Chapter 4

Controversies of total mesorectal excision for rectal cancer in elderly patients

Harm J.T. Rutten, Marcel den Dulk, Valery E.P.P. Lemmens, Cornelis J.H. van de Velde, Corrie A.M. Marijnen

ABSTRACT

The cornerstone of treatment for rectal cancer is resectional treatment according to the principles of total mesorectal excision (TME). However, population-based registries show that improvements in outcome after resectional treatment occur mainly in younger patients. Furthermore, 6-month postoperative mortality is significantly increased in elderly patients (≥ 75 years of age) compared with younger patients (< 75 years of age). Several confounding factors, such as treatment-related complications and comorbidity, are thought to be responsible for these disappointing findings. Thus, major resectional treatment is not advantageous for all older patients with rectal cancer. However, the Dutch TME trial showed a good response to a short course of neoadjuvant radiotherapy in the elderly patients. Biological responses to cancer treatment seem to change with age, and, therefore, individualised cancer treatments should be used that take into account the heterogeneity of ageing. For elderly patients who retain a good physical and mental condition, treatment that is given to younger patients is deemed appropriate, whereas for those with diminished physiological reserved and comorbid conditions, alternative treatments that keep surgical trauma to a minimum and optimise the use of radiotherapy might be more suitable.
INTRODUCTION

The effectiveness of surgery for rectal cancer in the elderly (≥ 75 years of age) can be measured by survival, postoperative morbidity and mortality, and the ability of the patient to regain the independence they had before the surgery. The incidence of rectal cancer is highest at around 80 years of age. However the incidence of comorbidity, which renders the patient vulnerable to postoperative complications, is also highest after this age (Figure 1).1-3

Population-based studies have shown that the prognosis of patients with rectal cancer has improved over the past few decades. The Danish Nationwide Cancer Registry, a population-based registry with almost complete ascertainment, showed that between 1977 and 1999, 5-year survival gradually improved in all age groups, with the biggest improvement seen in the period between 1977 and 1989. In elderly patients, 30-day and 6-month mortality decreased substantially over time. Better anaesthesia, improved health awareness leading to earlier stage diagnoses, less emergency procedures (surgery within 24 h after first onset of symptoms), improved access to health-care services, and greater availability of effective treatments were considered factors responsible for these findings.4 In the Netherlands, Dutch cancer registries also noted an improvement in outcome after surgery for rectal cancer, which accelerated in the 1990s.5
An explanation for the improvement in the 1990s might be the introduction of total mesorectal excision (TME), which has become the standard for resectional treatment. Heald and colleagues\textsuperscript{6} introduced this technique, in which the rectum is removed enveloped within its mesorectal fascia, and Quirke and co-workers\textsuperscript{7} provided the anatomical basis for this concept by showing that an uninvolved circumferential margin is the most important independent factor for avoiding local recurrence.

In the Netherlands, TME surgery was introduced as a result of a trial done in 1996 that compared TME surgery with and without a short course of preoperative radiotherapy (5 fractions of 5 Gy).\textsuperscript{8} On the basis of the findings of this trial, TME combined with preoperative radiotherapy was rapidly accepted as the standard treatment for rectal cancer. However, the mean age of the patients included in the trial was 63 years, and, although no upper age limit was used, there is concern that the elderly population was under-represented. In most population-based studies, the mean age of patients with rectal cancer is 70 years and the relative incidence increases with age, reaching a maximum at 80 years of age.\textsuperscript{9} Therefore, whether the findings of the TME trial are applicable to the elderly population is unclear.

Other reports of under-representation of the elderly in clinical trials also exist.\textsuperscript{10,11} The opinion that geriatric patients do not tolerate cancer treatment well might be a reason for why they are not always included in prospective randomised studies. Other possible explanations are exclusion criteria for comorbidity, which is increasingly present in older patients, and the reluctance of investigators to include frail patients in such trials. Despite this issue, the findings from most studies are presented irrespective of participant age. The exclusion of older populations from these trials leaves important questions unanswered - i.e., are biological behaviour and responsiveness to treatment independent from age; and how do cancer treatments interact with the vulnerability of ageing people? In this paper, we will address the above mentioned topics and propose alternatives for the treatment of elderly patients with rectal cancer.

**METHODS**

Two datasets were used for our analyses: data from the Dutch TME study and data from the Dutch Comprehensive Cancer Centres (CCC) South and West combined. Both datasets have been published before.\textsuperscript{12,13} However, for this review new, unpublished analyses have been done. In the TME study 1356 patients had curative resection (1126 patients aged < 75 years and 230 patients aged ≥ 75 years). 99% of patients had complete follow-up. In this dataset, we focused on mortality in elderly patients. In the Dutch CCC South and West combined dataset, 4567 patients had curative resection during the period 1990-2002, of whom 28% were aged 75 years or more.\textsuperscript{12}
Data were analysed with the SPSS package (version 15.0 for Windows; SPSS Inc., Chicago, IL, USA), and SAS (version 9; SAS Institute Inc., Cary, NC, USA). Forest plots were drawn with software from Biostat (Comprehensive Meta-analysis Version 2; Biostat, Englewood, NJ, USA).

The prevalence of comorbidity, including hypertension, in the area of the Comprehensive Cancer Centre South was recorded according to a slightly adapted version of the Charlson Index. Patients with missing data were excluded from the comorbidity analysis. European standardised incidence rates of rectal cancer in the Netherlands were downloaded from the website of the Dutch Comprehensive Cancer Centres. Age-specific life expectancy tables were used from the Dutch Central Bureau of Statistics to calculate relative risks of dying for patients with rectal cancer compared with the general population, by means of Cox regression. \( P \)-values lower than 0.05 were considered significant. All eligible Dutch patients from the Dutch TME trial who underwent a resection and had no evidence of distant metastasis at the time of surgery were included in the analysis of the relative risk of dying from a complication within 6 months of surgery for patients aged 75 years or more compared with those aged less than 75 years. 95% confidence intervals (CIs) not including 1 were considered to indicate significant differences between the respective age groups. No imputation methods of missing values were used because completeness of data in the TME trial exceeded 99%.

Findings from the analyses were compared with the published work. We searched Medline, Scopus, and the Cochrane database for articles published in English back to January 1997. The following search terms were used: “rectal cancer and elderly (ageing)”, “preoperative irradiation”, “local excision”, and “chemoradiation”. Reference lists were used for further search.

RESULTS

The combined cancer registries of the CCC South and West failed to show a beneficial effect of the use of TME surgery in elderly patients (Figure 2). Table 1 provides the relative risk of dying of rectal cancer according to 3-year age groups compared with the general population, and shows that age is an independent risk factor. Therefore, the effectiveness of TME surgery for rectal cancer in the overall population cannot be simply derived from the findings of studies that involve a predominantly younger age group. In a younger patient group with a high relative risk of dying from cancer, a small treatment benefit might be worthwhile. However, in elderly patients, such a benefit might be overshadowed by their increased vulnerability and decreased tolerance, resulting in greater postoperative mortality than in younger patients.

Table 1 also shows postoperative 30-day mortality and 6-month mortality for each
age group after curative surgery for rectal cancer. An increase can be seen in both 30-day mortality and 6-month mortality in elderly patients, representing one of the major drawbacks of surgery for rectal cancer in this population. In patients above 75 years of age, 6-month mortality increases compared with patients aged 75 years or younger. This proportion increases to almost 40% in patients older than 90 years of age. Unfortunately, the introduction of TME surgery has not resulted in a decrease in 6-month mortality.12

Figure 2. Overall survival per age group before and after the introduction of total mesorectal excision (TME) in the Netherlands. Data from the Dutch Comprehensive Cancer Centres South and West combined database. CI = confidence interval.

Table 1. Relative risk of dying after curative rectal cancer surgery compared with the general population. Data from the Dutch Comprehensive Cancer Centres South and West. CI = confidence interval.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P-value</th>
<th>30-day mortality (%)</th>
<th>6-month mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 61</td>
<td>1179</td>
<td>123</td>
<td>56-275</td>
<td>0.0001</td>
<td>1.1</td>
<td>2.1</td>
</tr>
<tr>
<td>61-63</td>
<td>354</td>
<td>127</td>
<td>20-806</td>
<td>&lt;0.0001</td>
<td>1.1</td>
<td>3.1</td>
</tr>
<tr>
<td>64-66</td>
<td>401</td>
<td>9.0</td>
<td>6.4-12</td>
<td>&lt;0.0001</td>
<td>2.0</td>
<td>4.7</td>
</tr>
<tr>
<td>67-69</td>
<td>481</td>
<td>4.7</td>
<td>3.7-6.1</td>
<td>&lt;0.0001</td>
<td>2.5</td>
<td>6.2</td>
</tr>
<tr>
<td>70-72</td>
<td>428</td>
<td>3.1</td>
<td>2.5-3.9</td>
<td>&lt;0.0001</td>
<td>1.6</td>
<td>4.9</td>
</tr>
<tr>
<td>73-75</td>
<td>452</td>
<td>2.8</td>
<td>2.2-3.4</td>
<td>&lt;0.0001</td>
<td>3.5</td>
<td>8.0</td>
</tr>
<tr>
<td>76-78</td>
<td>423</td>
<td>1.8</td>
<td>1.5-2.2</td>
<td>&lt;0.0001</td>
<td>6.9</td>
<td>13.0</td>
</tr>
<tr>
<td>79-81</td>
<td>329</td>
<td>1.6</td>
<td>1.3-2.0</td>
<td>&lt;0.0001</td>
<td>7.9</td>
<td>14.9</td>
</tr>
<tr>
<td>82-84</td>
<td>321</td>
<td>1.2</td>
<td>0.9-1.6</td>
<td>0.17</td>
<td>10.4</td>
<td>17.7</td>
</tr>
<tr>
<td>85-87</td>
<td>169</td>
<td>2.4</td>
<td>1.7-3.2</td>
<td>&lt;0.0001</td>
<td>14.8</td>
<td>27.2</td>
</tr>
<tr>
<td>88-90</td>
<td>71</td>
<td>1.5</td>
<td>0.9-2.5</td>
<td>0.09</td>
<td>18.3</td>
<td>26.8</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>31</td>
<td>1.5</td>
<td>0.5-2.5</td>
<td>0.14</td>
<td>25.8</td>
<td>38.7</td>
</tr>
</tbody>
</table>
DISCUSSION

Rectal cancer surgery is a major procedure, highlighted by the number of postoperative complications. The occurrence of complications is associated with a higher postoperative mortality, which, in elderly patients, persists for at least 6 months, compared with a few weeks after surgery in younger patients.

Table 2 presents the complications that occurred in elderly patients in the Dutch TME trial (unpublished), showing that elderly patients are liable to more complications than their younger counterparts. Furthermore, these complications were associated with higher mortality. Even complications in elderly that occurred at a similar or lower frequency compared with younger patients were associated with more severe consequences. The best example of such a complication is anastomotic leakage. This leakage occurred at a similar rate in younger and elderly patients, but the ensuing mortality in elderly patients was 57% compared with just 8.2% in younger patients. Furthermore, complications including abscesses, sepsis, and postoperative pulmonary and cardiac problems were related to a significantly increased risk of dying within 6 months post-surgery in elderly patients compared with younger patients.

Several studies have addressed the issue of why elderly patients benefit less than younger patients from surgical treatment for rectal cancer. Shahir and colleagues\textsuperscript{14}
showed in a regional setting that older patients (≥ 70 years) were at higher risk of developing treatment-related complications than younger patients (< 70 years). They noted that age, comorbidity, and the number of postoperative complications were sig-
significantly related with worse outcome. In a subset of patients, the presence of chronic obstructive pulmonary disease and deep vein thrombosis led to a higher occurrence of perioperative complications.\textsuperscript{15} An extended study\textsuperscript{4} of the Comprehensive Cancer Centre South showed that 65\% of patients aged 65–79 years and 70\% of patients aged 80 years or over had one or more comorbid conditions, and about half of these patients had two or more comorbid conditions. Additionally, comorbidity was shown to significantly decrease the chance of being treated with TME surgery and was strongly associated with diminished survival.

Similarly, in a systematic review by the Colorectal Cancer Collaborative Group,\textsuperscript{16} age was noted to be an important risk factor for 30-day mortality, with a 3.2 times increased risk in the 75–84-year age group and a 6.2 times increased risk in the 85-years-and-older age group compared with younger patients. Although all types of general complications were significantly increased in the older age groups (i.e., pneumonia, thromboembolism, and cerebrovascular complications), anastomotic leakage was not correlated with age.\textsuperscript{16}

In addition to the risks of anastomotic leakage, functional outcome after bowel restoration should also be taken into account. When confronted with the choice between a permanent colostomy and restoration of bowel continuity, most patients will opt for the latter choice. Technically, the restoration of bowel continuity is feasible in most patients with rectal cancer. With the protection of a diverting stoma, more than 90\% of the anastomoses at the pelvic floor level or lower will heal, and, in elderly patients, the number of anastomotic failures is similar to that in younger patients.\textsuperscript{17} However, there are several disadvantages of this procedure. In addition to an increased risk of mortality in case of anastomotic failure, 20\% of diverting stomas in elderly patients will not be reversed for many reasons.\textsuperscript{18} Furthermore, a return of manageable bowel function is not guaranteed. After removal of the rectal ampulla, bowel function will change and can take up to 2 years before an end stage is reached. Side studies of the Dutch TME trial have shown that, in most patients, a high frequency of defecation, fractionated defecation, urge, and incontinence will occur, at least temporarily. If the anal sphincter was included in the radiation field, incontinence will be a problem in almost all patients.\textsuperscript{19} The consequences of the changes in defecation patterns can be grave in elderly patients. The increase and urge of bowel movements can prevent patients from leaving their home and can, therefore, lead to social isolation. Loss of functionality, which is a threat to the delicate balance between living an independent life and depending on others, often leads to a depersonalised, institutionalised life. Several researchers have shown that quality of life can be better with a stoma than with a low anastomosis.\textsuperscript{20,21} Multidimensional assessment of individual cases is needed for deciding whether an anastomosis is technically feasible, safe, but above all desirable.
**Future perspectives**

The current evidence shows that findings from randomised studies on the treatment of rectal cancer cannot be automatically applied to elderly patients, in whom treatment of rectal cancer is a multidimensional issue. Apart from being an oncological problem, this issue is also associated with the physiological changes caused by aging, whereby patients become more vulnerable to noxious effects, which are often exaggerated by comorbid conditions. Population-based studies often claim that elderly patients, who undergo the same cancer treatment as their younger counterparts, have a more favourable outcome than elderly patients who do not have these treatments, and undertreatment of the elderly has been suggested as the reason for decreased rectal-cancer-specific survival in this population. However, these studies do not provide convincing evidence that elderly patients should have the same treatment as younger patients. The factors responsible for the obvious selection bias when recruiting elderly patients into clinical trials are not well explained. Sufficient evidence exists to support the statement that cancer-specific survival after major resection is not age dependent. However, all researchers agree that postoperative mortality is at least doubled in elderly patients after resection compared with younger patients after resection and that careful selection should be made. None of the studies provided data for 6-month mortality, but, as can be noted from our analysis presented in Table 1, a further doubling of postoperative mortality at 6 months and thereafter is very likely.

Thus, major surgical treatment might not be the best option for all elderly patients with rectal cancer. However, biological age is not the only factor to be taken into account when including patients in this at-risk group, and more reliable parameters are mandatory when selecting patients for certain treatments. Obviously, in the very fit (i.e., American Society of Anesthesiologists (ASA) grade I) and the very ill (ASA IV-V) the decision to treat with curative intent or to provide palliative care is not difficult to make. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) has developed an excellent scoring system for 30-day mortality on the basis of a prospective survey of more than 8077 patients with colorectal cancer in 79 hospitals (ACPGBI Colorectal Cancer Study). Several other scoring systems (i.e., Possum, P-Possum, and CR-Possum) have also been developed, which take into account physiological status and the extent of the procedure, and have produced similar findings. Validation studies have confirmed the usefulness of these systems to predict mortality. For example, the operative mortality risk for patients aged 75-95 years with ASA II-III ranges from 5.4% to 13.5%, as shown in Figure 4 on the basis of the ACPGBI score for resected rectal cancer (Tumour Node Metastasis stage 2 and 3).

Although these scoring systems can help to identify and quantify the risk associated with resectional treatment for a given physiological performance status, they cannot be used as a definite decision aid. A 20% operative mortality risk might be acceptable for a disease that leads to debilitating symptoms if left untreated, but is probably not
acceptable for a small, well-differentiated tumour. Furthermore, the most important question for older patients is not whether they will survive, but, rather, how their quality of life will be affected after surgery - i.e., will their functional status deteriorate and will an independent life still be possible? Mortality scoring systems do not help to answer these questions.

**Alternatives for TME surgery for elderly patients**

The standardised approach of TME is certainly the best way to avoid local recurrence. However, with the extremely high 6-month postoperative mortality associated with this procedure in elderly patients, the search for safer alternatives is imperative.

In a paper describing the effects of introducing TME surgery in the general population, we showed that radiotherapy was not responsible for the increased mortality in elderly patients and that surgical trauma remained the heaviest burden on mortality. Figure 5 shows cancer-specific survival in the Dutch TME trial. Cancer-specific survival in elderly patients was significantly improved in the study group that received five fractions of 5 Gy preoperative radiotherapy, whereas this improvement did not occur in younger patients.

Future research should take advantage of this finding. The important question is whether radiotherapy can have a more prominent role in the treatment of rectal cancer in the elderly and, thus, avoid the morbidity and mortality associated with major resectional treatments. A concern of omitting mesorectal excision in these patients is the possibility of leaving positive lymph nodes behind, which might cause local recur-
rence. However, Read and colleagues $^{33}$ showed that in patients whose tumours were downstaged to T0-1 after neoadjuvant radiotherapy and chemoradiotherapy, nodal metastases were rare. Furthermore, publications by Hughes and colleagues $^{34}$ and Ratto and colleagues $^{35}$ confirm that good responders to neoadjuvant treatment have little chance of persisting nodal metastases. On the basis of these findings, we now discuss several alternative treatment options for rectal cancer in elderly patients.

**Chemoradiotherapy alone**

In a study by Habr-Gama and colleagues, $^{36}$ which included patients with mainly T3 rectal cancers, 71 patients who had a complete clinical response after chemoradiotherapy were closely observed and not operated on. With a mean follow up of 57 months, two patients developed a local recurrence, of which one underwent a successful salvage operation. An additional three patients developed distant metastases. Up to now, no other studies to our knowledge have confirmed these findings.

**Radiotherapy in combination with local excision**

Less invasive surgical techniques than TME, such as local excision or transanal endoscopic microsurgery (TEM), have resulted in promising findings in the treatment of early rectal cancer, especially in terms of low morbidity and mortality. However, the benefits of these less invasive treatments should be carefully weighed against the increased risk of local recurrence.

For early-stage rectal cancer (T1N0), a trial that randomly assigned patients to either TEM or anterior resection showed significantly less blood loss in the TEM group than in the anterior resection group (143 mL versus 745 mL) and shorter hospitalisation times (5.7 days versus 15.4 days). Local control in the anterior resection group was 100% compared with 95.8% in the TEM group.$^{37-43}$ On the basis of these findings, TEM has become a widely accepted treatment modality for T1N0 rectal cancers.
For T2 and T3 tumours, the findings for TEM surgery are less satisfactory, even when combined with postoperative radiotherapy of chemoradiotherapy. Local recurrence of these tumours varies from 10% to 36%, suggesting that postoperative radiotherapy or chemoradiotherapy is incapable of eradicating possible lymph node involvement. However, the combination of preoperative radiotherapy or chemoradiotherapy with TEM seems to be more promising. Only one small randomised trial to our knowledge has been done for low T2N0 tumours (situated in the distal rectum), which showed no difference in local control between patients who underwent local excision or laparoscopic resection after chemoradiotherapy. In accordance with this finding, several researchers have reported local control between 90% and 95% for patients with T2 or T3 tumours treated with this approach. However, the addition of chemotherapy to radiotherapy, which has produced promising findings in younger patients for downsizing tumours, might become a problem in elderly patients who are unfit for resectional treatment. By contrast, elderly patients respond well to radiotherapy alone, and this might also be an option to be investigated, in terms of a short or long course radiotherapy, without chemotherapy, followed by a longer waiting period before re-evaluation for local excision.

Radiotherapy as radical treatment option

In this context, the role of radiotherapy is limited to the (neo)adjuvant or palliative setting, because a very high dose of radiation (at least 60 Gy, but probably more than 80 Gy) needs to be given for control of rectal carcinomas by radiotherapy alone. However, external-beam radiotherapy doses higher than 50 Gy will result in increased late toxic effects, which are the limiting factor for dose escalation in external-beam radiotherapy. To overcome this dose limitation, intracavity irradiation, either by contact X-rays or by intraluminal brachytherapy, which enables the delivery of a high dose of radiation to the tumour with low doses to the surrounding normal tissue, might be explored.

Papillon and Berard described the value of contact X-rays for early rectal cancers (T1 and favourable T2 lesions) and reported 4.5% local failure and 74% survival after 5 years. Several other investigators have confirmed these findings in studies with contact X-rays for patients with T1N0 and small T2N0 rectal cancer. For patients with more advanced tumours, the risk of nodal involvement is high and a combination of contact treatment or interstitial brachytherapy with external-beam radiotherapy is needed to address this problem. Several publications have shown that the combination of local and external radiotherapy leads to 63%-85% local recurrence in T2 and T3 tumours.

These findings show that radical radiotherapy might be a good alternative to TME, especially for elderly patients who are unable to undergo any surgical procedure. For patients with small tumours with a low likelihood of nodal involvement, locally applied radiotherapy might be appropriate, as long as the total dose to the tumour is about
80 Gy. For larger tumours with possible lymph node involvement, a combination of external-beam radiotherapy and brachytherapy can be an option.

CONCLUSION

After major resectional treatment, elderly patients with rectal cancer have an increased 30-day and 6-month mortality compared with younger patients. Treatment-related mortality is an important competitive risk factor, which obscures the positive effect of modern rectal cancer treatment in those aged 75 years and above. Easy and applicable physiological and clinical scoring systems have been developed and validated as instruments for the identification of those with a high operative risk. Additionally, in frail patients, a multidimensional assessment of the relevant medical, functional, social, and mental parameters is necessary to define an appropriate treatment goal. In such an individualised treatment plan, the optimum oncological outcome might not be the most important objective. Less invasive treatment options for rectal cancer in the elderly patients are gaining increased interest. Furthermore, elderly patients seem to respond well to radiotherapy, and might, therefore, become the main beneficiaries from the use of radical radiotherapy in this setting. As such, the elderly population might be a suitable patient group for research in this field.

Despite the fact that we have limited knowledge of the biology of rectal cancer in the elderly patients, treatment options for this population need to be explored, and individualised treatment approaches should be considered in order to maintain a good quality of life for each patient. Such treatment needs to involve specialised services that are capable of obtaining optimum outcomes for this multifactorial issue.
REFERENCES


