Available online at www.sciencedirect.com
ScienceDirect
EJSO 36 (2010) 470–476
EJSO the Journal of Cancer Surgery
www.ejso.com

Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial

M. Kusters [a,b], C.A.M. Marijnen [c], C.J.H. van de Velde [a,*], H.J.T. Rutten [b], M.J. Lahaye [d], J.H. Kim [f], R.G.H. Beets-Tan [d], G.L. Beets [e]

[a] Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands
[c] Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands
[d] Department of Radiology, University Hospital Maastricht, Maastricht, The Netherlands
[e] Department of Surgery, University Hospital Maastricht, Maastricht, The Netherlands
[f] Department of Radiology, Yonsei University College of Medicine, Seoul, Republic of Korea

Accepted 19 November 2009
Available online 21 January 2010

Abstract

Aim of the study: In patients from the Dutch TME trial patterns of local recurrence (LR) in rectal cancer were studied. The purpose was to reconstruct the most likely mechanisms of LR and the effect of preoperative radiotherapy.
Methods: 1417 patients were analyzed; 713 were randomized into preoperative radiotherapy and total mesorectal excision (RT + TME), 704 into TME alone. Of the 114 patients with LR, the subsites of LR were determined and related to tumor and treatment factors.
Results: Overall 5-year LR-rate was 4.6% in the RT + TME group and 11.0% in the TME group. Presacral local recurrences occurred most in both groups. Radiotherapy reduced anastomotic LR significantly, except when after low anterior resection (LAR) distal margins were less than 5 mm. Abdominoperineal resection (APR) mainly resulted in presacral LR. Even after resection with a negative circumferential resection margin, LR-rates were high. Thirty percent of the patients had advanced tumors, which resulted in 58% of all LRs. Lateral LR comprised 20% of all LR. Presacral and lateral LR resulted in a poor prognosis, in contrast to anterior or anastomotic LRs with a relatively good prognosis.
Conclusions: RT reduces LR in all subsites and is especially effective in preventing anastomotic LR after LAR. APR-surgery mainly results in presacral LR, which may be prevented by a wider resection. In the TME trial many advanced tumors were included, rather requiring chemoradiotherapy instead of RT. Currently, with good imaging techniques, better selection can take place. Especially lateral LR might be a problem in the future.

Keywords: Local recurrence; Rectal carcinoma; Abdominoperineal resection; Low anterior resection; Distal margin; Preoperative radiotherapy

Introduction

Optimal local control is an important goal in the treatment of rectal cancer. Since the introduction of the total mesorectal excision (TME) local control has improved drastically, with further improvement through the addition of preoperative radiotherapy.[1,2] In the Dutch TME trial, surgeons were trained in TME-surgery by workshops and tutorials in order to achieve optimal surgical quality. Although locally advanced tumors were supposed to be excluded, only fixed tumors at rectal examination could be identified, since routine imaging was not mandatory at that time.[2] However, histological evaluation of the circumferential resection margins (CRM) suggested that a substantial proportion of advanced tumors had been included.[3] Suspected CRM involvement, T4 disease and massive lymph node involvement, all risk factors for local recurrence, can currently be well identified by preoperative MR imaging.[4,5] In the presence of these risk factors, nowadays a long course of neoadjuvant (chemo)radiation would be given in order to achieve downsizing and downstaging before surgery.[6]

The purpose of this study is to analyze the patterns of local recurrence in the TME trial, reconstructing the most

* Corresponding author. Department of Surgery, Leiden University Medical Center, 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).

0748-7983/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejso.2009.11.011

likely mechanisms of local recurrence and the effect of preoperative radiotherapy.

Patients and methods

Patients

Patients were selected from a large prospective randomized multi-center study that analyzed the effect of short-term preoperative radiotherapy (5 × 5 Gy) in patients operated with a total mesorectal excision (RT + TME), compared to patients with TME alone (TME). Inclusion criteria were primary adenocarcinoma of the rectum, without evidence of metastatic disease and tumor location within 15 cm from the anal verge. Patients with other malignant diseases or with fixed tumors were excluded. Standardized techniques for surgery, radiotherapy and pathology were used.[2]

For the current study only the Dutch patients were selected and the following patients were excluded from the analysis: ineligible patients ($n = 50$), no resection ($n = 37$) and no tumor at operation ($n = 26$), leaving 1417 patients for analysis.

Methods

All patients with a local recurrence, defined as any rectal cancer recurrence in the small pelvis, were identified. Local recurrence was diagnosed clinically, radiologically or histologically. All patients with a local recurrence were studied individually. Sources of information additional to the standard trial database items were the operative report, the histological report, specimen photographs when available, initial preoperative imaging when available, imaging of the local recurrences, and the clinical history and follow-up after the diagnosis of the local recurrence. The data were reviewed case by case by a team consisting of 2 radiologists, 1 radiation oncologist and 2 surgeons.

Examining the images and data, the location of the recurrence was classified into one of the following subsites:

- Presacral: predominantly midline, in contact with sacral bone
- Anterior: predominantly midline, involving bladder, uterus, vagina, seminal vesicles or prostate
- Anastomotic: after low anterior or low Hartmann, at the staple line
- Lateral: pelvic sidewall, immediately behind posterior ischiac spine, in the obturator lymph node compartment or along iliac vessels
- Perineal: perineum, anal sphincter complex with surrounding perianal and ischiorectal space

Although the distal margin for the low anterior resections and low Hartmann's was prospectively recorded, the database did not contain reliable information on the completeness of the mesorectum distally. For the patients with a local recurrence the operative reports were studied to define whether the distal mesorectum was transected below the tumor, or if a distally complete mesorectal excision was performed.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 12.0 for Windows; SPSS Inc, Chicago, IL). *T*-tests and chi-square tests were used to compare individual variables. Survival was estimated using the Kaplan–Meier method. Differences were assessed using the Log-Rank test. *P*-values were two-sided and considered statistically significant at a value of 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk.[7] Similarly, cumulative incidences were calculated for subsite of local recurrence, with death and other types of local recurrence as competing risks, and for survival, with death due to other causes as competing risk.

Results

Clinical and pathological characteristics

Clinical and pathological characteristics are listed in Table 1. Low tumor location, abdominoperineal resection (APR) surgery, higher TNM stage and involvement of the circumferential resection margin are associated with local recurrence, as previously reported.[8] After a median follow-up of 7.0 years (range 2.5–9.8) 114 of the 1417 patients developed a local recurrence; 36 patients in the RT + TME group (5-year 4.6% LR-rate) and 78 patients in the TME group (5-year 11.0% LR-rate).

The mean time to local recurrence was 2.6 years in RT + TME group and 1.5 years in the TME group. Nineteen of 36 patients (55%) in the RT + TME group had distant metastases at the time of local recurrence diagnosis. This was in 32 of 78 (41%) patients in the TME group ($p = 0.264$). If distant metastases diagnosed within 1 month of local recurrence diagnosis were also considered as occurring simultaneously, distant metastases rate was 74% in the RT + TME group and 40% in the TME group ($p = 0.004$).[9]

Patterns of local recurrence

The subsites of local recurrence are presented in Table 2. Presacral local recurrences (Fig. 1) occurred most in both randomisation groups (5-year local recurrence rate RT + TME: 2.0% and TME: 3.6%). There was a significant difference between the two randomisation arms in the anastomotic subsite, with 0.7% 5-year local recurrence in the RT + TME group and 2.7% in the TME group ($p = 0.003$). Lateral local recurrences comprised about 20% of all local recurrences.