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Conservative Treatment of Rectal Cancer with Local Excision and Postoperative Radiation Therapy

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The conventional surgical treatment for patients with potentially curable transmural and/or node positive rectal cancer is a low anterior resection or abdominoperineal resection. Recently, there has been increasing interest in the use of local excision and postoperative radiation therapy as primary therapy for selected rectal cancers. The limited data suggest that the approach of local excision and postoperative radiation therapy should be limited to patients with either T_1 tumours with adverse pathological factors or T_2 tumours. Transmural tumours, which have a 24% local failure rate, are treated more effectively with standard surgery and pre- or postoperative therapy. The results of local excision and postoperative radiation therapy are encouraging, but more experience is needed to determine if this approach ultimately has similar local control and survival rates as standard surgery.

Key words: rectal cancer, sphincter preservation, conservative management
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INTRODUCTION

THE CONVENTIONAL surgical treatment for patients with potentially curable clinically transmural and/or node positive rectal cancer is a low anterior resection or abdominoperineal resection. If the tumour is transmural (T_3) or involves the pelvic lymph nodes, the incidence of local failure is at least 10% and adjuvant chemotherapy plus pelvic radiation therapy is recommended [1–3].

Given the morbidity of standard surgery and the frequent need for radiation therapy for many rectal cancers, there is increasing interest in the use of local excision and postoperative radiation therapy as primary therapy. The use of local excision and postoperative radiation therapy is not a new concept. This organ sparing technique has been used successfully for a variety of other tumours such as breast cancer, soft tissue sarcomas, and head and neck cancer. More recently, this approach has been used in the treatment of rectal cancer.

Local excision has been performed both pre- and postradiation therapy. The advantage of performing a local excision prior to radiation therapy is that the pathological features, such as margins, depth of bowel wall penetration, and histological features, can be identified. Knowledge of these details are useful in the development of selection criteria. The pathological details can be obscured by pre-operative radiation therapy [4]. Therefore, the approach of initial local excision and, if necessary, postoperative adjuvant therapy is preferred.

OVERVIEW OF THE CLINICAL SERIES

Local excision followed by postoperative radiation therapy has been performed at a limited number of institutions (Table 1) [5–14]. In most series, patients had T_{1-3} tumours and underwent a local excision followed, 4–6 weeks later, by 4500–5000 cGy to the whole pelvis. Some patients received an external beam or brachytherapy boost. A limited number of patients received 5-FU.

At the University of Florida, U.S.A. 17 patients (13:T_{0-1}, 4:T_2) underwent local excision and postoperative radiation therapy (4500 cGy ± 1000 cGy boost) [9]. All tumours were < 3 cm, and one had positive margins. With a minimum follow-up of 24 months (mean 64 months), 2 (12%) developed local failure. One of the two was salvaged with an abdominoperineal resection. Absolute survival was 76%.

The initial report from the New England Deaconess Hospital U.S.A. included 26 patients with stages T_{1-3} rectal cancer [5]. The majority (81%) were located < 5 cm from the anal verge. The total dose was 4300–6863 cGy in patients with grossly positive margins and 4140–6000 cGy in patients with negative margins. Some patients received an intracavitary or brachytherapy boost. In the 17 patients with no gross residual tumour, the local failure rate was 6% and the disease-free survival was 88%. Less satisfactory results were seen in the 9 patients with grossly positive margins. The incidence of local failure was 56% and disease-free survival was 44%.

In a more recent report from the New England Deaconess, 12 patients with T_2 rectal cancers underwent a full thickness local excision and postoperative radiation therapy (5000–5400 cGy) [6, 7]. 10 had 5-FU chemotherapy. All tumours were exophytic, well–moderately differentiated with no colloid, ≤ 4 cm, and <30% circumference. With a median follow-up of 30 months (2–48.5 months), none have developed local failure. Functionally, all were "continent".

At the Massachusetts General Hospital (MGH) U.S.A., Willett and associates treated 26 patients (T_1:11, T_2:11, T_3:3, not evaluable:1) with local excision followed by

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Table 1. Local excision and postoperative pelvic radiation therapy

Series (Ref.)	Number of patients	Median follow-up (months)	5-FU (%)	Size (cm)	T_3 (%)	Margins	Number	% Local* failure	Survival	Sphincter function†
U Florida [9]	17	64	0	< 3	0	Negative	16	12	76%	N/A
						Positive	1		Absolute	
NE Deaconess [5]	26	23	0	3.7 mean	19	Negative	17	6	88% DFS	N/A
						Positive	9	56	44% DFS	
NE Deaconess [6]	12	30	83	< 4	0	Negative	12	0	100%	All continent
MD Anderson [10]	46	36	17	3	33	N/A	9		93% 3-year	Good in > 90%
U Penn [11]	16‡	33	0	4.0 median	32	Uneval	16	20	94% 3-year actuarial	92% satisfactory
MGH [8]	26	26	27	4.0 mean	12	Negative	19	16	—	Satisfactory
						Positive	6	0	70% 5-year	
						Uneval	1	1/1	Actuarial	
MGH update [14]	56	48	N/A	N/A	0	N/A		4–32§	72% DFS	N/A
MSKCC [13]	22	37	9	3.0 median	27	Negative	21	18	79% 4-year	93%
						Uneval	1		Actuarial	good–excellent

DFS, disease-free survival; N/A, not available from the manuscript; * Crude incidence of cumulative local failure as a component of failure except the series from U Penn and the MGH update which report actuarial data; † Sphincter function in locally controlled patients; ‡ Patients received 500 cGy pelvic radiation therapy pre-operatively followed by local excision and postoperative radiation therapy; § 4% with favourable pathological features and 32% with unfavourable pathological features.

4500 cGy ± 500–2250 cGy boost [8]. The local excision was performed by a Kraske or transanal approach. The boost was limited to those 21 patients in whom the margins were positive or where there was deep muscle invasion or invasion into fat by the tumour. 7 received 5-FU during the first and last 3 days of radiation therapy. The incidence of local failure was 15% and distant metastasis was 8%. In contrast with the original series from the New England Deaconess [5], there was no difference in the incidence of local failure in those 6 patients with microscopic positive margins compared with the 19 with negative margins. All locally controlled patients maintained satisfactory sphincter function.

The MGH update was limited to 56 patients with T_{1-2} disease [14]. With a median follow-up of 48 months, the 5-year actuarial disease-free survival was 72%. The actuarial local failure rate was 13% for stage T_1 and 20% for stage T_2. The 28 patients with "favourable" pathological features (well–moderately differentiated without evidence of blood or lymphatic vessel invasion) had a lower actuarial local failure rate (4% versus 32%) and increased disease-free survival (87% versus 57%) compared with those 28 patients with "unfavourable" pathological features (poorly differentiated and/or blood or lymphatic vessel invasion).

The MD Anderson Hospital experience of local excision and postoperative radiation therapy for 46 patients with rectal cancer was reported by Ota and colleagues [10]. This approach was limited to locally resected tumours which were mobile, ≤ 4 cm (median 3 cm), and located <5 cm from the anal verge. Patients received 4500 cGy to the pelvis followed by a boost to a minimum of 5300 cGy. 8 received 5-FU. With a median follow-up of 36 months (18–73 months), the 3-year survival was 93% and the 3-year local recurrence-free survival was 90%. Local failure by stage was T_1:0% (0/16), T_2:7% (1/15), and T_3:20% (3/15), for a total incidence of 9%. Anal continence was "good" in >90% of patients.

Rosenthal and associates from the University of Pennsylvania, U.S.A. reported the results of 16 patients with adenocarcinomas extending to within 6 cm of the anal verge who received 500 cGy × 1 pre-operatively, followed by a local excision and postoperative radiation therapy [11]. Postoperatively, patients received a median of 5040 cGy. The margins were not assessable and 5 patients had T_3 tumours. The 3-year actuarial local failure rate was 20% and survival was 94%. The 3-year colostomy-free rate was 77% and overall sphincter function was satisfactory in 92% of patients with an intact sphincter.

The series by Minsky and colleagues from the Memorial Sloan-Kettering Cancer Center (MSKCC), U.S.A. included 22 patients of whom 21 underwent a full thickness local excision (11: transanal, 2: transsphincteric, 8: Kraske) followed by postoperative radiation therapy [13]. One patient underwent a snare excision of a T_1 polyp. Patients received 4500–4680 cGy ± a boost to 5040 cGy. With a median follow-up of 37 months, the 4-year actuarial disease-free survival was 56% and the overall survival was 79%. The 4-year actuarial colostomy-free survival was 73%. Margins were negative in 21 patients and unassessable in one patient who underwent a snare excision. The incidence of local failure was 18% and increased with T stage: T_1:0%, T_2:17%, and T_3:33%. Of the 15 eligible patients, 14 (93%) had good or excellent sphincter function.

There are two series excluded from the discussion since the data are difficult to interpret. First is the series by Wong and associates [15]. In their report, some patients had electrocoagulation, many had fragmented resections, and only 9 of the 25 had assessment of the margins (6/9 were positive). Similarly, the series by Rouanet and colleagues [16] was excluded since patients were selected for pre-operative and/or postoperative radiation therapy based on a variety of selection factors such as size and the presence of residual disease.

MANAGEMENT ISSUES

Among the many unresolved issues in the treatment of rectal cancer with local excision and postoperative radiation therapy are: (1) are the results comparable with standard surgery?; (2) which clinicopathological features are important?; (3) what are

the functional results of this approach?; and (4) is there a role for chemotherapy?

Results compared with standard surgery

Depending on the series, the overall survival rates vary from 70 to 100%. Since the pelvic lymph nodes are not pathologically examined at the time of a local excision, it is not possible to accurately compare, stage for stage, the results of local excision and postoperative radiation therapy with standard surgery.

In the MGH update [14], the 56 patients were compared to a retrospective group of 69 patients with stage $T_{1-2}N_0M_0$ disease who underwent an abdominoperineal resection. For patients with favourable pathological features, the 5-year actuarial local failure rates (local excision: 4% versus abdominoperineal resection: 9%) as well as the disease-free survival (local excision: 87% versus abdominoperineal resection: 91%) were similar. However, the results were not equivalent in the subset of patients with unfavourable pathological features. The 5-year actuarial local failure rate was higher (local excision: 33% versus abdominoperineal resection: 11%) and the disease free survival was lower (local excision: 57% versus abdominoperineal resection: 79%).

Although there are data to help predict the incidence of positive nodes based on the clinical and pathological features of the primary tumour [17–23], only a randomised trial could adequately address this issue. Since the accrual to a randomised trial may be difficult, there is an ongoing Intergroup Phase II trial examining the approach of local excision and postoperative radiation therapy (CALGB 8984/RTOG 9109). The results are pending at this time.

Clinicopathological features

Most series in which patients are treated with local excision alone exclude tumours with unfavourable clinical and pathological features. For example, in the series of 12 patients from the New England Deaconess Hospital, all tumours were exophytic, well–moderately differentiated with no colloid, $\leq$ 4 cm, and <30% circumference [6, 7]. Historically, clinically unfavourable features have included tumours which are greater than 3 × 5 cm, annular, fixed, or have perforated the bowel wall. Unfavourable pathological features have included blood vessel invasion, lymphatic vessel invasion, colloid histology or transmural disease.

The MGH update [14] revealed a significant increase in local failure in patients with poorly differentiated versus well–moderately differentiated tumours (36% versus 12%) as well as the presence of blood and/or lymphatic vessel invasion (positive: 53% versus negative 15%).

T stage. As seen in Table 2, there is an increase in local failure with extension of tumour through the bowel wall in patients who undergo local excision and postoperative radiation therapy. Combining the series, the incidence of local failure by stage is T_1:3%, T_2:10% and T_3:24%.

Table 2. Local failure by T stage

Series (Ref.)	T_1	T_2	T_3
NE Deaconess [6]		0% (0/12)	
MD Anderson [10]	0% (0/16)	7% (1/15)	20% (3/15)
MSKCC [13]	0% (0/4)	17% (2/12)	33% (2/6)
MGH [8]	10% (1/10)	18% (2/11)	33% (1/3)
MGH update [14]	17%*	20%*	
Total (Crude only)	3% (1/30)	10% (5/50)	24% (6/25)

* 5-year actuarial.

Resection margins. Owing to the high local failure rate, when there are positive margins, most authors recommended either a re-excision or proceeding with an abdominoperineal resection. In the setting of positive margins, is local excision and postoperative radiation therapy a reasonable option? In the original New England Deaconess series [5], the local failure rate was 56%. In contrast, none of the 6 patients in the MGH series who had positive margins developed local failure [8]. Since the boost doses were routinely increased to 6000–6500 cGy in this group of patients, the local control rate may have been a function of the high radiation doses delivered. Of the 4 patients who developed local failure in the MGH series, all had negative margins but 2/4 had fragmented resections. In the MD Anderson series, all patients had negative margins and none had fragmented resections [10]. At MSKCC, one patient had unassessable margins (who was locally controlled), otherwise all patients had a full thickness local excision and negative margins [13]. Although it cannot be determined with certainty from the available data, most investigators would recommend that negative margins be obtained if possible. If not, doses of >5040 cGy are reasonable.

Other selected clinical and pathological features. In the MGH series, there was a suggestion that tumour size >3 cm was associated with an increased local failure rate [8]. The MSKCC series reported a similar increase in local failure (>3 cm: 25% versus $\leq$ 3 cm: 14%) [13]. In the MD Anderson [10] and the recent New England Deaconess series [6], all tumours were $\leq$ 4 cm and in the University of Florida [9] series all were <3 cm.

The MGH reported an increase in local failure in patients with tumours with blood and/or lymphatic vessel invasion [8]. In the MSKCC series, patients with blood vessel positive tumours had a slight increase in local failure compared with blood vessel negative tumours (21% versus 13%) [13]. This increase may have been due to the increased incidence of T_3 tumours in the blood vessel invasion negative group (25% versus 5%). The only factors associated with an increase in local failure, which could not be explained by the presence of other features, were tumour size > 3 cm and ulceration. However, since none of the series have adequate numbers to perform a multivariate analysis, the influence of these selected criteria on one another cannot be determined. Therefore, until more complete data are available, we do not recommend exclusion of a patient from treatment with local excision and radiation therapy based solely upon the above selected clinical and pathological features.

Sphincter function

Most series report "satisfactory" sphincter function in locally controlled patients. The median follow-up varies from 26 to 36 months. However, it must be emphasised that sphincter function has not been carefully examined in many of the series. Furthermore, the change in sphincter function with longer follow-up cannot be predicted.

The role of chemotherapy

There are few data examining the use of adjuvant chemotherapy in patients who undergo local excision and postoperative radiation therapy. In the MGH series, 7 patients received concurrent 5-FU (500 mg/m^2 × 3 during the first and last week

of radiation therapy) and none developed local failure [8]. In the recent New England Deaconess report, 10/12 patients received 5-FU [6]. With a median follow-up of 30 months, none have developed local failure [6, 7]. At the MD Anderson, 17% of patients received 5-FU. In the MSKCC series, only 2 patients received 5-FU [13]. Since the number of patients is small and the data are not stratified by the T stage, the impact of chemotherapy is unclear. However, given the statistically significant impact of chemotherapy on survival in patients with resectable rectal cancer reported in the randomised postoperative adjuvant trials [1–3, 24], it is reasonable to add chemotherapy to this group of patients.

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