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ScienceDirect

EJSO 41 (2015) 1204–1209

EJSO the Journal of Cancer Surgery

www.ejso.com

Remaining cancer cells within the fibrosis after neo-adjuvant treatment for locally advanced rectal cancer

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Accepted 27 May 2015
Available online 12 June 2015

Abstract

Aim: To analyse the incidence and distribution of remaining cancer cells within the fibrosis induced by preoperative chemo-radiotherapy (CRT) for locally advanced rectal cancer.
Methods: The histopathological specimens from 46 patients operated on with extensive surgery for locally advanced rectal cancer after CRT were examined. The extension of fibrosis in relation to the mesorectal fascia (MRF) and the distribution of cancer cells within the fibrosis was examined using routine haematoxylin-eosin staining. In addition, immunohistochemical staining with CK20 was done to examine if cancer cells were missed by routine pathological work up.
Results: All specimens showed CRT induced fibrosis. Two specimens showed complete response without viable cancer cells (ypT0). The fibrosis was limited inside the MRF in three cases, adherent to or involved the MRF in ten cases and in 33 cases the fibrosis was obvious outside as well as inside the fascia. Twenty-one cases showed fibrosis on the surgical resection margin, and in 9 of these cancer cells were found on the surgical margin (R1, R2-resection). 37 patients had R0 resections and among those 24 showed fibrosis beyond the MFR and 13 had scattered cancer cells in the fibrosis along or outside the MRF.
Conclusions: The rate of remaining cancer cells within the fibrosis was high in patients with locally advanced rectal cancer treated with CRT. Frequently cancer cells were detected near the border of the fibrosis. A complete resection of the fibrosis is therefore recommended to achieve an R0 resection after neo-adjuvant treatment.

Keywords: Locally advanced rectal cancer; Preoperative chemoradiotherapy (CRT); Fibrosis; Mesorectal fascia (MRF); Local recurrence

Introduction

The implementation of total mesorectal excision (TME) has dramatically improved local control and survival in patients with rectal cancer.[1,2] However, some patients still develop a local failure. A significant risk factor for recurrence is the presence of tumour cells less than 1 mm from the circumferential resection margin (CRM).[3,4] This may be due to an incomplete TME or by tumour growth at, or close to the mesorectal fascia (MRF), which anatomically is the surgical resection margin and the key structure when proper TME surgery is performed.[5] In patients with advanced T3 tumours infiltrating close to the MRF or with T4 tumours, infiltrating other structures or organs, the resection must extend beyond the MRF in order to avoid tumour involved margins. This is often done by an extended procedure, including en bloc resections of involved organs or structures. Neo-adjuvant chemo-radiotherapy (CRT) is recommended in locally advanced rectal cancer to induce down-sizing/down-staging in order to permit a less extensive procedure.[6–8] CRT often results in a significant tumour response with development of fibrosis or even a complete pathological response.[9,10] Thus, clinically staged T4 tumours on preoperative assessment may

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http://dx.doi.org/10.1016/j.ejso.2015.05.019
0748-7983/

be reported as ypT0 – ypT4 tumours on histopathology, depending on treatment response. This is a clinical dilemma, since extensive en bloc resections may be considered unnecessary in advanced tumours after neo-adjuvant treatment if only fibrosis remains outside the MRF and if the tumour is well confined within the mesorectum. Especially since extensive surgery of locally advanced rectal cancer is associated with high morbidity.[11,12] However, if the post-treatment fibrosis contains cancer cells extended procedures may be warranted even after neo-adjuvant treatment.

The aim of this study was to analyse the incidence and distribution of remaining cancer cells within the fibrosis induced by preoperative chemo-radiotherapy (CRT) for locally advanced rectal cancer.

Material and methods

Since 1995, all patients with rectal cancer in the county of Stockholm are prospectively reported to the Regional Cancer Center in Stockholm. Registered data include patient- and tumour characteristics, preoperative staging, neo-adjuvant treatment, surgical procedure, histopathology of the resected specimen and follow up data on recurrence and survival.

From the database, information was extracted on patients fulfilling the following criteria: A preoperative diagnosis of primary locally advanced rectal cancer (cT4), no preoperative signs of distant metastases (except potentially resectable metastases), a surgical procedure including resection of another organ or structure *en bloc* with the rectum, and surgery performed at the Karolinska University Hospital.

After a cross match between the registry at the Regional Cancer Center and the local patient registry at the Karolinska University Hospital, 46 patients operated on until December 2005 fulfilled these criteria and were included in the study.

A thorough review of patient medical records, concerning preoperative work-up, surgical procedure and histopathology report, was performed to obtain information on tumour extension, type of surgery performed and on tumour stage. The patients were followed for local recurrence until death or end of follow up (May 31, 2012).

Based on radiological and/or clinical findings at surgery, the tumours were considered as involving adjacent anatomical organs (such as bladder, prostate, female genitals, small bowel), adjacent anatomical structures (such as pelvic floor, pelvic sidewall or sacrum) or both. The surgical procedure was defined as an en bloc resection if another organ or part of another organ was removed with the tumour or as an extended TME if a part of an adjacent structure was removed with the tumour. The completeness of tumour removal, residual tumour stage, was defined as R0 if the surgeon reported a complete resection and the pathologist reported tumour free resection margins of the specimen, as R1 if the pathologist reported a tumour involved resection margin and as R2 if the surgeon reported locally remaining tumour after resection.

For the purpose of this study, histological slides from all patients were reviewed and assessed by one surgeon (S.T.) regarding the extent of peri-tumoural fibrosis, its relation with the MRF and to the actual circumferential resection margin (CRM) outside the MRF and subsequently revised and confirmed by one pathologist (J.L.). In addition, an assessment was made on whether tumour cells were present within the fibrosis close to the MRF (<1 mm), in the fibrosis outside the MRF or on the actual surgical resection margin (CRM).

In addition to the review of conventionally stained slides (Haematoxylin–Eosin), immuno-histochemical staining with cytokeratin 20 (CK 20) was performed in 40 patients. In the six remaining patients CK 20 staining was not performed, due to lack of paraffin embedded tissue blocks.

Results

Clinical characteristics of the 46 patients are shown in Table 1. The median age was 63 years and two thirds of the patients were male. The diagnosis of a locally advanced rectal cancer was based on MRI or CT findings in 31 patients, on findings at explorative laparotomy preceding neo-adjuvant treatment in 14 patients and on digital examination revealing a fixed tumour in one patient. Potentially resectable distant metastases were found in five patients.

All patients had received neo-adjuvant treatment, the majority long course radiotherapy (50 Gy), with or without 5-fluorouracil (5FU)-based chemotherapy. The median time interval between completion of preoperative treatment and surgery was 8 weeks (0–36 weeks). The patients were followed in 63 (6–152) months in median.

Table 1
Preoperative evaluation of patient, tumour, and treatment characteristic in 46 patients with locally advanced rectal cancer.

	Total $N = 46$
Age, median (range)	63 (28–79)
Women/Men	16/30
Follow up time, median (range) months	63 (6–152)
Assessment of tumour	
Radiology MRI/CT	31
Explorative laparotomy	14
Digital examination	1
Distant metastases	5
Extension of T4	
Towards other organ	18
Towards other structures	9
Both	19
Preoperative treatment	
Long RT (50 Gy)	18
Long RT and chemo	20
Short RT (5 × 5 Gy)	7
Short RT and chemo	1
Intraoperative RT (IORT)	13