Risk-adapted adjuvant chemotherapy after concomitant fluoropyrimidine-radiotherapy neoadjuvant treatment for patients with resectable cT3-4 or N+ rectal cancer

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Adjuvant chemotherapy in rectal cancer is not well defined. After neoadjuvant chemoradiation and surgery, at least a short period of treatment with 5-fluorouracil is recommended, and some investigators claim a more aggressive approach, in particular, for those patients with a high risk of systemic relapse. Nevertheless, there are few studies about adjuvant combination therapy tolerance and efficacy, and no randomized trials have been conducted comparing fluoropyrimidines versus combination therapy such as folinic acid plus 5-fluorouracil plus oxaliplatin (FOLFOX), considered the standard of care in stage III colon cancer. We present an institutional series of risk-adapted adjuvant therapy. Sixty evaluable patients who had received treatment with neoadjuvant fluoropyrimidine radiotherapy and surgery now received adjuvant fluoropyrimidines in the case of pT0-2N0 or oxaliplatin-based combination in the case of pT3-4 or N+. Overall, 33 patients experienced downstaging to pT2-0N0 (55%) and 27 patients were restaged as pT3-4 or N+ (45%) after surgery. Local recurrence rate was 5% (three patients), one local and one local plus systemic in the adjuvant single-agent group and one local plus systemic in the adjuvant FOLFOX group. Systemic relapse occurred in 14 patients (23.3%), five (15%) in the single-agent group and nine (33.3%) in the FOLFOX group. Disease-free survival at 3 years for patients in the good prognostic group (pT0-2N0) and poor prognostic group (pT3-4 or N+) were 78.7 and 62.2%, respectively. Severe diarrhoea was more frequent with fluoropyrimidines and neutropenia, mucositis and peripheral neuropathy were more common with FOLFOX. There were no toxic deaths. A risk-adapted adjuvant therapeutic decision is feasible with an acceptable safety profile even with the use of oxaliplatin-based combinations. Three-year disease-free survival compares favourably with historical controls, especially in those patients with high risk factors for relapse. Phase III controlled trials are needed. ***Anti-Cancer Drugs*** **22:185–190 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

In the early 1990s, surgery followed by adjuvant chemoradiotherapy was considered the standard of care for stage II or III rectal cancer patients, not only in the United States but also in some countries in Europe. Disease-free survival (DFS) and local recurrence rates ranged between 42–59% and 11–16%, respectively [1–3]. The introduction of a preoperative approach and the results of subsequent randomized trials including a large number of patients in Europe have led to a change in the standard of care, because of a clear advantage in local recurrence rate, less toxic adverse events and better survival in some studies. A 2-year local recurrence rate may be as low as 2.4% by combining total mesorectal excision (TME) with preoperative radiotherapy [4]. Preoperative chemoradiation resulted in better control for local relapse than the same postoperative regimen and is less toxic [5]. The response to preoperative chemoradiotherapy was earlier associated with lower local recurrence and improvement in DFS and overall survival [6,7]. In contrast with the great effort made to improve local control in rectal cancer, the systemic approach for the control of micrometastases has been limited in most cases to a short period of adjuvant 5-fluorouracil (5-FU) with or without leucovorin. In contrast, at that time, in the setting of colon cancer, oxaliplatin plus 5-FU modulated with leucovorin was established as a new standard regimen for stage III colon cancer. The rate of DFS at 3 years was significantly better than bolus and continuous infusion of 5-FU modulated with leucovorin alone [8,9]. In 2003, our practical dilemma as medical oncologists was how to manage these patients after neoadjuvant chemoradiation and surgery. As it was reasonable to assume that distant micrometastatic disease has to be

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similarly sensitive to fluoropyrimidines as the local rectal tumour, a risk-adapted protocol was initiated in our single institution. The election of adjuvant chemotherapy was based on the quality of response to the neoadjuvant fluoropyrimidine radiotherapy treatment.

Here, we present the 3-year results of our institutional series with this approach.

Patients and methods

Between 2003 and 2007, 113 consecutive patients were submitted to our oncology department to be assessed for neoadjuvant chemoradiation. All of them had pathological rectal adenocarcinoma that involved the distal 12 cm. The patients had to be in good general condition (performance status: 0–1), with adequate bone marrow, hepatic and renal functions. The patients selected for neoadjuvant chemoradiation were cT3-T4 and/or N + , determined by ultrasound endoscopy and pelvic computed tomography (CT) scan. In some patients, MRI was added. Metastatic disease was ruled out by CT or abdominal ultrasound and chest radiograph.

Neoadjuvant chemoradiation

Radiotherapy consisted of 45 Gy in 25 fractions with a 5.4 Gy boost to a restricted pelvic volume. Concomitant chemotherapy with fluoropyrimidines from the first to the last day of radiotherapy without rest, was used as a radiosensitizer: capecitabine (825 mg/m^2/12 h) in 45 (75%) patients, protracted infusion 5-FU (225 mg/m^2/day) in 10 (16.6%) patients and UFT (400 mg/8 h) in 5 (8.3%) patients.

Surgery

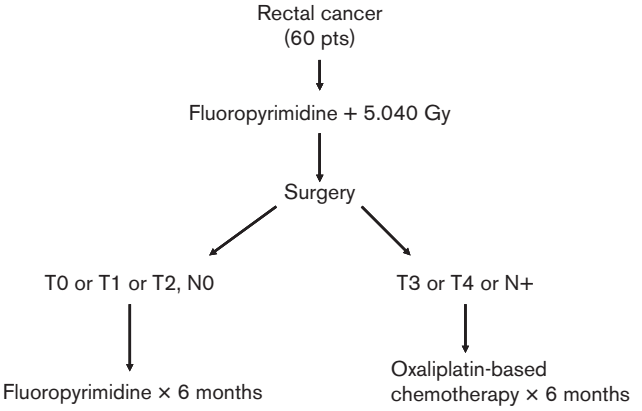
The TME surgical procedure had been implemented in our centre by the time of this series and was generally performed between 6 and 8 weeks after neoadjuvant chemoradiation. Quality control of the surgical procedure was not done.

A sphincter preservation surgical procedure was performed in 39 patients and an abdominoperineal resection was performed in 21 patients.

Adjuvant chemotherapy

The decision to use adjuvant treatment was based on TNM pathological classification according to the following criteria (Fig. 1). Group 1: pathologic downstaging to T0-2N0 was achieved in 33 patients and received single-agent fluoropyrimidines [capecitabine (1000–1250 mg/m^2/12 h) for 14 days every 21 days (72.7% of patients); bolus 5-FU (400 mg/m^2) for 2 days modulated by intravenous leucovorin (200 mg/m^2) for 2 days and 22-h continuous infusion of 5-FU (600 mg/m^2) for 2 days (De Gramont schedule), every 2 weeks (18.2%) or bolus 5-FU (425 mg/m^2/day) modulated with leucovorin (20 mg/m^2/day), both for 5 consecutive days every 4 weeks (Mayo Clinic schedule) (9.1%)]. Group 2: pathologic T3-4 and/or nodal positive status (N +) was observed in 27 patients after neoadjuvant chemoradiation. These patients were treated with folinic acid plus 5-fluorouracil plus oxaliplatin (FOLFOX) regimen [oxaliplatin (85 mg/m^2) on day 1 followed by bolus 5-FU (400 mg/m^2) for 2 days modulated by leucovorin (200 mg/m^2) for 2 days and 22-h continuous infusion 5-FU (600 mg/m^2) for 2 days, every 2 weeks]. Planned adjuvant chemotherapy duration was 6 months and dose adjustment for toxicity was made according to the standard rules for every schedule. Toxicity was recorded according to the National Cancer Institute Common Toxicity Criteria 2.0 version (NCI 1999, Maryland, USA).

Fig. 1



Risk-adapted adjuvant therapy decision.

Follow-up

The patients were followed at approximately 6-month intervals with clinical history, physical examination, serum carcinoembryonic antigen level, abdominal ultrasound and pelvic CT or abdominopelvic CT information being recorded. Chest radiograph was taken annually and colonoscopy 1 year after operation and then every 3 years if no polyps were found.

Statistical considerations

DFS was defined as the time from surgical procedure to the date of cancer relapse confirmed by histological or radiological findings. DFS curves were calculated using the Kaplan–Meier method. The two groups were independently analysed and a formal statistical comparison was not planned.

Results

Among the 113 patients submitted for neoadjuvant chemoradiation evaluation, 15 patients did not receive neoadjuvant fluoropyrimidines for contraindication and were excluded. Among the 98 patients who received neoadjuvant chemoradiation, 32 did not receive adjuvant chemotherapy and six patients received adjuvant chemotherapy

not risk-adapted according to downstaging (Fig. 2). The characteristics of the 60 evaluable patients analysed in this series are summarized in Table 1. It should be pointed out that almost half of the patients were initially classified as clinical T3N0 stage and slightly more than one third as clinical T3N+.

Complete pathological response to neoadjuvant chemoradiation was achieved in 11 patients (18.3%). Overall, 33 patients experienced downstaging to pT2-0N0 (55%), and 27 patients were restaging as pT3-4 or N+ (45%) after surgery.

Local recurrence rate was 5% (three patients), one local and one local plus systemic in the adjuvant single-agent group and one local plus systemic in the adjuvant FOLFOX group. Systemic relapse occurred in 14 patients (23.3%), five (15%) in the single-agent group and nine (33.3%) in the FOLFOX group. Only one out of the 11 patients who achieved complete pathological response after neoadjuvant chemoradiation relapsed. Figure 3 summarizes systemic tumour location recurrences, with the lung being the most common site of metastatic disease. After a median follow-up of 37 months, 45 patients (75%) were alive and free of recurrence. DFS at 3 years for patients in the good prognostic group (pT0-2N0) and the poor prognostic group (pT3-4 or N+) were 78.7 and 62.2%, respectively (Fig. 4).

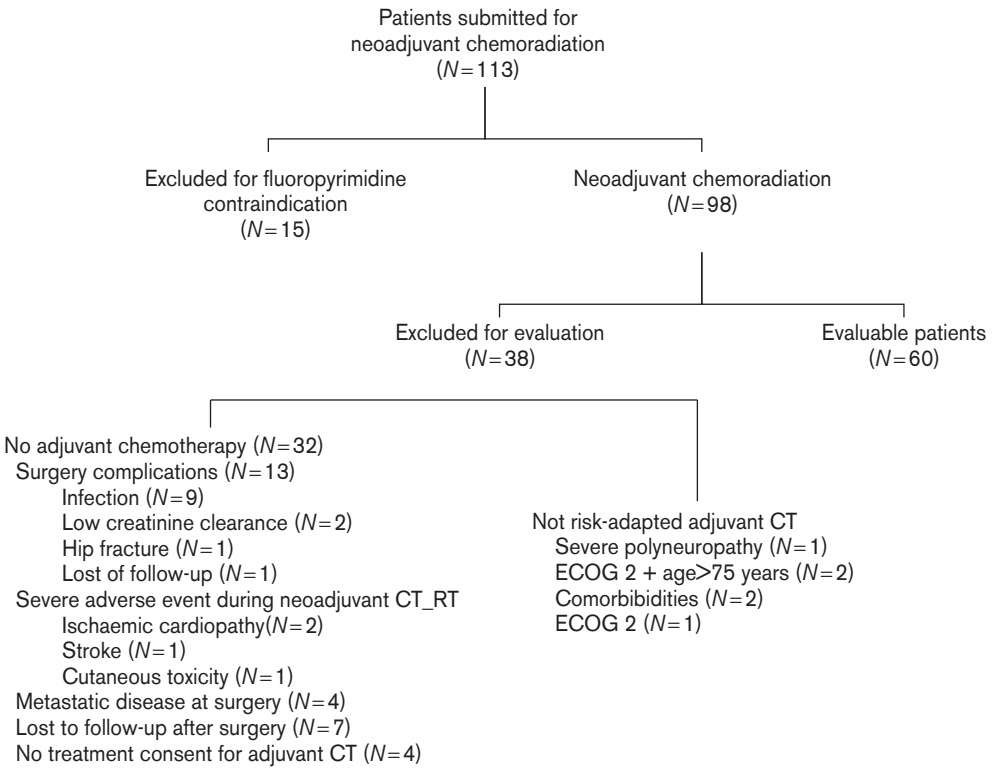
Toxicity was generally mild to moderate. The most common grade 2 or higher adverse events according to the National Cancer Institute Common Toxicity Criteria are shown in Table 2. Peripheral neuropathy, neutropenia and mucositis were more common with polychemotherapy and hand–foot syndrome and severe diarrhoea were more frequent with single-agent fluoropyrimidines.

Table 1 Patients characteristics ($n=60$)

		Endoscopic T-stage	
Median age	68 (37–86)	uT1	0
<65	23 (38.3%)	uT2	2 (3.3%)
>65	37 (61.7%)	uT3	52 (86.7%)
		uT4	6 (10%)
Sex		Endoscopic N-stage	
Male	35 (58.3%)	uN0	31 (51.7%)
Female	25 (41.7%)	uN1	23 (38.3%)
		uN2	6 (10%)
ECOG			
0	35 (58.3%)	Clinical stage	
1	18 (30%)	IIA	28 (46.7%)
≥ 2	7 (11.7%)	IIB	3 (5%)
Location		IIIA	2 (3.3%)
Intermediate third	36 (60%)	IIIB	21 (35%)
Lower third	24 (40%)	IIIC	6 (10%)

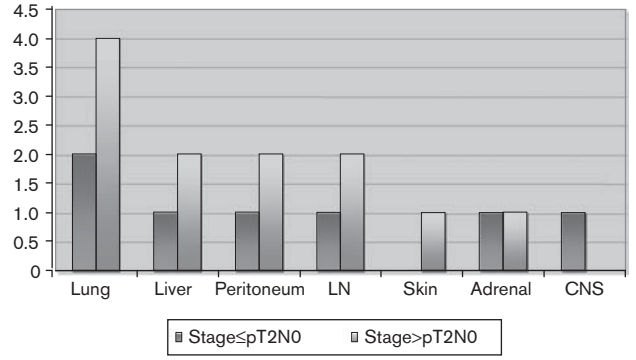
ECOG, Eastern Cooperative Oncology Group

Fig. 2



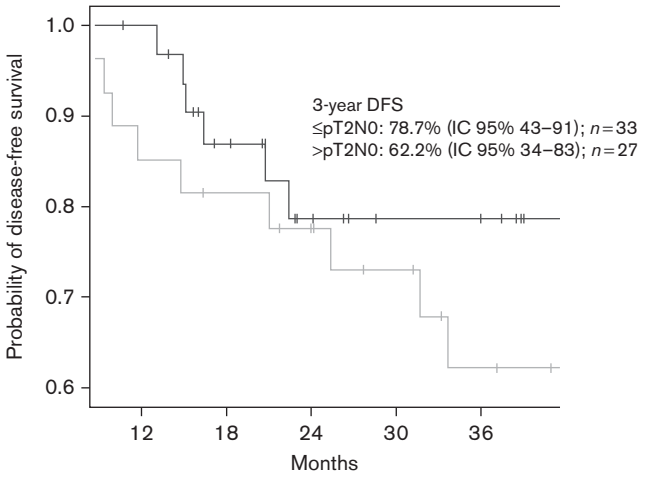
Trial profile. ECOG, Eastern Cooperative Oncology Group.

Fig. 3



Location of tumour recurrence according to pathologic stage group. CNS, central nervous system; LN, lymph nodes.

Fig. 4



Disease-free survival according to pTNM by Kaplan–Meier method. Good responders to neoadjuvant chemoradiation had a better disease-free survival (DFS) in spite of the poor responder subgroup received more intensive adjuvant chemotherapy.

Table 2 Grade 2–4 adverse events according to the National Cancer Institute Common Toxicity Criteria (scale-specific for neuropathy)

	Grade 2		Grade 3 or 4	
	Single agent[a]	Polychemo-therapy[b]	Single agent	Polychemo-therapy
Diarrhoea, *n* (%)	3 (9)	8 (29.6)	7 (21.2)	3 (11.1)
Mucositis, *n* (%)	2 (6)	6 (22.2)	1 (3)	5 (18.5)
Emesis, *n* (%)	2 (6)	3 (11.1)	1 (3)	1 (3.7)
HFS, *n* (%)	7 (21.2)	3 (11.1)	3 (9)	0
Neuropathy, *n* (%)	0	6 (22.2)	0	6 (22.2)
Neutropenia, *n* (%)	0	0	0	6 (22.2)

HFS, hand–foot syndrome.
[a]Single agent included Xeloda-De Gramont-5-FU/leucovorin Mayo Clinic schedules.
[b]Polychemotherapy included folinic acid plus 5-fluorouracil plus oxaliplatin and capecitabine + oxaliplatin schedules.

Discussion

Adjuvant chemotherapy in rectal cancer is not well defined. The second European Rectal Cancer Consensus Conference established that there is insufficient evidence on the benefit of adjuvant postoperative chemotherapy after preoperative chemoradiation [10]. Nevertheless, other institutions, such as European Society of Medical Oncology, support the use of adjuvant chemotherapy based on colon cancer adjuvant outcomes [11]. A short period of bolus 5-FU has been frequently included as adjuvant chemotherapy in the most important trials during the last decade. Some investigators claim a more aggressive approach, in particular, in patients with a high risk of systemic relapse. The possible benefit of the addition of oxaliplatin to fluoropyrimidines, in terms of DFS and its balance with the complications of such an intervention, is still a matter of debate.

During the last decade, most randomized clinical trials in rectal cancer have been designed under the premise that local tumour control may have a potential impact on DFS and overall survival. Preoperative radiotherapy added to TME resulted in better local control [4]. Preoperative chemoradiation showed a lower rate of local recurrence compared with radiotherapy alone [12]. Furthermore, preoperative chemoradiation was shown to be better tolerated than adjuvant chemoradiation and in some studies was shown to reduce local recurrence [5,13]. With the exception of the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial, in which preoperative multimodality therapy obtained a benefit of DFS over adjuvant chemoradiation [14], all these trials failed to improve outcomes in terms of survival. Several reasons may be suggested to explain the lack of benefit for DFS and overall survival with these chemoradiation approaches. First, the high rate of local control with the new surgical procedures (TME) makes it difficult to obtain a large benefit by adding radiotherapy and concurrent chemotherapy. Although local control was better with neoadjuvant radiotherapy or chemoradiation, that difference did not translate into a benefit in DFS and overall survival. Second, the chemotherapeutic regimens used in those trials was limited to fluoropyrimidines during a short period of time (less than 6 months). In the past, various regimens of 5-FU/leucovorin showed an improvement in DFS in stage III colon cancer, but in all these regimens chemotherapy was administered during 6 months [15]. A retrospective analysis of the Surveillance, Epidemiology and End Results-Medicare database in elderly patients with stage III colon cancer treated with adjuvant 5-FU-based chemotherapy, suggested that less than 5 months of treatment may jeopardize treatment outcome [16]. Nowadays, oxaliplatin plus 5-FU/leucovorin combination has become the new standard in stage III colon cancer, as two randomized trials have shown an advantage in DFS [9] and overall survival [17] when compared with 5-FU/leucovorin alone. Our series

shows that 6 months of adjuvant chemotherapy after initial chemoradiation and surgery is feasible, even on using a more toxic regimen such as FOLFOX. Nevertheless, it should be remarked that one third of our patients did not receive adjuvant treatment because of surgical complications, severe toxicity during induction therapy, metastatic disease at surgery or loss to follow-up after surgery.

With the introduction of neoadjuvant chemoradiation, medical oncologists have to deal with the practical dilemma of how to manage the patient in the postoperative setting. Should preoperative clinical stage be taken into account or, in contrast, have new predictive factors arisen in this setting? Is pretreatment evaluation reliable enough to take a postoperative decision (i.e. adjuvant chemotherapy only in clinical stage III rectal carcinomas)? Are there randomized trials comparing 5-FU/leucovorin with oxaliplatin-based combinations as in colon cancer? Is adjuvant chemotherapy mandatory after complete pathologic remission? Qua *et al.* [18] found that postoperative pathologic stage is the strongest predictor for DFS. Preoperative clinical stage alone was a poor predictor of outcome in patients receiving preoperative chemoradiation, even adding the effect of tumour response to neoadjuvant treatment. In contrast, the pathologic stage separated the two groups with a different prognosis. Those patients who exhibited downstaging of pathologic stage 0 or I experienced excellent outcome, whereas patients who did not have an optimal response (pathologic stage II or III) had a significantly worse outcome ($P = 0.001$). Response to neoadjuvant fluoropyrimidines concurrent with radiotherapy may select a group of favourable tumour behaviour, sensible to the drug and then, a low rate of local and distant disease recurrence can be achieved. In contrast, it is reasonable to assume that micrometastatic disease cannot be eliminated with a short time adjuvant single-agent fluoropyrimidine if the primary tumour expressed poor sensitivity to the neoadjuvant treatment. Results from a secondary analysis of the European Organisation for Research and Treatment of Cancer (EORTC) *22921* trial further supported this statement. Only patients with pathologic T0–2 after neoadjuvant 5-FU/radiation therapy who received four courses of adjuvant intravenous 5-FU 350 mg/m^2 + leucovorin 20 mg/m^2, both by five consecutive days every 3 weeks, obtained a benefit in DFS and overall survival compared with no adjuvant therapy [19]. Our results also suggest that the risk-adapted adjuvant decision may have an impact in the final outcomes. Almost 80% of our patients with pathologic stage 0–I were disease-free at 3 years, similar to those in the EORTC trial, which means that single-agent fluoropyrimidine is a safe and active treatment for micrometastatic disease for this subgroup of patients. The addition of oxaliplatin might be prospectively tested, but, in the meantime, the FOLFOX regimen is not justified because of its higher toxicity (neuropathy, neutropenia and diarrhoea). Our poor responders to neoadjuvant chemotherapy who received adjuvant FOLFOX regimen for 6 months achieved a DFS of 62% at 3 years. Similar results have recently been reported by Chua *et al.* [20] in the poor-risk rectal cancer patients who received 6 months of XELOX chemotherapy (3 months as induction chemotherapy and 3 months as adjuvant chemotherapy). Sixty-eight percent were disease-free at 3 years. In contrast, in the EORTC trial, among those patients who did not exhibit downstaging to pathologic pT0-2, who received 5-FU adjuvant chemotherapy for 4 months, only 45.1% of them were disease-free at 5 years. In the NSABP R-03 trial all patients received four cycles of bolus 5-FU (500 mg/m^2) per week for 6 weeks modulated by high-dose leucovorin. The 5-year DFS for those patients included in the preoperative arm was 64.7%, including patients with and without response to neoadjuvant chemoradiation. In our series, 3-year DFS for the whole group was 75%. In the German Cancer Group Study all patients were treated with four courses of adjuvant bolus 5-FU (500 mg/m^2) for 5 consecutive days every 4 weeks. The overall 5-year DFS in the preoperative group (low and high risk) was 68%, very similar to that reported in the NSABP R-03 trial. The German trial failed to show the expected absolute difference of 10% in overall survival between preoperative and postoperative chemoradiation, in spite of the preoperative group obtaining a significant benefit in local recurrence. The authors concluded that more effective adjuvant chemotherapy to prevent distant recurrences should be tested in the future [5].

The toxicity profile found was what we expected for those regimens of chemotherapy and the frequency of severe adverse events can be considered as acceptable. There were no toxic deaths. Severe diarrhoea was higher in the single-agent arm, probably in relation to a selective bias in the polychemotherapy arm. Those patients in the high-risk group after surgery who had to be treated with polychemotherapy but were judged as not fit enough to receive oxaliplatin-based combination by their physicians, finally received single-agent therapy and were excluded from this analysis. Recently, it has been reported that 16% of the patients receiving adjuvant CAPOX after neoadjuvant chemoradiotherapy and surgery experienced grade 3 diarrhoea [21]. Peripheral neurosensory symptoms, neutropenia and mucositis were more frequent in the oxaliplatin-based chemotherapy arm and hand–foot syndrome appeared more commonly with single-agent treatment mainly because most of the patients received capecitabine.

Our results are obviously limited by the fact that they represent a small single-centre series. Although quality control of surgical procedures and radiotherapy techniques were not done, our 5% local relapse compares with the best reported in the literature and then did not represent a bias in DFS outcomes. Almost half of the patients were initially cT3N0, which could be in favour of better outcome.

For future research in the adjuvant setting of rectal cancer, good and poor prognostic subgroups should be separated or comparative arms should be stratified by them. Important questions should be addressed such as the role of adjuvant therapy in complete responders to neoadjuvant treatment or duration of 5-FU chemotherapy in the good prognostic group. The role of adding oxaliplatin to 5-FU/leucovorin in the poor prognostic group should be proved in a prospective randomized trial, although in the meantime our results suggest that FOLFOX may be an alternative for these patients as some opinion leaders are currently recommending [22,23].

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