A cohort study of local excision followed by adjuvant therapy incorporating a contact X-ray brachytherapy boost instead of radical resection in 180 patients with rectal cancer

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Abstract

Aim Recent data have suggested near-equivalent oncological results when treating early rectal cancer by local excision followed by radio- ± chemotherapy rather than salvage radical surgery. The aim of this retrospective study was to assess the use of contact X-ray brachytherapy within this paradigm.

Method All patients had undergone local excision and were referred to our radiotherapy centre for treatment with contact X-ray brachytherapy. Postoperative (chemo)radiotherapy was also given in their local hospital in most cases. Variables assessed were local excision method, postoperative therapy received, follow-up duration, disease-free survival, salvage surgery and stoma-free survival.

Results In total, 180 patients with a median age of 70 (range 36–99) years were assessed. Following local excision, pT stages were pT1 = 131 (72%), pT2 = 44 (26%), pT3 = 5 (2%). All patients received contact X-ray brachytherapy boosting at our centre and, in addition, 110 received chemoradiotherapy and 60 received radiotherapy alone. After a median follow-up of 36 months (range 6–48), 169 patients (94%) remained free of local recurrence. Of the 11 patients with local recurrence (three isolated nodal), five underwent salvage abdominoperineal excision. Eight patients developed distant disease, of whom five underwent metastasis surgery. At last included follow-up 173 (96%) patients were free of all disease and 170 (94%) were stoma free.

Conclusions Contact therapy can be offered in addition to external beam radio (±chemo) therapy instead of radical surgery as follow-on treatment after local excision of early rectal cancer. This combination can provide equivalent outcomes to radical surgery. The added value of contact therapy should be formally assessed in a clinical trial.

Keywords Rectal cancer, radiotherapy, chemotherapy, local excision, 'watch and wait'

What does this paper add to the literature?
In this series, following local excision of early rectal cancers, radical surgery could be avoided in over 94% of patients by treating the retained rectum with a contact X-ray brachytherapy boost, usually in combination with external beam (chemo)radiation. After all salvage treatments, 96% were disease-free and 94% were stoma-free.

Introduction

The introduction of bowel cancer screening programmes internationally has increased the number of patients who are being diagnosed with early rectal cancer [1,2]. Although, traditionally, radical surgery incorporating total mesorectal excision has been recommended as the standard treatment for rectal cancer, the risks and functional sequelae of this approach have generated interest in alternative less invasive approaches, especially for patients with early stage disease [3–7].

It is now accepted that local excision alone for rectal cancers staged as T1sm1 R0 can constitute definitive treatment as the risk of local relapse is very low [3,6]. In clinical practice, however, because of limitations in

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preoperative staging, after initial local excision, tumours are often found to be at a more advanced stage or have adverse features such as involved or R1 margins or lymphovascular invasion when examined pathologically [7–9]. In addition, rectal cancer is increasingly being diagnosed after excision of polyps that were thought to be benign at endoscopy [6]. In these scenarios, because of the high chance of finding no further disease after radical surgery (with all of its incumbent risks and the possibility of a stoma), it can be unclear what represents the best follow-on strategy. As such, patients are often offered radical surgery as a 'fail-safe'.

The aim of this study was to analyse the outcome of a large number of patients who had been diagnosed with rectal cancer after local excision and who were referred to our institution for treatment with contact X-ray brachytherapy (CXB). Patients who were referred usually also received postoperative long-course chemoradiotherapy (LCCRT) or external beam radiotherapy (EBRT). Patients have been referred for attempted organ preservation to our centre since 1993 because of its unique position (until recently) within the UK of being able to offer CXB [10–12]. This technique allows very high doses of radiation to be delivered very precisely transanally to the site of the local excision and can be given in addition to conventional EBRT [10–12]. The technique uses low-energy X-rays (50 kVp) which are confined to the aperture of the treatment applicator; therefore, uninvolved portions of the rectum can be completely excluded from the boost volume. In addition, treatment delivery time is approximately 60 s, it is relatively comfortable for the patient and is generally given on an outpatient basis. Broadly, the cohort of patients referred to our centre for CXB were either frail/elderly/comorbid patients or patients who were offered an abdominoperineal excision but wished to avoid a colostomy.

The aim of this study was to analyse the oncological outcomes from the series of patients treated in this manner at our institution.

Method

Initial patient selection and exclusions

All patients referred for CXB after prior local rectal cancer excision from January 2003 to November 2012 were identified from a prospectively maintained institutional database. In order to assess at least 2 years of follow-up, data were censored at November 2014. Referrals were received from UK clinicians for patients who had already undergone local excision and were felt to be at high risk of local recurrence and were either

(1) medically unfit or elderly or (2) fit enough for surgery but had refused completion surgery at the time of informed consent. On these grounds, specific ethical approval was not deemed to be necessary by our trust but this study was approved by the local audit committee (no. 01-02/26).

Importantly, the patients analysed in this series were referred from surgeons from across the UK and the high proportion of adverse features in this group is reflective of our centre being the main national referral centre for organ preservation rather than this being a consecutive series of patients who had been treated locally with poor surgical or endoscopic technique. Prior to treatment, all patients had been diagnosed with biopsy-proven adenocarcinoma of the rectum, had undergone full endoscopic and radiological staging and had been discussed in a local colorectal cancer multidisciplinary team meeting. Local T and N staging was determined using pelvic MRI except in those with cardiac pacemakers. All patients were free of distant metastases as determined by a baseline contrast-enhanced CT scan of the chest, abdomen and pelvis. Patients agreed to treatment after informed consent and counselling. Patients who required EBRT or LCCRT usually had this delivered locally and attended our institution solely for CXB.

Patients who had developed local recurrence following prior local excision and patients who had received prior radiation therapy followed by local excision were excluded from this study.

CXB dosage schedule

In the majority of cases, CXB was administered as an outpatient treatment every 2 weeks. At each visit, 30 Gy of 50-kV X-rays, targeted directly on the scar from local excision, was given under direct vision through a stainless rigid applicator sized at 2.2, 2.5 and 3 cm diameter. The standard dosage schedule was 60 Gy in two fractions over 2 weeks.

Surveillance protocol

The surveillance protocol that was used was identical to our 'watch and wait' protocol that has been described in detail in previous publications from our unit [12,13]. In brief, the most intensive monitoring was undertaken within the first 2 years after therapy, when the risk of recurrence was highest. If any active recurrence of tumour was suspected or detected, the patient was restaged and offered surgical salvage, provided no inoperable distant metastases were detected and he or she was fit and agreeable to the surgical procedure.

Data integrity and statistical analysis

As data had been accrued over many years, we commissioned an external, independent validator to ensure the accuracy and integrity of our data. This process identified that 94% of initial entries were accurate. All identified inaccuracies were corrected. All data were analysed using SPSS Version 21 (IBM, UK). The chi-square test was used for all categorical data analysis. Binary logistic regression was used for multivariate analyses. Survival analyses were performed using Kaplan–Meier estimation and Cox proportional hazard regression models.

Results

Our database identified 204 patients for whom CXB had been delivered after a prior local excision between 2003 and 2012. Twenty-four of these patients were excluded for the following reasons: five received palliative CXB, nine had multiple primary cancer types, four had additional high dose rate brachytherapy, five were lost to follow-up and one patient was from overseas. After exclusions, 180 patients were therefore suitable for inclusion in the present study. This group constituted 113 men and 67 women with a median age of 70 years (range 36–99 years); 148 (82%) had a performance status of 0 or 1.

Local excision was performed by endoscopic mucosal resection (EMR) ($n = 57$, 32%), transanal resection (TAR) ($n = 64$, 35%) and transanal endoscopic microsurgery (TEMS) ($n = 59$, 33%) (Table 1a). Pathological stages at the time of referral to our centre were pT1 = 131 (72%), pT2 = 44 (26%) and pT3 = 5 (2%) (Table 1). A more detailed breakdown of pathological characteristics for patients with T1 tumours prior to receiving CXB can be found in Table 2.

Tumours were located at an average of 5.9 cm from the anal verge and had a mean size of 2.6 cm on histopathological analysis; the vast majority (92%) of patients were clinically lymph node negative. Only six were lymph node positive and nodal stage was unknown in eight.

Initial histology showed R0 resection in 69, R1 in 60 and R2 in 1. In 50 patients resection status was not known (RX) as the tumour was removed piecemeal.

One hundred and ten patients had LCCRT (of whom two had to stop early because of toxicity). Of these, the majority had 45 Gy in 25 fractions over 5 weeks. A further 60 patients who were not fit for chemotherapy had had EBRT alone, the majority of whom had 25 Gy in five fractions over 5 days or its biological equivalent.

Table 1 Breakdown of local excision method for rectal cancers prior to contact X-ray brachytherapy ± (chemo)radiotherapy.

T stage (group)	Surgery type	R margin	Number
pT1	EMR	R0	8
		R1	21
		RX	17
	EMR total		46
	TAR	R0	9
		R1	18
		RX	17
	TAR total		44
	TEMS	R0	31
		R1	5
		RX	5
	TEMS total		41
pT1 total			131
pT2	EMR	R0	1
		R1	4
		R2	1
		RX	4
	EMR total		10
	TAR	R0	5
		R1	8
		RX	6
	TAR total		19
	TEMS	R0	13
		R1	1
		RX	1
	TEMS total		15
pT2 total			44
pT3	EMR	R1	1
	EMR total		1
	TAR	R1	1
	TAR total		1
	TEMS	R0	2
		R1	1
	TEMS total		3
pT3 Total			5
Grand total			180

EMR, endoscopic mucosal resection; TAR, transanal resection with retractors; TEMS, transanal endoscopic microsurgery.

Oncological outcomes

The median follow-up was 36 months (range 6–48 months) from the time of the last given treatment. Only four patients had follow-up of less than 24 months because they died within this period from comorbidities. At the end of the study period, only 15 patients (9%) had evidence of any form of disease regrowth. These patients, along with their subsequent treatments, are detailed in Table 3. Eight patients developed endoluminal local recurrence within a median of 15.6 months (range 10–

Table 2 Pathological features of pT1 rectal cancers prior to receiving contact X-ray brachytherapy.

| T1 depth invasion | Differentiation | R status | | | |
		R0	R1	RX	Total
SM1	Well		1	1	2
	Moderate	1	3		4
	Not known	1	1		2
SM1 total		2	5	1	8
SM2	Well	1		1	2
	Moderate	5	6	1	12
	Poor		2		2
	Not known			1	1
SM2 total		6	8	3	17
SM3	Well	2			2
	Moderate	16	7	1	24
	Poor		1		1
	Not known	4		1	5
SM3 total		22	8	2	32
Not known	Well	3	3	6	12
	Moderate	14	15	20	49
	Poor		1	1	2
	Not known	1	4	6	11
Not known total		18	23	33	74
Grand total		48	44	39	131

55 months), three developed an isolated regional nodal recurrence and eight (4%) developed distant metastases. Five of the 11 patients who had local regrowth underwent salvage surgery with an abdominoperineal excision (four were R0 resections). Within this group, three of the seven patients with no evidence of distant metastases underwent radical salvage. Five patients with distant disease underwent resection of metastases. Five patients with disease recurrence were not fit for salvage surgery and were managed by best supportive care.

Because of the small number of events, there was insufficient power to determine if specific high-risk features such as R1, tumour diameter or lymphovascular invasion had an effect on local recurrence.

Using Kaplan–Meier survival estimation, the local recurrence-free survival of the group was modelled at 95% (CI 92–99%) at 3 years and overall survival was modelled at 91% and 83% at 3 and 5 years, respectively (Fig. 1a,b).

Treatment-related toxicity

The only toxicity that was formally assessed in the study group was per rectum bleeding, as from experience this is by far the most common side effect. This was experienced in 43 (24%) patients and was measured using the Common Terminology Criteria for Adverse Events Score (Version 4) [14]. Twenty-nine of these 43 were grade 3 and 24 required argon plasma coagulation.

Summary of outcomes from our group

At the end of all treatments (including surgery for metastatic disease and local salvage), 173 (96%) patients were free of disease and 170 (94%) were stoma free. Bleeding was the main adverse effect and required argon plasma coagulation in 24 (13%) patients.

Discussion

Currently, radical completion surgery is recommended as the optimal oncological treatment for patients with adverse tumour features after local excision of early rectal cancer [3–6]. Our data, however, derived from patients who were referred to our centre because they either chose not to, or were too unfit to, have a radical resection in this setting, have shown local regrowth rates of only 4% for T1 tumours and only 7% for T2 tumours after the addition of a contact boost when CXB was delivered to the local excision scar in addition to postoperative radio- ± chemotherapy as an alternative to radical surgery. These data highlight that empirical radical surgery can safely be avoided in many patients who have been diagnosed with early rectal cancer and have undergone local excision.

There are already several published reports of managing patients with adverse features after local excision with radio- ± chemotherapy instead of radical surgery. A recent meta-analysis by Borstlap et al. assessed data from studies which included at least 10 patients with pT1/pT2 adenocarcinomas removed transanally followed by adjuvant chemoradiotherapy [15]. This study showed that the weighted average for local recurrence was 10% (range 4%–21%) for T1 tumours and 15% (range 11%–21%) for T2 tumours. This study also assessed the outcomes after radical completion total mesorectal excision and found that the weighted average of local control was 6% (range 3%–15%) and 10% (range 4%–22%) for T1 and T2 tumours, respectively. There are, however, only limited data reporting outcomes of the addition of a contact boost to this regimen [10–12,16–18].

In the 'watch and wait' literature, there is now mounting evidence that the addition of a CXB boost to external beam (chemo)radiotherapy both increases the rate of complete clinical response and decreases the rate of local regrowth in the setting of rectal cancer [13,16–18] This benefit is likely to be derived from the known dose–response effect of increasing the dose of radiotherapy to induce tumour cell death. The benefit of contact

Table 3 Details of the 15 patients who had disease recurrence.

Patient no.	T stage	N stage	Surgery	R margin	Chemotherapy	RT dose (Gy)/no.	End of CXB to relapse (months)	Site of recurrence	Treatment for recurrence
1	pT2	cN0	TAR	RX	No chemo	No EBRT	15.84	Local	Palliative treatment and symptom control
2	pT1	cN0	TAR	RX	No chemo	45/25	19.82	Local and distant	APR
3	pT1	cN0	EMR	Rx	Raltitrexed	45/25	7.92	Local and distant	APR
4	pT2	cN0	TEMS	R0	Capecitabine	45/20	11.18	Local	Palliative treatment and symptom control
5	pT1	cN0	TAR	R1	Capecitabine	45/25	33.89	Local	APR
6	pT2	cN0	TEMS	R0	5-Fluorouracil	45/25	18.01	Local	APR
7	pT1	cN0	TAR	RX	Capecitabine	50.40/28	10.09	Local	APR
8	pT1	cN1	TAR	R0	No chemo	45/25	55.46	Local	Palliative treatment and symptom control
9	pT1	cN0	TEMS	R1	5-Fluorouracil	45/25	16.77	Distant	Lung surgery
10	pT1	cN0	TEMS	R0	Capecitabine	45/25	6.31	Distant	Liver surgery
11	pT1	cN0	EMR	R1	No chemo	45/20	38.86	Regional node and sistant	Palliative treatment and symptom control
12	pT1	cN0	TAR	R1	Capecitabine	45/25	23.34	Distant	Lung surgery
13	pT1	cN0	EMR	R0	Capecitabine	45/25	20.74	Distant	Lung surgery
14	pT2	cN0	TAR	Rx	No chemo	20/4	64.56	Regional node	Palliative treatment and symptom control
15	pT1	cN0	TAR	RX	5-Fluorouracil	45/25	48.55	Regional node and distant	Liver surgery

EMR, endoscopic mucosal resection; TAR, transanal resection with retractors; TEMS, transanal endoscopic microsurgery; RT, external beam radiotherapy; APR, abdominoperineal excision.

therapy in this paradigm is that it uses low-energy X-rays that only penetrate a few millimetres into the rectal wall and thus do not affect surrounding normal tissues. Our data suggest that a similar benefit is likely to be achieved in the setting of patients who have undergone local excision of early rectal cancer and wish to avoid surgery. While we do not have a control group with which to directly compare our data, we note that our data are equivalent to the very best outcomes reported in a recent meta-analysis using postoperative adjuvant treatment without contact therapy. Here, the weighted average for local recurrence for T1 disease was 10% and for T2 disease 15% [15]. Our data also compare favourably with the weighted average local regrowth rates for equivalent disease stages after radical salvage surgery [15]. Importantly, by adding external beam (chemo)radiation to the contact boost, we still

treat mesorectal nodal disease which we believe explains our favourable outcomes in patients with a more advanced tumour stage. It remains to be clarified in exactly what circumstances contact therapy may be beneficial in an organ-preserving approach. R1 resection is a definite indication in our centre. We do sometimes offer treatment for R0 resections, if LVI/poor differentiation or T2, as we know that most local recurrences are at the mucosal level. The contact boost can deliver very large additional doses to a depth of around 1 cm to the excision scar and so theoretically reduce local regrowth by sterilizing cells in this area. We propose that the main role of EBRT is to treat the mesorectal lymph nodes. We appreciate that the true benefit of adding contact therapy to EBRT alone and the degree to which it benefitted patients with R0 resections would best be investigated in a clinical trial. We also propose
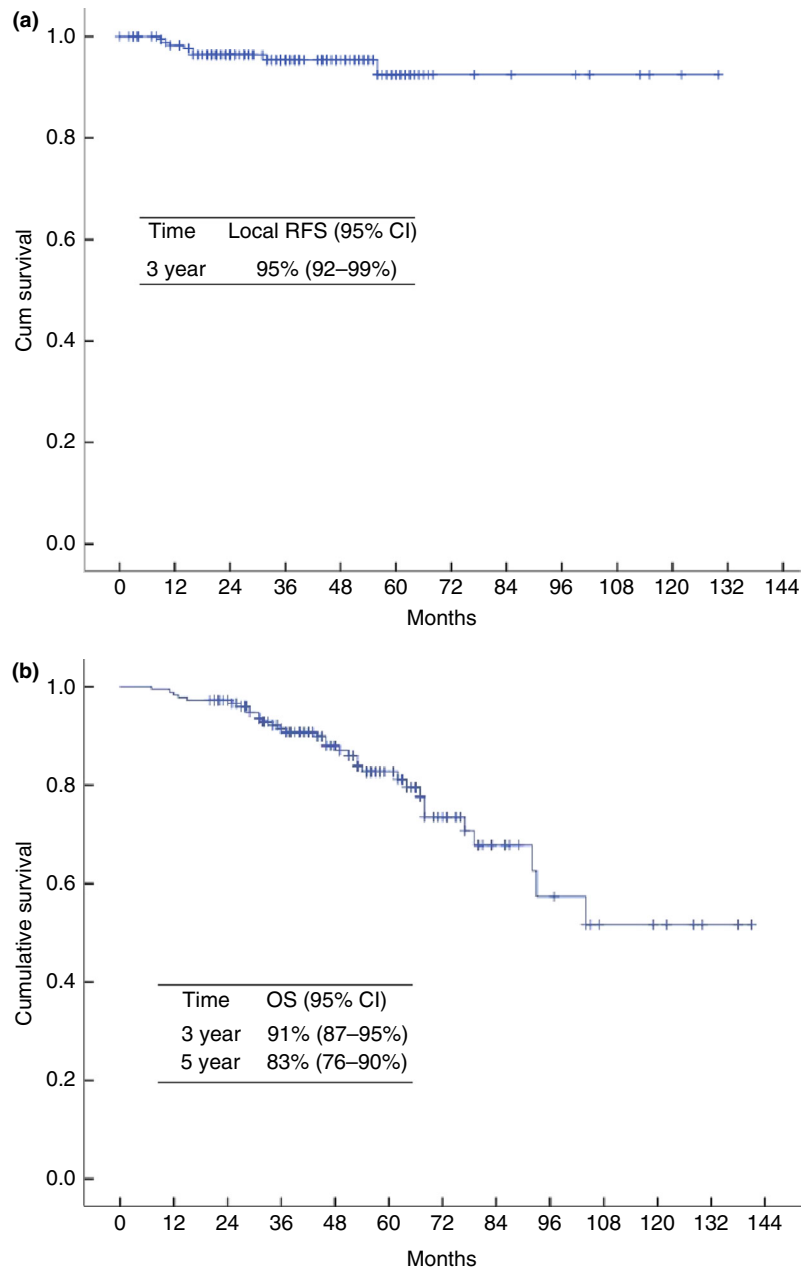
Figure 1 Kaplan–Meier survival curves showing (a) estimated 3-year local recurrence-free survival (RFS) and (b) estimated overall 3- and 5-year survival.

that in tandem there is increased awareness amongst clinicians of the importance of achieving R0 resection and avoiding piecemeal resection of large polyps as part of good practice.

We believe that our data are therefore important, because increasingly in surgical practice there is a 'trade-off' between oncological risk and the actual risks of surgery itself. Colorectal cancer is known to be a disease of the elderly with approximately 70% of

people who develop rectal cancer being over the age of 65. The age of highest likelihood of developing rectal cancer is 80 [19]. Increasing data show that intermediate-term mortality after radical surgery for rectal cancer can be considerable in elderly patients when compared with baseline mortality [19–22]. As such, the excellent local control seen in our patient cohort questions the need for radical surgery being offered as the 'safer option'.

Similarly, we believe our data are important because of the changing patterns of disease with increasing prevalence of early stage disease. Data from a review of 31 223 patients diagnosed with rectal cancer and who underwent a major abdominal procedure within the National Health Service in England found that 32% of patients were Dukes A. This same review found that 40% of these patients that received radical surgery for Dukes A rectal cancer were over the age of 80 years [23].

Even for younger patients who are otherwise fit and well, in order for consent for radical surgery to be valid they must also understand the risks of the surgical intervention being offered and any alternative treatments available to them. In this setting, some patients may wish to avoid a temporary or permanent stoma or the risks of pelvic nerve damage incurred by radical surgery and so may opt for chemoradiotherapy as a definitive treatment on that basis. Several recent publications have highlighted that patients are not always fully informed about the different options available to them and often feel that they were not involved in choosing the treatment that they ultimately received [24–26].

There are several accepted weaknesses of our study. The first is that it was not part of a randomized clinical trial; it therefore lacks a control group, and includes a disparate patient cohort. In some respects, though, it was not possible to generate a control group from within our own data because all patients were referred specifically to receive CXB in an attempt to attain optimal local control. CXB has been the standard of care in our unit for over 20 years and so it was not delivered as part of a trial. We believe, however, that an advantage of our data is that we report 'real-world' outcomes from a large and unique study group, which in turn can be broadly compared with the numerous reports of management without CXB [13]. Notwithstanding this, however, we do accept that definitive proof of the benefits of CXB in addition to postoperative EBRT ± chemotherapy would be best assessed in a prospective, randomized setting.

A further weakness is that we did not formally assess toxicity induced by external beam radiation or chemotherapy for the patients in our dataset because most patients had this treatment delivered at their referring local centres. Our data showed, however, that all patients received the full dosage of CXB and there was no immediate toxicity from it. We also did not formally assess rectal function in our study group, nor did we specifically assess late toxicity other than per rectum bleeding. We are, however, in the process of assessing rectal function in patients who are currently undergoing treatment. Despite this lack of data, the

side effects of CXB have recently undergone intensive study by the National Institute for Health and Care Excellence and the technique has formally been deemed safe [27].

A final criticism of our data is that aspects of the pathological analysis could be improved. For example, analyses were not standardized as they were done in local referring centres, which is a potential source of bias. Our data also lack full details of submucosal invasion status for a proportion of T1 tumours (Table 2). We are unable to give clarity as to why submucosal invasion depth was not recorded on a case-by-case basis, but we note that many of the T1 lesions were attributed to this stage after a prior EMR polypectomy where it is not possible to accurately measure the degree of submucosal invasion. In addition, tumours with positive margins following local excision were often low and TEMS excision of the scar may not have been deemed possible or the patient may have been unfit for or refused surgery. Lastly our data had limited reporting of adverse pathological features such as lymphovascular invasion and tumour budding.

Conclusion

Current guidelines accept radical surgery as the standard of care following local excision of early rectal cancer staged >T1sm1. The data we present highlight the oncological safety of nonoperative management of such patients who have received a CXB boost in combination with EBRT ± chemotherapy within our institution. Importantly, our data show equivalent local control to radical completion surgery as reported by a recent systematic review on the subject and better than average results than with chemoradiotherapy alone [13]. These data suggest that all patients should be made aware of the alternative treatment options for early rectal cancer at the time of informed consent and their views should be taken into account when final treatment decisions are made. A randomized trial which includes CXB in addition to EBRT would help to formally clarify its role in this area.

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