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Review

Size of invasive breast cancer and risk of local recurrence after breast-conservation therapy

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Abstract

Risk of local recurrence is one important factor that determines a woman's suitability for breast-conservation therapy. With the evolution of oncoplastic surgery, tumours of a size that traditionally require mastectomy may be treated by breast conservation and partial breast reconstruction. This article reviews the evidence relating to tumour size as a risk factor for local recurrence to assess whether this change in practice is appropriate. A literature review through Medline and Pubmed was performed. All pathological studies analysing tumour size as a predictor of multifocality and all randomised trials and large case series of breast conservation including tumours larger than 2 cm were reviewed and critically interpreted. Pathological studies report consistent evidence that tumour size is not predictive of multifocality. Randomised trials and clinical series of breast conservation report conflicting evidence relating to tumour size as a risk factor for local recurrence, although most studies report no association. Evidence relating to cancers over 3 cm is limited. There is little evidence to justify the use of tumour size alone as an exclusion criterion for breast-conservation therapy. A registration study of patients with cancers larger than 3 cm treated by breast conservation with or without partial breast reconstruction is proposed.

Keywords: Breast; Cancer; Size; Local; Recurrence; Risk; Breast conservation

1. Introduction

Long-term results of randomised trials have shown that for selected patients breast-conservation therapy combined with postoperative radiotherapy has equivalent survival to mastectomy in the treatment of breast cancer [1–3]. Outcome measures that indicate the success of breast-conservation therapy are a low rate of local recurrence, an acceptable cosmetic result and patient satisfaction. Recently, the role of breast-conservation therapy has expanded to include women who might traditionally have been treated by mastectomy using techniques such as breast reshaping, breast reduction and breast-volume replacement [4–11]. Using such techniques, a large percentage of the breast may be removed whilst still achieving an acceptable cosmetic result. Thus, large cancers may be treated by breast-conservation therapy.

Local recurrence represents a failure of breast conservation and usually requires a mastectomy to treat it. Tumour size was a dominant factor for selecting patients for breast-conservation therapy in many randomised trials and case series of breast conservation. This was in part due to concern that the excision of large tumours with anything less than a mastectomy would compromise treatment effectiveness.

Can large tumours safely be treated with breast-conservation therapy? In this article, we analyse the evidence relating to tumour size as a risk factor for local recurrence after breast-conservation therapy, and aim to answer this question.

2. Tumour size and pathological multifocality

True tumour size may be underestimated using current methods of pathological specimen handling. Hence, without radiotherapy after breast-conservation surgery,

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early local recurrences are relatively common and tend to occur at the site of previous excision, even when the pathological excision margins were clear [12–14]. The likely reason for this is tumour multifocality. As there are many different interpretations of the term 'multifocality', we use the following definition in this article: Multifocality refers to a cancer that is locally more diffuse histologically or on imaging than appreciated by palpation prior to surgery. It is thus the same disease process and the same phenotype as the main tumour mass. Where there are two or more distinct and separate cancerous lesions in a breast, this would be termed multicentricity.

Holland and colleagues demonstrated the extent of tumour multifocality in an analysis of mastectomy specimens subjected to serial sectioning from 282 patients with cancers less than 5 cm that clinically had unicentric breast cancer and were theoretically suitable for breast-conserving surgery [15]. In only 37% of cases was the cancer in the breast restricted to the main tumour mass. The remainder had microscopic tumour foci extending for varying distances. This was not determined by tumour size. For tumours less than 2 cm, 42% harboured residual cancer foci at 2-cm margins (28% intraductal, 14% invasive) and 10% at 4-cm margins (5% intraductal, 5% invasive). For tumours less than 4 cm, 41% had residual cancer foci at 2-cm margins (27%, intraductal, 14% invasive) and 11% had residual disease at 4-cm margins (4% intraductal, 7% invasive). In a similar smaller study by Vaidya and colleagues, the presence of residual cancer foci in 30 modified radical mastectomy specimens was assessed with 5-mm sections and radiological imaging [16]. Residual foci were identified in 63% of cases. The investigators found that 53% of patients had foci within 2-cm margins and 90% within 5-cm of the tumour edge. This study found that the presence of multifocality was related to tumour size. Four out of 12 breast specimens with tumours smaller than 3 cm harboured residual cancer foci, whereas this was identified in 12 out of 15 breast specimens with tumours equal to or larger than 3 cm ($P = 0.02$). However, the theoretical margin required to excise the multifocality did not differ with tumour size [16]. Larger tumours were more likely to have multifocal disease, but not any more likely to have residual disease after a wide local excision of any given margin width (i.e. the radial extent of multifocal disease was not related to tumour size).

Analysing the tumour bed following breast-conservation therapy is another way of identifying residual microscopic foci of cancer. In a study by Macmillan and colleagues, detailed histological assessment on cavity shavings was performed in 300 patients following wide local excision of their tumours with 1–2-cm macroscopic margins. Cancer foci were found in the cavity shavings for 118 of 300 patients (39.3%), 55 (18.3%) having residual invasive disease and 63 (21.0%) *in situ* disease only. There was no significant association between tumour bed positivity and tumour size [17].

In a study by Ohtake and colleagues, subgross and stereomicroscopic techniques were used to obtain computer-generated three-dimensional graphic reconstructions of the mammary ductal systems. Of 20 quadrantectomy specimens analysed from patients with invasive breast cancer, intraductal tumour extension was found in 16 of 20 specimens (80%), extending continuously from the primary invasive carcinoma through the mammary ductal tree. The distances and angles of extension were larger in tumours with certain characteristics but, notably, this was not associated with tumour size [18].

3. Tumour size and local recurrence

In randomised trials comparing breast-conservation therapy with mastectomy, enrolment criteria were largely based on tumour size. Some trials included only cancers smaller than 2 cm [19,20]. As shown in Table 1, four randomised trials comparing breast-conserving surgery and radiotherapy with mastectomy included tumours over 2 cm [1,2,21–27]. The percentage of patients with tumours equal to or larger than 2 cm varied from 39 to 80%. Three trials comparing breast-conserving surgery plus radiotherapy with breast-conserving surgery alone, included 16, 41 and 57% of patients, respectively, with tumours greater than 2 cm [28–33]. Two further trials, the European Organisation for Research and Treatment of Cancer (EORTC) 22881/10882 (breast-conservation therapy and radiotherapy versus breast-conserving radiotherapy plus boost) and Milan II (quadrantectomy and radiotherapy versus tumorectomy and radiotherapy), included 22 and 14% of patients with tumours of this size [34,35]. All but one of these nine trials analysed tumour size as a predictive factor for local recurrence [3,36]. Seven of these nine trials found no significant association between these variables (Table 1).

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, 1851 patients were randomised into three treatment arms; mastectomy ($n = 589$), breast-conservation therapy and postoperative radiotherapy ($n = 628$) and breast-conservation therapy alone ($n = 634$) [2,21,23]. In 46% of all patients, the tumours were larger than 2 cm. Histological margins were required to be free of tumour. In the most recent follow-up publication, the actuarial risk of local recurrence in the ipsilateral breast after a mean follow-up of 20.7 years was 14% in the breast-conservation therapy and radiotherapy group compared with 39% in the group treated with breast-conservation therapy alone [2]. The only published analysis on the association between

Table 1
Randomised trials including tumours ⩾2cm and local recurrence

Trial [Ref(s).]		No. of patients	Size criteria	%[a] > 2 cm	%[a] > 3 cm	Follow-up to date (years)	Clearance/ margins	LR (%) (all patients)	Analysis of size as risk factor for LR after BCS + RX	When size analysis performed (years)	Size risk factor for LR	*P* value
EORTC 10801 [1,24]		868	⩽5 cm (clinical)	80	NR	13.4	1 cm (macroscopic)		Multivariate on LRR (2.1–5.0 cm, mastectomy versus BCS)	13	NA (yes for LRR) (see combined analysis with Danish trial)	NA
	Mastectomy	420						8[b]				
	BCS + Rx	448						10[b]				
National Cancer Institute [25–27]		237	⩽5 cm (clinical)	39		10.1	Not defined		Univariate (⩽2.0 cm versus >2.0 cm)	10	No	NR
	Mastectomy	116			9 (4.1–5 cm)			NR				
	BCS + Rx	121			7 (4.1–5 cm)			16[c]				
NSABP B-06 [2,21–23]		1851	⩽4 cm (clinical)	46	NR	20.7	Not transecting (microscopic)		Univariate (>2.0 cm versus <2.0 cm)	5	No	0.16
	Mastectomy	589						NR				
	BCS + Rx	628						14[c]				
	BCS	634						39[c]				
DANISH DBCG-82TM3 [36]		859	⩽5 cm (clinical)	NR	8	3.3	Macroscopically clear		NR	NA	NA	NA
	Mastectomy	429						4[d]				
	BCS + Rx	430						3[d]				
MILAN III [28,29]		579	⩽2.5 cm (histology)	16	NA	9.1	Not transecting (microscopic)		NR	9	No	NR
	Quadrantectomy + Rx	299						5				
	Quadrantectomy	280						22				
SCOTTISH [33]		585	⩽4 cm (clinical)	57	NR	5.7	1 cm (macroscopic)		Univariate on LRR (⩽2.0 cm versus > 2.0 cm)	6	NA (no for LRR)	NA
	BCS + Rx	291						6				
	BCS	294						24				

(continued on next page)

Table 1 (*continued*)

Trial [Ref(s).]		No. of patients	Size criteria	%[a] > 2 cm	%[a] > 3 cm	Follow-up to date (years)	Clearance/ margins	LR (%) (all patients)	Analysis of size as risk factor for LR after BCS + RX	When size analysis performed (years)	Size risk factor for LR	*P* value
Ontario [30–32]		837	⩽4 cm (histology)	41	NR	7.6	0.5–1 cm (microscopic)		Multivariate (>2.0 cm versus ⩽2.0 cm)	8	Yes	0.0006
	BCS + Rx	416						11				
	BCS	421						35				
EORTC 22881/10882 [34]		5318	⩽5 cm (clinical)	22		5.1			Uni- and multivariate (palpable versus non-palpable tumour)	5	Yes	0.007
	BCS + Rx	2657		22	6		1 cm (macroscopic)	7				
	BCS + Rx + Rx boost	2661		22	5			4				
Milan II [35]		705	<2.5 cm	14	NA	9.4			Multivariate (⩽1 cm versus >1 cm)	10	No	NR
	QUART	360		15			2 cm (macroscopic)	7				
	TART	345		12			⩽1 cm (macroscopic)	18				
Voogd AC (EORTC10801 + Danish) [37]		1772	See EORTC and Danish	31	NR	9.8	See EORTC and Danish		Multivariate (⩾2.1 cm versus ⩽1.0 cm)	10	No	0.1
	Mastectomy	893						9				
	BCS + Rx	879						9				

LR, local recurrence; LRR, locoregional recurrence; NR, not reported; NA, not applicable; Rx, radiotherapy; BCS, breast-conserving surgery; QUART, quadrantectomy, axillary dissection and radiotherapy; TART, tumourectomy, axillary dissection, external radiotherapy and ^{192}Ir implantation boost; No., number; EORTC, European Organisation for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; DBCG, Danish Breast Cancer Cooperative Group.

[a] Percentage of all patients in study.

[b] After 8 years at follow-up.

[c] Actuarial risk.

[d] After median follow-up of 40 months.

Table 2
Local recurrence after breast-conserving surgery: retrospective studies

Study [Ref.]	No. of patients	Size criteria	Median/mean tumour size (cm)	% > 2 cm	% > 3 cm	Follow-up (years)	Clearance/margins	LR (%) (all patients)	Analysis of size as risk factor for LR after BCS + RX	Size risk factor for LR	*P* value
Fredriksson and colleagues [38]	4694	⩽5 cm	1.4	NR	1.8	6.4[a]	Microscopically clear	12.4	Multivariate[b]	No	NR
Veronesi and colleagues [13]	2233	NR[c]	1.4	10.2[d]	NR	8.5	NR	6.8[e]	Multivariate (>2.0 cm versus ⩽0.5 cm)	Yes	0.02
Bartelink and colleagues [39]	585	⩽5 cm	NR	NR	NR	6	Not defined[f]	1.5	Univariate	No	NR
Dalberg and colleagues [40]	759	⩽5 cm	NR	NR	NR	10	Microscopically clear	11.6	Uni and multivariate (>11 mm versus 0–5 mm)	No (on multivariate analysis)	0.21[g]
Fowble and colleagues [41]	697	⩽5 cm	NR	41	NR	4.8	Not defined[h]	8.7	Univariate ⩽2 cm versus > 2 cm)	No	NR
Kurtz and colleagues [42]	496	⩽5 cm	NR	NR	NR	5.9	Not defined[i]	12.3	Uni and multivariate	No (on multivariate analysis)	NR[j]
Fourquet and colleagues [43]	518	⩽5 cm	2	NR	4	8.6	Not defined[k]	10.8	Uni and multivariate (⩽1 cm versus ⩽2 cm versus > 2 cm)	No	NR

LR, local recurrence; NR, not reported.

[a] 30 151 person years of observation.

[b] Relative Hazards with 95% Confidence Intervals for 1–10, 11–20, 21–30 and > 30 mm.

[c] This series included 707 patients enrolled in the Milan I or II trials (maximum size 2.5 cm) and 1526 patients not included in any trial.

[d] 2109 patients had information on tumour size.

[e] Of the 151 local recurrences, 32 (1.4%) were classified as new primary cancers.

[f] 32 patients had incomplete margins.

[g] $P = 0.014$ on univariate analysis.

[h] 71 patients had incomplete margins.

[i] Margins were indeterminate for 165, and incomplete for 49.

[j] $P = 0.0183$ on univariate analysis.

[k] 57 patients of 351 assessed had incomplete margins.

tumour size and ipsilateral breast recurrence from this trial was after 5 years of follow-up [12]. In the group treated with breast-conservation therapy alone, 12% of patients with tumours equal to or larger than 2 cm developed local recurrence, whereas this was 7% for those with tumours smaller than 2 cm. This difference was statistically significant ($P=0.02$). However, in the group treated with breast-conservation therapy and post-operative radiotherapy, no such association between tumour size and local recurrence was seen (Table 1).

In the National Cancer Institute trial, 237 patients were randomised to mastectomy ($n=116$) or breast-conservation therapy and radiotherapy ($n=121$) [25,27]. 39% of all patients had tumours larger than 2 cm, and in 7% of patients in the breast-conserving arm the tumours were between 4.1 and 5 cm in size. Patients who were randomised to breast-conservation therapy had gross tumour excision, but histologically-free margins were not required. After a median follow-up of 10.1 years, 19 patients (16%) in the breast-conserving arm developed local recurrence and on univariate analysis these recurrences were not associated with tumour size [27].

The two randomised trials to report tumour size as a risk factor for local recurrences are the Ontario trial [30–32] and the EORTC 22881/10882 trial [34]. In the Ontario trial, 837 women with node-negative breast cancer were randomised to receive radiation therapy or no radiation therapy after breast-conservation therapy. After a median follow-up of 7.6 years, 148 (35%) patients in the non-irradiated group and 47 (11%) patients in the irradiated group developed a local recurrence. On multivariate analysis, tumours larger than 2 cm had a significantly higher risk of local recurrence than tumours smaller than or equal to 2 cm in size (Relative Risk 1.73, 95% Confidence Interval (CI) 1.26–2.37; $P=0.0006$). In the EORTC 22881/10882 trial, 5318 women were randomised to receive the standard 50 Gy of radiotherapy or an additional boost of 16 Gy after breast-conservation therapy. After a median follow-up of 5.1 years, local recurrences were observed in 182 of the 2657 (7%) patients in the standard-treatment group and 109 of the 2661(4%) patients in the boost group. Analysis of size as a risk factor for local recurrence was based only on whether the tumour was palpable or not. On multivariate analysis, palpable tumours were associated with a significantly higher risk of local recurrence development compared with non-palpable tumours (Hazard Ratio 2.14, 95% CI 1.23–3.72; $P<0.007$).

Because of the small number of patients enrolled in several of these trials and the relatively low rate of local recurrence in many, the number of events has limited risk-factor analysis. In order to address this, Voogd and colleagues re-analysed pooled data from the EORTC 10801 trial and the Danish trial [37]. Information on local recurrence (as opposed to regional) in relation to tumour size was obtained, which had not been published in the individual trial publications. The results showed that the 10-year actuarial risk of local recurrence after breast conserving surgery was 17% for tumours smaller than 2 cm and 11% for tumours larger than 2 cm. On multivariate analysis, tumour size was not one of the risk factors identified for local recurrence (Table 1).

Numerous retrospective studies have analysed the association between tumour size and local recurrence [13,38–43] (Table 2). In these studies, only one found an association between tumour size and local recurrence [13]. In this study by Veronesi and colleagues, the medical records of 2233 women who received quadrantectomy and axillary lymph node dissection followed by radiotherapy at the Milan Cancer Institute were analysed. The results showed that the yearly risk of local recurrences was approximately 1% up to the 10th postoperative year. One hundred and nineteen local recurrences were identified, 106 of which had information available on tumour size. 14 of 215 patients (6.5%) with tumours equal to or larger than 2 cm developed local recurrence, whereas this occurred in 87 of 1768 patients (4.9%) with tumours between 0.6 and 2.0 cm and 5 of 126 patients (4.0%) with tumours equal to or less than 0.5 cm. On both univariate and multivariate analysis, tumours greater than 2.1 cm had a significantly higher risk of local recurrence compared with tumours 0.5 cm or smaller (risk ratio 3.159, $P=0.0183$).

Two case–control studies have found no association between tumour size and local recurrence after breast-conservation therapy [44,45]. In the study by Voogd and colleagues, 279 patients with local recurrence after breast-conservation therapy were identified. Each case was matched with two controls without local recurrence by their date of surgery. Only 5% of the case tumours were larger than 3 cm. The adjusted relative risk of local recurrence after excision of tumours greater than or equal to 2.0 cm was 1.1 (95% CI 0.74–1.7) compared with 1.0 for tumours less than 2.0 cm. Tumour size was therefore not one of the identified risk factors for local recurrence.

Finally, studies on patients treated with preoperative chemotherapy followed by breast-conservation therapy for operable breast cancer have included large tumours (>5 cm) [46–50], although only a few have assessed tumour size as a risk factor for local recurrence in these patients [51,52]. In the NSABP B-18 trial, 1495 patients were randomly assigned to either preoperative or post-operative chemotherapy with doxorubicin and cyclophosphamide [51]. 954 were treated with breast-conservation therapy. When both groups were analysed together after 5 years of follow-up, clinically estimated tumours equal to or larger than 3 cm had a marginally

higher rate of local recurrence than tumours smaller than 3 cm, although this difference did not reach statistical significance ($P = 0.09$). In a retrospective study by Rouzier and colleagues, 257 patients with operable tumours up to and larger than 5 cm were treated with preoperative chemotherapy, breast-conservation therapy and radiation therapy [52]. Before chemotherapy, 174 patients (68%) had tumours clinically larger than 3 cm. At time of surgery, only 58 (23%) patients had tumours larger than 2 cm. The local recurrence rates were high; 16% at 5 years and 21.5% at 10 years. On multivariate analysis, a clinical tumour size of more than 2 cm at the time of surgery was shown to be significantly associated with an increased local recurrence rate compared with smaller tumours (Risk Ratio 2.09, $P = 0.04$).

4. Should tumour size alone be an exclusion criteria for breast-conservation therapy?

Tumour multifocality not recognised at the time of surgery is most likely to be the cause of early recurrences. The risk of such recurrence can be minimised by ensuring pathologically-clear margins and increasing the margins of excision. Late local recurrences may be due to the development of second primary cancers [14]. Evidence from pathological studies suggests that tumour size is not a risk factor for tumour multifocality for cancers less than 4 cm. Evidence from clinical studies suggests that tumour size is not a risk factor for local recurrence for cancers less than 3 cm. However, there is little data on which to base a conclusion on the risk of local recurrence for cancers larger than 3 cm and none for cancers over 5 cm.

For breast cancers up to 3–4 cm, breast-conservation therapy may be considered a safe option, providing of course that the margins of excision are clear, postoperative radiotherapy is given and an acceptable cosmetic result can be achieved. For cancers larger than 3–4 cm, there is no clear evidence of the oncological safety of breast conservation. We propose that Breast Units who offer breast-conservation therapy for tumours of such size, with or without partial breast reconstruction, should audit this practice and, ideally, this data should be compiled within a registration study, taking into account the known risk factors for local recurrence.

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