Available online at www.sciencedirect.com

ScienceDirect

EJSO 40 (2014) 227–233

EJSO the Journal of Cancer Surgery

www.ejso.com

Impaired continence function five years after intensified chemoradiation in patients with locally advanced rectal cancer

K. Horisberger [a,*], S. Rothenhoefer [a,c], M. Kripp [b], R.D. Hofheinz [b], S. Post [a], P. Kienle [a]

[a] Department of Surgery, University Hospital of Mannheim, Faculty of Medicine, Mannheim, Germany
[b] TagesTherapieZentrum am Interdisziplinären Tumorzentrum, III. Medizinische Klinik, University Hospital of Mannheim, Faculty of Medicine, Mannheim, Germany
[c] Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Accepted 29 November 2013
Available online 14 December 2013

Abstract

Aims: While the influence on survival is only seen in patients with complete regression after neoadjuvant treatment in locally advanced rectal cancer the impairment of the continence capacity weighs even more for patients with little oncological benefit.
Methods: Patients treated with intensified preoperative radiochemotherapy patients treated only by TME surgery were asked five years after treatment to complete the Wexner and SF-12 quality of life questionnaire.
Results: 25 after neoadjuvant treatment had a median Wexner score of 14 [3–20] after 63 [42–78] months. Histopathological stage or grade of regression did not influence the Wexner score ($p = 0.76$, resp. $p = 0.9$). 12% describe themselves as being permanently continent; 40% are stool incontinent "always" or "most of the time". 68% are always wearing pads.

29 patients after TME only showed a median Wexner score of 5 [range 0–17] after 66 months [26–133].

SF-12 showed significantly lower values in physical ($p = 0.02$) as well as mental summary scales ($p = 0.015$) in patients after RCTX while patients after radical surgery showed no difference to the norm population.
Conclusion: This study shows that continence is significantly worse five years after neoadjuvant treatment. Moreover, patients after neoadjuvant treatment and surgery have impaired quality of life compared to norm population. These results may contribute to the discussion of only applying neoadjuvant chemoradiation selectively in patients with advanced rectal cancer.

Keywords: Rectal cancer; Radiochemotherapy; Fecal incontinence; Quality of life

Introduction

Total mesorectal excision (TME) as described by Heald has been implemented as the standard surgical procedure for rectal cancer. Preoperative radiotherapy significantly reduces the rate of local recurrences.[1] Nonetheless, long-term data indicate that this reduction does not translate into improved survival with the exception of patients with stage III cancer.[2] On the basis of the data of the German Rectal Cancer,[3] as well as the MRC CR07 Trial,[4] neoadjuvant radio(chemo)therapy is regarded as a standard of care for locally advanced rectal cancer patients. Meanwhile, several studies have shown better survival rates for patients with complete pathological remission (pCR) after neoadjuvant treatment.[5,6] Consequently, several phase-II and–III studies have been initiated with the aim to increase the pCR rates.

A main drawback of neoadjuvant radiotherapy, however, is that long-term functional results may be compromised. Late results of the Dutch Trial revealed that irradiated patients suffered from a significantly higher rate of incontinence at day and night as well as from anal blood and

* Corresponding author. Department of Surgery, University Hospital of Mannheim, Theodor-Kutzer-Ufer 1-4, D-68167 Mannheim, Germany. Tel.: +49 621 383 2225; fax: +49 621 383 3809.
E-mail address: k.horisberger@gmx.de (K. Horisberger).

0748-7983/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2013.11.029

mucus loss.[7] In a randomized study, patients after neoadjuvant chemoradiation showed even worse functional results than patients after only radiotherapy.[8] Patients with low coloanal anastomosis show particularly bad functional results in such a setting.[9] Beyond these publications, data on late functional results after intensified neoadjuvant chemoradiation are scarce.[10] In the present analysis we sought to evaluate late functional results and health-related quality of life (HrQoL) data of patients undergoing intensified chemoradiation within a phase I and II study and compared these data to those of patients after a TME procedure without any neoadjuvant or adjuvant treatment.

Patients and methods

Study group

All patients included in the present analysis participated in phase-I and II clinical trials investigating the triple–drug combination of capecitabine, irinotecan and cetuximab in conjunction with radiotherapy. The efficacy results were presented earlier.[11,12] Here we only give a short overview of the eligibility criteria and the treatment regimen applied in the clinical trial.

The clinical study protocol for study patients and the control group was reviewed and approved by the local institutional ethics committee and the study was performed according to the Declaration of Helsinki. All patients provided written informed consent for participation in the study.

Eligibility criteria

Patients with histologically confirmed, locally advanced non-metastatic rectal adenocarcinoma (endorectal ultrasound stage cT3-4, any N and cT2, N+ distal rectum) were included in the clinical trials.

Pretreatment evaluation

All patients underwent physical examination, biopsy with confirmation of adenocarcinoma, digital rectal examination, rectoscopy, transrectal ultrasonography, rectal manometry, pelvic and abdominal computed tomographic (CT) scans, pelvic NMR, colonoscopy, and chest X-rays.

Chemoradiation regimen

Starting at Day 1 of RT, patients received weekly cetuximab (400 mg/m^2 loading dose day 1 and 250 mg/m^2 weekly thereafter on days 8, 15, 22, 29; weekly irinotecan (40–50 mg/m^2 Days 1, 8, 15, 22, 29), and capecitabine orally twice daily throughout the period of radiotherapy (500–1000 mg/m^2 twice daily days 1–38). Radiotherapy (RT) was delivered with a linear accelerator using 18–23 MeV photons and a three-field box technique consisting of a posterior-anterior and 2 lateral fields. A total dose of 50.4 Gy was given in daily fractions of 1.8–Gy, 5 days a week. The clinical target volume (CTV) included the sacrum, the presacral space, and the posterior wall of the bladder and prostate or vagina. The common iliac lymph nodes were included in the CTV. The upper border of the CTV was at the L5–S1 interspace for cN0 and at L4–L5 for cN + patients. The lower field border was 5 cm below the macroscopic tumour. After a dose of 45 Gy, an additional dose of 5.4 Gy was given to the boost volume using a shrinking field technique. To keep the boost volume as large as possible, it was defined as the initial CTV minus the small bowel as identified on the treatment planning CT or on simulation films after oral contrast administration in prone position using a belly board. The maximal dose to small bowel was limited to 46 Gy, accepting potential underdosages to small parts of the gross tumour volume in tumours of the upper third.

Surgery and histopathology

4–6 weeks after completion of chemoradiation resection of the primary tumour was scheduled. Grades of histopathological regression were described as defined by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (Japanese Society for Cancer of the Colon and Rectum (JSCCR).[13] Regression 0 = no histopathological signs of regression; 1 = little regression in at most 2/3 of the tumour; 2 = moderate regression in more than 2/3 of the tumour, but still vital tumour cells; 3 = complete regression.

For the present study patients were excluded in case of persisting or permanent ileo- or colostomy, local recurrence or distant metastases at time of the interview, death, or if they had been treated in between for local recurrences.

Control group

The control group was extracted from a prospective research database from our hospital that collects rectal cancer patients since 1999. All patients underwent radical oncological resection along the TME criteria without having had neoadjuvant or adjuvant treatment. Patients who would have had the indication for neoadjuvant or adjuvant treatment along the TNM stage but were prevented from for medical reasons (e.g. severe diseases) were excluded from the study. Along that, the histopathological analysis in all cases of the comparison group revealed a stage UICCC I disease.

Methods and statistical analysis

Five years after initial surgery patients were asked to fill out the Wexner questionnaire. Additionally, HrQoL was evaluated with help of the SF-12. The control group was asked to fill out the questionnaires five years after surgery. A portion of patients was already asked to fill out the Wexner score questionnaire before starting neoadjuvant treatment patients.

Patients were excluded from the present analysis in case of persisting or permanent stoma, local recurrence or