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Intensified neoadjuvant chemoradiotherapy in locally advanced rectal cancer – impact on long-term quality of life

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Abstract

Aims: In spite of advances in rectal cancer surgery and the use of preoperative 5-fluorouracil-(5-FU) based chemoradiotherapy (CRT) in stage II and III disease distant metastases still occur in about 35–40% of the patients. Intensified preoperative CRT (ICRT) using other drugs in conjunction with 5-FU has been investigated in order to improve the pathological complete remission (pCR) rate and thereby prognosis of patients with locally advanced rectal cancer. However, acute toxicity, especially diarrhea, was reported to be high and no improvement in pCR rates has been observed in randomized trials. Long-term results of these trials are pending. In the present analysis we investigated the impact of ICRT on health related quality of life and long term toxicity.
Methods: The present study included 119 patients with locally advanced rectal cancer who underwent neoadjuvant CRT followed by surgery within controlled clinical trials. Patients received ICRT ($n = 83$) or standard CRT ($n = 36$). Evaluation of HRQoL was performed using EORTC QLQ-C30 and QLQ-CR29 questionnaires.
Results: The overall rating of global health status/QLQ scale of the EORTC QLQ-C30 questionnaire was identical in both patient groups but patients in the CRT group showed better results in four out of nine function scales. Concerning symptom scales, patients in the CRT arm exhibited significantly less diarrhea ($p = 0.028$) and less disorders with taste (0.042).
Conclusions: This data suggests that higher gastrointestinal acute toxicity caused by ICRT might lead to a higher risk of long-term deterioration of "gastrointestinal QoL". Future results of randomized trials investigating ICRT versus CRT should be discussed in the light of long-term QoL data.

Keywords: Neoadjuvant chemoradiotherapy; Quality of life; Rectal cancer

Introduction

Advances in surgery have significantly improved the prognosis of rectal cancer. In addition to an optimized resection technique using total mesorectal excision surgery, preoperative radiotherapy further reduces local recurrence rates.[1] Based on the results of three randomized trials neoadjuvant 5-fluorouracil-(5-FU)-based chemoradiotherapy (CRT) is regarded as a treatment option for locally advanced rectal cancer (LARC).[2–4] In these trials local recurrence rates in patients undergoing preoperative 5-FU-based treatment ranged between 6% and 8% but distant metastases represented the most common type of treatment failure in approximately 35–40% of the patients.

In an attempt to improve the results of 5-FU based CRT neither biomodulation of 5-FU[5] nor combination of 5-FU with older cytostatics (e.g. semustine[6]) or the prolongation of chemotherapy[7] have improved disease-free or overall survival. Recently, capecitabine has been shown to decrease the rate of metastases and to improve disease-free survival in comparison with 5-FU with the 5-year overall survival as the primary endpoint of the study being non-inferior.[8]

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The pathological complete remission (pCR) rate has been identified as a favorable prognostic marker for patients with LARC.[9] Therefore, the intensification of neoadjuvant treatment by using two-drug CRT regimens as a strategy to increase pCR rates and to prolong disease-free and overall survival has been pursued. The pCR rates observed in phase-II trials with two-drug combination chemotherapy regimens appeared to be at least twice as high than with 5-FU-based CRT alone.[10] Nevertheless, randomized trials investigating the addition of oxaliplatin to 5-FU or capecitabine failed to demonstrate an improvement in pCR while substantially increasing acute toxicity especially diarrhea.[11,12]

Finally, the impact of intensified neoadjuvant CRT (ICRT) on health related quality of life (HRQoL) or long term toxicity has not yet been reported. Regarding the impact of different surgical techniques or radiotherapy on long-term sequelae and HRQoL in patients with colorectal cancer several studies have been published. Two studies recently reported on the influence of the addition of chemotherapy to long-course radiotherapy on HRQoL in patients with LARC.[13,14] Patients treated with CRT showed significantly more symptoms of diarrhea and a significantly worse role-function and social functioning and general HRQoL in comparison to patients receiving radiotherapy alone.[13,14] This raises the question if the intensification of CRT by adding a second drug may further worsen long-term HRQoL, however no data on the influence of ICRT on HRQoL has been reported yet.

In the present analysis we sought to investigate HRQoL of patients receiving ICRT and compared the results to the HRQoL of patients receiving standard CRT.

Patients and methods

Study design and study population

119 patients with histologically confirmed, locally advanced non-metastatic rectal adenocarcinoma (uT3-4, any N *or* any T N-positive), who underwent neoadjuvant CRT and surgery at the departments of oncology, radiation oncology and surgery of the University Medical Center Mannheim, University of Heidelberg were evaluated for HRQoL after CRT. All patients were either treated within a phase III trial (standard CRT group; July 2005 until November 2007)[8] or within phase I/II trials (ICRT group; May 2002 until June 2008).[15,16] Selection criteria for both studies were identical. Both trials were approved by the local institutional ethical committee, and patients provided written informed consent for study participation.

83 patients (70%) received ICRT consisting of capecitabine and irinotecan (CapIri) ± cetuximab, 36 patients (30%) received standard CRT. The clinical data of these trials have been reported before.[15,16] The standard CRT group comprised patients participating in the MARGIT trial which compared 5-FU with the oral pro-drug capecitabine.[8]

HRQoL questionnaires were sent to patients at two time points, in May 2008 and in May 2009. All patients were required to have completed rectal cancer therapy including adjuvant chemotherapy after curative resection and all patients had to have had their diverting stoma closed in cases of low anterior rectal resection. Patients with recurrence were excluded. Questionnaires were completed by the patients without the assistance of physicians or nurses. Patients were asked to return questionnaires within four weeks. If questionnaires were not returned, patients were contacted by phone call and were asked to fill in the questionnaires.

Health related quality of life questionnaires and statistical methods

Quality of life was assessed with two questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC), the QLQ-C30 questionnaire (version 3.0)[17] and the colorectal cancer-specific module QLQ-CR29 (version 2.1).[18] The QLQ-C-30 is a validated, brief, self-reporting, and cancer specific questionnaire which consists of 30 items that generate nine multi-items scales: five function scales, three symptom scales as well as the global health status/QLQ scale. The colorectal cancer specific module EORTC QLQ-CR29 questionnaire consists of 29 questions: one functional scale, three symptom scales and nineteen individual questions. Some questions are phrased differently depending on whether patients have a stoma or not, these concern gastrointestinal symptoms such as frequency of stool or ability to control defecation.

The linear transformation to a 0–100 point scale of the EORTC QLQ-C30 and QLQ-CR29 questionnaires was performed according to the EORTC scoring manual.[19] In both questionnaires high numerical values in function scales as well as in the global health status correspond to higher levels of functioning. In symptom scales/single-items high values indicate more symptoms.[19] Overall mean scores in the respective groups were calculated by adding all mean values per patient and dividing this value by the total number of patients. Functions, symptoms as well as the global health status were observed over time and an exploratory hypothesis-generating comparison of the two treatment groups at distinct time points was made for each item.

In addition to the EORTC questionnaires patients were asked to fill in a questionnaire comprising five closed "*yes or no*"-questions on symptoms compromising the QoL the most including fatigue, pain, stool frequency, incontinence (urinary/stool), and "*other*". Moreover, patients were asked to comment on their level of satisfaction with the perioperative treatment received and if they would recommend this treatment to other patients.

Statistical analysis was performed by SAS (Version 9.2). Results are presented as mean values. As QoL does not follow normal distribution the Mann–Whitney-U-Test was applied and the level of significance was set at $p < 0.05$.