



Lymphedema and Axillary-Lateral Thoracic Vessel Juncture Irradiation: A Clinical Dilemma

İ Şükran Şenyürek¹, İ Merve Duman¹, İ Sena Birsen Güçlü², İ Nilüfer Kılıç Durankuş¹, İ Duygu Sezen¹, İ Yasemin Bölükbaşı¹

¹Department of Radiation Oncology, Koç University Faculty of Medicine, İstanbul, Türkiye

²Koç University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Regional nodal irradiation (RNI) is one of the main causes of breast cancer-related lymphedema (BCRL). However, studies on the relationship between the radiation dose to the axillary-lateral thoracic vessel juncture (ALTJ) region and BCRL have reported conflicting results. Based on these findings, we aimed to evaluate the clinical relevance of the dose to the ALTJ region in our patient cohort.

Materials and Methods: Patients diagnosed with breast cancer and who were treated at Koç University Hospital between 2016 and 2022 and received RNI were included. BCRL was defined as a difference in arm circumference between the ipsilateral and contralateral limb >2.5 cm at any single encounter or ≥2 cm on ≥2 visits. ALTJ was retrospectively contoured, and doses were recorded as equivalent dose ($\alpha/\beta = 3$).

Results: Of the 129 patients (median age 49 years) who met the inclusion criteria, 12 (9.3%) had lymphedema. Two-thirds of the patients (66.7%) were stage II, and one-third (33.3%) were stage III. The median follow-up was 22 months. The median (range) ALTJ D_{mean} dose was 18.11 (1.87–50) Gy, the median ALTJ D_{max} was 44.53 (12.8–71.1) Gy, and the median ALTJ V35 was 38% (1–100%). No significant association was determined between ALTJ parameters and BCRL.

Conclusion: There is insufficient data to define ALTJ as an OAR for decreasing BCRL risk. It is not appropriate to define dose and target based on ALTJ. Prospective studies with larger patient populations are needed to clarify the relationship between ALTJ and lymphedema.

Keywords: Breast cancer; lymphedema; radiotherapy

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Key Points

- The aim of study was investigate the accosiation of reciving dose axillary-lateral thoracic vessel juncture and breast cancer related lymphedema.
- Patients were treated whole breast radiotherapy/chestwall radiotherapy and regional nodal radiotherapy were evaluated retrospectively.
- The dose axillary-lateral thoracic vessel juncture region was not detected significant factor for the development of breast cancer-related lymphedema.

Introduction

Breast cancer-related lymphedema (BCRL) is a common and significant complication following breast cancer treatment. A meta-analysis of 84 cohort studies, including 58,358 patients, found the pooled incidence of lymphedema to be 21.9%, indicating that approximately one in five breast cancer survivors developed BCRL as a consequence of multimodal treatment (1).

The lymphedema in randomized studies evaluating the oncological results of axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) showed that the risk of lymphedema in the

SLNB group was between 7–11%, where this rate increases to 14–23% in patients who underwent ALND (2, 3). In a more recent meta-analysis of studies comparing SLNB and ALND, the prevalence of lymphedema was 13.7% and 24.2%, respectively (4).

There is a well-established relationship between radiotherapy and lymphedema. Specifically, the risk of lymphedema is significantly higher in breast cancer patients who receive regional nodal irradiation (RNI) compared to those who undergo whole-breast irradiation alone. This risk is more significant in patients who receive RNI following ALND, underlying the additive impact of these treatments on the lymphatic system (5).

Corresponding Author:
Yasemin Bölükbaşı MD; ybolukbasi@kuh.ku.edu.tr

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The axillary-lateral thoracic vessel juncture (ALTJ) area has been identified as a structure at risk for lymphedema in patients who have undergone lymphatic irradiation in the last five years (6-8). Notably, the three studies advocating for recognizing ALTJ as an “organ at risk” (OAR) have published different dosimetric parameters significantly associated with lymphedema risk. Besides that, the latest study by Healy et al. (9) failed to find clinically meaningful importance of the ALTJ as an OAR. This topic remains an open question in the literature, warranting further research and discussion. Therefore, we aimed to assess the controversial relationship between ALTJ and BCRL through a retrospective analysis of our patient cohort.

Materials and Methods

Patients Selection

Patients diagnosed with breast cancer who were treated at Koç University Hospital between 2016 and 2022 and received whole breast radiotherapy/chest wall radiotherapy and regional nodal radiotherapy were evaluated retrospectively. The study population included patients presenting with lymph node positivity and/or tumors classified as T3 or T4 according to the TNM staging system. Patients who had complete arm measurement information for lymphedema monitoring and had at least one year follow-up were included in the study. Patients who presented with lymphedema either prior to radiotherapy or at the time of their initial clinical diagnosis were excluded from the study to avoid confounding factors related to pre-existing disease. In addition, patients who developed local, regional, or distant metastases during the follow-up period were excluded, as metastatic progression and its associated treatments could independently influence the risk of lymphedema. Furthermore, patients for whom radiotherapy treatment planning data were unavailable were also excluded to ensure the accuracy and consistency of the dosimetric analysis. Patients who used adjuvant capecitabine, immunotherapy, or CDK4i during radiotherapy were excluded from the study as the effect of new chemotherapy agents on lymphedema is unknown.

Treatment Protocol

All patients were simulated with a Siemens 4DCT scan and a 1.25 mm slice thickness. All patients were immobilized with arms upsid and customized vac-lac. The conventional (50 Gy/25 fr) or hypofractionation schema (42.56 Gy/16 fr) were used for adjuvant radiotherapy of breast

cancer for RNI. The most commonly used treatment technique is Field in Field (FinF).

Axillary-Lateral Thoracic Vessel Juncture Delineation

The ALTJ area was contoured retrospectively by a single radiation oncologist (Ş.Ş.) for all patients according to the guideline of Gross et al. (6) (Figure 1a-b).

The borders were defined as:

The cranial border: One axial slice below the humeral head

The caudal border: The inferior of the axillary vessels

The anterior border: The plane defined by posterior of pectoralis major

The posterior border: The anterior surface of the subscapularis and latissimus dorsi muscles.

The lateral border: Included the axillary vessels

The medial border: The lateral border of the pectoralis minor muscle.

To validate contouring, one patient for every ten patients was randomly selected and checked by another radiation oncologist (Y.B.). The mean dose, maximum dose and V35 values of ALTJ were recorded as equivalent dose (EQD2) which $\alpha/\beta = 3$ was settled for late toxicity.

Lymphedema Definition

Limb circumferences were taken routinely with a tape measure before and at three-month intervals for the first two years using the same landmarks to avoid excessive pressure during evaluation. The arm circumferences were measured in centimeters using a standardized flexible tape measure for all patients. Measurements were performed in the affected and unaffected limbs at 10 cm above (proximal) and below (distal) the elbow, circumference of outstretched inner hand, and wrist crease. BCRL was defined as a difference in arm circumference between the ipsilateral and contralateral limb >2.5 cm at any single encounter or ≥ 2 cm on ≥ 2 visits.

Statistical Analysis

The primary objective was to evaluate the relationship between ALTJ dosimetric parameters and BCRL. The secondary objective

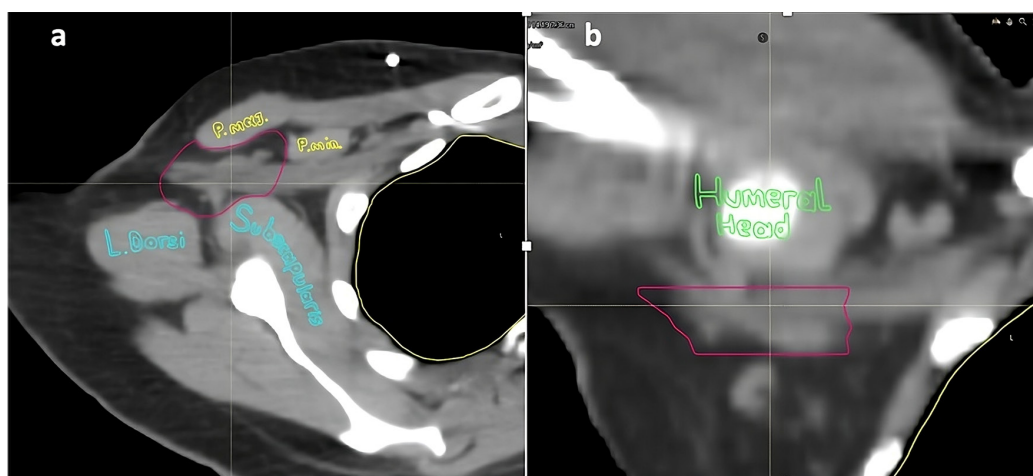


Figure 1. Axial plan of axila (a), coronal plan of axilla (b)

P.min.: Pectoralis minor muscle, P. maj.: Pectoralis major muscle, L. Dorsi: Latissimus Dorsi muscle

was to investigate the association between clinical and pathological characteristics and the development of BCRL. Cox proportional hazards regression models were used to test these associations. Univariate analyses were initially performed to assess the association between potential risk factors for BCRL, including body mass index (BMI), type of surgery, presence of axillary seroma, number of dissected lymph nodes, number of positive lymph nodes, clinical stage, radiotherapy scheme, radiotherapy technique, and ALTJ dose parameters. Variables demonstrating statistical significance ($p < 0.05$) in the univariate analyses were subsequently entered into a multivariate logistic regression model to identify independent predictors of BCRL. The most optimal cut-off values for ALTJ D_{mean} , ALTJ D_{max} , and ALTJ V35 Gy were determined using receiver operating characteristic (ROC) curve analysis to investigate how they related to BCRL.

Ethical Approval

The retrospective research design of this study (approval number: 2024.350.IRB2.149, date: 14.10.2024) was approved by the Institutional Review Board at Koç University.

Results

Patients eligible for inclusion numbered 129, with a median (range) age of 49 (26–86) years. Of these, 86 patients had clinical stage II, and 43 patients had clinical stage III breast cancer (Table 1). The median follow-up was 22 (12–89) months. Lymphedema was observed in 12 patients (9.3%).

The majority of patients had undergone mastectomy (80.6%) and 19.4% had lumpectomy. Of the patients, ALND was performed in 58.9% and SLNB in 41.1%. Axillary seroma was observed in 20% of patients. The number of removed lymph nodes was >15 in 28% of the patients. A total of 26 patients (20.2%) had ≥ 4 positive lymph nodes. In 25.5% of the patients, the BMI value was 30 kg/m² or higher.

In terms of pathological receptor status, 84 patients (65.1%) identified as hormone receptor (HR)(+)/human epidermal growth factor receptor 2HER2(-), 29 patients (22.5%) as HER2(+), and 16 patients (12.4%) as triple negative. Regarding systemic treatment, 82 patients (63.6%) received neoadjuvant chemotherapy, 36 patients (27.9%) received adjuvant chemotherapy, and 11 patients (8.5%) did not receive any chemotherapy.

Radiotherapy schemes were used in 70 patients (54.3%) whereas hypofractionated schemes were used in 59 patients (45.7%). The radiotherapy technique used was predominantly the FinF technique in 107 patients (82.9%), while 22 patients (17.1%) were treated with intensity-modulated radiotherapy (IMRT).

Dosimetric parameters of the ALTJ in EQD2 terms were: median ALTJ D_{max} was 44.53 (12.8–71.1) Gy, the median ALTJ D_{mean} was 18.11 (1.87–50) Gy, and the median ALTJ V35 Gy was 38% (1–100%).

In the univariate analysis, the number of removed lymph nodes, BMI and axillary dissection type were evaluated in terms of predictor of lymphedema. In the multivariate analysis, more than 15 removed lymph nodes ($p = 0.002$), ALND ($p = 0.015$), and BMI ≥ 30 kg/m² ($p = 0.006$) were identified as significant predictive factors for lymphedema (Table 2).

Furthermore, ROC analysis performed for ALTJ D_{max} , ALTJ D_{mean} , and ALTJ V35 Gy parameters in predicting lymphedema development did not identify any significant threshold values (Figure 2). In the patient group treated with IMRT, ALTJ doses were found to be significantly higher ($p = 0.003$) than those receiving the FinF technique, but this had no significant effect on the development of lymphedema.

Discussion and Conclusion

In this retrospective study, we analyzed breast cancer patients who had undergone regional lymph node radiotherapy, and no significant association was detected between the dose to the ALTJ region and the development of BCRL. The results indicated that the number of removed lymph nodes (>15), the type of axillary intervention (ALND), and a high BMI (≥ 30 kg/m²) were identified as predictive risk factors for BCRL. The current study is the first Turkish breast cancer cohort evaluating the delivered dose to the ALTJ in relation to the development of lymphedema.

Table 1. Patients characteristics

	All patients (n)	All patients (%)
Age, median, years	49 (26–86)	-
Follow-up duration, months	22 (12–89)	-
Clinical T-stage		
T1	46	35.7
T2	66	51.2
T3	9	7
T4	8	6.1
Clinical N-stage		
N0	25	19.4
N1	74	57.4
N2	15	11.6
N3	15	11.6
Stage groups		
II	86	66.7
III	43	33.3
Pathological receptor status		
HR(+)/HER2(-)	84	65.1
HER2(+)	29	22.5
HR(-)/HER2(-)	16	12.4
Systemic treatment		
Neoadjuvant chemotherapy	82	63.6
Adjuvant chemotherapy	36	27.9
No chemotherapy	11	8.5
Lymphedema		
No	117	90.7
Yes	12	9.3

HR: Hormone reseptor; HER2: Human epidermal growth factor receptor 2

The relationship between the ALTJ region and lymphedema has been established based on the distinction of breast and arm lymphatic drainage. The upper limb drainage nodes, which are identified via the axillary reverse mapping (ARM) technique, were distinctly separate lymph nodes from the sentinel nodes draining the breast in 90% of cases. A systemic review by Ahmed et al. (10) indicated an overlap rate of up to 10%; moreover, Ngui et al. (11) confirmed this low overlap rate of 9.6%. Moreover, the majority of ARM nodes (72%) were located in the upper level 1 axilla, outside the tangential whole-breast radiotherapy fields (12). One of the studies supporting distinct

lymphatic drainage systems was performed by Clough et al. (13). They mapped the sentinel lymph nodes of 242 patients diagnosed with stage I breast cancer and indicated that, apart from the site of the tumor in the breast, 98.2% of sentinel lymph nodes were found in the medial part of the axilla, alongside the lateral thoracic vein.

Based on data suggesting that the use of the ARM technique in surgical series reduces BCRL (14) and the knowledge that arm and breast drainage are distinct in most patients, Gross et al. (6) proposed that there could be a significant relationship between radiotherapy dose to

Table 2. Results of univariate and multivariate analysis for BCRL

Characteristics	All patients (n = 129)	BCRL (n = 12)	Univariate <i>p</i> -value	Multivariate <i>p</i> -value
BMI, kg/m²				
<30	96	5	0.01	0.006
≥30	33	7		
Surgery, primary				
Lumpectomy	25	3	0.42	-
Mastectomy	104	9		
Surgery, axilla				
SLND	53	1	0.01	0.01
ALND	76	11		
Seroma, axilla				
Yes	26	0	0.58	-
No	103	12		
Removed lymph nodes				
15	93	4	0.004	0.002
>15	36	8		
Positive lymph nodes				
<4	103	9	0.45	-
≥4	26	3		
Stage groups				
II	67	6	0.42	-
III	50	6		
Radiotherapy scheme				
Conventional	70	7	0.50	-
Hypofraction	59	5		
RT technique				
Field in Field	107	12	0.09	-
IMRT	22	0		
ALTJ D_{max} (EQD2), median Gy	44.53 (12.8–71.1)	42.1 (36.8–67.95)	0.72	-
ALTJ D_{mean} (EQD2), median Gy	18.11 (1.87–50)	16.45 (1.87–35.57)	0.17	-
ALTJ V35 Gy (EQD2), median (%)	38 (1–100)	27 (2–74)	0.18	-
ALTJ V35 Gy (EQD2)				
≤66%	99	11	0.18	-
>66%	30	1		

ALTJ: Axillary-lateral thoracic vessel junction; ALND: Axillary lymph node dissection; BCRL: Breast cancer-related lymphedema; BMI: Body mass index; EQD2: Equivalent dose; N: Number of patients; SLNB: Sentinel lymph node biopsy; Gy: Gray; RT: Radiation therapy; D_{mean}: Mean dose; D_{max}: Maximum dose; V35 Gy: Percentage of volume receiving 35 Gy; IMRT: Intensity-modulated radiotherapy

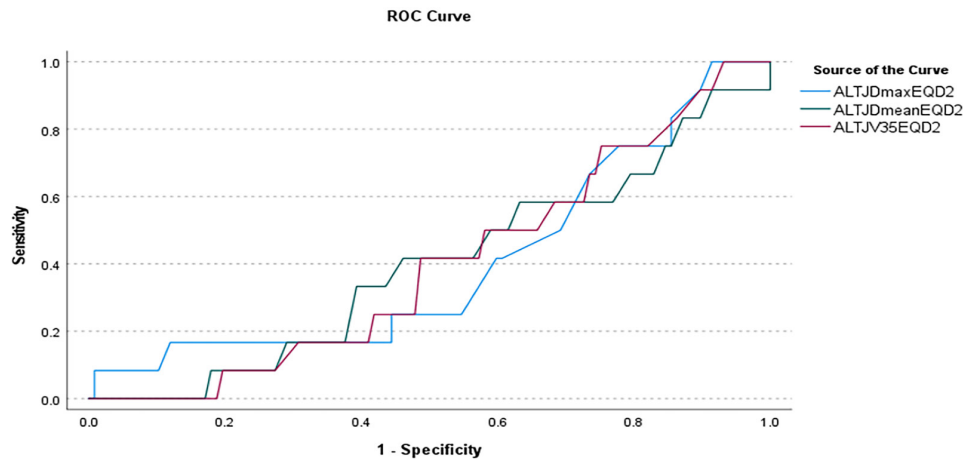


Figure 2. The outcomes of a receiver operating characteristic curve analysis examining the correlation between the ALTJ and EQD2 doses

ROC: Receiver operating characteristic; ALTJ: Axillary-lateral thoracic vessel juncture; EQD2: Equivalent dose

the upper level 1 axillary region, an area predominantly involved in arm drainage, and the development of BCRL. This study indicated that the most significant dosimetric variable and the cut-off point was ALTJ $D_{min} < 36.8$ Gy, which was associated with a 6.6-fold decrease in 3-year lymphedema rates (5.7% *vs.* 37.4%). Following this new OAR definition by Gross et al. (6), three studies have been published investigating the impact of radiotherapy doses on the ALTJ region and the risk of developing lymphedema. Two of these three studies have demonstrated that the ALTJ appears to be an OAR. Lei et al. (15), reported a significant reduction in ALTJ dose with VMAT, and we found higher ALTJ doses in patients treated with IMRT compared to the FinF technique. One of the studies validating the ALTJ as an OAR was conducted by Suk Chang et al. (7), which revealed that ALTJ V35 Gy of $\leq 66\%$ in patients with ≤ 6 removed lymph nodes and ALTJ maximum dose of > 53 Gy in patients with > 15 removed lymph nodes, were identified as important factors using decision tree analysis. Another study by Park et al. (8) developed and validated a multivariable normal tissue complication probability model to predict lymphedema in breast cancer patients receiving radiation therapy. According to this model, patients were classified into three risk categories: high-risk [number of lymph nodes dissected (LNDno) > 10 and ALTJ V35 $> 39.9\%$], moderate-risk (LNDno > 10 and ALTJ V35 $\leq 39.9\%$ or LNDno ≤ 10 and ALTJ V35 $> 39.9\%$), and low-risk (LNDno ≤ 10 and ALTJ V35 $\leq 39.9\%$). The risk of lymphedema was significantly higher in high-risk patients where both LNDno and V35 exceeded the cut-off values. In contrast to these three studies, a more recent study by Healy et al. (9) did not demonstrate a significant relationship between the dose to the ALTJ region and the development of BCRL. In the current study, which represents the fifth study in the literature analyzing the relationship between ALTJ and BCRL, no threshold value for ALTJ dose parameters was identified that could predict the risk of lymphedema. Additional analyses were conducted based on the threshold values of 39.9% and 66% for ALTJ V35 Gy reported in the literature; however, these analyses also did not yield significant results.

In patients with breast cancer, the type of surgical intervention to the axilla is among the most well-known risk factors for the development of lymphedema. In a meta-analysis of 67 studies published in 2023, focusing on upper limb morbidity associated with SLNB and ALND, it was once again shown that ALND significantly increased the risk of

lymphedema compared to SLNB (13.7% and 24.2%) (4). Contrary to this clear relationship, studies investigating the relationship between the number of removed lymph nodes and the risk of lymphedema have reported conflicting results. Although Goldberg et al. (16), in their series of 600 patients, did not demonstrate a significant relationship between the number of lymph nodes removed and the risk of lymphedema, a meta-analysis of 84 studies published in 2022 by Shen et al. (1) concluded that removing more than 15 lymph nodes is a risk factor for lymphedema. In the present study, removing more than 15 lymph nodes and ALND were also significantly identified as a predictive factor for lymphedema.

High BMI is another parameter that has been identified as one of the most significant factors increasing the risk of lymphedema in breast cancer patients. Both BMI at diagnosis and weight gain in the postoperative period have been shown to contribute to this risk. In Chinese data, a BMI over 25 kg/m² has been shown to pose a risk for lymphedema due to physical differences, whereas in Western populations, this risk is observed when the BMI exceeds 30 kg/m² (1, 17). Our results demonstrated that a BMI of 30 kg/m² or higher was a significant risk factor for BCRL.

The nodal burden of the disease, age, and long follow-up duration are also risk factors for lymphedema and have been integrated into various lymphedema risk stratification models (18, 19). While our study did not demonstrate a significant association between the number of positive lymph nodes and lymphedema, presumably due to the small cohort size, the role of nodal disease burden as a strong predictive factor for lymphedema is well recognized in the literature. The progressive fibrotic changes induced by radiotherapy, compounded by age-related factors, underscore the importance of extended follow-up periods in capturing the full spectrum and incidence of lymphedema among BC survivors (20).

Study Limitations

This study has potential limitations. Firstly, due to the retrospective nature of the study, we included only the patients with sufficient arm measurements. Secondly, even though the study explored a new concept in breast cancer treatment planning, it was limited by the small sample size. The relatively small sample size of the study may have limited statistical power, reducing the ability to detect significant

associations between variables. A lower number of patients increased the risk of type II errors, where actual differences or effects may go undetected. Thus, our findings should be considered as preliminary, necessitating confirmation through studies with larger, adequately powered populations. Thirdly, longer follow-up after 5 years could provide more meaningful and robust findings due to the high cure rates of breast cancer. Lastly, patients with lymphedema prior to radiotherapy were excluded in order to minimize the impact of surgery on lymphedema. Therefore, patients who developed acute postoperative morbidity related to surgery were not evaluated within the scope of this study and should thus be considered a separate group in terms of risk of developing lymphedema.

Although our study did not demonstrate a significant association between the radiation dose to the ALTJ and the development of BCRL, delineating the ALTJ as an OAR in clinical practice and incorporating it into treatment plan optimization, but without compromising the clinical target volume, may offer a clinically safe and beneficial strategy, particularly for long-term breast cancer survivors.

Ethics

Ethics Committee Approval: The retrospective research design of this study (approval number: 2024. 350.IRB2.149, date: 14.10.2024) was approved by the Institutional Review Board at Koç University.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.Ş., M.D., S.B.G., N.K.D., D.S., Y.B.; Concept: Ş.Ş., M.D., S.B.G., N.K.D., D.S., Y.B.; Design: Ş.Ş., M.D., S.B.G., N.K.D., D.S., Y.B.; Data Collection or Processing: Ş.Ş., M.D., S.B.G., N.K.D., D.S., Y.B.; Analysis or Interpretation: Ş.Ş., M.D., S.B.G., N.K.D., D.S., Y.B.; Literature Search: Ş.Ş., M.D., S.B.G., N.K.D., D.S., Y.B.; Writing: Ş.Ş., M.D., S.B.G., N.K.D., D.S., Y.B.

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