

Original Article

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Clinical audit of breast cancer patients treated with helical tomotherapy for irradiation of the internal mammary chain

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Abstract

Aim: To evaluate efficacy of helical tomotherapy (HT) for treatment of breast cancer with internal mammary lymph node involvement.

Methods: This is a retrospective clinical audit of planning, dosimetry, toxicity and short-term survival of a cohort of 65 patients. Patients were treated between November 2014 and May 2019. The primary and nodal region was prescribed a dose of 50 Gray (Gy) in 25 fractions, while all cases of breast conserving surgery received a simultaneous integrated boost to a dose of 61 Gy in 25 fractions.

Results: The 95% coverage for the primary, supraclavicular, internal mammary node and tumour bed was 93.4%, 96.8%, 90.7% and 98.3%, respectively. Mean dose to total lung, heart and contra-lateral breast was 10.6 Gy, 6.92 Gy and 4.32 Gy, respectively. None developed grade III skin or oesophageal toxicity. Twenty-one patients had progression; of which eighteen developed only distant failure while three also had loco-regional recurrence. At a median follow-up of 36 months, the 3-year loco-regional control, disease-free survival and overall survival were 93.5, 73.9 and 85.9%, respectively.

Conclusion: We report encouraging clinical outcome for patients treated uniformly with HT. The predominant pattern of failure was distant metastases which suggests the need for systemic control intensification.

Introduction

Locally advanced breast cancer (LABC) accounts for 10–20% in the West, while in India, it represents 30–40% of all cases.¹ LABC is a heterogeneous group characterised by large primary tumour (>5 cm), with/without skin or chest wall involvement and/or presence of matted axillary lymph nodes (ALN) and/or involvement of internal mammary nodes (IMN) or supraclavicular fossa (SCF) nodes without distant metastases. Thus, LABC includes all stage III patients and some with stage IIB disease (T3N0).²

A clinical presentation of LABC merits adjuvant radiotherapy regardless of type of surgery done or use of neoadjuvant or adjuvant chemotherapy used. Adjuvant radiotherapy has been proven to be effective for tumour control as well as improving overall survival. The benefit from adjuvant radiotherapy is proportionally larger for LABC compared to early breast cancer.^{3,4}

With regard to target volume for adjuvant radiotherapy, some controversy exists on the prophylactic inclusion of the internal mammary chain (IMC) in the radiation targets. A recent meta-analysis of 3 randomised trials: EORTC 22922–10925, MA.20, and French showed that comprehensive regional nodal irradiation significantly improves progression-free, distant metastasis-free and overall survival in stage I–III breast cancer.⁵ The main challenge lies in the identification of the sub-group that will benefit the most from prophylactic IMC irradiation as the inclusion of IMC makes planning as well as delivery complex.⁶

Delivering IMC irradiation with conventional techniques like partially wide tangents and photon-electron combination leads to significant dose inhomogeneity as well as excessive exposure of heart and lung. Over the few decades, there are significant technological advancements in radiotherapy. Intensity-modulated radiotherapy (IMRT) has emerged as a promising option, which can also be utilised to deliver simultaneous integrated boost (SIB) to the lumpectomy cavity in case of breast conservation. The SIB technique improves dose conformity at the tumour bed, reduces spillage in the adjacent breast as well as to the organs at risk (OAR) compared to a sequential boost.^{7–10} The IMPORT HIGH trial currently in follow-up is a randomized trial

testing the benefit of concomitant boost (SIB) at two doses levels: 48 Gray (Gy) or 53 Gy in 15 fractions(F) versus standard radiotherapy 40 Gy/15F to whole breast +16 Gy/8F sequential boost.¹¹ It intends to study whether high dose using IMRT can reduce radiation-induced side effects while maintaining cure rates. The initial 3-year result of late adverse effects are similar in the standard and low dose level test arm but significantly higher in the 53 Gy arm.

Helical tomotherapy (HT) is a unique platform that permits daily 3D image verification coupled with IMRT technique. It is akin to a helical computed tomography (CT) scanner delivering radiation in a helical rotational manner using a modulated fan beam.¹²

Its advantages include online correction of set-up errors due to daily imaging and delivery of continuous radiation in cranio-caudal direction suppressing junction problems from multiple fields while treating larger complex volumes, that too with excellent dose conformity.¹³

Few series have reported outcome of patients with initially positive IMN receiving optimal systemic therapy, surgery, and loco-regional radiotherapy including IMN.^{14,15} These studies report heterogeneous use of radiotherapy dose, fractionation as well as techniques. In the current study, we intend to report the outcomes of HT for IMN irradiation in clinically positive nodes diagnosed radiologically and includes dosimetric evaluation, early toxicity as well as short-term clinical outcome.

Methods and Materials

Study design and patients

All consecutive patients with LABC who received adjuvant breast/chest wall irradiation along with SCF and IMN using HT technique at our institute between November 2014 and May 2019 were identified. Electronic medical records of 65 patients were reviewed for clinico-pathological details, and treatment history including the radiotherapy treatment planning parameters and acute toxicities. The clinical, treatment and pathological details have been reported in Tables 1, 2, and 3, respectively. The diagnosis of IMN involvement was made on the cross-sectional imaging done for staging. No cytological or histological confirmation of the IMN involvement was attempted. None of the patient received prophylactic IMN irradiation. This study was approved by the institutional ethics committee, and waiver of consent was granted.

The median age was 45 years (range 23–68). All patients treated with curative intent were included. Eight patients had oligometastatic disease: 4 had disease in the sternum out of which one patient also had ipsilateral 5th rib metastases and one also had parasternal disease. Two patients had solitary nodule in liver which were treated with radiofrequency ablation (RFA). Two patients with contra-lateral axillary metastases underwent bilateral axillary dissection.

Sixty-one patients received neo-adjuvant chemotherapy (NACT), while 4 patients underwent upfront surgery followed by chemotherapy as they were operated outside. All patients received anthracycline and taxane-based chemotherapy. Thirty-four patients had partial response and 23 patients had complete response, 2 had stable disease whereas 2 had progression (response assessed clinic-radiologically). All 36 hormone-receptor-positive patients received appropriate hormonal therapy as per institutional protocol. Nineteen of the 22 patients who were HER 2neu positive received trastuzumab in neo-adjuvant or adjuvant setting of which

Table 1. Clinical characteristics

Characteristics		n	%
Age grouping	< 45 years	30	46.2
	≥45 years	35	53.8
Menopausal status	Pre-menopausal	39	60.0
	Post-menopausal	22	33.8
	Peri-menopausal	04	06.2
Laterality	Right	37	56.9
	Left	28	43.1
Quadrant ^a	Outer	25	39.0
	Inner	24	37.5
	Central	15	23.5
cT	cT0	01	01.5
	cT1–2	13	20.0
	cT3–4	51	78.4
cN	cN3	65	100.0
cM	cM0	57	87.7
	cM1*	08	12.3
ER	Positive	35	53.8
	Negative	30	46.2
PR	Positive	27	41.5
	Negative	38	58.5
Her2neu	Positive	22	33.8
	Negative	41	63.1
	Equivocal	02	03.1
Staging investigation	CT scan	40	61.5
	PET CT scan	25	38.5

^aOne patient had occult primary.

*2 patients had contralateral axillary nodal metastases, 2 patients had solitary liver metastases and 4 patients had sternal metastases.

cT: clinical tumour stage; cN: clinical nodal stage; cM: clinical metastatic stage; ER: estrogen receptor; PR: progesterone receptor; CT: computed tomography; PET: positron emission tomography.

only 12 patients received maintenance therapy due to affordability issues.

Immobilisation and volume delineation

All patients were immobilised in supine position in a customised vacuum bag with both arms abducted over head. Planning images without contrast with 3–5 mm slice thickness were acquired from the level of mandible to mid-abdomen on CT simulator (GE DISCOVERY IQ). Images were exported to the tomotherapy treatment planning system (Accuray Inc., Sunnyvale, CA, version 5.1.0). Clinical reference using wire placement on patient's body during CT acquisition aided in the delineation of clinical target volume (CTV) for the breast and/or chest wall. The target volumes were contoured according to the ESTRO guidelines.¹⁶ In all patients, primary (breast/chest wall) and regional nodes comprising of SCF and IMC were included in the radiotherapy targets, while sternum was included in four patients with sternal

Table 2. Treatment characteristics

Characteristics		n	%
Neo-adjuvant hormonal therapy	Yes	04	06.2
	No	61	93.8
Neo-adjuvant chemotherapy	Yes	61	93.8
	No	04	06.2
Type of surgery*	BCS	17	26.2
	MRM	47	72.3
Adjuvant chemotherapy	Yes	47	72.3
	No	18	27.7
Adjuvant hormonal therapy	TAM	20	30.8
	AI	12	18.5
	AI + ovarian ablation	02	03.1
	TAM + OS	02	03.1
	Not indicated	29	44.6
Trastuzumab in adjuvant or neoadjuvant setting	Received	19	29.2
	Not received	03	04.6
	Not indicated	43	66.2
Maintenance Trastuzumab	Received	12	18.5
	Not received	10	15.4
	Not indicated	43	66.2

*One patient had occult primary hence did not undergo primary surgery.

BCS: breast conserving surgery; MRM: modified radical mastectomy; AI: aromatase inhibitor; TAM: Tamoxifen; OS: Ovarian suppression.

metastases. Axilla was not irradiated as full axillary clearance was performed in all patients as per institutional protocol.

A uniform 5 mm margin to the CTV was given for generating the planning target volume (PTV) for the primary as well as nodes and tumour bed (TB). The PTV primary was cropped from the skin by 5 mm. The CTV was restricted to the pectoral muscles posteriorly but included only in T4 disease especially post mastectomy. For IMN, one intercostal space below the involved space was included in the target volume. Additional targets like the sternum was treated in 4 patients, whereas 2 patients had bilateral IMN irradiation. Departmental guidelines for TB delineation were followed taking into account the seroma, base clips, post-operative changes and wired surgical scar. Thoracic OARs: individual lung, total lung, heart, left anterior descending artery (LAD), contra-lateral(C/L) breast, oesophagus, spinal cord and thyroid were contoured. Brachial plexus dosimetry was not included as none of the patients had axillary radiation and also dose prescribed was below the tolerance limit of brachial plexus.

Helical tomotherapy planning

A jaw width of 5.02 cm was used for planning with pitch of 0.287 and maximum modulation factor used was 3. The dose prescribed to the primary and nodal targets was 50 Gy in 25 fractions, and all cases of breast conserving surgery (BCS) received a SIB to the PTV_Boost. SIB was given in 16 patients out of which 12 received 61 Gy and 4 received 58 Gy and one received sequential boost. One

Table 3. Pathological characteristics

Characteristics	n	%	
Grade	III	65	100.0
Histology	IBC	63	96.9
	Mucinous	01	01.5
Extranodal extension	Others	01	01.5
	Present	22	33.8
Ductal carcinoma in situ	Absent	41	63.1
	Unknown	02	03.1
Lymphovascular invasion	Present	21	32.3
	Absent	43	66.2
	Not known	01	01.5
Perineural invasion	Present	16	24.6
	Absent	48	73.8
	Not known	01	01.5
Skin	Present	04	06.2
	Absent	60	92.3
	Not known	01	01.5
	Free	54	83.1
Nipple-alveolar complex	Epidermis	04	06.2
	Dermis	03	04.6
	Not known	04	06.1
	Free	62	95.4
Extensive intraductal component	Involved	02	03.1
	Not known	01	01.5
	Present	03	04.6
Margin status	Absent	61	93.8
	Not known	01	01.5
	Close	06	09.2
pT	Negative	58	89.2
	Not reported	01	01.5
	pTx	01	01.5
	pTis	02	03.1
pN	pT0	21	32.3
	pT1–2	28	43.1
	pT3–4	13	20.0
	pN0–1	42	64.6
	pN2–3	23	35.4

IBC: invasive breast carcinoma; Tis: tumour insitu; pT: Pathological tumour stage; pN: pathological nodal stage.

patient with occult primary did not receive boost. The planning objectives were defined to achieve coverage of 95% of the target volume with 95% of the prescribed dose (it was difficult to achieve 98% dose coverage). However, in cases with unfavourable anatomy, a coverage up to 90% was considered acceptable (Figure 1). Target objectives were chosen according to priority – PTV IMN followed



Figure 1. Coverage of <95% of target volume.

by PTV SCF then PTV CW/BR. For OARs, the planning objectives were set as V20 Gy < 35% for total lung, whereas V25 Gy < 10% for heart as per QUANTEC guidelines.¹⁷ OARs according to priority were set LAD > Heart high dose (high dose region defined as area within 2.5 margin from PTV; whereas low dose is area obtained after subtracting OAR from high dose region) > Lung HD > C/L Breast > Heart LD > Lung LD > C/L Lung > Oesophagus > Spine > Body.

Standard criteria for target volumes (volumes receiving 95, 90 and 107%, mean dose) and OARs (mean, maximum, volume receiving 5 Gy (V5 Gy), V10 Gy, V20 Gy, V30 Gy, V40 Gy) were used for reporting the dose volume parameters (Tables 4 and 5).

Statistical analysis

The patient, treatment and pathological characteristics have been reported as numbers and percentage. The dosimetric characteristics have been reported as mean value with range. Actuarial survival curves were generated by Kaplan–Meier method and compared using log – rank test for univariate analysis. Disease-free survival (DFS) was measured as the time between initial treatment (date of surgery) and first evidence of disease progression. Overall survival (OS) was calculated from the date of initial treatment to date of death from any cause or last follow-up. Disease recurrence in the ipsilateral breast/chest wall was defined as local recurrences and those in ipsilateral axillary, supraclavicular, or IMN were defined as regional recurrences. Multivariate analysis was done by Cox proportional–hazards model and it included factors significant (p -value < 0.05) on univariate analysis. The analysis was done in Statistical Package for Social Sciences (SPSS) version 22.

Results

Dosimetric results

Tables 4 and 5 summarise the dosimetric parameters achieved for the target volumes and OARs. The 95% PTV coverage for the primary, SCF, IMN and tumour bed was 93.47, 96.85, 90.72 and 98.39%, respectively. The inconsistent dose/volume parameters may be due to being a retrospective analysis. The mean dose to the total lung, heart and contra-lateral breast was 10.6 (7.8–13.7) Gy, 6.92 (2.34–14.89) Gy and 4.32 (2.04–10.67) Gy, respectively. The mean dose maximum to the LAD was 21.5 (2.91–52.60) Gy. The dosimetric results in relation to the type of surgery and

Table 4. Dosimetric parameters indicative of planning target volume (PTV) coverage

PTV_Primary	Volume (cc)	771.3 (229.2–1453.4)
	Mean (Gy)	50.2 (47.6–53.3)
	Min (Gy)	50.2 (17.5–87.7)
	Max (Gy)	80.7 (52.5–55.7)
	V95%	93.4 (79.1–97.4)
	V90%	97.6 (91.2–99.5)
	V107 (cc)	03.1 (0.0–83.8)
	D2 (Gy)	53.7 (51.0–63.4)
	D98 (Gy)	45.5 (34.6–51.8)
PTV_TB	Volume (cc)	79.1 (53.3–170.9)
	Mean (Gy)	60.8 (56.8–63.2)
	Min (Gy)	78.7 (49.6–93.7)
	Max (Gy)	93.3 (60.1–112.5)
	V95%	98.3 (94.7–99.7)
	V90%	99.7 (98.3–100.0)
	V107 (cc)	08.8 (0.0–20.8)
	D2 (Gy)	66.2 (59.4–76.9)
	D98 (Gy)	57.2 (43.3–66.8)
PTV_SCF	Volume (cc)	78.4 (47.0–253.1)
	Mean (Gy)	49.5 (46.0–52.1)
	Min (Gy)	63.8 (31.6–96.3)
	Max (Gy)	78.4 (51.4–108.8)
	V95%	96.8 (90.1–99.9)
	V90%	99.2 (96.3–100.0)
	V107 (cc)	00.2 (0.0–5.7)
	D2 (Gy)	52.1 (50.2–54.0)
	D98 (Gy)	48.0 (44.2–50.6)
PTV_IMN	Volume (cc)	42.6 (3.1–92.2)
	Mean (Gy)	49.1 (43.2–52.1)
	Min (Gy)	55.6 (28.2–90.1)
	Max (Gy)	78.8 (50.1–109.4)
	V95%	90.7 (74.9–99.9)
	V90%	97.0 (89.0–100.0)
	V107 (cc)	00.8 (0.0–26.0)
	D2 (Gy)	52.0 (48.1–55.0)
	D98 (Gy)	45.7 (36.4–50.0)

TB: tumour bed; SCF: supraclavicular fossa; IMN: internal mammary node.

inclusion of sternum in the target volumes have been provided in the Supplementary Tables 1–4.

Acute toxicities

Radiation Therapy Oncology Group (RTOG) grading criteria was used to assess toxicity. No patient developed grade III skin or oesophageal toxicity. Forty-seven patients had grade I and 18 patients

Table 5. Dose and volume parameters for organs at risk

Parameter	B/L tot lung	Heart	C/L breast	LAD
Mean dose (Range)	10.6 (7.8–13.7) Gy	6.92 (2.3–14.8) Gy	4.3 (2.0–10.6) Gy	21.5 (2.9–52.6) Gy*
V5 Gy (Range)	56.4 (41.9–84.0) %	47.1 (16.5–91.0) %	46.4 (2.1–88.0) %	57.6 (3.0–100.0) %
V10 Gy (Range)	33.5 (18.6–60.1) %	23.9 (1.5–65.4) %	16.7 (0.0–39.5) %	30.2 (0.0–100.0) %
V20 Gy (Range)	17.7 (7.9–30.5) %	9.3 (0.0–28.6) %	3.5 (0.0–10.9) %	16.1 (0.0–81.3) %
V30 Gy (Range)	11.4 (4.2–20.2) %	4.0 (0.0–18.7) %	0.8 (0.0–3.5) %	7.5 (0.0–46.7) %
V40 Gy (Range)	6.5 (1.5–16.5) %	1.3 (0.0–9.5) %	0.2 (0.0–1.6) %	2.3 (0.0–34.3) %

*Dose maximum (not mean dose).

C/L: contralateral, LAD: left anterior descending artery.

had grade II skin toxicity, whereas 39 patients had grade I and 4 patients had grade II oesophageal toxicity.

Disease-related outcome

The median follow-up for the study cohort was 36 months (95% CI 34–42.8). Twenty-one patients had progression out of which 18 patients had distant metastasis alone, while 3 also had locoregional recurrence. The sites of progression were multiple with brain, liver metastasis being common sites. Ten patients died of disease progression.

LRC, DFS and OS

The median survival times for DFS and OS have not been reached. The 3-year loco-regional control, DFS, and OS were 93.5% (95% CI 86.1–100.0), 73.9% (95% CI 62.9–84.9) and 85.9% (95% CI 76.9–95.0), respectively (Figures 2, 3 and 4). On univariate analysis, age, menopausal status, laterality, hormone receptor status, Her2 status, presence of oligo-metastatic disease, response to NACT, type of surgery and pathological nodal status were analysed to see the impact on the DFS. Of these, absence of oligometastatic disease at presentation and significant response to chemotherapy were associated with improved outcome. The 3-year DFS for patients with oligometastatic disease was 34% (95% CI 7–60.7) versus 74% (61.1–86.9) for non-metastatic patients (p 0.003). With regard to OS, only response to chemotherapy predicted survival on univariate analysis.

Discussion

It is seen that IMN metastases occur in 28–52% of patients having positive ALN and in 5–17% of patients without ALN.^{18,19} The authors have not come across any series reporting on a homogenous cohort of patients who underwent IMN irradiation with single fractionation schedule and uniformly treated on HT. Albeit a small series, we report our initial clinical experience of IMN irradiation on HT.

IMN irradiation invariably leads to increased cardiac and pulmonary irradiation thereby increasing the risk of developing late effects.^{20–22}

In our study, mean dose received by the heart was 6.92 (2.34–14.89) Gy. In the 37 right-sided patients, Dmean of heart was 4.68 (2.34–7.70) Gy. Totally, 28 patients had left-sided cancers, Dmean was 9.89 (5.29–14.89) Gy while concomitant boost was delivered in 16 patients to a dose of 58–61 Gy of which 8 were left sided, Dmean for heart in these patients was 10.37 Gy.

Median Follow up time =35.8 (95% C.I. 34 -42.8)months

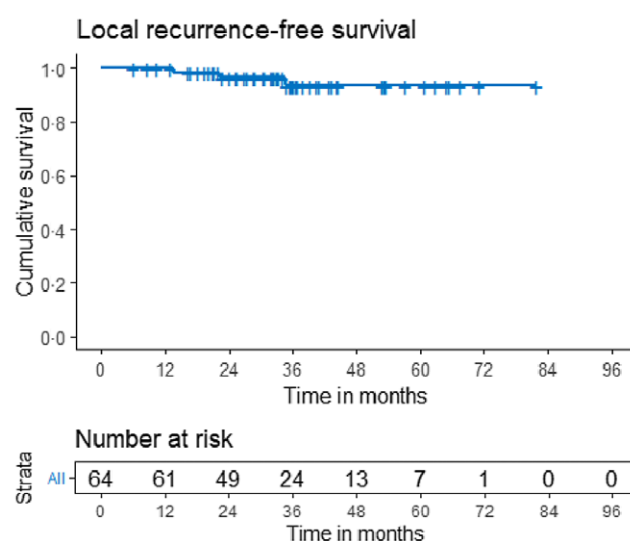


Figure 2. Kaplan–Meier curves for loco-regional control.

Dosimetric comparison of 3–4 field technique IMRT with HT by Caudrelier et al. in stage III left-sided breast cancer reported cardiac sparing potential of HT in terms of significant reduction of V30 Gy but not with respect to Dmean.²³ Initial dosimetric experience with HT reported by Goddu et al. reported a decrease in mean V35 Gy but also an increase in heart Dmean compared to 3D conformal radiotherapy (CRT).²⁴

The incidence of radiation pneumonitis has been associated with volume of the lung receiving low dose spill. A cut-off of 42% has been reported by Wang et al.²⁵ Therefore, planner has to achieve reasonable dosimetric goals by maximum reduction of lung V20 Gy, V5 Gy, and mean lung dose. Practically, it is difficult to achieve the stringent cut-off of V5 Gy as observed in the current series as well as by Goddu et al.²⁴ In our study, mean V5 Gy of the I/L lung was 81.83% (50.30–99.34) and of C/L lung was 41.31% (11.80–71.14).

However, the follow-up period of the study is less to comment on whether the dose achieved for heart and lung has any effect on late cardiac and pulmonary toxicity.

While for acute toxicity, due to nil acute grade III events, dosimetric comparison has not been possible.

Matching of the field junctions is a challenging task while delivering IMN irradiation. Traditional junctional solutions

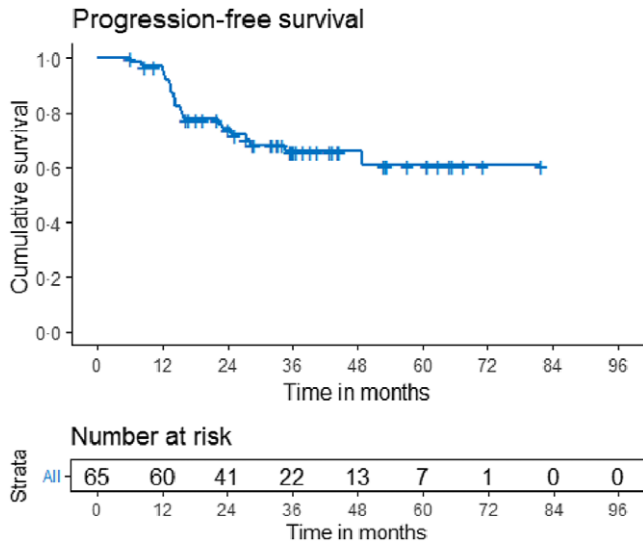


Figure 3. Kaplan–Meier curves for disease free survival.

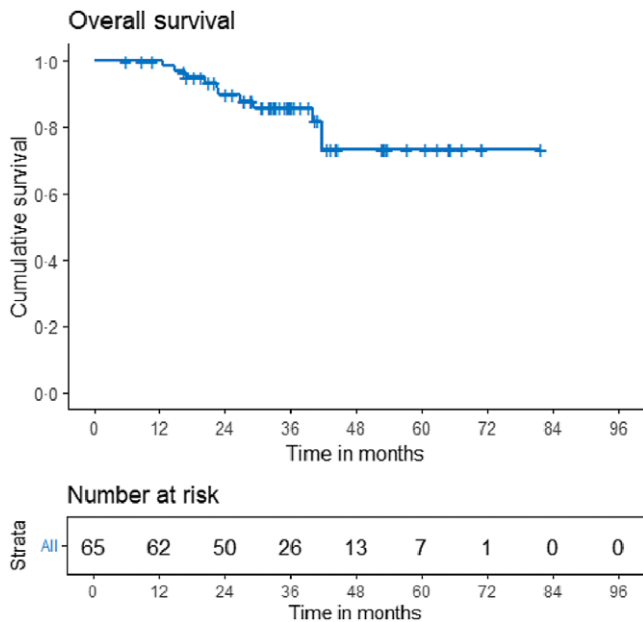


Figure 4. Kaplan–Meier curves for overall survival.

(asymmetric jaws and photon-electron combination) make patient's set-up complex and time-consuming.²⁶ Moreover, dose homogeneity is very difficult to achieve resulting in either hot/cold spots within the target volumes. Most of these challenges are circumvented by HT that delivers radiation without any issue of field junctions. Moreover, daily image guidance provides the opportunity of correction of daily set up errors.

A dosimetric study including 13 patients (eight left sided) evaluated the feasibility of SIB comparing 3DCRT with HT.²⁷ Dose prescribed was 50.68 Gy and 64.4 Gy in 28 fractions. With comparable coverage, conformity was better with HT with significantly less spillage outside the tumour bed (V107 = 12.47 versus 30.83%). It is important to control spillage as high doses

to adjacent breast lead to increase in fibrosis and poor cosmetic outcome.²⁸ In our study, 16 patients received SIB to a dose of 58–61 Gy/25F, in whom the mean of V107 = 8.88% (0.00–20.89).

The largest series by Kyubo Kim et al of patients with baseline supraclavicular and/or IMN, treated with conventional radiation to a median dose of 50.4 Gy, reported 5-year DFS and OS of 57.8 and 75.1%, respectively.¹⁵ Similarly in a recent study by Kim et al. in patients with clinically positive IMN, treated by NACT followed by surgery and radiation, the 5-year DFS and OS was 68.6 and 81.8%, respectively.²⁹ In our study, the 5-year DFS and OS were 51.8 and 68%, respectively. The relatively inferior outcome is probably related to the differences in patient profile as the current study included oligo-metastatic patients as well as infrequent use of targeted therapy. The authors have reported multiple adverse prognostic factors predicting outcome which include initial clinical T stage, histologic grade 3, triple-negative (TNBC) subtype, response to NACT, lymphovascular invasion, involvement of both SCL and IMN, ≥ 4 ALN, Ki67 > 10%. In the current study, response to NACT was predicted for both DFS and OS, while oligometastatic presentation impacted only DFS.

Conclusion

This is a study for analysing efficacy of HT for radiating IMN, and it shows similar encouraging results compared to already published literature. It is tolerated well and results in minimal toxicity. However, the sample size is small, and follow-up is relatively short. The predominant pattern of failure was distant metastases that suggests need for intensification of systemic control especially in the non-responders. Patients having oligo-metastatic disease have a worse outcome.

Supplementary Material. To view supplementary material for this article, please visit <https://doi.org/10.1017/S1460396921000625>

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Conflicts of Interest. None.

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