Section A-Research paper

An Overview about Radiotherapy and its lateToxicity in Management of Breast Cancer

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Abstract

The most prevalent neoplasm in the world to be diagnosed in women is breast cancer, which also kills more women than any other malignancy. The American Cancer Society estimates that one in eight American women could develop breast cancer at any time in their lives. In the treatment of both early and local advance disease, radiation is important. It is applied as follows:
When required, post-operative adjuvant radiation after modified radical mastectomy (MRM) in the locally advance stages of disease. In early-stage disease, radiation is the main local therapy after breast conservation surgery (BCS). In cases of locally advanced breast cancer, surgery (MRM or BCS) followed by post-operative radiation therapy when tumor downsizing after neoadjuvant chemotherapy. Palliative radiation for metastatic cancer. To improve local disease management, post-operative radiation was first employed in the fifth decade of the previous century and has been used ever since. In the early stages of breast cancer, local, post-operative radiation reduces local recurrence from 25% to less than 10%, according to numerous studies conducted over the course of nearly 80 years. Although radiation may not increase survival rates, it does improve quality of life by preventing local recurrence, which is otherwise very difficult to treat. A stage of breast cancer known as locally advanced breast cancer (LABC) is defined as having an advanced local breast tumor without any distant metastases. The American Joint Committee on Cancer (AJCC) classifies LABC as stage III AJC breast cancer. In systemic therapy for meta-static and advanced disease, radiation is utilized as a supportive and palliative measure with the following goals. Late radiotherapy toxicity is defined as side effects of treatment that occur 3 to 6 months following radiotherapy.

Keywords: Radiotherapy, Toxicity, Breast Cancer

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The most prevalent neoplasm in the world to be diagnosed in women is breast cancer, which also kills more women than any other malignancy**.** The American Cancer Society estimates that one in eight American women could develop breast cancer at any time in their lives**.** Breast cancer is the most common disease in women diagnosed globally; 2.26 million [95% UI, 2.24–2.79 million] new cases were reported in 2020**.** By 2050, it is expected that the number of new instances of female breast cancer worldwide would be close to 3.2 million**,** The overall incidence of cancer is 157.0 per 100 000 Egyptian women with the highest incidence being BC (32%) **(1).**

Staging:

It has undergone numerous revisions since the AJCC published its first edition in order to take into account significant advancements in our knowledge of oncology and survival statistics. The eighth iteration of the staging system was revealed in 2017 (**2).** Clinical, radiological, and pathological data are the foundation of TNM staging.

Since the 1st edition by AJCC was published, it has been regularly revised to incorporate major updates in the understanding of oncology and survival data. In 2017 **(2).,** the 8th edition of the staging system was announced. NM staging is based on clinical, radiological and pathological data.

There are different guidelines for treatment of breast cancer like: NCCN guideline and ESMO guideline and others which assure that there are 4 type of treatment the main one is surgery then chemo, radiotherapy, and immunotherapy.

(I) SURGERY:

The last 20 years have seen significant advancements in breast cancer surgery. The idea of treating a patient by performing radical surgery has been effectively replaced by BCT using the same OS**,** and The seriously related morbidities were decreased to nearly no influence on upper limb functionality when SLNB was used in place of ALND in negative axilla**.** BCS and SLNB have now been standard procedures for nearly 20 years. However, research did not end there. The idea that an SLNB should replace an ALND in an axilla where fewer than three nodes are positive was adopted as standard procedure even prior to the trials' findings that ALND is not inferior to regional node radiation (RNI)**.** In the early stages of breast cancer, tumor biology now plays a major role in guiding regional treatment, which was previously primarily driven by disease burden and staging. The understanding of tumor biology has led to the replacement of upfront surgery with neo-adjuvant treatments (primary systemic therapy, PST) for all triple-negative and HER2-positive stage II and III breast cancers, as well as for some Stage 1 (T1c) tumors in several countries. In addition to enabling less invasive surgery, PST also makes it possible to examine the sensitivity of tumors in vivo and more effectively customize postoperative systemic therapy for patients without pCR **(3).**

Once more, therapeutic mammaplasties and partial local flaps offered maybe other options to the traditional BCS with superior cosmetic results without sacrificing the oncologic outcome **(4)**

Last but not as every female who were previously offered a total mastectomy without reconstruction, the prognosis was significantly altered by the utilization of skin sparing procedures with prompt reconstruction if possible**.** As long as patient preferences and the benefits and disadvantages of various approaches were taken into account during the multidisciplinary discussion and careful preoperative evaluation, all these advancements were made without having an impact on oncologic outcomes **(5).**

Most significantly, this evolutionary route with so many new opportunities that will eventually result in the best care possible for breast cancer patients is primarily obtained and maintained inside a skilled, multidisciplinary setting with access to the required technology- technological arsenal **(6).**

Quality Criteria in Surgery*:*

In 2010, EUSOMA published its first paper on quality indicators in breast cancer care. The article described a set of benchmark quality indicators (QIs) that breast centers should implement to enable standardized auditing and quality assurance, as well as to establish a minimum standard of care that has been agreed upon **(7).**

Table (1): EUSOMA quality indicators: breast cancer surgery **(6)**

Quality indicator	LOE	Mand/Recom	Minimum standard	Target
Waiting time				
5—Time interval ≤6 weeks from the date of first diagnostic examination within the breast centre to the date of surgery or first treatment	IV	R	80%	90%
Multidisciplinary approach				
8—Proportion of patients to be discussed pre and post operatively by a multidisciplinary team	III	M	90%	99%
Appropriate surgical approach				
9a—Proportion of patients (invasive cancer only) who received a single (breast) operation for the primary tumour (excluding reconstruction)	II	M	80%	90%
9b—Proportion of patients (DCIS only) who received just one operation (excluding reconstruction)	II	M	70%	90%
9c—Proportion of patients receiving immediate reconstruction at the same time of mastectomy	III	R	40%	NA
Surgery and quality of life: avoidance of overtreatment				
11a—Proportion of patients with invasive cancer and clinically negative axilla who underwent sentinel lymph node biopsy (SLNB) only (excluding patients who received PST)	I	M	90%	95%
11b—Proportion of patients with invasive cancer who underwent sentinel lymph node biopsy with no more than 5 nodes excised	I	R	90%	95%
11c—Proportion of patients (BRCA1 and BRCA2 patients excluded) with invasive breast cancer not greater than 3 cm (total size, including DCIS component) who underwent BCT as primary treatment	I	M	70%	85%
11d—Proportion of patients with non-invasive breast cancer not greater than 2 cm who underwent BCT	II	M	80%	90%
11e—Proportion of patients with DCIS only who do not undergo axillary clearance	II	M	97%	99%

1- Mastectomy:

Thirty to forty percent of individuals with breast cancer still have a mastectomy. In the multidisciplinary treatment of breast cancer, the availability of breast reconstructive treatments should be considered as it mostly reflects patient demand.

According to the EUSOMA guidelines, a minimum threshold of 40% should be met by patients who have urgent reconstruction at the same time as a mastectomy, with a target specified as not applicable. However, these figures need to be fully debated, aiming that the number of women not undergoing breast reconstruction should be in our opinion very low.

Beyond the already accessible indicators (e.g., rate of breast conservation, rate of rapid reconstruction, reinterventions for insufficient margins), a modern assessment of QI in the breast cancer surgical scenario should be updated. Keeping in mind the fun- damental aspect of the patient's satisfaction and the cosmetic result. One easily assessed factor, for example, that can be used to determine the caliber of the service provided is the number of patients for whose pictures were taken both before and after surgery and throughout a suitable follow-up period (6–12 months**) (8).**

2- Conservative breast surgery:

This is level I evidence that BCT is at least as effective as modified radical mastectomy (MRM) in treating early-stage breast cancer. Consequently, when early sporadic breast cancer patients are having primary surgery, BCT ought to be their first choice. Because breast preservation has a significant influence on life quality and that breast reconstruction primary or secondary, autologous or implanted comes with supplementary risks and expenses—as well. Even in individuals with an unfavorable breast/tumor relation or tumor site, oncoplastic methods or primary systemic treatments are important strategies to boost breast

conservation rates. Additionally, meta-analyses have provided evidence that in cases of invasive disease, "no ink on tumour" might be regarded as a sufficient margin width **(9).**

There is still a great deal of effort to be done to improve BCT rates following PST, which is becoming more and more common in the treatment of patients with early-stage breast cancer. There aren't many guidelines that particularly address the best loco-regional therapy and quality measures in this context. To debate clinical evidence and offer professional guidance on the technical management of patients with early-stage breast cancer, an international group was formed. A new paper was released to give doctors a toolkit covering all important clinical queries **(10).**

3- Axillary Approach:

In the field of axillary surgery, the surgical de-escalation technique has proven to be highly effective because the procedure's original motivation was changed from treatment to staging. In clinically node-negative patients, SLNB is unquestionably considered the gold standard for determining the status of the axillary lymph nodes. The minimum standard for the proportion of patients with invasive cancer and clinically negative axilla who undergo SLNB only, excluding those who received PST, should be 90%, and the target should be 95%. There has been a persistent decrease in the dissection of axillary lymph nodes, particularly with the release of significant randomized studies such as AMAROS and Z-0011 **(11).**

(II) RADIOTHERAPY:

In the treatment of both early and late diseases, radiation is important. It is applied as follows:

A. When required, post-operative adjuvant radiation after modified radical mastectomy (MRM) in the early stages of disease.

B. In early-stage disease, radiation is the main local therapy after breast conservation surgery (BCS).

C. In cases of locally advanced breast cancer, surgery (MRM or BCS) combined with post-operative radiation therapy after tumor downsizing after neoadjuvant chemotherapy.

D. Palliative radiation for metastatic cancer. **(12)**

a-Adjuvant Radiation Therapy after modified radical mastectomy (MRM) in the early stages of disease:

To improve local disease management, post-operative radiation was first employed in the fifth decade of the previous century and has been used ever since. In the early stages of breast cancer, local, post-operative radiation reduces local recurrence from 25% to less than 10%, according to numerous studies conducted over the course of nearly 80 years. However, most of the series did not significantly boost survivability. Although radiation may not increase survival rates, it does improve quality of life by preventing local recurrence, which is otherwise very difficult to treat**. (13)**

After MRM, radiation is not recommended for every patient. Patients who have a high risk of having a local recurrence should have it. Either the chest wall alone or the areas with draining lymph nodes receive radiation. The indications for post-operative radiation therapy are as follows:

1. Pathological Positive results from four or more lymph nodes, clinical involvement (N1), or unclear axilla histology
2. Tumors of grades 2 and 3.
3. Positive lymphatic invasion
4. A tumor larger than 4 cm
5. Cancer at or close to the resection margin
6. Medial or central quadrant tumor
7. Axiallary nodes' further capsular expansion
8. Locates the invasion of the skin or muscles on histology
9. Sometimes if a straightforward mastectomy is performed
10. At a very early age of ≤35
11. Triple negative tumour
12. Surgeon not satisfied with clearance

(**14)**

All of the aforementioned are signs that the ipsilateral axilla and supraclavicular lymph node regions should also be exposed, in addition to the chest wall. If the axilla is fully and adequately dissected and only one to three lymph nodes are positive and have favorable characteristics, the axilla may not be irradiated. In several cases, adding radiation to the axilla has improved disease control, even in individuals who have one to three positive lymph nodes and exhibit cellular and genetic unfavorable prognostic characteristics **(15).** Internal mammary lymph nodes are often spared from radiation since doing so would needlessly increase the exposure to the heart and lungs. Clinically positive internal mammary lymph node metastases are seen in just 1% of patients.

However, internal mammary lymph node radiotherapy may be taken into consideration for patients whose illness is in the central or medial quadrant, have a positive axilla, and exhibit other unfavorable prognostic factors **(16).**

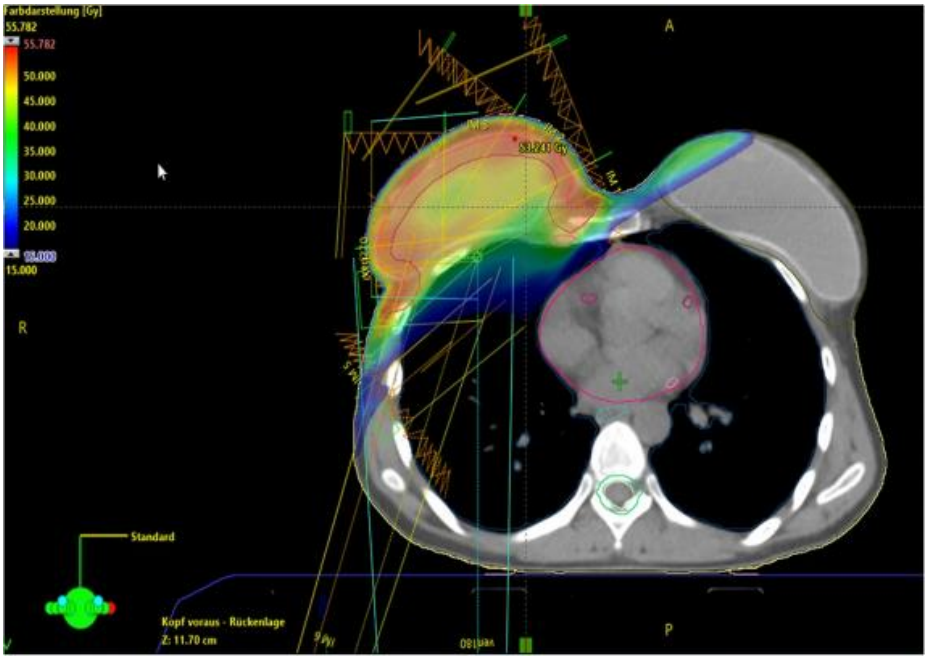

Figure (1): Postmastectomy patient with immediate implant-based reconstruction undergoing right sided breast and regional nodal radiotherapy including supra−/infraclavicular and internal mammary lymph nodes using a 6-field sliding window IMRT **(17).**

B. Breast Conservative Surgery & Radiation:

At first, radiation was not regularly added to BCS. A 40–60% local recurrence rate was noted. Radiation addition reduced recurrence to less than 10%. It was conducted that randomized studies in Milan, Italy in 1983, Hayward, UK in 1983, and Bernard Fisher in the USA in 1983, 1989**(17).**

After a lengthy follow-up period of 10–20 years, the trials comparing MRM with BCS + radiation concluded. The results showed similar outcomes in terms of local control and survival, with the added benefit of maintaining a nearly normal breast. Over the past 40 years, other randomized studies with comparable findings have been published **(18).**

In addition to lowering the risk of a local recurrence to less than 10% after adjuvant chemotherapy and BCS/MRM, adding radiation has been linked to an increase in overall and disease-free survival, according to studies from British Columbia and Denmark. For the greatest local disease management in early-stage breast cancer, BCS + Radiation has thus emerged as the recommended standard of therapy. However, because this modality involves a lengthy course of therapy, excellent patient compliance is essential. Additionally, the patient must be willing to receive radiation and be well monitored **(19).**

Boost: is applied to the entire breast following the conclusion of external radiotherapy. Boost aims to further decrease local recurrence. Research using randomized trials has demonstrated that adding boost to the lumpectomy cavity can lower the risk of recurrence to 3% or less when compared to not adding boost **(20)**

C. Accelerated Partial Breast Irradiation (APBI):

Radiation oncologists, like surgeons, are currently using a conservative approach and have developed Accelerated Partial Breast Irradiation (APBI), which is an alternative to whole breast radiation that allows more women to consider BCS while maintaining a 2 cm margin of safety around the lumpectomy cavity and sparing the remainder of the breast. The reasoning behind this is that within 2 cm of the cavity's edge, 80% of local recurrences are visible**.** APBI is only recommended for older patients (over 45 years old) who have invasive tumors (T1 or T2) that are less than 3 cm in size, have negative margins, and are visible within 2 cm of the cavity's edge **(21).**

D. Role of Radiation in Locally Advanced Breast Cancer (LABC):

A stage of breast cancer known as locally advanced breast cancer (LABC) is defined as having an advanced local breast tumor without any distant metastases. The American Joint Committee on Cancer (AJCC) classifies LABC as stage III AJC breast cancer **(22).**

When distant metastases are absent, the following conditions are present:

- Tumors larger than 5 cm (T3, T4) accompanied by localized lymphadenopathy (N0–3)
- Any size tumor that directly extends to the skin, the chest wall, or both (including satellite nodules or ulcers), independent of the presence of regional lymphadenopathy
- Regional advanced lymphadenopathy, defined as clinically fixed or matted axillary lymph nodes or any combination of internal, supraclavicular, or infraclavicular lymphadenopathy, irrespective of the stage of the tumor.

e- Role of Radiation in Metastatic and Advanced Breast Cancer:

In systemic therapy for meta-static and advanced disease, radiation is utilized as a supportive and palliative measure with the following goals (**22):**

1. Pain relief, especially for bone metastases.
2. Management of symptoms related to pressure.
3. Management of breast tumor hemorrhage or fungal growth.

Indications for palliative radiation are:

1. Bone metastases—.
2. Brain metastases.
3. Extradural spinal deposits.
4. Soft tissue metastasis.
5. Choroidal metastases
6. Impending fracture.
7. Large local growth with pain, ulceration, bleeding.
8. Fixed nodal recurrences.
9. Liver and lung metastasis
10. For ovarian ablation

(23)

Dose:

A standard radiation dosage of fifty grays is given over the course of five weeks in twenty-five parts.
This results in the least amount of late radiation morbidity and the best disease control.

These days, hypo fractionated regimens are becoming more and more common. A dose of 40–42.5 Gys is administered in three weeks in 15 fractions under this regimen. Benefits of this region include short treatment times, which improve compliance and comfort, lower costs, and radiation reactions that show up after radiation is finished, which prevents treatment interruption. Radiation Therapy's Function in Breast Cancer: 412 Randomized Trials START (Standardization of Breast Radiotherapy) A and B with a 40–42.5 Gy hypofractionation regimen from UK. and a trial from Canada have demonstrated that, in comparison to a typical regimen of 50 Gys, hypofractionation provides the same local control and survival as well as comparable or lower late radiation damage. Since then, other studies have demonstrated the effectiveness of hypofractionation in the treatment of breast cancer, and it is already the norm in most centers. **(24).**

(III) CHEMOTHERAPY:

Over the past few decades, the development of human epidermal growth factor receptor 2 (HER2) focused medicines, chemotherapy, and endocrinology has resulted in a notable improvement in the survival rate of women with breast cancer **(25),** Chemotherapy uses medications, either alone or in combination, to kill malignant cells. These medications are given according to predetermined timetables called treatment cycles. In order to maximize response, medications are administered at various time periods (e.g., Day 1, Day 8, Day 15, etc.) during each treatment cycle, which lasts 21 days on average. The next treatment cycle is started and the same routine is followed after 21 days. A patient typically undergoes four to six therapy cycles.

Though, chemotherapy is mostly administered as an infusion into the vein (intravenously), some drugs can be taken in the form of pill or capsule as well.

Based on the stage of disease, the hormonal receptor status and Her2/neu status of the tumor, systemic management of breast cancer can be divided into three broad categories.

(a) Adjuvant systemic therapy in early and locally advanced stage disease

1. Adjuvant Chemotherapy
2. Adjuvant hormonal therapy
3. Adjuvant Targeted therapy

(b) Neo-adjuvant Chemotherapy in early and locally advanced stage disease

(c) Therapeutic systemic therapy in metastatic disease

1. Chemotherapy
2. Hormonal/endocrine therapy
3. Targeted therapy

Adjuvant Chemotherapy:

A single medication, either cyclophosphamide or melphalan, was administered as adjuvant systemic therapy in 1950s and 1960s, with somewhat improved survival rates. The CMF (Cyclophosphamide + Methotrexate + 5-Fluorouracil) combination chemotherapy treatment was created in Milan, Italy, towards the end of 1970 by **Bonadona et al. (26)** which significantly added to the survival of breast cancer. Results of anthracycline-based regimens FAC or CAF (5-Fluorouracil + Adriamycin + Cyclophosphamide) were published by bonadona et al. in late 1970, which increased survival even further. Since the addition of taxanes in 1990 increased survival rates as well, systemic adjuvant chemotherapy regimens based on anthracyclines and/or taxanes are currently the standard of care for breast cancer patients. An optimal adjuvant chemotherapy treatment for patients who are at high risk involves using a regimen comprising anthracyclines and taxanes, according to the American Society of Clinical Oncology's adaption of the Cancer Care Ontario Clinical Practice recommendations **(27).**

When compared to no treatment, anthracycline-based chemotherapy regimens reduced the 10-year breast cancer mortality by one-third, according to a 15-year meta-analysis of 100,000 women treated across 123 randomized trials **(27).**

Radiotherapy Toxicity

Radiotherapy-Related Skin Toxicity:

Acute Skin Toxicities

Acute skin reactions are experienced by up to 95% of patients undergoing radiation treatment to the breast. Radiation dermatitis is the general term used to describe a wide spectrum of skin toxicity, ranging from mild erythema to desquamation to rare tissue necrosis. Although patient-to-patient variability does exist, acute toxicities generally start around the 2nd to 4th week of radiation treatment**.** By definition, acute skin toxicities occur within 30 days from completion of therapy. The maximal peak response occurs 1–2 weeks following the conclusion of radiotherapy **(28)**

Late Skin Toxicity

Late skin toxicity is defined as side effects of treatment that occur one to 3 months following radiotherapy. Like acute toxicities, these can range from mild to significantly bothersome; thus, these outcomes should be considered as important factors relative to maintaining quality of life after treatment.

Types of Late Skin:

Toxicity Radiation-Induced Fibrosis:

Radiation-induced fibrosis, or a thickening or hardening of skin with or without associated pain, is one of the more common late sequelae of radiotherapy**.** Histopathologically, fibrosis is described as a marked abundance of fibrous scar tissue within the dermis **(29).**

Atrophy:

Atrophy related to radiation treatment is identified as a thinning of the subcutaneous tissue within the treatment field**(30)**

Hyperpigmentation:

Hyperpigmentation within the radiation treatment field results from skin melanocyte activation. This side effect may occur acutely but may also persist and progress following treatment **(31)**

Telangiectasia:

Telangiectasias are found as a late and progressive complication of radiation toxicity. These vascular aberrations represent dilated blood vessels close to the skin surface that may be cosmetically bothersome to some patients

Morphea:

Morphea is described as a localized scleroderma condition, distinct from radiation fibrosis **(32)**

Fatigue Prevalence During and After Breast Cancer Radiotherapy:

Women who receive radiotherapy often experience fatigue during and after treatment. The reported prevalence of CRF before radiotherapy ranges from 25% to 76%**,** while the prevalence at the end of radiotherapy ranges from 42–93% **(33).** The number of women who develop CRF is typically greatest at the completion of radiotherapy and then decreases thereafter.

Delayed Radiation-Induced Brachial Plexus Neuropathy (RIBPN):

Delayed radiation-induced brachial plexus neuropathy (RIBPN) is one of the late effects of RT that occurs after a latent period varying from a few months to more than 10 years after completion of treatment with the peak onset of neurologic symptoms being at 2–4 years after RT. RIBPN is characterized as slowly progressive wasting and weakness of the upper extremity, which is often frequently observed among breast cancer patients who had received radiation to the supraclavicular fossa along with the breast and axilla **(33)**

The incidence of RIBPN has been reduced according to the improved irradiation techniques and the reduced RT dose per fraction in the past decade **(33)**

Lymphedema:

Lymphedema is the most common chronic morbidity resulting from breast cancer treatments. The incidence of lymphedema ranges from 3–65% patients may experience some degree of functional impairment, psychological morbidity, and diminished quality of life **(34).**

Many factors affect development of arm lymphedema as age at the time of breast cancer diagnosis, post-treatment weight gain, extent of axillary lymph nodes dissected, pathological status of the axillary lymph nodes removed during the surgery, nodal irradiation, systemic therapy, arm infection, or arm trauma , and level of the hand use **(35)**

Lymphedema is a result of pathologic condition in the lymphatic system in which protein-containing fluid accumulates in the interstitial tissue leading to tissue inflammation, fibrosis, and adipose hypertrophy. Clinical manifestations of lymphedema include swelling, induration, skin changes, and decreased function of the affected limb **(36)**

Cardiotoxicity:

Radiation-related injury of the heart manifests as pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, coronary artery disease, and/or possibly valvular disease and arrhythmia. A single-institution analysis of mean heart dose as a function of two-dimensional vs. three-dimensional planning showed that mean heart dose decreased from 3.45 Gy in 2003 to 2004 when all were planned Cardiotoxicity Associated with Radiation for Breast Cancer 132 with two-dimensional (2D) treatment planning to 2.13 Gy between 2007 and 2013 when all were planned with 3D planning **(37)**

Factors Influencing Cardiac Dose:

Anatomy:

Women with left-sided breast cancer had mean heart doses ranging from just less than 1 Gy to over 15 Gy. While the average mean heart dose for left-sided breast cancers was 4.4 Gy, a great deal of variability in mean heart dose was noted **(38)**

Treatment Volume:

In addition to individual patient anatomy, mean heart dose is also dependent upon target volume. As highlighted in the dosimetric study from the United Kingdom, internal mammary radiation resulted in higher radiation dose to the heart than other treatment field arrangements **(38)**. Internal mammary (IMN) chain RT delivered heart doses of 3–17 Gy and 2–10 Gy for left- and right-sided irradiation, respectively

Cardiac Risk Factors:

An individual's history of pre-existing cardiac risk factors such as diabetes, hypertension, obesity, smoking, and prior ischemic events is critical to assessing risk of cardiac toxicity **(39)**

Age:

On a biological level, elderly patients may be more susceptible to coronary artery atherosclerosis and diffuse myocardial fibrosis due to radiation interaction as RT likely accelerates these age-related processes **(40)**

Lung toxicity:

Radiation Pneumonitis:

Perhaps the most widely studied pulmonary toxicity from lung cancer radiation is radiation pneumonitis (RP); however the prevalence of this condition is low due to the tolerance of lung tissues to the relatively low exposure from typical breast radiation treatments. A significant challenge in defining the risk of RP is the heterogeneity in defining this process 6. The most common grading system used for reporting pulmonary toxicity is the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE commonly uses a grading system from 1 to 5, with 5 always defined as death. In regard to pneumonitis, Grade 1 is considered asymptomatic inflammation of the lung without requirement for intervention; this RP would be noted incidentally on radiographic findings. Grade 2 pneumonitis is symptomatic with limitations warranting intervention, and Grade 3 is defined as that requiring oxygen supplementation. Grade 4 pneumonitis includes more severe life-threatening respiratory compromise requiring intervention such as tracheotomy or intubation **(41).**

The clinical factors found to be linked to radiation pneumonitis after RT for breast cancer include regional nodal irradiation, prior exposure to chemotherapy, volume of lung irradiated, as well as age **(42)**

Pulmonary Fibrosis:

Like RP, pulmonary fibrosis is similarly uncommon and develops as a late toxicity most often 6–24 months post-RT, with stabilization at 2 years **(43)**

Like pneumonitis, fibrosis may be defined either clinically or radiographically and is most commonly identified as an asymptomatic radiographic finding. Pulmonary fibrosis in the CTCAE relies more heavily on radiographic assessment. Grade 1 fibrosis is defined as 50–75% radiographic changes). Lastly, Grade 4 fibrosis is defined as any fibrotic change requiring intubation with ventilatory support, radiographic changes to >75% of lung parenchyma with honeycombing, or hemodynamic instability.

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