



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

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Abstract *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 post-operative 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

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due to awareness of the clinicians who avoided delayed surgery after radiotherapy since the results have been presented during congresses. A longer than recommended interval between radiotherapy and surgery should be avoided. Besides, the verification set suggests that radiotherapy duration of 7 days is acceptable.

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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.^{1–4} 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.^{5,6} In a large Swedish trial, short-course preoperative RT has proven to be more effective compared to postoperative radiotherapy with conventional surgery.⁷ The TME-trial and the CR07 trial showed, additionally, that with total mesorectal excision (TME) surgery, preoperative radiotherapy improved local control even further.^{8,9} 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).^{6,10} Radiotherapy is generally well tolerated, although postoperative morbidity and mortality is increased in some patients.^{8,11–16} The increased postoperative mortality may be contributed to the use of anterior–posterior beams, resulting in large irradiated volumes, from the earlier trials.^{11,13}

A more recent study has shown that short-course radiotherapy has significant impact on the perioperative leucocyte response.¹⁷ 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 distant 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 in 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 trial¹⁸). Radiotherapy duration has been divided into two groups: 5 days (Monday till Friday) or 7 days of radiotherapy (with a weekend included). Overall

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