



Short Communication

Patterns of loco regional failure in women with breast cancer treated by Postmastectomy Conformal Electron Beam Radiation Therapy (PMERT): Large scale single center experience



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ARTICLE INFO

Article history:

Received 2 February 2017

Revised 24 March 2017

Accepted 24 March 2017

Available online 7 June 2017

Keywords:

Adjuvant chest wall radiotherapy

Electrons

Mastectomy

Loco regional recurrences

ABSTRACT

Purpose: To evaluate loco regional control and describe the patterns of loco regional failure in women with breast cancer irradiated by a previously described post-mastectomy highly conformal electron beam radiotherapy technique.

Materials and methods: We included all women irradiated by PMERT for non-metastatic breast cancer (BC) between 2007 and 2011 in our department. All cases of bilateral BC were excluded. All patients who experienced loco regional recurrence have been studied. Mapping patterns of regional recurrences was also performed and compared with the ESTRO and RTOG Guidelines of volume definition and delineation guidelines.

Results: Among the 796 women included, 10.1% were triple-negative (TN) and 18.8% were HER2-positive and 24.6% of them had received neoadjuvant chemotherapy (CT). Internal mammary chain (IMC), supraclavicular (Level IV), infraclavicular (Levels III and II) and axillary LN (Level I) were treated in 85.6%, 88.3%, 77.9% and 14.9% of cases, respectively. With a median follow-up of 64 months (range: 6–102), 5-year locoregional (RFS and OS were 90% (95% CI: 88.1–92.4) and 90.9% (95% CI: 88.9–93), respectively. Twenty-three patients (2.9%) presented locoregional recurrences. Most of them presented aggressive biological features with grade III tumors in 17 patients (74%) with high mitotic index in 16 cases (70%) and triple negative tumors in 12 (52%). Lymphovascular invasion (LVI) was observed in 11 cases (48%). In 14 cases the locoregional recurrences were diagnosed at the same time as the metastatic disease whereas 4 patients presented distant metastases secondarily. Local (Chest wall) recurrences occurred in 13 cases (56%) with the coverage by the isodose of 47.5 Gy (isodose 95%). Fifteen regional recurrences (lymph nodes) were observed in 13 patients. Only 3 regional recurrences occurred within irradiated volumes and 12 regional recurrences occurred outside irradiated areas.

Conclusion: In presented series, the local recurrences were related mostly to the tumor biological aggressivity and radio resistance. Small number was caused by geographical miss. Further follow-up and careful registration of the recurrences is needed to improve their understanding.

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Introduction

After mastectomy, chest wall (CW) radiation therapy (RT) reduces local recurrences and breast cancer (BC) mortality in high-risk patients, especially patients with lymph node (LN) involvement [1–3]. It is therefore essential to propose an adapted RT technique with minimal early and late side effects. For several

decades, CW irradiation has been performed at the Institut Curie by electron beam radiotherapy, which provides both good coverage of target volumes and decreased dose to organs at risk (OAR), especially the heart and lungs [4]. In previously published study, we reported the results of our technique in terms of efficacy and toxicity. The primary objective of the present study was to evaluate locoregional control and describe the patterns of locoregional failure in women with breast cancer irradiated by a previously described post-mastectomy highly conformal electron beam radiotherapy technique [4]. The secondary objective was to analyze the tumor characteristics and radiation volumes/doses

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that may have resulted in locoregional failure. The essential question investigated this study is whether locoregional recurrence is mainly related to clinical target volume (CTV) coverage or to tumor biology.

Materials and methods

This retrospective study was based on the electronic health records of all patients treated by post-mastectomy chest wall electron beam radiotherapy between 2007 and 2011 at the Institut Curie [5]. The following patients were excluded: patients with ipsilateral recurrences, patients with previous chest wall irradiation or synchronous bilateral chest wall irradiation, patients with metastatic disease, photon beam therapy, all forms of hypofractionated RT, and male BC. Data were recorded until November 2015. The study was approved by the Institutional Scientific and Ethics committee and by the Institut Curie Breast Cancer Research and Treatment Group.

The indications for post-mastectomy RT, according to the REMAGUS (Institut Curie and Institut Gustave Roussy) guidelines used in our department are as follows: i) T3–T4 N0, and/or ii) all T \geq pN1 and/or iii) combination of 2 risk factors (age <40 years, macroscopic multifocality, grade III, lymphovascular invasion, Her2+, triple-negative and pT2).

Lymph node (LN) irradiation included the internal mammary chain (IMC) and supraclavicular (Level IV) and infraclavicular regions (Level II&III) in patients with histologically documented LN involvement. The axilla (Level I) was also treated only in cases with more than 50% of positive LN on the resection specimen and when LN dissection was not performed. The IMC and only level IV LN were irradiated for an inner quadrant or central tumor in the presence of 2 of the following 3 criteria: age \leq 40 years, tumor size >2 cm, lymphovascular invasion (LVI).

All patients underwent radical mastectomy with either axillary lymph node dissection or sentinel lymph node biopsy. Chemotherapy was administered to the majority of patients in the neoadjuvant or adjuvant setting, in combination with Trastuzumab in the presence of Her2 overexpression. Hormone therapy was administered to all patients with hormone-sensitive tumors. The radiotherapy technique has been previously described in detail [4]. Briefly, the chest wall and IMC volumes were included in a unique field at a gantry angle of 20–30° of the vertical. Doses of 50 Gy and 46–50 Gy were delivered to the chest wall and lymph nodes, respectively. A personalized bolus was designed according to the thickness of the chest wall. When the IMC dose per fraction became less than 1.8 Gy, a photon boost completed the dose to a total of 50 Gy.

The following characteristics were analyzed: patient and tumor characteristics, treatments received and short-term and long-term radiation toxicity. Survival was defined as the time between the end of radiotherapy and the date of last follow-up. Locoregional recurrence-free survival (RFS) and metastasis-free survival (MFS) were defined as the time from the end of radiotherapy until locoregional recurrence or death, or the date of metastases or death, respectively. Patients who did not experience any events were censored at the date of last news. Time-to-event endpoints were estimated by the Kaplan–Meier method.

For each patient, positioning (from photos during simulation CT), radiation fields, dosimetries, organ-at-risk (OAR) shielding, and bolus characteristics were retrieved from technical files.

We subsequently compared locoregional recurrences with the initial radiation fields in a standard simulation positioning of the patient (ipsilateral arm abducted and externally rotated). The second step consisted of determining the precise site of node metastases based on computed tomography (CT) or positron emission

tomography (PET) CT. Geographic spatial sites of regional recurrence were defined according to ESTRO and RTOG CTV N [5].

Results

Outcome

Among the 796 women included, 10.1% were triple-negative (TN), 18.8% were HER2-positive and 24.6% of them had received neoadjuvant chemotherapy (CT). Internal mammary chain (IMC), supraclavicular, infraclavicular and axillary LN were treated in 85.6%, 88.3%, 77.9% and 14.9% of cases, respectively. With a median follow-up of 64 months (6–102), 5-year locoregional recurrence-free survival, metastasis-free survival and overall survival were 90% (95% CI [88.1;92.4]), 83.3% (95% CI [80.6;86]) and 90.9% (95% CI [88.9;93]), respectively, for the whole population.

Twenty-three patients (2.9%) presented locoregional recurrences at a median age of 60.5 years (range: 37–87). Synchronous distant metastases occurred in 14 cases. The mean latency period between the end of the radiotherapy and the diagnosis of recurrence was 32 months (range 5.2–89.3 months). The median survival after locoregional failure was 26.4 months in this study, similar to that observed for metastatic breast cancer (although 14 patients had metastatic disease at the time of local failure). As previously reported, considering the molecular profile, locoregional recurrence free survival was comparable between Her2+ and HR+, but was significantly worse for the triple negative tumors (6).

Clinical and pathologic features

The characteristics of the 23 studied patients with locoregional recurrence s +/- metastatic disease are presented in Table 1. Most patients presented aggressive biological features: grade III lesions in 17 patients (74%), high mitotic index in 16 patients (70%) and triple-negative status in 12 patients (52%). Lymphovascular invasion (LVI) was present in 11 cases (48%). One to three lymph nodes (LN) were involved in 10 cases and more than 4 positive lymph nodes were reported in 10 cases. Among the 13 patients who experienced LN recurrence, 10 had triple-negative and/or grade III tumors. One patient was presented with HER2 positive tumor but did not receive Trastuzumab in the adjuvant setting. Chemotherapy was administered in 20 patients (87%), in the neoadjuvant setting in 12 patients (52%) and in the adjuvant setting in 8 cases (35%).

Mapping of local (chest wall) and regional (LN) recurrence

Chest wall recurrences occurred in 13 cases (56%) with the coverage by the isodose of 47.5 Gy (isodose 95%) in 12 cases. In one patient (# 7), the local recurrence was diagnosed under the lung protection, in a region covered by isodoses between 40 and 46 Gy. Only two patients presented recurrences in the mastectomy scar. Chest wall recurrences consisted of a nodular or infiltrative mass in 10 cases and corresponded to skin invasion in 3 cases. Only two patients presented recurrences close to the original tumor site.

Fifteen regional recurrences were observed in 13 patients. Only 3 regional (lymph node) recurrences occurred within irradiated volumes, as follows: 1 in level III (under the lung protection), 1 involving both level III/IV (optimal coverage) and 1 in the IMC (optimal coverage). Twelve LN recurrences occurred outside of irradiated areas. Interestingly, four lymph node recurrences occurred outside the ESTRO CTV definition (3 axillary and 1 supraclavicular LN) and among them two were located within the RTOG CTV.

Table 1
Patients' characteristics: initial treatment and recurrences.

Patient	Initial treatment	Radiotherapy field	Latency (time to loco regional relapse)	Age at relapse	infield	locoregional recurrence		Dose delivered in the recurrence area	secondary treatment	Metastases	metastatic sites	delay between locoregional recurrence and distant metastases	PET CT at locoregional recurrence	Follow up		
						local	regional							months	disease	
						marginal/outfield	infield									
1	neoadjuvant-CT + Surgery + RT + Herceptin	chest wall,supra-subclavicular, IMC and axillary field	8.6	81	cutaneous			>46 Gy	HT	yes	cutaneous lymphangitis carcinomatosa of the left arm	0	no	22.4+	yes	
2	Surgery + RT	chest wall,supra-subclavicular and IMC field	32.9	86	chest wall			>46 Gy	CT	yes	lungs	0	no	41.6	yes	
3	Surgery + RT	chest wall,supra-subclavicular and IMC field	89.3	64			LN number1:level I/II junction LN number2: supraclavicular LN outside ESTRO and RTOG CTV	≈20–40 Gy	CT	yes	bone and pleura	0	yes	95+	yes	
4	Surgery + adjuvant-CT + RT	chest wall,supra-subclavicular and IMC field	85.9	61	chest wall			>46 Gy	Surgery + CT + RT	no	no	-	no	97.7+	no	
5	neoadjuvant-HT + Surgery + concurrent-CT-RT	chest wall,supra-subclavicular and IMC field	41.2	80			level I/II	≈40–46 Gy	CT	yes	Mediastinal LN and bone	0	no	42.5	yes	
6	Surgery + adjuvant-CT + RT	chest wall, supraclavicular and IMC field	19.4	44	chest wall		level I/II junction	≈20–40 Gy	CT	yes	bone and liver	47.7	no	67.2	yes	
7	Surgery + adjuvant-CT + RT	chest wall,supra-subclavicular, axillary and IMC field	31	44		chest wall (pectoral muscle infiltration)		40 Gy	Surgery + CT	yes	pleura	17.1	yes	72.8	yes	
8	Surgery + RT	chest wall field	12.3	75			axillary LN outside ESTRO and RTOG CTV but included in the chest wall CTV	≈25–40 Gy	(Surgery + CT + RT) x 2	yes	pleura	9	no	55.3	yes	
9	Surgery + adjuvant-CT + RT	chest wall,supra-subclavicular and IMC field	77.6	53			level I/II junction	≈10–25 Gy	Surgery + CT	no	no	-	yes	98.7+	no	
10	neoadjuvant-CT + Surgery + RT	chest wall,supra-subclavicular and IMC field	71.3	56			axillary LN partially included ESTRO and RTOG CTV	40 Gy	Surgery + CT	no	no	-	yes	90.2+	no	
11	neoadjuvant-CT + Surgery + RT	chest wall,supra-subclavicular and IMC field	5	59	chest wall subcutaneous nodules		level III/IV	>46 Gy	CT	yes	controlateral supra-subclavicular LN + chest wall infiltration	0	no	8.4	yes	
12	Surgery + adjuvant-CT-Herceptin + concurrent-RT-Herceptin	chest wall,supra-subclavicular and IMC field	35	39	subcutaneous nodules			>46 Gy	CT	yes	bone, mediastinal LN,lungs, liver, adrenal gland and brain	0	no	41.5	yes	

Table 1 (continued)

Patient	Initial treatment	Radiotherapy field	Latency (time to loco regional relapse)	Age at relapse	infield	locoregional recurrence			Dose delivered in the recurrence area	secondary treatment	Metastases	metastatic sites	delay between locoregional recurrence and distant metastases	PET CT at locoregional recurrence	Follow up	
						local	regional	marginal/outfield							months	disease
13	neoadjuvant-CT + Surgery + concurrent-CT-RT	chest wall,supra-subclavicular, axillary and IMC field	15.7	77	subclavicular mass				≈40–46 Gy	CT	yes	mediastinal and retroperitoneal, iliac LN, lungs and liver	0	no	32.3	yes
14	neoadjuvant-CT + Surgery + concurrent-CT-RT	chest wall,supra-subclavicular, axillary and IMC field	5.2	37	pectoral muscle infiltration		level III		>46 Gy	CT	no		-	no	13.4	yes
15	Surgery + adjuvant-CT + RT	chest wall,supra-subclavicular and IMC field	6.2	67		IMC	axillary LN outside ESTRO CTV but inside RTOG CTV (level I)		≈20–40 Gy	CT	yes	bone	0	no	45.3	yes
16	neoadjuvant-CT + Surgery + HT + RT	chest wall,supra-subclavicular and IMC field	46.4	47			level I/II junction		≈20–40 Gy	CT	yes	bone and lungs	0	yes	83.9+	yes
17	neoadjuvant-CT + Surgery + concurrent-CT-RT	chest wall,supra-subclavicular and IMC field	14.1	54	subcutaneous nodules				>46 Gy	Surgery + CT	yes	lungs	0	no	22.4	yes
18	neoadjuvant-CT + Surgery + adjuvant-CT + RT	chest wall,supra-subclavicular and IMC field	19.4	42			level II		≈20–40 Gy	CT	yes	controlateral supraclavicular axillary nodule	0	no	28	yes
19	Surgery + HT + RT	chest wall,supra-subclavicular and IMC field	30.6	75			level I		≈20–40 Gy	Surgery + CT + RT	yes	bone	26.4	no	68.5+	yes
20	neoadjuvant-CT + Surgery + concurrent-CT-RT	chest wall,supra-subclavicular and IMC field	30.6	87	chest wall				>46 Gy	CT	no		-	no	40.1	yes
21	neoadjuvant-CT + Surgery + RT	chest wall,supra-subclavicular and IMC field	21.6	83			level I/II junction		≈20–40 Gy	CT	yes	lungs	0	yes	41.7	yes
22	neoadjuvant-CT + Surgery + RT	chest wall,supra-subclavicular and IMC field	6.3	32	chest wall				>46 Gy	CT	yes	brain, peritoneum	0	no	17	yes
23	Surgery + adjuvant-CT + RT	chest wall,supra-subclavicular, axillary and IMC field	54.1	40	supra-subclavicular mass				>46 Gy	Surgery + CT	yes	controlateral axillary LN, skin	0	yes	79.4+	yes

LN: Lymphadenopathy, RT: radiotherapy, CT: chemotherapy, HT: hormonotherapy, +: alive.

* This patient has twice recurrence which has been treated twice.

Discussion

We recently reported the largest experience of PMERT based on a series of 796 patients [6]. The outcomes comprising five-year loco regional recurrence-free survival and overall survival were excellent for the overall population. However, a less favourable prognosis was observed for patients with loco regional and metastatic recurrence. Loco regional control therefore appears to be a critical determinant of survival. As previously reported, considering the molecular profile, locoregional recurrence free survival was comparable between Her2+ and HR+, but was significantly worse for the triple negative tumors (6). Furthermore, patients with uncontrolled disease often present very poor quality of life.

Only 2 of the 13 chest wall recurrences were detected in the mastectomy scar, which is a much lower rate than the usual 50–60% reported in other series, but which can be explained by the adequate dose delivered to the skin by the use of electrons and bolus. Chang et al. reported that a thin chest wall (<10 mm) was associated with a higher risk of recurrence using the reverse hockey stick technique, in which electron beam radiation appears to be particularly attractive [7]. Feigenberg et al. proposed an electron boost for patients with close or positive margins [8]. Eleven of the 13 cases of chest wall recurrences were associated with triple-negative and/or grade III tumors. The main reason for this pattern of failure was therefore the biologic characteristics of the tumor.

The issue of lymph node recurrence has been studied by various teams [7]. Due to the need for optimization of volume coverage and sparing of OAR, international guidelines have been developed, such as the ESTRO or RTOG contouring guidelines designed to reduce between-physician variability of delineation. However, only limited data are available concerning the patterns of recurrence related to application of these guidelines.

In the present study, only three regional recurrences occurred in irradiated volumes and involved non-irradiated areas. In most cases (n = 12), recurrences were observed in non-irradiated volumes such as level I and II nodes.

Four LN recurrences were observed outside of ESTRO recommended volumes. These guidelines were designed for early stage breast cancer and probably need to be modified for advanced tumors [9]. The RTOG postmastectomy delineation atlas appears to be more reliable in this context by proposing more generous target volumes. In a recently published Korean mapping study, geographic miss outside the ESTRO CTV and inside the RTOG CTV was observed in 14% of cases [7]. Further studies are therefore needed to evaluate the relationship between irradiated volumes and patterns of recurrences in order to improve these international guidelines.

Very rare recurrences were also observed, generally corresponding to the ectopic position of axillary LN (2 cases in our study). In a study using lymphotropic nanoparticle-enhanced MRI for LN detection in patients with breast cancer, Mac Donald et al. demonstrated that lymph nodes outside target volumes were located anteriorly to a line drawn between the pectoralis major and latissimus dorsi muscles [10].

Another region of interest is the supraclavicular fossa, known as level IV. Two mapping studies have provided detailed patterns of failure [7–11]. The conclusion of these two studies was that, for locally advanced tumors, supraclavicular nodes are insufficiently covered by the CTV proposed by ESTRO or RTOG, especially in the poster lateral region of the supraclavicular fossa (patient 3 in our study) [7]. In the Korean study, multiple lymph nodes, young age (<45) and triple-negative status were predictive of recurrences in the supraclavicular fossa. In the age of intensity-modulated radiation therapy (IMRT), the CTV must be very carefully delineated, as

it can result in unintentional sparing of certain areas previously covered by conventional fields.

This study presents several limitations including its retrospective nature and the small population of patients who experienced local or regional recurrence. The strength is that all patients were treated by a highly conformal technique using CT scan for treatment planning in single institution, allowing reconstruction and analysis of recurrences and the reconstruction of volumes and doses were feasible.

Conclusion

This study suggests that chest wall recurrences are rare after PMERT and are related to biologic aggressiveness of the disease than to inadequate irradiation of target volumes. Altogether, recent mapping publications and this study demonstrate the limits of strictly following international guidelines for a given patient and highlight the need to adapt volumes in high-risk cases. Further studies are needed to evaluate the relationship between irradiated volumes and patterns of recurrences in order to refine these international guidelines.

Acknowledgements

Dominique Peurien, Emilie Costa, Nathalie Fournier-Bidoz, François Campana, Anne Chilles, Christelle Hemart, Christelle Logerot, Anne Stilhart, and all our patients.

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