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Overview

Adjuvant Chemotherapy in Rectal Cancer after Chemoradiotherapy

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Abstract

The aim of this overview was to investigate whether adjuvant chemotherapy has a favourable effect on the outcome of patients with rectal cancer who had preoperative (chemo)radiotherapy. A review of randomised clinical trials that allocated patients between fluorouracil-based and observation or between fluorouracil-based and oxaliplatin-based adjuvant chemotherapy after preoperative (chemo)radiotherapy was carried out, including their corresponding meta-analyses. None of the five randomised trials has shown a significant benefit of fluorouracil-based adjuvant chemotherapy for overall survival or disease-free survival. Also, the three corresponding meta-analyses failed to show a benefit of adjuvant treatment. Of three randomised trials – two phase III and one phase II with a 3-year disease-free survival end point – two showed a small benefit of adding oxaliplatin to fluorouracil, one failed. The corresponding meta-analyses showed that the pooled difference was not significant. In conclusion, the use of postoperative 5-fluorouracil-based chemotherapy with or without oxaliplatin in patients with rectal cancer after preoperative (chemo)radiotherapy is not scientifically proven.

Key words: Adjuvant chemotherapy; meta-analysis; preoperative chemoradiotherapy; preoperative radiotherapy; rectal cancer

Statement of Search Strategies Used and Sources of Information

A literature search was carried out on PubMed and Web of Science. Abstracts from international meetings such as ASCO, ECCO, ESTRO, ESMO were also searched.

Introduction

In 1990, postoperative chemoradiotherapy (CRT) was recommended in the USA in patients with stage II–III resected rectal cancer [1]. This was based on the results of two randomised trials that showed improved survival with postoperative CRT in comparison with surgery alone or with postoperative radiotherapy alone [2,3]. The recommended treatment scheme was pelvic radiotherapy and concurrent 5-fluorouracil (5-FU) followed by additional 5-FU-based chemotherapy. Although subsequent US trials were variations of the same model, preoperative radiotherapy using either short- or long-course schemes showed improvement in treatment-related outcome for resectable rectal cancer [4]. In 2004, the results of a German randomised trial that compared preoperative and postoperative CRT in patients with stage II and III rectal cancer were reported [5]. Adjuvant chemotherapy (aCT) with 5-FU was given in both arms. Five year local control was significantly improved in the preoperative treatment arm, but overall survival was unchanged. The rate of distant recurrence at 5 years was 36% in both arms, whereas the rate of local recurrence was only 6% in the preoperative treatment arm and 13% in the postoperative treatment arm.

The US and German trials did not question the value of aCT on survival.

Nowadays, the standard of care for stage II and III rectal cancer is preoperative short-course radiotherapy (SRT) or CRT followed by total mesorectal excision, but oncologists are uncertain about aCT, given different contradictory guidelines [6]. The 2015 version of the National Comprehensive Cancer Network guidelines recommended preferably oxaliplatin-based aCT in all patients who received a

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preoperative CRT irrespective to the pathological stage (p stage) [7]. ESMO guidelines stated that aCT can be given in p stage III and 'high risk' p stage II [8], whereas it is not recommended in the Netherlands nor in Norway [9,10]. No consensus was reached to apply aCT in patients with a stage II or III disease after preoperative treatment in the 2012 European consensus conference on colorectal cancer [11].

The objective of this review was to determine whether aCT after preoperative (chemo)radiotherapy is relevant, through the analysis of the results of randomised clinical trials (RCT) and their related meta-analyses.

Materials and Methods

A literature search was carried out on PubMed and Web of Science, with the following key words: rectal cancer, preoperative (chemo)radiotherapy, adjuvant chemotherapy. The corresponding abstracts from international meetings such as ASCO, ECCO, ESTRO, ESMO were also searched. We selected RCT with either preoperative SRT or CRT and postoperatively a chemotherapy arm and an observation arm without aCT, and RCT that compared 5-FU-based and oxaliplatin-based aCT. Meta-analyses of these RCT were examined. The primary end point was overall survival. Secondary end points were disease-free survival (DFS) and distant recurrence.

Results

We found eight RCT, seven phase III and one phase II and four meta-analyses. A Chinese trial accessible only in abstract form was excluded because accurate evaluation was not possible, as well as a meta-analysis that included retrospective series and RCT [12,13].

Randomised Clinical Trials that Compared Adjuvant Chemotherapy with Observation (Table 1)

The EORTC 22921 trial allocated 1011 patients to preoperative radiotherapy versus preoperative CRT and postoperative aCT versus observation, following a 2×2 factorial plan design. Radiotherapy consisted of 45 Gy to the pelvis over 5 weeks. Each course of chemotherapy consisted of 5-FU (350 mg/m^2 per day intravenous bolus) and folinic acid (leucovorin; 20 mg/m^2 per day intravenous bolus) administered in 5 day courses. For preoperative chemotherapy, two courses were given (during weeks 1 and 5 of radiotherapy). aCT was given in four cycles, every 3 weeks. The primary end point was overall survival. The aCT arms included 506 patients; the observation arms included 505 patients. The trial was powered to detect a 10% overall survival benefit in an intent-to-treat analysis. After a median follow-up of 10.4 years, the 10 year overall survival was 51.8% for the aCT arms and 48.4% for the observation arms (hazard ratio 0.91, 95% confidence interval 0.77–1.09, $P = 0.32$). Adding chemotherapy to radiotherapy significantly decreased local failure but had no effect on overall survival. The rates of 10-year distant recurrence were about 35%. The overall adherence to aCT was 43% [14].

The I-CNR-RT Italian trial allocated 655 patients to preoperative CRT with or without aCT. The chemotherapy was identical to the EORTC 22921 trial, but six courses were planned instead of four. The 5-year overall survival rate in resected patients was 70% in the observation arm and 69% in the aCT arm (hazard ratio 1.045, 95% confidence interval 0.775–1.410, $P = 0.772$). The 5-year distant recurrence rates were around 20% in both arms. About 60% of patients received three to six courses of aCT [15].

In these two RCT, randomisation took place before preoperative treatments.

The PROCTOR-SCRIPT RCT allocated patients with p stage II–III who were able to start aCT within 6 weeks of surgery, to 5-FU-based aCT or observation. Patients could have preoperative SRT or CRT. Surgery was standardised total mesorectal excision. In total, 840 patients were needed to detect an improved 5-year overall survival from 60 to 70%. The trial was closed after 470 patients were enrolled. The 5-year overall survival rates were 79.2% and 80.4% in the aCT and observation arms, respectively (hazard ratio 0.97, 95% confidence interval 0.81–1.17, $P = 0.775$). aCT was completed in 73.6% of patients [16].

The CHRONICLE trial allocated patients with p stage III after preoperative CRT to observation or to six aCT courses that combined capecitabine and oxaliplatin [17]. In total, 800 patients were planned to detect a 5-year DFS from 40 to 50.5%. The trial was closed after 113 patients were enrolled. After a median follow-up of 44.8 months, the 3-year DFS was 71.3 and 72.5% in the observation and aCT arms, respectively (hazard ratio 0.80, 95% confidence interval

Table 1
Survival data from randomised clinical trials comparing adjuvant chemotherapy with observation

Study	Objective	Adjuvant chemotherapy arm	Observation arm	*P* value
EORTC 22921	10-year overall survival	$n = 506$ 51.8%	$n = 505$ 48.4%	0.32
I-CNR-RT Italian trial	5-year overall survival (in resected patients only)	$n = 296$ 69%	$n = 294$ 70%	0.77
PROCTOR SCRIPT	5-year overall survival	$n = 216$ 79.2%	$n = 221$ 80.4%	0.77
CHRONICLE	3-year disease-free survival	$n = 54$ 72.5%	$n = 59$ 71.3%	0.56