Impact of Tumour Location and Incidental Radiation Dose to the Internal Mammary Lymph Nodes on Breast Cancer-Specific Mortality

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Introduction

The internal mammary lymph nodes (IMLN) constitute a pathway of lymphatic cancer spread from the breast but their inclusion in breast radiotherapy remains controversial.[1,2] Randomized trials investigating IMLN irradiation may not have shown a benefit due to the incidental dose delivered to IMLNs by conventional breast tangents.[3-5] Conventional tangent beam geometry produces substantial heterogeneity in incidental IMLN doses, where tumours located closer to the IMLNs are more likely to result in higher incidental doses and also are more likely to drain to the IMLNs. **This study investigates the interplay of seroma position (relative to lymphatic drainage pathways) and incidental IMLN dose and their impact on breast cancer-specific mortality as another step towards identifying which patients may benefit from IMLN irradiation.**

Materials and Methods

Retrospective review of 10,221 patients curatively treated with breast-conserving surgery and radiotherapy from 2005 – 2014

Inclusion Criteria:
- Pathologically node-positive
- CT-based planning
- Contoured seroma

Exclusion Criteria:
- Neoadjuvant systemic therapy
- Non-standard RT
- Therapeutic IMLN irradiation (D_{mean} > 40 $Gy_{3.5}$)
- Cosmetic breast implants

Internal mammary vessels contoured with Limbus Contour (version 1.8.0-B3) and edited as needed to include the first 3 intercostal spaces per RTOG guidelines

Data extraction for 475 patients meeting study criteria:
- Baseline patient, tumour, and treatment characteristics
- Mean IMLN dose (D_{mean}) converted to equivalent dose in 2 Gy fractions ($\alpha/\beta = 3.5$)
- Minimum surface distance between seroma and IMLN contours
- Minimum surface distance between seroma and ipsilateral lung contours

Estimate subdistribution hazard ratios (sHR) using multivariable Fine-Gray competing-risk regression with interaction terms of the D_{mean} quartiles and minimum distances.

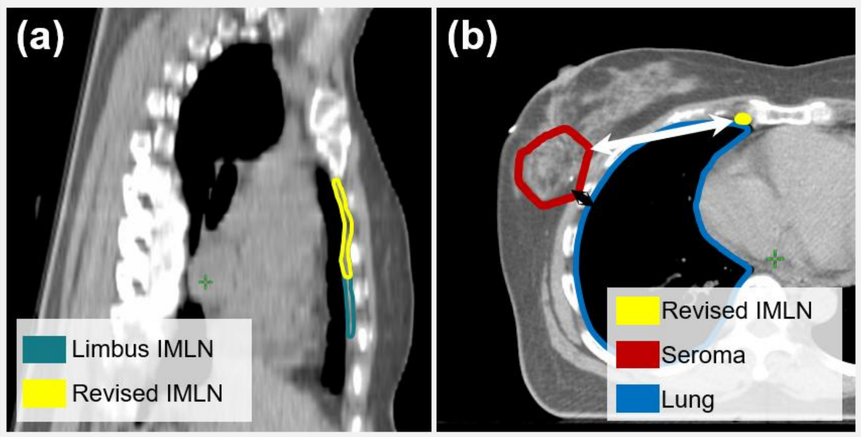

Figure 1: (a) Sagittal CT slice showing the Limbus-generated (teal) and revised IMLN (yellow) contours. (b) Axial CT slice showing the minimum seroma-to-IMLN (white arrow) and seroma-to-lung (black arrow) distances, calculated in 3D using the bidirectional local distance.[6] Seroma-to-lung distances were used as a surrogate for tumour distance from the deep mammary plexus that drains to the IMLNs.

Results and Discussion

Table 1: Patient, tumour, and treatment characteristics of the 475 patients included in the study cohort and results of the multivariable Fine-Gray subdistribution model for breast cancer-specific mortality, including interaction terms of mean radiation dose quartiles and centered distance metrics. A p-value < 0.05 is considered statistically significant.

Baseline Variables	Levels	Study Cohort, Median (Range) or Count (%) N = 475	Multivariable Analysis sHR (95% CI)	Multivariable Analysis p value
Follow-up time (years)		13.7 (0.8 – 20.3)		
Age at Diagnosis		59 (27.0–92.0)	1.02 (0.99, 1.05)	0.171
Lymphovascular invasion				0.385
	Negative	292 (61.5)	–	
	Positive	164 (34.5)	1.44 (0.85, 2.45)	0.172
	Unknown	19 (4.0)	1.16 (0.33, 4.17)	0.815
Stage				0.212
	1	78 (16.4)	–	
	2	347 (73.1)	2.08 (0.81, 5.33)	0.128
	3	50 (10.5)	2.97 (0.87, 10.1)	0.082
Subtype				0.137
	Lum A	254 (53.5)	–	
	Lum B	**108 (22.7)**	**1.89 (1.03, 3.49)**	**0.041**
	HER 2+	78 (16.4)	2.26 (0.94, 5.43)	0.067
	Triple Negative	35 (7.4)	1.08 (0.27, 4.31)	0.912
Hormone Therapy				0.877
	Yes	79 (16.6)	–	
	No	396 (83.4)	0.94 (0.43, 2.07)	0.877
Chemotherapy				0.596
	Yes	193 (40.6)	–	
	No	282 (59.4)	0.82 (0.40, 1.69)	0.596
Radiation Therapy				0.112
	Breast only	103 (21.7)	–	
	Breast + regional nodes	372 (78.3)	1.81 (0.87, 3.76)	0.112
Seroma-IMLN Distance (mm)*		71.5 (7.4–158.9)		
	IMLN D_{mean}, 1st Quartile ($Gy_{3.5}$)	**2.1 (0.3–3.1)**	**0.96 (0.94, 0.98)**	**<0.001**
	IMLN D_{mean}, 2nd Quartile ($Gy_{3.5}$)	5.0 (3.1–9.3)	1.00 (0.98, 1.02)	0.863
	IMLN D_{mean}, 3rd Quartile ($Gy_{3.5}$)	15.3 (9.4–24.3)	1.00 (0.98, 1.02)	0.684
	IMLN D_{mean}, 4th Quartile ($Gy_{3.5}$)	33.9 (24.3–40.0)	0.99 (0.97, 1.01)	0.527
Seroma-Lung Distance (mm)*		10.9 (1.3–96.7)		
	IMLN D_{mean}, 1st Quartile ($Gy_{3.5}$)	**2.1 (0.3–3.1)**	**0.64 (0.52, 0.79)**	**<0.001**
	IMLN D_{mean}, 2nd Quartile ($Gy_{3.5}$)	5.0 (3.1–9.3)	0.93 (0.85, 1.02)	0.121
	IMLN D_{mean}, 3rd Quartile ($Gy_{3.5}$)	**15.3 (9.4–24.3)**	**1.04 (1.01, 1.07)**	**0.016**
	IMLN D_{mean}, 4th Quartile ($Gy_{3.5}$)	33.9 (24.3–40.0)	1.03 (0.92, 1.16)	0.545

*Separate models were fit for each of the distance variables.

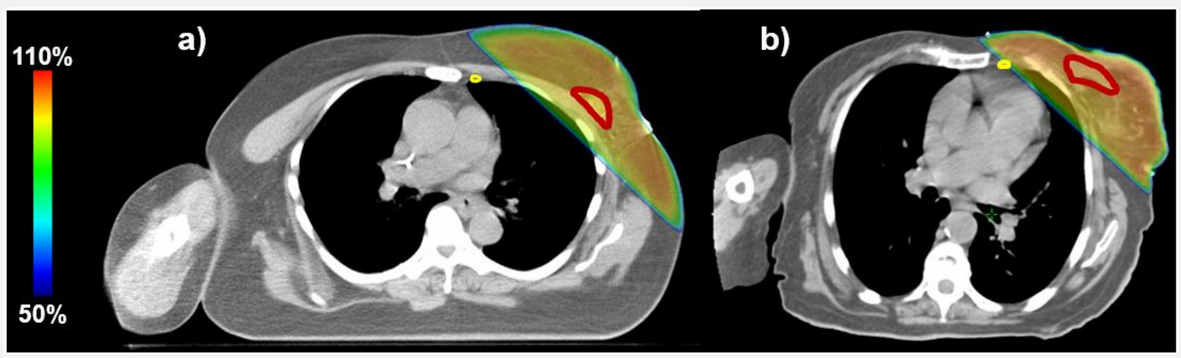

Figure 2: Axial CT images and radiotherapy plans for breast cancer patients where the IMLNs receive (a) a low mean dose and (b) a high mean dose. The seroma is outlined in red and the IMLNs in yellow. The dose distribution is shown in colour wash (50 – 110% of the prescribed dose).

Conclusions

For patients with lower incidental IMLN doses, shorter seroma-to-IMLN and seroma-to-lung distances were associated with increased risk of death from breast cancer. This effect was absent as the incidental IMLN dose increased. Future work will investigate whether this trend holds true in high-risk node-negative patients.

References

[1] Rodin *et al.*, *Int. J. Radiat. Oncol. Biol. Phys.* 2023; 117(4): 779–782.
[2] Recht., *J. Clin. Oncol.* 2024; 42(16): 1871–1874.
[3] Kaija *et al.*, *Radiother. Oncol.* 1995; 36(3): 172–176.
[4] Hennequin *et al.*, *Int. J. Radiat. Oncol. Biol. Phys.* 2013; 86(5): 860–866.
[5] Kim *et al.*, *JAMA Oncol.* 2022; 8(1): 96–105.
[6] Kim *et al.*, *Med. Phys.* 2012; 39(11): 6779–6790.

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