Surgical treatment of rectal cancer: results of a strategy for selective preoperative radiotherapy

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SUMMARY

Aim — The indications for preoperative adjuvant therapy in rectal cancer are still a subject of debate. The objective of this study was to analyze the results of surgical resection and selective radiotherapy in a group of high-risk patients (Dukes B and C) taken from a series of 148 consecutive patients with rectal cancer.

Methods — All patients with rectal cancer considered for resection during the period 1994-2004 were prospectively included. The policy was to deliver preoperative radiotherapy in cases of fixed or tethered tumors or when imaging predicted T3 tumors with positive circumferential margins. Other tumors were resected without neo-adjuvant therapy. All resections were done using the total mesorectal excision (TME) technique.

Results — One hundred and forty-eight consecutive patients underwent rectal resection during the study period. A sphincter-saving technique was carried out in 134 patients (90%). No patient was excluded from the analysis. The perioperative mortality was 2/148 (1.5%). Curative surgery was obtained in 135 patients. The mean follow-up in this group was 58 months (range 24-120). Twenty patients (21%) received preoperative radiotherapy (PRT) and 74 (79%) underwent surgical resection alone. A positive circumferential margin, defined as one that was ≤ 1 mm, was found in seven of the 85 patients (8.2%) for whom this measure was available. The actuarial five-year overall survival was 74%. Local recurrence developed in eight patients (8.4%): four in the PRT group (20%), and four in the non-PRT group (5.4%). Only two patients developed an isolated local recurrence.

Conclusions — Preoperative adjuvant therapy can be safely omitted in patients who demonstrate clear circumferential margins on preoperative imaging, provided that adequate surgery is subsequently performed.
Introduction

In the management of rectal cancer, the role of preoperative radiotherapy (PRT) is still controversial. There is general agreement over the use of PRT in fixed tumors and the use of surgery alone in small tumors graded T1 or T2 on preoperative imaging. With T3 and/or N+ tumors, where the risk of local recurrence is high, the majority of clinicians advise PRT [1] whereas several prestigious centers propose that it be used more selectively on the grounds that adequate surgery with total mesorectal excision (TME) can remove most tumors confined within the mesorectum [2-4].

Many trials have shown that a short course of PRT can significantly reduce the rate of local recurrence. Three Swedish randomized trials have shown the benefits of PRT [5-8], but the significance of these trials has been questioned, as the local recurrence rate with surgery alone was as high as 30% [6]. A Dutch trial, performed with TME-trained surgeons, showed a significant effect of PRT at 2 years [9], but the 5-year results were less optimistic: the overall rate of local recurrence was 5.8% with PRT vs 11.4% with surgery alone; the reduction of local recurrence was observed only with tumors situated between 5 and 10 cm from the anal verge, and had no effect on those <5 cm or >10 cm away; PRT also had no effect in patients undergoing abdominoperineal resection (APR), and its impact was limited to Dukes C tumors [10].

Although radiotherapy is an effective treatment, it has been shown to induce both short- and long-term complications [11-22]. The former includes an increased rate of anastomotic leakage, perineal sepsis and small-bowel obstruction [15, 16, 22], while the latter includes small-bowel obstruction, unspecified infections [13], and excess rates of intercurrent deaths [7] and secondary cancers [13]. PRT also alters functionality, with increased rates of incontinence, urgency, stool frequency, blood loss, and evacuation and discrimination problems [16, 17, 21]. Sexual function is also affected, with impaired erection, orgasm, ejaculation and general sexual activity seen in men [18, 19], and sexual dysfunction seen in women [19].

Another prognostic factor in the treatment of rectal cancer is the quality of surgery. The resection technique, and the surgeon’s skill and experience, have all been shown to have a major impact on the outcome and, particularly, on the local recurrence rate, where the surgeon represents an important variable [22-30]. A local recurrence rate of around 5% or less has been obtained by surgery alone in several studies from centers of expertise [2-4, 31-39], and a rate lower than those obtained with PRT in more recent trials [8, 10].

Given our intention to add new data to the debate, we present here the results of our policy of selective PRT in a consecutive series of 148 patients. To avoid any bias as noted in some TME series — such as the exclusion of patients by the surgeon after surgery on the grounds that the resection was deemed not curative [35, 36] — no patients were excluded from our analysis.

Patients and methods

One hundred and forty-eight consecutive patients with rectal cancer (lower margin at 15 cm or less) underwent surgical resection in the period 1994-2004. During the same period, resection was not attempted in 12 patients with advanced metastatic disease, and one patient had a laparotomy prior to resection, but underwent a colostomy alone because of diffuse peritoneal carcinomatosis.

During the preoperative workup, the extent of the cancer was evaluated by rectal examination, endo-ultrasound, CT scanning and, since 2003, pelvic MRI. When the tumor was mobile and imaging predicted free margins, the patient was operated on without PRT. When at rectal examination the tumor was fixed or tethered, or appeared bulky, pelvic irradiation was performed. Histopathological techniques

The resected specimen was received straight from the operating room, opened anteriorly on the peritoneal aspect and fixed in 10% formalin without being pinned to a corkboard. The mesorectum was dyed with India ink. Dissection consisted of taking 5-mm slices of the tumor and surrounding mesorectum in the transverse plane. The slice(s) containing the most lateral spread and its neighboring slices were selected for multiple block sections, and embedded for routine processing. The other slices were processed by hyperfixation using Bouin’s fluid for careful examination of the lymph nodes. The longitudinal and circumferential margins were measured on the fixed specimens. The circumferential (radial) margin was defined as the dyed soft-tissue margin closest to the deepest tumor penetration. A positive circumferential margin (CRM) was defined as one that is ≤1 mm on the specimen. The following features were also determined: histological type (OMS classification); the UICC pTNM staging; and the states of the longitudinal and radial margins.

In the postsurgical period, patients with affected nodes or unfavorable signs on the specimen (such as vascular/neral invasion or free tumor deposits beyond the main tumor mass) received postoperative chemotherapy. Patients with involved margins (either longitudinal or circumferential) on the specimen were offered postoperative radiotherapy.

Data were collected prospectively on a computer-based chart, and included age, gender, surgical details, pathological findings (including, since 1998, CRM size), adjuvant treatment, complications and outcome. Follow-up was carried out by surgical and oncological teams twice a year for a minimum of 5 years. A colonoscopy was performed 1 year after the operation and every 5 years thereafter. Symptoms suggestive of recurrence were investigated using imaging and biopsy. Survival curves were calculated with the Kaplan-Meier method, using the R statistical package.

All patients with Dukes B or C tumors were included in the “high-risk” group; also included in this group were patients with an A-stage tumor on the specimen after preoperative radiotherapy where preoperative staging had shown a T3 tumor.

Results

One hundred and forty-eight patients, comprising 83 men and 65 women, mean age 66 years, underwent surgery. Twenty patients (13.5%) received preoperative radiotherapy (radiotherapy alone in 10 patients and radiochemotherapy in 10); 128 patients (86.5%) had surgical resection alone.
A sphincter-saving resection was performed in 134 cases (90%): colorectal anastomosis in 85 cases; colo-anal anastomosis in 46 cases; Hartmann’s operation in 3 cases. A temporary defunctioning ileostomy was constructed in all cases of colo-anal anastomosis and in 64/85 cases of colorectal anastomosis. An APR was performed in 14 cases (10%).

Postoperative mortality was 1.3% (2/148). Surgical complications arose in 30 patients (20%) in the postsurgical period and 14 (10%) required a repeat operation. Among the 134 sphincter-saving resections, definitive continuity was established in 128, while two patients died postoperatively and four patients did not benefit from reestablishment of continuity due to colonic necrosis, medical complications or disease progression.

The 146 patients who survived the operation were followed-up for a mean period of 58 months (range 24-120). Eleven patients had non-resectable metastases at the time of presentation and underwent palliative rectal resection to control local symptoms: nine of these patients died during the follow-up at a median time of 15 months after operation (range 6-29), and two patients were still alive at 20 months. None of these patients developed a local recurrence.

The 135 remaining patients experienced a successful operation, 133 of whom had no metastases at the time of operation, while two had liver metastases that were resected. No patients were excluded from the ‘cured’ group on the basis of non-resectable tumor tissue left behind in the pelvis. In these 135 patients, distant metastases occurred in 24 (17%), of which 16 died at a mean follow-up time of 35 months (range 14-68), and eight were still alive at follow-up 53 months later (range 28-88). Actuarial overall survival at 5 years was 80% and disease-free survival was 75% (figure 1). Local recurrences occurred in eight patients (6% crude, 12.5% actuarial). Four in the group without (3%) and four in the group with (20%) radiotherapy. Overall, of the 135 patients surviving a “curative” operation, 26 (19%) experienced a recurrence, either distant or local.

### High-risk group

To identify those patients with a high risk of local recurrence and in whom it is currently advised to give preoperative radiotherapy [1], B- and C-stage patients were analyzed separately; this group included 90 patients with T3/T4 and/or N+ tumors on the specimen, and four patients with a tumor staged T3 preoperatively, irradiated before surgery and staged T2 on the specimen. The pathological data are shown in table I. The mean number of harvested lymph nodes was 15. Thirteen patients were stage T4: 12 had serosal invasion and two had extension to an adjacent organ. In all patients, total macroscopic resection of the tumor could be performed and, in two cases, this required ablation of a neighboring organ (vagina in one, seminal vesicle in the other).

A positive circumferential margin (CRM), defined as one that is ≤1 mm on the specimen [42], was found in seven of 85 patients with available data (8.2%), of whom one had received PRT and six, surgery alone. Two had actual involvement of the CRM with no margin at all; one of these patients received postoperative radiotherapy while the other did not, due to severe co-morbidity. Of the 20 patients undergoing PRT, the circumferential margin was present in 17; the mean margin was 7.14 mm (range 1-19).

Perforation of the rectum at the tumor site or elsewhere on the rectum during surgery occurred in four patients (4.1%).

Local recurrence developed in eight patients (8.5% crude, 12.5% actuarial at 5 years) — six men and two women — after Table I. — Pathology data in the high-risk group of 94 patients.

<table>
<thead>
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<th>Stage</th>
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</tr>
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<tr>
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<td>48</td>
</tr>
<tr>
<td>T</td>
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<td>7</td>
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<td>Longitudinal margin on specimen after fixation</td>
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<td>5</td>
</tr>
<tr>
<td></td>
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</tr>
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<td></td>
<td>&gt;5 cm</td>
<td>14</td>
</tr>
<tr>
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<tr>
<td>Circumferential margin (N=85)</td>
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<td>7</td>
</tr>
<tr>
<td></td>
<td>1-2 mm</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt;2 mm</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Serosal involvement</td>
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</table>

Fig. 1 — Overall and disease-free survival among the 135 patients who underwent “curative” surgery.

Survie globale et sans récidive des 135 malades opérés curativement.
a median follow-up of 21 months (range 15-60). The tumor was located 15 cm from the anal verge in one patient, 8 cm in one patient, and 5 cm or less in five patients (table II). The local recurrence was in the lower pelvis along the posterior or lateral wall in seven patients and in the anal canal in one. There was no anastomotic recurrence. Among the eight patients with local recurrence, four had received preoperative adjuvant treatment — radiotherapy (N=2) or radiochemotherapy (N=2) — and four had undergone surgery alone. The local recurrence rate in the PRT group was therefore 4/20 (20%) vs 4/74 (5.4%) in the surgery-alone group. The local recurrence was the first recurrence in five patients, associated with distant metastases in two cases and a second site of recurrence in one. Among the five patients with localized disease as the first recurrence, distant metastases were seen in three cases after 3, 13 and 20 months, respectively. Only two patients had an isolated local recurrence. Resection of the local recurrence was performed in three patients. Five of the eight patients with local recurrence died of their disease at a mean follow-up of 38 months after the primary operation (range 26-48), and three patients are living with disease at 32, 51 and 88 months, respectively. None of the seven patients with a positive CRM developed local recurrences. Node-positive patients had a local recurrence rate (LRR) of 10% (5/48): 3/43 (7%) after surgery alone and 2/5 (40%) after PRT plus surgery.

Patients in this group had a 5-year actuarial overall survival of 74.1% and a disease-free survival of 64.6%.

**Low-risk group**

This group comprised the 45 stage-T2 N0 patients in the “cured” group. The mean follow-up in this group was 70 months. Their overall actuarial survival was 90% at 5 years, and none experienced a local recurrence. Only one patient (2%) had a distant recurrence (hepatic metastasis).

**Discussion**

The present series illustrates the results of adequate surgery and selective radiotherapy, a strategy aiming to obtain the best possible results with the least amount of exposure to radiotherapy. The series exhibits good results in terms of sphincter preservation (90%), overall survival at 5 years (80%), disease-free survival (75%) and local recurrence rate (6% crude, 5-year actuarial 8%). As our study is prospective, our results are not biased by exclusion of patients a posteriori on the grounds of incomplete excision (“palliative cases”) and, as our minimum follow-up was 24 months, our figures are reasonably accurate.

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**Table II.** — Local recurrences.

<table>
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<tr>
<th>#</th>
<th>Sex</th>
<th>Age</th>
<th>D</th>
<th>PRT</th>
<th>Primary operation</th>
<th>T</th>
<th>N</th>
<th>Longitudinal margin (cm)</th>
<th>Circumferential margin (mm)</th>
<th>Chemotherapy</th>
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<td>O</td>
</tr>
<tr>
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<td>F</td>
<td>63</td>
<td>6</td>
<td>No</td>
<td>CAA</td>
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<td>1</td>
<td>1.5</td>
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</tr>
<tr>
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<td>M</td>
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<td>RCT</td>
<td>CAA</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
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<td>N</td>
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<tr>
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<td>15</td>
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<td>CRA</td>
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<tr>
<td>6</td>
<td>F</td>
<td>57</td>
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<td>RXT</td>
<td>CAA</td>
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<td>1</td>
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<td>O</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>50</td>
<td>2</td>
<td>RCT</td>
<td>APR</td>
<td>3</td>
<td>1</td>
<td>5</td>
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<td>O</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>67</td>
<td>3</td>
<td>No</td>
<td>APR</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>NA</td>
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<table>
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<tr>
<th>#</th>
<th>Follow-up (months)</th>
<th>Site of first recurrence</th>
<th>Time of first recurrence (months)</th>
<th>Treatment of first recurrence</th>
<th>Site of second recurrence</th>
<th>Time of second recurrence (months)</th>
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<th>Status at follow-up</th>
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<td>32</td>
<td>Liver, pelvis</td>
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<td>Liver</td>
<td>36</td>
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<td>5</td>
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<td>Lungs, liver, pelvis</td>
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<td>DOD</td>
</tr>
<tr>
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<td>55</td>
<td>Pelvis</td>
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<td>Surgery</td>
<td></td>
<td>51</td>
<td></td>
<td>AWD</td>
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<td>8</td>
<td>28</td>
<td>Pelvis</td>
<td>18</td>
<td>No treatment</td>
<td></td>
<td>18</td>
<td></td>
<td>DOD</td>
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</table>

PRT: preoperative radiotherapy; D: distance from anal margin; NA: not available; CAA: colo-anal anastomosis; CRA: colorectal anastomosis; APR: abdominoperineal resection; RXT: radiotherapy; RCT: radiochemotherapy; CT: chemotherapy; AWD: alive with disease; DOD: dead of disease.
While it has been reported that centers of expertise have obtained local recurrence rates of 5% or less with surgery alone or selective PRT [1-3, 32-40], whether such results are reproducible is a matter for debate. Our results attest that they may indeed be reproduced. In fact, it has already been shown that good results are not the exclusive province of experts, but may be attained after adequate training; in the 1990s, technical training was implemented in Scandinavia, with impressive results [42-45]. In Sweden, the TME Project included training sessions and supervision of volunteer surgeons by experts; after the program, the rate of non-conservative surgery fell from 60% to 27%, the local recurrence rate fell from 20% to 8%, and the 5-year survival rate rose from 66% to 77% [44]. Furthermore, recent studies from other groups have reached the same excellence as the major centers [3, 4, 32, 34].

In our series, we used the following criteria as indications for preoperative radiotherapy: fixed or tethered tumors and, more recently, tumors reaching the limits of the mesorectum or invading neighboring organs in imaging studies. Overall, 13.5% of our patients received PRT. The use of selective preoperative radiotherapy is widespread in the prestigious Anglo-Saxon centers, using approximately the same criteria, and the percentage of patients undergoing PRT in those studies ranges from 10% to 30% [4, 33-35, 37]. In all of those studies, and ours as well, selective PRT was validated by the quality of the overall results, in terms of both survival and local recurrence rates.

It is interesting to focus on our stage B and C patients, in whom PRT is currently advised [1], to see whether our results equal those from series of patients treated with both PRT and surgery. In our high-risk study group, the overall 5-year survival was 74% and the 5-year cumulative local recurrence rate was 12.5%. These results are comparable to those in the PRT arm of the Dutch trial (overall survival, 64%; local recurrence rate, 8.4%).

In our patients receiving radiotherapy, the local recurrence rate was 20% vs 5% in the patients undergoing surgery alone while, in PRT trials, the local recurrence rate in the PRT arm is usually lower or equal to that of the surgery-alone arm. It is difficult to explain this finding. Fixed tumors were included in our study and, as such tumors are treated with PRT and surgery, this may have worsened the results in these patients. Patient selection may also have accurately identified the most aggressive tumors with the greatest risk of local recurrence. Further studies are needed to clarify this point.

The concept of selective radiotherapy is based on the fact that high-risk patients can be identified. Originally, patient selection was clinical, based on rectal examination with or without anesthesia. It is common knowledge that fixed or tethered tumors are not amenable to complete resection and are likely to recur locally, so these patients were given radiotherapy prior to surgery. However, since the mid-1980s, two factors have brought about improvements in preoperative evaluations: the significance of involvement of the circumferential resection margin (CRM); and the information obtained from modern imaging technologies, mainly MRI.

The link between involvement of the CRM and local recurrence was first shown by Quirke et al. [46] and, subsequently, by others [47-51]. Involvement of the CRM may be related to inadequate surgery, as the incidence of positive CRMs has been shown to vary widely among surgeons [22, 49]. These differences are particularly marked in low-lying tumors, where obtaining free CRMs may be especially challenging [50]. In a subsequent paper from Quirke's group looking at the significance of CRM involvement in the context of optimal surgery, a positive CRM was considered a sign of an aggressive tumor with a high potential for distant as well as local recurrences [51].

In the high-risk group in our series, a positive CRM was found in seven patients out of the 85 in whom this measure was available (8.2%). Of these patients, one had received PRT and six, surgery alone. There were five cases of stage C, and two stage B5, and none of these patients developed local recurrences. This is surprising and deserving of comment. There is currently broad agreement in defining a positive CRM (CRM+) as a margin ≤ 1 mm, but there is room for debate if the issue is probed more deeply, as done by Dent et al. in a recent review [52]: in that review of nine studies, the LRR in CRM+ patients varied greatly, from 9% to 92%. According to the authors, this variability was accounted for by many causes, the most important being the definition of a positive CRM itself. Initially, in 1986, Quirke et al. defined a positive CRM as the actual presence of tumor at the resection margin [46], based on a prospective study showing an LRR of 85% with an involved CRM vs 3% with a clear CRM. Then, in 1994, Quirke's group proposed another definition: the presence of tumor “1 mm or less from the circumferential margin” [53], without justification for this change. The first paper to support this new definition was published by Birbeck, from Quirke’s team, in 2002: the LRR was 55% for an involved CRM; 28% for a CRM 0.1-1 mm; and 3% for a CRM greater than 1 mm [22]. But this study was based on a heterogeneous group of patients from several hospitals, with a wide range of results across centers, suggesting major variability in surgical technique. That same year, Nagtegaal et al. published a study based on the Dutch trial suggesting that 2 mm may be the threshold of positivity, but the data shown in this study were not convincing either, as the LRR was 20% for an involved CRM, and 6-15% for CRMs ranging from 0.1 to 10 mm [48]. Dent concluded that there was too much variability among the studies to draw firm conclusions and that, pending further research, “the definition of CRM involvement should be simply histological evidence of tumor in a line of resection, that is, a margin of 0 mm”, meaning that tumor was transected and a part left behind [52]; he retained a zero CRM as a strong predictor of recurrence, and a narrow margin (less than 1-2 mm) as a weaker risk factor, in the context of the surgical technique.

In our study, only two patients had involvement of the CRM with no margin at all; the five other patients had a clear margin, but smaller than 1 mm. The two patients with a zero CRM had undergone surgery alone; one of these patients received postoperative radiotherapy and died of peritoneal carcinomatosis 12 months after the operation, without local recurrence; the other patient received no adjuvant treatment due to severe comorbidity, and died of this co-morbidity 28 months after the operation, with no recurrence. The five patients with a free but narrow CRM received no postoperative radiotherapy, and are alive at a median follow-up of 50 months: three with no recurrence and two with distant metastases.

Despite a clear definition of a positive CRM, it appears that a narrow margin is a risk factor and should be avoided whenever possible. It is also sensible to offer PRT to those patients with a potentially positive CRM on preoperative imaging in order to shrink the tumor and obtain a wider margin. MRI is currently the most accurate tool for detecting a potentially positive CRM, as it shows accurately the limits of both the tumor and the mesorectum, thus predicting the size of the circumferential margin. This indicator has been proposed as a useful criterion in the selection for neoadjuvant therapy [54, 55]. Following this policy, Gandy et al. have obtained a 0% local recurrence rate at a follow-up of 16 months [34], and Horgan et al. have reported a 4% local recurrence rate at 58 months of follow-up [4].

In our current practice, an MRI is ordered whenever the clinical examination shows a bulky tumor, and the findings are used to select cases for neoadjuvant therapy. When the MRI shows that a tumor lies close to, or at, the predicted margin of resection,
the patient is given PRT. Recently, we have adopted a policy of PRT indications with greater latitude for very low-lying tumors, in an effort to increase the longitudinal margins of resection and allow safe conservative surgery. Nevertheless, we acknowledge that this point remains open to discussion [56].

In conclusion, our present study confirms the quality of the results obtained by TME surgery. It provides, in line with other studies, further evidence in favor of selective radiotherapy in T3 and/or N+ tumors. The indications for preoperative radiotherapy are based on clinical examination and MRI findings. This strategy has been acknowledged as a possible choice in the latest version of the Recommendations for Clinical Practice issued by the Association Française de Chirurgie in 2007 [56].

Further research will allow further refinement of these indications in the future, allowing the clinician to accurately select those patients who should receive neoadjuvant therapy to prevent local recurrences of tumors following TME surgery.

REFERENCES