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Scientific Article

Axillary lymph node coverage with 3-dimensional tangential field irradiation and correlation with heart and lung dose

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Abstract

Purpose: The American College of Surgeons Oncology Group Z0011 trial indicated no benefit from axillary lymph node (LN) dissection after a positive sentinel LN biopsy in patients receiving breast irradiation, suggesting that level I-II LNs were covered in tangential fields.

Methods and materials: We evaluated 50 computed tomography–based tangential breast plans and contoured level I-III axillary LNs using the Radiation Therapy Oncology Group guidelines. The volumes of level I-III LN regions covered by 90% and 95% of the prescription dose (PD) were calculated and correlated with the V20 ipsilateral lung and mean heart dose. We calculated field length, distance from the humeral head, and separation. The Pearson correlation method and linear models were used in the correlative study.

Results: Level I LN mean and median volume (MMV) covered by 90% of the PD were 46.8% and 47.2%, respectively. MMV covered by 95% of the PD was 30.8% and 29.62%. Mean and median dose to level I LNs were 29.03 Gy and 30.13 Gy, respectively. The MMV of level II LNs covered by 90% of the PD was 2.49% and 0%. The mean and median dose to level II LNs were 6.09 Gy and 2.12 Gy, respectively. The MMV of level III LNs was 0% with a mean and median dose of 1.04 Gy and 0.92 Gy, respectively. There was a moderate correlation between the 95% prescription coverage of level I LNs and V20 ipsilateral lung and a smaller correlation between 95% prescription coverage of level I LNs and mean heart dose. Distance from the humeral head was inversely correlated with coverage of level I and II LNs and positively correlated with V20 lung.

Conflicts of interest: The authors declare no conflict of interest.

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Conclusion: In most patients, <50% of the level I LN volume was covered by 90% of the PD and <30% was covered by 95%; <5% of the level II nodes were covered by 90% of the PD; and coverage was 0% for level III LNs.

Introduction

The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial changed surgical management of the axilla in patients with early breast cancer.[1] Multiple previous trials demonstrated that the omission of axillary LN dissection had no adverse effect in women with negative lymph nodes (LNs).[2,3] The ACOSOG Z0011 trial randomized patients with T1 or T2 breast cancer who were treated with breast-conserving surgery and sentinel LN (SLN) dissection (SLND) with a positive SLN to either axillary LN dissection (ALND) or no axillary-specific treatment. The protocol specified that third-field radiation would not be used. All patients received opposing-field whole breast radiation. At a median follow-up of 6.3 years, there was no statistically significant difference in local or regional recurrence between the 2 groups. Ten-year follow-up demonstrated that locoregional control and survival with SLND alone was comparable to that with ALND.[4]

A postprotocol analysis of radiation field design of enrolled patients showed that high tangents (ie, cranial tangent borders ≤2 cm from the humeral head) were used in 50% of patients assigned to the ALND arm and 52.6% of patients assigned to the SLND only arm. Third-field radiation was used in 18.9% of patients, 22 in the ALND arm and 21 in the SLND arm. There were no significant differences in these deviations between the 2 groups.[4,5] A review of the protocol deviations showed that 11% of patients did not receive radiation, which was required by the protocol, and 18.9% of patients received third-field radiation, including areas outside of those specified by the protocol; patients were equally distributed in both arms. Omission of radiation was associated with increased local recurrence risk and reduced overall survival. The addition of third-field radiation did not improve survival.

Twenty-seven percent of patients who were randomized to the ALND arm of the Z0011 trial had additional nodal metastases identified on histopathology, implying that patients who were randomized to receive no ALND had residual axillary metastatic disease that was not removed by surgery. The study results showed no difference in locoregional recurrence or survival, which suggests that not all microscopic axillary metastases develop into clinically detectable disease.

The After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial, which completed accrual 6 years after the Z0011 trial, explored an alternative approach to axillary LN dissection for patients with positive SLNs.[6] Patients with T1-2 primary breast cancer with a positive SLN were randomized to ALND or axillary radiation therapy. Axillary radiation therapy included the contents of all 3 levels of the axilla and the medial part of the supraclavicular fossa. Thirty-three percent of patients who received ALND were found to have additional positive LNs. Axillary radiation was found to be noninferior to axillary dissection with regard to local recurrence and resulted in less morbidity.

Data from both studies demonstrated a significant risk of residual axillary disease in patients with a positive SLN. In the AMAROS trial, this was addressed with comprehensive axillary LN irradiation. In the Z0011 trial, approximately 18% of patients received third-field irradiation and approximately 50% received high tangents; distribution was equal in both arms. More than 95% of patients in the Z0011 trial received systemic hormonal therapy or chemotherapy, which could have contributed to local control. In addition, the authors suggested that standard opposed tangential fields irradiated the SLN operative field, much of the level I axilla, and a portion of the level II axilla, and that whole breast radiation treated a significant portion of the axilla in these patients. This concept was based on a reference using 2-dimensional planning with surgically placed clips as surrogates for nodal regions.[7]

Contemporary radiation therapy uses 3-dimensional computed tomography (CT)-based planning, which allows for assessment of the volumes receiving the radiation dose. We hypothesized that an evaluation of the radiation dose delivered to the nodal regions based on volumetric CT planning would demonstrate subtherapeutic doses to the level I and level II axillary LNs from standard tangential breast radiation. The purpose of our study was to evaluate contemporary CT-based intact breast radiation plans for coverage of regional LNs based on Radiation Therapy Oncology Group (RTOG) contouring guidelines.[8] We sought to identify the volume of each axillary LN level receiving 95% and 90% of the prescribed dose, the mean and median dose to each level, and the correlation of nodal coverage to V20 lung and mean heart dose (MHD). We also sought to identify the tradeoffs between increasing coverage of the nodal regions in tangential fields by extending coverage superiorly (ie, high tangents) or increasing the chest wall coverage with increased dose to heart and lung.

Methods and materials

We obtained treatment planning data from 50 consecutive patients with breast cancer who received treatment to the intact breast during the previous 12 months. Because our purpose was to evaluate potential nodal coverage in a whole breast plan, we did not select for stage and included patients with invasive cancer and ductal carcinoma in situ (DCIS) who had whole breast treatment without regional node coverage. All patients had undergone a prior lumpectomy, and the majority had SLN biopsy or ALND. Patients were simulated with both arms extended overhead on a dedicated CT scanner using a breast board and Vac-Lok (CIVCO Radiotherapy, Coralville, IA) setup combination. CT scans were obtained from mid-neck to below the breast at 3-mm intervals. External wire markers were placed by the attending physician to outline the superior, inferior, medial, and lateral borders. An external wire was placed along the patient's lumpectomy scar and axillary scar when present. CT data were transferred to an Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning system.

Treatment plans were created using opposed tangential fields with field-in-field multileaf collimator modification, which allowed for modulation of the dose with reduced hotspots. Planning constraints addressed the target volume (D Max <115% Rx; D95 >95% Rx), ipsilateral lung (mean dose <15 Gy and V20 <25%), and heart (mean dose <4 Gy). The target volume was the breast tissue, including the lumpectomy site. No effort was made during treatment planning to include or exclude nodal volumes. For this study, the level I-III LNs were retrospectively contoured by a radiation oncologist and radiologist on the simulation CT image using RTOG breast contouring guidelines.[8] Volumes of level I-III LN regions covered by 90% and 95% of the prescription dose (PD) were calculated from the treatment plan. LN coverage by the PD was correlated with the MHD and V20 lung from the dose volume histogram of the completed treatment plan. We calculated field length, distance of superior field from the humeral head, and field separation and correlated these parameters with LN coverage, MHD, and V20 lung.

A descriptive statistical analysis was performed to summarize the data, including summary tables, proportions, mean, median, and range. The Pearson correlation method and linear models were used to assess the association between continuous variables.

Results

Twenty patients received treatment to the left breast and 30 patients to the right breast. Fourteen patients had DCIS stage 0, 25 had stage I, and 11 had stage II (Table 1). Thirty-two patients had undergone an SLN biopsy, 4 had undergone ALND, and 14 patients with DCIS did not have axillary surgery.

The PD to the breast ranged from 42.56 Gy in 16 fractions for patients treated with hypofractionation to 46.8 to 50.4 Gy in 26 to 28 fractions in patients treated with standard fractionation. A boost of 10 to 14 Gy was prescribed at the discretion of the radiation oncologist. Only the whole breast dose, excluding boost, was evaluated in this study.

Table 1 Summary of patient staging information

Stage	TNM	Number
0	Tis	14
I	T1N0M0	25
IIa	T1N1M0	3
IIa	T2N0M0	5
IIb	T2N1M0	3

The level I LN mean and median volume (MMV) covered by 90% of the PD was 46.8% and 47.2%, respectively (range, 8.77%-88.95%); the MMV covered by 95% of the PD was 30.8% and 29.62% (range, 0%-82.9%). The mean and median dose to the level I LNs was 29.03 and 30.13 Gy, respectively (range, 5.47-46.74 Gy). The MMV of level II LNs covered by 90% of the PD was 2.49% and 0% (range, 0%-32.98%). The mean and median dose to the level II LNs was 6.09 and 2.12 Gy, respectively. Coverage of level III LNs was 0% for MMV (Table 2).

Mean and median V20 ipsilateral lung was 6.73% and 6.7%, respectively (range, 0.018%-22.9%). There was a moderate correlation between 95% prescription coverage of level I LNs and V20 ipsilateral lung (Pearson correlation = 0.51, $P = .0001$).

For patients who received treatment to the left breast (20 of 50 patients), the mean and median MHD were 1.39 and 1.24 Gy, respectively (range, 0.48-5.10 Gy). There was a small correlation between 95% prescription coverage of level I LNs and MHD (Pearson correlation = 0.49, $P = .029$).

Field length without reference to distance from the humeral head was not correlated with nodal coverage, MHD, or V20 lung. Decreasing the distance from the humeral head was correlated with increased level I and II nodal mean dose ($P = .001$, $P < .001$, respectively) and with increased V20 lung ($P = .037$). Maximum field separation was associated with increasing V20 lung ($P = .037$) but not with nodal coverage or MHD.

Table 2 Dose coverage of levels I-III lymph nodes

Axillary lymph node levels	Prescription dose coverage	Mean	Median
Level I	Vol (%) covered by 90%	46.79	47.22
	Vol (%) covered by 95%	30.80	29.62
	Mean dose (Gy)	29.03	30.13
Level II	Vol (%) covered by 90%	2.49	0.00
	Vol (%) covered by 95%	0.65	0.00
	Mean dose (Gy)	6.09	2.12
Level III	Vol (%) covered by 90%	0.00	0.00
	Vol (%) covered by 95%	0.00	0.00
	Mean dose (Gy)	1.04	0.92

Vol, volume.

Discussion

Current breast cancer treatment is multimodal and includes surgery, systemic therapy, and radiation. Ideally, the minimum effective treatment is selected for each patient. Over the past several decades, primary surgery has transitioned from radical mastectomy to modified radical mastectomy or breast-conserving surgery. Management of the axilla has evolved from ALND to SLN biopsy. The identification of prognostic molecular markers and gene assays has refined selection of systemic therapy.

The context of the ACOSOG Z0011 randomized trial included the established prognostic value of SLND,[3] the known morbidity associated with ALND,[9] and the questionable therapeutic benefit of ALND.[10] On the basis of the initial published results of this study, which showed no difference in locoregional recurrence or survival, SLND has become the predominant surgical approach to the axilla in patients with early stage breast cancer. Ten-year follow-up demonstrated locoregional control and survival with SLND alone to be comparable to that with ALND.[4]

The contribution of radiation to local control and survival after breast-conserving surgery has been demonstrated in multiple randomized clinical trials.[11] The Z0011 trial raises the question of the respective roles of axillary surgery and radiation in controlling axillary metastases and subsequent effects on survival. An initial report on the trial stated that standard opposed tangential fields irradiated “the SLND operative field, much of the level I axilla, and a portion of the level II axilla” when the cranial border was 2 cm below the humoral head and 2 cm deep to the chest wall–lung interface.[1] This statement was based on a retrospective analysis of patients who were treated from 1997 to 2000.[7] During that era, breast radiation was based on clinical landmarks and 2-dimensional fluoroscopic imaging without volumetric anatomic information. Current radiation oncology practice uses CT-based 3-dimensional planning with definition of treatment target volumes and dose volume histogram analyses of organs at risk, including the heart and lung, in breast treatment plans. To provide a standardized approach to 3-dimensional breast cancer planning, the RTOG published consensus guidelines to contour the target volumes for the breast, chest wall, and draining lymphatics, which are currently available online in the RTOG Breast Cancer Atlas.[8]

An earlier study of nodal coverage in CT-based plans with standard tangential fields, using anatomic landmarks and surgical clips to define the regional nodes, found that surgically placed axillary clips failed to define the level I-II axilla and that the 95% prescription isodose line encompassed an average of 55% of the level I-II LN volume.[12] A retrospective study of patients with an undissected axilla who were treated with standard tangential fields with 1.5 to 3.0 cm of lung measured from the chest wall demonstrated an average dose of 66%, 44%, and 31% to the level I, II, and III nodal volumes, respectively.[13] Axillary coverage may have been higher in these earlier studies, reflecting a less conformal approach to treatment planning. This study, which included 1.5 to 3.0 cm of lung to cover potential nodal regions, did not take lung or cardiac doses into consideration. A CT-based retrospective evaluation of nodal coverage in tangential fields found that adequate coverage, defined as 95% of the volume receiving 95% of the dose, was achieved in none of the patients with standard tangential fields.[14] A prospective study of SLN coverage, using clips to identify the SLN biopsy site, showed a mean dose to the SLN of 29 Gy for a standard tangent field and 28 Gy with a high tangential field.[15] A volumetric study of 10 patients with breast cancer with 3 types of plans created for each case found the median V95 of level I LNs to be 26.4% for 3-dimensional plans, 8.6% for static intensity modulated radiation therapy plans, and 2.6% for volumetric modulated arc therapy plans.[14] Although this is a small study, the implication is that the more conformal the treatment plan is to the breast, the less the volume of nodal coverage.

A review of these studies demonstrates that an evaluation of CT-based plans with contoured LN demonstrates inadequate (<95% of PD) coverage of level I and II LNs in standard tangent fields. LN coverage is less in more modern studies, which is consistent with more attention to lung and cardiac dose and more conformal treatment plans.

The American Congress of Obstetricians and Gynecologists Z0011 trial accrued patients between 1999 and 2004. An analysis of the radiation field design in the trial noted that high-tangent fields were used in 50% of the patients assigned to the ALND arm and 53.6% of patients assigned to the SLND arm.[5] The use of high-tangent fields refers to increasing axillary coverage in tangential fields by increasing the superior field border to within 2 cm or less of the inferior border of the humeral head. Schlembach et al reported that the level I and II dissection field could be covered in 80% of patients by extending the superior field border to 2 cm below the humeral head and the posterior border to 2 cm deep to the chest wall interface.[7] This was based on the use of surgical clips as surrogates for the dissected area in a 2-dimensional fluoroscopic planning image without volumetric information.

Subsequent CT-based studies of nodal coverage show less complete nodal coverage. Reznik et al, who used retrospective contouring of CT-based plans, showed that the average dose to level I and II nodes with standard tangents was 66% and 44 %, respectively, of the prescribed dose.[13] With high tangents, coverage was increased to 86% and 94% of the prescribed dose. Our data confirm that decreasing the distance between the cranial field border and humeral head results in increased nodal coverage and an increase in the V20 lung. Increasing field separation is also associated with increasing V20 lung.

Sixty percent of patients in the Z0011 trial had documentation of 3-dimensional planning; a significant percentage may have had 2-dimensional planning. CT-based planning became widespread after 2000, and use of

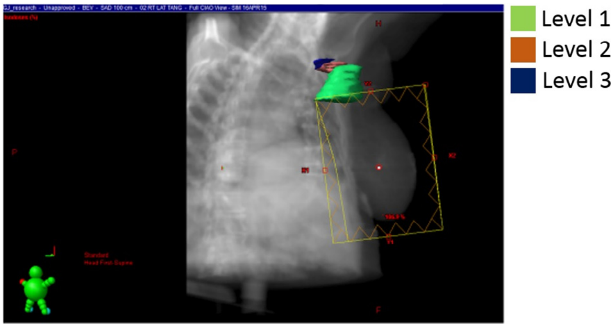

Figure 1 Poor nodal coverage lateral.

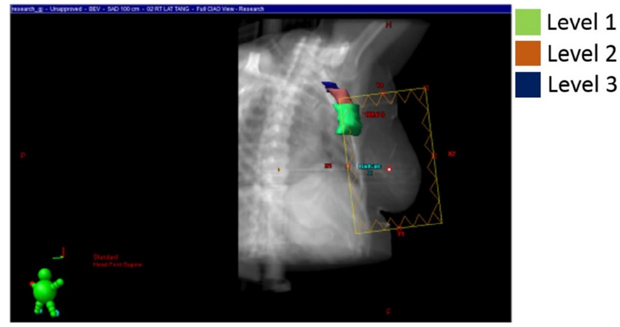

Figure 2 Average nodal coverage lateral.

field-in-field, static, and volumetric intensity modulated radiation therapy plans developed during the following decade. Reed et al demonstrated that, in CT-based plans treated before 2002, standard breast tangential fields failed to deliver a therapeutic dose to the level I-II axillary LNs.[12] De Santis et al suggested that increasing planning conformality of tangential breast plans would decrease nodal coverage. This concept is supported by our data.[14] The Z0011 trial raises the question of optimal treatment of LNs in SLN-positive breast cancer. The explanation of nodal coverage by tangential radiation fields is not sufficient because multiple studies demonstrate incomplete nodal coverage, and the modern trend of more conformal therapy reduces LN coverage in tangential fields.

Our goal in this study was to address the widely held idea that standard tangential fields encompass a significant portion of the axillary LN region. To evaluate the coverage of level I-III LN regions in breast-conserving, tangential treatment fields, we reviewed 50 plans of patients who were treated in the previous 12 months after contouring level I-III nodal regions in accordance with the RTOG Breast Cancer Atlas. Our plan review attests to the changes in surgical management of the axilla. Of 50 patients, only 4 (8%) had an ALND. The majority (64%) had SLN biopsy, and a significant number with DCIS had no axillary surgery (Table 2). Our treatment planning goals were to encompass the clinical breast tissue, including the lumpectomy site, and to minimize radiation to the heart and ipsilateral lung. We found significant variability in the coverage of nodal volumes in our breast tangential fields. Although the MMV of level I LNs covered by 90% of the PD was 46.8% and 47.2%, the range was broad (8.77%-99.95%). Examples of minimal and significant coverage of level I LNs are shown in Figures 1 and 2.

We questioned whether there was a tradeoff between increasing nodal coverage and increasing the dose to the heart and lungs. We found a moderate correlation between 95% prescription coverage of level I LNs and V20 lung, which suggests that greater coverage of this nodal region would increase the volume of lung treated. There was a smaller correlation between coverage of nodal volume and MHD. Increasing the cranial border closer to the humeral head (ie, high tangents) improved nodal coverage but also increased V20 lung. In our patients, increasing the field separation did not ensure greater nodal coverage but was associated with increased V20 lung.

Conclusion

In this review of contemporary CT-based 3-dimensional conformal tangential breast plans, less than 50% of level I LNs were covered by 90% of the PD and less than 30% were covered by 95% of the PD in the majority of patients. Mean (29 Gy) and median (30 Gy) doses to level I LNs were subtherapeutic. Doses to level II LNs were negligible, and doses to level III LNs were 0. There was a modest correlation between MHD and level I LN coverage and a moderate correlation between V20 ipsilateral lung and coverage of level I LNs, which suggests that increasing the prescription coverage for these LNs could increase V20 ipsilateral lung. In this group of patients, a standard tangential radiation field did not provide significant therapeutic coverage of level I LNs and provided negligible coverage of level II and III LNs.

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