2-YEAR SINGLE CENTER CLINICAL EXPERIENCE IN PATIENTS WITH COLON CANCER STAGE II AND III RECEIVING ADJUVANT CHEMOTHERAPY

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ABSTRACT

INTRODUCTION: Colorectal cancer is the most commonly diagnosed gastrointestinal cancer worldwide. For patients without metastatic disease, surgery is the first option used with curative intention, for stage I disease the adequate treatment consists only of surgical excision. In stage III additional adjuvant chemotherapy post-surgery is recommended. In stage II colon cancer, adjuvant treatment remains controversial.

We aim to stratify patients according to different criteria, identify those with recurrence within the first year post last cycle of adjuvant chemotherapy and discuss those primary results.

MATERIALS AND METHODS: a total of 52 patients who were subject to curative resection of stage II and III colon adenocarcinoma and who were administrated 5 FU based adjuvant chemotherapy were included and were followed for a period of two years. Data analysis was performed.

RESULT: After a mean of 2 years of follow-up, recurrence was identified in 16 patients. None of stage II patients (n=6) and 3 patients in stage III (n=16) experienced recurrence. Patients with Nx cancer (n=30) were detached in separate group. Thirteen of them experienced recurrence (9 patients had relapse within 6 months after surgery – defined as synchronous metastatic disease).

CONCLUSION: Surgery remains the cornerstone of treatment for the majority of colon patients. The selection of optimal chemotherapy for each patient is a complex process and there is a practice evidence gap which remains a significant problem. Our results for relapse are comparable with the reported ones worldwide. The reports suggest that there is still lack of evidence in the adjuvant colon cancer chemotherapy worldwide.

Keywords: *colon cancer, adjuvant chemotherapy, recurrence, early stages colon cancer, follow-up*

INTRODUCTION

Colorectal cancer (CRC) is the most commonly diagnosed gastrointestinal cancer worldwide (nearly 1.4 million new cases in 2012); it is the fourth most common cause of cancer-related death, following lung, stomach and liver cancer (1). In Bulgaria for 2012 there have been 2370 newly diagnosed colon cancer and 1664 rectal cancers cases. The total number of registered patients is 29995 (2).

The currently used TNM staging system for colorectal cancer is version 7 and is based on sever-

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al criteria: the extent of primary tumor invasion into intestinal wall (T), the number of involved metastatic regional lymph nodes (N), and the presence of distant metastasis (M). The oncological management of colon cancer patients is based on the initial clinical staging of the disease. For patients without metastatic disease (cM0), surgery is the first option, used with curative intention. It is actually considered that for stage I disease the adequate treatment consists only of surgical excision of the primary tumor and the regional lymph nodes. The surgery should excise the tumor with wide margins and regional lymphadenectomy such that at least 12 lymph nodes are available for pathologic evaluation. For lesions above the rectum, resection of the tumor with a minimum 5-cm margin of grossly negative colon is considered adequate. Laparoscopic colectomy approaches have been developed and appear to be equally effective staging and therapeutic approaches to open colectomy, with modest decreases in hospital stay and pain medication use and improved cosmetic results (3). Variations in the use of radiotherapy (RT) alone or combined with chemotherapy and in surgical technique only for rectal cancer have been investigated in attempts to improve local control rates. Numerous randomized controlled studies of both preoperative and postoperative RT alone have demonstrated no improvement in survival; at best, there has been a small decrease in the rate of local recurrence.

In stage III additional adjuvant chemotherapy post-surgery is recommended as standard of care. Oxaliplatin based chemotherapy is now emerging as the new standard of care in adjuvant treatment of stage III colon cancer. Adjuvant chemotherapy for stage III colon cancer (lymph node involvement) with 5-FU plus Levamisole (historical) or 5-FU plus Leucovorin reduced the incidence of recurrence by 41% ($p < 0.001$) in a number of large prospective randomized trials. The MOSAIC study in Europe randomized 2 200 patients (40% stage II, 60% stage III) to receive 5-FU infusion and Leucovorin without or with Oxaliplatin (FOLFOX) (4,5). In stage II colon cancer, adjuvant treatment remains controversial – according to the current guidelines of the American Society of Clinical Oncology adjuvant chemotherapy is not routinely recommended in all stage II cases, but could be considered in several subgroups of patients, including poorly differentiated histology (G3), T4 lesions, bowel perforation at presentation or inadequately sampled regional lymph nodes (<12). A meta-analysis of five trials involving about 1,000 patients showed a statistically insignificant difference in 5-year survival rates of 82% versus 80%, treated versus untreated, respectively, for patients with stage II disease. The QUASAR group did show a 3% survival advantage at 5 years for FU/L over observation in a trial that enrolled >3 200 patients. There was no survival advantage for the 40% of stage II patients enrolled in the MOSAIC trial. The ASCO recommends against the routine use of chemotherapy in stage II colon cancer (6-8).

Oxaliplatin based chemotherapy (FOLFOX) shows effectiveness including after radical liver resection in stage IV patients (pseudoadjuvant therapy) – 35.4% vs. 28.1% without recurrence in a 3 years follow-up (9).

Cetuximab and Panitumumab are monoclonal antibodies that target the epidermal growth factor receptor (EGFR) and have been approved for use in advanced, refractory colorectal cancer (There is no evidence in adjuvant aspect). Multiple clinical trials have convincingly established that mutations in RAS render these two antibodies ineffective in colorectal cancer. Consequently, Cetuximab and Panitumumab should only be used in RAS wild-type colorectal cancer. Both have single agent activity resulting in response rates of 10% to 15% in third-line therapy in RAS wild-type cancers.

Currently, the relative 5 year survival rates for all stages colon cancer is reported as about 62%, but in cases of localized disease it increases to 90%. For stage IIA it is 66.5%, stage IIB – 58.6%, stage IIC – 37.3%, respectively IIIA – 73.1%, IIIB – 46.3%, IIIC – 28% (10).

In our study we collected data for patients with colon cancer stage II and III, who underwent surgery, adjuvant chemotherapy in our institution – University hospital "St. Marina" and agreed to collection of serum/plasma (for the needs of further tests, planned additionally as a second trial, aiming to identify different potential predictive/prognostic markers). As a first step we aim to stratify patients according to different criteria, identify those with recurrence within the first year post last cycle of adjuvant chemotherapy and discuss those primary results.

Scripta Scientifica Medica, vol. 47, No 2, 2015, pp. 43-48

METHODS

Patient selection

We conducted a prospective non-experimental clinical study of a total of 52 patients who were subject to curative resection of stage II and III colon adenocarcinoma. The patients were followed for a period of 2 years after surgery which was performed at the University Hospital "St. Marina" from August 2011 to November 2013. Prior to inclusion in our study we obtained ICF for collection of biological material (plasma/serum) from all patients willing to participate.

We included patients with colon cancer stage II and III as per AJCC, 7th ed. who underwent radical surgery in our hospital; there was no residual disease or compromised edges post-surgery and patients have completed 5-FU based adjuvant chemotherapy. We obtained plasma/serum after last cycle of adjuvant chemotherapy and patients started follow-up regularly (every 3-6 months) with CT/PET-CT until progression or 2 year of follow-up. Follow-up time was measured from date of surgery until date of progression or 2 years.

Clinical and pathologic features

We collected the following clinical and pathologic data: demographical data (age at initial staging, sex, etc), date of surgery, extent of surgery, tumor characteristics – localization, histology, grade of differentiation and TNM classification, total number of histologically examined lymph nodes and type of adjuvant chemotherapy, date of last cycle.

Follow-up and recurrence of disease

Recurrence was defined as appearance of any new lesion(s) or local recurrence (anastomotic or regional). Patients were followed for 2 years after date of surgery or until recurrence was documented. The follow-up included: a colonoscopy one year following end of adjuvant chemotherapy, a CT of the thorax and abdomen every 3-6 months or upon presentation of clinical symptoms.

Statistical methods

Data analysis was performed with the statistical analyzer SPSS for Windows, ver. 21. Descriptive statistics was used. Categorical features were summarized with frequencies and percentages.

RESULTS

Stage II

Six patients with stage II disease were included in our study. Their data was summarized in Table 1. All patients had moderately differentiated adenocarcinomas (G2). The total number of dissected and histologically examined lymph nodes was at least 12. All patients had T3 tumors and were treated with 5 FU based adjuvant chemotherapy (n=4 Mayo Clinic, n=2 De Gramont). After 2 years of follow-up surgery none of them experienced recurrence.

Stage III

Sixteen patients with stage III colon cancer were included in our study. Their data was summarized in Table 1. One patient had well differentiated tumor (G1), 12 patients had moderately differentiated tumors (G2) and 3 patients had poorly differentiated (G3) tumors. Fifteen patients had T3 tumors and 1 had T4a tumor. The total number of dissected and histologically examined lymph nodes was at least 12. All patients were treated with 5 FU based adjuvant chemotherapy (n = 9 FOLFOX4, n = 4 Mayo Clinic, n = 1 De Gramont and n = 1 monotherapy Capecitabine). After a mean of 2 years of follow-up 3 of them experienced recurrence (18.7%) (Table 2). These 3 patients had all received FOLFOX4 as adjuvant chemotherapy; 2 of them had G2 tumors and one had a G3 tumor.

Nx group *(no description of lymph node involvement possible due to lack of data)*

Thirty patients with Nx cancer were included in our study. Their data was summarized in Table 1. One patient had a well differentiated tumor (G1), 26 patients had moderately differentiated tumors (G2) and 3 patients had poorly differentiated (G3) tumors. The total number of dissected and histologically examined lymph nodes was less than 12. Six patients had T2 tumors, 19 patients had T3 tumors and 5 patients had T4a tumor. All patients were treated with 5 FU based adjuvant chemotherapy (n = 4 FOLFOX4, n = 12 Mayo Clinic, n = 11 De Gramont and n = 3 Capecitabine monotherapy). After a mean of 2 years of follow-up 13 of them experienced recurrence (43.3%). Nine patients had a recurrence within 6 months after surgery (30% of Nx group). Two of the other 4 patients who had recurrence (G1 and G2 tumors) have received Mayo Clinic as adjuvant chemo-

Table 1. Summary of clinical, pathologic and treatment features for all patients

Sex %	
Male	44.2 (n=23)
Female	55.8 (n=29)
Age at diagnosis (years, mean ± SD)	
Male	**66.09 (±7.734)**
Female	**64.76 (±8.118)**
Total	**65.35 (± 7.901) Min. 44, Max. 77**
Tumor localization (N, %)	
Colon ascendens	16 (30.8)
Colon tranversum	2 (3.8)
Colon descendens	8 (15.4)
Sigma	26 (50)
Total	52 (100)
TNM (N, %)	
pT2NxM0	6 (11.5)
pT3NxM0	19 (36.5)
pT3N0M0	6 (11.5)
pT3N1M0	12 (23.1)
pT3N2M0	3 (5.8)
pT4aNxM0 6	(11.5)
Total	52 (100)
Stage (N, %)	
II	6 (11.5)
III	16 (30.8)
Nx N/A	30 (57.7)
Total	52 (100)
Histology (N, %)	
Adenocarcinoma 45 (86.5)	45 (86.5)
Mucinous	6 (11.5)
Signet ring	1 (1.9)
Grade (N, %)	
Gr 1	2 (3.8)
Gr 2	44 (84.6)
Gr 3	6 (11.5)
Total	52 (100)
Surgery (N, %)	
Right hemicolectomy	16 (30.8)
Left hemicolectomy	8 (15.4)
Sigma resection	26 (50)
Colon transversum resection	2 (3.8)
Total	52 (100)
Adjuvant chemotherapy regimen (N, %)	
Mayo clinic	18 (34.6)
FOLFOX4	16 (30.8)
De Gramont	14 (26.9)
Capecitabine monotherapy	4 (7.7)
Total	52 (100)

Scripta Scientifica Medica, vol. 47, No 2, 2015, pp. 43-48

therapy, one (G3 tumor) received De Gramont and one (G2 tumor) received FOLFOX4.

Data for recurrence, evaluation methods of recurrence and location of recurrence is shown on Table 2.

Table 2. Recurrence, evaluation methods of recurrence and location of recurrence

Recurrence (N, %)	
Non recurrence	36 (69.2)
Recurrence	16 (30.8)
Total	52 (100)
Time to recurrence (N)	
Under 6 months	9
Over 6 months	7
Total	16
Time to recurrence (mounts, mean ± SD)	**5.5 (± 4.487) Min. 1, Max. 12**
Evaluation method (N, %)	
CT	8 (73.1)
PET/CT	14 (26.9)
Recurrence location (N, %)	
Lung	4 (25)
Pleura	1 (6.3)
Bone	1 (6.3)
Liver	6 (37.5)
Per	2 (12.5)
Lymph nodes	2 (12.5)
Local recurrence	6 (37.5)

DISCUSSION

The results of this study, analyzing the data of a total of 6 patients with stage II colon cancer at high risk, demonstrated a two-year recurrence rate of 0%. The stage III colon cancer population of 16 patients, as expected, had a much higher two-year recurrence rate of 18.7%, with most recurrences occurring within the first year after surgery. Compared with other studies, the findings for risk of recurrence for stage II and III colon cancer are similar to those in our study (11).

We have separated patients with Nx disease in a different group. As we expected, those 30 patients within this group had a much higher two-year recurrence rate of 43.3%; again most recurrences occurred within the first year after surgery. According to Cunliffe et al. synchronous metastases can be two or more in number, detected for a period up to 6-month-period postoperatively (12). Thus we considered patients with recurrence within 6 months after surgery (30% of Nx group) to have had synchronous metastasis.

Prognostic factors are particularly useful in the context of stage II colon cancer, where benefits of cytotoxic adjuvant therapy are more controversial than in stage III disease (13).

In our study for all patients the mean number of histologically examined lymph nodes was less than 10 due to the large number of Nx group patients. Several studies focusing on stage II disease suggest that patients with fewer total lymph nodes dissected at surgery encounter more often micrometastases and have higher risk for recurrence (14,15). Others studies do not confirm those findings (16).

We consider the diagnosis of Nx disease a poor prognostic factor as those patients could receive suboptimal adjuvant therapy; they also have increased recurrence rate that could imply the need of intensified follow-up, especially during the first year after surgery of the primary tumor. Variety of adjuvant chemotherapy regimens have been used in this Nx subgroup, because recent post-hoc exploratory anal-

ysis of the MOSAIC trial did not show a significant DFS or OS benefit of FOLFOX over 5FU/LV for patients with high-risk stage II disease (including patients with less than 10 lymph node examined) (4,5).

CONCLUSION

Surgery remains the cornerstone of treatment for the majority of colon patients. The selection of optimal chemotherapy for each patient is a complex process and there is a practice evidence gap which remains a significant problem. There are differences in the chemotherapy regimen pattern in the different institutions, regions and countries. The results suggest that there is still lack of evidence in the adjuvant colon cancer chemotherapy worldwide (1). The identification of accurate predictive and prognostic markers will help clinicians in choosing appropriate use of adjuvant chemotherapy in patients with colon cancer which we plan to study in further research.

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