Impact of the interval between short-course radiotherapy and surgery on outcomes of rectal cancer patients

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Aims: Pre-operative radiotherapy has proven to reduce local recurrences after curative surgery for rectal cancer. Radiotherapy is generally well tolerated, although postoperative morbidity and mortality was increased in some patients. Current study was undertaken to analyse whether the interval between preoperative radiotherapy and surgery influences postoperative mortality and recurrence for two cohorts.

Methods: All Dutch patients included in the total mesorectal excision (TME)-trial receiving radiotherapy for resectable rectal cancer were included in this study (n = 642). The verification set consisted of all patients receiving short-course radiotherapy for resectable rectal cancer in two radiotherapy clinics in The Netherlands (n = 600). Univariate and multivariable survival analyses for overall survival, disease-free survival, local recurrence-free survival and non-cancer related survival were calculated.

Results: Patients aged 75 years and older treated during the TME-trial showed a worse overall and non-cancer-related survival when surgically treated 4–7 days after the last fraction of radiotherapy. No differences in survival between the interval groups were found in the verification set.

Conclusion: Present study found that elderly patients aged 75 years and older operated 4–7 days after the last fraction of radiotherapy had a higher chance of dying due to non-cancer-related causes during the TME-trial as compared to patients with an interval of 0–3 days. In the verification set similar differences could not be confirmed, which could be

KEYWORDS
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Radiotherapy
Surgery
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Elderly
1. Introduction

In the treatment of rectal cancer, local recurrences are a major problem, occurring in 15–45% of the rectal cancer patients without total mesorectal excision (TME) surgery and radiotherapy. These local recurrences often have severe disabling symptoms and are difficult to treat. To reduce local recurrences after curative surgery, several studies have used either preoperative or postoperative radiotherapy. In a large Swedish trial, short-course preoperative RT has proven to be more effective compared to postoperative radiotherapy with conventional surgery. The TME-trial and the CR07 trial showed, additionally, that with total mesorectal excision (TME) surgery, preoperative radiotherapy improved local control even further. Preoperative radiotherapy has been given in varying regimens, either short-course (25 Gy in 5 fractions during one week) or long course combined with chemotherapy (45–50 Gy during 5 weeks). Radiotherapy is generally well tolerated, although postoperative morbidity and mortality is increased in some patients. The increased postoperative mortality may be attributed to the use of anterior–posterior beams, resulting in large irradiated volumes, from the earlier trials.

A more recent study has shown that short-course radiotherapy has significant impact on the perioperative leucocyte response. Short-course radiotherapy followed by surgery after 5 or more days since the last fraction of radiotherapy was significantly correlated with leucopenia or falling leucocytes rates on day one postoperatively. The patients with an abnormal leucocyte response developed sepsis more often (31% versus 13% in patients with a normal leucocyte response), and had an increased risk of death within 90 days after surgery compared to patients with a normal leucocyte response, suggesting that surgery should occur within 5 days after the last day of radiotherapy.

This study was undertaken to analyse whether the interval between preoperative radiotherapy and surgery, or the duration of radiotherapy (5 or 7 days) influences the outcome of patients regarding one year post-operative mortality and five year local recurrence free survival and disease free survival for two cohorts; patients from the TME-trial from 1996 to 1999 (DUT-KWF-CKVO-9504, EORTC-40971, EU-96020) and patients from a more recent cohort from 2000 until 2010 as a verification set.

2. Methods

2.1. Patients and follow-up

2.1.1. Dataset from the TME-trial

From January 1996 until December 1999 1861 patients with resectable rectal cancer without evidence of distance disease were randomly assigned to TME preceded by 5 × 5 Gy radiotherapy or TME alone. There was no age limitation. For this subset analysis, only Dutch patients receiving pre-operative radiotherapy are included (n = 642), since the follow-up of the Dutch patients has been more thorough and complete.

2.1.2. Verification set

From January 2000 until 15th July 2010, all patients receiving short-course preoperative radiotherapy for resectable rectal cancer without evidence of distant metastases followed by TME surgery at Leiden University Medical Center and Catherina Hospital Eindhoven were included retrospectively. Information on the patients’ characteristics, such as gender and date of birth, as well as tumour characteristics, location (according to the International Classification of Diseases for Oncology (ICD-O)), histology, stage (clinical and pathological TNM classification 5th edition), grade and primary treatment, were obtained from the medical records. The vital status was obtained either directly from the patients’ medical record or through linkage of the hospital with the municipal population registry which records information on their inhabitants’ vital status. Exclusion criteria were: patients without information available on their vital status (n = 2), patients without information on the date of radiotherapy or surgery (n = 30) and missing data on the age (n = 2).

For both datasets, stage was based on pathological TNM classification. For patients in whom pathological stage was unknown, clinical stage was used. Patients were divided into two age groups (<75 years and ≥75 years). The majority of the patients were operated 1, 2, 3, 4 or 5 days after the last fraction of radiotherapy. To compare the effect of the interval, we have divided the patients into four groups. Patients operated within 3 days since the last day of radiotherapy, from 4 until 7 days, from 8 until 27 days and from 28 days or more (in line with one of the arms of the Stockholm III trial). Radiotherapy duration has been divided into two groups: 5 days (Monday till Friday) or 7 days of radiotherapy (with a weekend included). Overall
treatment time (OTT, as shown in Fig. 1) has been divided into two groups: OTT ≤10 days (with the exception of a radiotherapy duration of 8 days) or OTT >10 days (as shown in Tables 1a and 1b with the light grey shaded area). A radiotherapy duration of 8 days was in violation with the protocol and has therefore been included as an OTT >10 days. An interval between radiotherapy and surgery ≥8 days (dark shaded grey area in Tables 1a and 1b) has been excluded from the OTT analyses since this was in violation with the recommendations.

When patients received radiotherapy for 5 days, from Monday till Friday, surgery was either performed on Monday (within 3 days since the last fraction of radiotherapy), or later in that week (from 4 until 7 days since the last fraction of radiotherapy).

2.2. Statistical analyses

All analyses were performed with STATA 10. Differences between the groups were tested with a Chi-Squared test. Follow-up was calculated as the time from surgery to death or date of last contact. Overall survival, disease-free survival, local recurrence-free survival and non-cancer related survival (including death due to post-operative complications) were calculated, by using Kaplan–Meier survival curves, for both univariate and multivariable survival analyses. Overall survival and

![Fig. 1. Relation between duration of radiotherapy, interval between radiotherapy and surgery and overall treatment time.](image)

Table 1a
Relation between radiotherapy duration and the interval between radiotherapy and surgery during the total mesorectal excision (TME)-trial.

<table>
<thead>
<tr>
<th>Interval between radiotherapy and surgery</th>
<th>Total</th>
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<tr>
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<td>≥28</td>
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<tr>
<td><strong>Radiotherapy duration</strong></td>
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<td>3</td>
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<tr>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>546</td>
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</tbody>
</table>

The area is light grey shaded area in case of OTT >10 days, and the dark shaded grey area has been excluded from the OTT analyses. Both were in violation with the protocol. Radiation duration of 8 days was in violation with the protocol and these patients were therefore included in the OTT >10 days.

Table 1b
Relation between radiotherapy duration and the interval between radiotherapy and surgery during the verification set (2000 until 2010).

<table>
<thead>
<tr>
<th>Interval between radiotherapy and surgery</th>
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<td>7</td>
<td>8</td>
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<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>275</td>
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</tbody>
</table>

The area is light grey shaded area in case of OTT >10 days, and the dark shaded grey area has been excluded from the OTT analyses. Both were in violation with the recommendations. Radiation duration of 8 days was in violation with the protocol and these patients were therefore included in the OTT >10 days.
non-cancer related mortality were truncated at one year, since recently a study has shown that post-operative mortality can be increased up to one year after surgery due to differences in comorbidities and fragility. Disease-free survival and local recurrence-free survival were truncated at 5 years, since recurrences or metastases are not expected to occur often within one year after surgery. Univariate and multivariable survival analysis was performed using a Cox proportional hazard model. Statistical significance was defined as \( p < 0.05 \). All analyses are done separately for the group of patients from the TME trial and the verification set.

3. Results

3.1. Dataset from the TME-trial

3.1.1. Patients

A total of 642 patients from the TME-trial were included in this study. The median follow-up since surgery of these patients was 9.1 years (range 0.01–13.7 years). The median age of the patients at time of surgery was 65.1 years (range 26.6–89.0 years).

3.1.2. Radiotherapy duration and interval between radiotherapy and surgery

Table 1a demonstrates the relationship between the duration of radiotherapy and the interval between the last fraction of radiotherapy and surgery for patients during the TME-trial. Most patients received radiotherapy from Monday till Friday, so 5 days continuously (85.0%). For the other patients, the radiotherapy duration was 6 days (2.6%), 7 days (9.8%) or 8 days (2.5%); including a weekend and/or bank holiday. Surgery within 3 days of the last fraction of radiotherapy was performed in 293 patients of the 642 patients, an interval of 4–7 days was the most common (340/642). Intervals of 8 until 27 days and 28 days or more occurred less often (5 and 4 patients, respectively).

In Table 2a the characteristics of the patients divided into the four interval groups are shown. There were no significant differences between the four interval groups in age and gender during the TME-trial (\( p = 0.5 \) and \( p = 0.2 \), respectively). Pathological stage was lower in the patients with an interval of \( \geq 8 \) days as compared to patients with an interval of <8 days (\( p < 0.001 \)), but no difference was detected between the group of patients with an interval of 0–3 days and 4–7 days (\( p = 0.3 \)), neither when the interval of 28 days and more only was excluded (\( p = 0.4 \)).

3.1.3. Survival

Due to small numbers in the interval group of 8 until 27 days and 28 days or more, these patients (\( n = 9 \)) were excluded for survival analysis. 30-day mortality analyses showed no significant difference between an interval of 0–3 days and 4–7 days for all ages combined (30-day mortality for interval of 0–3 days was 2.1% and for the interval of 4–7 days 4.7%, \( p = 0.08 \)). Neither difference in one-year overall survival between an interval of 0–3 days and 4–7 days was found for all ages combined (hazard ratio (HR) 1.67; 95% confidence interval (CI) 0.94–2.96; \( p = 0.08 \)). However, the 1-year overall survival showed an age disparity (Fig. 2a). Where patients younger than 75 years of age showed no difference in 1-year overall survival between both intervals (HR 1.11; 95% CI 0.54–2.30; \( p = 0.8 \)), patients \( \geq 75 \) years showed worse survival for the 4–7 days interval compared to those with 0–3 days interval (HR 3.58; 95% CI 1.32–9.71; \( p = 0.01 \)). Adjusted for age, gender and stage these differences remained significant (HR 3.65; 95% CI 1.31–10.16; \( p = 0.01 \)). The difference between the two interval groups in elderly patients arose within the first month, which suggested non-cancer-related mortality (including post-operative complications), as
confirmed in Fig. 2b (HR 2.92; 95% CI 1.05–8.12; \(p = 0.04\)). No significant differences were found for both age groups between the two interval groups in 5 year disease-free survival (HR 1.00; 95% CI 0.71–1.39; \(p = 0.9\) for patients <75 years and HR 2.07; 95% CI 0.90–4.79; \(p = 0.09\) for patients \(\geq 75\) years), neither for the 5 year local-recurrence free survival (HR 0.79; 95% CI 0.37–1.67; \(p = 0.5\) for patients <75 years and HR 3.98; 95% CI 0.41–38.34; \(p = 0.2\) for patients \(\geq 75\) years).

### 3.2. Verification set

#### 3.2.1. Patients

A total of 600 patients receiving radiotherapy between 2000 and 2010 were included in this verification set. The median follow-up since surgery of these patients was 4.3 years (range 0–11.4 years). Median age of these patients at time of surgery was 67.2 years (range 26.5–94.5 years).

#### 3.2.2. Radiotherapy duration and interval between radiotherapy and surgery

In this cohort most patients received radiotherapy during 5 days (45.8%) or 7 days (50.2%) (Table 1b). The remaining patients received radiotherapy during 6 days (0.5%) or 8 days (3.5%). Most patients (425/600) were operated on 0–3 days after the last fraction of radiotherapy. The interval of 4–7 days, 8–27 days and \(\geq 28\) days were less common (112/600, 18/600, and 35/600 patients, respectively). Over time there was an increase in patients who were operated on more than 28 days after the last fraction of radiotherapy (from 2.9% in 2000, to 10.7% in 2009; \(p < 0.001\)).

As shown in Table 2b, in the verification set elderly patients of 75 years and older more often had an interval of \(\geq 28\) days, and less often \(\leq 3\) days (\(p = 0.006\)). Furthermore, with a longer interval between the last fraction of radiotherapy and surgery, there was a decrease in pathological stage (\(p < 0.001\)). The pooled rate of pathological complete response in patients with...
an interval of 28 days or more was 13% (3 of 39 patients).

3.2.3. Survival

3.2.3.1. Interval. The 30-day mortality for all ages combined was 1.7% for an interval of 0–3 days, 1.6% for an interval of 4–7 days and 2.9% for an interval of 28 days or more, which was not statistically different ($p = 0.9$).

Both the 30-day mortality and the one-year overall survival of the patients from the verification set did not show the age disparity found in the dataset from the TME trial (Fig. 3a). Due to small numbers, patients with an interval of 8 until 27 days between radiotherapy and surgery ($n = 18$) were excluded from survival analysis. There was no significant difference found between the interval of 0–3 days compared to 4–7 days both for patients <75 years (HR 0.65; 95% CI 0.14–2.93; $p = 0.6$) and patients $\geq 75$ years (HR 0.59; 95% CI 0.13–2.66; $p = 0.5$). This remained after adjusting for age, gender and stage. Similarly, no differences in overall survival were found between the interval of 0–3 days and $\geq 28$ days in neither patients <75 years (HR 3.70; 95% CI 0.82–16.72; $p = 0.09$), nor in patients $\geq 75$ years (HR 0.97; 95% CI 0.22–4.38; $p = 0.9$).

The non-cancer-related survival of younger and elderly patients showed no significant differences between the interval of 0–3 days compared to 4–7 days either (HR 0.40; 95% CI 0.05–3.13; $p = 0.4$), for patients <75 years, and HR 1.08; 95% CI 0.22–5.36; $p = 0.9$, for patients $\geq 75$ years, respectively) (Fig. 3b). Besides, no differences were found in 5 year disease-free survival (HR 0.93; 95% CI 0.57–1.52; $p = 0.8$), 4–7 day interval compared to 0–3 days for patients younger than 75 years, HR 0.77; 95% CI 0.29–2.05; $p = 0.6$, 4–7 day interval compared to 0–3 days for patients of 75 years and older).

Furthermore, no differences were found in 5-year local-recurrence free survival, (HR 0.27; 95% CI 0.04–2.06; $p = 0.2$, HR 0.89; 95% CI 0.19–4.29; $p = 0.9$, for younger and elderly patients with an interval of 4–7 days compared to 0–3 days, respectively).

![Fig. 3a. Comparison of one-year overall survival per interval group stratified for age group (verification set).](image-url)
3.2.3.2. Duration of radiotherapy. Since the TME-trial the radiotherapy treatment was more often interrupted with a weekend, which increased the duration of radiotherapy from 5 days (85.0% in the TME trial) to 7 days (50.2% in the verification set). When radiotherapy during 5 days and during 7 days were compared in the verification set, no differences were found in 1-year overall survival (HR 0.75; 95% CI 0.37–1.52; \( p = 0.4 \)), 1-year non-cancer-related mortality (HR 0.91; 95% CI 0.39–2.10; \( p = 0.8 \)) or 5-year local-recurrence free survival (HR 0.89; 95% CI 0.39–2.01; \( p = 0.8 \)). Furthermore, no differences in overall survival, non-cancer-related survival or local-recurrence free survival were found in patients aged <75 years, neither in patients aged \( \geq 75 \) years.

3.2.3.3. Overall treatment time. Since both the duration of the radiotherapy and the interval between radiotherapy and surgery have changed over time, overall treatment time (OTT, as explained in Fig. 1), could have been a factor influencing mortality. However, in the verification set OTT was not associated with 1-year overall survival, 1-year non-cancer-related mortality (HR 0.91; 95% CI 0.39–2.10; \( p = 0.8 \)) or 5-year local-recurrence free survival (HR 0.89; 95% CI 0.39–2.01; \( p = 0.8 \)). Furthermore, no differences in overall survival, non-cancer-related survival or local-recurrence free survival were found in patients aged <75 years, neither in patients aged \( \geq 75 \) years. Because most patients were seen by the anaesthetist during admission prior to surgery, postponement of surgery by the anaesthetist should then result in a longer interval between admission and surgery for the longer interval group. However, no difference was found, with a similar median time between admission and surgery in both interval groups (2 days). Furthermore, no differences were found in age, gender, stage (see Table 2a), WHO performance scores (data not shown) and toxicity (data not shown) between the two interval groups. Even though, comorbidities were not administered during the TME trial, and might explain differences between both interval groups.

For this reason we tried to confirm the above mentioned findings in a separate retrospectively collected verification set. In this verification set, no differences were found in one-year overall survival and non-cancer-related survival between the interval groups. Several possible reasons could explain this. Firstly, over time perioperative care might have improved, resulting in less post-operative mortality. 30-day mortality was 2.1% in the interval of 0–3 days and 4.7% in the interval of 4–7 days, compared with 1.7% in the interval of 0–3 days, 1.6% in the interval of 4–7 days and 2.9% in the interval of 28 days or more in the verification set; suggestion that perioperative care has improved. Finally, another possibility is that due to awareness of

4. Discussion

In this study we analysed the impact of the interval between the last fraction of short-course radiotherapy and surgery on 1-year survival and long-term recurrence, both in the TME-trial and in a verification set. Results from the TME-trial showed that elderly patients with a prolonged interval (4–7 days) between the end of radiotherapy and surgery had higher one-year overall and non-cancer related mortality. In the verification set this could not be confirmed.

Although the results of the TME cohort derived from a randomised controlled trial, we have to interpret these results with caution, since these analyses have not been evaluated in a randomised setting. Therefore the finding may be simply a random finding. Another possible explanation for the results found may be that surgery was postponed in patients with a poor condition, after consultation by the anaesthetist, which would result in bias. Elderly patients are expected to have a poor condition more often, which would explain that the results were only found in patients \( \geq 75 \) years.
the clinicians for the higher postoperative mortality, since the TME results have been presented on several congresses, elderly patients were less often treated with an interval between 4 till 7 days between radiotherapy and surgery in the verification set. The results showed that indeed fewer patients were operated on 4 till 7 days after the last fraction of radiotherapy, indicating that awareness of the physicians might have been present. Besides, the finding that there has been a shift in radiotherapy duration from mainly 5 days in the TME-trials to 7 days in the verification set, suggests that this was done in order to prevent logistical problems. During the TME trial most patients received radiotherapy from Monday till Friday, followed by surgery in the next week. The knowledge of possible worse outcome after an interval of more than three days might have triggered radiation oncologists to decrease the interval between the end of radiotherapy and surgery, with nowadays only 20% of patients having an interval of 4–7 days (122 out of 600 patients), which was over 50% during the TME-trial (340 out of 642 patients). This resulted in a shift in approach; approximately 10% of the patients had a radiotherapy duration of 7 days during the TME-trial, whereas this was over 50% in the verification set. The present study therefore analysed the relation between overall treatment time and postoperative mortality and non-cancer-related mortality, demonstrating no difference, neither for the whole group, nor for the elderly. This suggests that including a weekend in radiotherapy treatment is safe.

Several other studies have studied the influence of the interval between radiotherapy and surgery. Recently the interim analyses of the Stockholm III trial have been published. In these interim analyses an increase in postoperative complications for patients surgically treated 11–17 days since the start of radiotherapy compared to patients with a shorter interval was reported. Differences in postoperative mortality were not significant due to small numbers. Similar, Hartley et al. found in a retrospective population-based cohort that patients with an overall treatment time <10 days had a decreased risk of complications. Additionally, Hartley et al. published that the ratio between pre-operative and postoperative neutrophil leucocyte count was significantly higher in patients without complications. Even though, they did not find an association between the neutrophil ratio and the overall treatment time. Fokstuen et al. found clear indications that the differences between the interval groups are related to the perioperative leucocyte response. Patients with an abnormal leucocyte response developed sepsis more often and had an increased risk of death within 90 days after surgery. Besides, a longer than recommended interval also appeared to be detrimental for postoperative death independently of leucocyte response. From the above can be concluded that there are several indications in the literature that the increased postoperative mortality after a longer interval between radiotherapy and surgery could be caused by an impaired immune response, possibly reflected in the perioperative leucocyte count of the patient.

Currently a Swedish trial studies delayed surgery after short course radiotherapy, because clear indications have been found that short course radiotherapy could cause downstaging after an interval between radiotherapy and surgery of at least 4 weeks. Almost certainly due to these results and the currently running trial, delayed surgery was used more often in the verification set, mainly in elderly patients. In our study there were also indications that delayed surgery induces downstaging, as patients with delayed surgery had a lower pathological stage. Furthermore, the verification set showed no differences in short-term survival between direct surgery after radiotherapy (interval of 0–3 days or 4–7 days) compared to delayed surgery (interval of 28 days or more), which is in line with the results shown in the interim analyses of the Stockholm III trial. Possibly, the leucocyte response has normalised at the time those patients are operated on.

In conclusion, there are several indications that the interval between radiotherapy and surgery influences postoperative outcome. Results from the verification set demonstrate that avoiding a longer interval between radiotherapy and surgery and including a weekend in the radiotherapy treatment seems safe, both for postoperative mortality as for oncological outcome. Therefore we recommend to limit the interval to 3 days and accept a radiotherapy duration of 7 days. If logistically impossible, postponement surgery after more than 4 weeks seems an option, although results on oncological outcome have to be awaited.

**Conflict of interest statement**

None declared.

**References**


