How does knowledge of 3-dimensional excision margins following breast conservation surgery impact upon clinical target volume definition for partial breast radiotherapy?

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Abstract

Purpose: To compare partial breast clinical target volumes generated using a standard 15mm margin (CTV_{standard}) with those generated using 3-dimensional surgical excision margins (CTV_{tailored}) in women who have undergone wide-local excision (WLE) for early breast cancer.

Materials/ methods: 35 women with breast cancer underwent WLE with placement of titanium clips in the anterior, deep and four coronal excision-cavity walls. Distances from edge of tumour to anterior, deep and coronal excision margins were measured microscopically. Tumour bed was defined on kv-CT images using clips. CTV_{standard} was generated by adding a uniform 3-dimensional 15mm margin, and CTV_{tailored} by adding 30mm minus the excision margin in 3-dimensions. Concordance between CTV_{standard} and CTV_{tailored} was quantified using conformity (Col), geographical-miss (GMI) and normal-tissue (NTI) indices. An external-beam partial breast irradiation (PBI) plan was generated to cover 95% of CTV_{standard} with the 95% isodose. The percentage-volume coverage of CTV_{tailored} by the 95% isodose was measured.

Results: Median (range) coronal, superficial and deep excision margins were 15.0mm (0.5-76.0mm), 4.0mm (0.5-60.0mm) and 4.0mm (0.5-35.0mm) respectively. Median Col, GMI and NTI were 0.61, 0.18 and 0.20 respectively. Median coverage of CTV_{tailored} by the

PBI-plan was 97.7% (range 82.4-99.7%). In 25/30 cases, >95% CTV_{tailored} was covered by the 95% isodose. In 4/5 inadequately covered cases, the excision margin in the direction of inadequate coverage was ≤ 2 mm.

Conclusions: Three-dimensional excision margins following WLE vary widely. CTVs based on 3-D margin data are discordant with those defined using a standard 15mm margin. This may be clinically significant where excision margins are narrow in a sagittal plane.

Introduction

Whole breast radiotherapy following wide local excision (WLE) of breast cancer improves local control and survival but is associated with increased late morbidity and mortality (1). The aim of current studies of partial breast irradiation (PBI) is to reduce late radiation-related side-effects whilst maintaining local control and survival. Four of seven current PBI trials use external beam RT as a modality (2-5), all of which define the clinical target volume (CTV) as tumour bed (TB) expanded uniformly by 15mm in three dimensions (3-D). This definition is based upon data from mastectomy studies which suggest that 90% of subclinical multifocal and multicentric disease lies within 30mm of the edge of index tumour (6). If, on average, the index tumour is excised with a margin of around 15mm, a further 15mm TB-CTV margin might be expected to encompass the majority of subclinical disease.

The addition of a uniform margin is based on a further assumption that tumour is centrally placed within the excision specimen. However, WLE specimen radiographs and reports of histopathological excision margins (7) suggest that tumour is more often eccentrically placed. This raises the question of whether the current practice of adding a uniform 15mm margin to the edge of TB might, in some cases, result in a geographical miss of breast tissue considered to be at risk of local recurrence. Using knowledge of 3-dimensional excision margins, it is possible to generate a CTV which more closely reflects the original position of tumour and thereby more accurately encompasses tissue containing residual subclinical disease.

This study compares partial breast CTVs generated using a standard uniform 15mm margin (CTV_{standard}) with those generated using knowledge of 3-D surgical excision margins (CTV_{tailored}) in women who have undergone WLE of early breast cancer, and measures adequacy of coverage of CTV_{tailored} by CTV_{standard} -based tangential PBI fields. It

is hypothesized that CTVs will be discordant and that, in some cases, there may be a risk of geographical miss of breast tissue considered to be at risk of local recurrence.

Methods

The study was approved by the Royal Marsden Committee for Clinical Research and by the local ethics committee.

Surgery and clip placement

Patients with unifocal G1-3 invasive ductal carcinoma or intermediate- to high-grade DCIS were recruited prior to wide local excision (WLE). Informed consent was taken from all patients. All patients had titanium clips placed at the time of WLE according to the national UK IMPORT-Low (Intensity Modulated Partial Organ Radiotherapy) study protocol (8) in which each excision cavity boundary is defined by clips positioned in pairs at the centre of the cavity (deep boundary), half-way between skin and pectoral fascia (lateral, medial, superior and inferior walls) or in subcutaneous tissue close to the suture line (anterior boundary).

Pathological analysis

Each wide local excision specimen was oriented according to individual surgical practice e.g. superior margin marked by a short suture, deep margin (double suture) and lateral margin (long suture), and the orientation method annotated in the operation note. Prior to cut-up, specimen dimensions were measured and margins inked. Each specimen was cut into uniform slices of between 4 and 7mm. Orientation and width of slices was noted. Slices were laid out onto a blue board in the same orientation and photographed individually. 20 by 25mm blocks of tissue were taken from tumour and from each of the lateral, medial, superior, inferior, anterior and deep margins. From each of the blocks, 7µm-thick slides were prepared, stained appropriately and studied microscopically. Tumour dimensions and 3-D microscopic margins from edge of pre-invasive/ invasive

disease to the edge of the excision specimen were measured. All measurements were recorded to the nearest 0.5mm.

For the purposes of demonstrating graphically the 3-D position of tumour within the excision specimen, the digital photographs of specimen slices were reconstructed using software written with the MatlabTM computer package (Mathworks Inc., Natick, MA). This was run on a standard PC. Serial photographs were digitised, and boundaries of the specimen and tumour on each slice traced and represented in binary format. Using the known slice thickness, 3-D representations of the specimen and tumour were reconstructed and displayed. The 3-D reconstructed images could be rotated at any assigned angle around the x, y and z axes.

CT-imaging and target volume definition

Each patient underwent a standard supine radiotherapy-planning kv-CT scan. Radio-opaque wire was placed at the palpable edge of breast tissue circumferentially in order to define whole breast. CT data was transferred into the department's radiotherapy planning system (Pinnacle version 8.0, Philips Radiation Oncology Systems, Madison, WI).

Tumour bed (TB) was identified on supine CT images using clips and including seroma or architectural distortion. Delineation of TB was performed with a fixed window level of 0 Hounsfield Units (HU) and width of 500 HU. A CTV_{standard} was generated by adding a uniform 15mm margin to TB in 3-D, limited deeply by chest wall, superficially by 5mm beneath skin surface and radially by the edges of whole breast tissue. A CTV_{tailored} was created using a differential margin, reflecting the position of the tumour (GTV) plus 30mm (i.e. 30mm minus surgical excision margin), with skin/chest wall/ breast tissue limits as above. For the purposes of comparison with other literature (7) reflecting a different interpretation of data on pathogenesis of local recurrence, we also generated a tailored-15mm CTV (CTV_{tailored15mm}) by adding 15mm minus the surgical margin in each of the six directions.

Absolute volumes were calculated and compared using the two-tailed Student t-test. Concordance between CTV_{standard} and CTV_{tailored} was expressed as a conformity index (Col). The proportion of discordance attributable to CTV_{tailored} or CTV_{standard} underlap was expressed as geographical miss (GMI) and normal tissue (NTI) indices [defined in figure 1]. Col, GMI and NTI were also calculated for CTV_{standard} versus CTV_{tailored15mm}. Planning target volumes (PTV) were created for each of CTV_{standard}, CTV_{tailored} and CTV_{tailored15mm} by addition of a 10mm margin to each CTV, limited superficially to 5mm from skin surface.

Partial breast radiotherapy planning

PBI dose distributions were generated using multiple static tangential fields with the aim of encompassing the CTV_{standard} according to UK IMPORT-Low trial criteria (5) i.e. ≥95% of the CTV_{standard} should be covered by >95% of isocentre dose (50Gy in 2Gy fractions). Plans fulfilled ICRU dose homogeneity criteria (9). The percentage of CTV_{tailored} receiving ≥95% of the isocentre dose was measured.

Results

Thirty-five patients were recruited and analysed histopathologically according to protocol. The median age of patients was 63 years (range 34-79 years). Six patients had intermediate or high-grade DCIS, fourteen had grade 1 invasive ductal carcinoma (IDC), ten had grade 2 IDC and five had grade 3 IDC.

Photographs of serial slices from a single specimen are shown in figure 2. Tumour is demonstrated in photograph 'e'. Table 1 displays the margin data for all patients. Tumours were eccentrically placed within the excision specimens in the majority of women (examples of which are shown in figure 3). In 34/35 patients, there was a >10mm difference between the closest and widest margins of excision. In 15/35 women there was a >30mm difference between the closest and widest margins. The mean difference between the closest and widest margins was 28.2mm. The population mean anterior

(6.5mm) and deep (6.7mm) surgical margins were significantly narrower than the mean coronal margin (16.6mm). The median coronal margin was 15mm.

Five patients required re-excision of surgical margins at a subsequent procedure and were excluded from subsequent radiotherapy planning analysis. Thirty remaining patients each had 6 clips placed according to protocol, and also underwent CT-imaging and radiotherapy planning according to protocol. There was no significant difference between the mean (SD) volumes of CTV_{standard} 94.8(32.3)cm³ and CTV_{tailored} 94.6(40.4)cm³ (p=0.97). However, CTV_{tailored15mm} were significantly smaller at 24.1(10.4)cm³ (p<0.001). Concordance and discordance between CTV_{standard} and CTV_{tailored}, and between CTV_{standard} and CTV_{tailored15mm} are summarized in table 2. Tangential-beam PBI plans based on CTV_{standard} did not adequately cover CTV_{tailored} in 5/30 cases. In 3/5 cases, coverage was inadequate in the superior-inferior plane, as illustrated in figure 4. The mean difference in the position of the geometric centres was also greatest in the superior-inferior axis. In 3/5 cases, coverage was inadequate anteriorly. In the case with the least adequate coverage, the CTV_{tailored} was adequately encompassed by the 80% isodose. This case (06) had narrow excision margins, including 1.5mm superior and inferior margins. In 4/5 cases of inadequate coverage, the excision margin in the direction of inadequate coverage was ≤2mm.

Discussion

The aim of wide local excision (WLE) surgery is to remove tumour with a margin of 10-20mm of normal tissue (10). Our median coronal excision margin of 15mm was consistent with this aim. Holland's data (6) suggests that, if *surgical* excision margins are symmetrically and uniformly 15mm in 3-dimensions (3-D), the standard approach of adding a further uniform *TB-CTV* margin of 15mm is reasonable. However, our study demonstrates, consistent with previous literature (7), that 3-D excision margins vary widely within and between patients. In the majority of cases, tumours were eccentrically placed within the excision specimens as reflected in a mean difference of nearly 30mm between

the narrowest and widest margins in each case. In most women, the coronal excision margins were greater than the anterior and deep margins, reflecting the anatomical shape of breast tissue.

Although there was no significant difference between absolute volumes, CTVs based on 3D-excision margins (CTV_{tailored}) were discordant to those defined using a standard uniform 15mm margin (CTV_{standard}). Nonetheless, clinically satisfactory coverage of CTV_{tailored} by CTV_{standard}-based tangential PBI fields was achieved in 83% of cases. This partly reflects the fact that the dose distribution from opposing tangential fields is likely to encompass most of the breast tissue within its axial plane, such that clinically significant differences in CTVs are more likely to occur in the sagittal plane. Indeed, in 3/5 inadequately-covered cases, coverage was inadequate in the superior-inferior plane, whilst in 3/5 patients coverage was inadequate anteriorly. In 4/5 inadequately covered cases, the surgical excision margin was ≤ 2 mm in the direction of inadequate coverage. In the fifth patient, the excision margin was 4mm in the direction of inadequate coverage. The current minimum histopathological dataset (11) requires that only the closest margin be reported but our data suggests that reporting of other close margins (≤ 5 mm) may be helpful in ensuring adequate coverage of subclinical disease by tangential PBI fields. In practice, most local guidelines recommend that re-excision be considered for margins of 1-2mm, and it is, in the authors' experience, commonplace for pathologists to report all margins of ≤ 2 mm.

The clinical implications of these findings will depend upon the mechanism of pathogenesis of local recurrence. If the hypothesis is correct that local recurrence of breast cancer arises from hitherto undiagnosed multifocal and multicentric disease, 90% of which is distributed within 30mm of the edge of index tumour (6), our data suggests that the use of a uniform 15mm margin around TB may be associated with a risk of geographical miss in women with narrow excision margins. Mastectomy studies (6, 12) may be overestimating the required margin as, firstly, they are associated with a 15mm

error in the mapping procedure and, secondly, the cases in these studies were higher-risk than those entered into current PBI studies. However, a recent detailed histopathological study of WLE specimens confirms that there is microscopic disease beyond 15mm from the edge of index tumour in 36% of cases undergoing WLE (13).

Alternative hypotheses regarding the pathogenesis of local recurrence have been discussed in a recent review (14). Data suggests that radiotherapy might work by sterilising genetically unstable, morphologically normal cells within 1-2mm of the edge of the excision cavity (15) as well as by reducing the stimulatory effects of surgical wound fluids upon proliferative, migratory and invasive abilities of breast cancer cells (16). Outcome data from studies of intra-operative radiotherapy (17) which deliver dose to only a 2mm peri-cavity rim of breast tissue are awaited with interest. Such data will shed light on whether or not residual multifocal/ multicentric disease is as relevant to local recurrence as currently supposed. Meanwhile clinical outcome data have shown that empirical use of a 15mm TB-CTV margin has achieved 5-year actuarial local control rates of up to 98.8% (18). However, only 6% of these patients had surgical margins ≤ 2 mm (whereas 13/30 (43%) of our non-re-excised patients had margins ≤ 2 mm).

In contrast to our study, other authors have set out to use 3-D margin data to reduce breast boost target volumes thereby potentially reducing doses to non-target tissues (7). Hanbeukers and colleagues compared CTVs defined using the standard uniform 15mm margin with those defined using 15mm minus the excision margins in 3D. They found, in agreement with our $CTV_{tailored15mm}$ data, that the tailored boost volumes were significantly smaller than standard boost volumes. In our study, all of the discordance between $CTV_{standard}$ and $CTV_{tailored15mm}$ was due to $CTV_{standard}$ encompassing a large volume of “normal tissue” as defined by the smaller $CTV_{tailored15mm}$. On this basis there might be scope to reduce CTV volumes for PBI thereby sparing normal tissues. The authors acknowledge however that, based on the Holland data, this choice of margin is likely to be too narrow to

accurately encompass sub-clinical disease. We suggest that a margin of 30mm minus the surgical margin more accurately reflects the findings of mastectomy studies.

The implications of our findings also depend upon the external-beam PBI technique used. The multiple static tangential field technique employed in the UK IMPORT-Low study spares approximately two-thirds of breast tissue whilst simultaneously reducing low-dose exposure of internal organs (5). The latter is particularly important in women in the most favourable prognostic subgroups and in those at greatest risk of radiation-induced cancers. Conformality to the partial-breast target volume can be increased using additional non-tangential and non-coplanar fields, although this may be at the expense of increased low-dose irradiation of non-target tissues. With increasing conformality however, awareness of close surgical excision margins, particularly in the axial plane, is likely to become even more relevant.

Limitations of our study include errors in relating histopathological findings to post-operative CT images. Although clips were placed according to protocol at the margins of excision, there is a possibility of clip migration. A recent study suggests however that clip migration is rare (19). Histopathological excision margins are likely to be underestimated due to tissue shrinkage and electrocautery, one study suggesting that tissue can shrink by up to 10% (20). With a median coronal margin of 15mm the median errors due to tissue shrinkage would be in the order of 1-2mm and, although these might have lead to a small overestimation of the margins required to generate CTV_{tailored}, they are unlikely to affect the conclusions of this study.

In conclusion, current PBI studies using external-beam radiotherapy define CTV as TB plus a 15mm margin in 3-D. A uniform margin does not take account of eccentricity of tumour within the excision specimen. This study suggests that failure to take account of narrow excision margins when planning PBI could result in a geographical miss of tissue considered to be at risk of local recurrence. Where re-excision does not take place, a

wider TB-CTV margin in the direction of the narrow surgical margin might therefore be considered.

Conclusion

Three-dimensional excision margins following WLE vary widely. CTVs based on 3-D margin data are discordant with those defined using a standard 15mm margin. This may be clinically significant where excision margins are narrow in a sagittal plane.

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Figure 1. Definitions of conformity, geographical and normal tissue indices

$$\text{Conformity index} = \frac{x}{x + y + z}$$

$$\text{GMI} = \frac{z}{x + y + z}$$

$$\text{NTI} = \frac{y}{x + y + z}$$

Figure 2a-l: Series of sequential macroscopic slices from a single patient's wide local excision specimen. Slice width= 4mm. Tumour is visible in slice (e).

Figure 3: Orthogonal views of reconstructed digital images demonstrating relationship between excision specimens (red) and pre-invasive/ invasive tumour (green)

Figure 4: Partial breast radiotherapy plan using tangential 6MV photon fields to cover $>95\%$ CTV_{standard} (magenta fill) by the 95% isodose (green line).

The CTV_{tailored} (thick yellow line) is inadequately encompassed at the superior and inferior aspects. (Blue line=PTV_{tailored}).

Table 1: Margins of excision for each patient (all measurements to the nearest 0.5mm)

Patient	Medial	Lateral	Superior	Inferior	Anterior	Deep	Direction of
	margin	margin	margin	margin	margin	margin	inadequate
	(mm)	(mm)	(mm)	(mm)	(mm)	(mm)	CTV _{tailored}
							coverage
01	15	15	25	2	5	3	
02	20	1	5	15	1	3	Re-excised
03	32	35	11	11	5	5	
04	35	11	13	1	16	16	Re-excised
05	5.5	13	28	7	3.5	9.5	
06	3	4	1.5	1.5	0	0.5	Sup-inf
07	36	12	1	10	5	0.5	Re-excised
08	10	14	10	14	3	0.5	
09	18	10	8	1.5	5	6	Re-excised
10	16.5	16.5	15	12	4	13	
11	10	20	15	35	1	7	
12	14	7	32	24	0.5	3	
13	1	3	8	3	20	35	Re-excised
14	18	13.5	6	19	2	5	Sup-Ant
15	17.5	7	11	5	2	4	
16	16	12	6	10	5	10	
17	24	16	10	20	1	8	
18	27	15	13	17	2	5	
19	20	35	30	15	6	2	
20	8	36	0.5	15	6	1	
21	20	15	9	11	1	0.5	Ant
22	20	25	15	30	60	1	
23	22	22	15	15	2	4	
24	30	25	15	15	1	3	
25	25	15	20	10	8	15	
26	36	18	18	20	4	10	
27	20	10	20	35	1	3	

28	30	5	15	9	2	4	
29	35	5	4	14	12	25	Sup-Lat
30	12	76	12	59	1	14	
31	19	33	8	3	1	11	Ant
32	5	30	16	11	9	3	
33	8	36	6	22	10	1.5	
34	55	10	20	10	7	12	
35	16	10	35	15	6	2	
Median							
excision							
margin (mm)	19	15	13	14	4	4	
Mean excision							
margin (±SD)							
(mm)	20.0±11.4	18.0±14.2	13.7±8.6	14.8±11.5	6.5±10.4	6.7±7.4	

Table 2: Conformity and discordance for CTV_{standard} vs. CTV_{tailored} and for CTV_{standard} vs. CTV_{tailored15mm} (n=30)

Median values (range)	CTV _{standard} vs. CTV _{tailored30mm}		CTV _{standard} vs. CTV _{tailored15mm}	
Conformity index	0.61 (0.25-0.88)		0.25 (0.10-0.50)	
Geographical miss index	17.5% (1.8-55.7%)		0.0% (0.0-2.9%)	
Normal tissue index	19.9% (0.0-51.0%)		74.7% (49.2-89.6%)	
Median percentage volume of CTV _{standard} covered by 95% isodose	98.9% (95.0-100.0%)			
Median percentage volume of CTV _{tailored} covered by 95% isodose	97.7% (82.4-94.2%)		99.9% (96.0-100.0%)	
Number of cases in which CTV _{tailored} was inadequately covered by 95% isodose	5/30		0/30	
Mean displacement in geometric centre of CTV _{tailored} in relation to CTV _{standard}	Medial- lateral	3.7mm	Medial- lateral	2.3mm
	Anterior- deep	3.3mm	Anterior- deep	2.2mm
	Superior- inferior	3.9mm	Superior- inferior	2.8mm