ACTA MEDICA LITUANICA. 2018. Vol. 25. No. 3. P. 161–165

Survival and time interval from surgery to the start of chemotherapy for patients with stage II and III colon cancer

Denis Ganenko[1],

Audrius Dulskas[1, 2, 3],

Žygimantas Kuliešius[4],

Edita Baltruškevičienė[5],

Vincas Urbonas[5],

Eugenijus Stratilatovas[1]

[1] *Department of Abdominal and General Surgery and Oncology, National Cancer Institute, Vilnius, Lithuania*

[2] *Faculty of Health Care, University of Applied Sciences, Vilnius, Lithuania*

[3] *Department of Surgery, National Cancer Institute, Clinic of Internal, Family Medicine and Oncology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

[4] *Department of Interventional Surgery, State Vilnius University Hospital, Vilnius, Lithuania*

[5] *Department of Chemotherapy, National Cancer Institute, Vilnius, Lithuania*

Background. Usually adjuvant chemotherapy is started within 12 weeks of surgery, but the evidence on the commencing time is lacking. Our aim was to investigate the association of initiating post-surgery treatment within six weeks *vs.* six to ten weeks *vs.* more than ten weeks with survival.

Methods. We analysed the association of treatment and its timing with survival among patients who were diagnosed and underwent surgery for stage II or III colon cancer from 2012 to 2013 at the National Cancer Institute, Lithuania.

Results. Of the 86 patients, 78% were still alive on December 31, 2013. Patients who received chemotherapy within six weeks after surgery were more likely to survive. However, those who received chemotherapy 6–10 weeks after surgery had better survival (p – 0.014, hazard ratio 0.80, 95% CI 0.60–0.99) than those who began chemotherapy treatment more than ten weeks after surgery (p – 0.173 hazard ratio 0.55, 95% CI 0.12–0.99).

Conclusions. The results from this study show that optimal timing of adjuvant chemotherapy for patients with resected colon cancer within six weeks and associated with better survival.

Keywords: colon cancer, survival, adjuvant chemotherapy

Correspondence to: Audrius Dulskas, Department of Abdominal and General Surgery and Oncology, National Cancer Institute, 1 Santariškių St., Vilnius 08406, Lithuania. Email: audrius.dulskas@gmail.com

INTRODUCTION

In 2013, colon and rectum cancer (CRC) ranked third for cancer incidence and fourth for cancer death worldwide (1) Surgical resection is the primary treatment for localized colon cancer. After curative resection, adjuvant chemotherapy is prescribed to lower the risk of tumour recurrence and metastasis (2, 3, 4, 5). The oncologic benefits of adjuvant chemotherapy have been proven (2), and adjuvant chemotherapy is suggested for stage II or III colon cancer patients in the current National Comprehensive Cancer Network (NCCN) guidelines (6).

One factor that may hamper the benefit of chemotherapy is an excessively long interval between surgery and the commencement of adjuvant therapy, which might give further time to micro-metastases to develop. This has been hardly assessed in CRC and available studies have shown conflicting results (7–9).

We used database of patients with stage II or stage III colon cancer from the National Cancer Institute to investigate the association of the timing of chemotherapy initiation survival.

PATIENTS AND METHODS

The study was approved by the Institutional Review Board.

From January 2012 to December 2013, 86 patients with stage II-III CRC, who had undergone surgical resection, were included in this study. All the patients had histologically proven stage II-III CRC after surgeries: high vascular resection (right-sided hemicolectomies, transverse colon resections, left-sided hemicolectomies, sigmoid resections and rectosigmoid resections) with D3 lymphonodectomy, and had received adjuvant chemotherapy. The medical records of patients were reviewed prospectively. Patients were categorized into three groups representing different times for adjuvant chemotherapy initiation after surgery: group 1 – patients having adjuvant chemotherapy within six weeks, group 2 – 6–10 weeks after surgery, and group 3 – more than 10 weeks after surgery. Patients had chemotherapy intravenously (oxaliplatin, 5-fluorouracil and leucovorin – FOLFOX4; 5-fluorouracil and leucovorin – 5-FU/LV), and orally (capecitabine – Xeloda, tegafur/uracil – UFT). To evaluate the efficacy of adjuvant chemotherapy according to the timing of its initiation, we analyzed and compared 5-year overall survival rates. Overall survival rates were estimated by using the Kaplan-Meier method. Multivariable Cox proportional hazards regression models were then used to analyze the association of treatment and the timing of treatment with mortality in univariate analysis (12). The differences between the groups were assessed using the log-rank test. A two-sided p-value of less than 0.05 was considered to represent statistical significance. All associations were considered to be statistically significant if the two-sided p value was 0.05 or less.

RESULTS

Of the 86 patients included in this study, 45 patients were male and 41 patients were female. The mean age of the patients was 63.3 ± 9.64 years (range from 31 to 75 years). The mean interval from the surgery to the initiation of adjuvant chemotherapy was 47.67 days, with a range of 24 to 206 days. Sixty-eight patients had chemotherapy intravenously (Oxaliplatin 85 mg/m^2; Folinic acid 200 mg/m^2; Fluorouracil 400–>600 mg/m (FOLFOX4); Leucovorin 200 mg/m^2; Fluorouracil 400–>600 mg/m^2 (de Gramont)), and 18 patients had it orally (Capecitabine 1250 mg/m^2 (Xeloda); tegafur 300 mg/m^2/uracil 672 mg/m^2 (UFT)) (Table 1). Twenty-two per cent of the patients are known to have died during the five-year study period.

A total of 57 patients (28 males and 29 females) in group 1 received chemotherapy within six weeks after surgery. The mean age was 60.8 years. A total of 20 patients (11 males and nine females) in group 2 received chemotherapy from six to ten weeks after surgery. The mean age of those patients was 60.5 years. A total of nine patients (five males and four females) in group 3, received chemotherapy more than ten weeks after surgery. The mean age of those patients was 62.3 years. There were no significant differences between the groups (p = 0.0001) (Table 2).

Kaplan-Meier survival analysis showed that the patients who received chemotherapy more than ten weeks after surgery had poorer survival than those whose chemotherapy treatment was started six to ten weeks following the surgery, and the patients who were treated within six weeks after surgery had better survival (Fig. 1).

Table 1. Demographic characteristics of patients in three groups (n = 86)

Characteristic	Value
Age, mean ± SD	63.3 ± 9.64
Sex (male:female)	41:45
Interval between surgery and chemotherapy (day), mean ± SD	47.67 ± 30.45
Regimen of adjuvant chemotherapy	
de Gramont or FOLFOX-4 (Group 1/2/3)	47/14/7
capecitabine – Xeloda or tegafur/uracil – UFT (Group 1/2/3)	10/6/2

Table 2. Differences in all three study groups

Variable	Group 1 (<6 weeks)	Group 2 (6–10 weeks)	Group 3 (>10 weeks)	*p* value (<0.05)
Number of patients	57	20	9	–
Age (years), Mean ± SD	60.8 ± 8.27	60.5 ± 12.73	62.3 ± 4.04	0.032
Sex (male:female)	28:29	11:9	5:4	0.0001
TNM (stage II/III)	37/20	9/11	3/6	0.0001

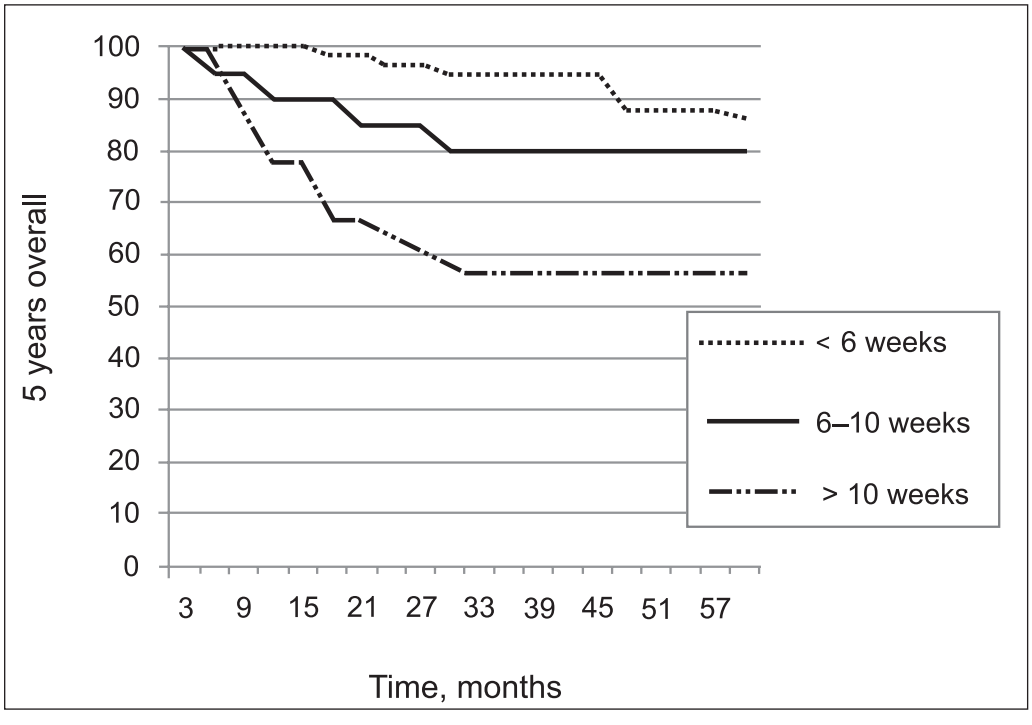

Fig. 1. Kaplan-Meier curves depicting 5-year overall survival

DISCUSSION

Numerous clinical factors may affect overall patient survival: stage III diagnosis, older age, and being male were all found to significantly decrease the probability of survival, after adjusting for treatment. Patients with stage III disease were almost twice as likely to die as those with stage II disease (HR 1.98, 95% CI 1.74–2.25). However, after adjusting for these factors, adjuvant chemotherapy was still associated with better survival (10).

Like our results, the results of studies by Kim et al. (9), Czaykowski et al. (11), Klein et al. (12), and Chau et al. (13) support the idea that adjuvant chemotherapy should be started as soon as possible after surgery, within six to eight weeks. A large meta-analysis published by Biagi et al. assessed the impact of delay to initiation of chemotherapy in ten cohorts of patients, involving 15,410 patients (14). The authors demonstrated that each incremental four-week delay in adjuvant chemotherapy resulted in a detriment to overall survival (HR: 1.14; 95% CI: 1.10–1.17) and disease-free survival (HR: 1.14; 95% CI: 1.10–1.18). Des Guetz et al. performed a complimentary meta-analysis of 17,645 patients and demonstrated similar findings, with delays beyond eight weeks associated with inferior overall survival (RR: 1.20; 95% CI: 1.15–1.26) (15).

However, there was a nonsignificant trend toward a higher risk of systemic recurrence when the delay of adjuvant chemotherapy was more than 12 weeks ($p = 0.068$). Additionally, a significant association was found between age, race, type of hospital, and timeliness of adjuvant chemotherapy (16).

Patients who received chemotherapy after surgery were less likely to die within the period of study. Our study showed that early initiation of chemotherapy may have better result. In summary, the study found that chemotherapy treatment after surgery improves the probability of survival for patients with stage II and III colon cancer. The study found strong evidence that the time interval between surgery and the start of chemotherapy affects survival. Further analysis on the relationship between treatment and survival, doses, durations, and types of chemotherapeutic agents is needed, especially as treatments and technology improve.

Our study obviously has some limitations. First of all, a small sample size and a retrospective nature of the trial. Secondly, we have not differentiated between various prognostic factors (localization of the primary tumour, inseparable left to right side of tumour localization, pathological grading), surgical complications, the number of metastatic lymph nodes. In addition, the age of our groups significantly varied statistically (in patients in the third group are older than in other groups, so they are likely to have more comorbidities).

CONFLICTS OF INTEREST

Authors have no conflicts of interest.

Received 30 June 2018
Accepted 22 November 2018

References

1. Global Burden of Disease Cancer Collaboration. The Global Burden of Cancer 2013. JAMA Oncol. 2015; 1: 505–7.
2. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009; 27: 3109–16.
3. Graham JS, Cassidy J. Adjuvant therapy in colon cancer. Expert Rev Anticancer Ther. 2012; 12: 99–109.
4. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009; 27: 3109–16.
5. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011; 29: 1465–71.
6. National Comprehensive Cancer Network (2016). National comprehensive cancer network guidelines, Colon cancer (Version 2.2016). National Comprehensive Cancer Network.
7. Kang KM, Hong KS, Noh GT, Oh B-Y, Chung SS, Lee RA, Kim KH. Optimal time of initiating adjuvant chemotherapy after curative surgery in colorectal cancer patients. Ann Coloproctol. 2013; 29: 150–4.
8. Nachiappan S, Askari A, Mamidanna R, Munasinghe A, Currie A, Stebbing J, Faiz O. The impact of adjuvant chemotherapy timing on overall survival following colorectal cancer resection. Eur J Surg Oncol. 2015; 41: 1636–44.
9. Kim YW, Choi EH, Kim BR, Ko WA, Do YM, Kim IY. The impact of delayed commencement of adjuvant chemotherapy (eight or more weeks) on survival in stage II and III colon cancer: a national

population-based cohort study. Oncotarget, 2017; 8: 80061–72.
10. Zeig-Owens R, Gershman ST, Knowlton R, Jacobson JS. Survival and time interval from surgery to start of chemotherapy among colon cancer patients. J Registry Manag. 2009; 36: 30–41.
11. Czaykowski PM, Gill S, Kennecke HF, Gordon VL, Turner D. Adjuvant chemotherapy for stage III colon cancer: does timing matter? Dis Colon Rectum. 2011; 54: 1082–9.
12. Klein M, Azaquoun N, Jensen BV, Gogenur I. Improved survival with early adjuvant chemotherapy after colonic resection for stage III colonic cancer: a nationwide study. J Surg Oncol. 2015; 112: 538–43.
13. Chau I, Norman AR, Cunningham D, Tait D, Ross PJ, Iveson T, et al. A randomised comparison between 6 months of bolus fluorouracil/leucovirin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Ann Oncol. 2005; 16: 549–57.
14. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011; 305: 2335–42.
15. Des Guetz G, Nicolas P, Perret G-Y, Morere J-F, Uzzan B. Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer. 2010; 46: 1049–55.
16. Yu S, Shabihkhani M, Yang D, Thara E, Senagore A, Lenz HJ, Sadeghi S, Barzi A. Timeliness of adjuvant chemotherapy for stage III adenocarcinoma of the colon: a measure of quality of care. Clin Colorectal Cancer. 2013; 12: 275–9.
17. Fritz A, Percy C, Kanagaratnam A, Shanmugaratnam J, Sobin L, Parkin DM, et al. International classification of diseases for oncology, 3rd Ed. Geneva: World Health Organization, 2000.
18. Rich JT, Neely JG, Paniello RC, Voelker CCJ, Nussenbaum B, Wang BJ. A practical guide to understanding Kaplan-Meier curves Otolaryngol Head Neck Surg. 2010; 143(3): 331–6.

Denis Ganenko, Audrius Dulskas, Žygimantas Kuliešius, Edita Baltruškevičienė, Vincas Urbonas, Eugenijus Stratilatovas

ADJUVANTINĖS CHEMOTERAPIJOS PRADŽIOS PO OPERACIJOS ĮTAKA PACIENTŲ, SERGANČIŲ II IR III STADIJOS GAUBTINĖS ŽARNOS VĖŽIU, IŠGYVENAMUMUI

Santrauka

Tikslas. Paprastai adjuvantinė chemoterapija pradedama taikyti praėjus ne daugiau kaip 12 sav. po operacijos. Tačiau kada ji turėtų būti pradėta, daug randomizuotų klinikinių tyrimų nėra. Darbo tikslas – įvertinti chemoterapijos skyrimo laiko po operacijos įtaką išgyvenamumui. Pacientai buvo suskirstyti į tris grupes: pirmoji – kuriems chemoterapija skirta iki 6 sav. po operacijos, antroji – 6–10 sav. ir trečioji – >10 sav. po operacijos.

Metodai. Chemoterapijos skyrimo pradžios įtaka pacientams, kuriems dėl II ir III stadijos gaubtinės žarnos vėžio buvo skirta pooperacinė chemoterapija Nacionaliniame vėžio institute 2012–2013 metais.

Rezultatai. Tyrimo pabaigoje (2013 m. gruodžio 31 d.) 78 % pacientų buvo gyvi. Pacientų, kuriems chemoterapija pradėta taikyti iki 6 sav. po operacijos, išgyvenamumo rodikliai buvo geriausi, o kuriems pradėta nuo 6 iki 10 sav., išgyvenamumo rodikliai (p – 0,014, rizikos laipsnis 080; 95 % CI 0,60–0,99) buvo geresni nei tų, kuriems chemoterapijos pradžia buvo paėjus 10 ir daugiau sav. po operacijos (p – 0,173, rizikos laipsnis 0,55; 95 % CI 0,12–0,99).

Išvados. Tyrimo rezultatai rodo, kad chemoterapija turi būti pradėta taikyti kuo anksčiau, geriausia – iki 6 sav. po operacijos. Ankstyvas chemoterapijos skyrimas lemia geresnius išgyvenamumo rodiklius.