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CLINICAL TRIAL

Comparing long-term local recurrence rates of surgical and non-surgical management of close anterior margins in breast conserving surgery

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Abstract

Purpose While it is known that histologically involved margins lead to a higher local recurrence rate, re-excision of anterior margins is less common than that of radial margins. However, there are minimal long-term data on the oncological safety of non-surgical management of anterior margins.

Patients and methods A retrospective study was performed of all patients who underwent breast conserving surgery for breast cancer between 2000 and 2008 at two tertiary referral centres. A close margin was defined as disease within two mm of the resection margin (including disease at the margin).

Results 6922 patients underwent surgery for invasive or in situ breast cancer of whom 277 patients had a close anterior margin alone after breast conserving surgery. Two hundred and twenty patients had non-surgical management of their margins, while 57 had re-excision surgery. Overall, there were 4/57 local recurrences in the surgical management group and 12/220 in the non-surgical management group. The local recurrence-free survival rate at 5 years was 98.2% (1 recurrence, 95% CI 87.8–99.7) in the surgical management group and 97.2% (6 recurrences, 95% CI 93.8–98.7) in the non-surgical management group. At 10 years, the rates were 92.2% (4 recurrences, 95% CI 80.3–97.0) in the surgical management group and 93.9% (12 recurrences, 95% CI 89.4–96.5) in the non-surgical management group. There was no significant difference found in the local recurrence rate between management groups (HR 1.24, 95% CI 0.40, 3.85; $p = 0.71$).

Conclusions Local recurrence rates are acceptable and similar in both the surgically and non-surgically managed groups. Non-surgical management of close anterior margins appears oncologically safe when combined with appropriate adjuvant therapy.

Keywords Breast neoplasms · Neoplasm recurrence · Local · Multicentre studies

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Introduction

Breast cancer is the most common cancer across Europe with over half a million new diagnoses every year [1]. Surgical treatment involves either a mastectomy or breast conserving surgery depending on pathological factors as well as patient choice [2]. Published local recurrence rates after breast conserving surgery range from 2 to 17% [3–7] with more recent publications reporting overall lower recurrence rates due to improved adjuvant treatment. Recent European guidelines recommend a local recurrence rate of less than 0.5% a year after breast conserving surgery [8]. One in four local recurrences result in systemic disease highlighting the survival benefit of reducing local recurrence [9]. While it is known that histologically involved margins lead to a

higher local recurrence rate [10–12], it is thought that anterior and posterior margins are less important than radial margins [6, 13]. To further complicate decision-making, there is no uniform definition of margin involvement and no randomised controlled trials of adequate margin clearance. Observational studies of patients with invasive and in situ carcinoma have produced conflicting results as to the significance of margin width on local recurrence rates [10, 14–22]. Recent European and American guidelines adopted no tumour on inked margin for invasive disease and at least 2 mm for in situ carcinoma [8, 23, 24] while a UK consensus statement advises at least a 1 mm margin for both in situ and invasive cancer [25]. The potential benefits of re-excision have to be balanced against the consequences of further physical, cosmetic and psychological harm for the patient, the delay to commencement of adjuvant therapy and associated financial cost. There are no guidelines for the management of involved anterior margins alone and nearly a third (29%) of surgeons would never excise an involved anterior margin in patients with invasive carcinoma [26]. The proportion of surgeons that would never excise an involved anterior margin increases to nearly half (44%) for patients with in situ carcinoma. Mullen et al. highlighted that re-excision of involved anterior margins yielded further disease in only 4% of patients, prompting the authors to discontinue routine re-excision of involved anterior margins [27]. A 2016 study from Edinburgh showed a 5-year local recurrence rate of 2.7% in patients who did not have re-excision of an involved anterior margin after surgery for invasive disease [28]. The study did not investigate the effect of re-excision on the local recurrence rates. A 2016 review found that there is no evidence of the effect of re-excision of anterior margins upon local recurrence rates [29] but the review only included six papers, three of which were cross-sectional surveys of surgeons views. Of the remaining three studies, one did not report local recurrence rates and the two others reported on patients who had positive anterior margins in combination with other margins. We aimed to compare the effect of surgical and non-surgical management of close anterior margins (including tumour at margin) on long-term local recurrence rates following breast conserving surgery.

Patients and methods

A retrospective review was performed of all patients who underwent surgery for invasive or in situ carcinoma between 2000 and 2008 at two tertiary referral units. One centre's policy was to re-excise all patients with a close anterior margin (surgical management centre, SMC), whereas the second centre did not routinely undertake re-excision surgery (non-surgical management centre, NSMC). Electronic patient records, pathology records, radiology records as well as the Somerset database were cross-checked to ensure data accuracy. The data extracted for each patient included original and re-excision histology, margin width, adjuvant therapy received and local recurrence. Study follow-up ceased in April 2016.

Surgical technique

During the study period, breast conservation surgery generally consisted of an incision placed over the tumour, dissection continued down to pectoralis major fascia followed by removal a cylinder of tissue and leaving behind thin anterior flaps. Skin was excised if involved by the cancer. All patients with clinically negative nodes had sentinel node biopsy, and this was followed by axillary node clearance if the nodes were positive for metastatic deposits. Specimens were orientated in three dimensions for pathological assessment. Re-excision of the anterior margin involved either skin resection or resection of the subcutaneous fat beneath the skin.

Adjuvant therapy

During the study period, both unit guidelines were for patients with oestrogen receptor positive invasive disease to receive endocrine therapy for 5 years. Radiotherapy was given to patients who had breast conserving surgery for invasive carcinoma, or those with DCIS lesions with a high risk of recurrence. Patients who had moderate or high risk disease were given chemotherapy. Both units used Van Nuys Prognostic Index for approximating risk [30]. In addition, Trastuzumab (Herceptin®, Roche) was used from August 2006 in patients who had disease that was positive for human epidermal growth factor receptor 2 (HER2).

Margins

A close anterior margin was defined as disease within two mm of the resection margin, and an involved margin as that with disease at the inked margin. We aimed to study patients who had only a close anterior margin with all other margins being clear, to avoid risk of close radial margins influencing local recurrence rates. The pathological findings were discussed at a post-operative multi-disciplinary team meeting.

Local recurrence

Local recurrence was defined as disease in the ipsilateral breast following breast conserving surgery for invasive or in situ breast cancer.

Statistical analysis

Categorical data was described using proportions and frequencies and formally compared using Chi squared tests or Fisher's exact tests, as appropriate. Continuous data was described with means, standard deviations and the range of the data and was compared formally using two sample *t* tests. Comparisons were made between management group and centre with respect to local recurrence-free survival time using a Kaplan–Meier curve. To compare the effect of management group on local recurrence-free survival time, a Cox proportional hazards survival model was fitted to the data. This approach allowed the computation of a hazard ratio and 95% confidence interval. A p value of < 0.05 was considered to be statistically significant. Statistical analysis was performed using Stata version 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results

There were 6922 patients that underwent surgery for invasive or in situ breast cancer across both units. Of these patients, 277 had a close anterior margin (< 2 mm) after breast conserving surgery, with all other margins being greater than two mm (Fig. 1). Median follow-up duration was 9.9 years for the non-surgical management patients ($n = 220$, range 0.2–16.3) and 10.4 years for the surgical management patients ($n = 57$, range 1.2–16.1). Tumour characteristics were compared by margin management (Table 1). More patients had disease at the margin or transected in the surgical management group ($p < 0.001$), potentially highlighting management being influenced by the pathology. Other tumour characteristics were generally comparable. There were no differences in the adjuvant therapy received between the two management types (Table 2).

Histology following surgical management

Six patients had disease found on histology following surgical management of a close anterior margin (11%). Of these, three had an involved margin, one a margin width of less

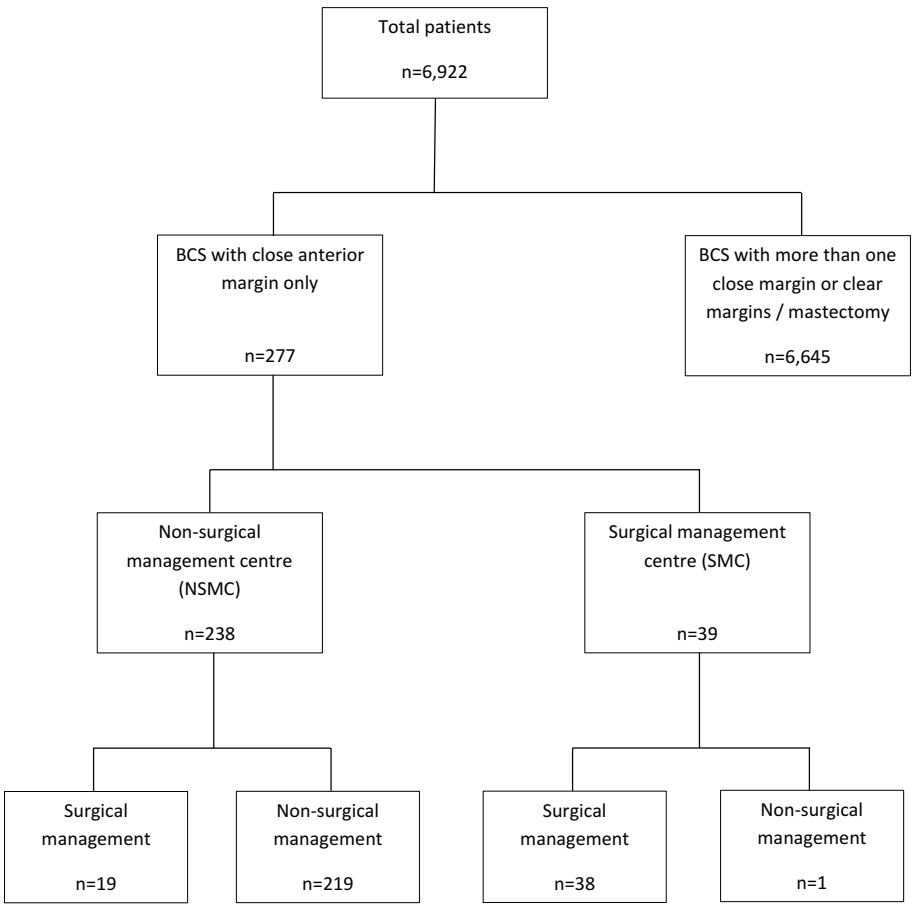

Fig. 1 Study profile showing the management of patients with a close margin after breast conserving surgery at two breast centres

Table 1 Patient and disease characterises by margin management

	Non-surgical management ($n=220$)	Surgical management ($n=57$)	p value
Age (years)	59.8 (8.1), 31.8–79.0	58.0 (9.1), 33.0–74.9	0.14
Disease type (%)			
Invasive disease only	46 (20.9%)	11 (19.3%)	0.31
Invasive and in situ disease	139 (63.2%)	32 (56.1%)	
In situ disease only	35 (15.9%)	14 (24.6%)	
Grade (%)	$N=184$	$N=43$	
Grade 1	37 (20.1%)	11 (25.6%)	0.23
Grade 2	79 (42.9%)	22 (51.2%)	
Grade 3	68 (37.0%)	10 (23.3%)	
T stage (%)	$N=180$	$N=37$	0.079
T1	149 (85.1%)	31 (73.8%)	
T2	26 (14.9%)	11 (26.2%)	
T3/T4	0	0	
In situ grade (%)	$N=35$	$N=14$	0.075*
Intermediate/low grade	12 (34.3%)	1 (7.1%)	
High grade	23 (65.7%)	13 (92.9%)	
Margin (%)			
Transected	3 (1.4%)	4 (7.0%)	< 0.001
At margin	49 (22.3%)	27 (47.4%)	
< 1 mm	84 (38.2%)	15 (26.3%)	
1–2 mm	84 (38.2%)	11 (19.3%)	
Positive nodes (%)	40 (18.2%)	11 (19.3%)	0.85
ER positive (%)	173 (78.6%)	44 (77.2%)	0.81
HER2 positive (%)	10 (4.6%)	1 (1.8%)	0.47*
Follow-up (years)	9.9 (3.2), 0.19–16.3	10.4 (3.1), 1.2–16.1	0.26

For continuous variables, results given as Mean (SD), Minimum–Maximum. p Value was taken from a two sample T test. For categorical variables, results given as Number (Percentage) and p value taken from Chi squared test, unless otherwise stated. *p Value from Fisher's Exact Test

Table 2 Adjuvant therapy by margin management

	Non-surgical management ($n=220$) (%)	Surgical management ($n=57$) (%)	P value
Endocrine treatment (%)	153 (69.6)	43 (75.4)	0.38
Radiotherapy (%)	171 (77.7)	43 (75.4)	0.71
Chemotherapy (%)	35 (15.9)	11 (19.3)	0.55
Herceptin (%)	6 (2.7)	0	0.35*

Results given as Number (Percentage) and p value taken from Chi Squared test, unless otherwise stated. *p value from Fisher's Exact Test

than one mm and two patients a margin width of between one and two mm.

Local recurrence by margin management

We detail outcomes according to how the margin was actually managed rather than by centre. Overall, there were 4/57 local recurrences in the surgically managed group and 12/220 in the non-surgically managed group. At 5 years, the local recurrence-free survival rate in the surgically managed group was 98.2% (1 recurrence, 95% CI 87.8–99.7) and 97.2% (6 recurrences, 95% CI 93.8–98.7) in the non-surgically managed group. The 10-year local recurrence-free survival rate was 92.2% (4 recurrences, 95% CI 80.3–97.0) in the surgically managed group compared to 93.9% (12 recurrences, 95% CI 89.4–96.5) in the non-surgically managed group (Fig. 2). In the 49 patients who had in situ disease only, there were three local recurrences in the surgically managed group (n = 14) and one recurrence in the non-surgically managed group ($n=35$). In the 228 patients who had invasive disease, there was one recurrence in the surgically managed group ($n=43$) and 11 recurrences in the non-surgically managed group ($n=185$).

Performing a Cox regression based on margin management alone confirmed that there was no significant difference in the local recurrence rate when comparing surgical management with non-surgical management (HR: 1.24, 95% CI 0.40, 3.85; $p=0.71$).

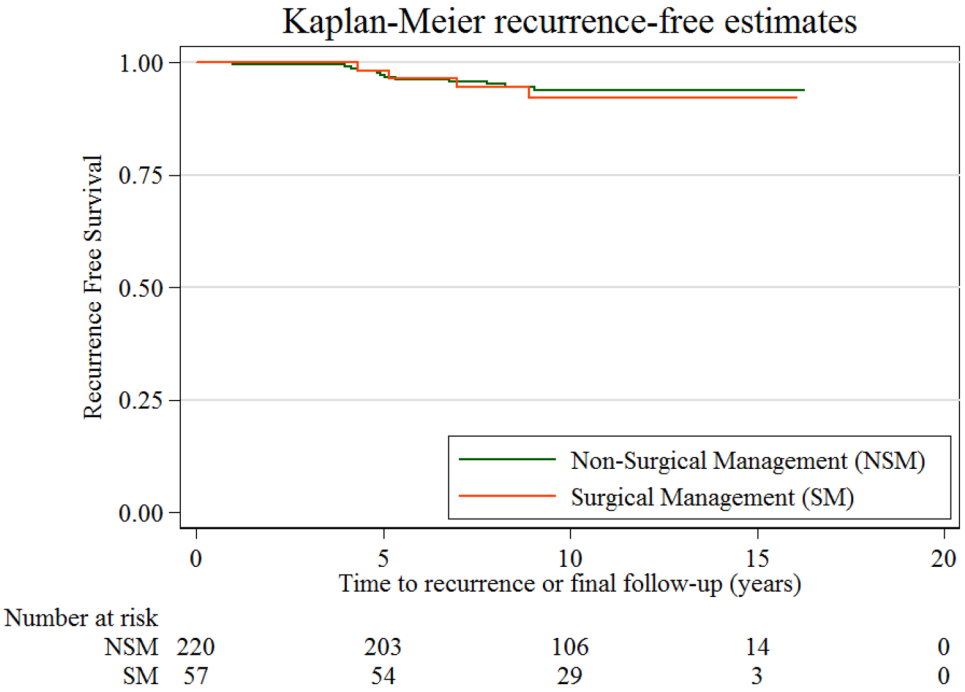

Fig. 2 Kaplan–Meier curve showing local recurrence-free survival comparing surgical and non-surgical management over time

Characteristics of patients who had surgical management at the NSMC

Eight percent of patients at the NSMC (19/238) had surgical management of their close anterior margin. These patients had less favourable disease characteristics. They were more likely to have positive lymph nodes (42.1% vs. 17.8%, $p=0.03$) or an involved (42.1% vs. 22.4%) or transected (21.1% vs. 1.4%) margin ($p<0.001$) compared to the rest of the patient population at the NSMC (Table 3).

Local recurrence by centre

At 5 years, the local recurrence-free survival rate at the SMC was 94.9% (2 recurrences, 95% CI 81.0–98.7) and 97.8% (5 recurrences, 95% CI 93.8–98.7) at the NSMC. The 10-year local recurrence-free survival rate was 91.5% (3 recurrences, 95% CI 75.6–97.2) in the SMC compared to 93.9% (13 recurrences, 95% CI 89.6–6.4) in the NSMC (Fig. 3).

Subgroup analysis for patients with a margin width of 1 mm or less

For this subgroup analysis, 95/277 (41.9%) patients with a margin of 1–2 mm were excluded. There were 3/46 local recurrences in the surgically managed group and 3/136 in the non-surgically managed group. The local recurrence-free survival rate for this subgroup at 5 years was 97.7% (1 recurrence, 95% CI 84.9–99.7) in the surgically managed group and 99.2% (1 recurrence, 95% CI 94.5–99.9) in the non-surgically managed group. At 10 years, the rate decreased to 92.5% (3 recurrences, 95% CI 78.2–97.5) in the surgically managed group and 97.7% (3 recurrences, 95% CI 92.8–99.2) in the non-surgically managed group. There was no significant difference found in the local recurrence rate between management groups (HR: 2.85, 95% CI 0.57, 14.12; $p=0.20$).

Discussion

Close anterior margins result in prolonged management discussions despite the lack of evidence to support decision-making. This study is the first to compare treatment options for close anterior margins. The classification of a close margin in this study was clearance of less than two mm from the edge of the specimen. While there is no consensus on the definition of an involved margin, 2 mm was widely used as a measure of margin clearance at the time of study set-up [31].

Re-excision of involved anterior margins yielded further disease in only six out of 57 patients (11%). This is similar to the rate reported by Mullen et al. using a one mm clearance at the anterior margin [27]. Other authors have reported disease at re-excision for any involved margin in 14–51% of patients [11, 32, 33]. A possible explanation for the low rate in our and Mullen's series is that thin anterior flaps left at breast conserving surgery contain little more than skin and a layer of subcutaneous fat.

Within 5 years of surgery, six patients who had non-surgical management of their involved anterior margin developed

Table 3 Disease characterises and adjuvant therapy in those treated surgically and non-surgically at the Non-Surgical Management Centre

	Non-surgical management ($n=219$)	Surgical management ($n=19$)	p value
Age (years)	59.8 (8.2), 31.8–79.0	55.9 (11.2), 33.0–74.9	0.053
Disease type (%)			
Invasive disease only	45 (20.6%)	3 (15.8%)	0.51*
Invasive and in situ disease	139 (63.5%)	11 (57.9%)	
In situ disease only	35 (16.0%)	5 (26.3%)	
Grade (%)	$N=183$	$N=14$	
Grade 1	37 (20.2%)	2 (14.3%)	0.60
Grade 2	79 (43.2%)	5 (35.7%)	
Grade 3	67 (36.6%)	7 (50.0%)	
T stage (%)	$N=174$	$N=13$	0.43*
T1	148 (85.1%)	10 (76.9%)	
T2	26 (14.9%)	3 (23.1%)	
T3/T4	0	0	
In situ grade (%)	$N=35$	$N=5$	0.30*
Intermediate/low grade	12 (34.3%)	0	
High grade	23 (65.7%)	5 (100%)	
Margin (%)			
Transected	3 (1.4%)	4 (21.1%)	< 0.001*
At margin	49 (22.4%)	8 (42.1%)	
< 1 mm	84 (38.4%)	4 (21.1%)	
1–2 mm	83 (37.9%)	3 (15.8%)	
Positive nodes (%)	39 (17.8%)	8 (42.1%)	0.030*
ER positive (%)	172 (78.5%)	14 (73.7%)	0.57*
HER2 positive (%)	10 (4.6%)	0	> 0.99*
Follow-up (years)	9.9 (3.2), 0.19–16.3	9.9 (4.1), 1.2–16.1	0.93
Endocrine treatment (%)	152 (69.4%)	14 (73.7%)	0.70
Radiotherapy (%)	170 (77.6%)	11 (57.9%)	0.09*
Chemotherapy (%)	34 (15.5%)	5 (26.3%)	0.21*
Herceptin (%)	6 (2.7%)	0	> 0.99*

For continuous variables, results given as Mean (Standard Deviation), Minimum–Maximum. p Value was taken from a two sample T test. For categorical variables, results given as Number (Percentage) and p value taken from Chi Squared test, unless otherwise stated. *p Value from Fisher's Exact Test

a local recurrence, this equated to a 97.2% local recurrence-free survival rate. This was not statistically different from the rate of local recurrence amongst patients who had surgical management of their margin (Cox regression $p=0.71$). The ten year local recurrence-free survival rate was 93.9% (12 recurrences) in the non-surgically managed group and 92.2% (4 recurrences) in the surgically managed group.

As current UK guidelines define a close margin as within one mm, we analysed the data for those patients and the local recurrence-free survival rates were similar at 5 (surgically managed group 97.7%, 1 recurrence and non-surgically managed group 99.2%. 1 recurrence) and 10 years (surgically managed group 92.5%, 3 recurrences and non-surgically managed group 97.7%, 3 recurrences). These data are in agreement with those from Edinburgh of 78 patients who had non-surgical management of their involved (< 1 mm) anterior margin after surgery for invasive disease [28].

The low rates of local recurrence are multifactorial, influenced by radiotherapy, chemotherapy, Trastuzumab and hormonal therapy [9, 34, 35]. Whether re-excision surgery contributes to the low local recurrence rates has long been debated. Notwithstanding the few local recurrences and the wide confidence interval, our data shows that re-excision surgery does not appear to improve local recurrence rates over that achieved by appropriate adjuvant therapy. In addition, of those patients who had surgical management of their close anterior margin, the vast majority had no macro- or microscopic disease on re-excision histology and could be regarded as having been over-treated. Further surgery to the breast is likely to have an impact on cosmesis, although this was not assessed in this study.

Although the policy at one centre (NSMC) was to not routinely re-excise close anterior margins, 19 patients underwent re-excision. These patients were more likely

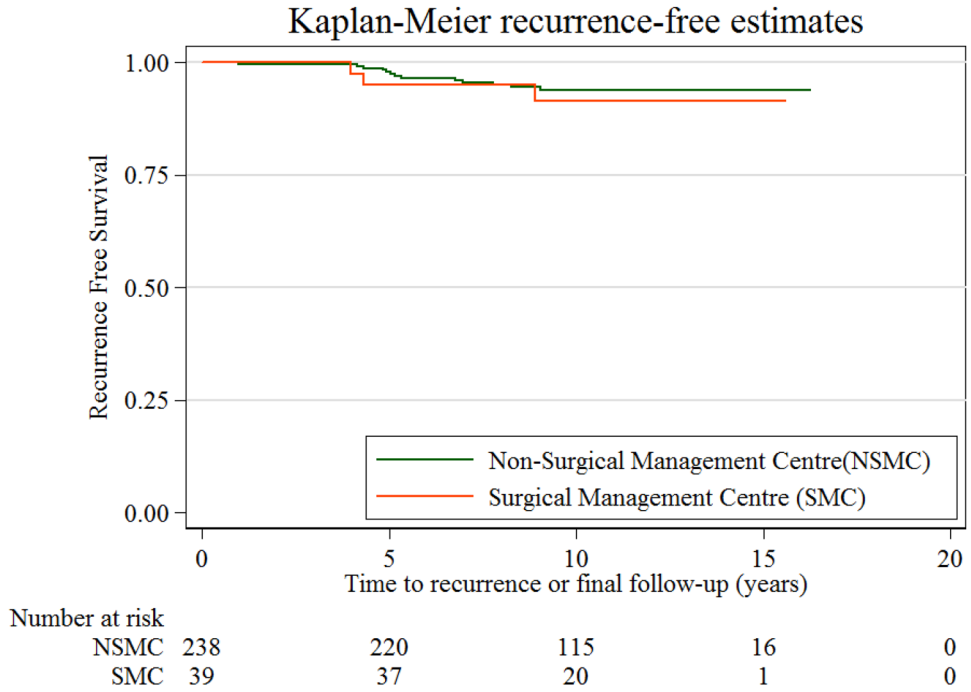

Fig. 3 Kaplan–Meier curve showing local recurrence-free survival comparing the surgical management centre with the non-surgical management centre

to have disease at the margin (63%) compared to the rest of the patients treated at this centre (24%). This is likely to have been a factor in the MDT discussion that preceded the decision to perform re-excision surgery. Indeed, these patients included four whose disease was transected at the margin. The MDT at the NSMC appears to have recommended re-excision surgery on the basis of the risk of residual disease or a perception of a higher risk of local recurrence in these patients. It is likely that patients with transected margins have more benefit from re-excision surgery but this study was underpowered to investigate this. In addition, although this is the largest study to date, the number of patients who had a local recurrence was not large enough to perform a multifactorial analysis of the data.

We have demonstrated that non-surgical management of close anterior margins is oncologically safe when combined with appropriate adjuvant therapy. In addition, this negates the need for a second operation that may increase patient anxiety, negatively impact on cosmesis and increase healthcare costs. However, there may be a benefit to re-excision surgery of a patient with a transected primary tumour.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study complied with all applicable laws in the United Kingdom.

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