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The volume of liver irradiated during modern free-breathing breast radiotherapy: Implications for theory and practice

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ABSTRACT

Introduction: Incidental liver irradiation during breast radiotherapy can increase the risk of second primary malignancy and induce adverse inflammatory states. This study establishes the volume of liver irradiated during free-breathing breast radiotherapy. Novel associations between liver dose-volume data and systemic interleukin-6 soluble receptor and blood counts are evaluated.

Methods: The volume of liver within the 10%, 50% and 90% isodose was determined for 100 women with stage 0 to II breast carcinoma undergoing 40Gy in 15 fractions over three weeks tangential irradiation. Blood counts and interleukin 6 soluble receptor concentration were recorded before, during and four weeks after radiotherapy. Dose-volume data for right-sided treatments was associated with longitudinal measures at bivariate and multivariable levels.

Results: A maximum of 226cm^3 (19%), 92 cm^3 (8%) and 62 cm^3 (5%) of the liver was irradiated within the 10%, 50% and 90% isodose. Liver irradiation was almost exclusively a feature of the 52 right-sided treatments and was strongly correlated with breast volume ($\rho = 0.7$, $p < 0.0001$). Liver V10% was significantly associated with interleukin-6 soluble receptor concentration four weeks post-radiotherapy (beta = 0.38, $p = 0.01$) after controlling for theoretical confounding variables.

Conclusion: Up to 8% of the liver is irradiated within the primary beam during local right-sided breast radiotherapy. Select use of a deep inspiration breath hold technique would reduce this volume, and minimise the risk of radiation-induced malignancy and acute systemic elevation of inflammatory interleukin 6 soluble receptor.

Background

Radiotherapy after breast conserving surgery halves the risk of carcinoma recurrence at 10 years.[1] Eight-out-of ten women treated are expected to be alive at that point,[2] so related morbidity assumes greater significance. Toxicity from incidental heart irradiation[3] has led to widespread adoption of deep inspiration breath-hold (DIBH) techniques for patients with left-sided breast tumours, which reduce cardiac doses by around 50%.[4]

The latency and incidence of a cardiac event are comparable to that for a second primary cancer (SPC) after breast radiotherapy.[5] Low dose to structures at the target periphery are thought to contribute to SPC incidence.[6] Depending upon patient anatomy and treatment technique, a superior portion of the liver lies within the irradiated volume during right-sided treatment: an effect enhanced by the rise of abdominal organs with arms abducted above the head. An in-silico study estimated liver irradiation in this setting confers a significant lifetime SPC risk, albeit much lower than for the lung.[7] The relevance of low-dose exposure to a liver volume has not been evaluated using real patient dosimetry.[8]

Abbreviations: BMI, Body mass index; CTV, Clinical target volume; DIBH, Deep inspiration breath-hold; Gy, Gray; HADS, Hospital anxiety and depression scale; HRT, Hormone replacement therapy; IL-6, Interleukin-6; IPAQ, International physical activity questionnaire; IQR, Inter-quartile range; MCV, Mean corpuscular volume; NHS, National Health Service; PTV, Planning target volume; SCF, Supraclavicular fossa; sIL-6R, Interleukin-6 soluble receptor; TNM, Tumour, node, metastases; Vliverx, Volume of liver irradiated within x% isodose.

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Very limited published evidence from four patients reports that between 4 and 31.5 cm^3 of the liver is irradiated within the 50% isodose during free-breathing radiotherapy breast tangents,[9] with a further single case citing 134 cm^3.[10] Our separate pilot study, of eight right-sided and six left-sided local breast targets, confirmed that up to 5%, mean 1.9%, of the liver was irradiated within the primary beam.[11]

Acute radiation damage to hepatic cells ranges from asymptomatic elevated liver function tests[12] and radiologically-detected focal parenchyma damage[13] to a significant veno-occlusive pathology late in the acute period encompassing liver inflammation, steatosis, fibrosis and necrosis.[14,15] Chemotherapy, volume irradiated and dose-per fraction all modulate the risk of liver toxicity.[16]

This study characterises the volume of incidental liver irradiation during free-breathing breast radiotherapy. The clinical implications for our participants, who received hypo-fractionated treatment with no prior chemotherapy, are evaluated with reference to novel associations between liver dose and systemic sIL-6R (a mediator of hepatic inflammation[17,18]) and blood counts.

Methods

A pragmatic sample size of 100 women with stage 0 to II breast carcinoma were prospectively recruited from new patient clinics at a major regional cancer centre. All had undergone breast conserving surgery or mastectomy and 40Gy in 15 fractions over three weeks adjuvant radiotherapy prescribed (±tumour bed boost). Patients who had received prior systemic anti-cancer therapy were excluded to enable a direct evaluation of radiation effects. Endocrine therapy was scheduled after radiotherapy. Uncontrolled heart, lung, thyroid and liver disease or pre-existing chronic fatigue, autoimmune or inflammatory disease excluded 15 potential participants. The study protocol was approved by NHS Ethics Committee 07/WSE04/82.

Radiotherapy planning data

A breast clinical target volume (CTV), comprising all subcutaneous tissue to the pectoral fascia, was defined during free breathing CT. An expansion margin excluding the most superficial 5 mm formed a planning target volume (PTV). Chestwall CTV extended from skin to rib-pleural margin. Tangential fields created a non-divergent posterior border and the beam arrangement optimised to achieve a maximum lung and heart field projection of ≤20 mm and ≤15 mm, respectively. Wedges were applied with the goal of achieving PTV dose homogeneity between 95% and 107% of reference dose. Beam energy was 6 MV unless a tangential separation of >20 cm meant 10 MV improved dose homogeneity. The couch was rotated to remove divergence from the tangential field superior margin if supraclavicular fossa (SCF) irradiation was indicated.

A researcher contoured the liver extent on contiguous 3 mm slices. Gall bladder and extra-parenchymal inferior vena cava and portal vein were excluded. An experienced radiologist prospectively checked the structure delineation on the first five cases and a random retrospective sample of a further five plans. A collapsed cone algorithm [Oncentra Masterplan v4.1] with 3 mm voxel size calculated the dose distribution.

Longitudinal data

Circulating blood counts and sIL-6R concentration were observed at baseline (between 10 and 22 days before radiotherapy), after 10 and 15 fractions and four weeks after radiotherapy. Enzyme-linked immunosorbent assay quantified sIL-6R serum concentration [R&D Systems]. Full blood counts were auto-analysed [Pentra XL 80]. Potential confounding variables depression and physical activity were self-reported via the hospital anxiety and depression scale (HADS) and international physical activity questionnaire (IPAQ), respectively and body mass index (BMI) was recorded.

Data analysis

Descriptive statistics included the absolute (cm^3) and relative (%) volume of liver irradiated to at least 10, 50 and 90% of the prescription dose ($V_{liver10,50,90}$), and maximum, mean (standard deviation) and median (interquartile range) liver doses. When the full extent of liver was not included in the scan, the volume of liver was imputed based on the weight of the participant.[19] The volume of external contour irradiated within the 95% isodose ($V_{breast95}$) was chosen as a breast size proxy.

Bivariate correlations were conducted between the liver dose-volume data and breast volume, longitudinal sIL-6R concentration and 12 blood count parameters. Non-parametric statistics were used where data did not fulfil assumptions underlying parametric tests. The relative contribution of liver dose-volume parameters to variance in sIL-6R was evaluated using multiple regression. Significance level was reduced to $p < 0.01$ to adjust for multiple testing.

Results

Forty-eight of the 100 participants had a left-sided tumour and 52 were right-sided (Table 1).

Liver dose-volume data is summarised in Table 2. Percentage liver volumes were imputed for four right-sided and six left-sided cases. The minimum liver dose for both left- and right-sided treatments was zero cm^3 at all dose levels. The lowest maximum liver dose was 0.5% and 1% of the reference dose for left- and right-sided, respectively.

As the liver dose-data was positively skewed, median values were more informative. Frequency of median doses, and a maximum liver dose of 4.5% (IQR 3–6.3), indicated liver irradiation was negligible for all but three left-sided treatments. Therefore, statistical tests were conducted on right-sided treatments only.

Spearman's rank test for right-sided treatments showed the breast size proxy $V_{breast95}$ correlated strongly with liver irradiation: $V_{liver\ 10}$ $\rho = 0.8$, $p < 0.0001$; $V_{liver50}$ $\rho = 0.7$, $p < 0.0001$; $V_{liver90}$ $\rho = 0.6$, $p < 0.0001$; max liver dose $\rho = 0.3$, $p = 0.01$. Significance levels remained when controlling for BMI.

Correlations between liver dose-volume variables and longitudinal sIL-6R and mean corpuscular volume (MCV) are summarised in Table 3. Mean corpuscular haemoglobin concentration returned similar results to those for MCV, but all other blood counts were statistically non-significant. Sample size is $n = 52$, except four weeks post-treatment data was $n = 49$ as three right-sided patients declined to return for blood sampling.

After adjusting for age, smoking pack years, depression and physical activity, a significant association remained between $V_{liver10}$ and sIL-6R concentration at four weeks post radiotherapy (beta = 0.38, $p = 0.01$). When BMI was added to the regression model the association was no longer statistically significant (beta = 0.30, $p = 0.07$). This is probably due to the significant correlation between these two variables ($r = 0.5$, $p < 0.0005$).

A one-way ANOVA explored a theoretical impact of BMI on baseline MCV. BMI was collapsed into tertiles approximating to WHO categories for low (<25 kg/m^2), pre-obese (25–29.9 kg/m^2) and obese (≥30 kg/m^2). There was no statistically significant difference in MCV for the three groups ($F = 0.32$, $p = 0.73$).

Table 1
Characteristics of participants, presented as means (SD) or number (%).

Characteristic	Left-sided (n = 48)	Right-sided (n = 52)
Age (years)	58.5. (9.3)	57.9 (8.1)
BMI (Kg/m^2)	28.1 (4.5)	28.2 (4.9)
Smoking history (pack years)	10.5 (14.2)	6.9 (11.5)
HADS anxiety score	5.1 (3.0)	6 (3.9)
HADS depression score	3 (3.2)	3 (2.8)
IPAQ score (MET-min/week)	2446 (2447)	2170 (1880)
HRT history		
Never	36 (75%)	34 (66%)
Previous	12 (25%)	18 (34%)
Histological diagnosis		
Ductal carcinoma in-situ	5 (10%)	8 (15%)
Invasive ductal carcinoma	33 (69%)	34 (66%)
Other	10 (21%)	10 (19%)
TNM stage		
0	5 (10%)	8 (15%)
I	30 (63%)	40 (77%)
II	13 (27%)	4 (8%)
Histopathological grade		
1	9 (19%)	22 (42%)
2	33 (68%)	18 (35%)
3	6 (13%)	12 (23%)
Surgical procedure		
Wide local excision	46	52
Mastectomy	2	0
Time from surgery to radiotherapy (days)	60 (16)	62 (14)
Electron breast boost [10Gy/5#/1 week]	1	1
SCF irradiation [40Gy/15#/3 weeks]	2	1

(BMI = body mass index; HADS = hospital anxiety and depression scale; IPAQ = international physical activity questionnaire; HRT = hormone replacement therapy; TNM = tumour, node, metastases; SCF = supraclavicular fossa). Italics denote categories.

Table 2
Liver dose-volume data for irradiation of left- and right-sided tumours.

Dose level	Liver variable	Maximum		Mean (SD)		Median (IQR)	
		Left	Right	Left	Right	Left	Right
10%	$V_{10absolute}$ (cm^3)	72	226	1.5 (10.4)	56.3 (52.8)	0	40.5 (61)
	$V_{10relative}$ (%)	4.1	18.7	0.9 (0.6)	4.5 (3.8)	0	3.7 (4.9)
50%	$V_{50absolute}$ (cm^3)	21	92	0.4 (3.0)	22.1 (22)	0	16 (29)
	$V_{50relative}$ (%)	1.3	7.9	0 (0.1)	1.7 (1.5)	0	1.2 (2.2)
90%	$V_{90absolute}$ (cm^3)	13	62	0.3 (1.8)	11.3 (14.3)	0	5 (18.2)
	$V_{90relative}$ (%)	0.5	5.0	0 (0.1)	0.9 (1.1)	0	0.5 (1.4)
	Max dose (%)	101.3	113.1	7 (14.4)	87.1 (32)	4.5 (3.3)	101.6 (17.3)

Discussion

Up to 226 cm^3, 92 cm^3 and 62 cm^3 of the liver was irradiated to at least 10%, 50% and 90% of the prescription dose during free-breathing local radiotherapy. This equates to about 19%, 8% and 5% of the liver irradiated within the respective isodose. Such doses were atypical, with the median point estimate being 1.2% (interquartile range 0.3–2.5%) of the liver irradiated within the 50% isodose for participants with right-sided tumours.

Table 3
Mean (SD) interleukin-6 soluble receptor (sIL-6R) and mean corpuscular volume (MCV) values and longitudinal correlations with liver dose-volume parameters.

	Before RT		+10 fractions		+15 fractions		+4 weeks post-RT	
	sIL-6R (ng/dL)							
	38.9 (11.7)		40.1 (10.2)		43.5 (12.2)		38.6 (11.5)	
Liver	ρ	(p)	ρ	(p)	ρ	(p)	ρ	(p)
V10 (cm^3)	0.15	(0.2)	0.29	(0.03)*	0.33	(0.01)**	0.40	(0.007)**
V50 (cm^3)	0.16	(0.16)	0.26	(0.06)	0.26	(0.06)	0.36	(0.01)**
V90 (cm^3)	0.17	(0.16)	0.21	(0.13)	0.22	(0.11)	0.33	(0.02)*
Max dose (%)	−0.07	(0.63)	−0.13	(0.93)	−0.03	(0.98)	0.04	(0.80)
	MCV (fL)							
	91.8 (4.3)		92.7 (4.2)		92.7 (4.4)		90.8 (6.7)	
Liver	ρ	(p)	ρ	(p)	ρ	(p)	ρ	(p)
V10 (cm^3)	−0.24	(0.08)	−0.28	(0.04)*	−0.28	(0.04)*	−0.32	(0.02)*
V50 (cm^3)	−0.35	(0.01)**	−0.36	(0.009)**	−0.36	(0.009)**	−0.40	(0.005)**
V90 (cm^3)	−0.30	(0.03)*	−0.34	(0.01)**	−0.31	(0.02)*	−0.39	(0.01)**
Max dose (%)	−0.10	(0.48)	−0.08	(0.56)	−0.17	(0.23)	−0.18	(0.22)

(Vx = volume of liver within the x isodose level; RT = radiotherapy; * sig at <0.05; ** sig at < 0.01).

It has long been assumed that liver exposure during breast radiotherapy is clinically insignificant. Population-level data indicate that patients with breast cancer have a small but existing risk of developing a second primary liver tumour after treatment, inferred largely to relate to genetic and lifestyle factors.[5,20] Santos et al. estimate a lifetime attributed risk of approximately 20 hepatic malignancies per 10,000 patient years across a range of modern radiotherapy techniques.[7] Radiation-induced cases are difficult to isolate in the absence of linked patient data[8] and reliance on anthropomorphic phantom dosimetry.[20] The current dose-volume data, established on real anatomy/plans, suggests that liver dose is negligible for approximately 70% of patients. However, a wide range of liver dose was evident: the likelihood of a substantial volume of liver being located within the high-dose region increasing significantly with breast size. This relationship was probably due to field borders extending to cover pendulous breasts falling more inferiorly under gravity and an angled breastboard.[21] Where a significant volume of liver irradiation is apparent at treatment simulation, with breast size being a good indicator, right-sided DIBH provides a feasible approach to flatten the diaphragm and displace the liver inferiorly.

DIBH has previously demonstrated reduced liver volume within the 50% isodose by a mean of 42.3 cm^3 (range 0–179 cm^3) for the use of 'wide tangents' localised to treat the internal mammary chain (IMC).[22] Recent review evidence supports IMC irradiation for medially placed axillary node-positive disease.[23] In this setting, there is a relative indication for the reduction of lung and potentially liver doses through right-sided DIBH. The upper range of liver exposure evident in the current participants could also be minimised for standard local breast tangents.[10] Leveraging the inherent stability of DIBH can reduce cranio-caudal intrafraction hepatic motion from 19 mm to 1–5 mm,[24,25] reduce liver volume by 63% (134 cm^3–50 cm^3) and mean liver dose by 46% (from 4.8 to 2.6 Gy) compared to a free breathing plan[10] and deliver superior ipsilateral and total lung dosimetry.[26,27]

The range of maximum liver dose in the current study was surprisingly large for left-sided treatments. Median data confirmed the phenomena of liver irradiation was negligible for all but one participant, who had a medially-placed tumour, a high BMI and SCF irradiation that exaggerated inferior beam divergence for tangential fields. Routine adoption of mono-isocentric field matching and left-sided DIBH are both likely to have additional benefits of reducing liver irradiation for such unusual cases.

Evaluating clinical significance

Classic radiation induced liver disease (RILD) would be extremely unlikely considering the dose-volume data established in this study.[28] Modest, statistically significant, positive correlations were evident between the volume of liver within the 10% isodose and circulating sIL-6R concentration during and after, but not before treatment. The pattern of data is consistent with a systemically discernible low-dose effect for right-sided treatments. The finding is best considered hypothesis generating, but suggests that radiation-induced shedding of sIL-6R could theoretically contribute to adverse inflammatory states and poorer outcomes.[29,30] Murine studies have shown hepatocytes to be a main source of systemic sIL-6R and that dysregulation of the IL6/sIL-6R complex plays a role in impairing the ability of the liver to regenerate after injury.[31–33] IL-6 and sIL-6R are negative prognostic markers for breast cancer proliferation, resistance and metastasis.[34–36] At a behavioural level, elevated sIL-6R has been associated with fatigue, depression and poor sleep hygiene in breast cancer populations.[37–39]

A negative association between liver irradiation and MCV was evident in the current data, before, during and after radiotherapy. The consistency of associations and lack of association with other blood counts indicate a modest statistically significant result, of unknown clinical significance. Maximum liver dose was neither a useful predictor of sIL-6R concentration nor blood counts.

The study design enabled original longitudinal data, but did not link dosimetry to clinical outcomes. Further studies could test the hypothesis that technical approaches can virtually eliminate the volume of liver tissue within the high-dose region and thereby minimise low-dose induction of sIL-6R and associated behavioural effects. Alternative free-breathing techniques with potential to reduce mean liver doses include proton therapy, partial breast irradiation, segmented intensity modulated radiotherapy and two-arc volumetric therapy.[40] This is important as the liver broadly functions as a parallel organ that is susceptible to damage from lower doses spread across a larger volume.[41] The exclusion of prior/concomitant systemic anti-cancer therapies helped to isolate the biological effects of radiation, but reduces generalisability to the wider population. The liver plays a central role in the metabolism of pharmacological agents. Tamoxifen, Lapatinib and other agents used in modern breast cancer protocols share a hepatotoxic profile.[16,42,43] The liver tolerance is also reduced by hypofractionated doses,[16] as prescribed to study participants.

Conclusions

Up to 8% of the liver is irradiated within the primary beam during contemporary local right-sided breast radiotherapy. Where treatment planning images demonstrate substantial liver exposure, right-sided DIBH provides a simple way to ensure the liver dose, the consequent risk of acute and chronic inflammatory toxicity and second primary liver cancer is as low as reasonably practicable; especially during IMC irradiation and extreme hypofractionation or for women with large/pendulous breasts or liver function is compromised.

Ethical approval

Ethics approval and consent to participate

South East Wales Research Ethics Committee D approved this study (07/WSE04/82).

Authors' contributions

NC and TG designed the overall study. MDM and PBL made substantial contributions to the conception and design of the study. NC analysed the data and data was interpreted by all authors. TO was involved in drafting the manuscript, revising it critically and providing intellectual content regarding right-sided DIBH and liver irradiation/motion. All authors read and approved the final manuscript.

Declarations of interest

Dr Nick Courtier: none.

Dr Tina Gambling: none.

Mr Theo Oliver: none.

Prof Peter Barrett-Lee: none.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radi.2018.12.003.

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