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Standardization of whole breast radiotherapy is required for safe omission of axillary lymph node dissection in breast cancer patients

M. Kong* and D.O. Shin

Department of Radiation Oncology, Kyung Hee University Medical Center, Kyung Hee University School of Medicine, Seoul, Republic of Korea

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Corresponding authors:
Dr. Moonkyoo Kong,
***Fax:** + 82 2 958 9469*
E-mail:
kongmoonkyoo@khu.ac.kr

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ABSTRACT

Background: The purpose of this study was to assess the dose distribution and coverage of level I-II axillary lymph nodes during whole breast tangential field radiotherapy (RT) after breast-conserving surgery in patients with breast cancer. ***Materials and Methods***: The level I-II axillary lymph node volumes were retrospectively contoured by a single radiation oncologist based on computed tomography simulation data from 44 patients who underwent breast-conserving surgery without axillary dissection and who received postoperative whole breast RT between January and December 2014. The dose distributions of the whole breast tangential RT fields were reassessed in relation to the axillary level I and II lymph node volumes. ***Results:*** **:** The average doses delivered to level I and I axillary lymph nodes were 49.4% (range, 14.2–94.6) and 30.8% (range, 2.6–71.5) of the prescribed radiation dose, respectively. The volumes receiving at least 95% of the prescribed radiation dose were 12.7% (range, 0–67.4%) for level I and 1.4% (range, 0–7.7%) for level II nodes. Compared to thin patients, the average doses delivered to axillary lymph node levels I and II were significantly higher in overweight patients. ***Conclusion:*** The radiation dose coverage of axillary lymph nodes by whole breast tangential RT varies greatly among patients. To safely omit axillary lymph node dissection from the treatment of clinically axillary lymph node negative T1-2 breast cancer patients with 1–2 positive sentinel lymph nodes, standardization and individualization of whole breast RT are necessary.

Keywords: *Breast, carcinoma, lymph nodes, radiotherapy.*

INTRODUCTION

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was a prospective trial investigating the survival of patients with clinical T1-2N0 stage breast cancer with 1–2 positive sentinel lymph nodes who underwent breast conserving surgery, whole breast radiotherapy (RT), and systemic therapy. This trial showed equivalent survival rates between patients who were randomly assigned to sentinel lymph node biopsy alone or biopsy followed by axillary lymph node dissection. Importantly, the regional recurrence rate among patients who underwent no axillary lymph node dissections was less than 1% [1,2]. Systemic chemotherapy and hormonal therapy may have played significant roles in achieving such a low regional recurrence rate [3,4]. Many investigators believe that incidental irradiation of the axilla with tangential whole breast radiation fields eradicate the axillary lymph node metastases and may provide excellent regional control [2,5-7]. However, the radiation dose distribution and coverage of the axilla with tangential whole breast RT fields in patients who enrolled in the

Z0011 trial have not yet been analysed in detail. Because dose distribution and RT field coverage are dependent on patient anatomy and the preferred treatment technique of the attending radiation oncologist, the results of the Z0011 trial should be interpreted with caution. Therefore, when considering whether to omit axillary lymph node dissection in patients with clinical T1-2N0 stage breast cancer with 1 or 2 positive sentinel lymph nodes, physicians at each hospital should first evaluate the exact dose distribution and the coverage of the axilla with tangential whole breast RT fields.

A number of studies have reported the range of axillary lymph nodes covered by tangential whole breast RT fields [7-11], most of which were conducted in America and Europe. Until now, only one study analysed the range of axillary lymph nodes covered by tangential whole breast RT fields in Korea [12]. The purpose of this study was to assess the dose distribution and the coverage of level I and II axillary lymph nodes with whole breast tangential field RT after breast-conserving surgery in patients with breast cancer, and to compare our results to those of other studies.

MATERIALS AND METHODS

Since January 2014, patients at our institution with T1-2N0 stage breast cancer and 1–2 positive sentinel lymph nodes have been receiving breast-conserving surgery without axillary dissection, as well as post-operative whole breast RT without axillary RT, pursuant to the findings of the Z0011 trial. The inclusion criteria for this study included a diagnosis of clinical T1-2N0 breast cancer with 1–2 positive sentinel lymph nodes, receipt of breast-conserving surgery, receipt of post-operative whole breast tangential RT, a good general condition with an Eastern Cooperative Oncology Group performance status of 1 or less, and available hospital records and RT planning data. Patients who received axillary dissection or axillary and/or supraclavicular nodal RT were excluded from this study. Patients with synchronous bilateral breast cancer, male breast cancer, and inflammatory breast cancer were also excluded. From January to December 2014, 102 patients with breast cancer underwent three-dimensional planning for RT at our institution. Of these patients, 44 met the eligibility criteria and were included in this study. The Institutional Review Board of our institution approved the retrospective review and analysis of patient data for this study (KMC IRB 1432-03), and all research was carried out in compliance with the Declaration of Helsinki.

All patients were placed in the supine position with both arms extended above their heads using Alpha Cradle immobilization. To reduce the movement of the chest wall during respiration, patients were instructed to take shallow breaths. All patients received intravenous contrast agents, and axial computed tomography (CT) images were acquired with a 5 -mm slice thickness. The CT images were transferred to the Eclipse planning workstation (Varian Medical Inc., Palo Alto, USA). After contouring of the whole breast parenchyma, all patients underwent forward field-in-field planning with medial and lateral tangential fields designed to encompass the entire breast. Because we conducted only whole breast RT without axillary nodal irradiation, we did not contour axillary lymph nodes. We evaluated each treatment plan by using a dose-volume histogram and by visually inspecting isodose curves. In general, we considered plans acceptable if the planning target volume (PTV) was covered by the 95% isodose curve and the inhomogeneity of the PTV ranged from 95% to 107%.

For this study, the level I-II axillary lymph node volumes were retrospectively contoured by the same radiation oncologist using the Danish Breast Cancer Cooperative Group guidelines [13]. We consulted a radiologist and a breast surgeon for proper identification of the axillary nodal volumes on the CT images. The dose distribution of the whole breast tangential RT fields was reassessed in relation to the axillary level I-II lymph node volumes. Dose-volume histograms were analysed to assess the volume encompassed by the 95% prescribed dose level ($V_{D95\%}$) and the mean dose

delivered to the axillary I-II lymph node volumes. The distances between the superior borders of the tangential fields and the humeral head were also assessed. The standard tangential field was defined with the superior borders set at 2 cm below the humeral head, while the high tangential field was defined with the superior borders placed within 2 cm of the inferior edge of the humeral head.

$V_{D95\%}$ and the mean dose delivered to the axillary I-II lymph node volumes between the groups were compared with independent t-tests or one-way analysis of variance between groups with Tukey's post-hoc tests. All tests were two-sided and $p<0.05$ was considered statistically significant. All analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, USA).

RESULTS

The characteristics of all patients are summarized in table 1. The whole breast RT doses were 46 Gy in 38 patients (86.4%) and 50 Gy in 6 patients (13.6%). The whole breast PTVs were covered by 95% isodose lines in all patients. Nine patients (20.4%) did not receive tumour bed boost RT. Of the remaining 35 patients (79.6%), 12 (27.3%) received tumour bed boost RT doses of 10 Gy, 20 patients (45.5%) received 16 Gy, and 3 patients (6.8%) received 20 Gy. The daily RT dose was 2 Gy in all patients.

In all patients, the average volumes of the level I and II axillary lymph nodes were 59.5 cc (range, 23.9–97.6 cc) and 33.5 cc (range, 12.5–68.7 cc), respectively. The radiation doses administered to level I and II axillary lymph node volumes are summarized in table 2. No patient had complete coverage of the axillary lymph node level I and II volumes by the 95% isodose line. The volume receiving at least 95% of the prescribed radiation dose for level I was less than 10% in 23 patients (52.3%), and for level II, it was less than 1% in 32 patients (72.7%). An example of axillary radiation dose coverage is depicted in figure 1.

Table 1. Patient characteristics (n=44)

Characteristic	Value
Age (years) Median (range)	 (77.2–38.1) 54.2
T stage 1 2	 (%59.1) 26 (%40.9) 18
Number of positive sentinel lymph nodes 1/2	 (%38.6) 17/(%61.4) 27
Tumour site Right/Left	 (%50) 22/(%50) 22
Histology Invasive ductal carcinoma Invasive lobular carcinoma Invasive papillary carcinoma Invasive tubular carcinoma	 (%93.2) 41 (%2.2) 1 (%2.2) 1 (%2.2) 1
Tumour size (cm) Median (range)	 (4.0–0.3) 1.5
Body mass index (kg/m^2) Median (range)	 (33.4–17.7) 24.8

Table 2. Dose distribution in axillary lymph node levels I and II (n=44).

	Level I	Level II
D_{ave} (%)* (range)	(94.6–14.2) 49.4	(71.5–2.6) 30.8
$V_{D95\%}$ (%)† (range)	(67.4–0) 12.7	(7.7–0) 1.4

*Average percentage of the prescribed radiation dose delivered to the axillary lymph node; †The volume encompassed by 95% of the prescribed radiation dose.

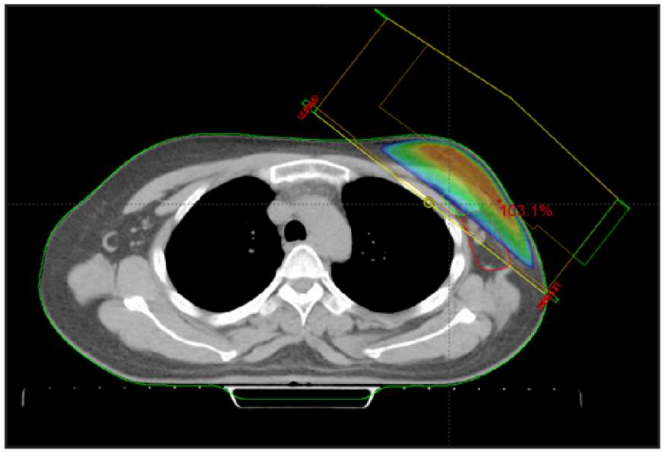

Figure 1. Example of radiation dose coverage of axillary lymph node levels. The coloured portion indicates the area receiving at least 95% of the prescribed radiation dose; the red and green lines indicate CT-defined axillary lymph node levels I and II, respectively.

The average distance between the superior border of the tangential fields and the humeral head was 2.0 cm (range, 0–5.3 cm). Among all patients, 24 (54.5%) received whole breast RT with standard tangential fields and the remaining 20 (45.5%) were treated with high tangential fields. The average doses delivered to the level I and II axillary lymph nodes were significantly higher in the patients who received whole breast RT with high tangential fields. Moreover, in the patients who received whole breast RT with high tangential fields, the axillary lymph node level I volumes receiving at least 95% of the prescribed radiation dose were significantly larger (table 3).

Table 3. Dose distribution in axillary lymph node levels I and II according to radiotherapy technique.

		Radiotherapy technique		*p*-value
		Standard tangential fields (n=24)	High tangential fields (n=20)	
D_{ave} (%)* (range)	Level I	41.2 (14.2–83.4)	56.2 (14.3–94.6)	0.029
	Level II	21.5 (2.6–47.5)	38.5 (6.8–71.5)	<0.001
$V_{D95\%}$ (%)† (range)	Level I	6.3 (0.7–20.5)	18.1 (0–67.4)	0.006
	Level II	1.3 (0–6.6)	1.5 (0–7.7)	0.801

*Average percentage of the prescribed radiation dose delivered to the axillary lymph node; †The volume encompassed by 95% of the prescribed radiation dose.

Dose distribution in the axillary lymph node levels was also analysed according to body mass index (BMI); patients were categorized as thin (BMI <20 kg/m2; n=9), average (20 ≤ BMI ≤ 25; n=15), and overweight (BMI >25; n=20). These analyses are summarized in Table 4. Compared to thin patients, the average dose delivered to level I axillary lymph nodes was significantly higher in overweight patients (p=0.001 in the post-hoc test). The average doses delivered to level II axillary lymph nodes were 17.9% in thin patients, 31.4% in average patients, and 36.2% in overweight patients (p=0.021). Overweight patients received a significantly higher average dose to their level II axillary lymph nodes compared to thin patients (p=0.016 in the post-hoc test). However, the axillary lymph node volumes receiving at least 95% of the prescribed radiation dose were not significantly different between patient groups.

Table 4. Dose distribution in axillary lymph node levels I and II according to body mass index.

		Body mass index (kg/m^2)			*p*-value
		Thin (BMI <20; n=9)	**Average (20 ≤ BMI ≤ 25; n=15)**	**Overweight (BMI >25; n=20)**	
D_{ave} (%)* (range)	Level I	28.5 (14.2–47.2)	48.7 (15.3–94.6)	59.3 (22.6–89.4)	0.002
	Level II	17.9 (2.6–40.6)	31.4 (5.7–71.5)	36.2 (15.4–62.9)	0.021
$V_{D95\%}$ (%)† (range)	Level I	4.9 (0–15.8)	12.9 (0–39.5)	17.3 (0–67.4)	0.129
	Level II	1.0 (0–6.8)	1.7 (0–6.3)	1.9 (0–7.7)	0.533

*Average percentage of the prescribed radiation dose delivered to the axillary lymph node; †The volume encompassed by 95% of the prescribed radiation dose
BMI=body mass index

DISCUSSION

In 2014, Jagsi *et al.* [6] reported the results of whole breast RT field coverage of the axillary lymph nodes in patients who enrolled in the Z0011 trial. However, because of the long period of time since treatment and because three-dimensional treatment planning was not performed for all patients during the era that the Z0011 trial was conducted, detailed RT records were evaluated for only 228 (25.6%) of all enrolled patients. Moreover, according to the results of Jagsi et al., the RT field designs in the ACOSOG Z0011 trial were very heterogeneous. Of the 228 patients, approximately half received whole breast RT with high tangential fields, and 43 (18.9%) received additional direct regional nodal RT which was prohibited in the Z0011 trial. Therefore, at present, we cannot draw any definitive conclusions regarding the optimal design of RT fields for breast cancer patients with 1–2 positive sentinel lymph nodes who did not undergo axillary dissection.

Several studies have reported the radiation dose coverage of axillary lymph node levels I and II by whole breast tangential RT [7-10, 12, 14]. The reported average doses delivered to axillary lymph nodes ranged from 66% to 86% in level I and from 29% to 71% in level II. Furthermore, the volumes receiving at least 95% of the prescribed radiation dose ranged from 10% to 79% in level I and from 1.2% to 51% in level II. In our study, the average doses delivered to levels I and II axillary lymph nodes were 49.4% and 30.8%, respectively, and the volumes receiving at least 95% of the prescribed radiation dose for levels I and II were 12.7% and 1.4%, respectively. Compared to previous investigations, our study revealed a relatively lower coverage of axillary lymph nodes by whole breast tangential RT, and the radiation dose coverage of axillary lymph node levels I and II by whole breast tangential RT appeared to vary greatly among various studies and hospitals. Moreover, despite the fact that a single radiation oncologist conducted the breast tangential RT, the coverage of axillary lymph nodes varied greatly among patients. In our study, the average radiation doses delivered to level I axillary lymph nodes ranged from 14.2%

to 94.6%, and the volumes receiving at least 95% of the prescribed dose for level I ranged from 0% to 67.4%. These discrepancies in coverage of axillary lymph nodes among patients and institutions may have been due to variable convexities of chest walls, axillary vein routes, somatotypes, and RT positions and techniques determined by the radiation oncologists administering the treatments. Therefore, the question remained whether axillary lymph node dissection can be safely omitted in patients with clinically axillary lymph node negative T1-2 breast cancer with 1–2 positive sentinel lymph nodes in all hospitals around the world.

An early study of the National Surgical Adjuvant Breast and Bowel Project (B-04) randomly assigned patients with clinically node negative breast cancer to radical mastectomy, total mastectomy with axillary nodal irradiation, or total mastectomy alone. Thirty-eight percent of patients who underwent axillary dissection had nodal metastases, whereas less than half developed clinically evident axillary recurrence in the group treated with total mastectomy alone [15]. This suggests that not all axillary metastases ultimately develop to clinically detectable disease, although some axillary nodal metastases clearly do. Meanwhile, the potential benefit of radiation in controlling metastatic disease in the axilla has been suggested in several studies [16-22]. Thus, for the safe omission of axillary lymph node dissection in patients with clinically axillary lymph node negative T1-2 breast cancer with 1–2 positive sentinel lymph nodes, sufficient dose coverage of level I and II axillary lymph nodes by whole breast tangential RT should be guaranteed. However, in our study, the volume receiving at least 95% of the prescribed radiation dose for level I nodes was less than 10% in 23 patients (52.3%), and for level II nodes was less than 1% in 32 patients (72.7%). Moreover, thin patients showed a significantly lower average dose to axillary lymph node levels compared to overweight patients. Because the radiation dose coverage of axillary lymph nodes varies greatly among patients, resulting in some patients receiving insufficient dose coverage, standardization and individualization of the whole breast RT technique are necessary. We therefore advocate exact evaluation of the dose distribution of axillary lymph nodes based on three-dimensional treatment planning to achieve more consistent coverage of these nodes by whole breast tangential RT. After contouring axillary lymph node levels, intentional targeting of the axilla via adjustments made to the tangential fields should be conducted to allow for individualized RT. We also advocate national prospective trials to achieve standardization of whole breast RT techniques, as this would enable us to deliver more consistent and individualized treatments to patients with breast cancer.

In conclusion, radiation dose coverage of axillary lymph nodes by whole breast tangential RT varies greatly among hospitals, and even among patients in a single hospital. In order to safely forego axillary lymph node dissection in patients with axillary lymph node negative T1-2 breast cancer with 1–2 positive sentinel lymph nodes, standardization and individualization of whole breast RT are critical.

***Conflicts of interest*:** *Declared none.*

REFERENCES

1. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM *et al.* (2010) Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg,* ***252:*** *426-32*.
2. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, *et al.* (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA,* ***305:*** *569-75*.
3. Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, von Minckwitz G, *et al.* (2008) Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. *J Clin Oncol,* ***26:*** *814-9*.
4. Gralow JR, Zujewski JA, Winer E (2008) Preoperative therapy in invasive breast cancer: reviewing the state of the science and exploring new research directions. *J Clin Oncol,* ***26:*** *696-7*.

5. Haffty BG, Hunt KK, Harris JR, Buchholz TA (2011) Positive sentinel nodes without axillary dissection: implications for the radiation oncologist. *J Clin Oncol,* ***29:*** *4479-81*.
6. Jagsi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, *et al.* (2014) Radiation field design in the ACOSOG Z0011 (Alliance) *Trial. J Clin Oncol,* ***32:*** *3600-6*.
7. Belkacemi Y, Allab-Pan Q, Bigorie V, Khodari W, Beaussart P, Totobenazara JL, *et al.* (2013) The standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I-II and the sentinel node area. *Ann Oncol,* ***24:*** *2023-8*.
8. Alco G, Igdem SI, Ercan T, Dinçer M, Sentürk R, Atilla S, *et al.* (2010) Coverage of axillary lymph nodes with high tangential fields in breast radiotherapy. *Br J Radiol,* ***83:*** *1072-6*.
9. Reznik J, Cicchetti MG, Degaspe B, Fitzgerald TJ (2005) Analysis of axillary coverage during tangential radiation therapy to the breast. *Int J Radiat Oncol Biol Phys,* ***61:*** *163-8*.
10. Reed DR, Lindsley SK, Mann GN, Austin-Seymour M, Korssjoen T, Anderson BO, et al. (2005) Axillary lymph node dose with tangential breast irradiation. *Int J Radiat Oncol Biol Phys,* ***61:*** *358-64*.
11. Schlembach PJ, Buchholz TA, Ross MI, Kirsner SM, Salas GJ, Strom EA, *et al.* (2001) Relationship of sentinel and axillary level I-II lymph nodes to tangential fields used in breast irradiation. *Int J Radiat Oncol Biol Phys,* ***51:*** *671-8*.
12. Park SH, Kim JC, Lee JE, Park IK (2015) Virtual lymph node analysis to evaluate axillary lymph node coverage provided by tangential breast irradiation. *Radiat Oncol,* ***33:*** *50-6*.
13. Nielsen MH, Berg M, Pedersen AN, Andersen K, Glavicic V, Jakobsen EH, *et al.* (2013) Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. *Acta Oncol,* ***52:*** *703-10*.
14. Aristei C, Chionne F, Marsella AR, Alessandro M, Rulli A, Lemmi A, *et al.* (2001) 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,* ***51:*** *69-73*.
15. Fisher B, Montague E, Redmond C, Barton B, Borland D, Fisher ER, et al. (1977) Comparison of radical mastectomy with alternative treatments for primary breast cancer. A first report of results from a prospective randomized clinical trial. *Cancer,* ***39:*** *2827-39*.
16. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N (2002) Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med,* ***347:*** *567-75*.
17. Hwang RF, Gonzalez-Angulo AM, Yi M, Buchholz TA, Meric -Bernstam F, Kuerer HM, *et al.* (2007) Low locoregional failure rates in selected breast cancer patients with tumor-positive sentinel lymph nodes who do not undergo completion axillary dissection. *Cancer,* ***110:*** *723-30*.
18. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, *et al.* (1989) Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med,* ***320:*** *822-8*.
19. Louis-Sylvestre C, Clough K, Asselain B, Vilcoq JR, Salmon RJ, Campana F, *et al.* (2004) Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. *J Clin Oncol,* ***22:*** *97-101*.
20. Haffty BG, Fischer D, Fischer JJ (1990) Regional nodal irradiation in the conservative treatment of breast cancer. *Int J Radiat Oncol Biol Phys,* ***19:*** *859-65*.
21. Ribeiro GG, Dunn G, Swindell R, Harris M, Banerjee SS (1990) Conservation of the breast using two different radiotherapy techniques: interim report of a clinical trial. *Clin Oncol, (R Coll Radiol)* ***2:*** *27-34*.
22. Recht A (1999). Should irradiation replace dissection for patients with breast cancer with clinically negative axillary lymph nodes? *J Surg Oncol,* ***72:*** *184-92*.