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ORIGINAL ARTICLE

Local excision after (near) complete response of rectal cancer to neoadjuvant radiation: does it add value?

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Abstract

Purpose Neoadjuvant radiotherapy is commonly used in rectal cancer. When used prior to radical surgery in locally advanced disease, up to one-quarter of patients have no residual cancer at surgery suggesting that radical surgery was unnecessary; those with complete clinical response may be managed on a rectal-preserving 'watch-and-wait' pathway. In those receiving radiotherapy for early stage cancer, local excision of small volume residual or recurrent tumour is possible, but its value is unclear.

Methods Data were collected from two institutions (UK and Denmark) which maintain prospective databases on all patients undergoing local excision by transanal endoscopic microsurgery (TEM). The study group was all patients who had TEM after neoadjuvant radiation for rectal cancer over an 11-year period.

Results Forty-five patients had TEM after neoadjuvant radiation, 18 after short course radiotherapy (SCRT) and 27 after chemoradiotherapy (CRT). Local recurrence occurred in 13 (29%) and distant metastases in 11 (24%). Complete pathological response was noted in 10 (22%), 28% after SCRT and 19% after CRT, $p = 0.02$. However, local recurrence still occurred in 60% of those with ypT0 after SCRT. The recurrence rate may be higher in those with residual disease at TEM compared with complete responders (40 vs 30%).

Conclusion If complete response can be determined clinically, local excision of the scar does not confer benefit, but follow-up should be maintained. If there is regrowth or residual tumour at TEM, further recurrence is common, and the benefits of TEM may not outweigh the risks, except in those unsuitable for radical surgery.

Keywords Rectal cancer · Radiotherapy · Organ preservation · Local recurrence

Introduction

Neo-adjuvant radiotherapy has become common practice in rectal cancer management, usually prior to standard radical surgery in locally advanced disease. The occurrence of complete response in up to one-quarter of patients treated with neoadjuvant radiotherapy [1] means that radical surgery may be avoided in some patients, leading to the use of radiotherapy as a potential organ-preserving strategy [2]. This group mainly comprises those patients who are opportunistic complete responders, in which radiotherapy was indicated because of advanced disease on MRI who happen to develop a dramatic response. However, there is a growing population of patients who have radiotherapy for early stage disease with the intention of seeking a complete response in order to avoid radical surgery. The motivation in this group may be unsuitability for radical surgery because of comorbidity or patients may be driven to avoid major surgery for personal reasons.

Assessment of response can be difficult as not all cases demonstrate typical features of complete clinical response leaving clinicians uncomfortable with a non-operative approach [3] and clinicians may look for verification of response, or excision of residual disease through local excision. The CARTS study showed that local excision after radiotherapy enables organ preservation in two-thirds of those with early rectal cancer, with good oncological and functional outcomes [4]. Following complete clinical response to

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radiotherapy, 25% of patients experience a regrowth in the first 24 months [5], and under some circumstances, it may be possible to manage this regrowth with local excision in patients who are unfit or refuse major surgery.

This paper aims to look at the group of patients undergoing local excision by TEM after neo-adjuvant radiation to determine what value the local excision adds to the patient's management pathway and whether any particular features of the tumour or neoadjuvant treatment regime define a subgroup which receives greater benefit from local excision for residual disease or limited regrowth.

Methods

A retrospective analysis of prospectively collected data in a dedicated TEM database from two centres was undertaken, one in the UK and one in Denmark. All patients had a diagnosis of invasive malignancy in the TEM specimen, or on pre-treatment biopsy for those who had TEM after complete response to neoadjuvant radiation, over an 11-year period from 2007 to 2017. Pre-treatment assessment included endoscopy, MRI and CT scan. Treatment decisions were made by the multidisciplinary team. Endoscopy was undertaken 4–6 weeks after radiotherapy to assess response. TEM was undertaken to remove the residual scar or tumour following radiation or because of regrowth following complete clinical response. Patients fit for radical surgery had this option, as an alternative to TEM, or if the resection margins at TEM were positive; those included in this study chose to pursue an organ-preserving strategy. Data collected included demographics, pre-operative staging, neoadjuvant treatment, details of surgical procedure, complications, histopathology of the tumour and outcome.

Patients were followed up according to the standard protocol: CEA (carcinoembryonic antigen), flexible sigmoidoscopy and pelvic MRI every 3–4 months for the first 2 years, then 6–12 monthly until 5 years. CT chest-abdomen-pelvis was performed yearly up to 3 years.

Radiotherapy

The CRT regime used was 45–50.4 Gy radiation in 25 or 28 fractions daily for 5 weeks with oral capecitabine. SCRT treatment involved 25 Gy in five fractions without chemotherapy. The irradiated fields comprised the rectum, mesorectum and lateral pelvic walls.

Statistical analysis

The data were collated in Excel (Microsoft) and descriptive statistics were obtained in Excel. Analysis was undertaken using R statistical software (www.r-project.org). Chi-square or Fisher's exact test was used to test for group differences for categorical data; Mann-Whitney was used for continuous data. Cox proportional-hazards regression was used to assess outcome. Kaplan-Meier estimates were obtained for local recurrence-free, disease-free and overall survival. Patients without recurrence were censored at date of last follow-up or death. This study was conducted according to ethical standards and reported according to STROBE guidelines.

Results

Pre-operative radiotherapy was used in 45 patients prior to TEM. This group included 28 males and 17 females, with a median age of 75 (range 43–96). Prior to commencing neoadjuvant radiation, the tumour was staged on MRI as cT1 in six, cT2 in 22, cT3 in 16 and cT4 in one. Nodal metastases were detected on pre-operative imaging in 15 (33%).

CRT was used in 27 (60%) and SCRT in 18 (40%); characteristics of these groups are shown in Table 1. In 27 (60%), patients TEM was undertaken with curative intent, while in 18 (40%), it was a compromise treatment as the patient was not fit for, or declined, radical surgery. In the SCRT group, treatment was considered compromise rather than curative in a significantly higher proportion.

The median interval between neoadjuvant treatment and TEM was 15 weeks (range 4–56 weeks), and for a third of patients (15/45), the interval was more than 16 weeks. It was not possible to clearly separate patients with residual tumour from those with regrowth.

Pathology

In 10 cases (22%), there was no residual tumour in the TEM specimen; this occurred significantly more frequently in the SCRT group (5/18, 28%) compared to the CRT group (5/27, 19%), $p = 0.02$. Pre-operative staging was cT1 in one, cT2 in four and cT3 in five. The median time from RT to TEM was 16 weeks; this was the same for the CRT and the SCRT subgroups.

In the 35 cases with regrowth or residual tumour in the TEM specimen, the stage was ypT1 sm3 in nine, ypT2 in 20 and ypT3 in six. The resection margin was positive in 13 specimens (29% overall, but 37% in patients with tumour present); this was mostly at the deep margin (10/11 where recorded). For the 18 patients where TEM was a compromise option, 17 TEM specimens contained residual tumour, and the resection margin was positive in seven (39%).

Table 2 compares pre-treatment staging on MRI with pathological staging at TEM and shows that in total 27 (60%) tumours were downstaged (61% in SCRT and 59% in CRT group). Staging was unchanged in 13, six (33%) in the SCRT

Table 1 Demographic and tumour characteristics of patients having TEM after CRT vs SCRT

Number of patients	SCRT 18	CRT 27	*p* value
Sex M: F	13 (72%): 5	15 (56%): 12	0.41
Age at TEM, median (range)	76 (47–90)	74 (43–96)	0.69
Tumour stage (MRI)			cT1/2 v T3/4
cT1	2 (11%)	4 (15%)	0.12
cT2	12 (67%)	10 (37%)	
cT3	4 (22%)	12 (44%)	
cT4		1 (4%)	
Nodal involvement (MRI)	8 (44%)	7 (26%)	0.33
Intention			
Curative treatment	7 (39%)	20 (74%)	0.04*
Compromise treatment	11 (61%)	7 (26%)	
Distance from anal verge			
≤ 6 cm	10 (56%)	21 (78%)	0.21
> 6 cm	8 (44%)	6 (22%)	
Tumour diameter	†		
≤ 3.0 cm	9 (69%)	18 (67%)	0.87
> 3.0 cm	4 (31%)	9 (33%)	
Interval RT to TEM (weeks), median (range)	11 (6–56)	15 (4–59)	0.23
Pathological tumour stage			ypT0 v others
ypT0	5 (28%)	5 (19%)	0.02*
ypT1	5 (28%)	4 (15%)	
ypT2	6 (33%)	14 (52%)	
ypT3	2 (11%)	4 (15%)	
Local recurrence	5 (28%)	8 (30%)	0.89
Distant metastases	6 (33%)	5 (19%)	0.26

† Size not stated in five

* Indicates $p < 0.05$

group and seven (26%) in the CRT group. The tumour had progressed in five (11%) in total.

Outcome

The median follow-up was 3.1 years (range 0.02–10.5). Three of the ten patients without residual tumour developed local recurrence, all in the SCRT group. One recurrence was nodal, and two were in the rectal wall. These recurrences were diagnosed at 0.5, 1.5 and 4.8 years following TEM. Two of these died of disease and one is alive with disease 5 years after TEM. The other seven patients without residual tumour remain disease-free at a median of 6.0 years after TEM (range 1.0–9.4).

Of the 35 patients with regrowth or residual tumour present at TEM, 10 (29%) developed local recurrence at a median 10

Table 2 Comparison of pre-treatment clinical staging and pathological staging at TEM by neoadjuvant treatment regime. Italic values on the diagonal indicate no change in stage; cells below and left are down-staged; cells above and right indicate tumours that have progressed

SCRT						CRT					
	ypT0	ypT1	ypT2	ypT3	Total		ypT0	ypT1	ypT2	ypT3	Total
cT1	1	**1**	0	0	2	cT1	0	**1**	1	2	4
cT2	3	4	**4**	1	12	cT2	1	3	**5**	1	10
cT3/4	1	0	2	**1**	4	cT3/4	4	0	8	**1**	13
Total	5	5	6	2	18	Total	5	4	14	4	27

months (range 4–51 months) after TEM. Eight recurrences were in the rectal wall and two were nodal. For those where the interval between RT and TEM was over 16 weeks, 5/15 (33%) developed local recurrence (5/12 if the ypT0 group are excluded), and where the interval was over 6 months, 2/9 (22%) developed local recurrence (2/7 excluding ypT0).

In four patients, the local recurrence was isolated while six also had distant disease. A further four had distant disease only, all diagnosed within 12 months of TEM. Of the 14 with any recurrence, 10 had died of disease at a median of 2.2 years after TEM (range 0.1–3.9 years), three were alive with disease at last follow-up at a median 1.6 years (range 1.5–4.3) after TEM, and one was well 10 years after salvage anterior resection. For the 18 patients where TEM was a compromise option, eight (44%) developed local and/or distant recurrence.

The estimated local recurrence-free, disease-free and overall survival risks for the subgroup that had no residual tumour at TEM compared with those with disease present are shown in Table 3. Survival curves are shown in Figs. 1, 2, and 3. In each, there is a tendency for those with no residual tumour at TEM to do better, but numbers are not large enough to reach significance.

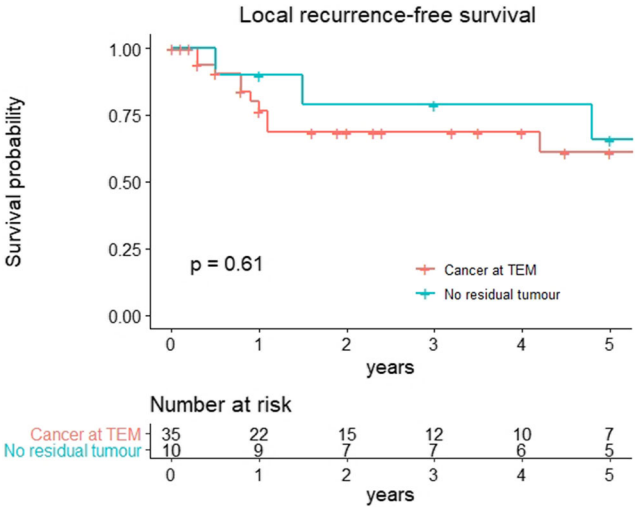

Fig. 1 Local recurrence-free survival after TEM for those with and without residual cancer after neoadjuvant radiation

Discussion

Local excision after neoadjuvant radiation has a role to play in patients pursuing a rectal-preserving strategy in the treatment of rectal cancer, although that role has not yet been clearly defined. The group considered here had an initial good response to radiotherapy and have had local excision of residual tumour or scar or limited regrowth as part of a 'watch and wait' pathway. The regrowth group could not always be distinguished from those with residual disease, but we defined a subgroup who had local excision more than 6 months after radiotherapy and only 2/7 with cancer in the specimen suffered a subsequent recurrence. Therefore, there may be a role for local excision in managing limited late regrowth in those unsuitable for radical surgery.

A complete pathological response (ypT0) was noted in the TEM specimen in ten patients, half of whom had SCRT and

Table 3 Estimated survival after TEM for those who had no residual tumour after neoadjuvant radiation, compared with those with residual tumour

	No residual tumour at TEM		Cancer present in TEM specimen	
	Number at risk	Risk (95% CI)	Number at risk	Risk (95% CI)
Local recurrence-free survival				
Estimated risk				
At 1 year	9	90.0 (73.2–100)	22	76.5 (62.6–93.5)
At 2 years	7	78.7 (56.4–100)	15	68.5 (53.2–88.1)
At 3 years	7	78.7 (56.4–100)	12	68.5 (53.2–88.1)
At 5 years	5	65.6 (40.2–100)	7	60.9 (43.2–85.7)
Any disease recurrence-free				
Estimated risk				
At 1 year	9	90.0 (73.2–100)	21	63.2 (48.6–82.3)
At 2 years	7	78.7 (56.4–100)	14	55.8 (40.7–76.5)
At 3 years	7	78.7 (56.4–100)	11	55.8 (40.7–76.5)
At 5 years	5	65.6 (40.2–100)	7	55.8 (40.7–76.5)
Overall survival				
Estimated risk				
At 1 year	10	100	29	85.5 (74.5–98.1)
At 2 years	8	88.9 (70.6–100)	22	82.0 (69.8–96.2)
At 3 years	8	88.9 (70.6–100)	16	64.7 (48.8–85.8)
At 5 years	7	88.9 (70.6–100)	8	54.7 (38.0–78.9)

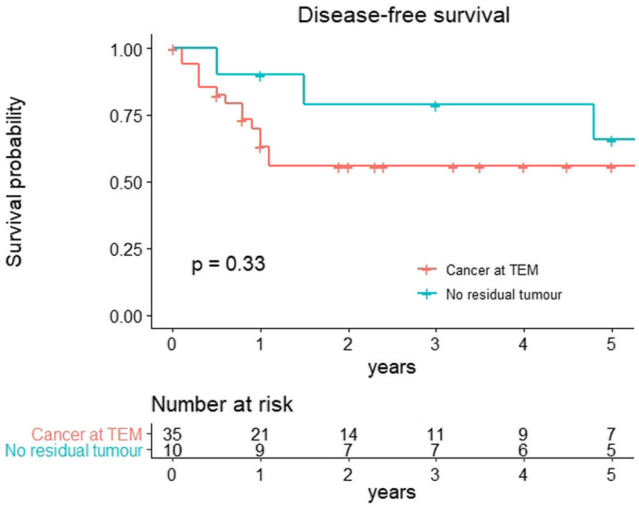

Fig. 2 Disease-free survival after TEM for those with and without residual cancer after neoadjuvant radiation

half CRT. Local recurrence occurred in three of those who achieved complete pathological response, all after SCRT. This indicates that while the SCRT dealt effectively with the primary tumour in these patients, residual nodal or vascular malignant deposits survived the radiation. This suggests that a complete pathological response after SCRT should not be viewed over-optimistically, although it is worth noting that SCRT was used more among those having compromise treatment, who may not have been fit for more aggressive treatment.

There was a high rate of positive resection margins, mostly at the deep margin, in excisions with residual tumour (37%). It is recognised that following radiotherapy the residual tumour may be fragmented within the bowel wall. Perez [6] observed that occult lateral spread of tumour beneath normal mucosa is a common finding after CRT. They recommend taking a margin of 1.5 cm around the visible tumour to reduce the positive

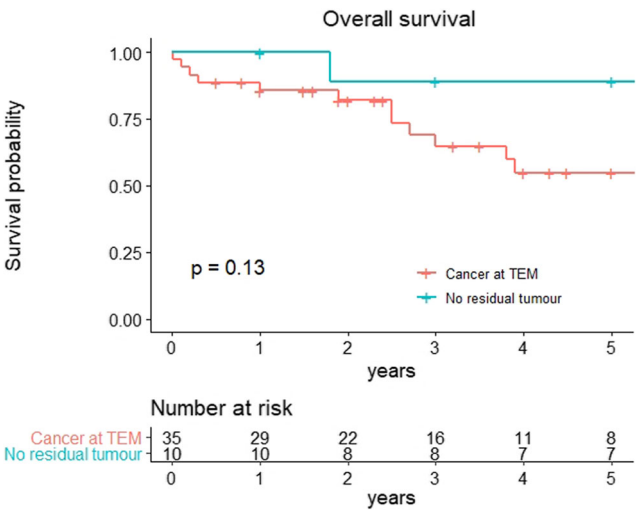

Fig. 3 Overall survival after TEM for those with and without residual cancer after neoadjuvant radiation

margin rate but note that there will still be instances of residual tumour beyond this distance. However, excision with such a margin is not always possible, for example if the cancer lies close to the sphincter muscle.

Most studies of local excision after radiotherapy have used CRT [7]. A study of 62 patients with cT1/2 N0 tumours who had SCRT followed 2 months later by TEM noted that 20 (32%) were ypT0 at TEM; among these, there was no local recurrence and one distant recurrence at a median 2-year follow-up [8]. A systematic review of over 1000 patients having local excision after neoadjuvant treatment, which involved CRT in around 95%, noted a pooled local recurrence rate of 4% among ypT0 tumours [7].

In the GRECCAR2 trial of patients with cT2/3 N0/1 tumours and 'good' response to CRT, similar to the present population, 81 had local excision 8 weeks after CRT of whom 44 (54%) were ypT0/1; among these, local recurrence occurred in 9% and metastatic disease in 14% at 5 years [9]. The 5-year disease-free survival was 70% and overall survival 82%, similar to the 66% and 89%, respectively, in our ypT0 patients. Completion TME was undertaken in 27 with ypT2/3 tumour at TEM; however, the authors note that the small volume of residual cancer in the ypT2 resections may not justify completion surgery.

A further French study [10] with 39 patients who had initial cT3/4 or N+ with a complete clinical response to CRT then local excision 10 weeks later found that only 28 (72%) in fact had a good response (ypT0/1). Of these, one (4%) had local recurrence at a median 4-year follow-up. Unfortunately, neither of these French studies presents separate results for the ypT0 cases.

A Polish study [11] with 14 tumours ≤cT3a N0 treated with CRT or SCRT followed by TEM also highlights the difficulty in clinically assessing response to radiotherapy. Nine clinically had incomplete response; one of these was ypT0 at TEM. Five had a clinically benign residual lesion, of these two in fact had residual cancer.

Assessment of clinical response is based on clinical examination, endoscopy and careful assessment of MRI scans. If such assessment concludes that there has been a complete response and local excision would yield a ypT0 specimen, the current results would indicate that local excision adds little value to the patient's management. However, if the patient had SCRT, there remains a risk of later recurrence, and close follow-up should be maintained.

On the other hand, where there is evidence for residual tumour or regrowth, further recurrence after local excision is a concern. While radical surgery would give oncological better outcomes, some patients refuse or are not fit for this option. In these patients, the decision to remove the tumour by local excision must weigh the risk of operative complications from

local excision after radiotherapy and impairment in functional outcome consequent upon multimodality treatment against the alternative of continued surveillance and possible further growth of the tumour which would cause further symptoms as the tumour became untreatable. A systematic review noted a pooled complication rate of 23% including 10% incidence of suture-line dehiscence [7]. The CARTS study noted a 50% incidence of major LARS (low anterior resection syndrome) at least 4 years after treatment in those having CRT then TEM [4], and a more recent study found worse LARS scores in those having multimodality treatment compared to those having TEM or CRT alone [12].

In conclusion, there seems little benefit to patients in local excision after neoadjuvant radiotherapy if there is no residual tumour on thorough clinical assessment. If there is regrowth or residual tumour, further recurrence is not uncommon and careful consideration should be given as to whether the benefits of surgery outweigh the risks.

Availability of data and material Data is not made available due to privacy.

Authors' contributions Study concepts: H Jones/I al-Najami/G Baatrup/C Cunningham
Study design: H Jones/I al-Najami/C Cunningham
Data acquisition: H Jones/I al-Najami/G Baatrup/C Cunningham
Quality control of data and algorithms: H Jones/I al-Najami
Data analysis and interpretation: H Jones/I al-Najami/C Cunningham
Statistical analysis: H Jones
Manuscript preparation: H Jones/I al-Najami/C Cunningham
Manuscript editing: H Jones/I al-Najami/C Cunningham
Manuscript review: H Jones/I al-Najami/G Baatrup/C Cunningham

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethics approval Formal ethical approval is not required as the data is routinely collected to enable follow-up.

Consent to participate Formal consent not required

Consent for publication Formal consent not required

Code availability n/a

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