



Effect of preoperative treatment strategies on the outcome of patients with clinical T3, non-metastasized rectal cancer: A comparison between Dutch and Canadian expert centers

A.J. Breugom^a, T.A. Vermeer^b, C.B.M. van den Broek^a, T. Vuong^c,
E. Bastiaannet^{a,d}, L. Azoulay^{e,f}, O.M. Dekkers^g, T. Niazi^c,
H.A. van den Berg^h, H.J.T. Rutten^b, C.J.H. van de Velde^{a,*}

^a Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

^b Department of Surgery, Catharina Hospital Eindhoven, Eindhoven, The Netherlands

^c Department of Radiation Oncology, Jewish General Hospital, McGill University, Montréal, Quebec, Canada

^d Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

^e Centre for Clinical Epidemiology, Lady Davis Institute, Montreal, Quebec, Canada

^f Department of Oncology, McGill University, Montreal, Quebec, Canada

^g Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

^h Department of Radiotherapy, Catharina Hospital Eindhoven, Eindhoven, The Netherlands

Accepted 3 May 2015

Available online 21 May 2015

Abstract

Aim: High-dose-rate brachytherapy (HDRBT) appears to be associated with less treatment-related toxicity compared with external beam radiotherapy in patients with rectal cancer. The present study compared the effect of preoperative treatment strategies on overall survival, cancer-specific deaths, and local recurrences between a Dutch and Canadian expert center with different preoperative treatment strategies. **Patients and methods:** We included 145 Dutch and 141 Canadian patients with cT3, non-metastasized rectal cancer. All patients from Canada were preoperatively treated with HDRBT. The preoperative treatment strategy for Dutch patients consisted of either no preoperative treatment, short-course radiotherapy, or chemoradiotherapy.

Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CIs) comparing overall survival. We adjusted for age, cN stage, (y)pT stage, comorbidity, and type of surgery. Primary endpoint was overall survival. Secondary endpoints were cancer-specific deaths and local recurrences.

Results: Five-year overall survival was 70.9% (95% CI 62.6%–77.7%) in Dutch patients compared with 86.9% (80.1%–91.6%) in Canadian patients, resulting in an adjusted HR of 0.70 (95% CI 0.39–1.26; $p = 0.233$). Of 145 Dutch patients, 6.9% (95% CI 2.8%–11.0%) had a local recurrence and 17.9% (95% CI 11.7%–24.2%) patients died of rectal cancer, compared with 4.3% (95% CI 0.9%–7.5%) local recurrences and 10.6% (95% CI 5.5%–15.7%) rectal cancer deaths out of 141 Canadian patients.

Conclusion: We did not detect statistically significant differences in overall survival between a Dutch and Canadian expert center with different treatment strategies. This finding needs to be further investigated in a randomized controlled trial.

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Keywords: Rectal cancer; External beam radiotherapy; High-dose-rate brachytherapy; The Netherlands; Canada; Outcome

Introduction

Colorectal cancer is the third most common cancer in men and the second in women worldwide, with a total of 1.36 million new cases in 2012.¹ Approximately one third of all colorectal cancers occur in the rectum.

* Corresponding author. Leiden University Medical Center, Department of Surgery, K6-R, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 71 526 2309; fax: +31 71 526 6750.

E-mail address: c.j.h.van_de_velde@lumc.nl (C.J.H. van de Velde).

In the past decades, several improvements in rectal cancer treatment have been achieved. Whereas the five-year local recurrence rate was up to 27% until the beginning of the nineties after surgery,² the introduction of total mesorectal excision (TME) decreased the five-year local recurrence rate to 5%–11%.^{3–5} The TME-trial showed that the addition of preoperative short-course external beam radiotherapy further decreased this rate to 5%.⁶ However, the improvement in local control should be weighed against the risk of side-effects due to short-course external beam irradiation.^{7,8} Acute as well as late side-effects occur, including more postoperative complications (48% in patients treated with preoperative short-course radiotherapy (RT) versus 41% in patients not treated with RT⁹), increased bowel dysfunction, and more sexual dysfunction.^{9–12}

In an attempt to reduce treatment-related toxicity, high-dose-rate brachytherapy (HDRBT) has been introduced as a preoperative treatment in patients with resectable rectal cancer.^{13–18} The five-year local recurrence rate was 5% and toxicity patterns seemed to be more favorable as compared to external beam radiotherapy.^{13,18} Moreover, no major differences in postoperative complications were demonstrated between short-course radiotherapy and HDRBT.¹⁹ To our knowledge, no studies (neither randomized nor observational) have compared the long-term effects between the different treatment strategies. Therefore, the objective of this study is to compare overall survival, cancer-specific deaths, and local recurrences in patients with cT3 rectal cancer treated with either no preoperative treatment, short-term preoperative radiotherapy or chemoradiotherapy (CRT) in an expert center in the Netherlands with patients treated with HDRBT in an expert center in Canada.

Patients and methods

Patients

We included all patients with magnetic resonance imaging (MRI) staged cT3 non-metastasized rectal cancer who were surgically treated between 2005 and 2010 in the Catharina Hospital in the Netherlands and four different centers in Canada with HDRBT centralized at the Jewish General Hospital. In the Catharina Hospital in the Netherlands, the treatment strategy consisted of either no preoperative treatment, short-course radiotherapy (5×5 Gy) followed by TME surgery within one week, or long-course radiotherapy (25×1.8 – 2 Gy) combined with chemotherapy followed by TME surgery within 6–8 weeks. All patients from Canada were treated with preoperative HDRBT with a daily dose of 6.5 Gy during 4 days, followed by TME surgery after 4–8 weeks. No detailed information was available on criteria that determined type of preoperative treatment in the expert center in the Netherlands. Therefore, we compared treatment strategies

as a whole, and not separated by type of preoperative treatment. Follow-up was completed until March 2015.

TME surgery was performed in all patients. Age, gender, presence or absence of comorbidity, cN stage, year of surgery, type of surgery, (y)pT stage, and (y)pN stage were collected from all included patients. Patients were divided into three age groups (<65 years, 65–74 years, and ≥ 75 years).

The primary endpoint was overall survival. Secondary endpoints were cancer-specific deaths and local recurrences. Overall survival was calculated from date of surgery. Overall survival was defined as time to death of any cause, or to end of follow-up (censored). Local recurrence was defined as evidence of tumor within the pelvic or perineal area, confirmed by imaging or pathology regardless the presence of distant metastasis. Cancer-specific death was defined as death due to rectal cancer, as confirmed by the treating physician.

Statistical analyses

The chi-square test was used to compare categorical patient characteristics. Median follow-up was calculated according to the reverse Kaplan–Meier method.²⁰

Kaplan–Meier curves were constructed comparing overall survival between the Dutch and Canadian expert center. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival. We adjusted for variables that differed between the two expert centers: cN stage (N0 vs N1 vs N2), (y)pT stage (T0 vs T1 vs T2 vs T3 vs T4), comorbidity (no vs yes), and type of surgery (LAR vs APR). Furthermore, we adjusted for age (as a continuous variable), as the primary endpoint was overall survival. Due to low number of events for cancer-specific deaths and local recurrences, we did not use Cox proportional hazard models, but calculated the proportions with 95% CIs for proportions of cancer-specific deaths and local recurrences. As a secondary analysis, we investigated crude and adjusted (for cN stage (N0 vs N1 vs N2), comorbidity (no vs yes), and type of surgery (LAR vs APR)) overall survival stratified by (y)pT stage ((y)pT0–2, (y)pT3–4), as the distribution between the expert centers was different and (y)pT stage was associated with overall survival.

A p-value of < 0.05 was considered as statistically significant. All analyses were performed with STATA 12.

Results

In total, we included 286 patients with cT3 non-metastasized rectal cancer. From the Catharina Hospital in the Netherlands, 145 patients were included. Eleven of these patients had no preoperative treatment, 52 patients were treated with short-course radiotherapy followed by TME surgery within one week, and 82 patients were preoperatively treated with long-course radiotherapy combined

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