Journal of BUON **14:** 219-224, 2009

ORIGINAL ARTICLE

Early and late results of adjuvant treatment in colorectal cancer. The experience of the Emergency County hospital Alba Iulia - Romania

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Summary

Purpose: *To present a comprehensive analysis of early and late results of adjuvant treatment in colorectal adenocarcinoma (CRC) patients treated at the Emergency County hospital Alba Iulia during a 54-month period.*

Patients and methods: *Our analysis included all records of CRC patients who had received adjuvant chemotherapy between 1 January 2001 and 30 June 2005. The Kaplan-Meier methodology was used in the analysis of survival data, while the regression Cox model and log-rank test were used in the analysis of prognostic factors.*

Results: *68 patients were included with a median follow-up time of almost 3 years. Overall survival (OS) at 3 years was 67%, and at 5 years 42.4%, while disease-free survival (DFS) was 52% and 39%, at 3 and 5 years, respectively. These inferior results compared with those reported in western Europe and USA for patients with similar major prognostic factors and similar adjuvant chemotherapy regimens is extensively discussed. The impact of the main prognostic factors on survival data is also reported.*

Conclusion: *Our hospital's experience is highly representative for the present status of adjuvant treatment of colorectal cancer patients in Romania. Results of our analysis can be used to design a strategy for improving quality of adjuvant treatment of colorectal cancer patients.*

Key words: adjuvant, chemotherapy, colorectal cancer, radiotherapy

Introduction

Colorectal adenocarcinoma represents 15% of all cancers, but with significant regional variations [1,2]. Adjuvant chemotherapy reduces the recurrence rate in stage III disease by about 20-30%, while for stage II CRC the benefit is still controversial (a maximum of 5% survival benefit) [3-7]. Therefore, current guidelines recommend adjuvant chemotherapy in stage II CRC only in patients with high risk of distant recurrence (grade 3-4; occlusion or perforation; lymph node or vascular invasion; positive, close or unknown resection margins; less than 12 resected lymph nodes) [8]. Widely-accepted adjuvant chemotherapy protocols are those including fluoropyrimidines i.e. bolus 5-fluorouracil (5FU)-folinic acid (Mayo Clinic regimen), infusional 5FU-folinic acid (DeGramont or AIO regimens), capecitabine, UFT, and, more recently, combinations with oxaliplatin (FOLFOX or XELOX). The latter add a benefit of about 25-30% compared with the regimens not containing oxaliplatin (meaning about 5% in terms of DFS) [9].

This study was conducted in order to assess the results of the adjuvant treatment of CRC patients treated at the emergency County hospital Alba Iulia. Because these results are highly representative for the majority of the oncology departments in Romania, the data could be used to design a strategy for improving the quality of adjuvant treatment of CRC patients.

Patients and methods

Our analysis included all records of CRC patients,

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Received 08-08-2008; Accepted 11-11-2008

who had received adjuvant chemotherapy between 1 January 2001 and 30 June 2005 (n=68).

The Kaplan-Meier methodology was used in the analysis of survival data, while the regression Cox model and log-rank test were used in the analysis of prognostic factors. As starting point was considered the first day of adjuvant chemotherapy, while the endpoint was the patients' status on 30 September 2007. All calculations were performed using SPSS 10.0 software.

Results

Patient characteristics are presented in Table 1. The average patient age was 56 years (range 37-73). Males predominated, with a male/female ratio of 1.26. Almost half of the patients had rectal tumors. The median patient follow up reached almost 3 years (mean 35.5 months, range 5-74).

Table 2 presents the patient distribution according to T and N status, and to 1997 TNM staging system. T3 tumors (75%) prevailed, while 40% (27 out of 68) of patients had N_x status. The average number of the removed lymph nodes was 6.18, but the median number was only 1.5.

Table 2 shows that accurate staging was possible only for 60% of the patients. Excluding those patients with N_x status, 70% of the patients were node-positive (III A-B-C stages).

Adjuvant chemotherapy regimens and the number of cycles administered are presented in Table 3. No patient received an oxaliplatin-based regimen. The predominant chemotherapy regimen delivered was bolus 5FU-folinic acid (92% of all patients), and the rest of the patients received infusional 5FU-folinic acid (De Gramont), and capecitabine. The median and mean number of adjuvant chemotherapy cycles was 6 and 5.5, respectively. The main reason of shortening the duration of chemotherapy was treatment toxicity,

Table 1. Patient characteristics

Characteristic	*Patients, n (%)*
Age (years), average (range)	56 (37-73)
Male/female ratio	1.26 (38/30)
Tumor site	
Ascending	9 (13.0)
Transverse	6 (9.0)
Descending	5 (7.0)
Sigmoid	16 (24.0)
Rectum	32 (47.0)

Table 2. TN status and TNM stage

	Patients, n (%)
T status	
2	3 (4.5)
3	51 (75.0)
4	14 (20.5)
N status	
0	11 (16.0)
1	15 (22.0)
2	11 (16.0)
X	31 (46.0)
TNM stage	
I	1 (1.5)
IIA	6 (9.0)
IIB	4 (6.0)
IIIA	3 (4.5)
IIIB	13 (19.0)
IIIC	10 (14.0)
T3-4NxM0	31 (46.0)

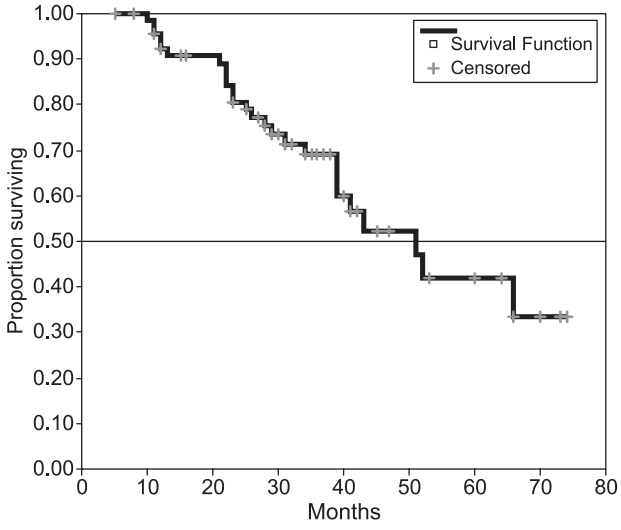

Figure 1. Overall survival.

Table 3. Adjuvant therapies

	Patients, n (%)
Adjuvant chemotherapy	
Fu Fol Mayo	63 (92.6)
Fu Fol DeGramont	4 (5.9)
Capecitabine	1 (1.5)
No. of chemotherapy cycles	
Median (range)	6 (1-6)
Mean	5.5
Radiotherapy (in rectal cancer)	
Before surgery	1 (3.2)
After surgery	21 (65.6)
Not performed	10 (31.2)

Table 4. Toxicity related to adjuvant chemotherapy according to CTCAE scale, version 3.0

Toxicity	*Grade 1 Patients, n (%)*	*Grade 2 Patients, n (%)*	*Grade 3 Patients, n (%)*	*Grade 4 Patients, n (%)*
Myelosuppression	9 (13.24)	2 (2.94)	–	–
Mucositis	2 (2.94)	2 (2.94)	1 (1.47)	–
Diarrhea	4 (5.88)	4 (5.88)	1 (1.47)	–
Emesis	3 (4.41)	1 (1.47)	–	–
Liver toxicity	1 (1.47)	1 (1.47)	–	–
Skin toxicity	–	1 (1.47)	–	–
Cardiovascular toxicity	–	1 (1.47)	–	–
Neurotoxicity	–	1 (1.47)	–	–

followed by treatment compliance. No dose reduction because of toxicity was necessary in any patient.

Tolerance to adjuvant chemotherapy was good, considering that only 24 (35.3%) patients developed treatment-related toxicity, and only one (1.5%) patient developed grade 3 toxicity, probably secondary to dihydropyrimidine dehydrogenase (DPD) deficiency.

Myelosuppression was the most frequent chemotherapy-related toxicity (16.2%), followed by diarrhea, mucositis and emesis - the others being infrequent (less than 5% of the patients; Table 4). This toxicity profile was consistent with the one expected from the 5 FU-based regimens used and the bone marrow suppression was related to the use of bolus 5 FU-folinic acid chemotherapy.

Postoperative adjuvant radiotherapy was given to 21 (65.5%) patients; only 1 (3.2%) patient received preoperative radiotherapy (Table 3). However, this proportion of patients who received radiotherapy (68.8%) was less than clinically indicated, mainly because it was hard to evaluate how many patients with rectal cancer benefited from total mesorectal excision (TME) in the absence of a TME-oriented pathology report.

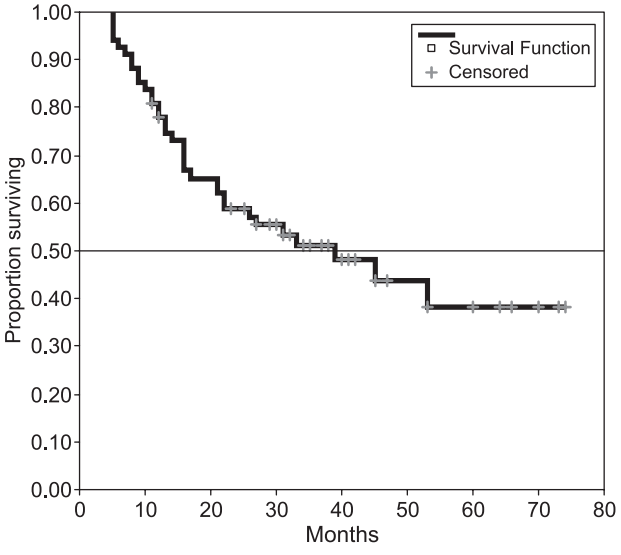

Figure 2. Disease-free survival.

Table 5 summarizes the main survival data, and Figures 1 and 2 present the OS and DFS, respectively. OS at 3 years was 67% and 42.4% at 5 years, while DFS was 52% and 39%, at 3 and 5 years, respectively.

In the last part of this study, an analysis was undertaken regarding the impact of the different prognostic factors on OS and DFS.

The first analysed prognostic factor was the primary tumor site (rectum vs. colon), resulting in no significant differences in median survival (52 vs. 51 months, p=0.76; Figure 3) or in DFS (45 vs. 39 months, p=0.90; Figure 4). Also, pathological grade did not prove as a significant prognostic factor neither for OS (p = 0.57; Figure 5), nor for DFS (p = 0.84, Figure 6). Similarly, age (< 50 vs. > 50 years) wasn't a significant prognostic factor neither for DFS (p = 0.23), nor for OS (p = 0.50).

On the other hand, as expected, TNM stage was highly significant for DFS (p = 0.004; Figure 7) and almost reached statistical significance for OS (p = 0.06; Figure 8). The lack of clear prognostic significance of TNM stage in terms of OS can be explained by the relatively important group of patients with $pT_{3-4}N_x$ (46% of the patients), a mixture of stage II and III disease, which finally reduced the statistical significance level.

Table 5. Overall survival and disease-free survival

Overall survival	*%*
Median (months)	51 (95% CI 38-64)
2 years	79.0
3 years	67.0
5 years	42.4
Disease-free survival	*%*
Median (months)	39 (95% CI 19-59)
2 years	59.7
3 years	52.0
5 years	38.8

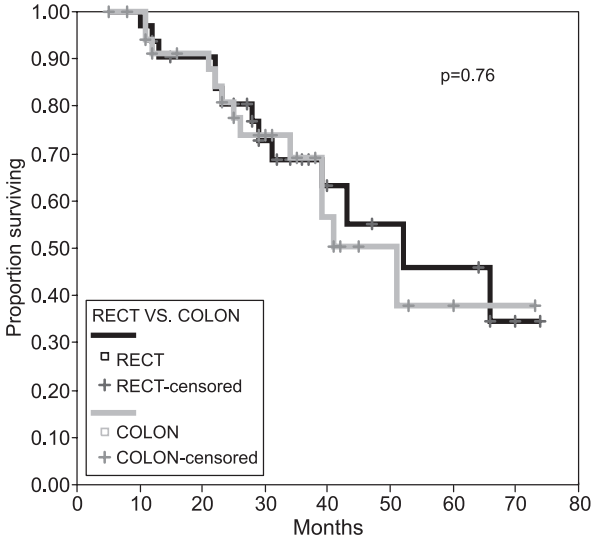

Figure 3. Overall survival according to the location of the primary tumor site.

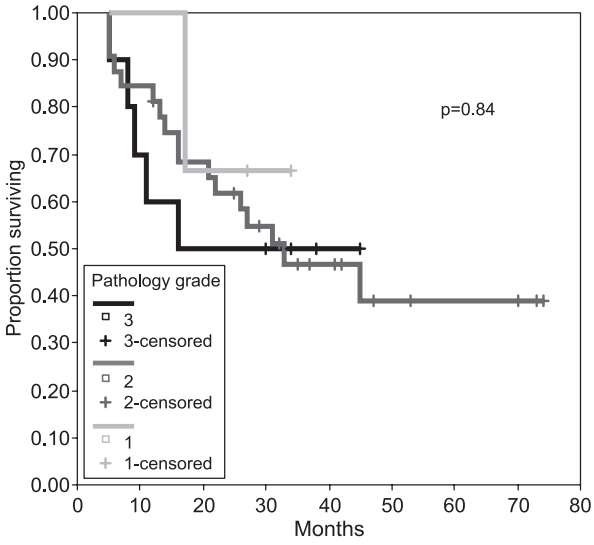

Figure 6. Disease-free survival according to grade.

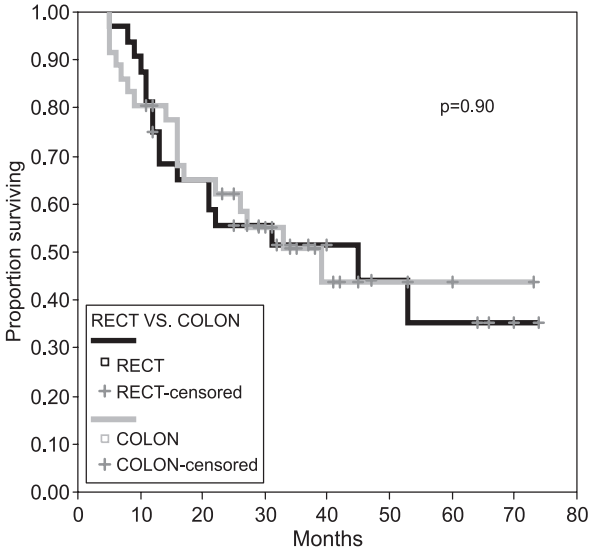

Figure 4. Disease-free survival according to the location of primary tumor site.

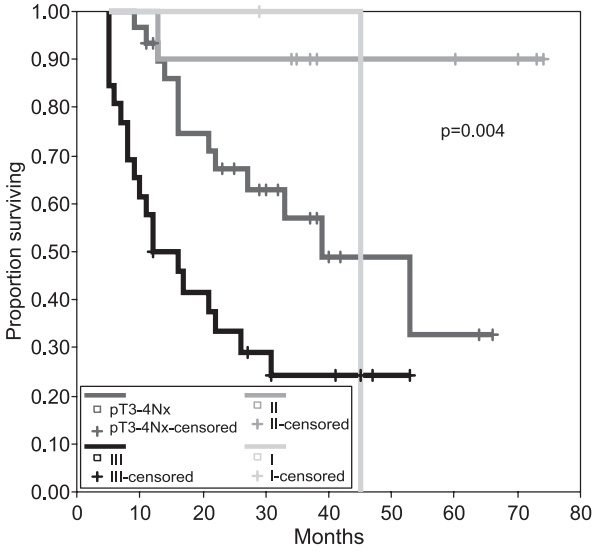

Figure 7. Disease-free survival according to TNM stage.

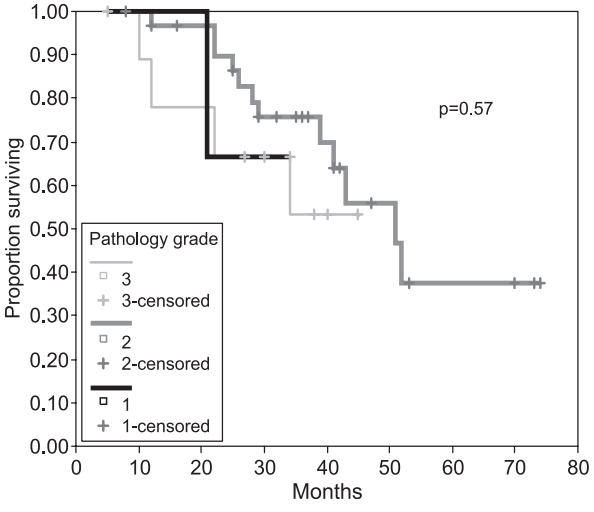

Figure 5. Overall survival according to grade.

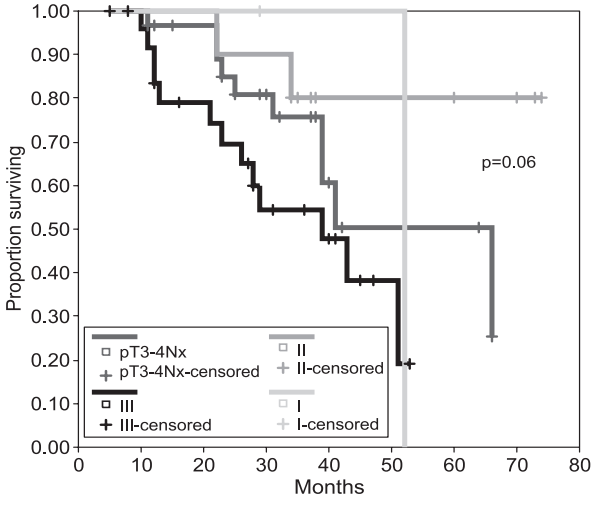

Figure 8. Overall survival according to TNM stage.

Discussion

The therapeutic benefits are most important from the patient's point of view. DFS and OS are the most reliable surrogates for the therapeutic efficacy of adjuvant chemotherapy, considering that the main endpoint of the overwhelming majority of adjuvant chemotherapy studies is to demonstrate an improvement in DFS and/or OS.

Our results are inferior to those reported in western Europe and USA for patients with similar major prognostic factors and similar adjuvant chemotherapy regimens [10-14]. For instance, the phase III study X-ACT, which compared adjuvant capecitabine with bolus 5FU-folinic acid in patients with exclusively stage III colon carcinoma, reported an OS at 3 years of 81.3 for the capecitabine arm vs. 77.6% for the 5FU/FA arm (67% in our study), and a DFS at 3 years of 64.2 vs. 60.2% (52% in our study) [10]. There may be multiple causes for our inferior results:

1. Almost half of our patients had rectal cancer, with a doubtful quality of the operation.

2. Only about two thirds of the rectal cancer patients received radiotherapy and only 1.5% received it before surgery.

3. The quality of the surgical therapy is hard to assess, since the pathology report is commonly concise, and in 40% of the cases the description of nodal status in the resected specimen is lacking, therefore making a correct staging impossible.

4. Late start of the adjuvant treatment (frequently at 6-8 weeks after surgery).

Moreover, no patient received an oxaliplatin-based regimen because of limited budget resources.

It should also be emphasized that 40% of the patients were not properly staged and no assessment of the operation in a TME-fashion was performed, therefore the pathology department of our hospital requires an improvement of the processing and reporting of the surgical specimens.

The rectal cancer group of patients deserves a special discussion, since it represented almost half of the reported cases. Notably, we observed an unacceptably high local recurrence rate. The incidence of local recurrence was not influenced by adjuvant radiotherapy (27.2% without radiotherapy vs. 23.8% with radiotherapy; p=0.87). This rate is similar with other studies coming from the surgical era before TME. However, there was a clear trend for improved DFS by using adjuvant radiotherapy (p = 0.08; Figure 9), while impact on OS was lacking (p = 0.31; Figure 10).

More than half of all patients (56%) underwent surgery in surgical clinics or at the Oncology Institute in Cluj Napoca, a city well known in Romania for its high-quality medical facilities. However, we found that the rate of local recurrence in these patients was not significantly different than in patients undergoing surgery in Alba county (even a little bit higher in Cluj Napoca; 27.7 vs. 21.4%). Moreover, DFS and OS were not influenced by the location of the operative center (Cluj Napoca vs. Alba). Therefore, the high local recurrence rate following rectal cancer surgery in our group of patients was not center-dependent, so maybe the main causes for this situation are the same for all surgical departments in Romania. Possible explanations are: inaccurate preoperative staging (without pelvic

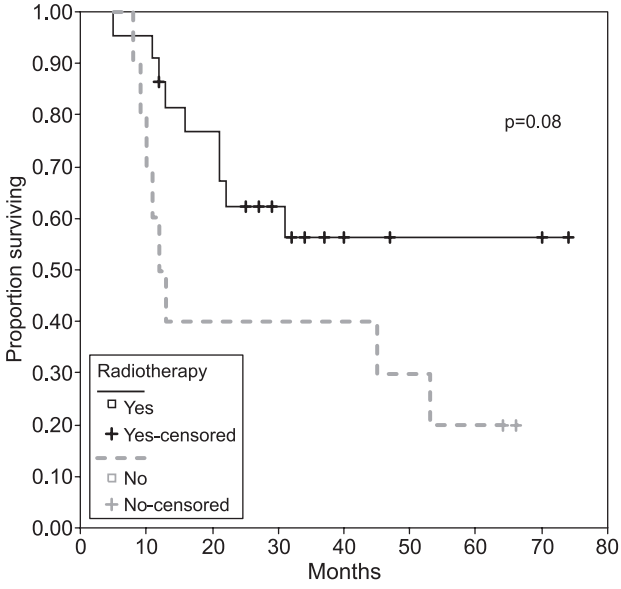

Figure 9. Impact of adjuvant radiotherapy on disease-free survival.

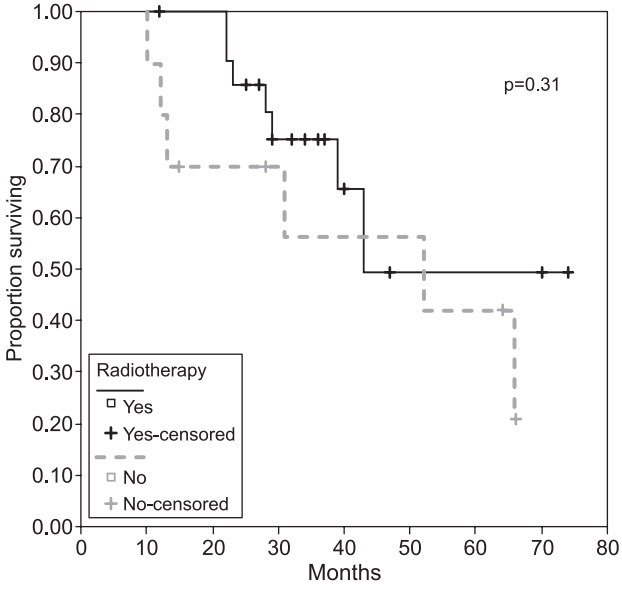

Figure 10. Impact of adjuvant radiotherapy on overall survival.

MRI) with upfront surgery in cases with circumferential margin involvement; minimal use of neoadjuvant radiation therapy or chemoradiotherapy; low-quality TME without proper pathology assurance control; insufficient access to adjuvant radiotherapy; and lack of patients' counseling regarding colostomy with lower acceptance of an abdomino-perineal resection. All these data impose the necessity of a extended training program in TME for surgeons operating rectal cancers and of a pathology-guided quality assurance of rectal surgery according to the TME standards. Nevertheless, a correct staging before surgery is highly advisable, best by using modern imaging techniques (MRI) to avoid a suboptimal upfront surgery. Furthermore, an expanding role of neoadjuvant chemoradiotherapy would be very beneficial as an accepted standard treatment in the EU states and also about to become the standard in the USA.

Conclusions

Our experience is highly representative for the present status of adjuvant treatment of colorectal cancer patients in Romania. Results of our analysis can be used to design a strategy for improving the quality of adjuvant treatment of colorectal cancer patients, which can and must be in the future similar with Western Europe and USA gold standards.

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