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Original article

# Multi-modality approach in curative local treatment of early rectal carcinomas

**M. J. Hershman*, A. Sun Myint† and C. A. Makin‡**

*MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool, †Clatterbridge Centre for Oncology, Bebington, Wirral and ‡Colorectal Unit, Wirral Hospital, Arrowe Park, Wirral, UK

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## Abstract

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**Objective** Despite recent advances, surgery remains the mainstay for the management of rectal carcinoma. The conventional surgical treatment for low rectal carcinoma is total mesorectal excision. This results in either abdomino-perineal excision of the rectum (APER) with permanent colostomy or low anterior resection (LAR) usually with a covering stoma. Local resection is an alternative treatment option and this could be offered either using manual trans-anal resection (TAR) or transanal endoscopic microsurgery (TEM) if the tumour is situated higher.

**Patients** Patient selection is an important factor if local resection is used. No further treatment is necessary for T1 tumours with clear surgical resection margins. Conventional radical surgery should be offered for T1 tumours with close resection margins (<1 mm) or T2 tumours with higher risk of lymph node metastases. Patients were treated by postoperative chemo-radiotherapy or radiotherapy, if further radical surgery was not considered appropriate or if the patient refused further surgery. Using this approach, we describe our experience of 100 patients treated from January 1992 to June 2002.

**Results** Only 13 patients had surgery alone and 87 patients had radiotherapy either pre-operative (33 patients), postoperative (25 patients) or radical radiotherapy alone (29 patients). Local recurrence occurred in 10% of patients and salvage surgery was offered in over half (6 patients) of these patients. At median follow up of 33 months (range 3–120 months), the overall survival was 77% reflecting the fact that the majority of these patients were elderly with coexisting medical problems. However, cancer specific survival was 96%. More importantly, only 9 patients had colostomies and colostomy-free survival in our cohort of patients from Liverpool was 91%.

**Conclusion** We concluded that in selected patients, who were not medically fit (ASA 111 or above) or those who were unable to accept a permanent colostomy, local treatment could be offered with curative intent using a multimodality approach. In our experience, relapses can be salvaged effectively and we recommend a long-term close follow up policy.

**Keywords** Rectal carcinoma, multimodality treatment, cure, transanal endoscopic microsurgery (TEM), transanal resection (TAR), radiotherapy

## Introduction

The conventional surgical treatment for low rectal carcinoma is total mesorectal excision (TME) [1]. This results in abdomino-perineal excision of the rectum (APER) or low anterior resection (LAR) usually with a covering stoma. The operative mortality for these operations is around 5%, with rates of up to 31% in

3 patients with ASA grade 111 and 1 V [2]. These patients have to cope with either a permanent or a temporary stoma and other morbidity such as genito-urinary and sexual dysfunction (30%). Moreover, even in patients with temporary stoma a second operation is necessary to reverse the stoma with the accompanying added risk and sometimes this is not performed. An alternative treatment option is local excision by either endoanal resection (TAR) [3] or by transanal endoscopic microsurgery technique (TEM) [4]. Local excision has a much lower operative mortality (0–2%) and morbidity (5–8%) [5]. Since 1992, we have offered

*Correspondence to*: Dr Arthur Sun Myint, Clatterbridge Centre for Oncology, Bebington, Wirral CH63 4JY, UK.
E-mail: Sun.Myint@ccotrust.nhs.uk

local resection to highly selected patients with rectal carcinoma [6,7]. In this paper, we describe our treatment policy and 10-year results of 100 patients treated in Liverpool.

## Method

From January 1992 to June 2002, local treatment was offered to 100 patients with a low rectal carcinoma (Table 1). The patients were selected after careful staging in Liverpool (42%) or investigation elsewhere and referral from outside our catchment area (58%). There were 55 males and 45 females with a median age of 73 years (range 49–91 years). All patients had a mobile tumour with no evidence of distant or lymph node metastases assessed by CT or MRI. They were further staged using either intra-anal ultrasound or intra-anal MRI to assess the radiological T and N stage. In our series, only 13 patients had surgery alone and 87 patients had radiotherapy either pre-operatively (33 patients), postoperatively (25 patients) or radical radiotherapy alone (29 patients).

### Rectal tumour <3 cm (T1/T2NOMO)

Patients with tumours less than 3 cm underwent transanal resection with either TEM or TAR (Table 2). If surgical resection margins were clear (at least 1 mm) no further treatment was offered other than close follow up. If the excision margins were involved (<1 mm), immediate radical surgery was offered. If the histology showed a T2 tumour with clear resection margins or a T1 tumour with uncertain resection margin then postoperative radiotherapy or chemo-radiotherapy was offered. If the patient was not fit for surgery at presentation (ASA 111 or above) or if surgery was refused, radical contact radiotherapy using the Papillon technique was offered.

The patients were assessed after two treatments with contact radiotherapy and if there was no response, then external beam radiotherapy was offered with or without chemotherapy. Patients were treated prone with either three or four fields' technique using megavoltage (6–8 MeV) radiation. Radiotherapy schedule used was either 39 Gy in 13 fractions over 2.5 weeks or 45 Gy in 20 fractions over 4 weeks. Chemotherapy, when used,

**Table 1** Patients and tumour characteristics.

| | Surgery | Surgery + postop RT | Pre-op RT + surgery | RT alone | Total |
|---|---|---|---|---|---|
| Groups | 1 | 13 | 2 | 3 | |
| Number | 13 | 25 | 33 | 29 | 100 |
| Sex | | | | | |
| Males | 5 | 14 | 13 | 23 | 55 |
| Females | 8 | 11 | 20 | 6 | 45 |
| Age | | | | | |
| Median | 77 | 69 | 74 | 71.5 | 73 |
| Range | (41–91) | (49–85) | (44–86) | (50–89) | (49–91) |
| Stage | | | | | |
| TO | | | 7 | | 7 |
| T1 | 10 | 19 | 11 | 13 | 53 |
| T2 | 3 | 6 | 11 | 9 | 29 |
| T3 | | | 4 | 2 | 6 |
| TX | | | | 5 | 5 |
| Surgery | | | | | |
| TEM | 10 | 12 | 26 | | 48 |
| TAR | 3 | 13 | 7 | | 23 |
| Local recurrence | | | | | |
| T1 | | | 1 | 2 | 3 |
| T2 | 1 | 2 | 2 | | 5 |
| T3 | | | 1 | | 1 |
| TX | | | | 1 | 1 |
| Distant metastases | | | 1(D)* | 1(D)* | |
| Deaths | | | | | |
| Cancer | | 1 | 2 | 1 | 4 |
| Non cancer | 8 | 1 | | 3 | 12 |

*(D) died.

**Table 2** Treatment strategy for early rectal carcinoma.

| |
|---|
| 1. <3 cm T1NOMO |
| 1.1 Local excision either TEM or TAR |
| CRM (– ive) – close follow up |
| CRM (+ ive) – immediate conventional radical surgery and if unfit for surgery or refuse surgery then postoperative radiotherapy or chemo-radiotherapy. |
| 1.2 Intracavity radiotherapy (Papillon technique) |
| 2. >3 cm T1/T2 NOMO |
| 2.1 External beam radiotherapy or Chemo-radiotherapy followed by local resection (TEM or TAR) |
| 2.2 Intracavity boost (Papillon) for patients unfit for surgery |

consisted of continuous 5 FU infusion 1G/m2 day 1–4 in week 1 and 4 [6].

#### Rectal tumours >3 cm (T1/T2NOMO)

Patients with tumours greater than 3 cm were offered pre-operative radiotherapy or chemoradiotherapy to downsize the tumour prior to transanal resection, which was carried out 6–8 weeks later (Table 2). If the resection margins were clear then no further treatment was offered other than close follow-up. If the resection margins were involved then standard radical surgery was given. Patients who were not fit for surgery were offered a contact radiotherapy boost using the Papillon technique [8].

#### Transanal endoscopic microsurgery

Trans anal endoscopic microsurgery (TEM) is a minimally invasive operation giving access to the rectum [4]. Marking dots are placed at 10 mm margin around the tumour and a full thickness excision is carried out. Anteriorly placed tumours in the upper rectum, however, which are situated above the peritoneal reflection, can only be resected by partial thickness resection. As the operative view is 6 times magnified, the different layers of the rectal wall and the perirectal fat can be clearly identified. After removal of the tumour, the defect is closed transversely. The specimen is pinned on a cork-board, fixed in formalin and sent to the pathologist who was expert in the field. Data were stored on a central database at the MASTER Unit in Liverpool and also at Clatterbridge Centre for Oncology. Data on patients who had TEM were subsequently forwarded to the national TEM database at Oxford and updated annually.

## Results

Of 100 patients treated, 71 patients had surgery including TEM (48 patients) and TAR (23 patients). Twenty-nine patients had radical radiotherapy alone. Local recurrence occurred in 10% and was usually in the lower third of the rectum. Salvage surgery was offered in over half of these patients. One patient had a local resection and five had a total rectal resection. At median follow up of 33 months (range 3–120 months), the overall survival was 77% reflecting the fact that the majority of these patients were elderly with coexisting medical problems. Cancer specific survival was 96%. Immediate rectal excision was carried out in 4 patients with involved margins after an initial local resection and in 5 patients after salvage surgery for local recurrence. Local resection was carried out in one patient who had local recurrence after radical radiotherapy using Papillon technique alone. Therefore, in our cohort of patients, colostomy-free survival was 91%.

The patients were divided into four groups for analysis:

- Surgery alone;
- Surgery followed by postoperative radiotherapy;
- Pre-operative radiotherapy or chemo radiotherapy followed by surgery;
- Radical radiotherapy alone.

#### Surgery alone

There were 13 patients; 8 females and 5 males with median age of 77 years (range 49–91 years). Ten patients had a T1 tumour and 3 patients a T2 tumour. The surgical technique used was TEM in 10 patients and TAR in 3 patients. One patient with close resection margins had an immediate rectal excision and is alive and well at 73 months. Another patient had a T2 tumour but refused further surgery or postoperative radiotherapy. He developed local recurrence and died 9 months later due to progression of a second primary advanced bladder cancer. There were two peri-operative deaths, one due to myocardial infarction and another due to overwhelming retroperitoneal sepsis. None of the six other deaths were related to colorectal cancer. The median follow up of the five surviving patients was 37 months (range 3–73 months). Cancer specific survival was 92%.

#### Local resection followed by postoperative radiotherapy

There were 25 patients; 14 males and 11 females of median age 69 years (range 49–85 years). There were 19 patients with a T1 and 6 patients with a T2 tumour. The surgical technique used for local resection was TEM in 12 patients and TAR in 13 patients. Two patients died, one due to extensive intra abdominal recurrence and the other due to medical cause. Two patients (8%) developed local recurrence, one at 7 months and the other at

10 months. Both patients had a salvage rectal excision and were alive and well at 85 months and 64 months, respectively. At a median follow up of 30.5 months, overall survival was 92% and cancer specific survival was 96%.

#### Pre-operative radiotherapy or chemoradiotherapy followed by surgery

Patients presenting with tumours greater than 3 cm were offered pre-operative radiotherapy ($n = 23$) or pre-operative chemoradiotherapy ($n = 10$). The rationale behind this strategy was to downsize the tumour before definitive surgery by full thickness local excision. There were 33 patients; 13 males and 20 females with a median age of 74 years (range 44–86 years). Seven patients had no residual tumour at the time of surgery in keeping with other series in the literature [9,10]. A T1 tumour was found in 11 patients and 11 patients had a T2 tumour after pre-operative treatment. There were 4 patients with a T3 tumour who were understaged at the initial assessment but were kept in the group as the analysis was based on intent to treat.

Twenty-six patients had a TEM and 7 patients a TAR. Local recurrence developed in 4 (12%) patients. In one patient with a T3 tumour, circumferential resection margins were involved but further surgery could not be offered due to post-operative wound dehiscence. He developed local recurrence 24 months later and had a salvage rectal excision. In three other patients with local recurrence, one had had a T1 tumour and the other two a T2 tumours. The patient with recurrence of a T1 tumour refused further surgery and died 12 months later. Two of the patients with recurrence of a T2 tumour had a salvaged rectal excision at 28 and 30 months. One developed pulmonary metastases 26 months later and is undergoing chemotherapy, the other is alive and well at 60 months. The overall survival in this group was 78% at a median follow up of 45 months with a cancer specific survival is 94%.

#### Radical radiotherapy alone

In this group there were 29 patients; 23 males and 6 females with median age of 71.5 years (range 50–89 years). It was not possible to assess T stage in 5 patients as they were treated at a time when intra-anal ultrasound scan was not carried out routinely. The remaining 24 patients had full radiological staging prior to treatment; there were 13 patients with a T1, 9 with a T2 and 2 with a T3 tumour. Twelve patients treated with contact radiotherapy alone using the Papillon technique [8,11]. The other patients had a tumour greater than 3 cm and underwent external beam radiotherapy ($n = 15$) or chemoradiotherapy ($n = 2$).

Our treatment policy was to remove the residual tumour by transanal full thickness resection [7,12]. However, patients in this group were elderly and had multiple comorbidities assessed as ASA grade 111 or above and were deemed to be a high risk for any form of surgery. They were offered local contact radiotherapy boost ($n = 26$), supplemented by iridium rectal implant in one case. There were three (10.3%) local recurrences at 6, 48 and 60 months, respectively. One patient recurred at 6 months and was salvaged by local resection. Therefore, local control after salvage was 93%. Overall survival was 79% at a median follow up of 35 months. There were no treatment related deaths. Two patients developed radiation proctitis resulting in persistent rectal bleeding and were treated successfully with Argon beam coagulation. One death was related to colorectal cancer (3.4%). Two patients had other malignancies (larynx and bronchus) and the other three patients died of medical causes. Cancer specific survival in this group was 96.6%.

## Discussion

Although total mesorectal excision of the rectum offers the best chance of cure, there is considerable morbidity and mortality associated with the procedure especially in patients with advancing age and comorbidity [3]. An alternative treatment approach is to offer local resection, which preserves ano-rectal function and avoids a permanent colostomy [3,4]. This is now accepted as a standard procedure for selected patients with T1NOMO where there are clear resection margins [13]. The question remains as to whether this approach offers an equivalent local control and survival compared with more radical surgery. The concern with local treatment is that the lymph nodes are not removed and therefore the treatment cannot be regarded as a radical oncological procedure with intent to cure [10]. Moreover, the important prognostic factor of lymph node status is not known which may compromise further treatment options that could reduce the chance of local, regional and distant relapses in the future. The advocates for local treatment have argued that the risk of lymph node metastases in low risk patients with T1 tumours is less than 5% [4,5]. Should recurrence occur, it can effectively be salvaged, as shown in our series of 100 patients treated over a 10-year period. In the whole group there were 10 local recurrences and we were able to offer radical salvage surgery in 75% of these patients (6 patients had surgery and one refused surgery although the recurrent tumour was operable).




 

The management of T2 tumoura is more complex. The risk of lymph node metastases is higher (10–20%) even in low risk groups and to improve loco-regional control, we recommend a course of radiotherapy or chemo-radiotherapy, if further radical surgery is thought to be inappropriate or if the patient refuses surgery.

In our series, local recurrence occurred in 5 (17%) of 29 patients with a T2 tumour as opposed to 3 (5.6%) of 53 patients with a T1 tumour. These recurrences have developed despite adjuvant treatment with either pre-operative (2 patients) or postoperative (2 patients) radiotherapy. As the number of patients in each group was small, the events occurring in each group has to be interpreted with caution. Nevertheless, there is a need to improve our results with either increasing the dose of radiation by using brachytherapy boost or adding newer chemotherapeutic agents such as Oxaliplatin or Irinotecan to the 5FU regime that was used in our study [6,7]. We were, however, able to offer salvage surgery to four patients with a recurrence of a T2 tumour and achieved 96% local control after salvage surgery at a median follow up of 36 months.

Transanal resection using TEM was first described by Buess in 1984 [4]. It was introduced as an alternative technique for local resection of large (>3 cm) rectal and recto sigmoid polyps, either benign or malignant. It also enabled tumour to be resected more proximally in the rectum than can be achieved with TAR.

TEM combines an endoscopic view of the rectum under gas insufflation via stereoscopic telescope with conventional surgical preparation. This enables the operator to remove the tumour using full thickness excision under direct magnified vision with sufficient margins of surrounding normal healthy tissue. The advantage of TEM is that it allows less invasive surgery with much more precise removal of the tumour [4,5,12]. Using conventional transanal surgical techniques, only tumours in the lower rectum can be reached and the operative view is somewhat limited, which may partly be responsible for high rates of local recurrence seen in the Mayo Clinic study and the Cancer and Leukaemia Group B CALGB Intergroup Phase 11 study (22%) [14]. Moreover, our patients were followed up much more closely at 4–6 weekly for the first two years compared to other investigators where follow up was usually typically 12–16 weeks. This may be one of the reasons why we were able to offer successful salvage surgery before the recurrent tumour became fixed and inoperable [7,12]. Although most of the recurrences developed within the first two years, our experience has shown that late recurrence could occur up to 5 years after treatment. Therefore, it is important to follow these patients up carefully beyond 5 years so that recurrence can be detected early enough to enable curative salvage surgery. Patient selection is important to achieve the best results and we recommend strict selection criteria (Table 3 and Table 4).

**Table 3** Selection criteria

| | |
|---|---|
| 1 | T1 or T2 tumour of the rectum. |
| 2 | Tumour <3 cm maximum diameter (one third circumference of lumen). |
| 3 | Well or moderately-well differentiated histology. |
| 4 | No evidence of lymphovascular invasion. |
| 5 | Mobile exophytic polypoid tumour with no ulceration. |
| 6 | No evidence of lymph node spread (NO). |
| 7 | No evidence of distant spread (MO). |
| 8 | Patient must agree on long-term follow-up. |

**Table 4** Exclusion criteria

| | |
|---|---|
| 1 | Poorly differentiated tumour. |
| 2 | T3/T4 Tumour. |
| 3 | Clinically tethered or fixed tumour of any radiological T stage. |
| 4 | Deeply infiltrative ulcerative tumour. |

The evidence for the efficacy of local treatment compared with conventional surgery in terms of local control and survival has been hampered by the fact that the number of patients presenting with T1NOMO tumour is usually below 1% of the total number of cancers presenting. There are several retrospective and case control studies [5,14,15] but only one randomised trial [16], which has attempted to address this question. Although the number of patients in each arm was small, this trial had elegantly shown that there is no difference in the procedure specific survival. The patients in the TEM group ($n = 24$) compared to the anterior resection group ($n = 26$) had shorter operative time (103 *vs.* 149 min), less blood loss (143 *vs.* 745 ml), shorter hospital stay (5.7 *vs.* 15.7 days), lower analgesic demand (5.7% *vs.* 15%) and less morbidity (20.8% *vs.* 34.5%). A large prospective randomised trial would be necessary to confirm these results. However, to accrue sufficient number of patients a multicentred international trial would be necessary. In the UK prospective data have been collected from each centre through the TEM group since 1996 and further detailed discussion of the data on surgery alone is presented in another article in this issue [17].

## Conclusion

The management of patients with small mobile rectal carcinoma (T1/T2NOMO) should be discussed within the multidisciplinary meeting. Patients and relatives

should be fully informed of the treatment options that are available and detailed information should also be given regarding the benefits and possible side-effects resulting from each treatment. It is likely that the number of patients for consideration of local treatment will expand with increasing use of endoscopy and early detection due to improved facilities in screening for colorectal cancer becomes a reality. We need a management plan in readiness for this time, so that these patients can be selected and treated appropriately without compromising their chance of cure. In the UK, there are now several centres, which are specializing in the local treatment of early rectal carcinomas and if necessary patients should be referred to dedicated centres with special interest to achieve best results.

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