Adjuvant Treatment for Locally Advanced Rectal Cancer Patients After Preoperative Chemoradiotherapy: When, and for Whom?

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Abstract

The role and type of adjuvant chemotherapy in patients with rectal cancer after neoadjuvant chemoradiotherapy and surgery is controversial. Based on the retrospective analysis, we analyzed the prognostic factors that may influence the choice of adjuvant treatment. ypTNM stage significantly affects disease-free and overall survival; in particular patients with ypN+ are candidates for intensified adjuvant chemotherapy.

Background: The standard treatment for patients with locally advanced rectal cancer (clinical tumor, node, metastases [TNM] stage II or III) is radiotherapy before surgery (with or without concomitant fluoropyrimidine-based chemotherapy) followed by surgery. The role of adjuvant chemotherapy in this setting of patients is controversial in terms of the overall benefit on survival, the subgroup of patients who might not need it, and the best regimen (combination regimens vs. fluoropyrimidine alone). **Patients and Methods:** Based on the retrospective analysis of the clinical outcome of all patients with locally advanced rectal adenocarcinoma treated at our institute during the past 9 years, we comment on prognostic factors for local and distant metastases of patients who received neoadjuvant treatment followed by surgery, and the scientific evidence that can help to decide the adjuvant chemotherapy. **Results:** We conclude that pathological TNM stage after neoadjuvant chemoradiation (ypTNM) stage after surgery significantly affects disease-free and overall survival. In particular, patients with pathologically positive lymph nodes (ypN+) after surgery have a high probability of developing distant metastases. **Conclusion:** ypN+ patients are candidate for intensified adjuvant chemotherapy.

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Introduction

Colorectal carcinoma (CRC) remains a predominant cause of oncologic death. In developed countries it is the third tumor for incidence and the second for mortality in men, and the second for incidence and the third for mortality in women.[1] Rectal cancer accounts for about a third of CRC incidence.[2]

Until the 1990s the gold-standard treatment for patients with locally advanced rectal cancer (clinical tumor, node, metastases [TNM] stage II or III) was surgery followed by radiotherapy and chemotherapy.[3] Currently, the standard strategy is preoperative combined fluoropyrimidine-based chemoradiotherapy followed by surgery and adjuvant chemotherapy.[2,4] Several studies have demonstrated a decreased risk of local recurrence and less treatment-related toxicity[5-9] in patients treated with preoperative chemoradiotherapy than in patients treated with radiotherapy alone or with postoperative chemoradiation. Preoperative radiotherapy significantly decreased the rate of local recurrence even in cases of total mesorectal excision.[10] However, neither decrease of distant recurrences nor improvement of disease-free (DFS) and overall survival (OS) has been reported in any study except the National Surgical Adjuvant Breast and Bowel Project (NSABP) R03 trial.[11] Intensification of preoperative chemotherapy with the addition of oxaliplatin to fluoropyrimidine resulted in a limited increase of complete pathological

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responses,[12,13] an increase in acute toxicity,[12,14,15] and no improvement in DFS or OS.[14]

In the "surgery first" era, 6 months of postoperative chemotherapy significantly improved DFS and OS in several trials,[3,16-19] and these results have been confirmed in a recent Cochrane meta-analysis.[20] However, when radiotherapy or chemoradiation are administered before surgery, the benefit of adjuvant chemotherapy is much less clear, even though it is suggested in European[2] and US[4] guidelines. Two systematic reviews of the major randomized clinical trials addressing this issue reached contrasting conclusions: Bujko et al identified 4 trials, all reporting negative results, and concluded that adjuvant chemotherapy is not warranted, and that a meta-analysis of individual data is required[21]; whereas Valentini and co-workers analyzed the data of 2795 cases from 5 European studies and found that adjuvant chemotherapy significantly reduced the risk of local recurrence, and increased survival.[22]

Here we report our experience in the treatment of patients with locally advanced rectal cancer. In detail, we analyze and discuss clinical and pathological factors that can help to select patients with a poor prognosis after preoperative chemoradiation followed by radical surgery, and who would benefit from adjuvant chemotherapy.

Patients and Methods

We retrospectively analyzed patients with locally advanced rectal adenocarcinoma (clinically T3-T4 and/or N-positive [N^+]) referred to our institute between July 2004 and February 2013. Staging was determined before treatment based on colonoscopy with biopsy and histological examination, contrast enhanced total body computed tomography (CT) scan, transrectal ultrasound or contrast enhanced pelvic magnetic resonance imaging, blood cell count, and biochemistry. All patients received concomitant neoadjuvant chemoradiotherapy with fluoropyrimidine alone or in combination with oxaliplatin[23] and long-course radiotherapy (45 Gy, fractioned in 25 sessions of 1.8 Gy each). Patients were restaged approximately 40 days after treatment completion, and their treatment response was evaluated. Patients with nonprogressive disease underwent surgery within 6 to 8 weeks since the end of chemoradiation, and were candidates for fluoropyrimidine-based adjuvant chemotherapy for 4 months.

Patients were evaluated at 6-month intervals with physical examination, complete biochemistry, and blood Carcino-Embryonic Antigen (CEA) level. Whole-body CT scan was performed yearly and colonoscopy at 1 year after diagnosis and every 3 years thereafter.

Disease-free survival was defined as the time between the date of diagnosis and the first tumor recurrence (local or distance metastases); OS was defined as the time elapsed between the date of diagnosis and the date of death from any cause or the last follow-up. Estimation of likelihood events for recurrence or death was calculated according to the Kaplan–Meier method. Statistical differences between curves were calculated using the log-rank test. The hazard ratio (HR) was assessed using stepwise multivariate analysis. A P value of $\leq .05$ was considered statistically significant. Statistical analysis was performed with SPSS (version 18.0; SPSS, Inc, Chicago, IL).

Results

We examined 118 patients; their characteristics are listed in Table 1. Most patients were diagnosed as clinically node-positive.

Table 1 Patient Characteristics (n = 118)

Characteristic	n	%
Sex		
Male	74	62.7
Female	44	37.3
Median Age (Range), Years	63.4 (32.7-80.1)	
Stage at Diagnosis		
cT3-4/N0	42	35.6
Any cT/cN-positive	74	62.7
Unknown[a]	2	1.7
Distance From the External Anal Margin		
≤5 cm	55	46.6
5-10 cm	54	45.8
>10 cm	7	5.9
Unknown[a]	2	1.7

[a]Patients staged and treated with neoadjuvant radiochemotherapy not at our center; no information about stage and tumor location available.

Fifty-nine patients received fluoropyrimidine as a single agent, and 59 received capecitabine with oxaliplatin, as preoperative chemotherapy. A total of 114 of 118 (96.6%) patients underwent surgery (1 patient received surgery but was lost to follow-up); 4 patients did not undergo surgery: 1 because of lung progression during neoadjuvant therapy, 1 died, and 2 refused surgery (Table 2). Among the 113 patients for whom postsurgical pathology data were available, 23 (20.3%) achieved a complete pathological

Table 2 Treatments

Treatment	n	%
Neoadjuvant Chemotherapy (n = 118)		
CAPOX[a]	59	50.0
Capecitabine[b]/5FU-FA[c]	59	50.0
Surgery (n = 118)		
Yes	114	96.6
No	4	3.4
Adjuvant Chemotherapy (n = 113)		
5FU-FA[d]/Capecitabine[e]	88	77.9
XELOX[f]/FOLFOX[g]	3	2.7
Nothing	21	18.5
Unknown	1	0.9

Abbreviations: CAPOX = capecitabine 825 mg/m^2 twice daily orally on days 1 to 14 every 21 days and oxaliplatin 50 mg/m^2 i.v., on days 1 and 8 every 21 days, for 2 cycles; FOLFOX = FOLinic acid - Fluorouracil - OXaliplatin; 5FU-FA = 5-fluorouracil and folinic acid; i.v. = intravenous; XELOX = XELoda - OXaliplatin.
[a]Capecitabine 825 mg/m^2 twice daily orally, day 1 to14 every 21 days and oxaliplatin 50 mg/m^2 i.v., day 1 and 8 every 21 days, for 2 cycles.
[b]Capecitabine 825 mg/m^2 twice daily orally during radiotherapy.
[c]Lederfolin 20 mg/m^2 i.v. and 5-fluorouracil 400 mg/m^2 bolus once a week during radiotherapy.
[d]Lederfolin 20 mg/m^2 i.v. and 5-fluorouracil 450 mg/m^2 bolus once a week for 4 months.
[e]Capecitabine 1250 mg/m^2 twice daily orally on days 1 to 14 every 21 days for 4 months.
[f]Oxaliplatin 130 mg/m^2 i.v. on day 1 and capecitabine 1000 mg/m^2 twice daily orally, on days 1 to 14 every 21 days for 4 months (6 cycles).
[g]Oxaliplatin 85 mg/m^2 i.v. on day 1 and lederfolin 100 mg/m^2 i.v. on days 1 and 2, and 5-fluorouracil 400 mg/m^2 bolus on days 1 and 2, and 5-fluorouracil 600 mg/m^2 i.v. as a 22-hour continuous infusion on days 1 and 2 every 14 days for 4 months (8 cycles).