

POSTMASTECTOMY RADIATION THERAPY IN LOCALLY ADVANCED BREAST CANCER

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Despite wide efforts for early detection of breast cancer using screening mammography, locally advanced breast carcinomas account for a remarkable proportion of all breast carcinomas, particularly in developing countries. Locally advanced breast cancer may have widely different clinical and biological features. Radiotherapy plays an important role in the management of locally advanced breast cancer. Postmastectomy radiotherapy has been shown to significantly reduce the risk of loco-regional failure and to improve disease free survival as well as overall survival in high-risk women with breast cancer. This review article summarizes the data from randomized trials revealing a significant benefit from postmastectomy radiation therapy in patients with locally advanced disease.

Key Words: breast cancer, locally advanced, radiotherapy.

INTRODUCTION

Breast cancer incidence rates increased rapidly in the 1980's, due to increased use of mammographic screening and have increased gradually then. Global breast cancer incidence increased from 641 000 cases in 1980 to 1 643 000 cases in 2010. Moreover breast cancer killed 425 000 (359 000–453 000) women in 2010, of whom 68 000 (62 000–74 000) were aged 15–49 years in developing countries. Worldwide, the incidence of breast cancer has increased at an annual rate of 3.1% and mortality from breast cancer has increased at an annual rate of 1.8%. Increases in the absolute number of cases and deaths are driven by the interaction of three distinct reasons: rising population numbers in women of at-risk age, population ageing such that the median age is rising in most regions and changes in age-specific incidence and death rates [1].

Locally advanced breast cancer (LABC) encompasses a heterogeneous collection of breast neoplasms and constitutes approximately 10–20% of the newly diagnosed breast cancers and even it is a very common clinical presentation in developing countries (30% to 60%) [2]. Patients with stage and III (IIIA, IIIB and IIIC) of the TNM classification are included in LABC [3, 4]. In this classification system patients are included if they have T3 tumors (tumors larger than 5.0 cm) with positive lymph nodes or T4 tumors with any N stage, or any T category with N2 or N3. T4 disease may represent invasion into the chest

wall (T4a), tumors associated with breast edema or skin ulceration or satellite nodules (T4b) both invasion and T4b characteristics (T4c), and inflammatory breast cancer (T4d). Invasion of disease into the pectoralis major muscle without chest wall invasion and dimpling or fixation of the overlying skin does not qualify as T4 disease.

Patients who present with LABC are at risk for both distant and locoregional disease recurrence. The prognosis of patients with LABC depends on tumor size, extent of lymph node involvement and presence of inflammatory breast cancer. The clinical management of LABC is complex and should be tailored to the individual patient. Optimal treatment of LABC requires a multidisciplinary approach that incorporates diagnostic imaging, chemotherapy, appropriate surgical intervention, radiation, and, if indicated, biological and hormonal therapies. Radiation therapy (RT) is an essential treatment modality in LABC. Post-mastectomy radiotherapy (PMRT), which generally includes radiation of the chest wall and regional lymph nodes, has been demonstrated in randomized controlled trials to improve loco-regional control in patients with LABC [5–8].

CLINICAL FEATURES AND DIAGNOSIS

LABC is heterogeneous disease, including disease which is either extensive within the breast and/or ipsilateral nodal areas. The rate of LABC in developed countries with organized population based screening mammography programs is about 5%, but this rate is more than 50% in low-middle income countries [9, 10]. Staging is based on TNM (tumor, nodes and metastasis) system. The staging system for breast cancer had varied over time; therefore categorization of LABC differs between studies. The clinical diagnosis of LABC is usually not difficult. Most patients with LABC present with an easily palpable mass that is often accompanied by additional findings such as fixation to the underlying fascia, erythema or edema (peau d'orange) of the surrounding tissue or even the entire breast, nipple retraction, pain, axillary mass and breast ulcerations.

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Abbreviations used: ASCO – American Society of Clinical Oncology; CAFTH – cyclophosphamide, doxorubicin, fluorouracil, tamoxifen and fluoxymesterone; CMF – cyclophosphamide, methotrexate and fluorouracil; EBCTCG – Early Breast Cancer Trailists' Collaborative Group; IM – internal mammary; IMC – internal mammary chain; LABC – locally advanced breast cancer; LRR – loco-regional recurrence; NAC – neoadjuvant chemotherapy; OS – overall survival; PMRT – postmastectomy radiotherapy; RT – radiation therapy; SCF – supraclavicular fossa; TNM – tumor, nodes and metastasis.

Breast imaging is essential for all women presenting with significant breast symptoms. Mammography may be inappropriate for patients with gross presentations of LABC like bleeding or fungating tumor, although ultrasound is valuable method of documenting tumor size and extent before initiation of treatment. In order to study the breast and lymph node areas a computed tomography or dynamic magnetic resonance should be used. LABC can be confirmed with biopsy.

MANAGEMENT

The management of LABC is a model for multidisciplinary oncology care. Surgery has been the first-line treatment for patients with operable breast cancer, with neoadjuvant chemotherapy (NAC) reserved for patients with locally advanced cancers. However the optimal management of LABC remains a major therapeutic challenge. NAC is now considered current practice and the standard of care for premenopausal patients [2]. Anthracycline and taxane based chemotherapy regimens are currently the most effective induction agents for women with locally advanced and operable breast cancer. Most patients will have objective clinical response to therapy; however approximately 10–20% will experience a complete clinical response [11]. Currently, most treatment approaches for LABC involve a delivery of primary chemotherapy or endocrine therapy, followed by surgery, RT or both. Such combined approaches associated with a five year survival probability of 30–55%, disease free survival of 30–50% and a five year local control of 70–90% [12, 13].

Even after mastectomy and systemic therapy occult disease may remain in the chest wall and/or regional lymph nodes. The residual disease may serve not only as a source of potentially morbid loco-regional recurrence (LRR), but also an important reservoir from which distant metastases may be seeded after the initial elimination of distant disease by systemic therapies. PMRT is an essential part of the treatment of LABC patients. PMRT may contribute both the improvement of local control and also to the reduction of breast cancer mortality [14].

POSTMASTECTOMY RADIATION THERAPY IN LOCALLY ADVANCED BREAST CANCER

PMRT has been a subject of considerable study over the past several decades. Most of these trials have shown that PMRT provided a substantial reduction in the risk of LRR in patients with LABC [15–17].

Most early studies failed to show the overall survival (OS) benefit of PMRT; however the treatment related toxicity, especially cardiotoxicity, prevented to observe the survival benefit [8]. In early 1980's operable breast cancer was accepted as a systemic disease, and it was thought that no survival benefit due to loco-regional treatment could be expected [18, 19]. However more recent developments in the field of breast cancer screening, long term follow-up studies of breast cancer and some trials on adjuvant RT underlined the curability of breast cancer and the importance of loco-regional relapse in the development of metastasis [18].

The Eastern Cooperative Oncology Group conducted a trial from 1982 to 1987 investigating patients with ope-

nable LABC, including patients with pathologic T4 lesions excluding T4d disease, T3 lesions with positive nodes and N2 disease [20]. Patients underwent modified or standard radical mastectomy with grossly tumor-free margins and had examined at least 8 axillary lymph nodes. All patients received 6 cycles of cyclophosphamide, doxorubicin, fluorouracil, tamoxifen and fluoxymesterone (CAFTH) and were randomized to PMRT or observation. After 9 years of median follow-up period it was concluded that PMRT decreased loco-regional failure (15% vs. 24%) without any survival benefit.

In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis 19 582 women with breast cancer from 40 randomized trials of RT were included [21]. RT fields generally included not only chest wall (or breast) but also axillary, supraclavicular and internal mammary nodes. In spite of a reduction in breast cancer mortality, and in systemic and LRR, a statistically significant improvement in OS was not demonstrated. It may be due to that many of its constituent trials, particularly those initiated before 1975, used old RT techniques which eventually resulted in higher cardiotoxicity. Van de Steene and colleagues re-analyzed the trials of EBCTCG study and concluded that adjuvant RT significantly improves OS and the benefit was probably present when heart sparing techniques and optimal fractionation doses were used [18].

Randomized trials from Denmark and British Columbia showed an impressive significant OS benefit in the RT group. In the Danish 82b trial, 1708 premenopausal women with high risk breast cancer (patients with positive axillary lymph nodes, tumor size >5 cm or invasion of the skin or pectoral fascia) were randomized to systemic chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) vs. CMF chemotherapy and PMRT to the chest wall and regional lymph nodes after total mastectomy [5]. After 114 months of median follow-up time 9% and 32% of women, who underwent CMF plus RT and CMF alone, had LRR with or without distant metastases ($p < 0.001$). OS at 10 years was 54% among those given RT and CMF and 45% among those who received CMF alone ($p < 0.001$). In the Danish 82c trial 1375 postmenopausal women with high-risk breast cancer (stage II or III) were randomly assigned adjuvant tamoxifen alone or with postoperative radiotherapy to the chest wall and regional lymph nodes [6]. Median follow-up was 123 months. Again PMRT decreased LRR (from 35% to 8%; $p < 0.001$) and improved OS time (10 year OS time improved from 36% to 45%; $p = 0.03$). In British Columbia trial 318 premenopausal women with breast cancer with pathologically positive axillary lymph nodes were randomly assigned to CMF or CMF and PMRT [22]. The radiation dose to the chest wall was 37.5 Gy in 16 daily fractions. The midaxilla received a dose of 35 Gy in 16 fractions through an opposed anterior supraclavicular/axillary field and a posterior axillary patch. A direct internal mammary-chain field delivered a dose of 37.5 Gy in 16 fractions. After 249 months of median follow-up time there were significant improvement in terms of loco-regional failure (from 28% to 10%) and OS time (20 year OS time improved from 37% to 47%; $p = 0.03$) (Table 1).

Table 1. Randomized trials comparing mastectomy with axillary dissection followed by systemic therapy to mastectomy with axillary dissection followed by systemic therapy and RT

Study	№ of patients	CT schedule	RT schedule	LRF		OS	
				CT (%)	RT (%)	CT (%)	RT (%)
DBCG 82b [5]	1708	CMF 9 cycles → RT(-)	Chest wall + regional lymph nodes 48–50 Gy (For 64 patients 36 Gy) +	32	9*	45	54*
DBCG 82c [6]	1375	CMF + Tamoxifen Tamoxifen alone	CMF → 8 cycles Chest wall+ regional lymph nodes 48–50 Gy (For 69 patients 36 Gy) +	35	8*	36	45*
British Columbia [7]	318	CMF Before 1981: 12 months After 1981: 6 months	CMF + Tamoxifen Chest wall+ regional lymph nodes 37.5 Gy + CMF (between 4 th and 5 th cycles RT applied)	33	13*	46	54
DFCI-AC [16]	123	AC 5–10 cycles	Chest wall + regional lymph nodes 45 Gy + AC	20	6*	63	59
DFCI-CMF/MF [16]	83	CMF or MF 8 cycles	Chest wall+ regional lymph nodes 45 Gy +	5	2	858	77
SECSG [17]	295	CMF 6–12 cycles	CMF/MF Chest wall + regional lymph nodes 50 Gy +	23	13*	44	55
ECOG stage III [20]	312	CAFTH 6 cycles	CMF → 6 cycles Chest wall + regional lymph nodes + CAFTH → 6 cycles	24	15	47	46

CT – chemotherapy; DFCI – Dana-Farber Cancer Institute; LRF – local-regional failure; MF – methotrexate and fluorouracil; SECSG – Southeast Cooperative Study Group.

*Difference between the groups was significant

Over the past 5 decades there have been at least 25 randomized prospective studies that have evaluated the benefits of radiation after mastectomy for patients with breast cancer [23]. Given the long time period over which this topic has been studied, it is not surprising that there is considerable heterogeneity in the surgical and RT treatments among these trials. The chance that a benefit in loco-regional control, relapse-free survival and OS rates were varied in different studies. Firstly, it may be related to trial sizes. In the 10 studies with fewer than 200 assessable patients sometimes control arm fared better, and sometimes RT arm did. Eight of the nine trials that contained 200 or more patients showed trends favoring the RT arm. It also should be pointed out that regarding to prognostic factors, such as the number of the positive nodes and tumor size, there are substantial heterogeneity between their populations.

In the British Columbia trial patients had a median of 11 axillary lymph nodes removed as part of level I and II axillary lymph node dissection. However in the Danish study the median number of removed axillary lymph node was 7, lower than that expected from a standard level I/II axillary dissection, which is at least 10, prompting the concern that inadequate regional surgery may underestimate the number of positive lymph nodes and eventually lead to increase risk of loco-regional failures.

The American Society of Clinical Oncology (ASCO) consensus panel recommended using PMRT in patients with 4 or more positive axillary lymph nodes as well as for patients with T3, node-positive disease [23]. In summary patients with tumors ≥5 cm or at least four involved nodes should be offered adjuvant irradiation. Additionally patients with one or three involved nodes and large tumors, extranodal extension or inadequate axillary dissections experience high rates of LRR and may benefit from PMRT. Therefore all patients with LABC should be evaluated with radiation oncologist because there is strong consensus regarding to the need for RT. The ASCO recommendation about the indications of PMRT was given in table 2 [23].

DEFINITION OF RADIATION FIELDS

The patients, most likely to benefit from adjuvant RT, are presumed to be those with an increased risk of loco-regional failure. Factors predictive of high rates of LRR were identified as four or more involved nodes, tumor size greater than 5 cm and the presence of tumor necrosis, negative estrogen receptor status and involvement of the pectoral fascia [24]. However the most important prognostic factor predicting the loco-regional failure rate is the involvement of axillary lymph nodes. Katz and colleagues reported that the 10-year actuarial rates of isolated LRR were 4; 10; 21 and 22% for patients with 0; 1–3; 4–9 or > 10 involved nodes respectively [24]. Recht and colleagues reported that the rate of chest wall recurrence in patients without axillary lymph node metastasis was 3% while 4.5%, 10% and 34% in patients with 1–3; 4–7 and > 8 axillary lymph node metastasis [25]. After PMRT, the most common site of LRR is the chest wall followed by the supraclavicular fossa (SCF) [24–26].

Chest wall

The chest wall is the site at greatest risk of recurrence in patients undergoing mastectomy [24]. The occult disease may remain in the chest wall and may serve as a source of systemic metastases. After chest wall recurrence 5 year OS rate was reported as 25–30% [24, 25]. Therefore treatment of chest wall is considered mandatory for all patient who undergone PMRT.

According to ASCO recommendations, there is insufficient evidence for chest wall irradiation as total dose, fraction size, the use of bolus and the use of scar boosts [23]. Most institutions in the United States treat the chest wall to total doses of approximately 50 Gy in 1.8 to 2 Gy daily fractions, given five times weekly. There are no data on whether giving doses to the entire chest wall in excess

Table 2. ASCO Guidelines for the use of PMRT [23]

1. Patients with Four or More Positive Axillary Lymph Nodes	PMRT is recommended for patients with four or more positive axillary lymph nodes
2. Patients with One to Three Positive Axillary Lymph Nodes	There is insufficient evidence to make recommendations or suggestions for the routine use of PMRT in patients with T1–T2 tumors with one to three positive nodes
3. Patients with T3 or Stage III Tumors	PMRT is suggested for patients with T3 tumors with positive axillary nodes and patients with operable stage III tumors
4. Patients Undergoing Preoperative Systemic Therapy	There is insufficient evidence to make recommendations or suggestions on whether all patients initially treated with preoperative systemic therapy should be given PMRT after surgery
5. Modifications of These Guidelines for Special Patient Subgroups	There is insufficient evidence to make recommendations or suggestions for modifying the above guidelines based on other tumor-related, patient-related or treatment-related factors
6. Chest Wall Irradiation	In patients, given PMRT, we suggest that adequately treating the chest wall is mandatory
7. Details of Chest Wall Irradiation	There is insufficient evidence for the panel to recommend or suggest such aspects of chest wall irradiation as total dose, fraction size, the use of bolus and the use of scar boosts
8. Axillary Nodal Irradiation	We suggest that full axillary RT not be given routinely to patients undergoing complete or level I/II axillary dissection. There is insufficient evidence to make suggestions or recommendations as to whether some patient subgroups might benefit from axillary irradiation
9. Supraclavicular Nodal Irradiation for Patients with Four or More Positive Axillary Lymph Nodes	The incidence of clinical supraclavicular failure is sufficiently great in patients with four or more positive axillary nodes that we suggest a supraclavicular field should be irradiated in all such patients
10. Supraclavicular Nodal Irradiation for Patients with One to Three Positive Axillary Lymph Nodes	There is insufficient evidence to state whether a supraclavicular field should or should not be used for patients with one to three positive axillary nodes
11. Internal Mammary Nodal Irradiation	There is insufficient evidence to make suggestions or recommendations on whether deliberate internal mammary nodal irradiation should or should not be used in any patient subgroup
12. Sequencing of PMRT and Systemic Therapy	There is insufficient evidence to recommend the optimal sequencing of chemotherapy, tamoxifen and PMRT. The panel does suggest, given the available evidence regarding toxicities, that doxorubicin not be administered concurrently with PMRT
13. Integration of PMRT and Reconstructive Surgery	There is insufficient evidence to make recommendations or suggestions with regard to the integration of PMRT and reconstructive surgery
14. Long-Term Toxicities	The potential long-term risks of PMRT include lymphedema, brachial plexopathy, radiation pneumonitis; rib fractures, cardiac toxicity and radiation induced second neoplasms. There is sufficient evidence for the panel to suggest that, in general, the risk of serious toxicity of PMRT (when performed using modern techniques) is low enough that such considerations should not limit its use when otherwise indicated. However follow-up in patients treated with current RT techniques is insufficient to rule out the possibility of very late cardiac toxicities
15. Toxicity Considerations for Special Patient Subgroups	There is insufficient evidence to make recommendations or suggestions that PMRT should not be used for some subgroups of patients because of increased rates of toxicity (such as radiation carcinogenesis) compared with the rest of the population

of approximately 50 Gy are of additional benefit. Twice-daily treatment has also been used at the M.D. Anderson Cancer Center to treat patients with locally advanced or inflammatory carcinomas after surgery [27, 28]. It is not clear whether one fractionation scheme has any advantages over another [23].

Supraclavicular fossa

The second most common site of recurrence after PMRT is SCF [24]. In patients without axillary lymph node metastasis or 1–3 axillary lymph node metastasis, the isolated SCF recurrence rate is less than 2% [24, 25]. The SCF recurrence rate increases when the number of axillary lymph node increased. Occult SCF node involvement was found in 18% (23 of 125) of patients with histologically positive axillary nodes (and none of 149 patients with negative axillary nodes) in one series in which SCF node biopsies were performed routinely [29]. The risk of clinical SCF recurrence after mastectomy seems to depend mainly on the extent of axillary involvement.

SCF nodal failures are more common in unirradiated patients with four or more positive axillary nodes. In one series SCF nodal failure appeared in 17% of unirradiated or inadequately irradiated patients (17 of 102), compared with 2% of 56 irradiated patients. In most series SCF recurrences occur in 1% to 4% of patients when only one to three nodes are positive [23, 30, 31]. There is insufficient evidence to state whether a supraclavicular field should or should not be used for patients with one to three positive axillary nodes.

In summary, the incidence of SCF failure is remarkable in patients with four and more axillary lymph node involvement; therefore SCF should be irradiated in all such patients. The doses of 45–50 Gy in 1.8–2 Gy daily fractions seem adequate in patients without macroscopic disease in SCF. If there is palpable lymph node in the SCF 10–15 Gy of boost, doses may be required.

Axilla

The risk of clinical axillary recurrence after mastectomy varies depending on whether axillary nodes are involved, how many are positive and by the type of axillary dissection performed [23, 32]. In most studies, which used a level I/II or complete dissection of levels I to III, axillary recurrences occurred in a few percent of patients, when only one to three nodes were positive, whether RT to the breast was a part of treatment or not [23, 30–32]. Axillary failures may be more common in patients with four or more positive nodes.

In Danish Breast Cancer Cooperative Group 82b study the frequency of LRR was 9% among the women, who received RT plus CMF, and 32% among those, who received CMF alone [5]. However in this study the median number of removed axillary lymph node was 7. It was reported in a study from Sweden that there was no axillary failures among either 46 unirradiated or 52 irradiated patients with four or more positive nodes [33]. Marks and colleagues reported that in a small series of patients, who underwent high-dose chemotherapy after complete dissection which revealed 10 or more positive nodes, there

was no difference in axillary failure rates whether a SCF field or full axillary field was treated [34].

ASCO recommended that axillary RT should not be given routinely to patients undergoing complete or level I/II axillary dissection [23]. There isn't any sufficient data about the benefit of axillary irradiation in certain patient subgroups. The doses of 45–50 Gy in 1.8–2 Gy daily fractions seem adequate for axillary irradiation.

Internal mammary lymph nodes

Internal mammary (IM) nodal irradiation was used in the majority of trials of PMRT, including the two Danish and the British Columbia trials. However the data regarding the value of routine IM nodal irradiation is limited [23]. In some studies which used mastectomy plus IM lymph node dissection as surgical treatment, the incidence of IM node metastases was approximately 10% in patients with a negative axillary dissection and 20% to 50% in patients with a positive dissection [23, 35–37]. The risk of IM lymph node metastasis increases when the number of axillary lymph node, tumor size and clinical stage increased [38–40]. The location of the primary tumor in the breast seems to have an impact on the risk of IM node involvement; patients with centrally or medially located tumor have higher risk of IM lymph node metastasis.

Arriagada and colleagues reported an analysis on 1195 patients with operable breast cancer and histologically positive axillary nodes treated by mastectomy and complete axillary dissection at the Institute Gustave-Roussy between 1958 and 1978 [41]. They suggested a beneficial effect of treatment of the internal mammary chain (IMC) on the risks of death and distant metastasis for only the patients with medial tumors. However they did not show any benefit of IM nodal irradiation for patients with laterally located tumors. They reported that the surgical IMC dissection and postoperative irradiation have similar effects on both the risk of death and of distant metastasis. Kaija and colleagues performed a randomized study of IM irradiation and concluded that there was no benefit of IM irradiation [42]. However in this study only 13% of the 270 patients had positive axillary lymph nodes and 18% of the patients had centrally or medially located tumor.

The lymph nodes, which located in the upper three interspaces, are most likely to be involved IM lymph nodes in patients with breast cancer [23, 39, 43]. These tend to be located less deeply than the ones located more inferiorly. Hence, in many patients most of the IM nodes will likely be included in tangential photon treatment fields [23, 44, 45]. Therefore techniques that attempt to more comprehensively treat the IM nodes may add only a small degree of benefit (if any) to standard chest wall irradiation fields [23].

The most important side effect of IM irradiation is known as cardiac toxicity. However in most of the studies, reporting the increased risk of cardiac toxicity the old RT technique, which used only photon beams to 6 cm of depth, was used. In Danish and the British Columbia studies, which did not show any increase in cardiac mortality and morbidity, IM irradiation was performed by using combination of photon and electron or only elec-

tron beams and the dose was prescribed to 3–4 cm depth [22, 46].

CONTROVERSIES

Although PMRT has been evaluated in more than 25 trials conducted over 40 years, some significant controversies over its use remain. There is insufficient evidence to make recommendations or suggestions for the routine use of PMRT in patients with one to three positive nodes. However increasing evidence accumulated in support of a role for PMRT even among patients with one to three positive lymph nodes. The Danish 82b and 82c trials were included node-negative patients who were eligible for this trial due to the presence of high-risk factors as invasion of pectoralis muscle or skin by the primary tumor [5, 6]. There were statistically significant differences in terms of loco-regional failure and OS rates favoring the irradiated patient arm for patients with negative, one to three positive and four or more positive nodes in the 82b trial. In the 82c trial the same results were found, but these differences were not reported [23]. The initial report of British Columbia trial showed statistically significant improvements in loco-regional failure in irradiated patients in the subgroups with either one, three or four to more positive nodes [7]. The reduction in the relative risk of a recurrence, that was obtained by adding radiation to chemotherapy, was similar in the subgroup with one to three positive nodes and the subgroup with four or more positive nodes. The British Columbia trial updated and 20 year results showed that the benefits of PMRT were similar relative magnitude for patients with one to three and four or more positive axillary lymph nodes [22] (Table 3).

Table 3. Results of prospective randomized trials according to positive lymph node numbers

	Isolated Local-Regional Recurrence, %		Overall Survival, %	
	No RT	RT	No RT	RT
Number of positive LN	26	10	37	47
British Columbia				
1–3	21	9	50	57
>4	41	16	17	31
DBC 82b	32	9	45	54
1–3	30	7	54	62
>4	42	14	20	32
DBC 82c	35	8	36	45
1–3	23	6	44	55
4	31	6	17	24
DBC 82b and c	49	14	–	–
>8 nodes removed	37	6	39	29
1–3	27	4	48	57
>4	51	10	12	21
EBCTCG				
1–3	20	6	55	59
>4	32	14	29	34

DBC 82b – Danish Breast Cancer Group; EBCTCG – Early Breast Cancer Trialists' Collaborative Group; LN – lymph node.

On the other hand the trial performed for patients with one, three, four or more positive nodes at the Dana-Farber Cancer Institute showed differences in disease free survival or OS [16]. Although the South-Eastern Cooperative study revealed the significant improvement in terms of loco-regional control in one to three positive lymph nodes, there did not report any significant difference in disease free survival and OS [17]. In the Danish studies the median number of axillary lymph nodes resected was only seven [5], which is approximately 50% of the number reported from studies conducted in the United States. Also 76%

of the patients had fewer than 10 lymph nodes removed and 15% had three or fewer lymph nodes removed [5]. In the British Columbia trial the median number of resected lymph nodes was 11 [7]. Given the less extensive axillary surgery done in these studies, it is highly probable that some of the patients in these studies, reported as having had one to three positive lymph nodes, would have had four or more positive lymph nodes if a standard axillary dissection had been performed. The Intergroup designed a randomized study to assess the role of PMRT in patients with one to three positive lymph nodes and failed to accrue and closed in 2003 [24].

The data regarding the value of routine IM nodal irradiation is limited. According to ASCO recommendations, there is insufficient evidence to make suggestions on whether deliberate IM nodal irradiation should or should not be used in any patient subgroup. Factors associated with an increased risk of IMN node positivity include age less than 35 years, medial tumor location, larger primary tumor size, the presence of lymphovascular invasion and positive axillary nodes. In summary, there is insufficient evidence for patients with T3, T4 tumors, ≥ 4 axillary lymph nodes involvement or centrally/medially located tumors with axillary lymph node involvement.

There is only limited retrospective data regarding, how the use of PMRT affects outcome of reconstructive surgery. These studies contain heterogeneous populations treated with different reconstructive techniques. The incidence of LRF does not seem to be different for patients undergoing reconstruction either immediate or delayed, than for patients not undergoing reconstruction [23]. According to ASCO panel, there is insufficient evidence to make recommendations or suggestions with regard to integration of PMRT and reconstructive surgery. Where reconstruction can be done with a low morbidity, such that systemic therapy and PMRT will not be delayed in the large majority of cases, the consensus of the panel was to perform immediate reconstruction of patients with stage I or II cancers. However there was no consensus regarding to use of immediate reconstruction in patients with stage IIIB disease and larger T3 tumors [23].

POTENTIAL SIDE EFFECTS OF POSTMASTECTOMY RADIATION THERAPY

The most frequent long-term risks of PMRT include lymphedema, brachial plexopathy, radiation pneumonitis, rib fractures, cardiac toxicity and radiation-induced second neoplasms.

Lymphedema

Lymphedema of the arm results from interruption and damage to lymphatics by surgery and/or radiation or may result from blockage of lymphatics by advanced cancer. Lymphedema may develop immediately after treatment or after many years. There is no way to predict which individuals will develop lymphedema or when it will develop. The rate of lymphedema after axillary dissection without radiation is reported as between 5% and 15%, but individual reports range as high as 30% [32]. The extent of the axillary dissection influences the incidence

of breast or arm edema, with this complication being more frequent when more extensive axillary dissections are carried out [47]. Dewar and colleagues [48] reported a greater incidence of upper limb sequelae in patients undergoing axillary surgery and irradiation (33.7%) or irradiation alone (24%) than in patients treated with axillary dissection only (7.2%).

In the Mayo Clinic trial, in which patients underwent complete axillary dissection, the risk of arm edema in irradiated patients was 54%, compared with 25% in 104 patients treated with the same chemotherapy alone [23]. In the British Columbia trial, in which a level I/II dissection was performed, the incidence of symptomatic arm edema (9%) and the number of patients who required intervention (3%) were higher among the patients randomized to PMRT, compared with the patients treated with chemotherapy alone [7]. 84 patients in the Danish trials of PMRT were prospectively studied for complications [46]. Ipsilateral arm edema occurred in 14% of the PMRT patients, compared with 3% of the control patients.

The compression pump, along with skin care, exercise and compression garments, complex decongestive physiotherapy or complex physical therapy are the treatment of options for lymphedema. Arm care, therapeutic exercises, manual lymph node drainage, and compression bandages or garments comprise this treatment regime. Decreases in lymphedema are noted if women are compliant with the prescribed treatment program.

In summary, the risk of lymphedema increased by irradiation of axilla after complete axillary dissection. However the incidence of breast or arm edema after surgery varies and is related to performance and technique of axillary dissection, regardless of whether the axillary lymph nodes were irradiated and the dose of radiation delivered.

Brachial plexopathy

Injury to the brachial plexus resulting in transient or permanent brachial plexopathy is uncommon in breast cancer patients. Brachial plexopathy must be distinguished from neuropathies, that are common after axillary dissection, characterized by numbness and paresthesias or the neuropathy that is caused by tumor recurrence [23].

The risk of developing brachial plexopathy seems to be increased with the doses above 50 Gy or large fraction sizes as well as the use of chemotherapy. It has been estimated that a dose of 60 Gy in 2 Gy fractions given to the entire plexus is required to result in a 5% risk at 5 years of permanent brachial plexopathy; a dose of 75 Gy was estimated to be required to cause a 50% risk [49].

The optimum treatment strategy for brachial plexopathy is still unknown. Therefore treatment planning should be carefully done and tolerance doses of normal tissues should be carefully evaluated.

Radiation pneumonitis

The most common radiographic finding in a patient, who received radiation treatment for breast cancer, is the infiltration in the lung parenchyma and localized interstitial fibrosis. These findings are self-limited and asymptomatic. However clinical radiation pneumonitis is characterized by a chronic cough, fever and nonspecific infiltrate on chest x-ray [23, 50, 51]. It usually develops in the

first few months after RT and is usually self-limited, with symptoms lasting an average of 4 weeks. Few patients require any specific treatment. Changes on x-ray may persist after the resolution of symptoms. The incidence of the radiation pneumonitis is about 1%; however it may increase up to 8% when concomitant chemotherapy is used. Moreover chemotherapy may cause pulmonary toxicity independently of RT.

Rib fractures

Rib fracture is an uncommon complication of chest wall irradiation. Metz and colleagues reported the risk of rib fractures as 2% (4 of 221) after 50 Gy of chest wall irradiation [52]. The risk of rib fracture is related to dose of total RT, use of chemotherapy, as well as the energy of the photon beam used [53]. Rib fractions usually heal without any intervention.

Cardiac toxicity

Acute and subacute complications caused by PMRT have been extensively evaluated. The overview analysis of RT phase III trials by Cuzick showed that the addition of irradiation reduced deaths secondary to breast cancer, but increased cardiac mortality in irradiated patients with the consequence that OS was similar in both irradiated and non-irradiated patients [54]. This overview analyzed many older trials, that used techniques and equipment that would now be considered suboptimal. Although the evidence from more modern trials, using techniques that minimize exposure to the normal cardiac structures, have reduced cardiac toxicity, the radiation oncologist must be aware of the potential for adverse cardiac effects irradiation, especially in patients with left-sided breast cancer and receiving other cardiotoxic therapies, including adriamycin, epirubicin and trastuzumab [55].

Analysis of the randomized postmastectomy Danish trials, with over 10-year follow-up, showed no excess cardiac mortality with the use of PMRT. Hojris and colleagues reported the relative hazard of morbidity from ischemic heart disease among patients in the RT compared with the no-RT group was 0.86 (95% CI 0.6 to 1.3), and that for death from ischemic heart disease the relative hazard was 0.84 (CI 0.4 to 1.8) [46]. The hazard rate of morbidity from ischemic heart disease in the RT group compared with the no-RT group did not increase with time from treatment. Similarly Nixon and colleagues reported that there was no difference in the incidence of cardiac events in patients with right- and left-sided lesions who had a potential follow-up time of at least 12 years, despite the fact that the IM nodes were commonly included in deep tangent fields [56]. In a retrospective review of 2128 women treated with irradiation for breast cancer, after a median follow-up of 10.2 years, it was reported that the incidence of myocardial infarction was comparable with that in an age-matched general population of women [57].

In summary, these studies suggest no excess cardiac morbidity using tangential fields to treat left-sided breast cancers. However it is important to minimize cardiac exposure in all patients, and particularly in those receiving left-sided radiation in combination with other potentially cardiotoxic drugs.

Radiation-induced second neoplasms

The risk for developing a subsequent malignancy secondary to PMRT is very small. Nonetheless, there is some evidence with very long-term follow-up of higher rates of secondary cancers. Although this may be more prevalent with older techniques, it is an important component of treatment planning to minimize dose to nontarget normal tissues. For younger patients the risk of developing a contralateral breast cancer likely is increased after PMRT, but soft tissue and bone sarcomas, lung cancer and esophageal cancer are known as the potentially lethal malignancies that appear in the radiation field. The risk of acute leukemia may be increased when PMRT is combined with multiagent chemotherapy regimens containing alkylating agents [23].

Angiosarcoma is the most common malignancy which develops after breast irradiation. The risk of developing angiosarcoma in the radiation field after 8–10 years of latent period is 0.0010% [55, 58]. It is important to differentiate atypical vascular lesions from angiosarcoma, but currently there is no evidence that they represent a precursor to radiation-induced angiosarcoma. The primary therapy is simple mastectomy if wide tumor-free margins can be achieved.

FUTURE POSSIBILITIES AND ONGOING STUDIES

Advances in molecular biology have also led to improvements in understanding a patient's prognosis and the likelihood of the disease responding to a particular treatment. The clearest example of such a strategy has been the successful use of trastuzumab for patients with tumors that overexpress the HER2/neu receptor. Incorporation of this targeted therapy has significantly improved the outcomes of patients with metastatic disease, has shown initial promise as a neoadjuvant treatment and is under active investigation as a component of adjuvant therapies.

In addition to the HER2/neu receptor, therapies have been developed against a number of other biologic targets, including other growth-promoting receptors, the tumor vasculature and products of other oncogenes. Targeting angiogenesis is one strategy that is being explored in the adjuvant setting to improve outcomes. Bevacizumab, a monoclonal antibody to the vascular endothelial growth factor, has been approved for use in a variety of tumor types, including colorectal cancer, non-small cell lung cancer and metastatic breast cancer. Compared with paclitaxel alone, the combination of paclitaxel and bevacizumab improved overall response rates and prolonged progression-free survival and in patients with breast cancer receiving their first line of chemotherapy for metastatic disease [59]. Based on this trial result, bevacizumab ECOG 5103 was designed as a randomized phase III trial studying doxorubicin, cyclophosphamide and paclitaxel with or without bevacizumab in the adjuvant treatment of patients with HER2-negative lymph node-positive or high-risk lymph node-negative breast cancer. Also based on results in the metastatic setting, lapatinib appears to be another promising agent

among patients with HER2-positive disease. The addition of lapatinib to capecitabine extended time to progression in patients who experienced disease progression after trastuzumab-based therapy [60]. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTO) trial is an international research study that will randomize more than 8000 patients to receive trastuzumab alone for 52 weeks, lapatinib alone for 52 weeks, trastuzumab for 12 weeks, followed by a 6-week break, followed by lapatinib for 34 weeks or lapatinib in combination with trastuzumab for 52 weeks.

Each of these trials will require substantial commitment on the part of patients to receive such prolonged courses of adjuvant treatment and will demand that providers including surgeons, medical oncologists and radiation oncologists communicate and coordinate patient care plans to minimize risks of multiple overlapping therapies.

CONCLUSION

RT is an integral component of the multimodal treatment of LABC. PMRT reduces the risk of LRR and increases the long term survival rate for a substantial proportion of women with positive axillary nodes treated with systemic therapy. PMRT is recommended for patients with tumors ≥ 5 cm or at least four involved. There is not enough data regarding to benefit of PMRT in patients with one or three involved nodes. However patients with one or three involved nodes and large tumors, extranodal extension or inadequate axillary dissections experience high rates of LRR and may benefit from PMRT. There is insufficient evidence to make recommendations or suggestions on whether all patients initially treated with preoperative systemic therapy should be given PMRT after surgery; however it is recommended that patients who require mastectomy after systemic therapy should receive PMRT.

After PMRT the most common site of LRR is the chest wall followed by the SCF. Chest wall irradiation is recommended for all patients receiving PMRT. SCF should be irradiated in patients with four and more axillary lymph node involvement.

In parallel to the developments in the field of radiation treatment deleterious side effects of PMRT have been decreased. Therefore the risk of such side effects should not prevent the use of PMRT when indicated. All patients with LABC should be evaluated with radiation oncologist, because there is strong consensus regarding to the need for RT.

CONFLICT OF INTEREST

There is no conflict of interest.

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