ORIGINAL

Impact and evaluation of the use of tri-dimensional over bi-dimensional plan for the breast and axillary lymph node irradiation with tangential fields for conservative breast cancer treatment

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Abstract

Background: A comparative study of dose distribution delivered to the anatomically defined breast, axillary levels I-III, supra clavicle nodal, cardiac and left lung volumes treated by standard tangent fields using conventional technique, planned by either two dimensional (2D) or tri-dimensional (3D) radiotherapy treatment-plan was performed to determine if the dosimetry for the breast, regional lymph nodes and normal tissues at risk can be improved. **Material and Methods:** Data of the charts and images of 10 consecutive patients who underwent breast-conserving surgery for left-sided breast cancer and received post-operative RT at the Department of Radiation Oncology, Hospital A.C. Camargo, São Paulo, Brazil were reviewed and re-planned. All sets of images used for the study were saved separately and no modification was performed to the initial programmed plan for each patient. For 2D irradiation plans, two opposed fields to treat the breast volume were used and one appositional field was used to treat the supra clavicle nodes. After 2D dosimetric planning, a second 3D treatment plan, with CT tomography at 5-mm intervals in the same position as predetermined in the 2D simulation, was used for plan dose coverage comparison. **Results:** The breast CTV dose coverage evaluated by the D85%, D90% and D100% presented statically significant differences favoring the 3D plan ($p = 0.017$; 0.011 and 0.005), with correlation indexes ranging from 42.6% to 57.2%. The same was observed for the supra clavicle nodes ($p = 0.003$; < 0.001 and 0.045) with correlation indexes ranging from 19.4% to 37.4%. For the axillary levels, a statistical significant difference on dose coverage was observed only for the axillary level III D100%, $p = 0.001$ and correlation index of 72.5%. For the cardiac area there was a statistical significant difference between the maximum and median given, $p = 0.002$ and $p = 0.01$, favoring the 3D plan. **Conclusion:** The use of 3D plan is necessary to include not only the breast but also the axillary nodes, with the advantage of significantly reducing the dose given to the cardiac area.

Keywords: axillary lymph node, breast cancer, imaging, plan, radiotherapy, three dimensional.

INTRODUCTION

Breast cancer is the second most frequent tumor in the world and the most frequent in women. In Brazil for 2010, 49,240 new cases were expected to be diagnosed[1]. Breast conserving therapy (BCT) is an effective treatment option for breast cancer patients[2,3] and the role of routine axillary dissection in the management of localized breast cancer is still controversial[4,5]. The treatment effectiveness is predicated by complete surgical therapy, combined with appropriate locoregional radiotherapy (RT). The irradiation of the regional lymph nodes, when indicated, remains an important but technically challenging part of the management of breast cancer. Unfortunately, for locoregional RT there are still several technical issues that can adversely influence the successful outcome of breast-conservative treatment. For a good cosmetic result and improved disease control, dose coverage and homogeneity must be maintained throughout the target reducing hot-volumes and sparing normal surrounding tissues to reduce complications[6].

Depending on the extent of metastatic axillary disease, additional RT may be directed toward regional lymph nodes. The traditional standard tangential fields for locoregional RT include the lowest part of the axilla, but fail to deliver therapeutic doses to any of the three axillary levels.

Historically, the tissue volume removed during level I-III axillary dissection is not routinely identified in locoregional RT. More importantly, the axillary level I and III areas are not typically incorporated into RT planning and dosimetric calculations, even for targeting or blocking. In cases of massive axillary involvement it is important to

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define accurately the volume at risk, as well as assessing its dosimetric coverage. The long-term survival rates observed in early-stage breast cancer have also driven efforts to decrease treatment-related morbidity, including that associated with the extent of axillary surgery and or RT.

Tridimensional conformal tangential radiotherapy (3D) and intensity- modulated radiotherapy (IMRT) using CT-based planning have been applied to improve the local control rate and reduce toxicity[7]. When the organs at risk are evaluated, special attention must be driven to the cardiac area. Fifteen--year cardiac mortality was higher for patients who received RT for left-sided compared with right-sided breast cancer[8-10].

This study was undertaken to carry out a comparative study of the dose distribution delivered to the anatomically defined axillary levels I-III, supra clavicle nodal, cardiac and left lung volumes treated by standard breast tangent fields using conventional technique (two dimensional 2D) or 3D-RT treatment-plans and to determine whether its use improve the dosimetry for the breast, regional lymph nodes and normal tissues at risk.

METHODS AND MATERIAL

The subjects were 10 consecutive patients who underwent breast-conserving surgery for left-sided breast cancer who were referred for locoregional post-operative RT at the Department of Radiation Oncology, Hospital A.C. Camargo, São Paulo, Brazil. Each patient was immobilized in the left arm-up position during treatment. All sets of images used for the study were saved separately and no modification was performed to the initial programmed plan for each patient. For 2D irradiation plans, two opposed fields to treat the breast volume were used and one appositional field was used to treat the supra clavicle nodes. The treatment field margins were determined by palpation of the breast parenchyma with the addition of a 2 cm margin in all directions. In general, the superior margin was at, or near, the base of the clavicle, the medial margin near the midline, the lateral margin near the mid-axillary line, and the inferior margin 2 cm below the inframammary fold. After this simulation, 2D dosimetric planning was performed and followed by a second 3D treatment planning with CT tomography at 5 mm intervals in the same position as predetermined in the 2D simulation. All patients underwent imaging by CT from above the clavicle superiorly to several centimeters inferior to the breast tissue.

The cardiac area and left lung volume (ORs), the anatomic axillary levels and supra clavicle (SCN) nodes were defined by analyzing the axial radiation planning CT images every 5 mm by the radiation oncologist. All volumes were delineated with Eclipse 3D treatment planning software (Varian, Palo Alto).

For 2D plans, the breast tangent fields were normalized approximately 1.5 cm anterior to the anterior lung surface, in a plane perpendicular to the central axis at mid-separation and for the SCN area the dose prescription was at 3 cm depth.

For the purpose of clinical evaluation and comparison the clinical target volume (CTV) included the whole breast. Independent structures were generated for the levels I to III axillary nodal regions and SCN.

The breast contour was defined medially at the lateral edge of the sternum, inferiorly at the inframammary fold, superiorly at the inferior edge of the medial head of the clavicle, and laterally to include all apparent breast tissue.

The axillary nodal region was divided into levels I to III, and the SCN. The level I region was defined as the area lateral to the lateral border of the pectoralis minor muscle and extending superiorly to the level of the axillary vein. Figure 1 shows a PET-CT of a left sided breast tumor with axillary level I and II positive capitation. The level II region was defined as the area between the medial and lateral borders of the pectoralis minor muscle, extending superiorly to the level of the axillary vein. The level III region was defined as the area medial to the medial margin of the pectoralis minor muscle and adjacent to the chest wall, extending superiorly to the level of the axillary vein. The SCN region was defined as the area within 5 mm of the surgical markers. The inferior border of the axilla was defined as being located at the level between the fourth and fifth thoracic ribs[11]. The planning target volume (PTV) was defined as the CTV with 5 mm margins, except for the skin area. The heart and left lung were contoured as the ORs (Figure 2). The dose-volume histograms were used to measure and compare doses received by each volume. The 85% (D85%), 95% (D95%) and 100% (D100%) prescribed dose coverage of the volumes were compared for the targets. For Ors, the maximum dose (Dmax), median dose (Dmed) and volumes of the lung and cardiac area receiving 20 Gy and 25 Gy, respectively, were evaluated.

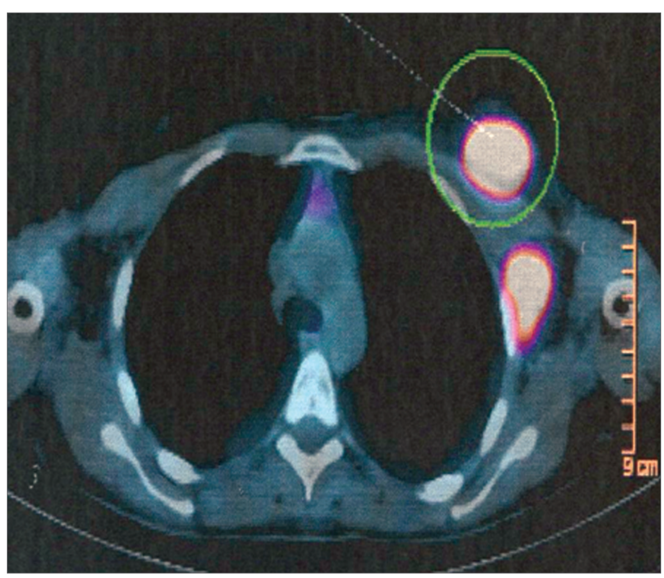

Figure 1. Left sided breast tumor with axillary level I and II pre-operative positive capitation on PET-CT.

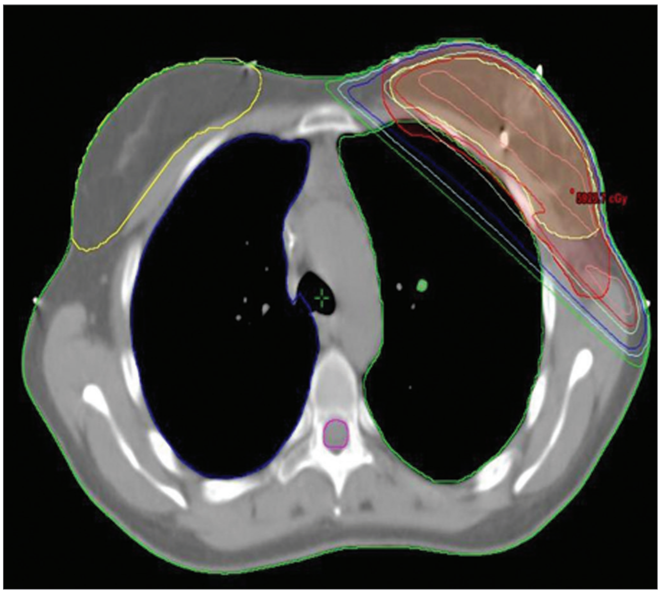

Figure 2. Central axis axial view of a plan showing the right and left breasts contoured (yellow), the left planned tumor volume including the left axillary level I-II plotted based pre-operative images.

RESULTS

The median volumes of the breast, axillary levels I, II, III, and SCN are shown in Table 1.

Table 1. Reconstructed volumes.

	Median (cc)	Range (cc)
Breast (CTV)	474	268-1186
Axillary level I	28	17-38
Axillary level II	32	22-45
Axillary level III	33	20-56
SCN	41	35-86
Left Lung Volume	1039	747-1387
Cardiac Area	487	350-525

The correlation index showed a wide range of variation. The most discrepant value between dose coverage was found for the D85% at axillary level III while for the axillary level I there was very good concordance between the D100% for 2D and 3D planning. The dosimetric parameters correlation of the breast, nodal regions and Ors are shown in Table 2.

No patient had complete coverage of the axillary I-III by the 95% isodose line by 2D plan when compared to 3D plan. The discrepancy ranged from 27.5% to 52.0% coverage for axillary level III and I, respectively. For 3D plan, 100% used forward planning to reduce dose inhomogeneity to the target.

The breast CTV dose coverage evaluated by the D85%, D90% and D100% presented statically significant differences favoring the 3D plan (p = 0.017; 0.011 and 0.005), with correlation indexes ranging from 42.6% to 57.2%. The same was observed for the SCN (p = 0.003; < 0.001 and 0.045) with correlation indexes ranging from 19.4% to 37.4%. In contrast to the breast CTV and SCN nodes for the axillary levels, a statistical significant difference on dose coverage was observed only for the axillary level III D 100%, p = 0.001 and correlation index of 72.5%.

Table 2. Dosimetric parameters correlation - 2D and 3D.

Anatomical Site	Dosimetric parameter	Correlation index
Breast	D 85%	0.543
	D 95%	0.574
	D 100%	0.428
SCN	D 85%	0.626
	D 95%	0.806
	D 100%	0.686
Axillary Level I	D 85%	0.988
	D 95%	0.806
	D 100%	0,520
Axillary Level II	D 85%	0.855
	D 95%	0.838
	D 100%	0.941
Axillary Level III	D 85%	0.869
	D 95%	0.763
	D 100%	0.275
	D 85%	0.899
Left Lung	D 20 Gy	0.422
	D 30 Gy	0.329
Cardiac area	D 25 Gy	0.427
	D Max	0.765
	D med	0.806

For the left lung, no statistical significant difference between the tissue volume receiving 20 Gy or 30 Gy, but for the cardiac area there was a statistical significant difference between the maximum and median dose received, p = 0.002 and p = 0.010, respectively, favoring the 3D plan (Table 3).

DISCUSSION

The prognosis for breast cancer patients has improved considerably in recent years, with five-year survival now around 90% in many countries[12]. Locoregional cancer control is an important aspect of BCT and may improve patient survival in selected patient subgroups The axillary lymph nodes status is crucial for directing therapy and predicting patient outcomes, but removal of the axillary nodes is a primary cause of locoregional morbidity and uncontrolled axillary recurrence is a clinical problem that impacts survival and quality of life[13]. Various alternatives

Table 3. Statistical analysis.

Anatomical Site	Dosimetric parameter (2D versus 3D)	Mean volume difference* (cc)	Significance (CI- 95%)
Breast	D 85%	-5.22	0.017
	D 95%	-10.46	0.011
	D 100%	-12.25	0.005
SCN	D 85%	-15.24	0.003
	D 95%	-17.07	< 0.001
	D 100%	-9.26	0.045
Axillary Level I	D 85%	-12.07	0.085
	D 95%	-23.29	0.003
	D 100%	-21.02	0.025
Axillary Level II	D 85%	-3.35	0.145
	D 95%	-3.31	0.129
	D 100%	-1.95	0.135
Axillary Level III	D 85%	2.24	0.531
	D 95%	5.31	0.369
	D 100%	-1.32	0.101
Lung	V20 Gy	-5.27	0.194
	V30 Gy	-3.45	0.213
Cardiac Area	V25 Gy	-3.15	0.159
	Dmax (Gy)	-14.64	0.002
	Mean Dose (Gy)	-5.3	0.001

to axillary node dissection are currently being investigated, including axillary lymph node sampling, selective dissection, and primary radiation therapy of the nodal region.

Axillary lymph evaluation is supported by results of the National Surgical Adjuvant Breast Project (NSABP) B-04 study. Clinical node-negative patients treated with total mastectomy without axillary dissection or radiation therapy direct to the axila experienced a 19% axillary failure rate. In contrast, clinical lymph node-negative patients undergoing axillary dissection without axillary RT experienced axillary recurrence rates of < 2%. Similarly low rates of axillary recurrence were seen in clinical node-negative patients undergoing primary nodal RT without axillary dissection, suggesting equivalency in terms of regional control for these two modalities in this group of patients[14].

The standard tangential technique is expected to irradiate all breast bed and remaining breast tissue. To some extent, the axillary lymph node region is in part also irradiated[15]. We observed a statically significant difference on the breast CTV coverage between 2D and 3D. This can be explained by the fact that planning 2D tangential field attempts are made more often to avoid the excessive volume of lung irradiation in detriment of the breast. The lateral extent of the SCN field has been implicated in the risk of radiation-associated of arm edema and limited arm mobility. Additional sparing of lateral tissues is possible with careful delineation of the SCN[15]. Better coverage of SCN nodes with 3D plan can be explained by the use of a second posterior field used to cover the SCN. Conversely, in 2D plan, only one anterior field with dose prescription at 3 cm depth is routinely used, which can explain this difference. Smitt and Goffinet evaluated 3D images of the axillary nodes and tissues in 5 of 6 patients who did not have axillary node dissection and in 1 patient who underwent axillary node dissection with the area marked by a clip, observing that only 1 of 6 patients had the lower axilla treated to 90% of the prescribed dose with traditional 2D treatment planning[16].

Our results, as others[11,17], have shown that no patient had adequate coverage of the anatomic axillary level I-III volume by 2D planning, results consistent with other studies that have demonstrated the lack of axillary nodes coverage with standard breast tangent fields. The discrepancy in volume coverage by D 95% ranged from 27.5% to 52.0% for axillary level III and I, respectively. McCormick et al. evaluating the dose received by the axillary level I-II area marked with metallic markers observed that area was encompassed by the 95% isodoseline when using tangent fields in only 38% of patients[18]. Reznik et al.[11] performed a study of 35 patients observing that axillary nodes get only partial radiation dose with 51% of Level I, 26% of Level II, and 15% of Level III receiving at least 95% of the dose prescribed to the breast. Reed et al. using 3D CT-based planning evaluated 50 consecutive patients treated by conventional breast tangential fields observing that all defined breast volumes received more than 95% of the prescribed dose and by contrast, the 95% isodose line encompassed only an average of 55% (range, 23-87%) of the axillary level I-II node anatomic volume, that ranged from 83.1 cc to 313.0 cc[19]. In contrast, Goodman et al. analyzing 3D images of 55 patients after sentinel lymph node biopsy and with axillary node dissection if the sentinel nodes were positive. The majority of their patients had Level I nodes covered by the 90% isodose line[20].

The use of metallic markers to help to define the axillary nodal area has also been investigated. Aristei et al.[21] observed on 3D plans that clip position does not exactly define the axillary-level borders, concluding that the anatomic delineation of axillary nodes on CT scans is much more precise than definition, based on clip position when compared tot the films of the two tangential fields, and that CT scans are essential for locating axillary nodes. They also noted that with the breast receiving 50 Gy, the median dose administered to the first and second level were about 30% and 60% of the prescribed dose, similarly to our own results. Takeda et al. checking the status of the surgical clips left at axillary lymph node sites by simulator films and planning CT scans of 63 patients noted that it is possible to irradiate almost all axillary lymph node regions by setting the dorsal edge of the irradiation field on lateral-view simulator films at the dorsal edge of the humeral head and the cranial edge at the caudal edge of the humeral head[22]. In our opinion, when using 3D plans, the placement of surgical clips would be not necessary, unless a marginal resection was performed and a boost dose is to be programmed to a specific area.

The standard tangential field techniques often result in the irradiation of the tip of the left ventricle and the left anterior descending coronary artery, potentially increasing cardiovascular morbidity. Minimizing radiation dose to these structures is crucial, especially for older patients or history of previous cardiac disease. Fifteen-year cardiac mortality was higher for patients who received RT for left-sided compared with right-sided breast cancer[8-10]. A recent large population-based study of 72,134 women diagnosed with breast cancer in Denmark and Sweden during 1976-2006 showed that from the total, 34,825 women (48%) received RT. Women with left-sided breast cancer were observed to receive substantial cardiac doses. The mean dose to the whole heart was 6.3 Gy for left-sided tumors and 2.7 Gy for right-sided tumors. Mortality was similar in irradiated women with left-sided and right-sided tumors, but incidence ratios of myocardial infarction, angina, pericarditis and valvular heart disease were raised[23]. The use of 3D plan in our study was able to reduce the Dmax and mean dose to the heart in 23.5% and 19.4%, respectively.

CONCLUSION

Standard tangential breast radiation fields used for 2D plan fail to treat the axillary node anatomic volume adequately, with approximately 50% of target receiving a therapeutic dose. Our results suggest that when the axillary levels have to be irradiated, an appropriate reconstruction of axillary nodal area with 3D treatment planning system is necessary. The use of 3D plan has also the advantage of reducing significantly the dose given to the cardiac area.

REFERENCES

1. Ministério da Saude. Instituto Nacional do Cancer. Estimtiva/2010 incidencia e mortalidade por cancer no Brasil. Rio de Janeiro: INCA, 2009.
2. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-41.
3. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast--conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;37:1227-32.
4. Haffty BG, Ward B, Pathare P, Salem R, McKhann C, Beinfield M, et al. Reappraisal of the role of axillary lymph node dissection in the conservative treatment of breast cancer. J Clin Oncol 1997;15:691-700.
5. Dent DM. Axillary lymphadenectomy for breast cancer: Paradigm shifts and pragmatic surgeons. Arch Surg 1996;131:1125-7.
6. Recht A, Houlihan MJ. Axillary lymph nodes and breast cancer: a review. Cancer 1995;76:1491-512.
7. Krueger EA, Fraass BA, McShan DL, Marsh R, Pierce LJ. Potential gains for irradiation of chest wall and regional nodes with intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 2003;56:1023-37.
8. Paszat LF, Mackillop WJ, Groome PA, Schulze K, Holowaty E. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: A population-based study in Ontario, Canada. Int J Radiat Oncol Biol Phys 1999;43:755-62.
9. Gyenes G, Rutqvist LE, Liedberg A, Fornander T. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. Radiother Oncol 1998;48:185-90.
10. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994;12:447-53.
11. Reznik J, Cicchetti MG, Degaspe B, Fitzgerald TJ. Analysis of axillary coverage during tangential radiation therapy to the breast. Int J Radiat Oncol Biol Phys 2005;61:163-8.
12. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
13. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival-A bayesian meta-analysis. Ann Surg Oncol 1999;6:109-16.
14. Fisher B, Bauer M, Wickerham DL, Redmond CK, Fisher ER, Cruz AB, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer: an NSABP update. Cancer 1983;52:1551-7.
15. Pierce LJ, Strawderman MH, Douglas KR, Lichter AS. Conservative surgery and radiotherapy for early-stage breast cancer using a lung density correction: the University of Michigan experience. Int J Radiat Oncol Biol Phys 1997;39:921-8.
16. Smitt MC, Goffinet DR. Utility of three-dimensional planning for axillary node coverage with breast-conserving radiation therapy: Early experience. Radiology 1999;210:221-6.
17. Krasin M, McCall A, King S, Olson M, Emami B. Evaluation of a standard breast tangent technique: a dose-volume analysis of tangential irradiation using three- dimensional tools. Int J Radiat Oncol Biol Phys 2000;47:327-33.
18. McCormick B, Botnick M, Hunt M, Petrek J. Are the axillary lymph nodes treated by standard tangent breast fields? J SurgOncol 2002;81:12-6.
19. Reed DR, Lindsley SK, Mann GN, Austin-Seymour M, Korssjoen T, Anderson BO, et al. Axillary lymph node dose with tangential breast irradiation. Int J Radiat Oncol Biol Phys 2005;61:358-64.
20. Goodman RL, Grann A, Saracco P, Needham MF. The relationship between radiation fields and regional lymph nodes in carcinoma of the breast. Int J Radiat Oncol Biol Phys 2001;50:99-105.
21. Aristei C, Chionne F, Marsella AR, Alessandro M, Rulli A, Lemmi A, et al. Evaluation of level I and II axillary nodes included in the standard breast tangential fields and calculation of the administered dose: results of a prospective study. Int J Radiat Oncol Biol Phys 2001;51:69-73.
22. Takeda A, Shigematsu N, Kondo M, Amemiya A, Kawaguchi O, Sato M, et al. The modified tangential irradiation technique for breast cancer: how to cover the entire axillary region. Int J Radiat Oncol Biol Phys 2000;46:815-22.
23. McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 2011;100:167-75.