to the wide medial tangential fields, which are out of the standard tangential fields, the incomplete dose to both breasts or chest wall PTV out of the standard the tangential fields and IMV PTV is completed. Standard tangential fields and the frontal electron fields overlap in maximal 10-mm distance. High-dose fields generated by this overlapping should be monitored (Fig. 16.11).

Based on the depth of IMN, electron beam energy is determined in the range of 8–14 MeV dose, whereas the dose normalization point is determined on the central axis at the highest dose level. Approximately 60% of the IMN PTV dose is delivered through electron fields, while the remaining dose is complemented by the wide medial tangential, by considering the dose received by the IMN dose-defining point. The total dose delivery of both the standard medial tangential field and the wide medial tangential field is balanced to the standard lateral tangential field. Wedge filters are used in these areas to obtain a more homogenous dose

distribution. By using photon and electron beams together, the skin and lung doses can be reduced [23, 24].

16.8 Chest Wall Irradiation Techniques

Radiotherapy after mastectomy includes chest wall, supraclavicular lymph nodes, and when indicated, axillary and internal mammary nodules. During CT, a radiopaque wire should be placed on the patient's mastectomy scar. On CT images, contours of the IMN and chest wall PTVs should be outlined. Different techniques are used in postmastectomy irradiation [32].

In chest wall irradiation, opposing two tangential photon beam irradiation is a widely used technique. The midpoint of the chest wall is identified as the isocenter for tangential beams. The gantry angle is adjusted to ensure the least volume to the lungs and heart included in the treatment field. A 0.5-cm bolus is used to avoid any dose decrease to the skin. A total of 50 Gy, as a daily dose of 2 Gy for 25 days, is delivered to the chest wall.

Many different techniques can be utilized for chest wall irradiation, one of which is the mixed photon-electron technique. For patients having wide chest walls, a separate field such mammary interna is used for irradiating the medial section of the chest wall PTV. Shielding of the lungs and heart is much better by dividing the chest wall. In this technique, most of the chest wall PTV is irradiated from standard medial-lateral tangential photon fields, while the medial part of the same PTV is irradiated with fixed electron beams. The gantry angle of the tangential photon beams is adjusted in a way to ensure maximal shield of the heart and lungs. Electron beams similar to the internal mammary field are adjusted with the gantry angle so that the medial chest wall PTV will be covered and overlapping with tangential photon beams will not exceed 5 mm. Another method is the electron arc therapy technique. This technique is preferred to the mixed photon-electron technique in patients having long scars or highly variable target tissue depths. The target volume of the boundaries are marked on the chest wall. In order to consider the changes in radius of the thorax in the superior-inferior direction, secondary collimators having different widths are used. According to the depths of different segments used in arc therapy, various energies can be used. Through this technique, a 45–50 Gy dose is delivered to the chest. The third technique is the overlapped electron technique. Administration of this technique is through overlapping of the three electron fields on the skin, such that joining lines of the central and lateral electron fields are shifted weekly depending on the differences in the gantry angles. Except for the lateral electron field, electron fields overlap at zero degrees of the gantry angle, while the lateral field angle is fit in accordance with the contour changes of the patient's body [32–34].

In all the chest wall irradiation techniques mentioned above, supraclavicular photon beam irradiation is administered to patients having supraclavicular and axillary lymph node involvement. When axillary irradiation is required, dosing

should be completed from the posterior, taking into account the supraclavicular field contribution. The optimal dose distribution is obtained by overlapping the upper margins of the inferior fields and the lower margin of the anterior supraclavicular photon field.

16.9 Conclusion

3D-CRT techniques offer the opportunity to develop custom-made therapy plans for breast cancer patients, thus exact dose delivery to the target tissues and redundant dose delivery to the organs at risk may be evaluated. Therefore, survival rates are determined to be increased and local recurrence risks and adverse effects affecting quality of life of the patients after treatment are significantly reduced. For this purpose, a number of 3D radiotherapy techniques have been developed.

Distinctive features for different methods of 3D-CRT need to be mentioned. One of these is the prone position of the patient. Compared with the supine position, the prone position during treatment is much more comfortable for breast cancer patients. Additionally, in the prone position, the breasts to be treated hang away from the chest wall, and eventually, organs at risk can be protected much more significantly. Due to the need for a special immobilization device and certain difficulties for some patients, it is less common than the supine position.

Another distinctive feature is whether the treatment technique is isocentric or multicentric. The isocentric technique is highly favorable due to its practical applicability in the treatment instrument and short duration. Moreover, missing dose regions or high-dose regions which are frequently seen in the 3D-CRT techniques demonstrating overlapping fields can be avoided. The patient's anatomy and technical possibilities, depending on the location of organs at risk, is the most appropriate form of treatment. This feature makes it superior to multi isocentric techniques.

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Chapter 17
Inverse Planning, Intensity Modulated Radiation Therapy, and Image-Guided Radiation Therapy

Isik Aslay, Halil Kucucuk, Oznur Senkesen, and Melahat Garipagaoglu

17.1 Introduction

Breast cancer has been postoperatively treated with conventional tangential beams using standard dose 46–50 Gy to the chest wall or whole breast and 10–16 Gy boost with or without regional lymphatics for many years. In addition to successful cosmetic results and low rates of cardiac-pulmonary complications, high rates of local control have been achieved [1–3]. Significant advances have occurred in the area of imaging and irradiation techniques over the past 15 years. Despite these advances, several studies have also shown that dose uniformities can occur in a high percentage of breast volume (Fig. 17.1) [4, 5]. To achieve dose homogeneity in the target is difficult using conventional two-dimensional (2D) or three-dimensional (3D) tangential beams because of the complicated geometry of the breast and different depths of regional lymph nodes (Figs. 17.2 and 17.3). During tangential breast irradiation, particularly in the nipple, the entrance and exit points, and in the superior and inferior portions of the fields may achieve an inhomogeneous dose distribution, which in turn, causes less favorable cosmesis related to breast size, wedge angles, and beam energies (Fig. 17.4) [6, 7]. Irradiated volumes of lung and heart within the treatment fields are sometimes unacceptably large and irradiation of regional lymph nodes, especially in the mammaria interna area, delivers high doses to the heart, lung, and contralateral breast. Cardiac perfusion defects have been documented even in patients treated with advanced 3D planning techniques, although the clinical consequences of these defects are not yet clear [8]. Potential interactions between cardiotoxic systemic agents such as doxorubicin and transtuzumab and radiotherapy (RT) must be considered [9, 10].

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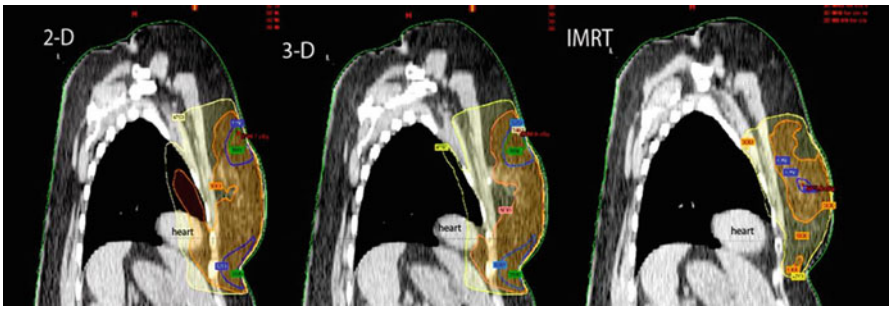

Fig. 17.1 Sagittal dose gradient of the 2D-conventional, 3D-conformal, and IMRT treatment plans presented for the same patient (*yellow*:47.5 Gy, *orange*:50 Gy, *blue*:53 Gy)

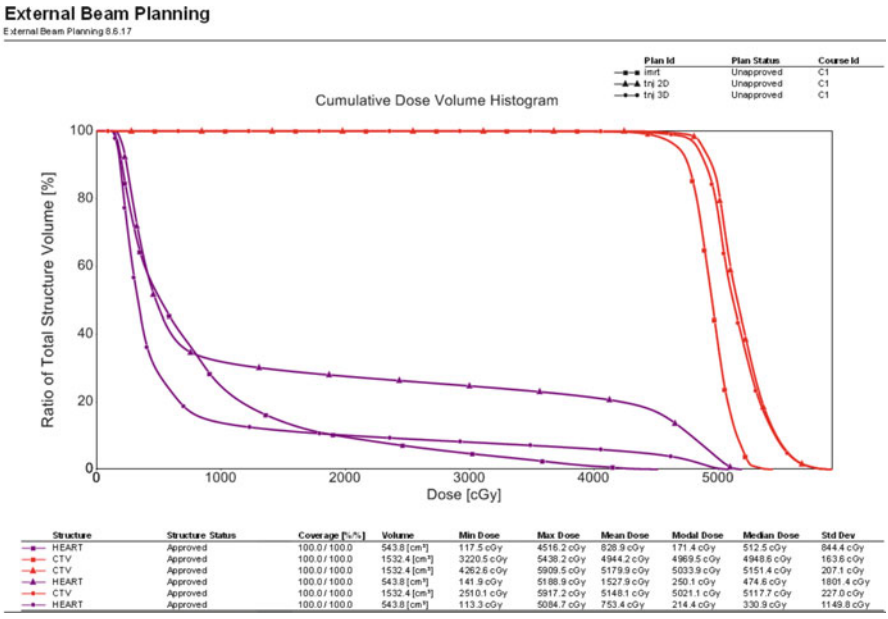

Fig. 17.2 Comparison of heart (*purple*) and CTV (*red*) doses on the DVHs. 2D-conventional (*triangle*), 3D-conformal (*round*), and IMRT (*square*) treatment plans obtained from the same patient's CT images. Better CTV homogeneity and lower cardiac volume irradiation at high doses can be seen with IMRT than with the other techniques

This section of the chapter focuses on the goals of intensity modulated radiation therapy (IMRT) in comparison with standard 2D or 3D breast radiation therapy. Several pioneer studies have demonstrated that IMRT planning provides better homogeneity and improved dose coverage in target, reduced dose in cardiac, lung and contralateral breast than 3D-conformal irradiation [11–18]. Vicini et al. reported the first clinical use of breast IMRT in a prospective series and suggested a reduced occurrence of acute skin adverse effects [13]. Freedman et al. reported the result of a matched-pair analysis of breast IMRT and found a significant reduction in the rate of moist desquamation in the IMTR group [19].

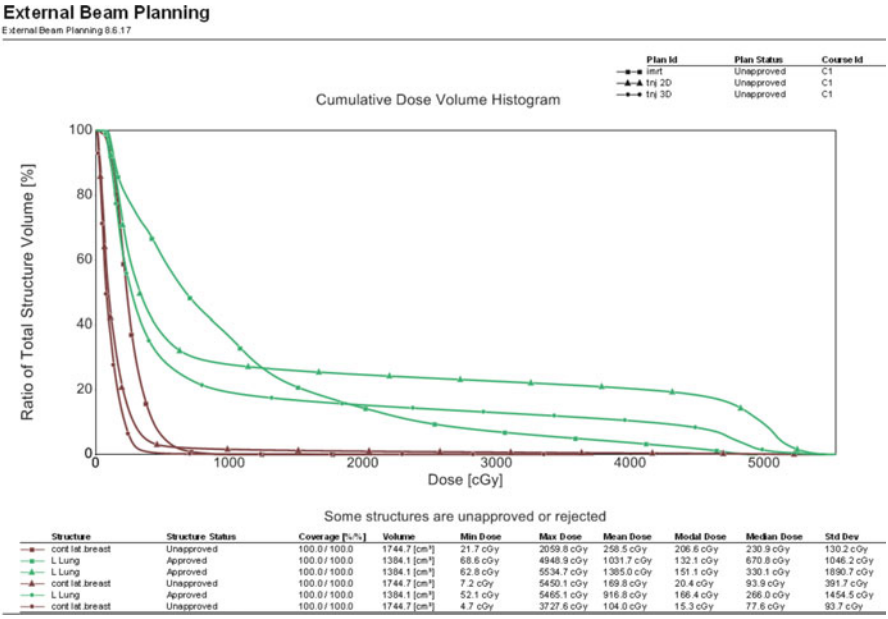

Fig. 17.3 Comparison of lung (*green*) and contralateral breast (*brown*) doses on DVHs. 2D-conventional (*triangle*), 3D-conformal (*round*), and IMRT (*square*) treatment plans obtained from the same patient's CT images. Lower ipsilateral pulmonary volume irradiation at high doses and lower contralateral breast doses can be seen with IMRT than with the other techniques

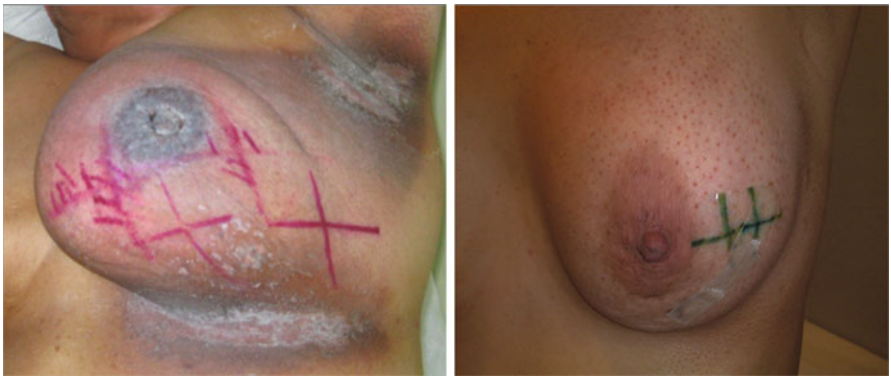

Fig. 17.4 Two weeks after completion of radiotherapy, early reactions can be compared for different treatment planning method. *Right side*: 3D-CRT. During tangential breast irradiations, especially in the nipple, the entrance and exit points, in the superior and inferior portions of the fields may achieve an inhomogeneous dose distribution, which in turn causes Radiation Therapy Oncology Group Grade 3 early reactions related to breast size, wedge angles, and beam energies. *Left side*: IMRT, skin reactions are lesser and life quality is better than the first one

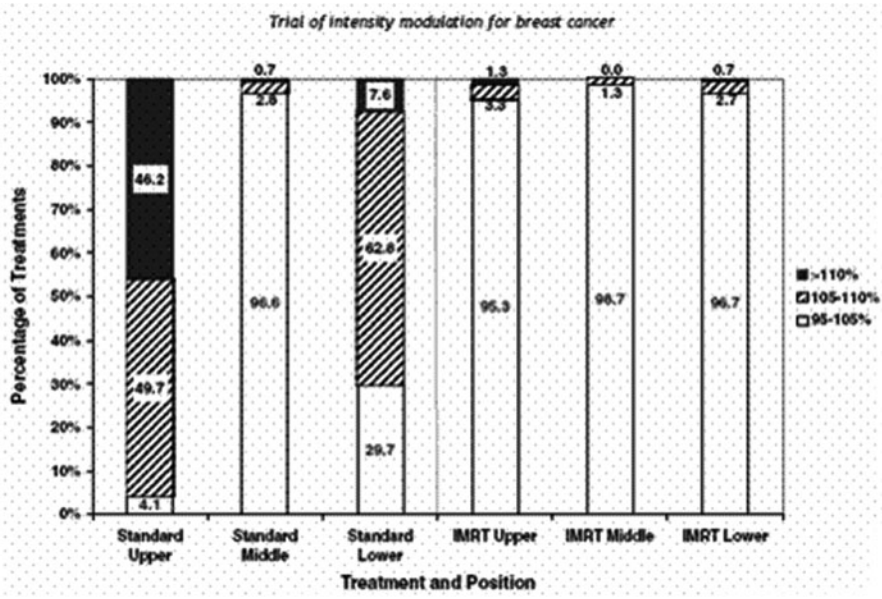

Fig. 17.5 Dose position data for each trial arm for each breast region. The data refer to the percentage of patients for each arm of the trial who scored a maximum dose in the indicated dose band. They are separated into each region of the breast. A dose band was scored if the area of the isodose was greater than 2 cm^2 in the orthogonal planes. The absolute area was not considered in the analysis. With permission of author [20]

The clinical implementation of IMRT has been researched in two prospective randomized studies. 2D wedge-based (control arm) and 3D IMRT (test arm) techniques have been compared with short- and long-term side effects after whole-breast RT in the Royal Marsden Study, which included 306 breast cancer patients after breast-conserving surgery between 1997 and 2000 [20]. All patients were treated with 6 or 10 MV photons to a dose of 50 Gy in 25 fractions in 5 weeks to the International Commission on Radiation Units and Measurements (ICRU) reference point in the center of the breast followed by an electron boost to the tumor bed of 10 Gy in five fractions. Patients were positioned in the supine position, 2D wedge plan, calculated in a single transverse contour and two IMRT delivery methods were used in the trial, namely physical 3D compensators and step-and-shoot IMRT. The primary endpoint was change in breast appearance scored from serial photographs taken before treatment and at 1-, 2-, and 5-year follow-up. Secondary endpoints included patient self-assessment of breast discomfort, quality of life was measured with questionnaire and BR-23 breast module, and physician assessment of breast induration related to dose inhomogeneity. At the close of the study, higher clinically assessed palpable induration related to the levels of dose inhomogeneity (particularly in the upper third of the breast) were found in the control group (2D) compared with the test group (3D IMRT) (Fig. 17.5). There were no significant differences between treatment groups with regard to patient-reported breast discomfort or quality of life.

A Canadian phase III multicenter double-blind, randomized clinical trial was performed to test whether breast IMRT would reduce the rate of acute skin reaction, particularly moist desquamation, and improve quality of life compared with standard RT [21]. Patients were randomly assigned to receive 50 Gy in 25 fractions to the whole breast using either standard RT with wedge compensation or breast IMRT. An additional boost dose of 16 Gy was used. The random assignment was stratified for the use of a boost and breast size, which were small, medium, and large. Based on treatment planning availability at each site, an inverse algorithm or forward-planning method was used [22]. Clinical outcomes included the intensity of acute skin reaction or pain and occurrence of moist desquamation. The European Organisation for Research and Treatment of Cancer C-30 general module and BR-23 module self-assessment questionnaires were used at baseline, the last week of treatment, and 1 month later. As a result, univariate and multivariate analyses of factors associated with increased moist desquamation in the breast were effected by large size of breast and standard RT. Breast IMRT significantly reduced the occurrence of moist desquamation compared with the standard wedge technique. Moist desquamation was correlated with increased pain and reduction in the quality of life. The surface doses (0–5 mm) were searched by Almberg et al. through a film-based phantom study [23]. Compared with the tangential standard plan, the surface doses were reduced with a seven-field IMRT plan on average of 20% and skin sparing level was achieved. McDonalds at al. evaluated long-term outcomes of adjuvant breast IMRT, with a comparison of cohort receiving conventional radiotherapy during the same period [24]. They found that treatment with IMRT, RTOG G2-3 acute skin reactions decreased from 52% to 39% ($p = 0.04$). Seven-year follow-up of stages I to III patients treated with IMRT has shown excellent local control similar to the cohort group treated with conventional RT, Kaplan-Meier freedom from ipsilateral breast tumor recurrence rates were 95% for IMRT and 90% for conventional RT ($p = 0.36$) and, for patients with DCIS were 92% and 81% ($p = 0.26$), respectively. Conventional locoregional control results can be obtained by IMRT techniques.

Cho and colleagues compared IMRT and non IMRT techniques in the treatment of the left breast and internal mammary nodes and demonstrated superior breast and internal mammary node target coverage (Fig. 17.6) [25]. One of the first clinical benefits of IMRT is in the treatment of concave structures such as the chest wall. The average ipsilateral lung volume and maximum heart doses can be decreased through IMRT planning, especially with deep inspiration breath-hold [26, 27]. The use of IMRT for women who require complex breast treatments, including the regional lymphatics, is an important ongoing research area [28].

17.2 Inverse Planning

RT planning in breast carcinoma has specific problems such as: (1) Target is wide and not solid; (2) Target location shows variation according to patient and tumor characteristics; (3) Target shape is very complex for patient, requiring regional

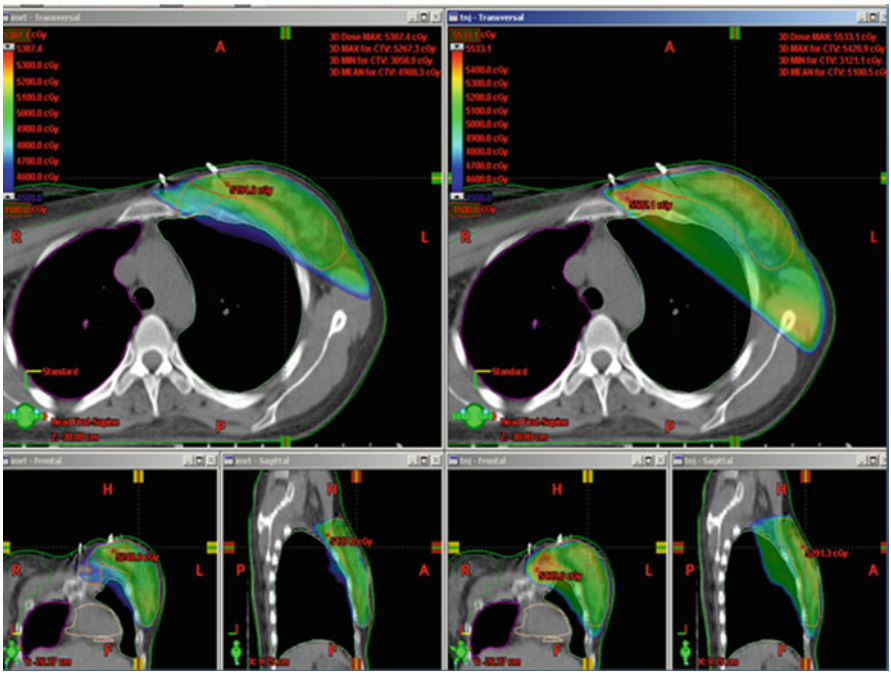

Fig. 17.6 The first three levels of mammaria interna (MI) lymph nodes were included by the 3D-conformal RT (on the *left side*) and IMRT plans (on the *right side*). Better target homogeneity and lower irradiated lung volume can be seen on the IMRT plan

lymph node irradiation; (4) Target is concave in shape, surrounding the heart and lung which should be protected from radiation exposure; (5) Sufficient skin dose requirement in certain patients; (6) Respiratory motion moving target and organ at risk (OAR) during RT fractions; (7) Target volume might change during the entire RT course; (8) Contralateral breast needs to be protected from radiation exposure. Breast RT planning should take into consideration all of the issues listed above. For these reasons, treatment planning is often very complex [29–31]. Unfortunately, all objectives cannot be fulfilled for all patients. Nonetheless, as treatment providers we need to do our best and strive to provide all requirements for an optimal plan. If we fail to achieve all goals, some issues need to be considered as primary goals. When primary goals are fulfilled, others can be neglected; this decision needs to be rationalized considering the clinical conditions of patients. IMRT is an advanced type of 3D conformal radiotherapy (3D-CRT) [4]. IMRT uses multileaf collimator motions and specific treatment planning software. It provides better dose homogeneity in target and reduced OAR doses in comparison with 3D-CRT (Figs. 17.1–17.4, and 17.6).

IMRT can be performed as a forward or inverse planning technique [30]. The forward planned segmental IMRT technique (for-IMRT) can be used as an alternative to conventional 3D-CRT. Similar beam orientations to 3D-CTR are utilized, but

instead of wedge, additional fields with manually created apertures are used to block specific hot spots in the original plan. The linac-based inverse-planned IMRT technique (inv-IMRT), uses optimization algorithms to create fluence maps to shape dose distributions [32]. Intended dose distributions for targets are achieved using the inverse IMRT technique while reducing OAR doses. This technique can be performed using linear accelerator furnished MLC (dynamic or static), arc therapy [33], tomotherapy [34] and topotherapy [35]. Irradiation is given to the patient while gantry rotates around the patient in intensity modulated arc therapy; MLC motion will continue throughout gantry rotation rate changes and in this way a fluence map is created. In regard to tomotherapy, there is a helical irradiation which continues during table movement and MLC motion creates fluency. Topotherapy uses inv-IMRT via static gantry position while the patient translates through the treatment field instead of rotational delivery [35]. Dosimetric comparison of left-sided whole-breast irradiation with 3D-CRT, for-IMRT, inv-IMRT, tomotherapy, and topotherapy were researched by Shubert et al. [32], who concluded that all of these planning techniques provide similar coverage of intact breast when ignoring the superficial tissue in the buildup region. The inverse planned modalities result in significant reduction of high doses to the target and normal tissues.

There are several published modulation methods which are classified as inverse planning; beam's eye view isodose contouring; plane compensation, tissue compensation and equivalent path length compensation; minimization of dose variation; and equalization of maximum dose. In a study comparing published modulation methods, Donovan et al. found that no modulation method showed a clear dosimetric advantage over the others [36].

Work flow: Patients are positioned supine (prone if necessary) with two arms or ipsilateral arm above the head and computed tomography (CT) images are obtained with 5-mm slice thickness in this treatment position. To apply the inverse planning algorithm, the target volumes and sensitive structures and OAR must be delineated. A recent study indicated that no consensus has been reached on the definition of breast clinical target volume among specialized radiation oncologist [37]. CTV/planning target volume can be defined as 0.5 cm inside the patient contour to prevent the inverse IMRT planning algorithm from delivering high dose to the skin. The target envelopes all radiographically visualized breast tissue plus a 7–10 mm margin posteriorly to account for set-up uncertainty and patient movement. Typically, the field borders are extended to the midline at the lower border of the clavicle superiorly, and 2 cm beyond the palpable breast tissue laterally and inferiorly. After creating tangent fields and calculations, hot spots are covered and new fields added to cold areas. These processes are continued until homogeneous dose distribution is achieved. In this way contralateral breast dose is reduced and homogenous dose within target can be obtained.

IMRT planning is based on contours delineated on planning CT images. The treatment planning system (TPS) recognizes target and OAR volumes as constant structures; creates sharp dose gradient around target(s), and protects OAR as much as possible. However, structures and organs can change because of either internal or

external conditions through time. Sharp dose gradient changes arising from IMRT can become a disadvantage if planning CT structure positioning is not matched throughout the treatment. Hence, patient set-up and immobilization are critical for IMRT. Patient comfort is essential to prevent unintentional body motion. Respiratory movement could alter target and OAR positions. These conditions need to be recognized and precautions such as respiratory-gated treatment should be considered. Furthermore, patient compliance is a key factor for IMRT.

Linear accelerator-based inverse IMRT is the most commonly used technique; several fields with different gantry angles are used in addition to conventional tangent fields. These fields have fixed gantry angles. However, multileaf collimator motions create a fluence map to obtain a homogenous dose in the target during irradiation using either sliding windows or step and shoot. Planners define energy level, gantry, collimator, and number of beams, etc. for routine RT planning procedures to obtain intended dose distribution. In contrast, for inverse planning dose definitions, constraints for targets and OAR are given, and then priority of constraints are decided. TPS provides optimal beam specification and arrangement for the proposed plan. Even so, proficiency of the user is very important. Experience in planning solutions for particular problems that arise in certain clinical conditions accumulates and this experience can be used for similar conditions. There should be dose limits within the target. The minimum dose should be greater than %95 of the prescription dose while volume receiving 105%, 110%, 115% of prescription dose should be lower than 14%, 5% and 1% of prescription dose, respectively [13]. Dose homogeneity and dose conformity are independent specifications of the quality of the absorbed dose distribution. Dose homogeneity characterizes the uniformity of the absorbed dose distribution within the target volume. Dose conformity characterizes the degree to which the high-dose region conforms to the target volume, usually the PTV. The rDHI is defined as the ratio of minimum dose (Dmin) to the PTV and the maximum dose (Dmax) to the PTV as defined by rDHI = Dmin/Dmax. In Report No. 83 from the ICRU, the following definition for homogenity index is suggested: $HI = (D_{2\%}\text{-}D_{98\%})/D_{50\%}$ [38]. The confidence interval was calculated according to the definition proposed by Knoos et al. [39] and recommended in ICRU Report No. 62 [40], to evaluate the degree of conformity of external beam treatment plans (radiation conformity index VPTV/V95%).

Simplified steps for an inverse planned IMRT case: (1) Proper set-up, (2) imaging and image transfer to TPS, (3) delineation of target(s) and OAR, (4) field placement, (5) dose limit definitions for target and OAR, (6) optimization, (7) tailoring field placement and features if needed, (8) dose calculation, (9) plan evaluation and validation, (10) quality assurance procedures performed for selected plan, and (11) plan transfer to treatment machine.

Field numbers are chosen according to patient anatomic characteristics and target localization. Additional fields facing boost volume are used for patients receiving simultaneous integrated boost (SIB) IMRT. Likewise, small additional fields for regional lymph nodes such as mammaria interna can be added. Preferably the number of fields is between five and nine; a higher number of fields could increase dose homogeneity within the target but at the expense of increasing lung V5 dose. OAR dose distribution should be meticulously planned. Frequently, 6MV

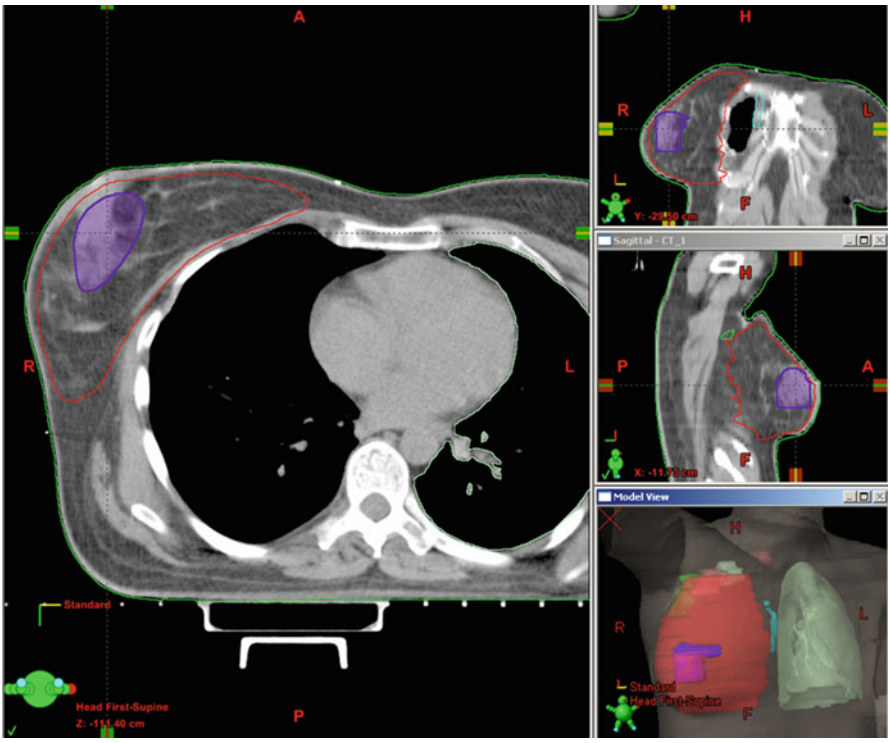

Fig. 17.7 Patients anatomy showing contours:PTV- eval: PTV volume from 3–5 mm underlying skin (shown in Figure as red color), PTV boost : Additional dose is given a primary tumor volume (shown in Figure as purple color)

energy is selected to obtain sufficient skin dose and to prevent hot spots in the target. Often tangential field gantry angles facing the target while avoiding OAR are preferred. Dose prescription for optimization is made according to the volume receiving maximum dose which is "target" for whole breast, lymph node for patient receiving lymph node irradiation, and "boost volume" for patients receiving SIB. Generally the prescription dose to whole breast/chest wall and regional lymph nodes will be 4,500–5,000 cGy, boost dose is 1,000–1,600 cGy. For SIB cases: 28 fraction 180 cGy (in total 5,040 cGy) to whole breast and 214 cGy (in total 5,992 cGy) to boost volume used. To compare SIB-IMRT fractionation with conventional sequential boost schedules, a biologically equivalent dose (BED) can be calculated using the linear quadratic (LQ) model [41]. BED values of this scheme were found (67 Gy_{10}, 102.6 Gy_3) comparable with the sequential schedule (fractional whole breast:1.8 Gy $\times$ 25 and fractional boost 2 Gy $\times$ 8 = nominal total dose 61 Gy = 65,5 $Gy_{10,}$ 98,7 Gy_3). Another dose schedule (1.8 Gy $\times$ 25 and 2.4 Gy $\times$ 25 = nominal total dose 60 Gy = 69.5 Gy_{10}, 108.0 Gy_3) can be compared (1.8 Gy $\times$ 25 and 2 Gy $\times$ 10 = nominal total dose 65 Gy = $69.4_{10,}$ 105.4 Gy_3) [42]. Some supplementary volumes such as body-PTV, PTV-eval PTV breast-boost, and dummy could be added to facilitate optimization (Fig. 17.7). Body-PTV means that the volume of body excluding PTV is useful to prevent hot

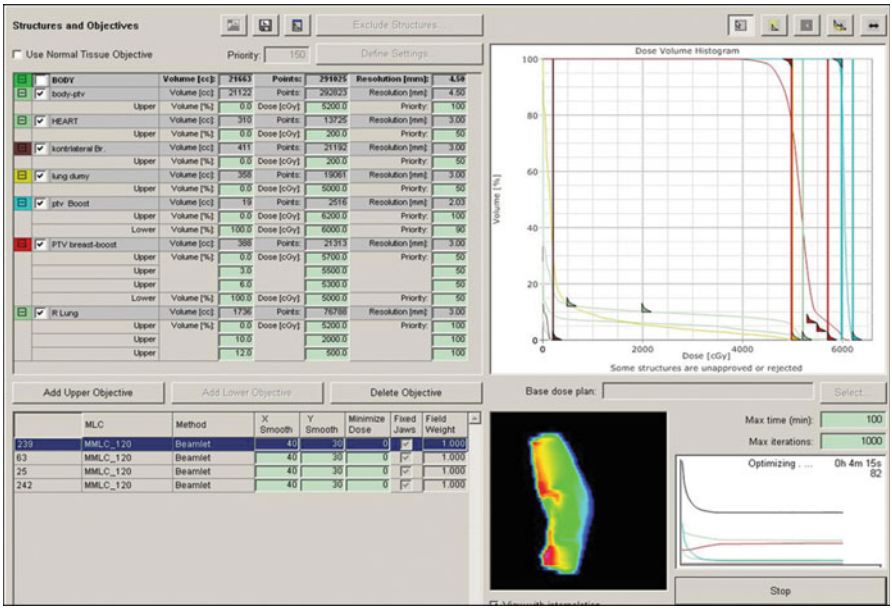

Fig. 17.8 Optimization sheet consists of dose constraints and priority

spots outside the target. RT planning software cannot accurately calculate skin dose. Sometimes fewer doses are calculated then real value and this incorrect estimation could lead to higher doses in skin and related side effects. For this reason it is useful to exclude skin from PTV. PTV-eval means exclusion of 3 or 5 mm of skin and underlying tissue from PTV. A high radiation dose creates a less optimal cosmetic result. PTV (breast-boost) is another volume useful for reducing irradiated nontarget breast tissue in boost treatment.

There are different algorithms used for optimization. In beamlet-based inverse planning IMRT, an optimization algorithm is used to divide each treatment beam into finite size pencil beams and to optimize the intensity then a leaf sequencing algorithm converts the optimized intensity profile into deliverable segments. This method is also named "two-step" IMRT [43, 44]. Another IMRT technique is direct aperture optimization in which the delivery parameters such as number of segments, shapes, and weights are directly considered during the optimization, which eliminates the need for the leaf sequencing step and limits the total number of segments [45].

Optimization is made according to defined dose constrains. Priorities are given to volumes and changed according to achieved dose values (Fig. 17.8). After dose calculations hot spots can be seen and defined as dummy volume (Fig. 17.9). During reoptimization priorities are changed and hot spots could be eliminated. In tangential breast irradiation, the region of the beam that has been deliberately planned to bypass the skin surface has been called the "flash region." In breast IMRT, PTV subdivision or relaxed absorbed-dose objectives for planning do not

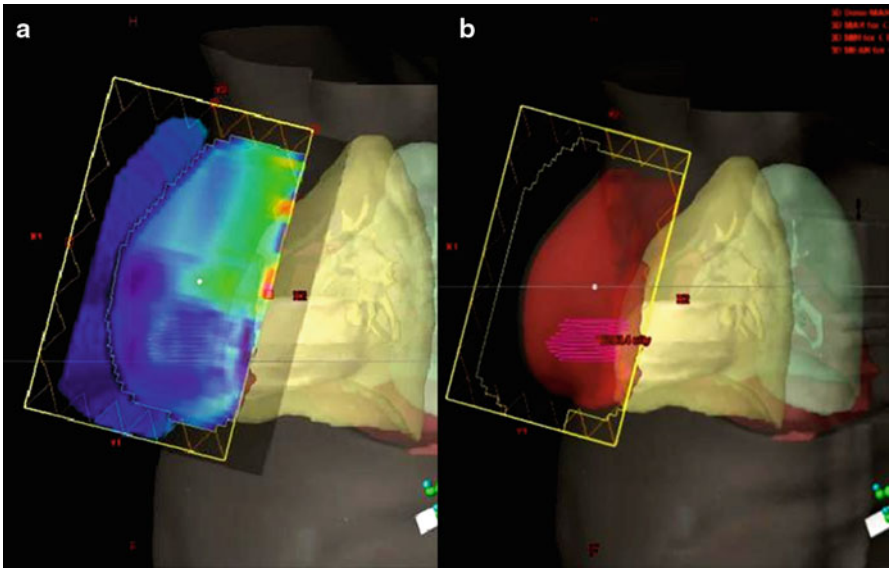

Fig. 17.9 a) Created additional fluence using skin flash tool (shown in left hand side), b) Treatment planning system calculates leaf motion considering retracted leaves until 2 cm fall of from skin (shown in right hand side)

solve the problem of fluence peaks extending beyond the treatment area. Various methods based on manual definition of beam apertures and beam intensities have been proposed for adequate treatment of the flash region [43]. Creation of flash by extending the same intensity values from the breast periphery to the regions of the PTV outside the breast BEV secure the "flash region" in IMRT [38]. Therefore, it must be noted that after optimization, a 2-cm skin flash is made to the tangential breast IMRT field by retracting the leaves (Fig. 17.10) [15, 38, 46]. The reason for doing so is to avoid missing the target during respiration and also decrement in skin dose. There is a tool called "skin flash tool" for this procedure in TPS.

Plans for quality assurance are made after plan acceptance and point dose measurement is done using an ion chamber, IMRT quality assurance phantom, and an electronic portal imaging device (EPID) (portal vision dosimetry), after the patient is ready for treatment. Set-up position accuracy will be ensured using kV, MV, or cone-beam CT images on the treatment table before treatment execution.

When do we particularly need IMRT?

In left breast cancer with large heart volume or close anatomy to the chest wall, use of cardiotoxic chemotherapy and heart diseases or inconvenient dose volume histogram for OAR with standard 3D-conformal planning can be causes for the preference of breast IMRT planning [47]. Moreover, IMRT can be a convenient choice for reirradiation, contralateral breast irradiation, internal mammary lymph node irradiation, partial breast irradiation, and deep placed tumor bed irradiation.

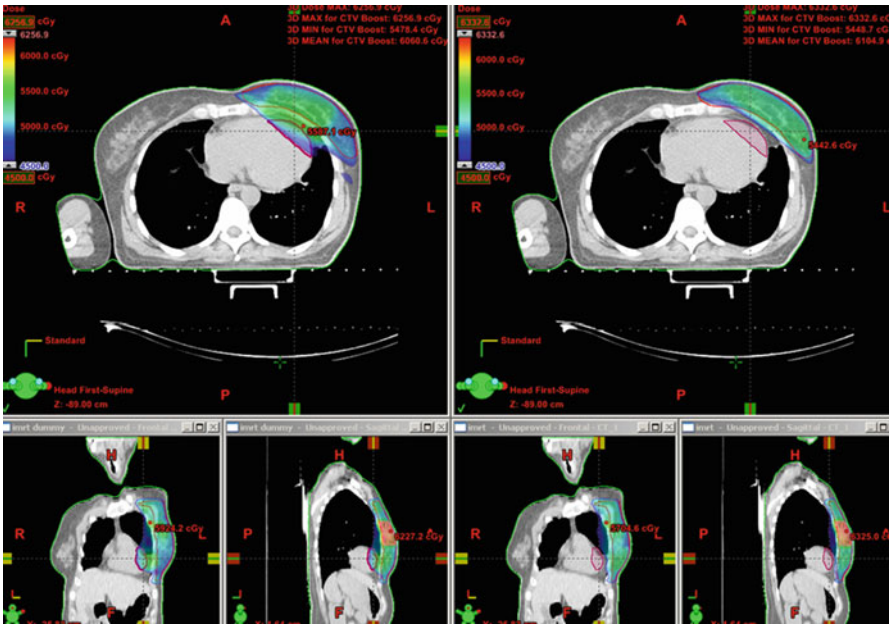

Fig. 17.10 Color-wash dose gradient that shows the hot spots in OAR (heart). After defining a dummy volume on heart and reoptimization, dose of the heart can be decreased

17.3 Image Guided Radiotherapy for Breast Cancer

Whole-breast irradiation is one of the essential parts of breast-conserving treatment in breast cancer patients. Diagnosis in the early stages and advances in chemotherapy and RT have led to increased life expectancy with more late side effects observed in breast cancer patients with long-term follow-up. Hence, adjacent normal structures such as the lung and heart are involved in external RT fields and limiting the dose to OAR requires more effort. Although 3D conformal and IMRT techniques limit the dose to adjacent OAR, there are still significant obstacles for accurate targeting because of large uncertainties in target localization. Image-guided RT (IGRT) has gained importance with the clinical use of techniques requiring precise localization of both target and normal tissues during planning and treatment.

17.3.1 Why Do We Need IGRT for the Breast?

IMRT defines specific treatments for breast irradiation with significantly reduced doses to the OAR. The goal of IGRT is to manage inter- and intrafraction motion to reduce margins and therefore to protect normal tissues by optimizing treatment plans. IGRT allows for more accurate targeting in breast cancer by providing

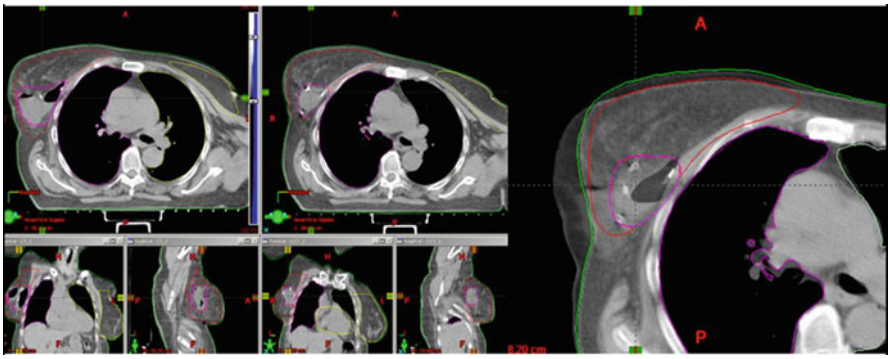

Fig. 17.11 The seroma volume changes during whole-breast RT affect the volume of normal breast tissue and the accuracy of boost planning. Therefore, CT-based boost planning is recommended before boost irradiation to ensure appropriate coverage

correct target volume delineation, obtaining simulation images, and set-up correction using images with the patient in the treatment position immediately prior to or during treatment. Verification with port films specific for RT inspired the idea of EPID systems integrated into the gantry. Portal imaging tools that became popular with the use of EPID since the early 1990s have enabled a more precise and safer treatment. Currently, in-room imaging technologies are becoming widely used in addition to EPID.

Inter- and intrafraction motions contribute to decreased treatment accuracy. Interfraction motion occurring between fractions includes movement of the target within the soft tissues, differences in patient positioning, and other types of set-up errors. In patients who have had a lumpectomy, the breast structure may change over time as tissue redistributes within and around the cavity (Fig. 17.11) [48]. Sharma et al. showed that the volume of seroma changes during whole-breast RT affected the accuracy of boost planning and the volume of normal breast tissue. They recommended CT-based boost planning before boost irradiation to ensure appropriate coverage [49]. Remouchamps et al. found that immobilization with a customized cradle resulted in decreased interfraction motion when compared with patients who were immobilized using a single-arm support system, suggesting that the higher the degree of immobilization, the lower the likelihood of set-up error [50]. Intrafraction motion occurring during the treatment session includes the position changes due to heart, lung, and patient movements. Organ movements secondary to respiratory motion are one of the main concerns during breast RT.

CT-based planning that allows incorporation of modern imaging techniques such as magnetic resonance imaging (MRI), magnetic resonance spectroscopy, and positron emission tomography/CT have been used since transition from 2D to 3D planning. Moreover, these advanced imaging techniques can be registered to CT images in order to allow more accurate tumor and lymph node delineation.

17.3.2 IGRT Technologies

A wide variety of imaging technologies have been incorporated into IGRT systems. The main groups for position verification in IGRT include gantry-mounted, room-mounted, and nonionizing systems.

17.3.2.1 Gantry-Mounted Systems

Gantry-mounted systems are the most common types of IGRT systems currently in use; they comprise the hardware for imaging that mounts directly to the gantry.

Megavoltage Electronic Portal Imaging Device System

In modern RT, the verification of treatment fields is crucial and it has been done with conventional port films for decades. Following the introduction of the scanning liquid ionization chamber system in the early 1990s, EPID quickly replaced the radiographic films and was integrated into the gantry [51]. EPIDs produce images using a therapeutic (megavoltage) beam. It not only provides immediate information to correctly position the patient, but also avoids the delays in film processing with port films, and with greater accuracy [52]. Furthermore, the cine acquisition mode of EPID could be used to observe intrafraction movements and to monitor the treatments where breath-hold technique is used for left side breast cancer patients [53].

In the daily practice of breast irradiation, increasing the frequency of treatment verification with portal imaging can reduce set-up errors. Some anatomic distances were defined to be considered for evaluation of portal and simulation images (Fig. 17.12) Central lung distance (CLD) is the distance between the posterior beam edge and inner thoracic wall, the inferior central margin (ICM) is the distance from the inferior beam edge to skin surface, and central field distance (CFD) is the distance between the anterior skin surface and beam edge [54–57]. CLD is probably the most important parameter as it gives an indication of both the volume of lung within the beam and the risk of pneumonitis, whereas CFD anteriorly ensures that the whole breast is enclosed within the beam and is more of a double check on what should be seen visually using the light field [58, 59].

Fein et al. showed that CLD, CFD, and ICM distances with margins of 7.70, 7.70, and 10.30 mm, respectively, were required for covering the breast target in 95% of cases [60].

Gantry-Mounted kV Systems

For IGRT applications, a kV imaging system is required with its capability of radiography, fluoroscopy, and cone-beam CT options. In this system, a kilovoltage

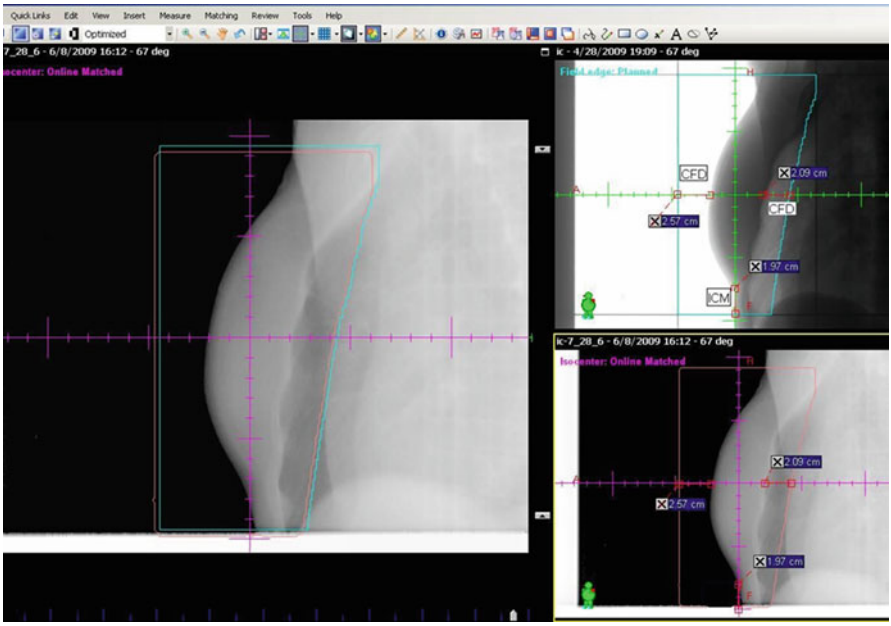

Fig. 17.12 Comparison of the simulation and portal images; anatomic measurements such as CLD, the ICM, and the CFD should be taken into consideration

x-ray tube is combined with a flat-panel image detector and they are mounted orthogonally on the linear accelerator. The system allows pretreatment set-up verification with 2D planar imaging and 3D volumetric imaging.

Two-Dimensional Planar Imaging System

There are commercially available system producing high resolution diagnostic quality radiographs of the patient in the treatment position; this constitute a considerably lesser dose exposure than EPID. kV imaging is usually used for confirmation of the isocenter while MV imaging is used for field verification (Fig. 17.13). Pretreatment orthogonal imaging via kV is preferred, given the more oblique treatment beams used in IMRT [61]. The fluoroscopy mode may help to visualize motion resulting from respiration or other causes, and it is usually used to follow up on respiratory control during the breast irradiation.

Three-Dimensional Volumetric Imaging Systems

kV cone-beam CT: Cone-beam CT provides high-resolution imaging of tumors and other soft tissues [61]. This system obtains multiple kV radiographs While gantry rotates and a filtered back projection algorithm is employed to reconstruct the volumetric images [62]. These images are registered to the planning CT. Then, any set-up error can be measured and corrected at the treatment unit [63]. Furthermore, the images provide soft-tissue information often allowing visualization of the actual target to be treated and surrounding OAR which cannot be provided by portal imaging.

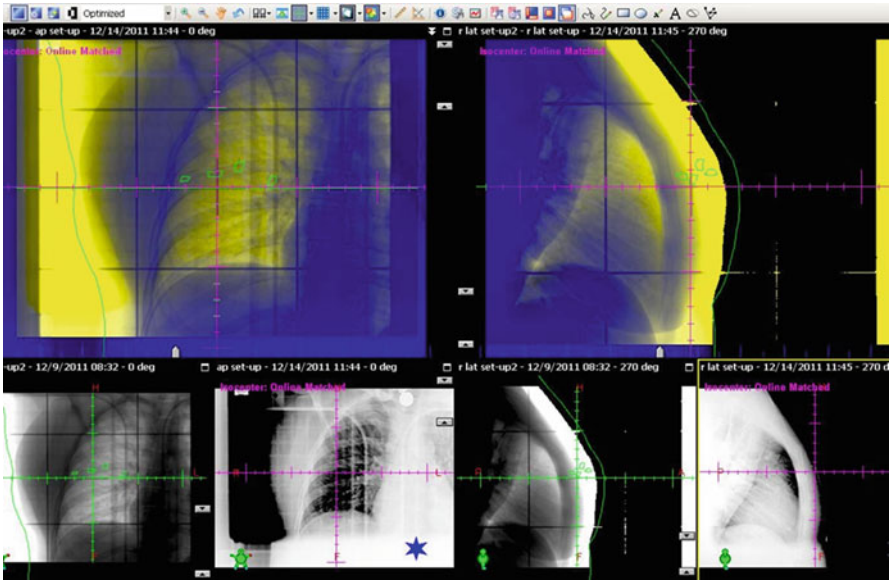

Fig. 17.13 Pretreatment orthogonal antero-posterior and lateral images are used for online set-up correction. These images provide an isocenter check instead of field check, is preferred fore more oblique fields confirmation such as IMRT.

Additionally, the relative absorbed dose of cone-beam CT is reduced compared with that of typical portal imaging techniques [64]. Fatunase et al. used cone-beam CT to examine the remaining residual error after patients were positioned using 2D kV/mv images before each accelerated partial breast irradiation session. They concluded that the use of cone-beam CT provided little additional benefit beyond kV/mv imaging for most patients, although it could be useful for improving targeting precision in patients with large breast volumes or patients who required tight margins [65].

White et al. [64] revealed increased accuracy of primary tumor imaging with the use of cone-beam CT when compared with skin reference landmarks. Kim et al. showed improved beam targeting with reduced margins when cone-beam CT was used to visualize surgical clips [66]. Furthermore, cone-beam CT allows monitoring of seroma volume and considering necessity of adaptive planning [49].

MV Imaging System

Tomotherapy

Tomotherapy (Hi Art TomoTherapy Inc., Accuray/TomoTherapy): Basically, a helical fan-beam megavoltage CT is combined with a linear accelerator in tomotherapy. The megavoltage CT gantry allows obtaining images prior to treatment and radiation therapy is given using the same ring megavoltage gantry that moves

around the patient in a circle to irradiate the tumor with smaller radiation beams from all directions. This combination is especially designed for delivering slit geometry of intensity modulated radiation. This approach also may provide better avoidance of heart and lungs in patients with left side breast cancer [67].

Megavoltage Cone-Beam CT

In this system, therapeutic megavoltage beam is the basic configuration for a CT imaging system and there is a traditional EPID mounted on a linac gantry. The most remarkable application advantage of a megavoltage cone-beam CT system is for the patient with implanted metal object where soft-tissue contrast is the limited factor for this system.

17.3.2.2 Room-Mounted Systems

A variety of fixed x-ray tube and detector combinations are included in in-room systems. They are also known as in-room mobile cone-based CT scanners, also referred to as CT on rails [68, 69]. Additionally, there is an in-room MRI system currently under development for IGRT that is not yet commercially used in clinical practice [61].

17.3.2.3 Nonionizing-Based Systems

Ultrasound

Ultrasound images of the tumor or nearby landmarks are superimposed on the planning CT images. It was shown that ultrasound is similar and superior to conventional CT imaging to delineate small lumpectomy cavities in patients with dense breast [70].

Video-Based Systems

Shape and volume changes in targets can be detected on the 3D camera system which is able to capture the accurate full-surface information of the target area. This feature is especially important for breast cancer because of its soft-tissue effectiveness. However, it is unable to detect the internal structures where knowledge of the internal data is necessary for accurate dose calculation, therefore, the internal structures are commonly correlated from the simulation CT data and can be verified with portal images of the target (i.e., the partial breast irradiation or the boost treatment after whole-breast irradiation) [71]. Gierga et al. compared the accuracy of different IGRT approaches for accelerated partial breast irradiation treatment and found that kV imaging of implanted surgical clips was superior to surface imaging using 3D video,

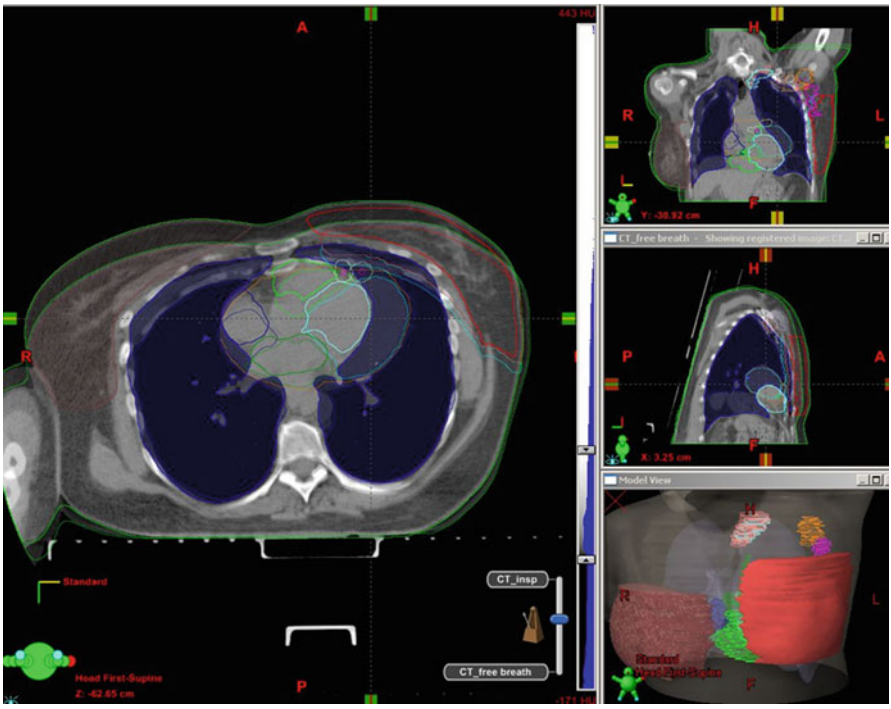

Fig. 17.14 Displacement of organs with deep inspiration and free breathing in a left breast cancer patient, especially heart displacement, effects heart and LAD doses

kV imaging of the chest wall, or laser alignment of skin surface marker [72]. Breathing was more important for breast movement in surface imaging.

17.4 Managing Respiratory Movement

Respiration is a significant source of variety for target and OAR movement in breast cancer patients secondary to chest motion during inhalation and exhalation (Fig. 17.14). A study comparing the radiation dose and volume changes during the breathing cycle revealed treatment planning without breath control was not capable of compensating heart and its components volume-dose changes and concluded that respiratory organ movement had to be considered when planning treatment [73]. Four-dimensional (4D) CT, a modality to visualize organ movement, has been used to capture images in each phase of the respiratory cycle [74–76]. Currently, there are few studies using 4D CT both to analyze and quantify the effects of respiratory motion on the target and normal tissue during breast irradiation [77]. Techniques developed to help control breathing movement include the voluntary breath-hold technique which limits motion and reduces the exposed heart volume by displacing the breast tissue

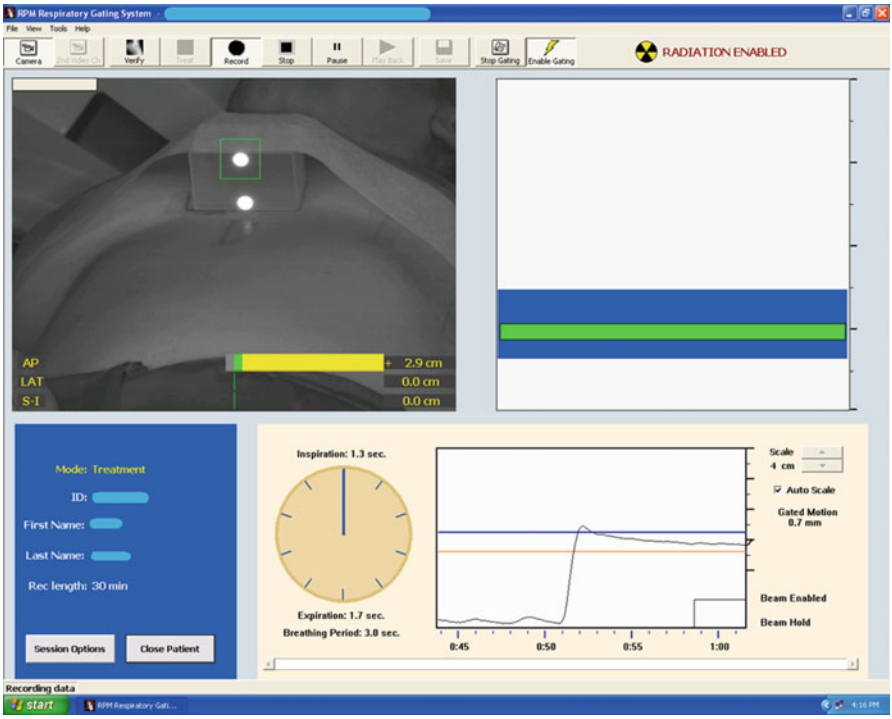

Fig. 17.15 The application of Deep inspirium breath-hold technique with real-time position management system (Varian Medical Systems, Palo Alto, CA.) Maintaining breath-hold position can be followed by the system with the help of two passive infrared reflective markers placed on the patient's chest and monitored by a charge-coupled-device video camera mounted on the treatment room wall. The beam is programmed to turn off when the chest position is out of range

away from heart or the use of active breathing control devices where the airflow during respiration is regulated by a computer-controlled valve [78–81]. However, patient compliance is crucial to application of these approaches [76]. There are respiratory gating methods that allow the beam to irradiate a moving target at the same point during each cycle. The real-time position management system (Varian Medical Systems, Palo Alto, CA) is an external gating system where both amplitude and phase gating are allowed (Fig. 17.15). It consists of a lightweight plastic block with two passive infrared reflective markers placed on the patient's anterior abdominal surface and monitored by a charge-coupled-device video camera mounted on the treatment room wall [82]. The beam is programmed to turn on and off with the patient's breathing in order to effectively control respiratory movement [76].

17.5 Conclusion

IMRT allows the shaping of the radiation dose distribution around critical structures while treating the target at full dose. Phase III trials have demonstrated superiority of IMRT over the standard treatment, for acute and late side effects in the intact breast. The use of IMRT improves breast and regional node coverage while decreasing doses to the lungs, heart, and contralateral breast when compared with 3D-CRT. A new version of the well-known technology, IGRT, has been developed and has become a candidate to more precisely control the potential sources of variability in tumor location such as shifting of soft tissues, breath motion, changes in organ filling, and patient positioning more. Therefore, this new technology allows reducing the margins to as little as millimeters. Various IGRT solutions of imaging tools for off-line and on-line application to optimize RT accuracy and to avoid the potential errors are available in breast RT. However, the circumstances of each individual center in daily routine might affected in choosing the best IGRT solutions for that clinic and for their breast cancer patients.

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Chapter 18
Forward Planning Intensity Modulated Radiation Therapy Techniques

Ferah Yıldız, Gozde Yazici, Pervin Hurmuz, and Ali Dogan

18.1 Introduction

Ionizing radiation has a major role in the treatment of breast cancer. For early-stage disease breast conserving surgery (BCS) with axillary or sentinel lymph node dissection followed by whole-breast irradiation is the standard of care. Adjuvant radiotherapy in patients with high risk for locoregional recurrence after mastectomy increases the overall survival, disease-free survival, and local control rates (LCR) [1–4].

Traditionally, a pair of tangential fields was used for whole-breast or chest wall irradiation. In order to improve dose homogenity within the treated volume, frequently, beam modifiers were utilized. However, due to the shape of the breast a homogenous dose distribution within the range of 95–105% is difficult to achieve. The planning target volume (PTV) coverage with the 95% isodose level often results in hot spots. Underdosage on the other hand is a problem in large breasts, with the tangential separation bridge more than 20 cm, when low-energy photons of 4–6 MV are used. Dose prescription to 90–95% of isodose line to overcome the cold spots in these patients frequently produces unacceptable hot spots, particularly in the most cranial and caudal parts of the breast.

Three-dimensional conformal radiotherapy (3D-CRT) provides precise information of the radiation dose distribution in all areas of the affected breast, regional nodes and adjacent normal tissues. With the routine use of 3D-CRT, optimal shielding of organs at risk (OAR) can be easily achievable, therefore, homogeneous dose distribution in the clinical target volume (CTV) became the main concern of the radiation oncologists. A further improvement in technology is the modulation of the intensity of the beams and is termed as intensity modulated radiotherapy (IMRT). This modality reduces the radiation-induced morbidity in patients with head and neck cancer and

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prostate cancer [5, 6]. Three randomized trials have demonstrated that IMRT increased the dose homogenity and decreased the acute complications in early-stage breast cancer in patients with BCS [7–9] In the recent SEER (Surveillance Epidemiology and End Results) data, it has been found that the prevelance of IMRT use in breast cancer was 0.9% in the year 2001 which rose to 11.2% by the year 2005, reflecting a greater than tenfold increase [10]. Although having advantages in dose homogenity and shielding of OARs, IMRT requires sophisticated technical resources and a long period of time for both planning and quality assurance tests. In addition the mean monitor units (MU), in a standard IMRT for breast cancer patients is around 800–1,000 MUs and the dose to contralateral breast and whole body is greater than the dose achieved with standard tangential fields. The consequences of the increased MUs in long-term follow-up are not yet clear. Forward planning IMRT is a quicker and less sophisticated form of intensity modulation that uses few additional segments or beams within the same tangentially arranged 3D fields. In this chapter we will describe the rationale, the techniques, and the optimization procedure of forward planning in breast cancer radiotherapy.

18.2 What is Forward Planning?

In a forward-planning technique, the radiation oncologist places the beams into the planning system to deliver sufficient dose to CTV, to spare the OAR and healthy normal tissues. In this technique, the therapist decides how many beams to use, which angles each beam will be delivered from, whether alternating wedges are to be used, and which multileaf collimator (MLC) will be used to shape the radiation from each beam. Once the therapist has created the treatment plan, the planning system calculates a predicted dose to the patient using different dose prediction models as pencil beam, Triple A and Monte Carlo simulation. In other words, forward planning is an extension of conventional treatment planning and its definition of the segment shaping is performed manually, similar to conventional 3D planning. In this planning technique more than one segment or additional beams within the tangential fields are used, and to achieve the desired dose distribution, the weights of the segments are optimized using a computer optimization algorithm. The manual definition of the segments is based on the beam's eye view (BEV) option of the planning system and the clinical implementation of this system is relatively easy compared with the inverse planning.

Several dosimetric studies comparing forward planning and inverse planning in the head and neck, prostate, and breast cancer have been performed [11–15]. In a study by Bär et al., IMRT treatment plans in head and neck cancer with inverse planning strategies produced improved dose distribution with better target coverage and better sparing of the parotids [11]. However, inverse planning increased the number of segments compared with forward planning. In another study, Metwaly et al. found that forward planned dynamic arc therapy in prostate cancer provided better protection of the rectum and the healthy tissues outside the treatment volume

compared with inverse planning [12]. However, Donovan et al. compared five different IMRT methods using either forward planning or inverse planning in breast cancer radiotherapy and found that no method showed a clear dosimetric advantage over the others [13].

18.3 Radiobiology of Forward and Inverse Planning IMRT

Accelerated repopulation is one of the major causes that jeopardizes tumor control probability. In the simultaneous integrated boost (SIB) technique in IMRT, at least two dose levels are used, aiming to reduce the overall treatment time and to minimize the number of the treatment phases. This may lead to better LCR, especially in tumors with short potential doubling time. In a study by Ferreina et al., different planning techniques including conventional, forward-planning, and inverse-planning IMRT with SIB technique in head and neck cancer patients were compared [16]. The tissue response in this study was calculated using the relative seriality model and the Poisson linear quadratic time model to simulate repopulation in the primary tumor. It was proposed that the average probability of tumor control increased from 38% to 89% with IMRT using the SIB technique compared with the conventional technique. The shorter treatment time and the larger dose per fraction in this study resulted in an increase in the probability of tumor control by 11%.

The α-to-β ratio (α / β) ratio of breast cancer is estimated to be in the range of 2.88–3.89, and the potential doubling time is around 14 days [17]. Therefore, the total treatment time in breast cancer radiotherapy is not as important as it is in head and neck cancer. Studies of the SIB technique in breast cancer generally used 1.8 Gy per fraction to the whole breast and 2.14–2.3 Gy per fraction to the tumor bed and demonstrated excellent LCR with a favorable acute toxicity profile in short-term follow-up. It is reasonable to increase the daily tumor bed dose because the α-to-β ratio of breast cancer is approximately 3 Gy [18, 19]. This fractionation model may produce even better LCR. An ongoing randomized IMRT-MC2 trial is now comparing IMRT with SIB to conventional radiotherapy with consecutive boost after BCS. The primary objectives of this phase 3 trial are the evaluation of cosmetic results at 6 weeks and 2 years posttreatment and the 2- and 5-year local recurrence rates [20].

IMRT is basically an advanced form of 3D-CRT. It allows far more precise shaping of dose to the target and reducing the dose to surrounding normal healthy tissues. One of the main problems of IMRT, which becomes more apparent as the complexity of the plan increases, is the number of MUs required to deliver a fractionated treatment. The increase in MU is associated with longer treatment time and increased leakage of radiation from the MLCs. This causes higher total body dose which may lead to secondary cancers. In a dosimetric study by Ruben et al., it was shown that the out-of field dose with IMRT was 80% higher compared with conformal radiation therapy mainly as a result of increased machine scatter and leakage [21]. It has been estimated that the maximum risk of fatal secondary cancer

was 1.7% for 3D-CRT, 2.1% for IMRT using 10 MV x-rays, and 5.1% for IMRT using 18 MV x-Rays [22]. In the era of modern medicine, breast cancer patients are offered effective systemic and local therapies resulting in long survival times. It is extremely important to reduce the complexity of IMRT plans in order to avoid unnecessarily high MUs and excessive radiation leakage particularly in patients with a long life expectancy. In this aspect, forward planning provides better dosimetry than 3D-CRT and less MU and leakage than inverse-planning IMRT.

18.4 Techniques in Forward-Planning IMRT in Breast Cancer

The methods used for beam modulation in forward planning IMRT of breast cancer are the use of compensators to optimize the 3D dose distribution, equivalent path length (EPL) missing tissue compensation, BEV dose contouring, and minimization of dose variation and equilization of maximum dose [13, 23–30]. In order to reduce the hot spots and to improve the dose homogenity, an individual compensator or a reusable compensator library is used in the first method. Several studies showed that the volume of breast tissue receiving more than 105% of the dose was significantly reduced in patients treated with this technique when compared with standard tangential fields with wedges [23–25]. In the EPL tissue compensation method, optimization of the dose distribution is achieved mainly by equalizing the dose in high-dose areas which is generally at the medial and lateral side of the lung and close to the apex of the breast. This method is based on the division of the PTV into segments with similar EPLs. In a dosimetric study by van Assalen et al., 2D EPM maps were generated from the CT dataset using homemade software and the distance between the minimum and the maximum path length, derived from the EPL map, was divided into four discrete, equally spaced intervals each which covers a range of path lengths [26]. The resulting map was used for optimal MLC settings, and approximately four MLC-shaped segments for each patient were used. Approximately 88% of the dose was delivered by two open fields covering the whole treated volume and the remaining 12% were equally divided among the other segments. It has been demonstrated that an improved dose distribution in CTV and approximately 10% dose reduction in the lungs could be achieved with this technique.

BEV dose contouring is a technique similar to the EPL missing tissue compensation but differs in the autoblocking utility of the treatment planning software used to compensate hot areas displayed in the BEV. The details of this technique, which is simply called “field-within-field technique,” will be described separately.

The rationale for the minimization of the dose variation technique is based on reducing dose variation in the direction parallel with the beam axis and hence minimize the total dose variation over the whole PTV. In this technique electronic portal imaging (EPID) is mainly used to obtain thickness maps of medial and lateral tangential fields and IMRT deliveries are designed to minimize the volume receiving greater than 105% of the prescribed dose based on these maps [13, 30–32]. The steps for EPID-guided compensation can be summarized as calibration of EPID

for thickness, obtaining radiologic thickness maps by EPID from open field, and obtaining treatment images of both tangential fields. The next step is to generate an estimated computerized tomography (CT) image of the breast with assumptions that the treatment volume contains only air, breast, and lung tissue and the whole breast is of the same uniform density and the lung tissue of different but uniform density [31, 32]. Intensity modulation based on these maps is achieved by combining wedged and multiple static MLC-shaped fields. Most of the dose is delivered by the wedged fields and then the MLC moves in to define fields that are progressively smaller. In a study by Donovan et al., a mean increase in PTV receiving 95–105% of the prescribed dose was 7.5% compared with wedged tangentials only and the volume that received greater than 105% was significantly low with this approach [32]. The algorithm and methodology of the modulation that uses equilization of the maximum dose is very similar to the previous method, however, it equalizes the maximum dose from the apex to the base of the breast [13, 33, 34].

18.5 BEV Dose Contouring: Field-Within-Field Technique

The primary goal of breast cancer radiotherapy is to treat the CTV, which is the whole breast or chest wall and/or regional lymphatics, with a homogenious dose distribution while minimizing the dose to the lung, heart, and contralateral breast. BEV dose contouring, or simply the field-within-field technique, uses multiple static MLC-shaped fields in order to achieve this goal. In this technique, a pair of conventional open tangential fields is produced first and MLCs are used to shape the fields and to spare the normal tissues and OARs. The wedge angles and relative weights of the beams are optimized using standard treatment planning methods in order to provide dose homogenity. The standard open or wedge tangential technique produces a dose distribution with 7–22% of hot spots in the majority of patients [35]. These hot spots occur mostly in the anterior, superior, and inferior parts of the breast and sometimes inaffordably in the lung tissue (Figs. 18.1 and 18.2). In the field-within-field technique, to obtain a homogenious dose distribution within the range of 95–105%, the dose delivered with these open fields is reduced typically to 90–93% of the total dose and new tangential fields are designed for the remaining 7–10% of the dose (Figs. 18.3 through 18.6). The trick of this technique is to use the new tangentials with the same gantry, and when wedges are used, with the same wedge angles. However, wedge filters in the medial tangential fields are no longer used in our department in order to not increase the dose to the contralateral breast. The new reduced fields are shaped to exclude the areas receiving more than 105% of the dose. Designing these new fields is an iterative process and additional static MLC-shaped fields may also be applied to improve the dose homogenity when needed. The other approach for the field-within-field technique is to delineate regions of nonuniform dose by contouring isodose surfaces in increments of 5% [28, 36]. These surfaces are then smoothed by sequentially blocking the 115%, 110%, and 105% of the dose clouds. In this method the weight of the medial and

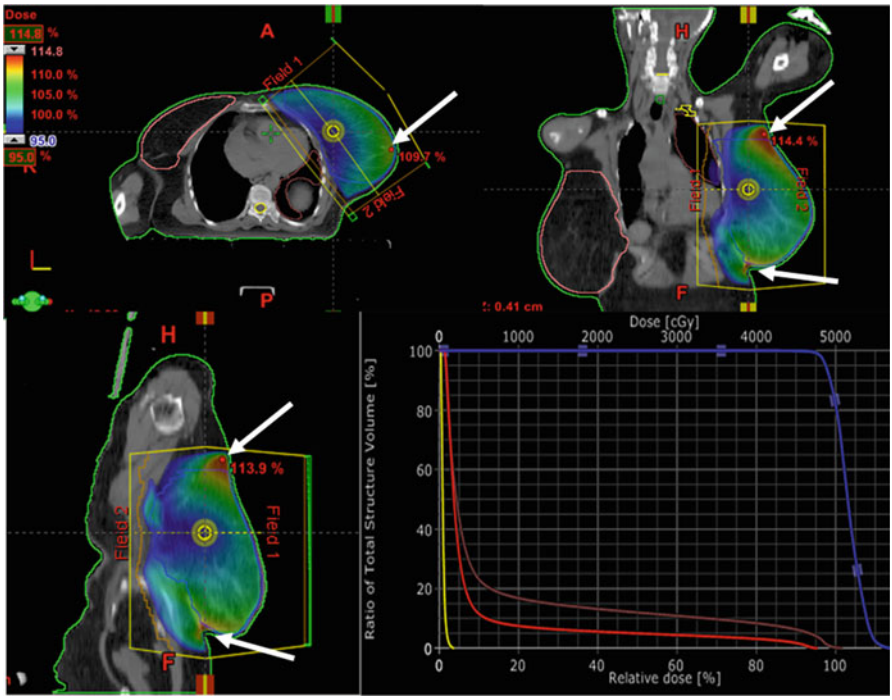

Fig. 18.1 Open tangential fields in transverse, coronal, and sagittal sections, and DVH. Twenty-five percent of breast receives more than 105% of the prescribed dose. Volumes receiving more than 105% of the prescribed dose are located in the upper, lower, and superficial parts of the breast, shown with *arrows*.

lateral open fields is generally in the range of 36–45% of the total dose and each field-within-field configuration contributes to 5–8% of the total dose [37].

Keeping the gantry and wedge angles the same for each set of multiple fields form another advantage of BEV shaped dose contouring. There is no increase in set-up complexity and treatment can be delivered quickly and reliably with this approach.

Studies of field-within-field technique have all reported an improved dose homogenity within the PTV in addition to reduced doses to the contralateral breast, lung, and heart when compared with conventional wedge compensated techniques [27, 28, 35–37]. In a dosimetric study, Smith et al. reported that three intensity modulated tangential beam radiotherapy plan types and one conventional wedge field tangential plan for breast cancer treatment were evaluated based on PTV homogeneity index, heart and lung doses, and time required for planning process [15]. The three IMRT plans consisted of forward-planned IMRT using the field-within-field technique, the surface compensated plan using two equally sliding window tangent fields, and the hybrid IMRT technique that contained a pair of open and a pair of dynamic MLC tangent fields with inverse optimization. All three

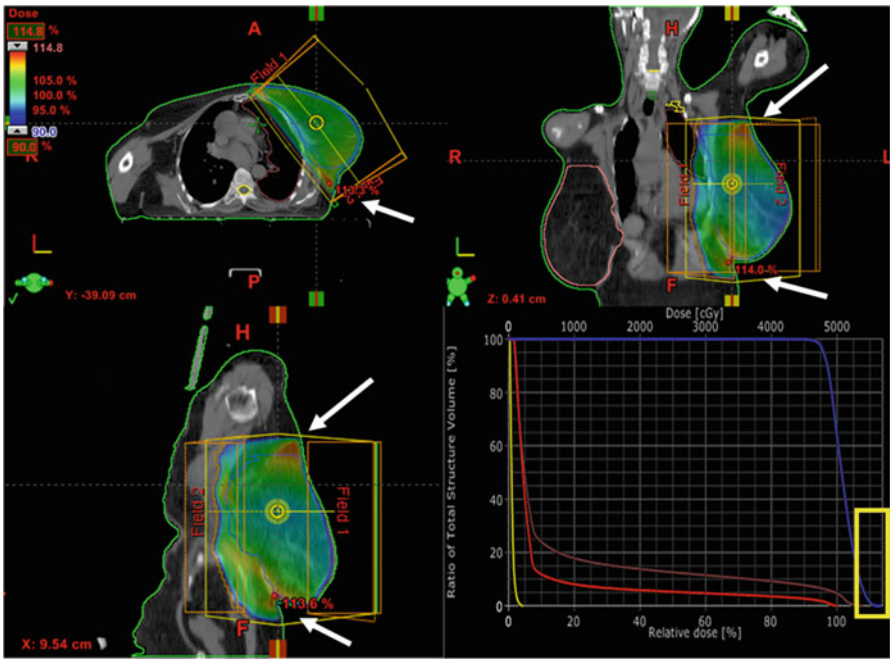

Fig. 18.2 Open tangential fields with wedges in transverse, coronal, and sagittal sections, and DVH. Wedge filters reduce the hot spots in the breast. Volumes receiving more than 105% of the prescribed dose are approximately 20%, and are located in the upper and lower parts of the breast, which are shown with *arrows*. The wedge filters mainly reduce the hot spots in the superficial region of the breast. The *yellow rectangle* in the DVH demonstrates the volume receiving $\geq$105% of the dose

IMRT plans showed significant improvement in PTV homogenity index in which hybrid technique produced the best homogenity index. However, no significant differences could be found among the three IMRT plans regarding the lung and heart doses. In another dosimetric study, Descovich et al. reported that forward-planned IMRT was compared with direct aperture optimized (DAO) IMRT in 15 patients with left side breast cancer and found no significant difference between DAO IMRT and forward-planned IMRT [38]. However, the time required for DAO IMRT planning was shorter than for forward-planned IMRT.

18.6 Randomized Studies with Forward-Planning IMRT

There are three phase III trials comparing forward-planning IMRT and conventional radiotherapy in patients with early-stage breast cancer [8, 9, 39]. In the study by Barnett et al., 815 patients with greater than or equal to 2 cm^3 of breast tissue receiving more than 107% prescribed dose with the standard breast plan were randomly assigned to either IMRT with BEV shaped dose contouring or standard wedge fields [39]. The mean volumes receiving more than 107% and less than 95%

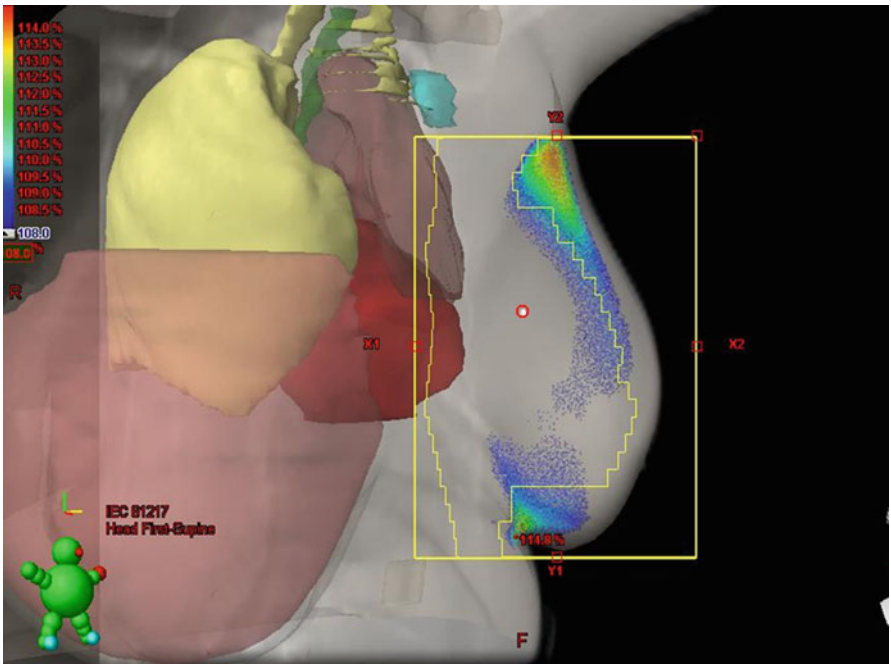

Fig. 18.3 BEV shaped forward planning; field-within-field technique. DRR showing the MLC segments closing the volumes receiving ≥105 % of the prescribed dose

of the prescribed dose in the IMRT arm compared with control arm were 34 and 48.1 cm^3, respectively, which showed significant difference.

In yet another study, Canadian researchers randomly assigned 358 women with early-stage breast cancer to forward-planned IMRT or to standard radiotherapy using wedges [9]. The primary endpoint was to analyse whether the new radiotherapy technique reduced acute skin reactions and pain and improved the quality of life for the patients. Results from 331 women who completed the study showed that significantly fewer patients suffered moist desquamation during, or up to 6 weeks after, the treatment with IMRT. Just less than one of three women (31.2 %) had an acute skin problem with IMRT compared with nearly half (47.8 %) of those undergoing standard treatment, which is statistically significantly important.

Three hundred and six women in a British trial prescribed whole-breast radiotherapy after BCS were randomized to IMRT or 2D radiotherapy delivered using standard wedge compensators [8]. The IMRT technique used in this study was minimization of dose variation and based on EPID-guided compensation. The primary endpoint in this phase III trial was change in breast appearance scored from serial photographs taken before radiotherapy and at 1-, 2-, and 5-year follow-up. Secondary endpoints included patient self-assessments of breast discomfort, breast hardness, quality of life, and physician assessments of breast induration. Five-year photographic evaluation was available in 79% of patients and change in breast appearance was

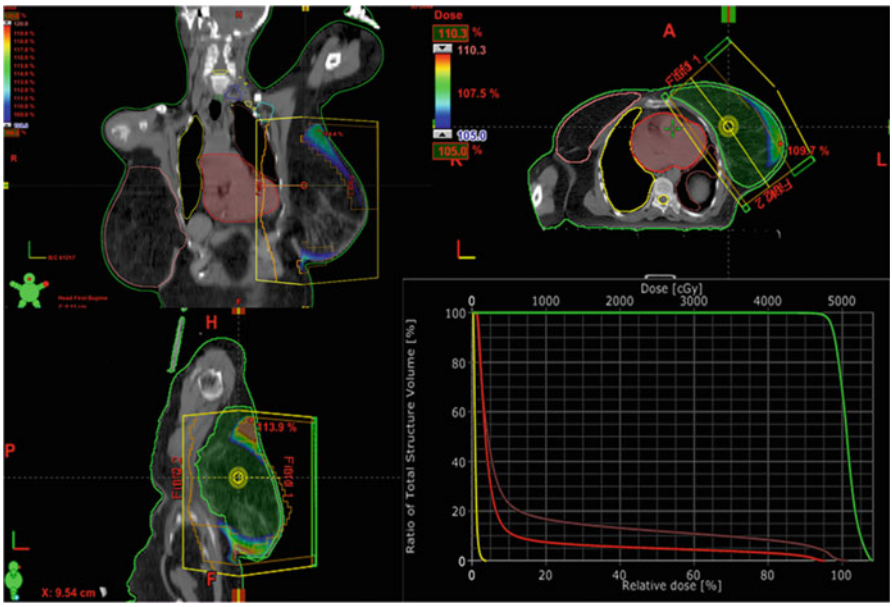

Fig. 18.4 BEV shaped forward planning; field-within-field technique. Transverse, coronal, and sagittal sections showing the reduced fields closing the volumes receiving $\geq$105% of the prescribed dose, and the resulting DVH which demonstrates the homogenious dose distribution in the CTV. Volume receiving $\geq$105% of the dose is below 5%. The minimum dose in the CTV is 4,800 cGy, and the maximum dose is 5,450 cGy

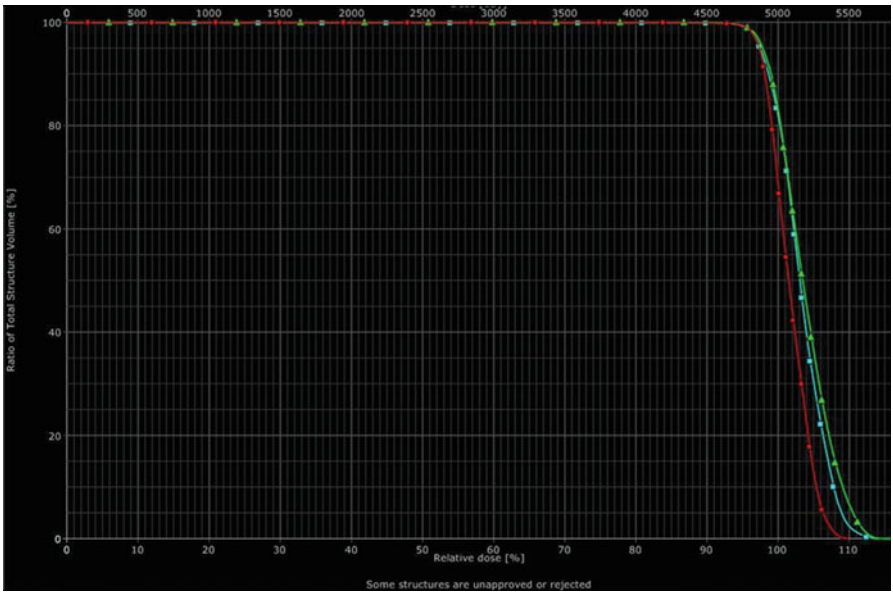

Fig. 18.5 DVHs of open field, open fields with wedge filters, and field-within-field technique. *Green line*: open field. *Blue line*: wedge field. *Red line*: field-within-field technique

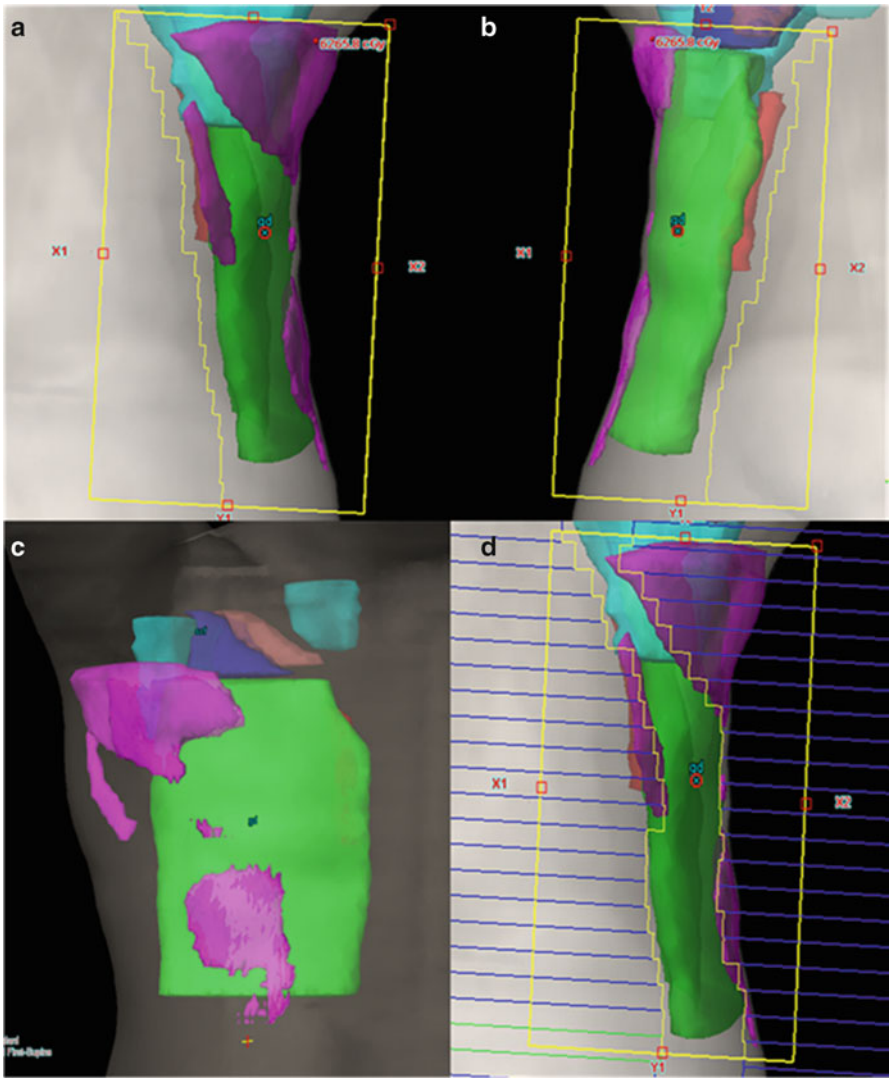

Fig. 18.6 BEV shaped forward planning; field-within-field technique in a patient who received chest wall and whole lymphatic irradiation after modified radical mastectomy (*green* = chest wall CTV; *cyan* = level I axilla CTV; *dark blue* = level II axilla CTV; *light blue* = supraclavicular fossa CTV; *purple* = volume receiving ≥110% of the prescribed dose). (**a–c**) Volumes receiving ≥110% of the prescribed dose. (**d**) Reduced field closing the volumes receiving ≥110% of the prescribed dose in the chest wall. Notice that the reduced fields are further coned down to shield the lung tissue

identified in 58% allocated to standard 2D treatment compared with only 40% of patients treated with IMRT. In the control arm, patients were 1.7 times more likely to have a change in breast appearance than the IMRT arm after adjustment for year of

photographic assessment. Additionally, significantly fewer patients in the IMRT group developed palpable induration assessed clinically in the center of the breast, pectoral fold, inframammary fold, and at the boost site.

In summary, all three published phase III trials of IMRT in breast cancer focused on the treatment of early-stage breast cancer, and the radiation target was breast only. The dosimetric results of these trials supported the significant advantage of IMRT in increasing the dose homogenity and the elimination of hot spots in PTV. Such improved radiation dosimetry resulted in significantly less acute radiation toxicity demonstrated both in Canadian and British trials. It seems that this dosimetric advantage of IMRT also converts to a cosmetic advantage in long-term follow-up.

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Chapter 19
Boost Techniques

Seden Kucucuk, Gonul Kemikler, and Aydin Cakir

19.1 Introduction

Breast-conserving therapy with surgery and radiotherapy in early breast carcinoma is a well accepted method. Survival rates and locoregional controls after mastectomy or breast-conserving therapy are similar and has been proved in many randomized trials [1–5]. Moreover, these results are confirmed in the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group [1].

Postoperative radiotherapy to the whole breast is required after lumpectomy. Most authors report that 65–80% of local recurrences after breast-conserving therapy occur at the primary tumor site [6–9]. As a result of this clinical observation, boost dose is routinely used. Although some authors suggested that boost is not necessary in tumors with surgically free margin [10–12], in prospective randomized trials it has been shown that local relapse rates are decreased with additional dose to the tumor bed [13–15]. The decrease in local recurrence with at least 10 Gy in addition to 50 Gy of whole-breast irradiation has been proved by the studies that analyzed dose response effects on local tumor control [14–18].

One of the keys to successful boost irradiation is obtaining a detailed and accurate definition of tumor bed. The target volume for boost is usually defined as the tumor bed with 1–2 cm safety margin. The delineation of tumor bed based on clinical findings (surgical scars) often leads to an insufficient dose delivery to the boost volume, therefore, a high rate of geographical omission [19, 20]. Accurate target volume is defined using various methods such as surgical clips, sonography, or computed tomography (CT) [21, 22]. Surgical clips are accepted as standard reference for tumor bed localization [21]. Ideally, they should be placed at the boundaries of the lumpectomy cavity at the time of surgery in order to aid in the localization of the tumor bed for implantation and to establish adequate dosimetric

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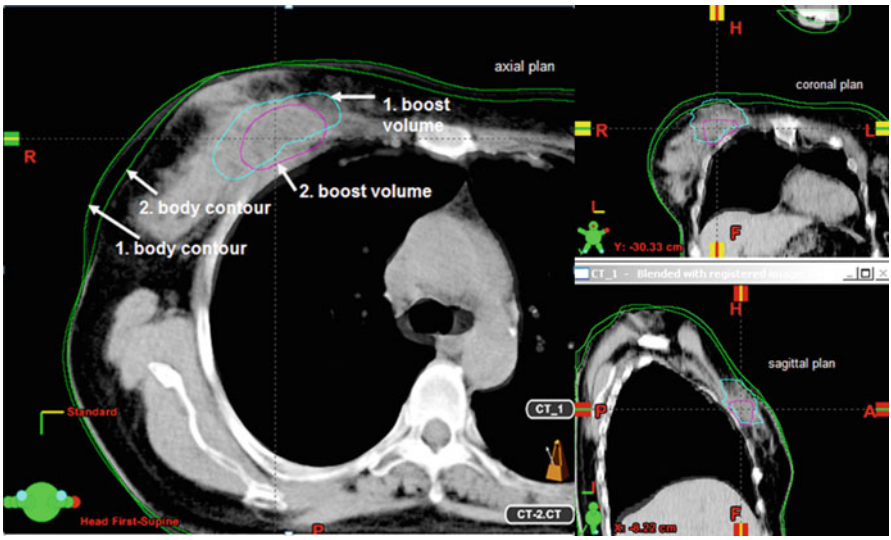

Fig. 19.1 The changes of the body contour and boost (seroma) volume between two CT images in the same patient with 28-day intervals (*left*), overlay of two boost volume on sagittal (*right upper*) and coronal (*right lower*) slices. The volume of seroma (*cyan line*) was 67 cm^3 on the first planning CT image and 16 cm^3 on the second CT image (*magenta line*). The smaller tumor bed volume allows for less normal breast tissue to be included within the radiation field

coverage for quality assurance purposes [21, 23]. Four to six radiopaque clips placed three-dimensionally (3D) are optimal to define the target volume. However, it must be taken into account that the position and number of clips are inconsistent and that they can move with respect to the changes of boost volume during irradiation [24, 25]. CT-based cross-sectional imaging allows delineation of the irregular excision cavity via 3D. CT-based planning also allows for 3D reconstruction; therefore, sagittal and frontal slices can be used in dose optimization. The use of surgical clips and CT images in combination seems to be the ideal method to determine the target volume [26]. In CT slices, clinical target volume (CTV) represents tissue scar and/or seroma within the surgical cavity. If clips present, they should be included in CTV.

Effective boost treatment is related to the tumor bed, so, with time, any changes in volume and position from planning will affect the delivered dose to the target and organs at risk [27, 28]. Seroma volume tends to shrink substantially over time during whole-breast irradiation. Such volume changes should be considered during boost planning. As the seroma shrinks and boost volume decreases, the irradiated normal breast tissue may be increased. Furthermore, breast contour alteration may occur (Fig. 19.1). Hence, repeated CT-based boost planning and "adaptive" therapy may be necessary.

Boost treatment is delivered mostly sequentially during whole-breast irradiation. However, recently, simultaneous integrated boost (SIB) treatment in which breast and boost irradiation are combined in one integrated treatment plan is defined. In this

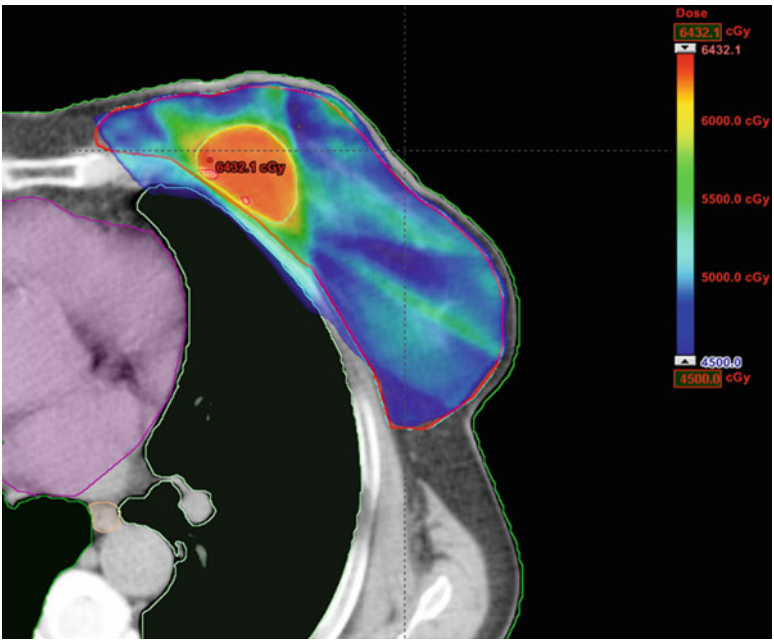

Fig. 19.2 Color wash of simultaneous integrated boost plan on axial views of a patient with left side breast cancer. Threshold is set to 45 Gy, which is 95% of the dose prescription to PTV breast and 60 Gy to PTV boost

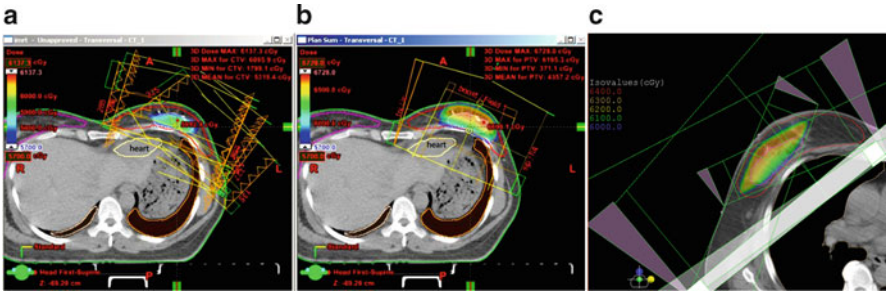

Fig. 19.3 Examples of total boost dose distribution for IMRT plan with concomitant boost (SIB) (**a**), 30° wedged standard plan plus electron boost (**b**), and 30° wedged standard plan plus photon boost (**c**). More conformed dose distribution is obtained for SIB with IMRT, while use of electron or photon beam can result in high radiation dose to the breast tissue

technique, the patients are treated with the combined plan at each fraction throughout the entire course of treatment (Fig. 19.2). SIB can be applied using electrons, photons, or intensity modulated radiotherapy (IMRT) [29–32] (Fig. 19.3). The treatment model used is 1.8–2.0 Gy to whole breast and 2.14–2.40 Gy to tumor bed in 25–28 fractions.

Although the use of a tumor bed boost is routine practice, there is no standard treatment delivery technique. Electrons, photons, and interstitial brachytherapy are the various treatment techniques to boost the tumor bed. Controversy exists regarding the optimal boost technique (electron vs. brachytherapy vs. photon), and their impact on local tumor control and cosmesis [33–38]. Each one has superiority over the others; therefore, a customized treatment technique is required for every case. Interstitial implantation has been widely used in the treatment of breast cancer as a boost or primary irradiation for partial radiotherapy. The widely accepted risk factors for indication to boost the tumor bed are a close or positive surgical margin, extensive intraductal component, grade 3 tumors, tumors greater than 3 cm in diameter, and young age. The technique for performing breast implantation has been well described in the literature [34–37]. However, technical supplies and experience are necessary for brachytherapy. After the widespread availability of electron radiotherapy, the en face electron field is the most selected method to boost the tumor bed because of its outpatient setting and ease in setup [33]. But, high-energy electron beams that are required in deep-seated tumors raise the skin dose and increase the doses at underlying adjacent normal tissues offering the possibility of unwanted side effects. In contrast, brachytherapy is preferable in some anatomic situations, particularly in cases of a deep-seated tumor bed in large breasts [36, 38]. Photon beam boosts have the advantage of giving a required dose to deep-seated tumors in which electron beams are unnecessary, although excessive dose to nontarget breast tissue is unavoidable. An analysis of the European Organisation for Research and Treatment of Cancer 22881–10882 boost vs. no boost trial data by Poortmans et al. revealed that there was no difference in local recurrence rates between photon and electron boosts [16].

Another approach to boost tumor bed is intraoperative external radiotherapy (IOERT) in which electrons or low-energy x-rays generating mobile devices are used. In an intraoperative session, radiotherapy is given with a single fraction. In this technique, direct tumor bed irradiation, homogenous dose distribution, and sparing critical adjacent structures are possible. Prevention of accelerated repopulation with very short irradiation time, as well as treatment of the target during surgery with intact vascularization, make oxygenation of the environment theoretical radiobiological advantages of IOERT [39]. The published trials of IOERT as a boost treatment reported similar local control in comparison with other boost techniques and acceptable toxicity rates [40, 41].

Primary goals of breast-conserving therapy are local control and cosmesis and are similar with brachytherapy, photons, and electrons, if patient selection is appropriate [16, 33, 42]. The different boost techniques should be used according to the depth and location of the tumor bed.

19.2 Boost Techniques

At the beginning, patients who are undergoing breast radiotherapy are positioned in a custom-formed vacuum cushion or breast board with the arm of the affected side raised above the head. For the boost treatment, CTV- boost and normal structures

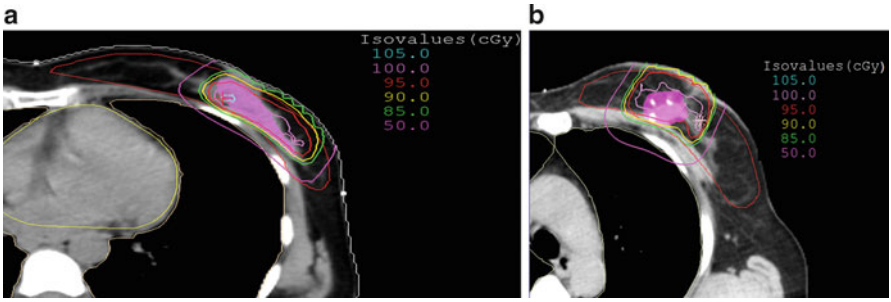

Fig. 19.4 Dose distributions of 9 MeV for shallow (**a**), and 15 MeV for deep seated (**b**) tumor beds in electron boost treatment

are delineated based on the CT data on the workstation of treatment planning system. Planning target volume (PTV) is defined with a 0.5–1 cm margin to CTV-boost. Tumor bed delineation is performed on the initial whole breast planning CT scan. If target volume change is expected, such as in seroma volume, repeat planning CT is necessary.

19.2.1 Electron Boost Technique

Usually a single perpendicular "en face" field to tumor volume with a 2–3 cm margin from every dimension is used for the electron boost. Selection of the electron energy (6–22 MeV) and the field size is based upon the depth and volume of the target. The 90% prescription isodose line is limited to the pectoral fascia to avoid the underlying organs at risk (OAR), such as the lung and heart (Fig. 19.4). For electron beam therapy, the skin surface overlying the treatment area should ideally be flat and free from irregularities such as the nipple and surgical scar. This could result in an uneven air gap, and corrections would need to be made to the dose distribution to account for the sloping surface [27].

The boost plans are generated for each patient using treatment planning software. For boost treatment, electron fields are based on the surgical clips at the time of excision and/or target volumes at CT slices. The beam orientation is based on the external contour to create an optimal en face beam. The beam energies are selected using 3D planning to obtain the optimal treatment volume coverage. All electron plans are normalized to the 90% isodose line. The plans are analyzed for dosimetric coverage of the PTV-boost via dose volume histograms.

In some situations with deep tumor locations and unsuitable body contour, electron beams are insufficient to wrap the tumor bed with prescribed dose. A repositioning technique called the lateral decubitus boost technique is performed to solve this problem [43, 44]. The patient is repositioned laterally toward the uninvolved breast which allows a decrease in depth of tumor bed and provides a flat

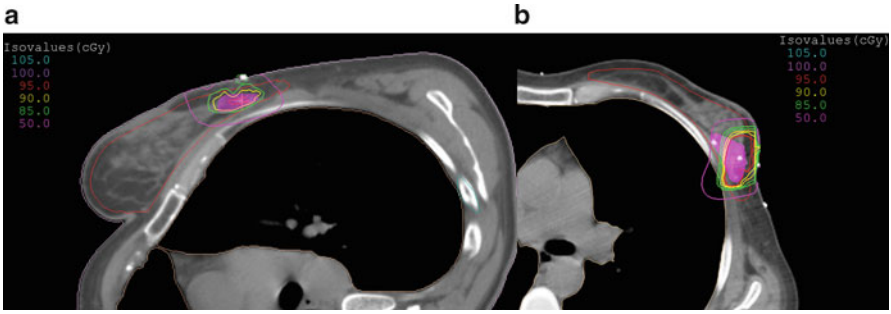

Fig. 19.5 A comparison of dose distribution in patient requiring lateral decubitus position (**a**) instead of supine position (**b**) because of unsuitable body contour

surface for optimum electron dosimetry (Fig. 19.5). On the other hand, it should be noted that combined isodose distribution of whole breast and boost irradiation could not be obtained from this technique.

19.2.2 Photon Boost Technique

In the photon boost technique, the dose to the tumor bed is delivered by using at least two or more photon beams. With the use of tangential or preferably noncoplanar beams, OARs must be avoided as much as possible. Beam directions, multileaf collimator settings, beam weights, and wedge angles are manually planned in such a way to cover the PTV with 90–95% isodose in three dimensions and to minimize the dose to OAR (Fig. 19.6).

19.2.3 Brachytherapy

Even though external beam therapy is currently used to boost the majority of patients treated with breast-conserving therapy, there are certain clinical, pathologic, or treatment-related situations where brachytherapy has been suggested as a more efficacious means of delivering a boost. These situations include: Patients with large breasts and/or deep-seated tumors where the integral dose with other boost techniques would be markedly greater than with brachytherapy (Fig. 19.7); and in patients with close, positive, or uncertain margins or those with an extensive intraductal component [45, 46]. Interstitial multicatheter breast brachytherapy has remained the most frequently applied technique for breast cancer [47]. The brachytherapy techniques have included mostly low-dose rate or high-dose rate Ir-192 implants. Although implantation can be done with local anesthesia, the interstitial administration is usually performed with the patient under general anesthesia. There are two ways of administering the dose. The first is the perioperative implant

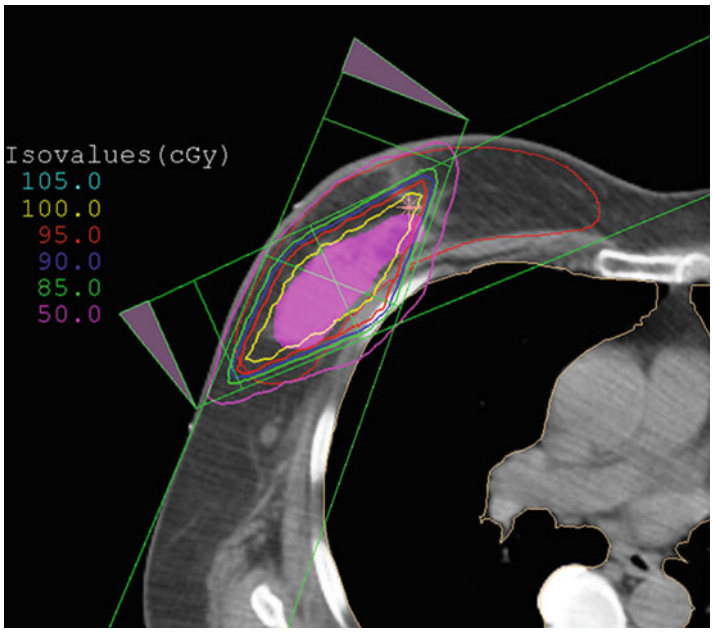

Fig. 19.6 Dose distributions in axial plane of deep seated tumor bed with photon beams with 45°-angle wedge filters. Isodose levels are shown at 105%, 100%, 95%, 90%, 85%, and 50%

procedure which is performed in conjunction with the main surgery of the primary tumor. Determination of the exact tumor bed thus proper implant placement requires interaction of surgeon and brachytherapist one-on-one, needs only one general anesthesia for two procedures, and decreased cost of the treatment are the advantages of this approach. However, in this procedure pathologic details such as status of the surgical margin should be obtained before planning and irradiation. The second is postoperative implantation, and is the procedure most often performed. This close cavity procedure is done after the completion of whole-breast irradiation.

Prior to application, the planning of the target volume to be implanted is performed under C-arm simulator control. The projection of implant area is drawn on the surface of the breast. Although it is feasible to perform the implantation using a free-hand technique, template-guided applications are strongly recommended [47].

A 2-cm margin around the lumpectomy cavity is utilized unless the skin surface or chest wall are limiting. The number of needles to be implanted is patient specific. A total dose of 10–20 Gy at 1–6 fractions, two fractions per day (with a minimal interfraction time interval of 6 h) are applied with a high-dose rate (HDR) remote afterloader. Brachytherapy can be delivered with a low-dose-rate (LDR), a pulsed-dose rate (PDR), and HDR radiation sources. A dose of 10–20 Gy is given to the target volume at 0.5 Gy/h (0.3–0.7 Gy/h) for LDR applications. A similar total dose is given as twice-daily fractions of 2–3 Gy for HDR.

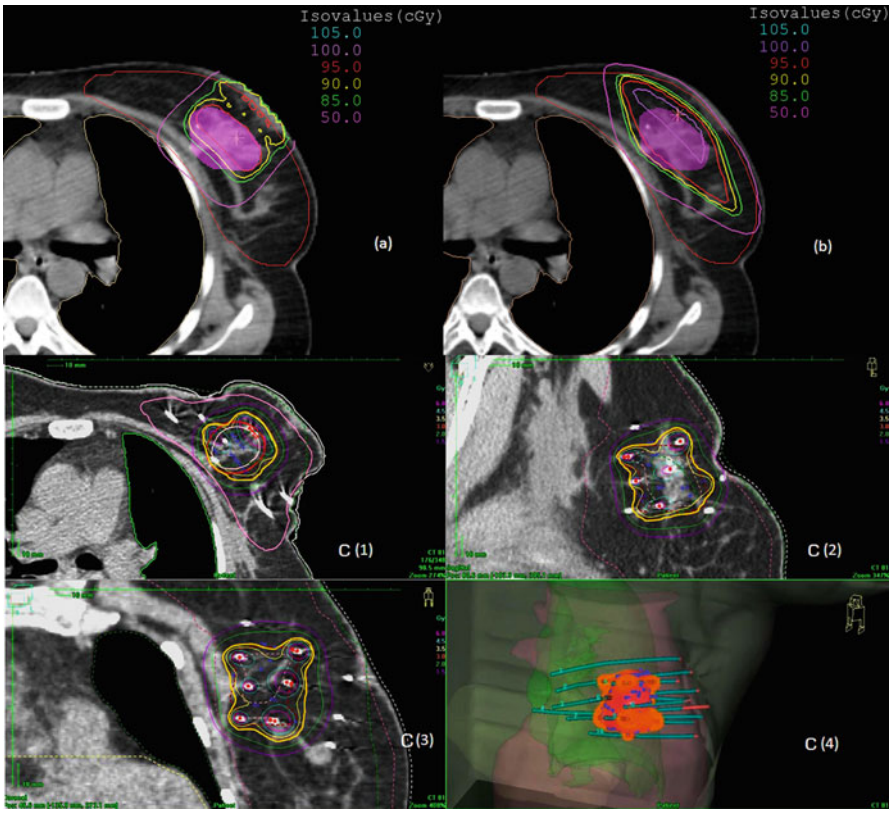

Fig. 19.7 Comparison of the isodose distributions of the boost treatment plans in the transverse section of a patient with left side breast cancer using an electron beam (**a**), photon beams (**b**), and brachytherapy (**c**1, axial view; **c**2, sagittal view; **c**3, coronal view; **c**4, 3D view). Isodose levels are shown at 105%, 100%, 95%, 90%, 85%, and 50% (**a**, **b**). Daily fraction dose is shown (**c**)

Rigid needles are passed through the breast with template guidance. After all the needles are applied, plastic catheters are inserted through them and then the needle guides are withdrawn progressively. Radiopaque buttons are put on the proximal and distal end of the plastic catheters at the skin surface for fixation. Excessive compression on the breast should be avoided.

Usually two planes of implantation are needed to compass the target volume. However, a single plane for flat, and multiple planes for large breasts are suitable. The implantation is preferably started at the deeper plane. The implant geometry should be planned according to the rules of the Paris System. The spaces are set 1.2–2.0 cm between the needles.

Following the application, treatment-planning CT images are obtained with 3–5 mm thickness slices for whole breast and 1–3 mm for tumor bed. These images are also used to confirm the postimplant adequate target volume coverage. The catheters and planes are identified and digitized from the CT images with a set of

radiopaque dummies. A 3D reconstruction of the implant is performed on the planning system. After loading of the dwell source positions in each catheter, the volume dose optimization is done. All catheters are removed after the completion of the boost treatment.

19.3 Conclusion

In summary, boosting the tumor bed in early-stage breast cancer is effective in improving local control rates and subsequently, survival. Accurate delineation of tumor bed is an important issue, and change in boost volume should be considered. Electrons, photons, interstitial brachytherapy, and IOERT are the various treatment techniques used to boost the tumor bed. The different boost techniques should be used according to the depth and location of the tumor bed. However, the combined dose distribution should be evaluated for external beam treatment in terms of hot or cold dose regions. For brachytherapy, it is not possible to obtain the combined dose distribution, regions of high-dose external beam therapy should be considered. Furthermore, the new approach of SIB has some radiobiological and practical advantages over the conventional boost technique.

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Chapter 20
Quality Assurance

Meltem Atamel and Ertugrul Erturk

20.1 Introduction

Treatment planning systems are computer software trying to predict the real dose absorbed by the patient using experimental data. Technologic progress in recent years has made it possible to obtain planning techniques for high-dose gradients by using inverse planning techniques. Obtained doses from three dimensional conformal radiotherapy (3D-CRT) can be validated by calculation of doses at different points. However, more knowledge and skill are expected from intensity modulated radiotherapy (IMRT) planning systems. Unlike the 3D-CRT, the IMRT field is made of many small, asymmetrical and irregular subfields. Subfields correctively obtained as a result of leaf positions are more important than in 3D-CRT. As subfields are created with multileaf collimators, naturally, accuracy of the multileaf collimator becomes more important. Multileaf collimator positioning error in IMRT causes worse results than in 3D-CRT. Furthermore, leaf transmission, output linearity, and similar data affect IMRT results much more than 3D-CRT results. Therefore, medical physicists must check the reality of results predicted by the planning system and each clinic must have its own specific quality assurance (QA) procedure [1].

20.2 Quality Assurance in Breast IMRT

The difference between the radiated and planned dose is obtained from QA programs. QA consists of clusters that overlap or intersect under hierarchy. Practical application of QA built over correct logical elements provides both reliable treatment opportunity

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Table 20.1 Summary of recommendations for linear accelerators in the AAPMTG 142 Report

Dosimetry	Limit	Frequency
X-ray output constancy	3%	Daily
X-ray output constancy	2%	Monthly
X-ray output calibration	1%	Annually
Dose rate output constancy	2%	Monthly
Photon beam profile constancy	1%	Monthly
X-ray flatness and symmetry change from baseline	1%	Annually
X-ray beam quality	±1 from baseline	Annually
X-ray monitor unit linearity	±5% (2–4 MU), ±2% ≥5 MU	Annually
X-ray output constancy vs. dose rate	±2% from baseline	Annually
X-ray output constancy vs. gantry angle	±1% from baseline	Annually
Laser localization	1.5 mm	Daily
Distance indicator at isocenter	2 mm	Daily
Collimator size indicator	2 mm	Daily
Light/radiation field coincidence	2 mm or 1% on a side	Monthly
Light/radiation field coincidence (asymmetric)	1 mm or 1% on a side	Monthly
Gantry/collimator angle indicators	1^0	Monthly
Gantry/collimator/couch rotation isocenter	±1 mm from baseline	Annually
Jaw position indicator (symmetric)	2 mm	Monthly
Jaw position indicator (asymmetric)	1 mm	Monthly
Cross-hair centering (walkout)	1 mm	Monthly
Treatment couch position indicators	2 mm/1.0^0	Monthly
Localizing lasers	1 mm	Monthly

and a saving of time. In general, QA can be examined under two topics. The first of these is machine QA and the other is patient-specific QA. Performing machine QA by a physicist on a routine basis directly affects the results of patient-specific QA within tolerance limits. Thus, errors in patient-specific QA can be reduced to a minimum. Because of this perspective, QA approaches in breast IMRT will be from general to specific. The concept of QA in breast IMRT is the application of patient-specific QA of a patient in the third even fourth degree for a specific region. Dose accuracy detection with QA at the end of the breast IMRT requires more than just two-dimensional (2D) and three-dimensional (3D) dose analysis. For the correct IMRT QA, an optimal device QA and treatment planning system should be made. In this way, defects in breast IMRT QA can be reduced to the lowest level and reasons can be understandable. In the case of a misplaced leaf, QA cannot be expected to give good results in a linear accelerator. However, if a clinic does not check the accuracy of leaf movements, errors can occur making precise predictions difficult [2–7].

The lineal accelerator (LINAC), which will be used for IMRT applications must have the essential sensitivity. The basis for this sensitivity includes QA programs, output, field size, gantry angle, collimator angle, gantry rotation axis stability, and leaf position controls and these must be kept within specified limits for IMRT that are provided by the international organization AAPM TG and ESTRO. Tables 20.1 and 20.2 are the summaries of LINAC and MLC QA which are adapted from the American Association of Physicists in Medicine Task Group (AAPM TG) 142 report [7].

Table 20.2 A summary of recommendations for multileaf collimator in the AAPMTG 142 Report

MLC	Tolerance	Frequency
Quantitative test (matched segments, picket fence)	Visual inspection	Weekly
Travel speed	Loss of leaf speed >0.5 cm/s	Monthly
Leaf position accuracy	1 mm	Monthly
MLC transmission	±0.5% from baseline	Annually
Leaf position repeatability	±1.0 mm	Annually
MLC spoke shot	≤1.0 mm radius	Annually
Coincidence of light field and X-ray field	±2.0 mm	Annually
Segmental IMRT test	<0.35 cm max. Error Root Mean Square (RMS), 95% of error counts <0.35 cm	Annually
Moving window IMRT	<0.35 cm max. Error RMS, 95% of error counts <0.35 cm	Annually

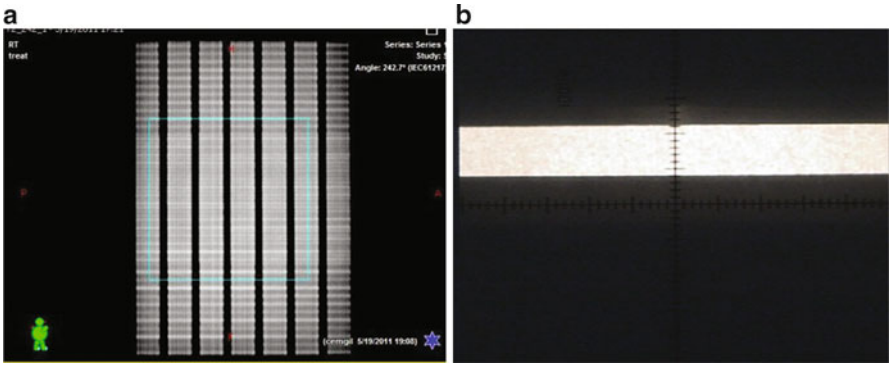

Fig. 20.1 **a** Picket fence test. **b** A frame from multileaf collimator motion video

The most popular Multi Leaf Collimator (MLC) positioning test is the "picket fence." The purpose of this test is to inspect leaf position according to the other leafs as shown in Figure 20.1a. The picket fence test has some variations. An alternative method to investigate MLC position and speed can be detected by using a commercial video camera. Motion of MLC can be recorded on film and can be investigated with various programs. As frames of video are a time indicator, it is possible to measure the speed of the MLC leaf and compare the position of each leaf according to the others [8–12].

If these basic requirements are provided, the causes of errors in QA can be understood better. Then, the treatment planning systems are programs that predict dose accurately under predefined conditions.

20.3 Patient-Specific Quality Assurance in Breast IMRT

Considering the anatomic structure and radiation interactions, the breast cannot be easily fixable in its placement with a target volume in the build-up zone and having neighboring organs such as the lungs and heart with different densities. Therefore, QA must consider these features.

20.3.1 Ion Chamber-Based Quality Assurance Methods

The basic approach in a patient-specific QA procedure in IMRT is to measure the absorbed dose using an ion chamber. As a result of the achievability and the availably of the equipment, this is the basic QA method. It is possible QA with an ion chamber and slab water equivalent phantom in the absence of special QA phantoms designed for IMRT. QA with large volume ion chamber and slab phantom requires more effort and attention regardless to QA by using phantoms which are specifically developed for IMRT. Even after these efforts, results may not be satisfactory, thus, the usability of this approach is limited. IMRT is a treatment with steep dose gradients. Detectors, which have high spatial resolution, are required in these steep dose gradient regions. Because of this requirement, an ion chamber with a small radius to a smaller active volume is needed. Ion chambers used in absolute dosimetry must be able to make correct readings even at the smallest subfield. On the other hand, decrease in volume will result with loss in dose response and make the signal-to-noise ratio an issue.

Measurements in high dose gradient regions as shown in Figure 20.2 will probably result with unexpected differences between planned and measured doses. This situation inserts another uncertain factor into the QA mechanism. In the case of a fail in QA, this uncertainty causes difficulties in the prediction of the error. Furthermore, errors resulting from the inability of the detector in steep dose gradient regions might be regarded as inability of the treatment planning system.

The workflow in an ion chamber-based QA is as follows:

1. Make a combination of phantom
   a. Do not place the ion chamber in the buildup region
   b. Put sufficient phantom between detector and coach for back scattering
   c. Put phantom combination to CT coach properly for taking scan
2. Obtain CT scan of the phantom
   a. Put marker on the phantom according to lasers or, if they already exist, arrange phantom according to lasers
   b. To avoid the artifacts during CT scan do not place detector in phantom
   c. Leave detector hole empty or use proper sticks

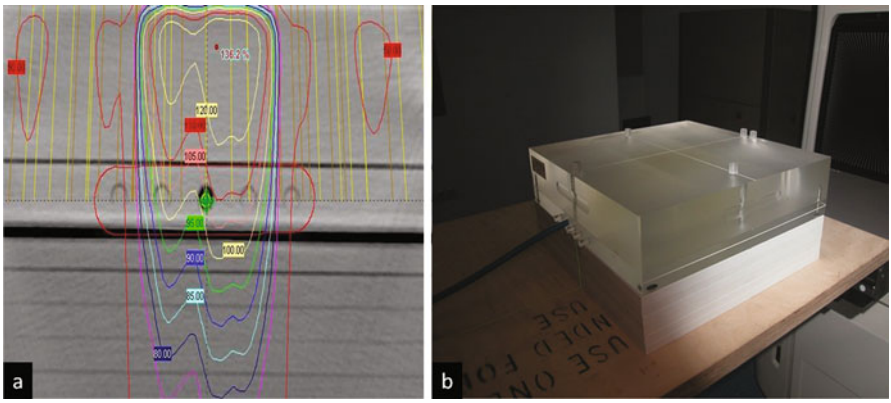

Fig. 20.2 **a** An ion chamber in high dose gradient region. **b** An ion chamber and a special phantom for IMRT QA

3. Transfer CT data to treatment planning system
    a. Create the plan
    b. Define planning target volume (PTV) at the active volume of the detector
    c. If the hole is empty set the PTV HU to zero
    d. Transfer IMRT plan to phantom, set the gantry and the collimator angles to zero
    e. Check the detectors to see if they are in high dose gradient region or low dose region
    f. Control the dose change in PTV volume
    g. Find the mean PTV dose
4. Irradiate the phantom
    a. Set the phantom in LINAC according to step 2a
    b. Check the laser and other equipment (i.e., Source Skin Distance (SSD), etc.)
    c. Put the detector into the hole and repeat step 4 at least two times for different points.

The number of measurements increases the reliability of PLAN but decreases the applicability of QA program, if there exists only one detector and a single-channel electrometer in the clinic. The difference between expected and measured dose must be within 3%.

A high dose gradient is observed and expected near the heart and lung. The breast is usually irradiated in tangential form and treatment planning algorithms include corrections for tangential irradiation. On the other hand, when suggested irradiation conditions are taken into account, the detector is beyond the build-up region because the gantry angle is at zero degrees and the field is orthogonal to the surface of the phantom, dose calculation for QA is not tangential. The irradiated structure is a semiinfinite medium instead of a body with different densities, concavities, and convex. These difficulties must be taken into account in clinical practice. Cylindrical phantoms may be used for testing tangential irradiation performance and inhomogeneity phantoms may be used for inhomogeneity correction performance of algorithms [4, 13].

20.3.2 Two-Dimensional Measurement Systems

Development in IMRT is accompanied by development in dosimetric systems. Currently, gamma analysis and distance to agreement methods are the most widely used methods for determining the accuracy of dose distribution obtained from the treatment planning system. These are the 2D analysis methods that examine the relationship between dose and ranges. It is very difficult to perform these two analysis methods with a single ionization chamber and solid phantom assembly. To use these analysis methods, 2D measurement systems are needed. Two-dimensional measurement systems can be grouped under three main topics: 2D diode or ion chambers, the use of electronic portal imaging devices (EPID) as a detector, and films. A 2D ionization chamber and diode detectors consist of many detectors which are placed on a matrix with a certain number of intervals. The measurement software offers different analysis opportunities to the user. Portal imaging devices act similarly to the dosimetry equipment, and they are part of the LINACs. Portal imaging devices in LINACs with software support become effectively used in QA for a dosimetric system in IMRT. Another type of 2D dose measurement system is film. As mentioned before, 2D ion chambers are made by detectors placed on a matrix at certain intervals. This structure brings the concept of a resolution of 2D detectors. Dose behavior is considered linear between two detectors. Also, a similar situation exists in portal dosimetry devices because they have certain resolutions. However, the film differs from the detectors with granular structure and almost has an infinite resolution. Depending on the developments in radiochromic film technology, and with the contribution of homemade dosimetry measuring, the popularity of films has increased. A variety of commercial software for analysis, as well as some scientific software used in analysis with film, has attracted the attention of curious users.

20.3.3 Two-Dimensional Detectors

As in the IMRT QA with an ion chamber, some 2D detectors combine solid phantoms. A combination of detector and phantom is illustrated in Figure 20.3. The QA flow chart for 2D detectors is similar to the ionization chambers, and the only difference is that the dose map plane is examined instead of the mean dose value. The combination of phantom and detector are reestablished in LINAC and then irradiated. As a result of irradiation, a dose map is composed in the detector plane. Exported dose maps from treatment planning systems are compared with the obtained dose maps after irradiation using the appropriate software. As a result of comparison, gamma analysis and/or distance to agreement value is examined.

Some 2D measurement systems do not require the use of CT and can be used in combination with phantoms as in other systems. The plan is transferred onto a virtual water phantom and the dose plane at the depth projectile in the detector's active plane is then exported for examination. Similarly to other detectors, the

Fig. 20.3 Combination of array and phantom

irradiated plane must have the same depth as the exported plane. With or without the need of CT, these detectors can be mounted to gantry heads as shown in Figure 20.4.

20.3.4 Quality Assurance With the Electronic Portal Imaging Device

Another effective measurement system for QA is an EPID mounted on LINAC. The use of EPID for relative dosimetry reduces the time spent on QA for IMRT. With an effective database management, acquired images can be directly compared with the data obtained from the treatment planning system and patient-specific data can also be saved for future use. EPID in IMRT QA methods is quite common and it is possible to perform analyses as in the other 2D QA methods, and gamma and distance to agreement analysis are possible with EPID electronic portal dosimeter (Figs. 20.5 and 20.6).

20.3.5 Quality Assurance With Films and Miscellaneous Systems

There are different types of radiation detection systems for IMRT QA, such as radiographic film, radiochromic film, thermoluminesance dosimetry (TLD), different types phantoms, gel dosimetry, or other types of 3D dosimetric systems.

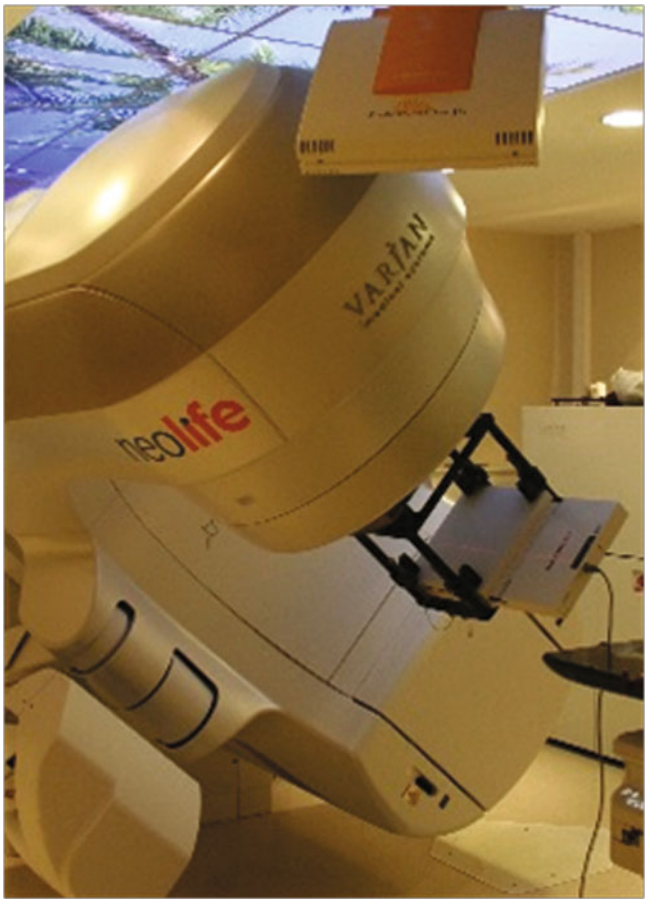

Fig. 20.4 Gantry mounted array

Films and TLDs are the most common miscellaneous measurement systems in radiotherapy. Both film and TLD chips can be used as planar 2D detectors with suitable phantoms. Like other 2D detectors for gamma analysis, distance to agreement analysis with films is also possible. Irradiated film is scanned with a suitable scanner, and with this process it becomes digital. Digitalized film can be analyzed with a commercial film analysis program or scientific software.

Films can be used in vivo dosimeter as TLD chips. In breast treatment, the target is close to the skin and it is hard to mobilize the breast. This situation raises the question whether the part of the target close to the skin is irradiated properly or not. Obtaining a good plan using a flash region in IMRT plan is suggested in ICRU 83 for adequate irradiation. Also, films can be used to validate repeatability of the treatment. It is also possible to check dose of incision scar.

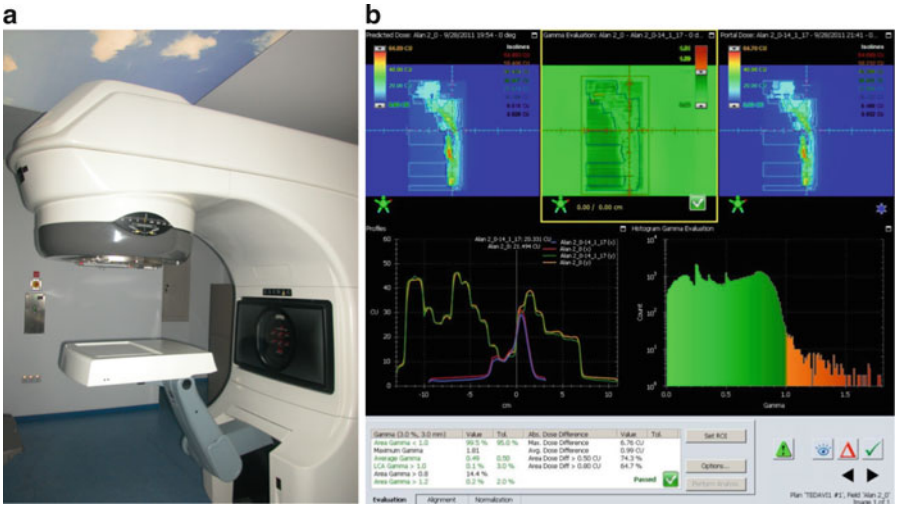

Fig. 20.5 **a** Electronic portal imaging device (EPID); **b** a sample of EPID dosimetry

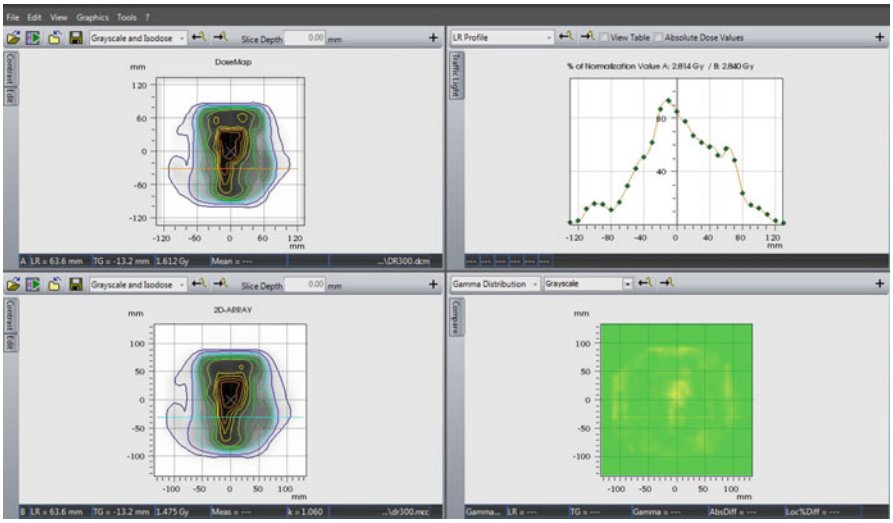

Fig. 20.6 A screen shot of gamma analysis report of a 2D array

20.4 Evaluation of Two-Dimensional Dosimetry Analyses

Distances to agreement and gamma analysis are the most common quantitative dose map comparison methods.

20.4.1 Distance to Agreement

(x_r, y_r) is the point on the measurement plane, where dose D_r is read. If dose D_c at (x_c, y_c), which is corresponding to the point (x_r, y_r), on calculated dose is in the acceptable interval $d\%$, then point is said to be acceptable. If D_c is not in the interval, then the algorithm seeks to find a point ($x1_c$, $y1_c$), where dose is equal to D_r, in the radius as defined as distance to agreement. So, if the user sets the distance to agreement value to 3 mm, the system tries to find a point with dose D_r in this radius. If there are two points with a dose higher than D_r and less than D_r in this circle, then it is said that there is at least one point with dose D_r in this circle [14, 15].

20.4.2 Gamma Analysis

(x_r, y_r) is the dose measurement point and $\gamma(x_r, y_r)$ is the gamma value of this point in the reference image. This value is

$$\gamma(x_r, y_r) = \min_{x_c/y_c}\{\Gamma_r(x_c, y_c, D_c)\} \tag{1}$$

where $\Gamma_r(x_c, y_c, D_c)$ is gamma value of point x_c, y_c on the calculated image according to point x_r, y_r on the reference image and equal to

$$\Gamma_r(x_c, y_c, D_c) = \sqrt{\frac{\Delta r^2}{\Delta {d_{max}}^2} + \frac{\Delta D^2}{\Delta {D_{max}}^2}} \tag{2}$$

where Δr is the distance between two reference points

$$\Delta r = |\overrightarrow{r_c} - \overrightarrow{r_r}| = (x_c - x_r)^2 + (y_c - y_r)^2 \tag{3}$$

and ΔD is the dose difference between two points

$$\Delta D = D_c(\overrightarrow{r_c}) - D_r(\overrightarrow{r_r}) \tag{4}$$

$r_r = (x_r, y_r)$ is the position in the reference dose distribution, $r_c = (x_c, y_c)$ is the position in the calculated dose distribution, ΔD_{max} is the dose tolerance (i.e., 3%), Δd_{max} is the space tolerance (i.e., 3 mm).

If (x_r, y_r) value is less than or equal to 1, then the point (x_r, y_r) is accepted as a passed point. If the ratio of the total number of passed point ratios to total number point is greater than 95%, then analysis is accepted as passed [3, 15].

The passing rate of the analysis is expected to be 100% in ideal cases, but in practice this may not be achieved. Medical physicists must investigate failed points. After analysis, the points that cannot pass must be searched and compatibility must

be checked because this point can occur in the lung, heart, or anywhere in the body except the critical organs. Analysis results should be evaluated clinically.

If an error is observed at the edge of the collimators which are parallel to the MLC motion direction, the error is usually caused by modeling of field size in the treatment planning system. During treatment, some leaves stay in the field without moving for a long time in respect to the beam time. In such cases, if the leaf transmission value is defined improperly in the treatment planning system, failed points are observed in low dose regions. This failure is an indicator of wrong leaf transmission value insertion.

20.5 Conclusion

Heartbreaking results of IMRT applications in the news prove the importance of QA. Obviously, there is no perfect system and for this reason, the desired treatment may not be given. Quality control is in effect from the beginning of system installation to the end of patient treatment. Measurements regarding LINAC should be made correctly and must be installed correctly in the treatment planning system. As in every process, this process must also be checked. The QA program for the LINAC should be applied in a sustainable way. After the approval of device suitability, it is still important to perform QA to avoid the errors that may occur. QA for patients gives feedback about the status of the system at the same. Different software can offer more than one analysis method, and the job of a medical physicist is not to search for the analysis methods where a plan exists, but to examine the analysis methods that fail.

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Chapter 21
Partial Breast Irradiation

Ilknur Birkay Gorkem

21.1 Introduction

There have been dramatic changes in the treatment of early-stage breast cancer during the last century. Quadrantectomies and even lumpectomy operations have replaced radical mastectomy procedures which were very popular at the beginning of the century. Breast-conserving surgery (BCS) began in the beginning of the 1970s in Europe and the United States. Based on the results of numerous randomized trials with follow-up periods longer than 20 years, BCS followed by radiation therapy (RT) is recommended as a standard treatment for selected patients with early stage breast cancer [1–6]. Numerous prospective randomized trials were published in the last 30 years proving that in selected cases, BCS followed by RT presents equivalent results with mastectomy using local recurrence and overall survival ratios as a reference [1–6]. Along with surgical advancements, irradiation protocols were updated and irradiation following BCS became the standard treatment modality [6]. In all these studies, RT was delivered as whole-breast irradiation (WBI). Because there has not been a long-term, well-controlled prospective randomized trial comparing WBI with partial breast irradiation (PBI), it is still too early to tell whether PBI can replace WBI in selected cases in the near future.

21.2 Rationale of Partial Breast Irradiation

After BCS and whole-breast RT, most of ipsilateral breast tumor recurrences (IBTR) occur in the primary tumor cavity [5, 7–11] and can be classified into two main categories; true recurrences and elsewhere recurrences. True recurrences

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occur at the excision cavities and at boost areas, while elsewhere recurrences occur a couple of centimeters from the primary tumor site and are defined as second primary breast cancer [12]. In various studies, true recurrence rates range from 44% to 86%, where elsewhere recurrence rates range from 0.9% to 6% with an average of 3% [5, 7–11]. An update of The National Surgical Adjuvant Breast and Bowel Project B-06 trial, in which 1,039 patients were treated with lumpectomy, it was reported through follow-up that 75% of local recurrences occurred at or near the lumpectomy site and that RT was irrelevant to the findings [4]. Freedman et al. reported on IBTR following BCS and WBI in 1,990 for women with stages 0-II breast cancer with a median follow-up period of 6.7 years. They classified recurrences according to their location. The 15-year actuarial rate of a true/marginal recurrence was 7% compared with an elsewhere recurrence rate of 6% and contralateral breast cancer rate 13% [13].

The likelihood of the presence of a multifocal or multicentric focus, along with an index invasive primary tumor is an important indicative for a local recurrence. The ratios of multicentricity and multifocality can be derived from the histopathologic studies from the past or from mammograms and/or more specifically, from current magnetic resonance imaging (MRI) studies [14].

In a study by Holland et al., 282 mastectomy specimens from women with localized T1-T2 tumors were studied with a combination of radiologic and pathologic techniques, and the tumor distribution was mapped in relation to index tumor [15]. The authors found that when the largest diameter of the index tumor was 2 cm or smaller, the likelihood of finding a focus of residual in situ or invasive carcinoma further than 2 cm from the primary tumor was about 28%. Does this mean that 28% of patients treated with PBI up to 2 cm from the lumpectomy cavity are at risk for breast failure? This is possible; however, the clinical data from the initial studies of PBI do not support this. Additionally, as almost all of these large tumors were detected only by physical examination, many clinical investigators suggest that the data from the Holland et al. study are not applicable to present-day smaller, mammographically detected tumors. Holland et al. also showed that the likelihood of finding residual tumors distant from the index invasive primary tumor was higher in the case of primary tumors with an extensive intraductal component (EIC) [15]. Forty-four percent of patients with EIC had residual intraductal carcinoma, compared with only 3% for patients without an EIC [15].

MRI has been introduced in preoperative staging of the breast in women with newly diagnosed breast cancer over past two decades. It can detect additional foci of cancer that are occult on conventional imaging. The diagnostic value of MRI is significantly prominent, particularly with younger age and dense breasts. The median detection increase using MRI has been estimated to add 16% over standard radiologic examinations and mammographic exams in numerous nonrandomized trials and meta-analysis [16–21]. In those trials, additional detection rates using MRI were 3.2–27.8% for multifocality and 5.2–14.6% for multicentricity. Women with breast cancer can currently be diagnosed at earlier stages and with smaller tumors. Occult foci away from index invasive tumor can be detected using MRI particularly in younger patients with dense breast tissues (Fig. 21.1).

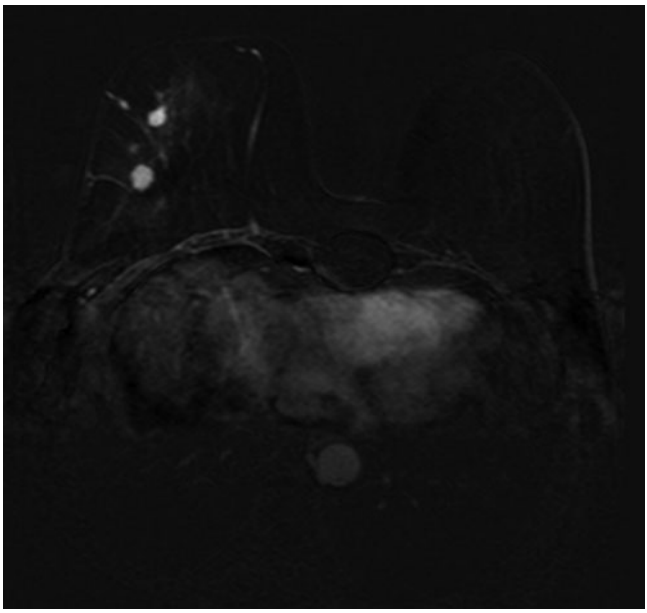

Fig. 21.1 A 32-year-old female patient with breast carcinoma, MR image shows occult foci away from index invasive tumor

Anderson et al. analyzed the prognostic significance of IBTR. They studied 3,799 women who were randomly assigned to five Adjuvant Breast and Bowel Project protocols of node-negative disease (i.e., B-13, B-14, B-19, B-20, and B-23) and were treated with lumpectomy and WBI with or without adjuvant systemic therapy [22]. As of March 2006, 342 of the 3,799 patients (9%) developed IBTR. Of the 342 IBTR, 127 (37.1%) occurred within 5 years, and 233 (68.1%) occurred within 10 years of the initial surgery. Young age ($p < 0.000$), race ($p = 0.04$), pathologic tumor size ($p < 0.003$), and adjuvant therapy ($p < 0.0001$) were significant predictors of IBTR. IBTR had a negative effect on 5-year distant disease-free survival and overall survival (OS). After IBTR was detected the survival rates were calculated as 66.9% and 76.6%, respectively. IBTR had a greater impact on mortality in estrogen receptor (ER)-negative than ER-positive patients (Hazard ratio (HR): 4.49 [95% CI; range, 3.29–6.19]).

Courdi et al. investigated the prognostic significance of early vs. late local recurrences (LLRs) in women who were treated by BCS followed by RT for breast carcinoma [23]. One hundred eighty of the 2,008 patients (8.9%) developed IBTR. Of the 180 who developed IBTR, 46 (25.5%) occurred within 36 months after treatment, called early local recurrence (ELR), and 90 (74.5%) occurred as LLRs after 60 months. Large tumor size ($p < 0.043$), a higher tumor grade ($p < 0.0002$), and negative hormone receptor tumors ($p < 0.0001$) were associated with ELR. The 5- and 10-year specific survival or patients with late local recurrence (LLR) were $88.1 \pm 2.4\%$ and $76.7 \pm 3.3\%$, respectively. Multivariate analysis of specific survival using the Cox model showed that only the timing of local recurrence and lymph node status retained an independent prognostic effect on specific survival.

Specific survival was 55.8% for patients with ELR and 79.5% for patients with LLR. Nevertheless, many clinical investigators have reported that elsewhere recurrences are associated with better prognosis than index breast carcinomas [11, 24]. Faverly and colleagues reported on a group of patients who would be very unlikely to have residual tumor foci further than 2 cm from the index tumor. These investigators confirmed that of women with a radiographic absence of calcifications or tumor density beyond the edge of the index tumor and 1 cm microscopically tumor-free margin, only 11% of patients will have residual carcinoma further than 2 cm from the primary tumor [25].

PBI is the irradiation of only the excision area and surrounding tissue with a 1–2 cm of a security margin, instead of the whole breast. The objective is to apply RT to the area with a higher recurrence risk while sparing the normal breast tissue with lower recurrence risk and completing the therapy in 4–5 days instead of the classic 5–6 weeks. In standard breast irradiation, 50 Gy is delivered to the whole breast in 25 days with 2 Gy of the daily fractional dose, this is followed by irradiating the excision cavity daily with 2 Gy of electron power (adjusting for the depth of the excision cavity) for 5 days, completing it to 10 Gy of boost dose, thus reaching a total dose of 60 Gy.

In PBI, therapy is completed within 4–5 days due to the high daily fractional doses. For working class women with busy schedules, it is a challenge to attend therapy for 25–30 days. Furthermore, there are a great number of patients who must complete their treatments without adjuvant RT due to the lack of suitable RT facilities in their local area. Low performance rates as a result of age and accompanying diseases also present a great obstacle for adjuvant RT, in addition to growing costs. In the late 1990s, it was reported that due to one or more of the reasons listed above, nearly 20% of all patients with partial mastectomies did not receive any RT at all [26]. The potential advantage of accelerated partial breast irradiation (APBI) is its ability to decrease the overall treatment time with a decrease in the volume of tissue treated, improvement of breast cosmesis, and a decrease in the acute and chronic toxicity to normal tissues, particularly the lung and heart. It can also be a good alternative to mastectomy for women with ipsilateral breast recurrence.

The current regimen typically delivers 34 Gy in 10 fractions with two fractions per day. The biologically equivalent dose (BED) for these fractions at 2 Gy per day is 45–50 Gy [27]. These calculations assume an α-to-β ratio of 10 Gy (for tumor control) using modifications of the linear quadratic model. For an α-to-β ratio of 4 Gy (for tumor control), the BED was calculated to be 63–76 Gy compared with 75 Gy for 50 Gy in 25 fractions and 90 Gy for 60 Gy in 30 fractions [27].

21.3 Patient Selection Criteria for Accelerated Partial Breast Irradiation

After the Christie Hospital experience of 1982, single-centered APBI studies became popular and there has been an increase in the number of studies. In some studies, due to the lack of patient selection criteria, a high number of local recurrences were observed and therefore patient selection criteria for APBI were established. Several centers pioneered the use of different APBI regimens for unselected patients in the 1980s and early 1990s [28–32]. However, in all these studies, results were poor with high local recurrence rates exceeding 1% per year (1.5–6.1%) and cumulative incidence. The high rates of local recurrence in the early APBI studies reflect inadequate patient selection criteria and/or suboptimal treatment technique and a lack of appropriate quality assurance procedures [33]. Hence, a large number of patients treated in those studies would not be considered eligible for breast-conserving therapy today. Thus, the results of the studies should not be used to underrate the APBI technique.

The American Society of Breast Surgeons has proposed eligibility criteria for APBI. The criteria include age over 50 years, invasive ductal cancer histology without an EIC, negative surgical margins, negative axillary nodes, and a tumor size less than 3 cm. Additionally, invasive lobular cancers are excluded and women with multicentric disease are not candidates for APBI [34].

Groupe European de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group has recommended guidelines on patient selection criteria for APBI [35]. The investigators determined three categories guiding patient selection for APBI: (1) A low-risk group for whom APBI outside the context of a clinical trial is an acceptable treatment option, including patient age of at minimum 50 years with unicentric, unifocal, p T1-2 ($\leq$3 cm) pN0, nonlobular invasive breast cancer without presence of an EIC and lymphovascular invasion (LVI) and negative surgical margins of at least 2 mm. (2) A high-risk group for whom APBI is considered contraindicated, including patient age of 40 years or less, having a positive surgical margin, multicentric or large tumor size (>3 cm), and/or EIC positive or LVI positive tumors, and/or four or more positive lymph nodes or unknown axillary status (pNx). (3) An intermediate-risk group for whom APBI is considered acceptable only in context of prospective clinical trials. Risk groups are listed Table 21.1.

American Society of Therapeutic Radiation Oncology also reported on patient selection criteria for APBI [36]. The task force proposed three patient groups: (1) A "suitable" group for whom APBI outside of a clinical trial is acceptable. (2) A "cautionary" group for whom caution and concern should be applied when considering APBI outside of a clinical trial. (3) An "unsuitable" group for whom APBI outside of a clinical trial is not considered.

Based on the controversial results of earlier studies, several investigators and groups designed APBI trial protocols incorporating stricter patient selection criteria including only low-risk early breast cancer and systematic quality assurance

Table 21.1 GEC-ESTRO recommendations on patient selection for APBI

Characteristic	Low-risk group	Intermediate-risk group	High-risk group
Patient age	<50 years	41–50 years	≤40 years
Histology	IDC	IDC, ILC	–
İLC	Not allowed	Allowed	–
Tumor size	p T1-2 (≤3 cm)	p T1-2 (≤3 cm)	p T2 (>3 cm), pT3-4
DCIS	Not allowed	Allowed	–
Associated LCIS	Allowed	Allowed	–
EIC	Not allowed	Not allowed	Present
LVI	Not allowed	Not allowed	Present
Surgical margin	Negative (≥2 mm)	Close (<2 mm)	Positive
Nodal status	pN0	pN1mi, pN1a (by ALND)	pNx, pN2a (4 or more)

procedures [37–39]. As a result, the outcomes of those studies have been improved considerably [37–41]. Long-term results of those trials proved similar efficacy of APBI in preventing local recurrence to those achieved in other breast-conserving studies using conventional WBI. It should be noted that a consequently low rate of local recurrence has been reported (less than 1% per year) [37, 38, 40, 42–49].

21.4 Partial Breast Irradiation Techniques

Several different treatment techniques have been developed for administering of APBI and are listed in Table 21.2. They each have their unique advantages and disadvantages. The goal of each technique is to comprehensively irradiate the target and to ensure homogeneous dose coverage, and to limit toxicity to healthy tissue.

21.4.1 Brachytherapy

In 1921, the English surgeon Sir Geoffrey Keynes used interstitial radium needles to treat primary breast tumors and the regional lymphatics [50]. In that technique, radioactive sources are placed within (interstitial brachytherapy), or very close to, the tumor bed (intracavitary brachytherapy). Brachytherapy has the main potential benefit of limiting toxicity to healthy tissue while delivering the maximum dose to the tissue at risk for disease.

21.4.1.1 Multicatheter Interstitial Brachytherapy

Multicatheter interstitial brachytherapy (MIB) is presently the most widely used technique. Generally, the radiation source is added to multiple catheters surrounding the tumor bed by automated afterloading technology for minimizes the health care

Table 21.2 Techniques for accelerated PBI

Brachytherapy
Multicatheter interstitial brachytherapy
Balloon intracavitary brachytherapy
External radiotherapy
Three-dimensional conformal radiotherapy
Intensity modulated radiation therapy
Intraoperative radiotherapy
Electron beam intraoperative radiotherapy
kV beam intraoperative radiotherapy

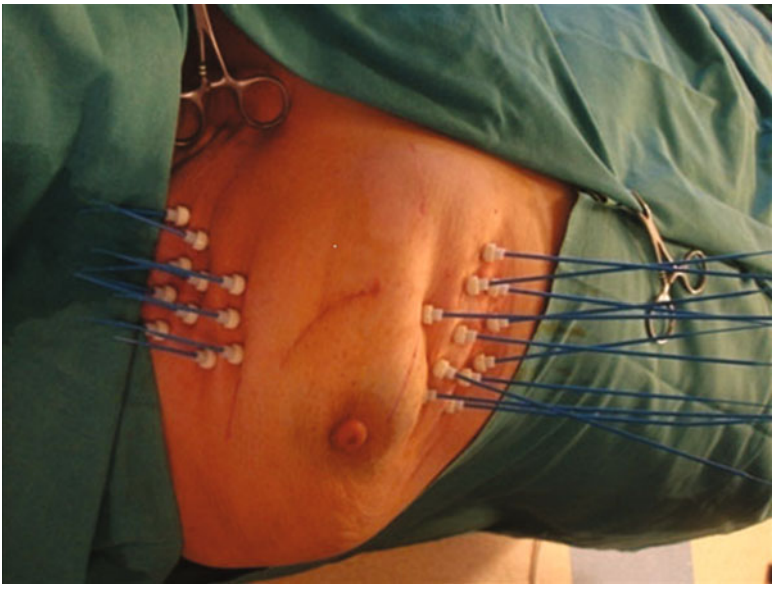

Fig. 21.2 External appearance of multicatheter interstitial brachytherapy

provider's potential radiation exposure. Brachytherapy can be performed with low dose rate (LDR) or high dose rate (HDR). LDR sources deliver 45–50 Gy over 3–5 days to the clinical target volume (at a rate of about 30–70 cGy per hour) and the patient remains hospitalized during this time. HDR irradiation is performed with the fractioned afterloading technique using HDR iridium-192 (e.g., 32 Gy in eight fractions with a 6 h interval or 30.1 Gy in seven fractions in two daily sessions) or as pulsed dose rate brachytherapy. Brachytherapy is an invasive thus painful procedure that requires extensive clinical experience in target volume definition, dosage, and fractionation. Therefore, it has a longer learning curve and also requires patient hospitalization and general anesthesia. Usually the implants are inserted in three places with a distance of 10–15 mm from each other to avoid hot and cold spots. Depending on the size and shape of the target, the implants require 14–20 catheters to ensure suitable dose coverage (Figs. 21.2 through 21.4).

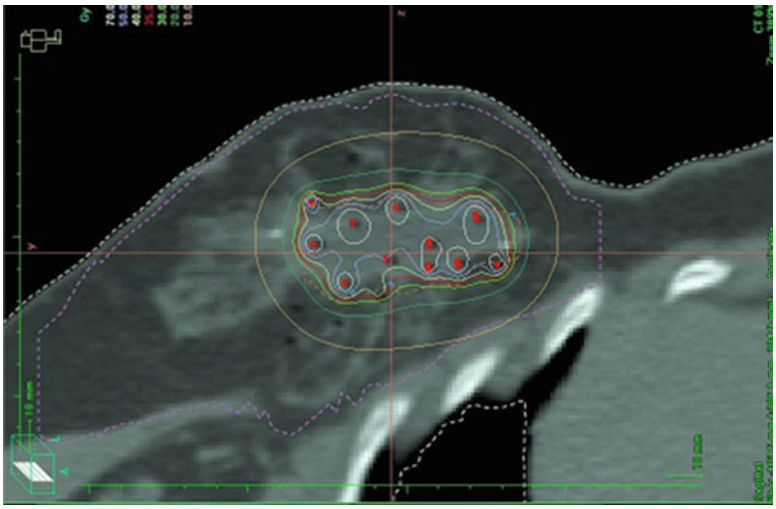

Fig. 21.3 Sagittal view of dosimetric target coverage. Nucletron Oncentra® Planning System. Sixteen implants were inserted in three plans with a distance of 12 mm. CTV is outlined in *red* (CTV defined as the lumpectomy cavity with 1.5 cm safety margin) and glandular breast tissue is outlined in *light pink*

The first study evaluating breast brachytherapy for unselected patients with breast cancer was performed at Guy's Hospital in London. Fentimen et al. reported a 37% local recurrence rate at 6 years [28]. The study had high local recurrence rates as a result of poor patient selection criteria, and having no quality assurance in either surgery or RT. A total of 27 patients were treated in the series with tumorectomy, and 56% of the patients had positive margins of resections. Tumorectomy was followed by LDR interstitial brachytherapy with iridium for a total dose of 55 Gy over 5 days. No increased rates of fibrosis on breast tissue were reported despite high doses. Parera et al. reported a pilot study from Ontario, Canada [51]. A total of 39 patients with clinical T1-T2 breast cancer were enrolled in the study. The first 13 patients had intraoperative implantation and the remaining 26 patients had outpatient postoperative implantation. HDR brachytherapy was given twice daily with at least a 6-h interval for a total dose of 37.2 Gy in 10 fractions over 5–7 days. Three patients had cellulites and four patients developed fat necrosis at the lumpectomy site. Patient-rated satisfaction for treatment was high. At a median follow-up of 91 months, the 5-year actuarial rate of ipsilateral breast recurrence was 16.2% [52]. Two of six ipsilateral recurrences occurred within the primary tumor site, which was the predominant pattern of recurrence. Telangiectasia was seen at 1.5% at dose points receiving 10 Gy or less, vs. 18% at dose points receiving more than 10 Gy ($p < 0.004$). Grade I or higher fibrosis occurred in 47.4% of patients with a 60-month follow-up and was significantly associated with a volume covered by 100% isodose [53]. In a study by Benitez et al., a total of 199 patients with stages I or II breast cancer were treated with lumpectomy followed by radiation restricted to the tumor bed using an interstitial

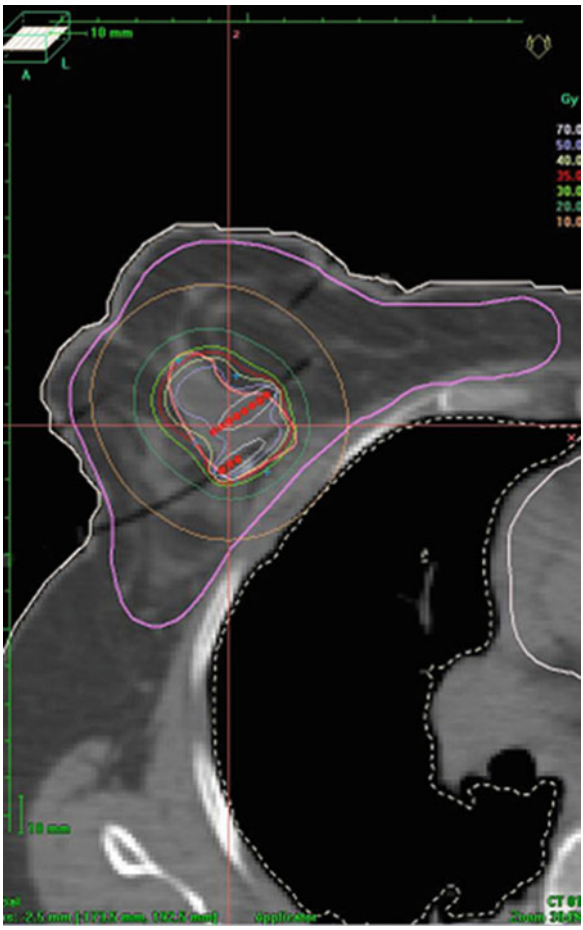

Fig. 21.4 Sagittal view of dosimetric target coverage. CTV is outlined in *red* and breast tissue is outlined in *light pink*. HDR irradiation was performed with the fractioned after-loading technique (35 Gy in 10 fractions with an 8-h interval in two daily fractions)

implant (delivered with either low-dose or HDR). Retrospective analyses were performed on early and late toxicities. Median follow-up was 5.7 years, and 54% of the patients had a follow-up period of 7 years. Fibrosis and fat necrosis were found in 26 of the 45 patients. The incidence of fat necrosis increased with time. More patients were found to have fat necrosis after 5 years. The majority of fat necrosis was asymptomatic (78%). According to the Harvard Criteria, good to excellent cosmetic results were observed in more than 90% of patients. A 5-year local recurrence rate was 1.2% [54]. The Radiation Therapy Oncology Group (RTOG) 9517 study reported a prospective phase I/II trial of APBI after lumpectomy in selected patients with breast cancer. Between August 1997 and March 2000, 100 women were enrolled in the study and 99 were evaluated. They were

treated with either LDR or HDR APBI. The median follow-up for all patients was 2.7 years (0.6–4.4 years). The rate of grade 3 or 4 early toxicity (erythema, edema, tenderness, pain, and infection) was 3% for the HDR groups, and 9% for the LDR groups. Late toxicities included skin thickening, fibrosis, breast tenderness, and telangiectasias. The rate of grade 3 toxicity was 18% for the LDR group and 4% for the HDR groups. No patient experienced grade 4 toxicity. In that study, at a median follow-up of 3.7 years, the breast recurrence rate was 3% [55].

21.4.1.2 Balloon Intracavitary Brachytherapy

Brachytherapy can be administeried with a balloon catheter. The introduction of the MammoSite® balloon catheter (Cytyc, Marlorough, MA) has provided an alternative to interstitial implants that decreases both the technical and application difficulties. The MammoSite breast brachytherapy applicator was developed to simplify the administration of the treatment. The advantage of this technique is its simple handling, which requires a short learning curve. The Food and Drug Administration approved the MammoSite balloon brachytherapy catheter in 2002. The balloon can be placed at the time of surgery (an open implant technique) or with the use of ultrasound guidance after lumpectomy (a closed technique). This technique is also invasive and requires training but results are less operator dependent. The MammoSite balloon catheter is composed of a 15-cm double lumen catheter that is 6 mm in diameter. The catheter is located centrally within a distally located balloon that is placed in the lumpectomy cavity and inflated with sterile saline solution. To accommodate the variation in lumpectomy cavity size, two balloon sizes are available. The sphere is inflatable to 4–5 or 5–6 cm in diameter. After inflation, balloon catheter placement is evaluated to ensure balloon symmetry and lumpectomy cavity conformance with the balloon surface [56]. Balloon surface and skin distance must be more than 5 mm. A catheter in which a balloon is filled with saline solution is inserted into the lumpectomy cavity to form a spatial geometry. Treatment planning is performed by using computed tomography (CT) imaging. The balloon surface and skin distance and the conformity of balloon surface and cavity are evaluated on CT images. Irradiation is performed with an iridium-192 source which is positioned at the center of balloon. The treatment is delivered in a spherical volume with a 10-mm safety margin. The treatment is delivered over 5 days with 8–10 fractions with a minimum 6-h interval between fractions for a total dose of 32–35 Gy using the high-dose technique.

Starting from late 2002, multicenter brachytherapy studies were done first in the United States and then in Europe. Keisch et al. published the initial clinical experience with the MammoSite® balloon applicator in women with early-stage breast cancer treated with breast-conserving therapy [57]. Women who were younger than 45 years with T1 invasive ductal carcinoma, pathologically node-negative disease, and no clinical evidence of distant metastatic disease were enrolled in the trial. Additionally, the edge of postsurgical cavity must be greater than or equal to 5 mm away from the skin surface. The total number patients entered

in the study was 54. Brachytherapy was not performed in 11 of the 54 patients. Investigators reported 88% good to excellent cosmesis at a median 2-year follow-up. The most common side effects were erythema, 57.4%; catheter site drainage, 51.9%; breast pain, 42.6%; ecchymosis, 31.5%; body pain, 22%; breast edema, 14.8%; dry desquamation, 13%; and seroma, 1.1%. Jennifer et al. reported the largest, mature, single-institution experience with the MammoSite brachytherapy applicator [58]. From May 2002 to March 2008, 111 women with early stage breast cancer were included in the analysis. At a median follow-up of 46 months, nine patients had experienced disease recurrence, including seven within the ipsilateral breast. Three of the recurrences were regarded as a tumor bed failure. The estimated 4-year outcomes for the entire cohort were ipsilateral breast control, 95%; event-free survival, 93%; disease-specific survival, 97%; and OS, 92%. Khan et al. reported the results of the American Society of Breast Surgeons MammoSite Radiation Therapy System trial [59]. A total of 1,449 primary early-stage breast cancer patients were entered in this prospectively planned study and 1,440 were treated. The crude local recurrence rate for the group was 1.7%. There was no statistically significant difference in local recurrence as a function of age. Female patients younger than 50 years developed local recurrences 3.1% of the time as opposed to 1.6% in the older patients. In patients with invasive disease, crude local recurrence rates were 2.8% and 1.7% in the younger and older groups, respectively. There were a total of four isolated regional recurrences, all of which occurred in women of at least 50 years of age. Women younger than 50 years were more likely to develop fat necrosis than women 50 years or older: 4.6% vs. 1.8%. The remainder of the toxicities was subcutaneous tissue change, fibrosis, palpable mass, breast deformity, seroma, infection, and telangiectasia.

In the European MammoSite trial, a total of 54 low-risk breast cancer patients were evaluated between June 2002 and March 2005 [60]. Twenty-eight patients were treated with primary brachytherapy with a total dose of 34 Gy (2×3.4 Gy) and 16 patients had a boost with a mean dose of 13.3 Gy combined with external-beam RT. Seroma was observed in 16 patients (36%), and abscess development in two patients (4.5%). The skin-related side effects were skin discoloration or inflammation in 36 patients (82%), and telangiectasia in eight patients (18%). Cosmetic evaluation was done 1, 3, 6, and 12 months after irradiation using the Harvard criteria. Cosmetic outcome data for 39 patients were as follows: 9 patients had an excellent cosmesis (23%), 20 patients had a good cosmesis (52%), seven patients had a fair result (19%), and two patients had poor cosmesis (6%).

Because the MammoSite balloon applicator has shown promising results, other forms of balloon-based brachytherapy have been developed. The novel Axxent electronic brachytherapy system (Xoft, Fremont, CA) and Contura (SenoRx, Inc, Aliso Viejo, Ca) device are a modified form of balloon-based brachytherapy [61, 62].

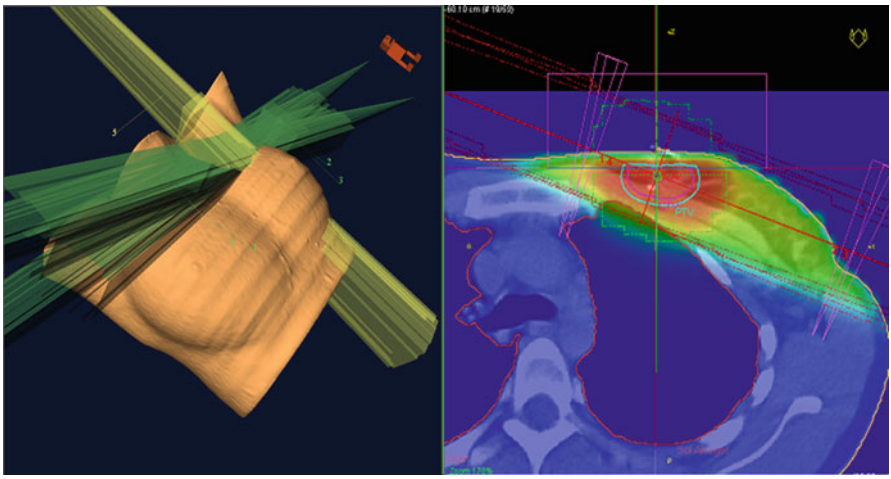

Fig. 21.5 3D-CRT. Four-field beam arrangement and conformal homogeneous dose distribution of the CTV and PTV. CTV is outlined in *dark pink* and PTV in *light blue*

21.4.2 External-Beam Radiotherapy

External-beam RT is a noninvasive procedure. It can be administered using 3D conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT). The technique is administered to the patient lying in a supine position with the ipsilateral arm elevated and the patient is then scanned. Baglan and colleagues suggest that the clinical target volume (CTV) should have a 1.5 cm safety margin which is uniformly expanded around the lumpectomy cavity and that it should be at least 5 mm from the skin surface as well as at least 5 mm from the lung-chest wall interface. The planning target volume (PTV) is defined as CTV plus a 1-cm margin to accommodate for breathing motion and set-up variations [63]. RT with 30–38.5 Gy is administered to the tumor bed in 5–10 fractions. External-beam APBI has several advantages over brachytherapy-based APBI, including noninvasiveness, treatment initiation based on the final pathology, and offering a more homogeneous dose distribution [64]. However, the integral dose to the lung, heart, or the remaining normal breast tissue could be higher than obtained with brachytherapy [65]. In a comparative study of APBI techniques, it was pointed out that better target coverage of 3D-CRT over brachytherapy could be obtained with a higher integral dose to the lung, heart, or the remaining normal breast [65]. Most planning studies have shown that IMRT is superior to 3D-CRT in treating the target volume adequately while sparing healthy organs and tissues (Figs. 21.5 and 21.6) [66–68].

Helical tomotherapy is another approach that enables effective intensity modulation of radiation delivery and its feasibility in APBI is still being tested [69, 70]. APBI could also be delivered using proton-beam therapy. Sun Ho Moon and colleagues reported a dosimetric comparison of four different external-beam APBI techniques: 3D-CRT, IMRT, helical tomotherapy, and proton beam therapy. Thirty patients were included in the study and treatment plans for four techniques

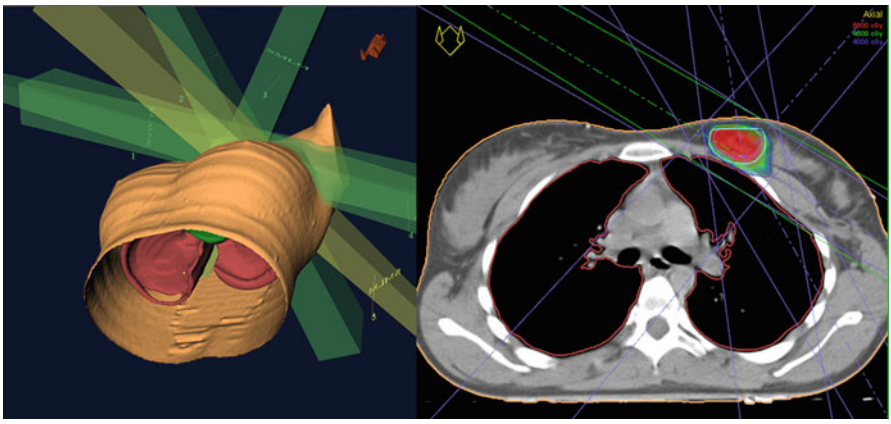

Fig. 21.6 PBI with IMRT. Five-field beam arrangement and dose distributions. Lower integral doses were delivered to the breast glandular tissue and normal tissues (heart, lung) with IMRT technique

were developed for each patient. The non-PTV breast volume delivered was 50% of the prescribed dose, proton-beam therapy (mean: 16.5%) was superior than tomotherapy (mean: 22.8%), IMRT (mean: 33.3%), and 3D-CRT (mean: 40.9%) ($p < 0.001$). The average ipsilateral lung volume percentage receiving 2% of the prescribed dose was significantly lower in proton-beam therapy (0.4%) and IMRT (2.3%) compared with 3D-CRT (6%) and tomotherapy (14.2%) ($p < 0.001$). The average ipsilateral heart volume percentage receiving 20% and 10% of the prescribed dose in left side breast cancer was significantly greater with tomotherapy (8%, 19.4%) compared with 3D-CRT (1.5%, 3.1%), IMRT (1.2%, 4.0%), and proton-beam therapy (0%, 0%) ($p < 0.001$) [70].

21.4.3 Intraoperative Radiotherapy

In this technique, the entire RT dose is given during surgery (quadrantectomy or lumpectomy). Different types of portable devices are available for intraoperative radiotherapy (IORT), including the mobile linear accelerator (Linac; Info&tech, Roma, Italy), Novac7 (Hitesys Srl, Latina, Italy), the Mobetron portable linear accelerator (IntrOp Medical Corp, Sunnyvale, CA), and Intrabeam Photon Radiosurgery System (Zeiss Inc, Germany) [71]. The University College of London has investigated the use of low-energy x-rays (maximum energy, 50 kV) delivered using a portable, spherical device that is placed into the lumpectomy cavity. For delivery of breast RT, the Intrabeam system is equipped with spherical applicators ranging in size from 1.5 to 5 cm. The prescribed dose is given in one 5–20 Gy fraction at depths of 1 and 2 cm, respectively [72]. A dose of 20 Gy at the applicator surface is equivalent to a fractionated dose of 70 Gy, while a dose of 5 Gy at 1 cm is

equivalent to a fractionated dose of 18 Gy. The chest wall and skin can be protected by tungsten-impregnated silicone barriers (providing >93% shielding) [71]. The European Institute of Oncology has used intraoperative electrons for APBI. IORT is given with one single fraction (21 Gy) with electrons, and offers a very precise delineation of target volume which is identified under visual control. Furthermore, immediate oncoplastic surgery can be performed, with excellent cosmetic results. IORT allows high sparing of normal tissue, as the critical structures can be easily shielded or moved away from radiation field. The most limiting aspect of the intraoperative technique is, as the definitive pathology findings may reveal, inadequate surgical margin or some aggressive tumor features for which a limited radiation field is contraindicated [73]. The TARGIT-A Trial was designed to compare IORT with WBI. It was a prospective randomized noninferiority phase III study, women 45 years or older with invasive ductal breast carcinoma undergoing BCS were enrolled from 28 centers in nine countries. One thousand one hundred and thirteen patients were randomly allocated to targeted IORT and 1,119 were allocated to external-beam RT. In the IORT group, 854 patients (86%) received targeted IORT only and 142 patients (14%) received targeted IORT plus external-beam RT. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1.2% in the IORT group and 0.95% in the external-beam RT group. The frequency of any complications and major toxicity was similar in the two groups [74]. Veronesi et al. reported results of a clinical trial that included 1,822 women treated off protocol. At 4 years, the actuarial rate of local recurrence was 4.84% (annual rate of 1.2%), two thirds of which were at the same quadrant of the primary tumors, while one third occurred in other quadrants. The complication rates were mild (1.8% of fibrosis and 4.2% of liponecrosis). Only six patients who received 21 Gy developed severe fibrosis [75]. The main criticism was that in both the TARGIT trial and the ELIOT study, follow-up was too short (median, 24 and 36 months, respectively) to consider APBI as an alternative to WBI for selected patients, and mature data on late toxicity are lacking [73].

21.5 Prospective Randomized Trials and Meta-Analysis of Partial Breast Irradiation

Ongoing prospective randomized trials comparing WBI with PBI are listed in Table 21.3.

In a study between 1998 and 2004, Polgar et al. reported that 258 of expected 570 patients with T1N0-N1mi, grades 1–2, nonlobular breast cancer, without the presence of EIC, and resected with negative margins were randomized after BCS to receive 50 Gy/25 fractions WBI ($n = 130$) or PBI ($n = 128$). The latter consisted of either 7 × 5.2 Gy HDR multicatheter brachytherapy ($n = 88$) or 50 Gy/25 fractions electron beam irradiation ($n = 40$). At a median follow-up of 66 months, the 5-year actuarial rate of local recurrence was 4.7% and 3.4% in the PBI and WBI groups,

Table 21.3 Prospective randomized trials comparing APBI with WBI

Study	Study design	*n*	Inclusion criteria	Standard arm	Experimental (APBI) arm	Status
ELIOT [75]	Equivalence	824	≥48 years, invasive carcinoma, $T < 2.5$ cm, pN0	WBI 50 Gy/25 fractions ± boost	IORT 21 Gy/1 fraction, electrons up to 9 Mev	Started Dec 2000
IMPORT LOW [76]	Non-inferiority	2,100	≥50 years, IDC, $T \leq 3$ cm, margin ≥2 mm, N0	WBI 40 Gy/15 fractions	EBRT (IMRT) Arm 1: 40 Gy/15 fractions to primary tumor + 36 Gy/15 fractions to low-risk area Arm 2: 40 Gy/15 fractions primary tumor	Started in 2006
GEC-ESTRO [77]	Non-inferiority	1,170	≤40 years, stage 0-II, ductal or lobular carcinoma, $T \leq 3$ cm, pN0-pN1mi, margin ≥2 mm	WBI 50–50.4 Gy/25–28 fractions optional 10–16 Gy boost	MIB 32 Gy/8 fractions HDR, 30.3 Gy/7 fractions HDR, 50 Gy PDR	Started 2004
NSABP/RTOG 0413 [78]	Equivalence	4,300	≥50 years, stage 0-II ($T < 3$ cm), DCIS or invasive adenocarcinoma, ≥3 nodes positive, margin negative	WBI 50–50.4 Gy/25–28 fractions ±10–16 Gy boost	MIB MammoSite 34 Gy/10 fractions (5–10 days) 3D EBCRT 38.5 Gy/10 fractions (5–10 days)	Started in 2005
RAPID [79] OCOG		2,128	≥40 years, DCIS or invasive carcinoma, pN0-pN1mic, margin negative	WBI 42.5 Gy/16 fractions + 10 Gy boost	3D EBCRT 38.5 Gy/10 fractions (5–8 days)	Started Jan 2006
IRMA [80]	Non-inferiority	n/a	≥49 years, pT1-2 (<3 cm), invasive carcinoma, pN0-N1, margins ≥2 cm	WBI 45 Gy/18 fractions, 50–50.4 Gy/25–28 fractions	3D EBCRT 38.5 Gy/10 fractions, twice a day with an interval of at least 6 h	Started in 2007

3D EBCRT three-dimensional external beam radiotherapy; *OCOG* Ontario Clinical Oncology Group; *EBRT* external beam radiotherapy; *NSABP* National Surgical Adjuvant Breast and Bowel Project; *RTOG* Radiation Therapy Oncology Group; ELIOT intraoperative radiotherapy with electrons; IORT intraoperative radiotherapy; WBI wide breast irradiation; EBRT external beam radiotherapy; IMRT intensity modulated radiotherapy; MIB multicatheter interstitial brachytherapy; HDR high dose rate; PDR pulse dose rate; NSAB/RTOG National Surgical Adjuvant Breast and Bowel Project/RTOG Radiation Therapy Oncology Group; DCIS ductal carcinoma in situ.

respectively ($p = 0.50$). There was no significant difference in the 5-year probability of overall survival (94.6% vs. 91.8%), disease-free survival (88.3% vs. 90.3%), and cancer-specific survival (98.3% vs. 96%). The rate of excellent-to-good cosmetic results was 77.6% and 62.9% in the PBI and WBI groups, respectively ($p = 0.01$). The trial was stopped prematurely because patients were offered entry into the GEC-ESTRO phase III APBI trial [81].

In a meta-analysis of randomized controlled trials reported by Valachis et al., 1,140 patients from three randomized PBI trials were entered. They found no statistically significant difference between the PBI and WBI groups associated with death (OR, 0.912; 95% CI; range, 0.674–1.234; $p = 0.550$), distant metastasis (OR, 0.740; 95% CI; range, 0.506–1.082; $p = 0.120$), or supraclavicular recurrences (pooled OR, 1.415; 95% CI; range, 0.278–7.202; $p = 0.560$). However, PBI was statistically significantly associated with an increased risk of both local (pooled OR, 2.150; 95% CI; range, 1.396–3.312; $p = 0.001$), and axillary recurrences (pooled OR, 3.430; 95% CI; range, 2.058–5.715; $p < 0.001$) compared with WBI. Investigators concluded that PBI can be used as an alternative treatment to WBI [82].

21.6 Conclusion

Currently, the standard of care after BCS is still WBI, not APBI. However, the role of APBI will continue to be defined by the mature results of ongoing randomized trials from large cooperative groups in the next 5–10 years.

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Chapter 22
Hypofractionation

Ayfer Haydaroglu

22.1 Introduction

Hypofractionation (HF) was first introduced in the 1960s and gained widespread use in practice as radiobiological parameters become widely known. Over the past 10 years, significant improvements in radiotherapy (RT) applications following breast-conserving surgery (BCS) have been realized in the whole or partial breast hypofractionated radiotherapy (HF-RT). More than 7,000 women with early-stage breast cancer were selected for the whole-breast HF [1]. Similar results were reported in all of the studies conducted until today for both HF-RT and conventional fractionation (CF) in terms of local recurrence and morbidity. In this chapter, the mechanisms of action of HF in the RT of breast cancer and the results of large randomized clinical trials will be discussed.

22.2 Fractionation

Single and high-dose RT was a common application at the beginning of the twentieth century, but withdrawals resulting from the high frequency of late and early adverse effects were observed, and consequently, RT was begun to be applied in divided fractions. Multifraction regimens were based on radiobiological experiments conducted in the 1920s in France. Delivering total treatment dose in small fractions may help reduce the damage in normal tissues [2].

The purpose of fractionation is to reduce the possible adverse effects of radiation on the normal tissues and allow proliferation, reoxygenation, rearrangement, and repair of normal cells during the time interval between two dose fractions.

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By dividing the total radiation dose into a number of fractions, and ensuring sufficient time for sublethal DNA damage repair and repopulation of normal cells, damage to normal tissues may be reduced. At the same time, because of reoxygenation occurring in tumor cells in the period between dose fractions, fractionation may increase hypoxic tumor responses to radiation. However, the benefits of fractionation may be mutually compensated by repopulation of tumor cells throughout the treatment [3].

Conventional fractionation radiotherapy (CF-RT) is delivering standard doses of 2 or 1.8 Gy for 5 days a week. Hyperfractionation is delivering smaller doses of radiation on a more frequent schedule compared with the standard fractionation method. Hyperfractionation, by reducing fraction dose, aims to improve late-term tissue tolerance and increase the efficiency of the total treatment dose [4]. The HF regimen refers to the use of relatively larger fraction doses over a smaller number of fractions [5]. Accelerated RT is administered in the shortest possible time [6] and there are different types of acceleration regimens. Accelerated hypofractioned RT regimen is given every day in larger fractions than CF in a short period of time [1]. A continuous hyperfractionated accelerated radiotherapy (CHART) regimen is administered twice a day or three times per day continuously, in small fractions of 1.1–1.5 Gy, with a minimum interval of 6 h between fractions, throughout the week and including the weekend. The aim of the accelerated RT is to shorten the total RT period in order to reduce repopulation risk [6] (Fig. 22.1).

22.3 The Mechanisms of Action of Hypofractionation

In RT applications, response of the tumor and the surrounding normal tissues to the increasing doses of radiation should be considered in determining the time interval between two fractions and the dose per fraction. Biological tissues and tumors may respond differently to the same amount of radiation. The repair capacity of each biological tissue is distinctive; therefore, the shoulder region of the survival curves raised at increasing doses of radiation may be different. Alterations in the slope of the equivalent curve with the fraction dose depend on the type of related tissue. Acute responding tissues display flatter curves, while late responding tissues have more steep curves, and α/β value determines this difference [7].

According to the linear quadratic (LQ) model, cell death occurs as a result of accumulation of a single-hit lethal and two sublethal events. The alpha (α) component represents a single lethal lesion, and indicates the intrinsic radiosensitivity. The beta (β) component represents cell killing resulting from accumulated damage, and reflects cellular repair mechanisms. The α-to-β ratio indicates the dose at which the linear and quadratic components of cell killing equate. It is considered that for early side effects in normal tissues, $\alpha/\beta = 10$ Gy, and for late side effects $\alpha/\beta = 3$ Gy. The LQ model demonstrates a linear-quadratic relationship between the fraction dose and the number of fractions [8, 9].

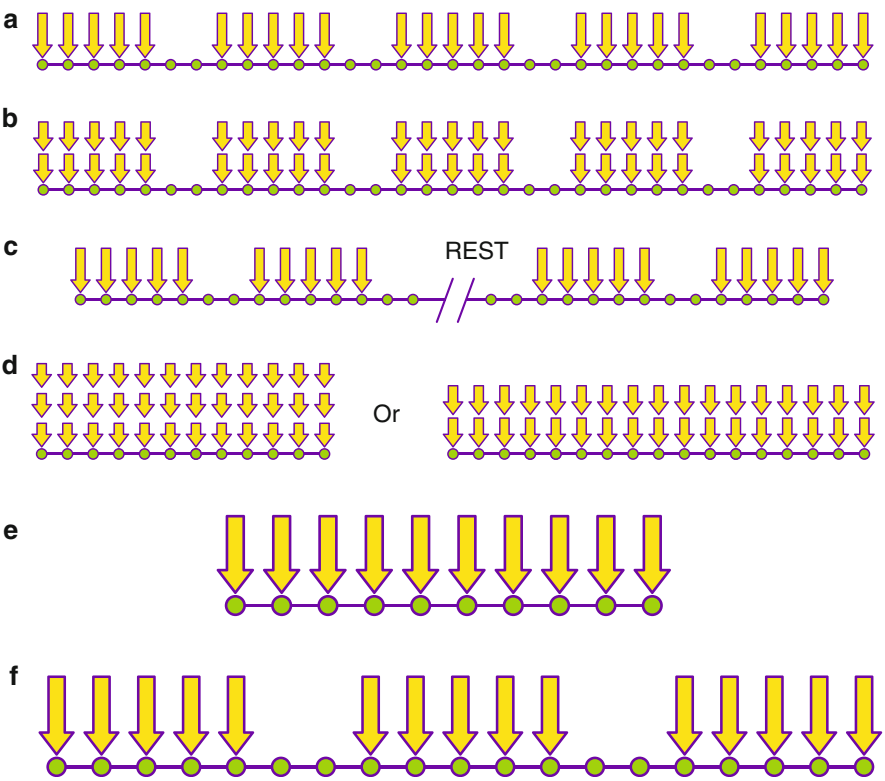

Fig. 22.1 Fractionation regimens. **a** conventional RT: 1.8–2 Gy/day, 5 days/week; **b** hyper-fractionated RT-1.15 GyX2/day, 5 days/week; SPLIT COURSE >2.5 Gy/day and REST; CHART: <2 GyX2-3 times/day/continuous days; accelerated hyporfractionated RT: >3 Gy/day/10 continuous day, short treatment time; hyporfractionated RT: >2 Gy/day, short treatment time

Application of an LQ model in HF-RT is controversial because of some limitations [10, 11]. For instance, the duration of the treatment is not taken into account in the LQ model, and fractions are assumed to be equal. High-dose fractions may cause endothelial apoptosis and vascular leakage more often. Given the accumulated damage, inflammation, and vascular damage, this formulation may not be appropriate. Reports advocating different opinions on this issue are available [10, 11].

Tumors with higher self-renewing capability reveal higher α-to-β ratios, while tumors with limited self-renewing capability have lower α-to-β ratios. At increasing radiation doses, the survival fraction is rather linear while the survival curve forms a shoulder at low doses. Repair capacity of each biological tissue is distinctive; therefore, the width of the shoulder at increasing radiation doses appears different. Late-responding tissues display more prominent and steep shoulders, with small α-to-β ratios. Early-responding tissues are characterized by survival curves with smaller shoulders with linear course, and larger α-to-β ratios. At low radiation doses, the curve inclines, and linear and quadratic components equate at 2 Gy.

A curve with significant slope may lead to an increase in the isoeffective dose as α-to-β ratio decreases at fraction doses exceeding 2 Gy, so utility of therapeutic ratio and HF may be enhanced. In fast renewing tumors, a linear survival curve may lead to a decrease in isoeffective dose, and consequently utility of HF may decrease. Slow growing tumors such as breast and prostate cancer, with lower α-to-β ratios, benefit from HF regimens. Fast growing tumors such as head and neck carcinomas, with higher α-to-β ratios, are expected to benefit from hyperfractionated and/or accelerated regimens.

Breast cancer has been the most commonly dealt with topic in studies conducted on RT-induced late-term normal tissue reactions, and radiation doses and fractions that may induce normal tissue reactions such as fibrosis, telangiectasia, brachial plexus neuropathy, and shoulder stiffness have been used in the studies as a model. For many late-term adverse effects following breast RT, an α/β value is considered to be somewhere between 1.5 and 4 Gy [12]. In different studies investigating fractionation sensitivity of various tissues to RT administered in breast cancer cases, an α/β value has been accepted as 4.2 Gy for telangiectasia [13], as 3.5 Gy for shoulder stiffness [14], as 1.5–2 Gy for brachial plexopathy [15], and as 2.5 Gy for fibrosis [16]. An α/β value is generally considered as 3 Gy for radiation-induced late-term adverse effects in the breast. In comparison of the CF-RT (50 Gy/25 fraction) and HF-RT (28.5 Gy/5 fraction) experimental arms of the FAST study, when the α/β value was accepted as 3 Gy, the doses reaching 100%, 105%, and 110% were determined as 50, 53.6 and 57.2 Gy in the CF arm, and as 49.6, 53.7 and 58.1 Gy in the HF arm, respectively. Dose increase in the HF arm become more prominent in the regions encountered with higher doses of radiation [17, 18]. Therefore, it was highly indicated in the ASTRO guidelines to comply with the ±7% rule regarding dose homogenization in the HF-RT applications [19].

Determining the molecular basis underlying the response of tumor cells in different radiation models is a problematic issue. The main problem is the ongoing controversy concerning the use of the LQ model which is used to calculate the isoeffective doses at high fraction doses in HF regimes as well [11]. Another problem is to establish the optimal time point for appropriate differences after irradiation. Tumor response to radiation may be achieved over a long period of time, and the cellular response may develop within different time frames in different radiation regimens. Research studies conducted to understand the molecular basis of radiosensitivity, and to identify gene mutations and single-nucleotide polymorphisms (SNPs) associated with radiosensitivity currently arouse particular interest [20]. As was shown for tamoxifen, SNPs may be associated with increased secretion of tumor growth factor-β-1. Interestingly, recent evidence has revealed that coadministered tamoxifen may potentiate radiation-induced fibrosis in patients with radiosensitive breast cancer [21].

22.4 Hypofractionated Radiotherapy Models

Curative or palliative therapies can be achieved with different HF-RT models (Fig. 22.2).

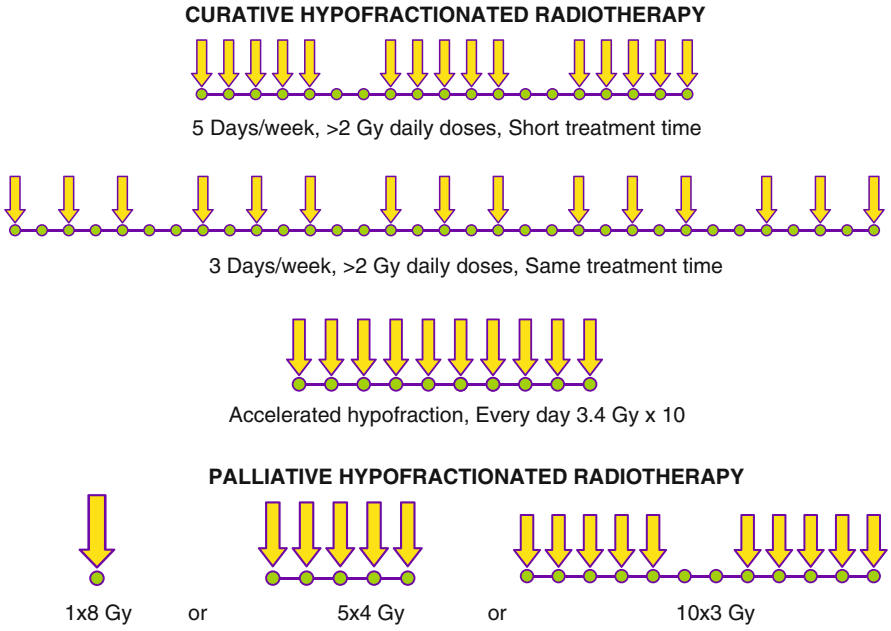

Fig. 22.2 Curative and palliative hypofractionated models

Curative hypofraction: Number of weekly fractions and duration of the treatment time may be the same or less. For instance, HF regimens of 3 days a week for 5 weeks [22] or 5 days a week for 3 weeks [23] have been used.

Palliative hypofraction: As a palliative therapy, it is generally used in metastasis, hemorrhages, and in oncologic emergencies such as vena cava superior. Treatments were usually given as a single 8-Gy dose, or 5 fractions of 4 Gy, or 10 fractions of 3 Gy treatments (Fig. 22.2). Studies reported that the palliations achieved were equivalent to the conventional methods [24, 25].

22.5 Effects of Hypofractionated Radiotherapy on the Risk of Secondary Cancer

As a result of the improved survival rates of cancer patients, the risk of late-term adverse effects including secondary cancers become crucial in long-term survivors [26].

Schneider et al. developed an analytic model as a function of the absorbed dose to the normal tissues and released a graph of the yearly cancer risk per 10,000 people, and investigated secondary cancer risk at 2, 3, and 5 Gy dose fractions. They found that each 1 Gy dose increase per fraction may lead to 10% decrease in carcinoma risk, whereas an average 15% decreases in sarcoma risk. They observed,

as with the sarcoma risk, that carcinoma risk decreased in parallel to an increase in fractionation dose. Actually, the rate of decrease in sarcoma risk was more significant compared with carcinoma risk, and for secondary cancer induction, HF was potentially useful [26].

22.6 Randomized Clinical Trials of Hypofractionation

Randomized clinical trials conducted on early breast cancer have demonstrated that following BCS, adjuvant whole-breast irradiation (WBI) may reduce ipsilateral breast tumor recurrence risk by approximately 70%, and produce 5% absolute improvement in 15-year overall survival [27]. In maximizing local control and overall survival in breast cancer, breast irradiation following BCS is the most important part of breast-conserving therapy. The most widely used fractionation model is to deliver 45–50 Gy to the entire breast in 1.8–2.0 Gy per daily fractions over 6–7 weeks plus 10–16 Gy to boost the dose on the tumor bed [28]. Despite the proved effectiveness and reliability, CF-RT has certain disadvantages. Daily treatments lasting for 6–7 weeks may generate discomfort in patients and cause problems regarding burden of the treatment cost, workload to RT clinics, and opportunity costs to the community [29]. However, as a result of practical advantages and biological effects, HF models attract intensive interest in breast cancer treatment. Moreover, HF models are considered attractive with regard to patient compliance and functioning of RT clinics.

In a comparison of HF and CF applications, four large multicenter randomized clinical trials were conducted; one in Canada and three in England: the Ontario Clinical Oncology Group (OCOG) Trial [30], the Royal Marsden Hospital/Gloucester Oncology Centre (RMH/GOC) Trial [31, 32], the UK Standardization of Breast Radiotherapy Trial A (START A) [22], and the UK Standardization of Breast Radiotherapy Trial B (START B) [23]. This chapter will also include other studies and reviews conducted with participation of a limited number of centers.

In the first trial, the OCOG enrolled 1,234 women, who had node-negative breast cancer and who undergone BCS and axillary dissection, and consequently had safe surgical margins. Women were randomized to accelerated HF-WBI as 42.5 Gy in 16 fractions over 22 days or standard WBI as 50 Gy in 25 fractions over 35 days [1, 33]. Local recurrence after 10-year follow-up was detected as 6.7% and 6.2% in standard and HF experimental arms, respectively (Table 22.1). Although there is no statistically significant difference between the groups, subgroup analysis displayed that local recurrence was less effective in high-grade tumors. In this group, local recurrence at 10 years was 4.7% in the control group and 15.5% in the HF-RT group ($p = 0.01$) [33]. Ten-year survival rates were 84.4% and 84.6% in control and HF-RT groups, respectively (Table 22.1). In terms of good and excellent cosmetic outcome at 10 years, the results were similar; 71.3% in the control group and 69.8% in the HF-RT group [33].

Table 22.1 Inclusion criteria, dose and fraction properties, local control and survival rates in randomized large hypofractionation trials

Study	Inclusion criteria	Total dose (Gy)/fraction/time	Local recurrence (%) 5 y/10 y	Survival (%) 5 y/10 y
OCOG [33]	BCS	50 Gy/25/35 d	3.2%/6.7%	91.7%/84.4%
	T1-T2, N0, M0	42.5 Gy/16/22 d	2.8%/6.2%	92.3%/84.6%
$n = 1{,}234$	<25 cm width			
	Uninvolved inked margin			
RMH/GOC [31]	BCS	50 Gy/25/5 wk	7.9%/12.1%	
$n = 1{,}410$	T1-3, N0-1, M0	42.9/13/5 wk	7.1%/9.6%	
	Complete macroscopic resection	39 Gy/13/5 wk	9.1%/14.8%	
START A [22]	BCS or mastectomy	50 Gy/25/5 wk	3.6%	88.8%
$n = 2{,}236$	T1-3,N0-1, M0	41.6 Gy/13/5 wk	3.5%	88.1%
	Clear tumor margins >1 mm	39 Gy/13/5 wk	5.2%	88.7%
START B [23]	BCS or mastectomy	50 Gy/25/5 wk	3.3%	87.5%
$n = 2{,}215$	T1-3, N0-1	40 Gy/15/3 wk	2.2%	90.4%
	Clear tumor margins >1 mm			

BCS breast-conserving surgery

In the START A, 2,236 women with node-negative and node-positive breast cancer were randomized after BCS or mastectomy [22]. Thirteen centers in England were included in the trial. In the standard arm of the trial, conventional 50 Gy was delivered in 25 fractions, whereas in two different HF programs, 41.6 and 39 Gy doses were delivered in 13 fractions. All programs lasted for 5 weeks and were designed to perform five fractions in 2 weeks. Women who had BCS (60.6%) were administered boost therapy. Regional RT was administered in 14.2% of the cases. Cosmetic controls were performed by photographic assessments [23]. The rate of local tumor relapse at 5 years was 3.6%, 3.5% and 5.2%, the rate of survival was 88.8%, 88.1%, 87.7%, after 50, 41.6, and 39 Gy applications in three arms of the trial, respectively (Table 22.1).

In the START B, 2,215 women with node-negative and node-positive breast cancer were randomized after BCS or mastectomy [23]. The standard regimen of 50 Gy in 25 fractions was administered over 5 weeks or the accelerated HF-RT regimen of 40 Gy in 15 fractions of 2.67 Gy daily doses was delivered over 3 weeks to the whole breast. Boost therapy was administered to patients who had BCS (42.6%). Regional RT was administered in 7.3% of the cases. Cosmetic controls were performed by photographic assessments. In the standard and HF arms of the trial, the rate of local tumor recurrence at 5 years was 3.3% and 2.2%, survival rate was 87.5% and 90.4%, and the rate of cosmetic differences was 42.5% and 36.5%, respectively [23].

Table 22.2 Skin toxicity and cosmetic outcome rates in large randomized hypofractionation trials

Study *n*	Total dose (Gy)/fraction/time	Toxicities skin (%) 5y/10y	Excellent/good cosmesis or no change (%)	Adverse cosmetic results (%) 5y/10y
OCOG [33]	50 Gy/25/35 d	17.7%/29.5%	79.2%/71.3%	20.8%/28.7%
$n = 1{,}234$	42.5 Gy/16/22 d	13.9%/33.2%	77.9%/69.8%	22.1%/30.2%
RMH/GOC [31]	50 Gy/25/5 wk	12.0%/18.1%	60.4%/46.6%	60.4%/46.6%
$n = 1{,}410$	42.9/13/5 wk	13.0%/18.0%	54.3%/42.0%	54.3%/42.0%
	39 Gy/13/5 wk	5.6%/12.0%	69.7%/43.9%	69.7%/43.9%
START A [22]	50 Gy/25/5 wk	31.1%	59.0%	42.9%
$n = 2{,}236$	41.6 Gy/13/5 wk	25.0%	58.1%	43.6%
	39 Gy/13/5 wk	2.6%	65.9%	32.1%
START B [23]	50 Gy/25/5 wk	42.3%	58.8%	42.2%
$n = 2{,}215$	40 Gy/15/3 wk	38.2%	64.5%	36.5%

n number of patients, *wk* week

According to the data obtained in all these randomized trials, standard and HF treatment models revealed similar results with regard to local recurrence, survival, and adverse cosmetic results. These results, especially long-term follow-up results of the Canadian study, confirm the acceptable morbidity results and support the applicability of selected HF programs into practice [34] (Table 22.2).

In the RMH/GOC trial, Owen et al. investigated 1,410 women with stages 1–3 breast cancer in the period between 1986 and 1998 [31]. Median follow-up was 9.7 years. One of three arms of the trial was a standard regimen of 50 Gy given in 25 fractions; the other two HF arms were 39 Gy given in 13 fractions and 42.9 Gy given in 13 fractions. All three regimens were completed in 5 weeks. Ipsilateral tumor relapse after 10 years was identified as 12.1% in the 50 Gy group, 14.8% in the 39 Gy group, and 9.6% in the 42.9 Gy group ($p = 0.027$) [31].

Available studies regarding the adverse effects of HF-RT and the interaction between HF-RT and chemotherapy (CT) are very few, and there is uncertainty on this issue. Hijal et al. reported that, all 162 patients were irradiated with HF-RT regimen, compared skin toxicity caused of patients with or without CT [34]. An HF-RT regimen of 42.4 Gy in 16 fractions was administered to the patients. In comparison of the patients with regard to acute and late-term skin reactions and cosmetic results, statistically significant differences were not found [34]. Although the updated results of the Canadian trial, regardless of the treatment arm, did not report that prior CT and increased risk of toxicity showed no correlation [33], anthracyclines and taxanes were rarely used in the period of this trial. Additionally, none of the patients enrolled in the trials were given trastuzumab or much newer targeted agents. Current CT regimens are different than those used in large randomized trials. In the ASTRO consensus group, team members were generally against the use of HF-WBI together with systematic treatment as a preventive measure, while available data today relating cytotoxic CT or targeted agents are not considered satisfactory [19].

Mannino et al. [35] reviewed five randomized HF studies which included 8,000 patients and compared them with regard to survival rates, local control, and

economic aspects. Treatment success rates were almost similar. Considering financial burden, total treatment cost was $6,100 US for the HF regimen of 16 fractions, whereas it was $8,500 US for the CF regimen of 25 fractions, and they concluded that HF regimens are more advantageous in an economic sense [35].

22.7 Uncertainties Regarding Hypofractionation Applications

In Canada and England, large randomized HF trials have been carried out, and today HF is a routinely used treatment method in numerous centers. However, despite all these positive approaches, there is still uneasiness in many countries about the use of HF. The main reservation is regarding late responding tissues due to insufficient relevant data. Additionally, for the patients who were given supraclavicular and axilla RT and CT, available data are not satisfactory. Uncertainties already exist regarding indifferent tumors in women 40 years and younger. The data about patients with large breast volume who irradiated HF-RT is little. It is also controversial whether the radiobiologically used LQ model is optimal for HF regimens or not.

In the OCOG study, compared with the conventional model, HF regime was found inadequate for local control in grade 3 breast cancer cases, whereas in a population-based cohort study conducted by Herbert et al. with 1,335 grade 3 breast cancer patients, HF and CF regimens were compared with regard to local control. Cumulative incidence of 10-year local relapse for HF and CF groups was found as 6.9% and 6.2%, respectively ($p = 0.99$). In terms of local control, no difference was detected between HF and CF regimes in grade 3 breast cancer cases [36].

Williamson et al. compared HF and CF in ductal carcinoma in situ (DCIS) cases in terms of relapse rates and couldn't find any significant difference (respectively, 7% and 6%, $p = 0.9$). However, the relapse rate was 11% for nuclear grade 3 cases, which was reported as a significant recurrence pattern ($p = 0.029$) [37].

Due to positive results obtained in randomized trials being accepted as very high evidence value, HF began to take place in consensus. In the 2010 version of the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, HF-RT was referred to as well as conventional methods in WBI; 45–50 Gy in 1.8–2 Gy fractions or 42.5 Gy in 2.66 Gy fractions were suggested for breast cancer [38].

The American Society for Radiation Oncology (ASTRO) evaluated randomized HF-RT trials and published evidence-based guidelines. In the guideline, based on the findings achieved in various randomized clinical trials, consensus was reached on the following criteria [19]: In women over 50 years, pT1-T2 patients who had BCS, and patients who were not given chemotherapy can use HF-RT safely. Homogeneity should be ensured by keeping the dose difference at ±7% (it should not be less than a minimum of 93% or more than a maximum of 107% of the identified dose). The ASTRO team accepted the data supporting the use of HF-WBI for early breast cancer cases, which also meet all these criteria [19]. Controversial

issues which need to be further supported with evidence-based new studies are the following: DCIS, nodal involvement, high-grade tumors, patients who had received CT, boost dose application in HF regimens, postmastectomy patients, cases with radiation area width larger than 25 cm, cases with insufficient cardiac shielding in left breast RT. The ASTRO team did not submit any positive or negative proposals regarding the use of HF-WBI in these controversial cases, but did not interpret them as contraindication criteria [19]. In the review from Canada by Holloway et al., it was suggested that 50 Gy in 25 fractions should not be further recognized as a standard application, HF should be approved as the new "standard" [39].

22.8 Conclusion

HF regimens improve the therapeutic index in slow-growing tumors with low α-to-β ratios, such as breast cancer. In phase III studies, adverse effects and therapeutic efficiency of HF-RT were found similar to standard therapy models. In economical evaluation of HF therapy, patients would visit hospitals less, duration of the therapy would be shorter, physical team would spend less time doing HF therapy, workload on RT instruments would be minimized, and productivity in RT departments would increase. Therefore, for the selected patients (having all of the following: age >50 years, pT1-T2 tumors, not receiving CT, achieving dose homogeneity of ±7%) HF-RT is an appropriate therapy option. However, in the ASTRO Evidence-Based Guidelines, applicability of HF-RT in all patient subgroups was discussed, and eventually it was recommended to conduct further studies for the patient groups which do not meet ASTRO criteria. In the 2010 version of the NCCN Practice Guidelines in Oncology, in addition to conventional methods, HF-RT was included to be used in WBI. HF-RT is reliable and safe, particularly for elderly patients and for those with good prognostic values.

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Chapter 23
Application of Tomotherapy in Breast Cancer Patients

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23.1 Introduction

Breast cancer is currently the most common carcinoma among women. Adjuvant radiotherapy (RT) plays an important role in the treatment of early breast cancer after lumpectomy and in selected cases after mastectomy. Adjuvant RT has traditionally been delivered using two tangential fields with or without direct fields for regional lymph node treatment after two-dimensional planning. Recently, new treatment planning and delivery options have emerged aiming to improve the dose distribution, reduce inhomogeneities, and clinically confer better locoregional control with reduced toxicities. Even more advanced RT techniques, such as helical intensity modulated radiotherapy (IMRT) (tomotherapy), might offer new solutions to further improve treatment planning and therefore, possibly clinical outcomes in comparison with traditional RT techniques. In this chapter, the current literature about applications of tomotherapy in breast cancer patients is being reviewed and our breast tomotherapy practice at the University of Lausanne, CHUV, Switzerland is being presented.

23.2 General Information on Tomotherapy

Helical tomotherapy (HT) is a hybrid between a 6-MV linear accelerator (LINAC) and a computed tomography (CT) scanner that delivers IMRT with megavoltage CT (MVCT) images for daily set-up verification. Target volume irradiation is

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helical with a rotating modulated fan beam using a binary multileaf collimator (MLC). The HT system does not offer electron beam therapy as traditional LINACs do.

HT had been developed at the University of Wisconsin and manufactured commercially with the name "TomoTherapy Hi-ART System" in 2002. Recently, "Tomodirect", previously called topotherapy, with nonrotating delivery options (via static gantry positions instead of rotating delivery) has been commercialized, and available clinically as of April 2010.

Tomotherapy treatment planning software (TPS) (TomoTherapy Inc., Madison, WI) is an inverse planning system with an optimization process. Prescribed dose to the target volumes, dose limitations for critical structures, the field width (FW), modulation factor (MF), pitch, and resolution of the calculated dose-grid should be defined primarily. FW (defined by the primary jaw) is the thickness of the fan beam at the isocenter and changes between 5.0-, 2.5-, or 1.0-cm dimensions. The bigger FW corresponds to the decrease in treatment duration while broadening the dose fall-off superior and inferior to the target. MF is the maximum leaf opening time divided by the average leaf opening time for all nonzero leaf openings. The initially chosen MF determines the upper limit for the amount of modulation allowed. Enhancing the MF increases conformity but also the treatment time. The pitch is defined as the ratio of the distance the couch travels per rotation to the FW at the gantry axis. HT TPS down-samples the CT image resolution to another pixel per slice. This is necessary to reduce the amount of memory required for optimization.

Each HT gantry rotation is divided into 51 projections. The MLC position is been calculated every 7°. The fluency of the fan beam is modulated by a single row of 64 binary tungsten leaves. Each leaf is 6.25-mm wide at the isocenter. With Tomodirect, each projection corresponds only to a different longitudinal position of the beam with a simultaneous couch translation and MLC modulation.

The Tomodirect technique is similar to IMRT with the use of "dynamic MLC sweeping window" except the sliding of the patient through the beam during Tomodirect treatment. Comparison of coplanar accelerated partial breast topotherapy with LINAC-based non-coplanar three-dimensional conformal radiotherapy (3D-CRT) and IMRT dosimetry in partial left breast irradiation, illustrates equivalent target conformity and uniformity [1]. Dosimetric comparison of two-field topotherapy with HT for the delivery of whole-breast radiotherapy (WBRT) showed improved target dose homogeneity and conformality in comparison to with topotherapy. However, topotherapy resulted into reduced amounts of the heart and ipsilateral lung receiving low doses while still maintaining adequate target uniformity. In the study, the higher number of the fields, up to five for the topotherapy plans, was correlated with increased conformality [2].

The HT beam from all gantry angles causes delivery of low doses to coplanar normal tissues, most of which would have received only a scatter dose with the conventional techniques. During HT treatment planning optimization, critical structures can be designated as a blocked region to prevent any beamlet from passing through the structure, or can be directionally blocked, thus inhibiting any entry of the beamlets to the structure, but still allowing their exit (Fig. 23.1).

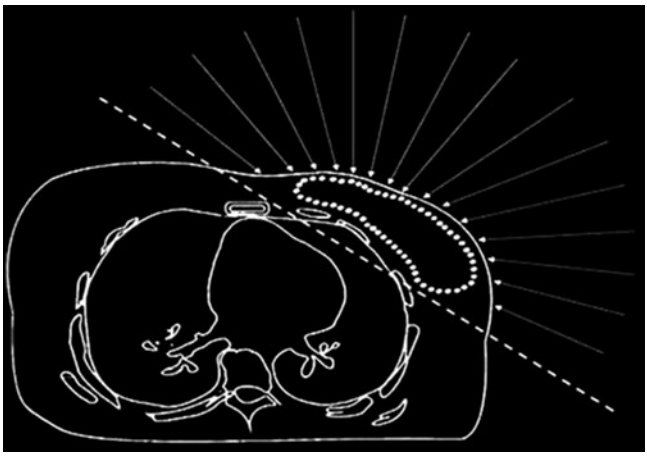

Fig. 23.1 Schematic illustration of directional blocking with HT [17]

This sort of blocking reduces treatment beam angles by minimizing dose to the contralateral structures; however, it reduces the potential conformality and sparing of the ipsilateral organs at risk.

23.3 Possible Indications of Tomotherapy for Breast Cancer

High locoregional control and survival rates have been reached with the contribution of conventional RT techniques to the other local (surgery) and systemic (chemotherapy, hormone therapy, targeted therapy) modalities implied in the treatment of early breast cancer over the last decades. The contribution of RT to local control and survival after breast-conserving surgery (BCS) and mastectomy has been consistently shown and recognized [3]. With the current technology advances in RT, further improvements in treatment outcomes and, most importantly, reduction of early and late RT toxicities emerge as a challenge. Furthermore, given the fact that breast cancer survivors currently live longer, late treatment sequelae, such as cardiac toxicity, that appear as long as 15 years after treatment, become of more pronounced importance and need to be minimized [4]. In addition to advances in imaging, IMRT represents one of the most important technologic advances in RT in all cancer sites; it is under vivid investigation how this promising technique will further improve the quality of treatment in the setting of early breast cancer.

The most common side effects of breast RT in the adjuvant setting with conventional techniques are lung and heart toxicity, lymphedema, brachial plexopathy, cosmetic problems, and secondary malignancies. There are situations such as bilateral disease, irradiation of the left breast, internal mammary chain (IMC) irradiation, pectus excavatum, and prominent prosthesis, that represent particular challenges during planning and implementation of RT in the adjuvant setting of early breast cancer.

Irradiation of the left breast is obviously associated to more important late cardiac toxicity that is attributed to irradiation of the left ventricle [5]; this becomes even more pronounced when cardiotoxic systemic therapy such as anthracyclines or trastuzumab have been or are being given concurrently to RT [6]. Respecting dose constraints of the heart and lung would minimize late toxicities to these organs, thus improving the quality of life in long-term survivors.

Despite the need to homogeneously irradiate the whole breast, quite often, in the adjuvant setting, regional lymph node irradiation is added. This was previously done with the addition of direct fields comprising the supraclavicular and/or IMC and sometimes the axillary regions, that were quite hard to design and match with the tangential fields, often resulting in areas of hyperdosage (hot spots) and therefore, increased toxicities. Matching field junctions with conventional RT is always challenging; IMRT currently emerges offering treatment planning advantages in terms of dose homogeneity, conformality, and organs at risk sparing in these cases. In addition, partial breast irradiation, a technique which has gained some evidence-based indications in the adjuvant setting of early breast cancer treatment might be optimally performed with the use of IMRT.

Compared with conventional treatment modalities, IMRT technique subjects a greater amount of normal tissue to low doses (5–10 Gy), and concerns regarding the increased risk of secondary malignancies with this technique may be raised. At the moment, this remains an open field of debate pending further long-term research. It is already known that with traditional RT techniques, secondary malignancy risk in breast cancer patients is higher compared with patients who did not receive RT [7–9]. To date, there is no clinical study answering the question if the recognized secondary malignancy incidents and mortality rates as with traditional radiation techniques increase with the use of IMRT, obviously due to the small time frame of IMRT implementation and the long (more than 10–15 years) follow-up needed to reach any meaningful conclusions.

HT is currently one of the most sophisticated forms of IMRT implemented in clinical practice. The clinical impact of modern techniques, including HT, on survival and local control outcomes, as well as long-term toxicities is not yet clear because these techniques are new. There are many dosimetric comparison studies to investigate the advantages or disadvantages of HT over traditional treatment modalities and static IMRT techniques. Differences among treatment planning details make it difficult to compare different studies and treatment modalities. Differences between planned and delivered dose distributions due to the interplay between respiratory and MLC motion and dose calculation inaccuracy for lesions close to the skin are other factors that make plan comparisons difficult [10, 11].

23.4 Left-Side Breast Carcinoma Irradiation With Tomotherapy

It is well established that women treated with WBRT for left breast cancer are at high risk of cardiac mortality due to the proximity of the heart [12, 13]. Correa and colleagues showed a significantly higher prevalence of stress test abnormalities

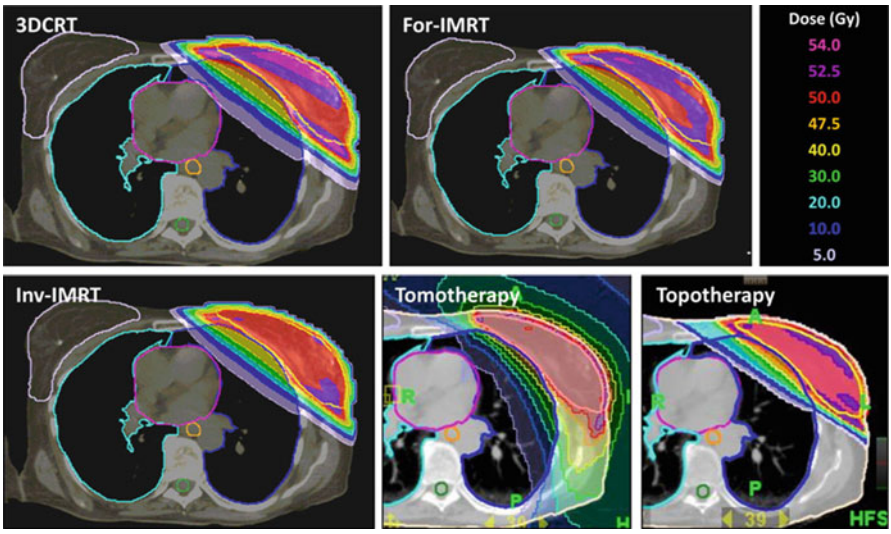

Fig. 23.2 Dose distributions of 3D-CRT, forward IMRT, inverse IMRT, HT, and topotherapy plans for one representative patient [16]

among left-side irradiated patients vs. right-side irradiated patients in their retrospective analysis. They also reported that 70% of left-side abnormalities were found in the left anterior descending (LAD) coronary artery area [14]. Right breast irradiation has been shown as a risk factor for cardiac mortality in several studies as well [14–16].

The maximum heart depth (MHD) has a linear relationship with mean heart and LAD coronary artery dose [17, 18]. The risk of cardiac mortality is much higher in women with anatomic variation of the heart and left ventricle location [19]. Coon et al. [17] made a dosimetric study to compare 3D-CRT, IMRT, and HT treatment planning in 15 selected patients with left side tumor postlumpectomy, who had MHD of greater than or equal to 1 cm. The mean heart V35, mean lung dose, and contralateral breast mean dose delivered with HT was significantly higher from the other two treatment techniques of 3D-CRT and IMRT.

Schubert et al. [20] did not find a significant difference for the coverage of the intact breast in their dosimetric study of 10 patients with left-side breast carcinoma, comparing inverse (HT, topotherapy, inverse IMRT) and forward (3D-CRT, forward IMRT) planned modalities. The inverse planned modalities result in significant reduction of high doses to the target and normal tissues. Figure 23.2 shows the dose distributions for different treatment modalities for one representative patient in this study.

23.5 Regional Lymph Node Irradiation With Tomotherapy

As already mentioned, inclusion of the IMC and axillary, as well as supraclavicular lymph node regions in the target volume is an additional challenge for locoregional breast RT due to matching field junctions. Treatment planning studies evaluating

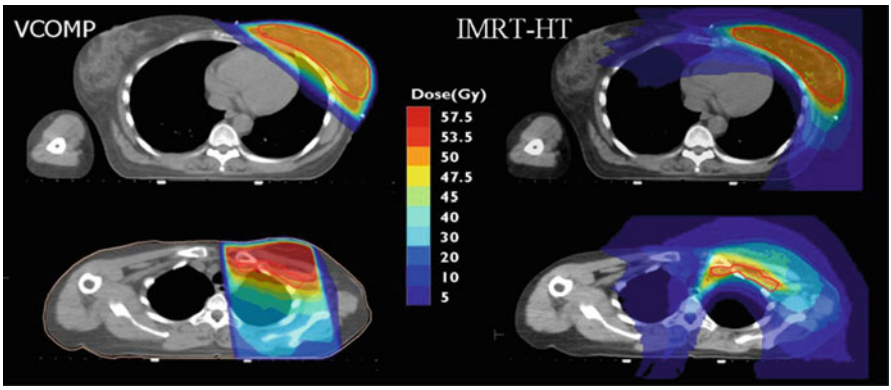

Fig. 23.3 Dose distributions of VCOMP plan (left) and IMRT-HT plan (right) for the same patient and CT image. With the IMRT-HT plan, the high-level isodoses are highly conformal to the target volume and spare the lungs and heart, but a larger volume of normal tissue receiving low radiation dose, (between 5 and 10 Gy) is observed [17]

LINAC-based IMRT techniques reported a decrease in the proportion of normal tissues irradiated to a high dose with similar target volume coverage [21]. Caudrelier et al. [21] compared a 3–4 field virtual compensation (VCOMP) forward-planned IMRT technique with HT treatment planning on 10 women with left-side breast carcinoma with a planning target volume (PTV) defined by breast ($n = 5$)/chest wall ($n = 5$) and regional lymph nodes including IMC. Homogeneity was superior with HT, while there was no significant difference in terms of PTV coverage, as measured by volume distribution (VD) 90% and VD 95%, between the two different techniques. The mean dose for the lungs was significantly lower in HT planning. The lung and heart volumes irradiated to a high-dose level were reduced with HT compared with the VCOMP technique [21]. Figure 23.3 shows the different dose distributions of the two treatment planning modalities with a prescription dose of 50 Gy in 25 fractions, through the CT image of a representative patient. High level isodoses are highly conformal to the target volume, yet a larger volume of normal tissue receives a low radiation dose with the HT planning.

23.6 Post-mastectomy Radiotherapy With Tomotherapy

There is no standard approach for the postmastectomy RT of the chest wall and regional lymph nodes [22]. Field junctions and chest wall dose heterogeneity are the main problems with conventional techniques. Krueger et al. [23] showed the dosimetric advantage of fixed-beam IMRT in terms of chest wall coverage over a conventional mixed-beam plan technique in their study. Another dosimetric study to compare a conventional mixed-beam plan technique with HT has been conducted by Ashenafi et al. [24]. They developed an HT plan for five patients that were previously treated with a conventional mixed-beam plan technique with a prescription

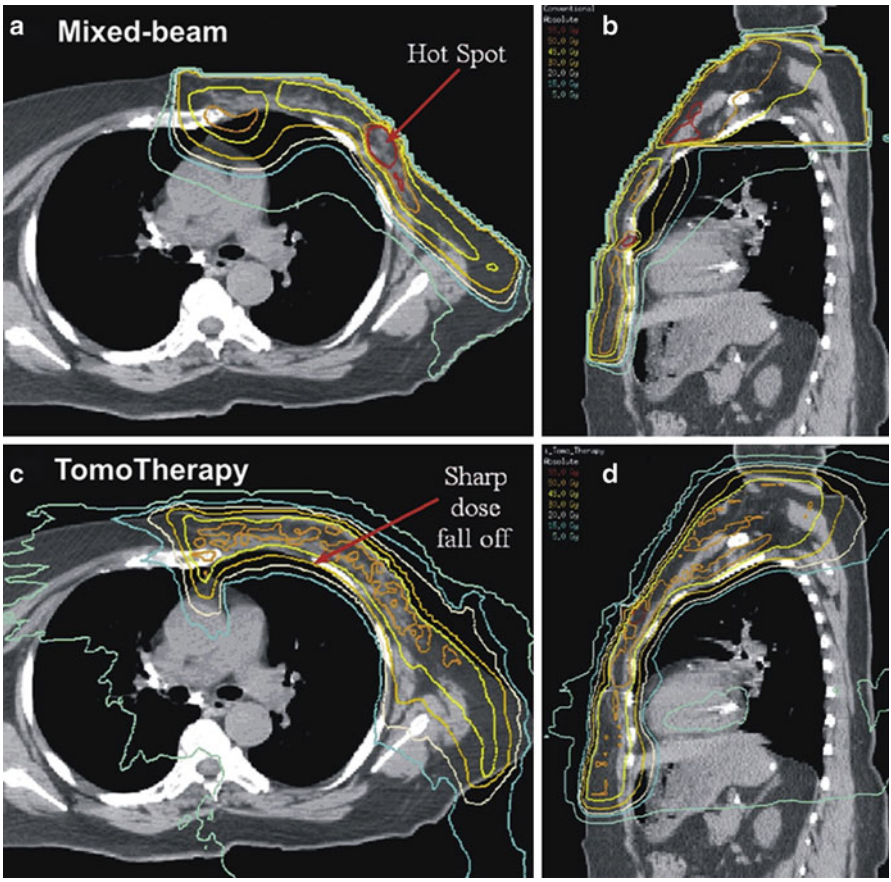

Fig. 23.4 Transverse and sagittal views of dose distributions (**a**, **b**) for conventional mixed-beam plan (**c**, **d**) and tomotherapy plan taken through internal mammary node region. Isodose contours are 5, 15, 20, 30, 45, 50, and 55 Gy [20]

dose of 50 and 45 Gy in 25 fractions for chest wall, IMC, supraclavicular lymph nodes and axillary lymph nodes, respectively. Figure 23.4 shows dose distribution differences among the conventional mixed-beam plans (Fig. 23.4[a] and [b]) and HT plans (Fig. 23.4[c] and [d]) for a patient from the study. With HT planning, dose inhomogeneity at the field abutments had not been observed. Dose homogeneity in the chest wall/IMN PTV was significantly better with HT plans, generally showing larger volumes of low dose (less than 5 Gy) for the lung and the contralateral breast. For the ipsilateral lung and the heart, HT plans delivered a higher dose to the smaller volumes and a lower dose to the larger volumes, compared to conventional mixed-beam plans. Improved dose homogeneity in target volumes offers improved posttherapy cosmesis. There is a slight improvement in the V20 of the ipsilateral lung with the HT technique. To ensure sufficient skin dose near the surface and to account for breathing movements, the authors suggest using a bolus on the chest wall for all or a part of the HT treatment.

Further studies are needed to evaluate the dosimetric and clinical benefits of HT application in postmastectomy cases. The results of four previously reported treatment planning studies comparing HT treatment planning with conventional techniques are summarized in Table 23.1 in terms of heart and ipsilateral lung protection.

23.7 Accelerated Partial Breast Irradiation With Tomotherapy

Accelerated partial breast irradiation (APBI) is a new kind of adjuvant RT concept for patients with early-stage breast carcinoma who underwent BCS such as lumpectomy, and who fulfill strict criteria, as well as a means for reirradiation for women who have already undergone adjuvant WBRT [25]. Although BCS has obvious advantages over mastectomy, its utilization remains a challenge mainly due to patient compliance with the adjuvant WBRT, related to the long treatment duration (6–7 weeks).

APBI emerges as an alternative to WBRT for selected patients not compliant to classic breast conservation therapy steps, and has additional advantages in terms of normal tissue protection. Despite many randomized clinical trials, the patient selection criteria, optimal techniques, target volume definition and delineation, as well as optimal dose and fractionation models for APBI are not yet clear.

There is a variety of techniques available for APBI such as interstitial brachytherapy (IB), intraoperative RT and external-beam conformal radiation therapy (EBCRT) including 3D-CRT, IMRT, HT, volumetric arc therapy, and proton beam therapy (PBT). Each technique for APBI has its own benefits and disadvantages. Breast size, location of the lumpectomy cavity, and sources of treatment center might dictate which technique to use. Breathing motion and treatment set-up variation are the main problems concerning EBCRT. The integration of IMRT and image-guided radiation therapy (IGRT) that incorporates a rapid automatching system for daily positional corrections before treatment delivery makes HT a potential candidate for APBI.

Dosimetric comparison studies of HT and different treatment modalities for APBI have been conducted by various researchers including Moon et al. [26], Oliver et al. [27] and Patel et al. [28]. Moon et al. [26] reported that all modalities showed acceptable coverage of the PTV, however, HT provided the most conformal plan compared with 3D-CRT, IMRT, PBT, while IMRT provided the most homogeneous plan. Ipsilateral lung volume percentage receiving 20% of the prescribed dose was significantly lower in PBT (0.4%) and IMRT (2. %), compared with 3D-CRT (6.0%) and HT (14.2%). PBT was found to be the best technique for sparing the ipsilateral normal breast. Although the contralateral breast and lung were completely blocked, and the stepwise directional blocking technique in each case of HT planning was used, the lower dose to the ipsilateral lung was considerable. Comparing APBI techniques with WBRT, Oliver et al. [27] showed significantly lower doses to organs at risk (OAR) for all APBI techniques (tangential fields, 3D-CRT, IMRT, HT), except for the mean dose of the contralateral breast and lung with HT, which were not significantly different as compared with WBRT.

Table 23.1 Summary of selected dosimetric breast RT studies for heart and ipsilateral lung dose metrics

Author	Population Studied	Structures and Metrics	HT	3D-CRT	Inverse IMRT	Forward IMRT
Coon [13]	15 patients left side. PTV: intact breast. Dose: 50.4 Gy	Heart				
		V35 (%)	0.5	3.6	0.7	–
		Ipsilateral lung				
		V20 (%)	18	15	22	–
Schubert [16]	10 patients left side. PTV: intact breast. Dose: 50 Gy	Heart				
		V5 (%)	26.5 ± 18.4	7.6 ± 3.5	5.0 ± 3.1	6.6 ± 3.5
		V10 (%)	4.8 ± 4.4	4.2 ± 2.5	2.5 ± 2.0	3.8 ± 2.4
		V20 (%)	0.5 ± 0.4	2.0 ± 1.6	1.2 ± 1.4	2.2 ± 1.7
		V30 (%)	0.0 ± 0.0	0.3 ± 0.5	0.0 ± 0.0	0.1 ± 0.2
		Ipsilateral lung				
		V20 (%)	19.4 ± 4.0	14.8 ± 3.9	11.8 ± 4.7	14.5 ± 0.7
Caudrelier [17]	10 patients left side. PTV ($n = 5$): intact breast + IMC + regional nodal area. PTV($n = 5$): chest wall + IMC + regional nodal area. Dose: 50 Gy	Heart				
		V5 (%)	38.3 ± 17.2	–	–	41.0 ± 22.8
		V30 (%)	1.5 ± 1.9	–	–	3.2 ± 2.2
		V45 (%)	0.02 ± 0.0006	–	–	1.6 ± 1.4
		Ipsilateral lung				
		V20 (%)	9.2 ± 3.8	–	–	31.2 ± 5.3
Ashenafi [20]	5 patients (4 left, 1 right side). PTV: chest wall + IMC + regional nodal area. Dose: 50 Gy (45 Gy for axilla)	Heart*				
		V15 (%)	9.5 ± 4.6	9.5 ± 6.2	–	–
		Ipsilateral lung				
		V20 (%)	17.6 ± 7.8	21.5 ± 8.5	–	–

*Patient with right side mastectomy excluded.

PTV planning target volume; *IMC* internal mammary chain; Vx = volume (%) receiving $\geq x$ dose

Data presented as mean or mean ± standard deviation

23.8 Other Issues: Prone Position and Patient Alignment

The standard patient is usually supine on a carbon fiber breast board and both arms are extended above the head during EBCRT administration. The prone position is not commonly used as it is uncomfortable to some patients and requires a special immobilization device. The patients with small breast volume or with a challenging anatomy are not suitable for the prone position. However, for some patients with large breasts, the prone position has some advantages over the supine technique. Furthermore, EBCRT can reduce the ipsilateral lung dose because of the separation of the lumpectomy site farther from the ipsilateral lung. Formenti et al. [29] suggest that the prone patient position may also minimize the target tissue movement during breathing.

To our knowledge, Patel et al. [28] are the first to study the prone position with HT for APBI. They compared IB, 3D-CRT, and prone and supine position HT in their dosimetric study. They reported that mean lung dose was significantly higher with the supine external-beam techniques in comparison with IB and prone position HT, while there was no difference for PTV coverage and heart doses. Kainz et al. [30] have also studied the feasibility of prone position HT for APBI and found conformal and uniform PTV coverage with adequate sparing of organs at risk, but the average maximum point dose for the contralateral breast was above the Radiation Therapy Oncology Group 0413 protocol dose constraints.

The verification of proper patient alignment should also be considered when evaluating different techniques. Langen et al. [31] studied the precision of MVCT alignments based on contrast differences between the seroma cavity and the soft tissue for APBI with HT. The precision of the MVCT-based alignment was better than 2-mm imprecision when averaged over the patient population. It should also be considered that patient set-up with MVCT-based alignment cannot reduce the effect of intrafraction breathing motion and this should be accounted for in the CTV–PTV margin. However, the lumpectomy seroma and the postsurgical clips are not necessarily visible on MVCT images for each case; hence, for these cases alignment should depend on other anatomic locations such as bony anatomy or the skin surface.

23.9 University of Lausanne (CHUV) Experience With Tomotherapy in Breast Cancer

The Radiotherapy Department in the Centre Hospitalier Universitaire Vaudois (CHUV) has been equipped with two tomotherapy solutions since 2009. Since that time, 94 patients with breast cancer have been treated with an HT technique. The HT technique was preferred in the most challenging cases such as:

- Adjuvant irradiation of the thoracic wall and the regional lymph nodes (supraclavicular and IMC), particularly in left breasts, after mastectomy and axillary resection (Figs. 23.5–23.7)
- Adjuvant irradiation of the whole breast and the regional lymph nodes (supraclavicular and IMC), particularly in left breasts in selected patient

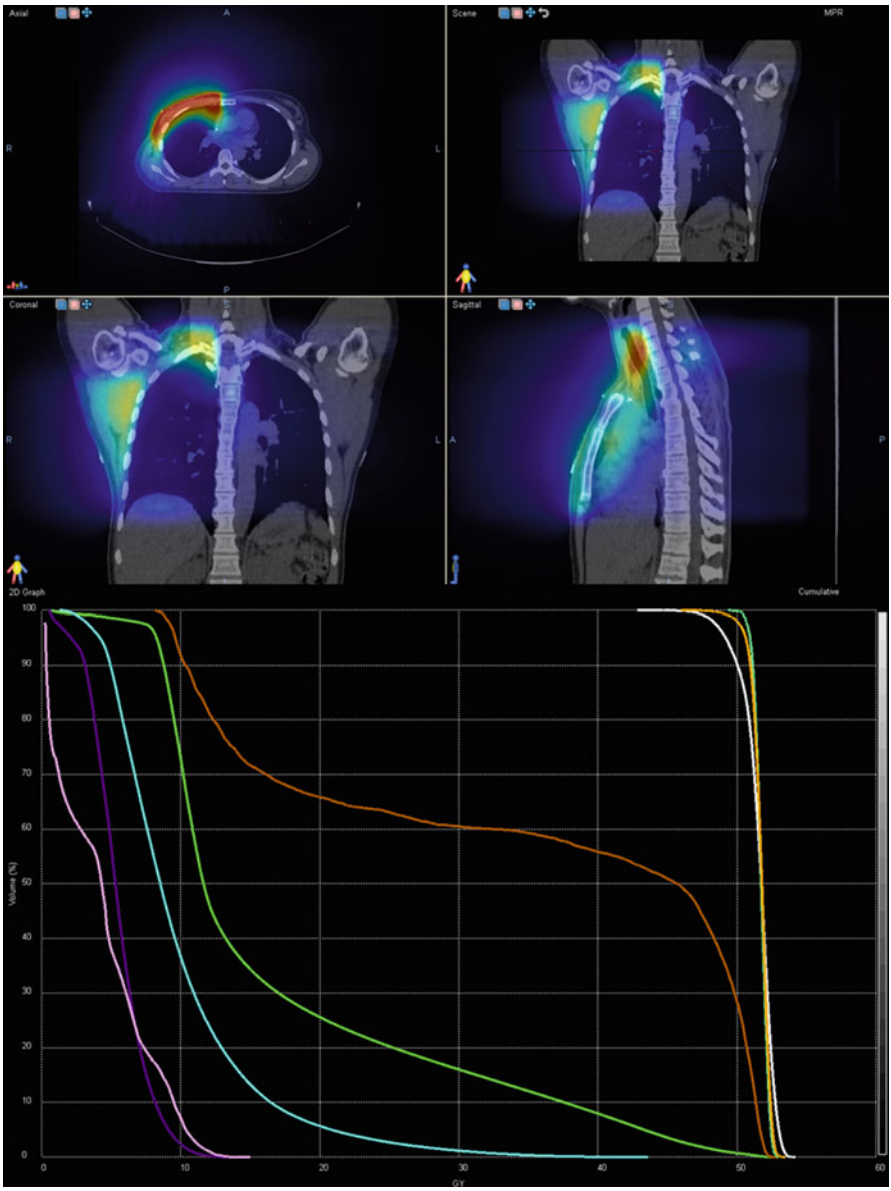

Fig. 23.5 Dose distribution and DVH of a patient in whom the right chest wall and regional lymph nodes have been irradiated. DVH: *pink*, spinal cord; *light green*, right lung; *mauve*, left lung; *orange*, *light green,* and *light pink*, PTV of supraclavicle, chest wall, and IMC, respectively; *brown*, clavicula; *light blue*, heart

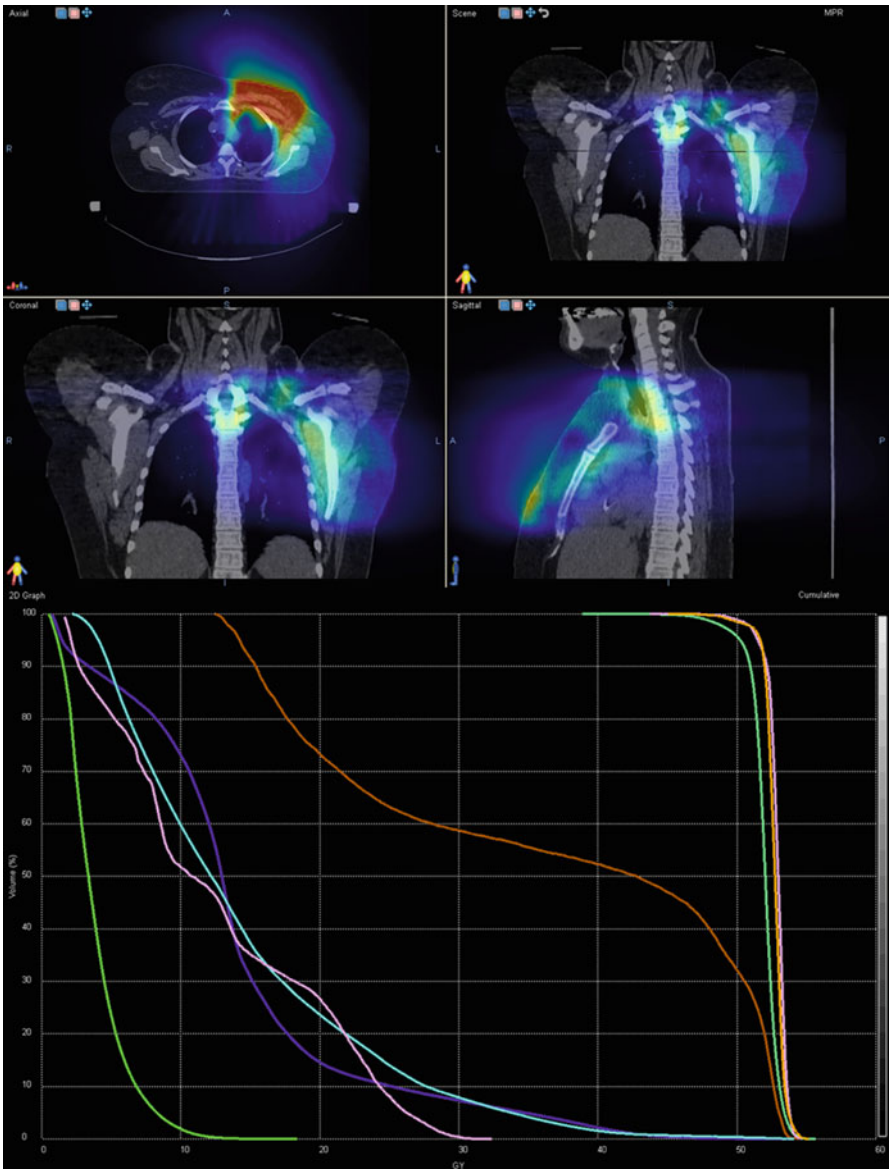

Fig. 23.6 Dose distribution and DVH of a patient in whom the left chest wall, supraclavicle, and IMC have been irradiated. DVH: *brown*, clavicula; *light blue*, heart; *pink*, spinal cord; *mauve*, left lung and PTV of left IMC; *light green*, right lung and PTV left chest wall; *orange*, PTV left supraclavicle

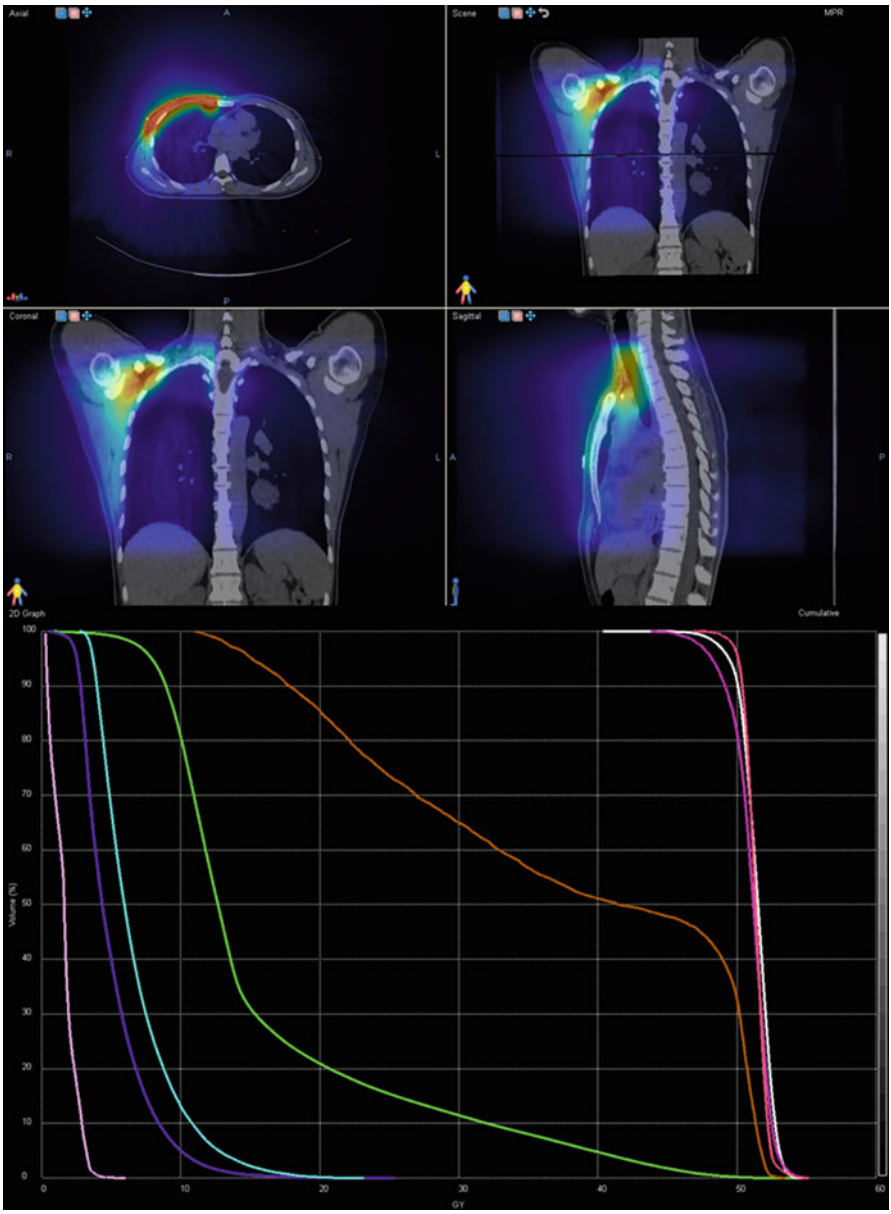

Fig. 23.7 Local (right chest wall) and regional (supraclavicular and IMC) irradiation after mastectomy (dose distribution and DVH). DVH: *pink*, spinal cord; *light green*, right lung; *mauve*, left lung; *vivid pink*, *white,* and *fuschia*, PTV of supraclavicle, chest wall, and IMC, respectively; *brown*, clavicula; *light blue*, heart

anatomies where too much heart and/or lung was otherwise irradiated with conventional techniques (Fig. 23.8)
- Reirradiation of a recurrence in the same breast, the thoracic wall, or in the axilla (Fig. 23.9)
- Irradiation of the contralateral breast for a second breast cancer
- Reirradiation of the breast after RT for other malignancies (lymphoma)
- Presence of breast implants during irradiation and challenging regional field irradiation (Fig. 23.6)
- Only local or only regional irradiation in cases with specific indications (Fig. 23.9).

In these cases, the HT technique provided the possibility to minimize the dose to normal tissues and to more conformally irradiate complicated volumes, while sparing completely, if desired specific normal tissue sites. This resulted in more satisfactory dose-volume histogram (DVHs) for a given patient, compared with a 3D technique. Toxicities were acceptable and compared well with traditional techniques (unpublished data). The following are several examples of cases where an HT technique was preferred and used instead of routine 3D-RT. Figure 23.5 illustrates the dose distribution and DVH of a patient in whom the right thoracic wall and regional lymph nodes are irradiated (supraclavicular and IMC), at a dose of 50 Gy (thoracic wall and regional nodes) with a boost to 66 Gy at the mastectomy scar for a ductal, Her-2 positive carcinoma pT1cpN2acM0 of the right breast, treated with mastectomy, sentinel lymph node dissection, followed by axillary dissection (2/23), and adjuvant chemotherapy.

- Irradiation of left chest wall, supraclavicular, and IMC is shown in Figure 23.6 in a patient with a ductal, Her-2 positive carcinoma of the left breast, cT4bcN2acM0, treated by neoadjuvant chemotherapy, mastectomy, and axillary dissection (ypTisypN0 [0/19]), as well as adjuvant trastuzumab. The thoracic wall and regional lymph nodes have been treated at a dose of 50 Gy.
- Figure 23.7 illustrates the local (right thoracic wall) and regional (supraclavicular and IMC) irradiation after mastectomy in a patient with ductal, luminal B carcinoma of both breasts: right breast: pT2pN3 (16/22)cM0, left breast: pT1cpN0cM0, treated by bilateral tumorectomy, sentinel node dissection, and right axillary dissection. This patient proved to be BRCA2 positive, therefore, a prophylactic left mastectomy followed, while a right mastectomy was performed for positive margins. The patient also received adjuvant chemotherapy and hormone therapy. The total dose to the left thoracic wall and regional lymph nodes has been 50 Gy with a boost to 66 Gy on the mastectomy scar.
- Below the images of left breast irradiation, as well as regional (supraclavicular and IMC) irradiation after tumorectomy (Fig. 23.8) in a patient with a ductal, triple-negative carcinoma of the left breast, pT2pN2a(4/15)cM0, treated with tumorectomy and axillary dissection, as well as adjuvant chemotherapy. The total dose to the whole breast and regional lymph nodes has been 50 Gy, followed by a boost to the tumorectomy bed to 66 Gy.
- In Figure 23.9(a), the dose distribution of the first irradiation for a patient who was then irradiated (Fig. 23.9[b]) in the contralateral axilla is given. Each dose distribution is followed by the respective DVHs.

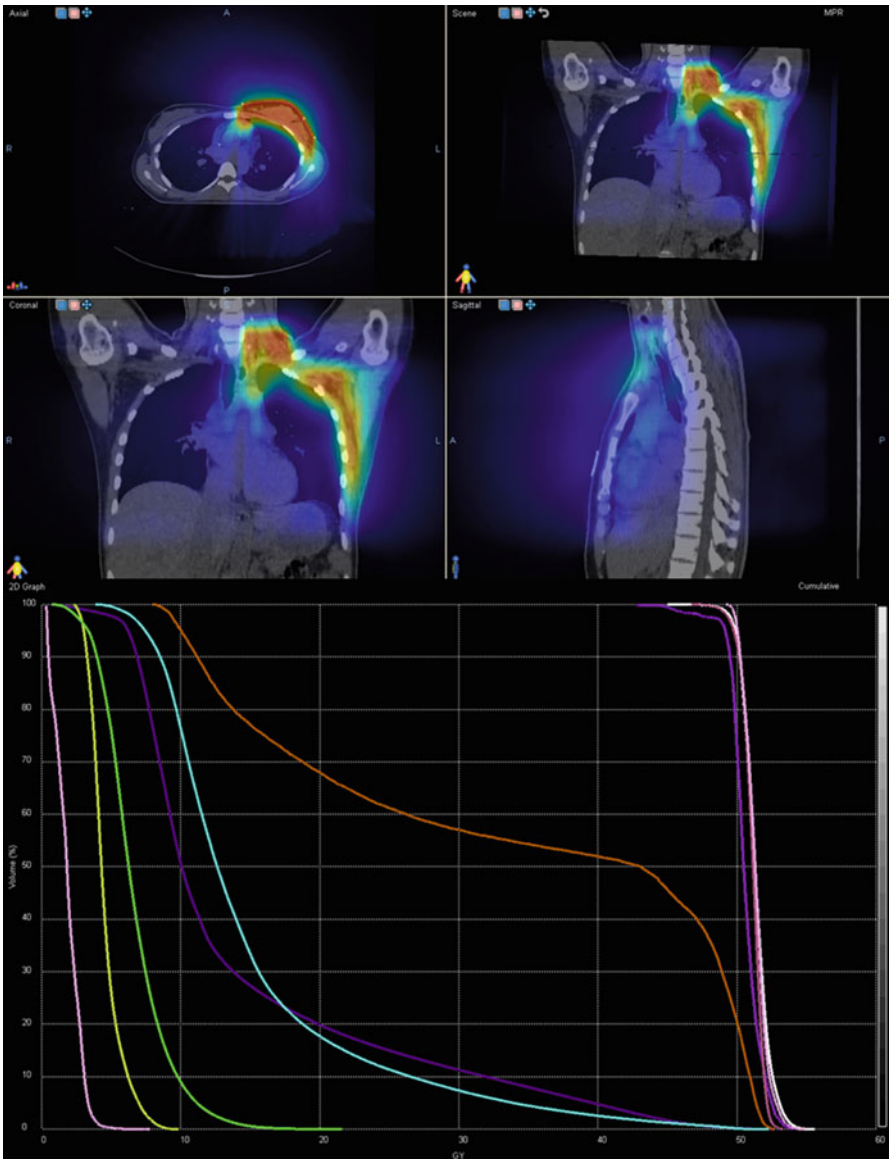

Fig. 23.8 Left breast irradiation as well as regional (supraclavicular and IMC) irradiation after tumorectomy (dose distribution and DVH). DVH: *brown*, clavicula; *red–brown*, clips; *light blue*, heart; *pink,* spinal cord; *light green*, right lung; *mauve*, left lung; *dark pink*, PTV boost; *fuschia*, PTV of left breast and IMC; *mauve*, PTV of left IMC; *white*, PTV of left breast; dark mauve, PTV of left supraclavicle; *yellow*, right breast

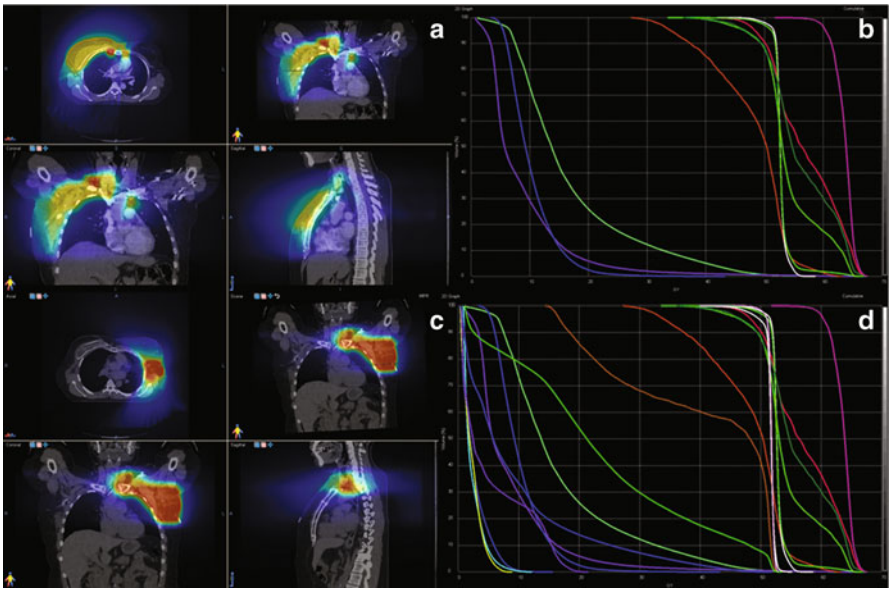

Fig. 23.9 (**a**) The dose distribution of the first irradiation for a patient, who was then irradiated, (**b**) in the contralateral axilla is given. Each dose distribution is followed by the respective DVHs (dose distribution and DVH). Treatment 1: DVH: *brown*, clavicula; *blue*, heart; *fuschia*, spinal cord and PTV boost 61.6 Gy; *green*, right lung; *mauve*, left lung; *light green*, PTV 50.4 Gy and PTV of right supraclavicle; *red*, PTV of right IMC; *dark green*, PTV of left IMC; *white-pink*, PTV of right chest wall. Treatment 2: DVH: *brown,* clavicula; *light blue*, heart; *mauve*, spinal cord; *green*, body; *blue*, right and left lung; *white*, PTV of axilla and interpectoral region; *pink,* PTV of supraclavicle; *yellow*, right breast; *green*, left breast

23.9.1 Treatment 1

The patient initially presented with a ductal, triple-negative cancer of the right breast (cT3cN3cM1 [IMC]) and was treated with neoadjuvant chemotherapy, radical right mastectomy. and right axillary dissection, followed by immediate reconstruction and adjuvant locoregional RT (50.4 Gy thoracic wall, and right axillary, supraclavicular and IMC regions with a boost to 61.6 Gy to positive lymph nodes), with an excellent outcome.

23.9.2 Treatment 2

One year later, the patient had a distant failure with axillary left nodes that were treated with chemotherapy and were excised (capsular effraction in three positive nodes). In view of the excellent response and the distant control of the disease, the

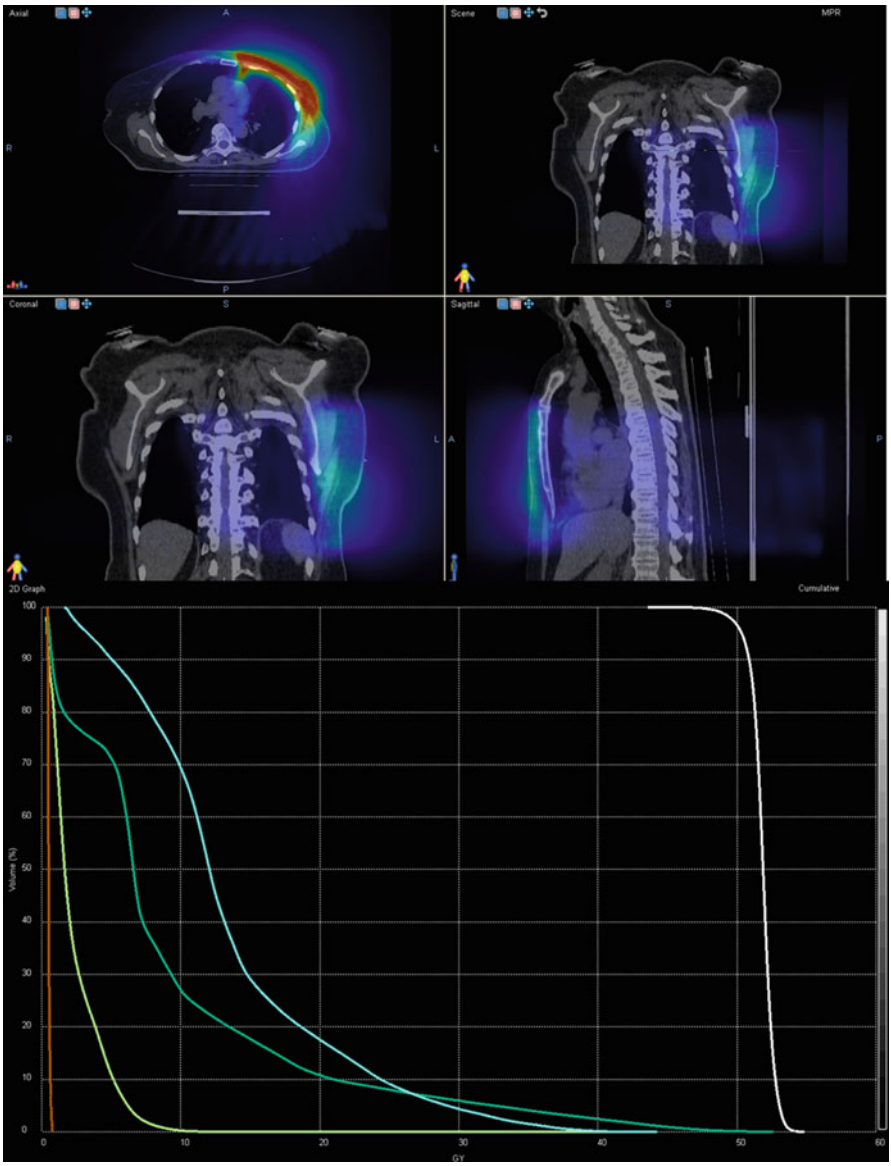

Fig. 23.10 Irradiation of the left chest wall alone (dose distribution and DVH). DVH: *brown*, clavicula; *light blue*, heart; *light green*, right lung; *dark green*, left lung; *white*, PTV of chest wall

patient was offered adjuvant locoregional RT to the left axillary and supraclavicular region, following a progression of the disease in the left axilla after resection, at a dose of 50 Gy.

- Images are shown of irradiation of only the left chest wall (Fig. 23.10) in a patient suffering from a left breast ductal, luminal cancer, initially cT3cN1cM0, for which the patient underwent neoadjuvant chemotherapy, mastectomy, and axillary dissection (ypT1ypN0 (0/12)cM0). Given the very large initial T stage (9 cm) and the cN1, ypN0 stage, the patient only received local adjuvant irradiation to the chest wall to a dose of 50 Gy.

23.10 Conclusion

We do not have robust clinical data to show the superiority of one technique over another. Because breast RT is one of the most frequently used techniques, it can be suggested that it should be made as simple as possible in order to rationalize departmental resources. Although the potential advantages of IMRT and HT over traditional techniques are easy to demonstrate qualitatively in dosimetric studies, the advantages are not yet fully appreciated. There is a need for clinical studies with long-term follow-up to show the clinical impact of advanced technologies and techniques. The positioning and treatment technique selection must be tailored to patient anatomy, location of the lumpectomy cavity, and comorbid factors. However, HT provides a valuable advantage when complex volumes need to be irradiated and specific structures need to be avoided in challenging breast cancer cases. Furthermore, it possibly provides the opportunity to improve breast cancer treatment overall, and the perspective, in a future setting, when toxicities should need to be minimized, to make that available to all patients.

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Part V
Radiotherapy Complications in Breast Cancer

Chapter 24
Radiotherapy Complications

Meltem Nalca Andrieu

24.1 Introduction

Cumulating data confirm the beneficial effect of radiotherapy in women with breast cancer. After mastectomy and breast-conserving surgery, this effect is expressed by a significant decrease in the local relapse rate and, in the former, by increased survival [1–4]. Postoperative radiotherapy, however, is associated with some complications that may affect patient quality of life (QOL) and possibly survival [5]. With an increasing number of breast cancer survivors, reducing the morbidity of treatment side effects is of high priority and has become the focus of research in recent years.

Radiation-induced complications are typically expressed in two, often quite distinct, waves (Table 24.1). The first wave is seen during or immediately after radiotherapy; it reaches a peak and will usually heal completely within a few weeks. The second wave is seen in patients after latent periods ranging from several months to several years. These are the late reactions that may become progressively more severe in individual cases and that are generally irreversible, sometimes severely affecting the patient's life [6]. Much research has been done on the clinical presentation and the pathophysiology of radiation-related morbidity. The pathogenesis is often complex, involving several possible pathways, and these may change in relative importance depending on the dose-fractionation details and the possible influence from other treatment modalities or patient-related factors. Furthermore, the symptoms and signs and the ability to cope with these morbidities vary considerably among patients [6].

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Table 24.1 Complications of breast radiotherapy

	Time	Complication
Early complications	During RT	Acute skin reactions
		Fatigue
		Breast edema
		Fat necrosis
Late complications	Weeks to months after RT	Dystrophic calcifications
		Radiation-induced pneumonia
		Skin retraction with breast fibrosis
		Telangiectazia
		Glandular atrophy
	Months to years after RT	Overlying bone fracture
		Lymphedema
		Shoulder immobility
		Brachial plexopathy
		Pulmonary fibrosis
		Pericardial disease
	10 years after RT	Cardiomyopathy
		Radiation-induced malignancy

24.2 Early Complications

The early complications of breast radiotherapy arise during the treatment, or weeks to months after the completion of radiotherapy, including acute skin alterations, breast edema, fat necrosis, dystrophic calcifications, radiation-induced pneumonia, and pleural effusion. Acute side effects of treatment are generally common in occurrence, self-limiting, and resolve within 4–6 weeks after radiotherapy is completed.

24.2.1 Acute Skin Reactions

Many patients who undergo radiotherapy treatment develop radiation-induced skin toxicity. The severity of the reaction has been attributed to treatment-related factors such as beam energy, dose per fraction, treatment duration, use of bolus, treatment site, as well as patient-specific factors such as skin type and diabetes [7–9]. Following the exposure of the skin to ionizing radiation, several distinct phases of response may be seen. The first is a transient early erythema seen within a few hours of irradiation, which subsides after 24–48 h. This is believed to be an inflammatory response [10]. The reddening of the skin is thought to represent a secondary inflammatory reaction or hyperemia. The main erythematous reaction, indirectly reflecting a varying severity of loss of epidermal basal cells; either a dry or a moist desquamatory response may be seen 3–6 weeks after beginning radiation treatment. It has been shown that the fields treated with 2 Gy daily fractionation do

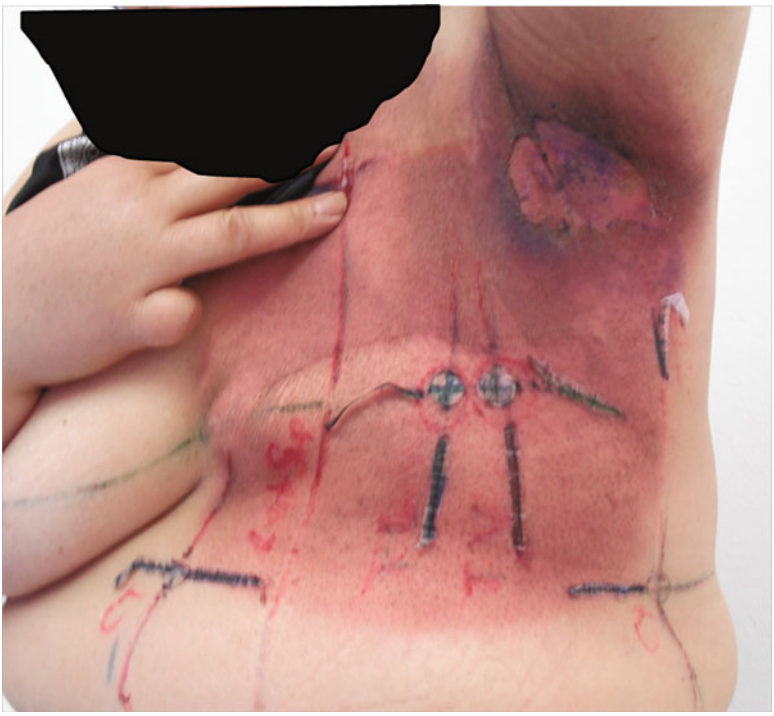

Fig. 24.1 Dry and moist desquamation

not exhibit changes in the basal cell density until total doses of 20–25 Gy are delivered [10, 11]. Induction of tyrosine kinase activity in the melanocytes may result in hyperpigmentation starting at the second and third weeks of treatment which may disappear in 3–12 months. 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 desquamation in the treated area. This is typically seen at doses greater than or equal to 45 Gy. If new cell proliferation is inadequate, moist desquamation occurs with exposed dermis and oozing of serum between the doses of 45 and 60 Gy. 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 the smaller boost volumes of the tumor bed. With this standard dosing, breast radiation will cause skin erythema and dry desquamation in 80–90% of patients, and in 30–50% the erythema may be more severe and associated with skin tenderness. Patchy moist desquamation confined mostly to skin folds such as the axilla or the inframammary fold can be seen in 5–10% of patients [10, 11]. A patient with dry and moist desquamation at the end of the treatment is shown in Figure 24.1. Acute skin reactions are mostly evaluated between grades 0 to 4 according to the Radiation Therapy Oncology Group acute toxicity scoring for skin [12].

Multiple studies have examined prevention and treatment of acute skin reactions. A meta-analysis and a systematic review of the literature on this topic was conducted to guide clinical decision making about prevention and treatment of acute skin reactions [13, 14]. In summary, it was demonstrated that there is limited and often conflicting information available on the management of radiation-induced skin toxicity. It is difficult to derive specific recommendations for management. The evidence available in the literature varied greatly in methodology, clinical outcomes, treatment site, radiotherapy regimes, and number of participants. However, evidence from the literature suggests gentle washing with water alone [15] or with mild soap and water [16], and the use of Calendula ointment in reducing grade 2 or higher skin toxicity during breast irradiation. Opinions of the supportive care guidelines recommended that the initial use of a plain, nonscented, lanolin-free, hydrophilic cream is helpful for patients experiencing radiation skin reactions. The cream should be discontinued when skin breakdown occurs. Low dose (i.e., 1%) of corticosteroid cream may be beneficial in the reduction of itching and irritation [17]. Caution must be used to avoid the overuse of a corticosteroid cream [18]. There was insufficient evidence to support or refute specific topical or oral agents for the prevention or management of acute skin reaction.

24.2.2 Fatigue

Radiation-related fatigue may be mild to moderate and mostly peaks at the fourth week of the treatment. Although it returns to the baseline levels by 4–6 weeks after the completion of the irradiation, it can have a significant effect on patients' daily functions and overall QOL [19, 20]. During a course of breast radiation, it is important to guide the patient regarding self-management of fatigue. Patients should be encouraged to give priority to essential activities and to postpone the nonessential ones [10]. Treatment of specific causes related to fatigue such as anemia, depression, anxiety, and insomnia should be undertaken [21]. There is also convincing clinical evidence showing that exercise can be an effective strategy to minimize fatigue symptoms during treatment when a patients feels well enough to undertake it [22].

24.2.3 Breast Edema

During the acute period after irradiation, inflammatory markers are induced and the expression of these proteins contributes to increased vascular permeability of breast tissue [23]. Breast edema that manifests as skin and trabecular thickening generally appears in the first several weeks following completion of radiotherapy. The edema usually resolves over a period of weeks, months, or sometimes even years. Radiographically, an irradiated breast with skin and trabecular thickening appears denser as compared with the contralateral normal breast [14].

24.2.4 Fat Necrosis

Intimal arterial damage caused by radiation exposure combined with surgical damage may result in tissue necrosis directly or indirectly [24]. Mammographically, the presence of a radiolucent oil cyst, round opacity, asymmetrical opacity, heterogeneity of the subcutaneous tissue, dystrophic calcification, clustered pleomorphic microcalcification, or the presence of a spiculated mass as noted on ultrasound examination can demonstrate the presence of a solid or anechoic mass with posterior acoustic shadowing or enhancement and can demonstrate the presence of a cyst with a mural nodule or internal echo or increased echogenicity of the subcutaneous tissue. On positron emission tomography imaging, fat necrosis may be seen with variable metabolic activities according to the process of inflammation. Therefore, a lesion with hypermetabolic activity can mimic tumor recurrence. As seen on magnetic resonance imaging, fat necrosis is characterized by the presence of a fatty signal intensity mass, often containing a fat–fluid level that exhibits variable enhancement following the administration of gadolinium contrast material. The presence of central fat signal intensity is the key to differentiate fat necrosis from tumor recurrence, as breast cancers do not contain central fat [14].

24.2.5 Radiation-Induced Calcifications

Radiation-induced calcifications are benign dystrophic calcifications that are a result of a combination of surgical trauma and radiation exposure. The calcifications are generally large and irregular in pattern, with central lucency and calcifications that always occur at the site of surgery. In addition, it is common for sutures to calcify after radiotherapy. Calcified sutures are typically characteristic because calcified sutures are equally spaced along the suture line and the presence of calcified knots is frequently evident [14].

24.2.6 Radiation Pneumonitis

Radiation pneumonitis is consolidation or ground glass opacity that is localized in the radiation field resulting from acute exudation in the alveolar space and migration of inflammatory cells. Radiation pneumonitis occurs 4–12 weeks after completion of radiotherapy, and in most patients the pneumonitis resolves completely in 6–8 weeks without any long-term effects, or evolves into fibrosis when present with a more severe grade. Lung alterations are scored according to a scoring system devised by Nishioka et al. [25]. Symptomatic radiation pneumonitis is uncommon when only the breast is

irradiated. A positive correlation was found between the incidence of pulmonary complications and increasing ipsilateral lung volumes receiving greater than 20 Gy (V_{20}) [26]. Radiation lung damage is rarely seen below 20 Gy, whereas it is common in areas receiving 30–40 Gy, and almost inevitable over 40 Gy [5, 26, 27]. The incidence increases to 3–9% when nodal irradiation and chemotherapy is added [5, 28–31]. The probability of lung damage is related to total dose, fractionation, and irradiated lung volume [5, 26, 27, 32, 33]. A good predictor of lung complications of breast or chest wall only irradiation is central lung distance, with values less than 2–3 cm considered safe [34–37]. The effect of other factors is less clear [26, 34, 38]. Suggested variables include age, performance status, the use of chemotherapy, tamoxifen (or both), smoking, preexisting reduced lung function, coexisting heart disease and short overall treatment time [5, 6, 26, 29, 32, 33, 37, 39–41]. The data on the effect of high-dose chemotherapy are contradictory, whereas concomitant paclitaxel was reported to increase the risk of pneumonitis [26].

The typical clinical symptoms of radiation pneumonitis are dry cough, fever, shortness of breath, and radiologic changes confined to the treatment field. If the patient has significant symptoms of pneumonitis, traditionally, treatment with corticosteroids is used, although no randomized trials have demonstrated efficacy. A typical regimen is prednisone, 1 mg/kg/day for 2–4 weeks, with the dosage gradually reduced over 6–12 weeks. Marked symptomatic relief may be obtained. Relapse may occur when treatment is stopped [41, 42]. Radiation-induced effusion which is a pure transudate associated with radiation-induced pneumonitis may also be seen and slowly resolves on serial follow-up imaging with improvement of the condition [14].

24.3 Late Complications

The late complications of breast radiotherapy which may arise months to years after the completion of radiotherapy are skin retraction with breast fibrosis, telangiectasia, glandular atrophy, overlying bone fracture, lymphedema, shoulder immobility, brachial plexopathy, pulmonary fibrosis, and pericardial disease. Radiation-induced heart disease (RIHD) and radiation-induced malignancy may be also seen 10–20 years after the treatment. The late side effects of radiotherapy are seen infrequently compared with the acute complications, but mostly they may become progressively more severe in individual cases and are generally irreversible, sometimes severely affecting the life of the patient. Importantly, these radiation reactions are specific biological events, related directly to loss of parenchymal cells, or to the response to treatment at the tissue level (i.e., radiation-induced fibrosis, vascular damage, or tissue atrophy) [6].

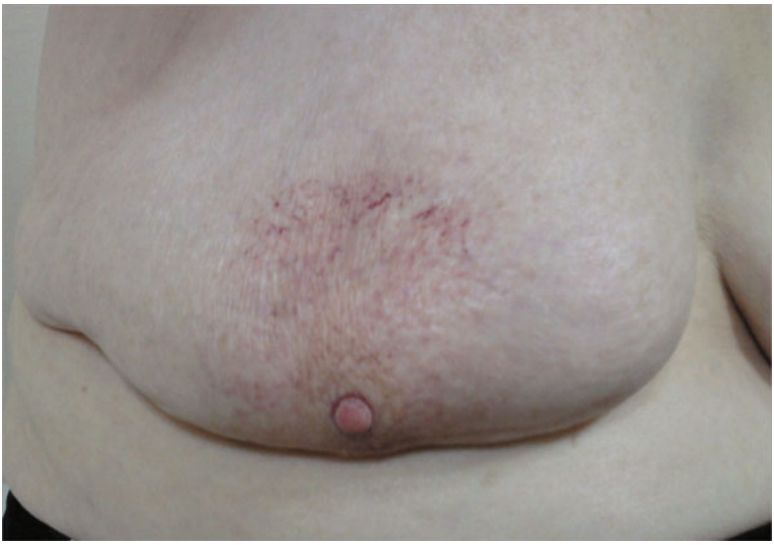

Fig. 24.2 Telengectasia over irradiated skin on the tumor cavity localization (boost dose field)

24.3.1 Glandular Atrophy, Breast Fibrosis, and Telangiectasia (Cosmesis)

The principal long-term effects that impair cosmesis are fibrosis, induration of the breast, and telangiectasia. Fibrosis and atrophy are the result of specific responses of skin and connective tissue to irradiation. Excessive abnormal fibroblast proliferation and excessive synthesis of extracellular matrix are the main reasons of fibrosis. In some cases, radiation-induced breast edema progresses to become a permanent fibrotic change with glandular atrophy. Dermal atrophy appears in 26 weeks and shows thinning of the dermal tissues associated with the contraction of the previously irradiated area. Depending on the severity of late normal tissue changes, the clinical picture includes induration, hardening, change in shape, and decrease in volume of the treated breast [43]. The breast parenchyma gradually shrinks and is denser as compared with the contralateral normal breast. Telangiectasia which is an atypical dilation of the superficial dermal capillaries can also occur following irradiation. Telangiectasia may be seen in a year and the incidence increases over time, like fibrosis. A follow-up study of mastectomy patients after radiotherapy showed that 90% of moderate or severe complications were present within 3.2 and 4.7 years for fibrosis and telangiectasia, respectively [44]. Although the frequencies of the complications seem to reach a stable level within 3–5 years, the clinical picture of damage may progress in individual patients over time [44, 45]. Figure 24.2 shows a patient with telangiectasia at the tumor cavity localization 5 years after irradiation. Additionally, hypopigmentation or hyperpigmentation of the irradiated skin may occur as a late toxicity. All these changes cause an unsatisfactory cosmetic

Table 24.2 Factors contributing to worse cosmetic outcome

Patient-related factors	Age [52]
	Smoking [52]
	Immunosuppression [52]
	Cardiovascular disease [52]
	Diabetes [52]
	Breast size [53]
	Radiosensitivity [54]
	Collagen tissue disease [55]
Tumor related factors	Localization of tumor [56, 57]
	Size of tumor (T stage) [58–62]
Radiotherapy-related factors	>50 Gy to the whole breast [63–67]
	Larger dose per fraction [44, 54, 62, 66]
	radiation boost to the tumor bed [46, 68, 69]
	Dose inhomogeneity [54, 58, 70]
	Nodal irradiation [69]
Other treatment-related factors	Type of breast surgery [50, 70–74]
	Concomitant chemotherapy [59, 75, 76]
	Tamoxifen [77]

outcome which should be considered as late toxicity particularly for patients with breast conservation surgery to preserve an acceptable cosmetic appearance of the breast [46]. In several studies, cosmesis was related to patient satisfaction, anxiety and depression, body image, feelings of sexual attractiveness, and self-esteem. There was also a strong correlation between body image and patient age, with younger women being more sensitive to alterations in body image [47–50]. Additionally, in the lactation period, it is possible to have poor glandular proliferation in the irradiated breast as a result of radiation-induced vascular injury, fibrotic change, and glandular atrophy, which causes lactation difficulty. In this condition, there is compensatory hyperstimulated glandular tissue in the contralateral breast [51].

Factors contributing to a worse cosmetic outcome can be separated according to the relation with patient, tumor, or treatment. These factors are shown in Table 24.2. The type of breast surgery is important for the volume of tissue excised, size and orientation of the scars, and utilization of surgical clips appropriately for localization of tumor cavity. There are some reports that concomitant chemotherapy and tamoxifen use may affect late cosmesis, but there are also studies showing that this effect is not statistically significant for chemotherapy [11, 78] and for tamoxifen [58, 59].

Although it has been shown in several studies that a larger dose per fraction may produce a worse cosmetic result [44, 54, 62, 66], the hypofractionated radiotherapy trials reported good or excellent cosmetic outcomes [12, 63, 79–87]. The hypofractionated schedule delivering 45 Gy in 20 fractions shortened the overall treatment time by 1 week with a reduction of skin acute toxicity and no increase of late effects compared with the conventional fractionation [83]. Strategies that have been used for established radiation fibrosis are consisting pharmacologic agents such as

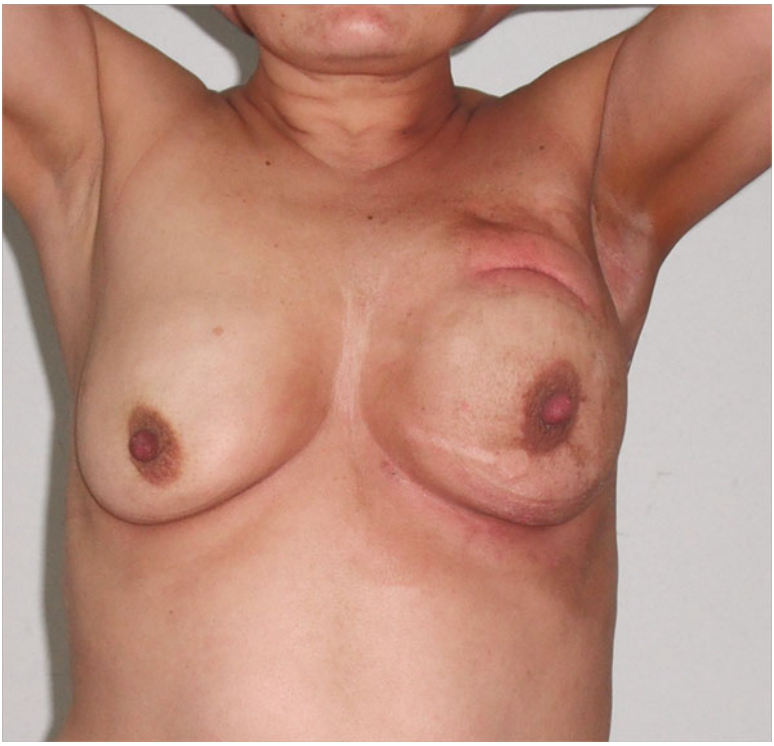

Fig. 24.3 Patient with hypopigmentation and hyperpigmentation areas and contraction

pentoxiphyline and alphatocopherol (vitamin E) [88], interferon-α [89, 90], glucocorticoids, hyperbaric oxygen, physiotherapy microcurrent therapy, and growth factors [88, 91, 92]. However, none of these methods are found to be successful as an effective treatment. The best method for avoiding a poor cosmetic result is prevention of side effects by appropriate treatments. Radiation-related factors contributing to a worse cosmetic result may be easier to modify than nonradiation-related factors. In addition to dose and fractionation, improvement of dose inhomogeneity, the selection of patients for boost treatment and the use of concurrent systemic treatment are important issues for the oncologist to consider. A patient with hypopigmentation and hyperpigmentation areas and contraction of the previously irradiated breast is seen in Figure 24.3.

24.3.2 Overlying Bone Fractures

Radiation-induced osteoradionecrosis occurs as a result of vascular compromise with obliterative endarteritis and damage to osteoblasts and osteoclasts [93]. To induce osteoradionecrosis, a dose greater than 6 Gy in adults is required and onset

occurs more than one year after completion of radiotherapy. Findings include focal lucency, periostitis, sclerosis, insufficiency fractures, and cortical thinning. Rib fractures usually involve anterior aspects of the third, fourth and fifth ribs; are frequently multiple, spontaneous, and asymptomatic; and may be slow to unite. Initially, a bone scan will show decreased uptake of radioactive material in the radiation field. In the late stage, radiation-induced bone fracture and increased radioactive material uptake are seen on a bone scan. Bone complications seemed to be particularly common in the orthovoltage era, most probably because of greater energy attenuation in bone [5, 94].

24.3.3 Pulmonary Fibrosis

Pulmonary fibrosis is a late injury resulting from interstitial damage involving the parenchyma as well as the pleura. Acute radiation pneumonitis may gradually clear and disappear completely or progress to permanent fibrous changes [5, 27]. Fibrosis results from cell death by irradiation and replacement by "scarring" or "fibrosis" without a precise mechanism being offered. On the basis of these studies it was concluded that pulmonary fibrosis after therapeutic irradiation is a consequence of the local release of cytokines and is confined to the area of irradiation [41]. It is also a consequence of the process of repair that is initiated by tissue injury or insult from irradiation and depends on the severity or frequency of the tissue injury. Severity seems to be related to a number of factors including the volume of the irradiated lung, radiation dose, fractionation dose, the use of additional nodal fields single or en face electron field, concomitant use of some chemotherapy regimens and tamoxifen, smoking habits, and age [51, 95]. Lung fibrosis appears after 6–24 months, usually remains stable after 2 years and is accompanied by limited, but irreversible, changes in pulmonary function tests [5, 33, 74, 96, 97]. Late pulmonary fibrosis is uncommon, and is usually identified radiologically in asymptomatic patients. It appears that relatively sharp marginated fibrosis is localized in the radiation field. Few data are available on the long-term consequences of radiation-induced pulmonary fibrosis from breast radiotherapy, suggesting that it rarely causes a clinical problem [43]. Late radiation fibrosis is refractory to treatment; therefore, minimizing the likelihood of developing it is particularly important. Lung protection may be achieved by treatment at deep inspiration [98] and the use of conformal three-dimensional (3D)planning [36].

24.3.4 Shoulder and Arm Complications (Lymphedema, Brachial Plexopathy, Impaired Shoulder Mobility)

Shoulder and arm complications are among the most troublesome sequelae of breast cancer treatment. Most important complications include arm lymphedema,

Table 24.3 Predisposing factors and symptoms of axillary morbidity in irradiated patients

Complication	Risk factors	Symptoms
Arm lymphedema	High RT dose per fraction [5, 6] Extent of axillary surgery [6] Concomitant CT or Tmx [6, 103] Advanced nodal stage [103, 104] Obesity [6] Older age [6] Hypertension [5]	Swelling of the arm [6]
Brachial plexopathy	Young age [6] Concomitant CT [6] Overdose irradiation [5] High RT dose per fraction [5]	Paresthesia [6] Pain [6] Weakness [6] Hypestesia, hypalgesia [6] Hyporeflexia [5] Muscular atrophy [5]
Impaired shoulder movement	High RT dose per fraction [5] Concomitant CT [5] Older age [6] Nonparticipation in physical exercise [6]. Subcutaneous fibrosis [6]	Reduced flexion and abduction [6] Pain by movement or at rest [6] Reduced working ability [6]

RT Radiotherapy; *CT* chemotherapy; *Tmx* tamoxifen

brachial plexus neuropathy, and impaired shoulder mobility [5, 6, 99, 100]. In a systematic review including 32 relevant studies, shoulder restriction was reported between 1% and 67 % of participants, lymphedema was between 0 and 34 %, shoulder/arm pain was between 9% and 68 %, and arm weakness was reported between 9% and 28 % of participants [101]. These morbidities often appear together and, to some extent, share common pathogenic elements and risk factors. The risk is mainly related to the treatment applied and consists of axillary surgery and/or axillary irradiation [102]. The predisposing factors and symptoms of axillary morbidity in irradiated patients are shown in Table 24.3.

24.3.4.1 Lymphedema

Lymphedema is considered the most significant complication of locoregional treatment of breast cancer [104]. It may result in significant psychological and functional morbidity, and markedly worsens QOL [5, 46, 105]. Once established, in most cases it cannot be cured. It is thus essential to prevent or minimize this condition [103]. The incidence of lymphedema in particular studies varied greatly, between 4% and 39 % [46, 101, 104, 106–108]. The risk after surgery only varies between 1% and 30 % [6, 46, 103], and depends primarily on the extent of lymph node dissection [6, 46, 100, 104, 106, 109]. Radiotherapy to the axilla considerably increases incidence and severity of this complication, with the relative risk ratio reaching 4.6 [46, 101, 106, 108]. The median latency is usually in the range of 1.5–4 years, but it may develop as many as 10 years after treatment.

The pathogenesis of lymphedema includes radiation-induced fibrosis, causing venous and lymphatic vessel obstruction and lymphocyte depletion with fatty replacement and local fibrosis [6]. These factors strongly interact with surgery, possibly due to reduced lymphatic regeneration after surgical interruption. The contribution of hemodynamic factors is also relevant [6]. The application of sentinel lymph node biopsy (SLNB) in the management of breast cancer has been associated with a reduced incidence of lymphedema formation. Current estimates suggest that secondary lymphedema affects approximately about 10–20 % of women who undergo treatment for breast carcinoma [33, 35, 36, 110, 111]. It is hoped that widespread use of the sentinel node technique will significantly decrease the risk of lymphedema [6]. Ongoing studies are researching whether full lymph node dissection in node-positive patients can be replaced by axillary radiotherapy. Decongestive lymphatic therapy, lymphatic massage, compressive garments, or bandaging or sleeves may be used for the treatment of mild lymphedema. The results of completed studies also support the safety of upper body exercise in breast cancer survivors with and at risk for lymphedema, but there is no complete cure [112]. A recommendation of the National Institutes of Health for patients with lymphedema to avoid injury is given in the literature [113].

24.3.4.2 Brachial Plexopathy

Brachial plexus neuropathy is a relatively rare complication of modern radiotherapy, although in the past, its incidence was much higher [114–119]. It has been predominantly observed in women treated with high dose per fraction or with overlapping fields [114, 118]. Pathologic studies have revealed fibrosis surrounding the brachial plexus, leading to entrapment of nerve fibers. The latency period for this complication ranges from 1.5 to 10 years (7–14 years for complete paralysis), and is similar for motor and sensory impairment [6, 114, 115, 117, 118, 120]. The risk factors and symptoms of brachial plexus neuropathy are shown in Table 24.3. When the biological effective dose was above 55 Gy, the risk of radiation-induced brachial plexopathy increased rapidly [105]. Treatment options remain limited and ineffective. Early physical therapy should be targeted toward maintaining range of motion and strength. Medical therapy may provide some relief from neuropathic pain [121].

24.3.4.3 Impaired Shoulder Mobility

Shoulder stiffness is usually caused by fibrosis of the major pectoralis muscle and damage to the vasculature or to the joints [6]. Movement range may also be decreased as a result of lymphedema or neural damage [6]. Symptoms usually appear after a median latency of 4 years [6]. The risk factors and symptoms are shown in Table 24.3. To diminish the consequences of shoulder and arm problems, patients should be recommended for a physical exercise program [6, 106]. However, some patients with edema or neurologic deficits may not be able to follow

such programs. The Cochrane Breast Cancer Group reviewed 24 randomized controlled trials and concluded that exercise can result in a significant and clinically meaningful improvement in shoulder range of motion in women with breast cancer. There was no evidence of increased risk of lymphedema from exercise at any time point [122].

From the point of view of management of the axilla, SLNB with or without additional information from biological markers raises the interesting possibility of identifying high- and low-risk patients with respect to axillary relapse and to optimize the combination of axillary lymph node dissection, adjuvant radiotherapy, and systemic therapy based on this prognostic profile [6]. It was reported that morbidity associated with the management of the axilla in breast conservation is limited when current treatment standards are used [107]. It was also mentioned that improved field matching to avoid overlapping problems would reduce the risk of such complications. Radiotherapy can be delivered with a minimal risk of severe, late morbidity provided that it is given using modern treatment techniques, appropriate dose-fraction schedules, and proper adjustment for other primary or adjuvant therapies. In this way, the optimal balance between surgery and radiotherapy in the axilla can be defined, depending on the risk profile of the patient [6]. A risk-adapted management algorithm for the patient with positive SLNB that incorporates risk estimates from the Memorial Sloan-Kettering Cancer Center nomogram suggest possible surgical or nonsurgical management paths for the axilla after the finding of a positive SLNB is presented in the literature [123].

24.3.5 Radiation-Induced Heart Disease

The most frequently diagnosed cardiac problems during radiotherapy are acute pericarditis, pericardial effusion, and arrhythmias. Acute radiation damage to pericardial and intimal coronary endocytes eventually leads to myocyte ischemia and fibrosis [124, 125]. The risk of cardiac disease seems to increase for decades after radiotherapy. The radiobiology of heart damage is not well understood due to the presence of various radiosensitive structures and their topographic heterogeneity. The dose–response curve for cardiac damage for large volumes is steep for doses exceeding 40 Gy, whereas small volumes (as in the case of breast cancer irradiation) can tolerate up to 60 Gy in 2 Gy fractions [126–128]. RIHD may be described as a result of damage to microvasculature and macrovasculature. Capillary swelling and progressive obstruction of the vessel lumen result in ischemia, which in turn leads to the replacement of cardiac tissue by fibrosis [129]. Additionally, animal models showed a significant reduction in the number of capillaries in relation to myocytes [125]. Macrovascular damage results from injury to larger vessels, leading to the exacerbation of the formation of atherosclerotic lesions [129]. From a functional point of view, the most significant seems to be myocardial damage [128]. This is usually demonstrated by nonspecific, diffuse interstitial fibrosis, which alters the compliance of the myocardium and contributes primarily to diastolic dysfunction.

Eventually, the decreased patency of capillaries results in ischemia and subsequent myocardial cell death, and these processes lead to their replacement by fibrosis [127]. Damage may also affect myocardial cells involved with conduction, leading to arrhythmias [127, 128, 130]. The injury to the pericardium may present as extensive fibrous thickening, pericardial adhesions, and excessive pericardial fluid [130]. The valve damage usually presents as thickening, fibrosis, and calcification of the cusp and/or leaflets of valves. The pathology and mechanism of coronary artery damage in irradiated patients appear to be similar to those of coronary disease in the general population with the presence of more fibrotic changes in media and adventitia, depletion of media smooth muscle, and predominance of proximal (ostial) coronary stenosis [131]. It was also postulated that atherosclerosis is a monoclonal process (like cancer), which begins within a single cell with somatic mutation induced, among other things, by radiation. This theory could possibly explain cardiac disease caused by low radiation doses [132]. Another possible phenomenon relating atherosclerosis and low-dose radiation damage is genomic instability.

Clinical presentations of RIHD include acute or delayed pericarditis, pancarditis consisting of pericardial and myocardial injury, coronary artery disease, and functional valvular and conduction defects [128, 133]. The acute effects usually resolve spontaneously and do not correlate with late cardiac complications [127]. Among the side effects, pericarditis is the most frequently seen acute cardiac toxicity of irradiation. Late onset clinical manifestations include coronary heart disease, restrictive cardiomyopathy, chronic heart failure with an increased decline of the diastolic function than systolic function, and valvular disease [134–137].

These cardiac manifestations occur within years or decades after treatment and can influence mortality and morbidity. Before 1980, the risk of cardiac failure was significantly higher in patients with left side irradiated tumors than right side tumors [138, 139]. Between the 1950s and 1970s, meta-analysis by the Early Breast Cancer Trialists' Collaborative Group consisting of approximately 20,000 women enrolled in 78 randomized trials of postoperative radiotherapy found a 30% increase in cardiac mortality for patients treated in the 1960s and 1970s was mainly due to heart disease and mainly in older trials, which used outdated radiation techniques that exposed more volume of the heart to larger doses of irradiation than current practice [140–143]. Most studies noting increased cardiac events in patients with breast cancer were from the "old" radiotherapy era (e.g., relatively high doses per fraction, photon irradiation of the [bilateral] internal mammary nodes, and orthovoltage/60Co equipment) [144–147]. An excess of cardiac deaths was also reported in other meta-analyses and trials [140, 145, 148–154]. The decrease in breast cancer deaths associated with postoperative irradiation was offset by an increase in cardiovascular deaths in some studies. By the 1980s, it was commonplace to use tangential fields delivered by a megavoltage linear accelerator. With modern techniques there were no increases reported in total cardiovascular mortality, total intercurrent mortality, or total mortality [139, 150, 155, 156]. More "modern" approaches (e.g., better targeting, higher beam energy, and better quality) have generally been reported to have fewer cardiac risks [139, 155, 157–162].

Recent technical changes facilitated sparing the heart and coronaries from unnecessary irradiation, but did not annihilate the risk for subsequent heart disease. High irradiation is still delivered to a small segment of the anterior wall, which partially includes the left anterior descending artery and other major vessels receiving a smaller dose [142]. New concerns regarding the safety of modern breast cancer radiotherapy have been raised by studies demonstrating increased cardiac mortality in individuals exposed to relatively low doses of irradiation. In atomic bomb survivors, a clear relationship was demonstrated between cardiac mortality and radiation dose in the range of 0–4 Gy [163–166]. Several studies have demonstrated a higher risk of cardiac disease when the internal mammary nodes were included in the treatment fields [12, 17–168]. However, it was not until the late 1990s that computed tomography (CT)-based 3D conformal treatment planning was routinely used. Internal mammary nodes should not be treated with 2D techniques in which the cardiac dose volumes cannot be measured. Additional heart protection has been achieved with the introduction of conformal 3D or intensity modulated radiotherapy (IMRT) techniques [35, 162, 169–173]. Estimates of noninvasive transcutaneous cardiac pacing or IMRT predict a 50% reduction in cardiac morbidity in left-sided tumors [171]. Additionally, with these techniques the decrease of high dose volume is usually achieved at the cost of increased heart volume encompassed by lower doses. Therefore, caution is needed in potential cardiotoxicity and radiation-induced secondary cancers of low radiation doses [174].

Factors associated with increased risk of cardiovascular morbidity after breast cancer radiotherapy include volume of irradiated heart (which is mainly a consequence of radiotherapy technique and choice of target volumes) [149, 152, 153, 175–178], total radiation dose [131, 153, 176], fractionation [147, 162, 179], the use of cardiotoxic chemotherapy [176, 180], and the coexistence of other recognized risk factors for cardiovascular disease [176, 181, 182]. Although the results of early trials, left-sided irradiation for breast cancer in and of itself is a minor contributor to heart disease in comparison with other risk factors such as hypercholesterolemia, hypertension, obesity and sedentary lifestyle, and family history. In the study by Harris et al., cardiac mortality was associated with several of these known risk factors, including age, smoking history, hypertension, hyperlipidemia, diabetes, and Framingham risk score [155]. It was mentioned that radiation should not necessarily be withheld when clinically indicated, even in women with cardiac risk factors [141]. It is known that doxorubicin-based chemotherapy concurrent with radiation is highly toxic [183]. Preclinical results suggested that trastusumab may enhance radiosensitivity with a dose-modifying factor of 1.11 [110, 142]. However, there is no strong demonstration that trastusumab may interact with radiation adversely.

While most studies have examined primarily mortality events, morbidity is also an important endpoint for cancer survivors, as treatment-related toxicities may affect QOL. The treatment and prevention of ischemic cardiac disease have improved greatly over the past two decades, and many women may be successfully treated for cardiac disease for many years. Thus, it is important to study the incidence of nonfatal events that affect the heart after cancer treatment in order to

inform patients of their risks and follow-up requirements and to improve treatment of these significant morbidities. Data on cardiac morbidity after breast cancer treatment from randomized trials are limited [141].

It is evident that radiation-induced cardiac injury is a late event. In most studies, excessive cardiac mortality was not seen until 10–15 years after breast cancer radiotherapy [138, 141, 143, 149, 159, 184, 185], although a latency period of only 4–5 years until increased ischemic heart disease mortality was also reported [177]. Therefore, long-term outcomes are necessary to evaluate the impact of any new techniques. More "modern" radiotherapy techniques, in contrast, have markedly reduced, but often have not completely eliminated, incidental cardiac irradiation. However, the follow-up duration in modern studies has generally been shorter than that in the older radiotherapy trials; thus, the long-term safety of modern techniques remains somewhat uncertain. Care should continue to be taken to minimize cardiac exposure, as much as is practical, in patients undergoing radiotherapy for breast cancer [144].

24.3.6 Radiation-Induced Malignancy

The data on the incidence of second malignancies in breast cancer survivors are contradictory. This general statement applies to contralateral breast cancer and to non-breast tumors [186, 187]. In some series, the use of radiotherapy was related to an overall increase in the risk of second tumors [151, 188, 189], whereas others demonstrated no effect [110, 190]. For example, breast cancer radiotherapy increases the risk of leukemia and lymphomas, but not of thyroid cancer [151, 191]. Several studies have reported an increased risk of contralateral breast cancer, with [192] or without radiotherapy [193, 194] in young women. Of the six randomized studies comparing the use of radiotherapy with the use of no radiotherapy, one showed increased risk in the irradiated group, two a trend toward increase, and three a decreased incidence of contralateral breast cancer [187]. As the carcinogenic effect of radiation on breast tissue was shown in many studies [151, 187–195], it is reasonable to make every effort to limit the doses of incidental irradiation. Introduction of conformal 3D radiotherapy allows for a decrease in radiation exposure of normal tissues, whereas the use of IMRT may significantly increase the doses to normal tissues (including opposite breast) [187, 196]. The total body dose is expected to be two to three times higher, predominantly owing to the increased number of beams used, as well increased leakage radiation (resulting from increased "beam on" time) [196]. IMRT may therefore increase the incidence of second tumors in 10-year survivors; this will predominantly include tumors resulting from low exposure, such as leukemia and carcinomas [195]. Three large studies confirmed a significantly increased incidence of ipsilateral (compared with contralateral) lung cancer after irradiation for breast cancer [194, 196–198]. Tumors with the largest relative increase of incidence in breast cancer survivors are soft-tissue sarcomas (SIR 13) [199]. Women exposed to radiotherapy harbor over a fourfold relative risk of sarcomas

compared with women not exposed to radiotherapy [199]. Radiation-related soft-tissue tumors appear after a mean latency of 10–12 years [188, 200, 201]. This has accounted for 20% of all angiosarcomas registered, whereas other soft-tissue sarcomas in breast cancer survivors constituted only 2% of all tumors of this type [188]. The risk of developing soft-tissue sarcomas other than angiosarcomas is related to integral radiation dose, although the risk decreased above a certain dose threshold, which is compatible with cell sterilization at high doses.

24.4 Conclusion

In general, breast radiotherapy is very well tolerated by most patients. Acute complications of irradiation are generally common in occurrence, self-limiting, responsive to symptomatic treatments and resolve within 4–6 weeks after the treatment is completed. Acute skin reactions and fatigue represent the most common toxicities. Late complications are seen rarely, however, may affect patient QOL and possibly survival. The more common late side effects of breast irradiation are breast edema, hyperpigmentation, and telangiectasia which may cause cosmetic problems. Breast cosmesis is an important issue for patients, and the oncologist should consider the effect of radiotherapy dose, fractionation, homogeneity, and concurrent systemic treatment on this outcome. In addition, late cardiac morbidity is an important issue, especially for good prognostic groups with early breast cancer or ductal carcinoma in situ, who will live with the late sequelae of treatment. As late effects tend to appear after long latency periods and damage may be progressive, women undergoing radiotherapy for breast cancer should undergo lifelong follow-up for complications. Long observation is particularly important before confirming the safety of new (in particular hypofractionated) irradiation schedules and techniques. Prevention is the best way to manage radiation-induced late toxicities and more advanced radiotherapy techniques such as conformal 3D radiotherapy, IMRT, and conformal partial breast irradiation may improve the therapeutic ratio. The role of the radiation oncologist is to perform individualized treatment planning using CT-based 3D planning with careful attention to normal tissue exposure and minimizing the parameters to allow long-term breast cancer survivors the optimal chance of survival without toxicity.

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