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ORIGINAL ARTICLE

Intensity modulated radiotherapy and 3D conformal radiotherapy for whole breast irradiation: a comparative dosimetric study and introduction of a novel qualitative index for plan evaluation, the normal tissue index

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Abstract

Introduction: We report on a retrospective dosimetric study, comparing 3D conformal radiotherapy (3DCRT) and hybrid intensity modulated radiotherapy (hIMRT). We evaluated plans based on their planning target volume coverage, dose homogeneity, dose to organs at risk (OARs) and exposure of normal tissue to radiation. The Homogeneity Index (HI) was used to assess the dose homogeneity in the target region, and we describe a new index, the normal tissue index (NTI), to assess the dose in the normal tissue inside the tangent treatment portal. **Methods:** Plans were generated for 25 early-stage breast cancer patients, using a hIMRT technique. These were compared with the 3DCRT plans of the treatment previously received by the patients. Plan quality was evaluated using the HI, NTI and dose to OARs. **Results:** The hIMRT technique was significantly more homogenous than the 3DCRT technique, while maintaining target coverage. The hIMRT technique was also superior at minimising the amount of tissue receiving $D_{105\%}$ and above ($P < 0.0001$). The ipsilateral lung and contralateral breast maximum were significantly lower in the hIMRT plans ($P < 0.05$ and $P < 0.005$), but the 3DCRT technique achieved a lower mean heart dose in left-sided breast cancer patients ($P < 0.05$). **Conclusion:** Hybrid intensity modulated radiotherapy plans achieved improved dose homogeneity compared to the 3DCRT plans and superior outcome with regard to dose to normal tissues. We propose that the addition of both HI and NTI in evaluating the quality of intensity modulated radiotherapy (IMRT) breast plans provides clinically relevant comparators which more accurately reflect the new paradigm of treatment goals and outcomes in the era of breast IMRT.

Introduction

Breast cancer is the most common cancer in women in developed countries, and the most common cause of cancer death worldwide.[1,2] It is well established that breast conservation with lumpectomy and adjuvant radiation treatment has equivalent oncological outcomes to mastectomy.[3] Advances in surgery and systemic treatment have translated to improved survival. Consequently, survivorship issues following radiotherapy including treatment toxicity and cosmetic outcomes have become increasingly pertinent.

Standard tangential beams, using 3D conformal radiation therapy (3DCRT), can achieve acceptable oncological outcomes, but the anatomy of the chest wall frequently results in in-homogenous dose distributions. Moreover, underlying lungs and, in the case of left-sided cancers, the heart, are at risk of radiation exposure and toxicity. Darby et al. reported that the risk of a major coronary event increased linearly with the mean dose to

the heart.[4] Intensity modulated radiation therapy (IMRT) can provide improved dose coverage and homogeneity, and minimise the cardiac, lung and contralateral breast dose in comparison to 3DCRT.[5] Freedman et al. reported a reduction in acute skin reactions with IMRT, which is hypothesised to translate to an improved long-term cosmetic outcome.[6] McDonald et al. reported on 7 year outcomes of patients treated with IMRT, and found reduced tumour recurrence rates.[7]

At the Northern Sydney Cancer Centre, adjuvant breast radiotherapy has been delivered using 3DCRT. Previously, we have compared the dosimetric parameters for 3DCRT to various IMRT techniques.[8] We have also compared dosimetric parameters for 3DCRT, IMRT and static tomotherapy for a left breast SIB technique.[9] In the first study, IMRT was used for 100% of the treatment. The second study consisted of a hybrid IMRT plan where IMRT tangents were used for 80% of treatment with open field tangents used for the remaining 20%.

While it has been shown that IMRT can improve dose homogeneity, concerns have been raised regarding the volume of normal tissue irradiated using IMRT. Hall et al. have postulated an increased risk of second malignancy from 1% to 1.75%.[10] To minimise the risk of normal tissue toxicity, including both stochastic and deterministic events, it is important to assess the volume of normal tissue irradiated, and the degree and volume of hot spots. Hot spots are defined by ICRU50 as a volume outside the planning target volume (PTV) which receives dose larger than 100% of the specified PTV dose and are generally considered significant if the minimum diameter exceeds 15 mm. Optimal plans have minimal hot spots, and meet the dose constraints that have been stipulated for the associated organs at risk (OAR). Our department OAR dose constraints, (Appendix), are based on QUANTEC data[11] and peer reviewed protocols. They include both optimal dose constraints and minor violations. Plans with minor violations are subject to clinical judgment.

Adjuvant breast irradiation presents unique challenges in minimising hot spots in the radiation portal. The anatomy of the breast and chest wall mandates the use of medial and lateral tangential fields, which inevitably results in hot spots in the tissue adjacent to the breast PTV. The goal, therefore, is to improve dose homogeneity throughout the PTV and reduce the hot spots in normal tissue, acknowledging that achieving normal tissue doses less than 100%, as per ICRU guidelines, is not a realistic aim. Mayo et al. acknowledged this, and compared the volume receiving greater than 100% and also the volume greater than 110%.[12]

We aimed to develop a clinically relevant, objective means to compare IMRT plans. We therefore developed a new index, the normal tissue index (NTI) to allow a quantitative comparison of the normal tissue inside the boundaries of the tangent treatment portal that is exposed to radiation using IMRT and 3DCRT.

The Homogeneity Index (HI) has previously been described by Yoon et al., and used to evaluate the quality of IMRT plans.[13] The HI is an objective tool to analyse the uniformity of dose distribution in the target volume.

The aim of this study was to compare the plan quality between 3DCRT and hybrid IMRT, consisting of 50% IMRT and 50% 3DCRT. We investigate the use of plan quality indices to assess the dose homogeneity in the target volume as well as the normal breast tissue inside the treatment portal. The HI was used to assess the dose homogeneity in the target region, and a new index, (NTI) was used to assess the dose in the normal tissue inside the tangent treatment portal.

Method and Materials

A site specific assessment (AU/7/B2E4112), and a low and negligible risk study (AU/6/A2E418) ethics application were both approved by the Human Research Ethics Committee of Northern Sydney Central Coast Health.

Patient selection criteria and sample size

A sample of 25 early stage breast cancer patients (T1–T2, N0–N1, M0–M1), sequentially selected from 2011 to mid 2013, were included for this study (Table 1).

Of the patients, 13 had left-sided tumours and 12 right-sided tumours. Sixteen patients were T1 and 9 were T2. Only 1 patient had nodal involvement. The mean age was 58.6 years. Median PTV breast volume was 655.37 cm^3 (range: 172.67–1841.54) and median separation was 21.84 cm (range: 17.06–26.50).

Planning

As this was a retrospective planning comparison study, the 3DCRT plans consisted of the treatment previously received by the patients. Plans were generated using the Varian Eclipse treatment planning system (v10.0.28; Varian Medical Systems, Palo Alto, CA). The hybrid IMRT plans were generated using Varian Eclipse 11.0.42, Algorithm = AAA_11030, Calculation grid size = 0.25 cm, delivered on Varian Trilogy silhouette linac, MLCs = 0.5 and 1 cm. All plans were developed to treat the breast to 50 Gy.

The 3DCRT plan utilised opposing medial and lateral rectangular beams with wedges. Additional medial or lateral beams were used in some circumstances to allow

Table 1. Patient characteristics.

Age	Laterality	T stage	N stage	PTV (cm^3)	Separation (cm)
52	Left T1c	T1c	N0	772	25
66	Left	T1c	N0	629	24
45	Left	T2	N0	588	23
70	Right	T1	N0	412	20
76	Right	T1	N0	342	19
63	Left	T2	N0	805	22
57	Right	T2	N0	726	23
48	Right	T1	N0	354	19
53	Left	T2	N0	1038	22
40	Left	T1	N1	518	23
56	Left	T1	N0	655	19
76	Right	T1	N0	703	23
48	Right	T1	N0	173	18
65	Right	T1	N0	396	22
54	Right	T1	N0	217	24
38	Left	T2	N0	912	17
64	Right	T1	N0	1036	25
63	Left	T1	N0	917	30
69	Left	T2	N0	460	18
56	Left	T1	N0	475	20
82	Right	T2	N0	880	21
62	Right	T2	N0	694	21
65	Right	T1	N0	848	24
40	Left	T1	N0	319	17
56	Left	T2	N0	1842	27

PTV, planning target volume.

for improved dosimetry by incorporating a mix of 6 MV and 18 MV. MLCs were designed to shield out OARs.

We used a hybrid IMRT technique, using 50% 3DCRT and 50% IMRT. The hybrid IMRT plan consisted of up to six opposing tangential fields; two to four open beams and two inversely optimised IMRT beams. All fields were half beam blocked at the lung. Only the 6- and 18-MV fields were used in the conformal component of the technique when deemed necessary by the planning radiation therapist, and only the 6-MV beams were used for the IMRT component.

Contouring

The PTV volumes that had been previously delineated on the 3DCRT plans by a radiation oncologist (RO) were used for the hybrid IMRT plans. The delineation of the breast tissue was guided by the clinical mark up, and using standard anatomical boundaries. The PTV Breast Eval structure is a modification of the PTV contour that excludes the pectoralis major and the skin surface, 5 mm deep from the body contour. We consider this volume to be a better surrogate than the PTV Breast for the evaluation of dose to the breast alone. (See Fig. 1).

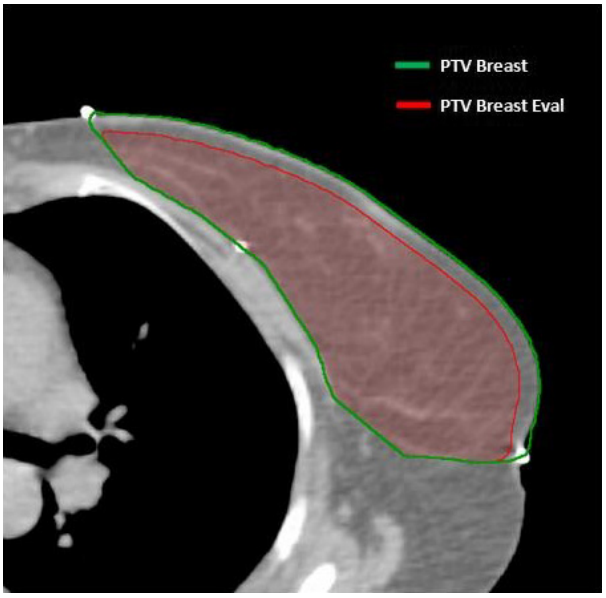

Figure 1. Planning target volume breast eval structure.

A planning volume, the IMRT PTV, was generated to facilitate the optimisation process. The IMRT PTV was created by converting the 50% isodose line from the open field plan into a structure. The IMRT PTV was then cropped 0.2 cm from the body and 0.3 cm from the posterior field edge. All OARs reported in this paper were contoured by the planning radiation therapist.

The normal tissue contour was created for the NTI analysis. This volume was created by subtracting the PTV Breast Eval from the 50% isodose structure. (See Fig. 2).

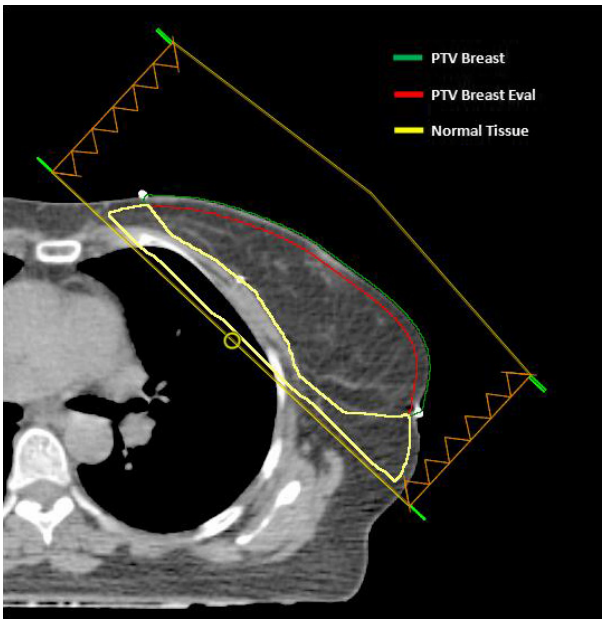

Figure 2. Normal tissue structure.

Data collection and analysis

From the normal tissue structure (NTS), the NTI was collected.

Development of the NTI

Initial comparison of plans using the volume of normal tissue receiving 110% of the dose, the value used by Mayo et al., was not useful as most plans did not have hot spots of 110%. As would be expected, using this as the comparator was not clinically significant. V107, was then chosen, as an extrapolation from ICRU50 evaluation of PTV coverage. A number of plans had hot spots of 107%, and comparison of plans on this basis did reach significance ($P = 0.002$). We subsequently compared plans based on the normal tissue volume receiving 105% of the dose, 103% of the dose and 100% to identify the most sensitive comparator. Of these results, use of V105 was the most significant ($P < 0.0001$), compared to V100 ($P = 0.037$), and V103 ($P = 0.001$). Based on this, we propose that the volume of normal tissue receiving 105% provides the most meaningful and clinically useful discriminator between the plans.

Therefore, the NTI is used to assess the percentage of normal tissue receiving a dose of 105% and above of the prescribed dose. NTI is calculated as the volume of normal tissue encompassed by 105% divided by the volume of normal tissue in the radiation portal (eq. 1). Using a percentage enables a more standardised comparison, independent of the patient's size, which is important for the breast patient cohort.

$$\mathrm{NTI} = \frac{V_{105\%}}{V_{\mathrm{NT}}}, \tag{1}$$

where, $V_{105\%}$, volume receiving 105%; V_{NT}, volume of normal tissue as defined by the Normal Tissue Structure (NTS) contour.

From the PTV Breast Eval structure, a HI was collected.

$$\mathrm{HI} = \left(\frac{D_{2\%} - D_{98\%}}{D_{\mathrm{P}}}\right) \times 100\%, \tag{2}$$

where, $D_{2\%}$, the dose received by 2% of the target volume; $D_{98\%}$, the dose received by 98% of the target volume; D_{P}, prescription dose.

ICRU83 recommends $D_{98\%}$ to cover 95% of the PTV for IMRT plans and ICRU50 recommends $D_{95\%}$ to cover 95% of the PTV for 3DCRT plans. As this study attempts to compare 3DCRT and IMRT plans, both $D_{98\%}/D_{2\%}$ and $D_{95\%}/D_{5\%}$ dosimetric data points were collected.

Maximum doses to OARs were collected as 2 cm^3. Mean doses to OARs were also collected.

Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS, Sydney, NSW, Australia) statistics version 22 was used for statistical analysis. The Wilcoxon-Signed ranks test was used for comparison and statistical significance was determined at $P < 0.05$.

Results

The IMRT plans and 3DCRT plans were compared using the HI and the NTI as defined above. The maximum dose and mean dose were used to compare the dose received by OAR.

Quality of PTV coverage – HI and NTI

The IMRT technique is significantly more homogenous than the 3DCRT technique at both $D_{98\%}/D_{2\%}$ ($P = 0.001$) and $D_{95\%}/D_{5\%}$ ($P < 0.0001$). The IMRT technique was also significantly better at minimising the amount of tissue receiving $D_{105\%}$ and above ($P < 0.0001$) (Table 2).

Dose to the OARs

The ipsilateral lung and contralateral breast maximum dose (Table 3) in the hybrid intensity modulated radiotherapy (hIMRT) plan was significantly lower ($P < 0.05$ and $P < 0.005$) than the 3DCRT plan. However, the clinical significance of this is not clear.

There was also a statistically significant difference seen in the mean dose received by the contralateral breast (Table 4), with hIMRT delivering less dose than 3DCRT ($P < 0.05$).

Table 2. Quality of PTV coverage – HI and NTI.

Parameter	3DCRT	IMRT	*P*
NTI			
Median	0.011	0.000	<0.0001
Range	0.000–0.065	0.000–0.009	
HI (D98/D2)			
Median	0.111	0.095	0.001
Range	0.014–0.341	0.079–0.130	
HI (D95/D5)			
Median	0.087	0.072	<0.0001
Range	0.075–0.124	0.054–0.091	

PTV, planning target volume; HI, homogeneity index; NTI, normal tissue index; 3DCRT, 3D conformal radiation treatment; IMRT, intensity modulated radiotherapy.

Table 3. Organs at risk maximum dose.

	3DCRT (cGy)	IMRT (cGy)	*P*
Ipsilateral lung			
Median	4672	4659	0.021
Range	3878–4979	3934–4953	
Contralateral breast			
Median	192	153	0.004
Range	5–307	5–254	
Heart (left-sided)			
Median	3719	4169	0.152
Range	361–4742	335–4615	
Heart (right-sided)			
Median	182	171	0.875
Range	88–225	112–208	
Contralateral lung			
Median	45	45	0.53
Range	1–121	1–116	

OAR, organs at risk; 3DRT, 3D conformal radiation treatment; IMRT, intensity modulated radiation treatment.

Table 4. Organs at risk mean dose.

	3DCRT mean (cGy)	IMRT mean (cGy)	*P*
Ipsilateral lung			
Median	627	594	0.493
Range	5–820	6–858	
Contralateral breast			
Median	20	20	0.033
Range	0–80	0–67	
Heart (left-sided)			
Median	184	215	0.011
Range	6–333	7–334	
Heart (right-sided)			
Median	29	28	0.388
Range	14–42	17–37	
Contralateral lung			
Median	4	4	0.651
Range	0–10	0–10	

OAR, organs at risk; 3DRT, 3D conformal radiation treatment; IMRT, intensity modulated radiation treatment.

The 3DCRT technique was able to significantly restrict the mean dose received by the heart in left-sided breast cancer patients compared with the hIMRT technique, ($P < 0.05$), (Table 4).

Discussion

We demonstrated a significant improvement in homogeneity in the hIMRT plans, compared to the 3DCRT plans, with minimal compromise on other dosimetric parameters. IMRT is reported to effectively reduce acute skin reactions, which is attributed to the more homogenous dose distribution,[14] and improve overall cosmesis. Homogeneity has been demonstrated to be a reliable surrogate marker for long-term outcomes, particularly fibrosis and cosmesis.[15] Moreover, the IMRT plans showed superior outcomes with regard to the irradiation of normal tissue.

A number of studies have assessed the quality of IMRT plans based on the dosimetric homogeneity and the dose of radiation received by normal tissues. Schubert et al.[16] performed a dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy and topotherapy. They found the most significant difference between treatment techniques involved the low- and high-dose irradiation of normal tissue. Of note, they reported that with regard to homogeneity the patient with the largest PTV volume had larger improvements in the IMRT plan compared to the 3DCRT plan. They postulated that the difference in homogeneity would be accentuated in a patient population with larger breast sizes. Nine of the 10 patients in their study population had PTV volumes less than 1000 cm^3. Donovan et al. evaluated methods of IMRT planning, and found improvements in dose uniformity in patients with breast PTVs greater than 500 cm^3.[17] Harsolia et al. stipulated a 'large breast' to be greater than or equal to 1600 cm^3,[3,18] and Dundas et al. defined it as cup size ≥D or a bra size ≥18.[19] In our patient population, the median PTV breast volume was 655.37 cm^3 (range: 172.67–1841.54). Over half of our patients (8) had a PTV less than 500 cm^3, and only one patient had a PTV greater than 1600. According to the definitions cited in the literature, our population would be predominantly 'average' breasted.

We demonstrated an improvement in homogeneity through the use of hIMRT, this improvement may be more appreciable in patients with larger breast volumes; however, it remains significant in our 'average' breasted population. While large breasted patients may have a more appreciable improvement in dose homogeneity, they may also have greater potential for unpredictable hot spots due to the fall of the tissue. Hence, we suggest that while hIMRT is the preferred technique for the majority of our patients, at the extremes of the spectrum of breast sizes, there may not be a demonstrable benefit in using IMRT compared to 3DCRT.

We have found a wide heterogeneity in clinical factors affecting the dosimetry of different techniques, and the variations in clinical definitions for these factors, as well as the heterogeneity in the measures used to evaluate the quality of plans. It highlights the need for consistent reporting and standardised means of both clinical and dosimetric evaluation.

There are a range of dosimetric parameters reported in the literature. As outlined earlier, the increasing application of IMRT has necessitated consideration of normal tissue irradiation. This has been evaluated in a number of studies. Beckman et al. looked at the dose received by the Healthy Tissue Volume (HTV = CTV set − PTV),[20] Stelzer et al. reported on maximum body dose and the volume of the body receiving >50 Gy and 55 Gy,[21] and Mayo et al. assessed the volume of tissue outside the breast receiving >100% and >110% of the prescribed dose.[12] There is an awareness and acknowledgement that this is an important factor to incorporate in plan evaluation. However, there is yet to be established a standard convention in reporting it.

The NTI represents an objective means to compare the quality of plans, based on the volume of normal tissues receiving >105% of dose. IMRT plans produced a significantly lower NTI compared with the 3DCRT plans. As demonstrated, the major benefits to be derived from breast IMRT are in the improved dosimetric homogeneity and minimisation of toxicity to normal tissue. Therefore, using both the HI and NTI presents a new means to evaluate plans.

We propose that this NTI represents the most clinically relevant tool to evaluate a breast IMRT plan, and is reflective of the changing paradigm in breast irradiation. As treatment techniques have evolved and become more refined, treatment goals have also changed. Traditional measures of plan quality, such as hot spots receiving greater than 110%, are no longer as clinically relevant using IMRT. This is evident not only in our results, but is supported in the literature. Vicini et al. reported on 281 patients receiving IMRT, and found the median breast volume receiving 115% of the prescribed breast dose was 0%, as was the median breast volume receiving 110% of the prescribed breast dose.[22] Therefore, more sensitive comparators than V115 and V110 are required and we recommend the use of the V105 as the most meaningful parameter.

For all techniques, it is important to have a means of evaluation that is objective, meaningful, clinically relevant and consistent. In particular, IMRT presents unique challenges, as it comprises different forms, such as forward-planned, inverse-planned and different-weighted hybrid plans. Therefore, we propose implementation of the NTI as a new standard by which to compare the quality of breast plans. As an index, rather than an absolute value, it accounts for clinical heterogeneity and allows a wider application.

Our study has demonstrated that for some patients 3DCRT remains an acceptable treatment option. In fact, in the case of left-sided tumours, the 3DCRT technique resulted in less cardiac dose than hIMRT. In 84% of patients, although, IMRT offered a superior plan compared to 3DCRT. Hence, while our results are promising, it is important to identify patients who are best suited to IMRT. It has been postulated that patients with left-ssided breast cancers, pectus excavatum or large sized breasts may have the most to gain from IMRT.[23] With greater expansion of IMRT use, future investigations lie in the definition of sub-populations best suited to IMRT.

Finally, efficient and accessible treatment planning and delivery is an important goal. IMRT planning requires experienced staff and, depending on the IMRT technique used, can require more time and resources than standard 3DCRT. However, with optimised semi-automated planning processes, as well as no use of dynamic wedges and little collimator spin, IMRT represents a potentially more efficient and effective use of resources. Farace reported their experience in planning large numbers of patients with IMRT and found little impact on human and departmental resources.[24]

Conclusion

In the majority of our patients, in comparison to 3DCRT, hIMRT plans provided improved dose homogeneity, with minimal difference in dose to OARs and a better quality plan based on the NTI. While hIMRT was superior in most cases, 3DCRT remained the preferred treatment technique in some patients, and should remain a treatment option for cases in which hIMRT produces a suboptimal plan.

We propose the implementation of a novel tool, the NTI, to use in the evaluation and comparison of breast plans. This is a more clinically relevant measurement that is tailored to the new standards of treatment goals established by the use of IMRT for breast irradiation.

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Conflict of Interest

The authors declare no conflict of interest.

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Appendix : Dose Constraints

Structure	Optimal-dose constraint	Minor violation
Contralateral breast	Max ≤5 Gy	8 Gy max
Heart		
Right-sided lesions	Max ≤2 Gy	N/A
Left-sided lesions	≤10 mm heart within tangent portal Mean <4 Gy V2.5 <40% V5 <10% V10 <5% V30 <20cc[25] V40 <10cc[25] V47 <2cc[25] V50 <1cc[25]	Mean = 4–5 Gy <3% of the heart should receive 95% of the prescribed dose ≤15 mm of heart within tangent portal
Left anterior descending coronary artery (LAD)	Max 2cc ≤45 Gy	
Ipsilateral lung	<3-cm lung within tangent portal Tang alone/	Tang alone -V20: 20% -V10: 40%

(*Continued*)

Continued.

Structure	Optimal-dose constraint	Minor violation
	Tang + Boost - V20: 15% - V10: 35% - V5: 40% - Mean ≤8 Gy Tang + SCF +/– Axilla & IMC - V20: 25% - V10: 35% - V 5: 50% - Mean ≤12Gy	-Mean = 9–10 Gy Tang + SCF +/– Axilla & IMC - V20: 30%- V10: 40%- Mean = 13–15 Gy
Contralateral lung	<15% of the lung can receive 5% of the prescribed dose	
Lungs combined	V20 <15% V30 <10% Mean ≤8 Gy	V20 <20%
Brachial plexus	Max ≤54 Gy	Max <55 Gy
Spinal cord	Max ≤45 Gy	
Thyroid	Max ≤55 Gy	No current dose limit – for review

NB, All constraints in *conventional fractionation*. Tang, tangent; SCF, supraclavicular fossa; IMC, internal mammary chain.