

Prognostic impact of Lymph node resection in stage II colon cancer: a prospective study from a tertiary hospital center

Diana Chetroui^{1,2}, Mircea Beuran^{1,3}, Petruta Violeta Filip^{1,2}, Sorina Diaconu^{1,2}, Carmen Orban¹, Corina Silvia Pop^{1,2}, Alexandru Laurentiu Chiotoroiu^{1,3}

¹ Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

² Department of Internal Medicine and Gastroenterology; University Emergency Hospital of Bucharest, Bucharest, Romania

³ Department of Surgery; Emergency Clinical Hospital of Bucharest, Romania

ABSTRACT

Background. The treatment of stage II colon cancer has been a subject of debate for a long time. In the last years, a few risk factors have been proposed in order to guide any treatment decision more accurately. One of these risk factors is the number of resected lymph nodes, and according to the latest guidelines, it is recommended that at least 12 lymph nodes should be resected for optimal staging.

The aim of this study is to evaluate the role of lymph node resection, in stage II colon cancer and the implication of sub-optimal lymph node resection on disease free survival and overall survival.

Patients and methods. This was a prospective study that included 130 patients with stage II colon cancer who were monitored between October 2014 and October 2016. The relation between patients' tumour characteristics that include number of lymph node resection and the use of adjuvant chemotherapy using Chi test and multiple logistic regression was analyzed. The disease-free survival and overall survival were estimated with the Kaplan-Meier method and compared with the log-rank test.

Results. 130 patients with stage II colon cancer were recruited. 56 patients were treated with surgery alone and 74 patients received fluorouracil-based chemotherapy after surgery. Patients' age varied from 37 years to 81 years. According to the number of resected lymph nodes, patients were divided into two groups - with less than 12 lymph nodes resected and at least 12 lymph nodes resected. The number of resected lymph nodes varied from 2 to 32 lymph nodes. Median follow up was 36 months. Suboptimal resections of lymph nodes confirmed to be a negative prognostic factor for survival without disease recurrence.

Conclusion. Data results confirmed the importance of lymph node resection as a prognostic factor for stage II colon cancer and the role of chemotherapy for patients with suboptimal lymph node resection.

Keywords: colon cancer, lymph nodes, resection, treatment

INTRODUCTION

Colon cancer is an important health problem around the globe, with an increasing incidence in the past several years [1-4]. Surgery remains the main treatment with curative intent for stage I-III colon cancers [1-4]. The recommended procedure is colectomy with en bloc removal of regional lymph nodes [4-7]. Studies correlated patients' survival

with the number of resected lymph nodes, demonstrating a positive association [4-7].

International Union Against Cancer, the 8th edition of the American Joint Committee on Cancer staging manual, College of American Pathologists and European Society of Medical Oncology have all recommended resection and evaluation of at least 12 lymph nodes in order to ensure adequate N staging,

Corresponding author:
Petruta Violeta Filip, MD, PhD
E-mail: petruta.filip@umfcd.ro

Article History:
Received: 25 May 2022
Accepted: 25 June 2022

with implications in patients treatment and prognosis [2, 4-10]. In spite of all these recommendations, inadequate number of resected lymph nodes is still reported in many retrospective studies. It has been reported that there are few factors that may influence the number of reported lymph nodes such as: the extent of surgical intervention and surgical technique, patients' age and tumours' location [2, 4-10].

In the present study, we pursue to evaluate the role of lymph node examined in stage II colon cancer and the influence of 5FU chemotherapy on disease free survival for patients with less than 12 nodes examined.

METHODS

Study Design and Patients

The current study was designed as a prospective study that included patients who underwent curative colonic resection for adenocarcinoma of colon in an academic hospital, University Emergency Hospital of Bucharest.

The study was conducted between October 2014 and October 2016. 130 patients with stage II colon cancer were included, of whom 56 patients received only surgery, and 74 patients received surgery plus 5FU-based chemotherapy.

All data on patient demographics, operative and pathological information were stored in a prospectively maintained database. Patients included in the study benefited from lymph nodes resection during the surgery, the resection pieces being independently examined by two pathologists (independent of each other.)

The follow-up period was of 36 months. In the first two years, patients were monitored every 3 months, and in the last year, every six months. During the follow-up visits, the patients underwent clinical examination, carcinoembryonic antigen (CEA) level tests, hematology and biochemistry tests were also being performed. Contrast computed tomography of the chest, along with abdomen and pelvis MRIs was performed annually for the first 3 years, but also whenever recurrence was suspected.

Patients who had undergone surgery for colon cancer were usually followed up to death. Patients' survival was monitored from the central electronic health system of our public hospital, but also by telephone monitoring during the study. Follow-up time, and time to recurrence or death were counted from the date of surgery. Patients were divided into two groups, according to the number lymph nodes resected: less than 12 lymph nodes, and at least 12 lymph nodes. The implications on disease-free survival (DFS) and overall survival (OS) of the number of lymph nodes resected in patients with stage II colon cancer were analysed.

Statistical analysis

All data were included in a data base using Microsoft Office Excel programme. The statistical analysis was performed using STATA 13/MP (StataCorp LLS US) software. The difference between these groups was analysed with the χ^2 test for categorical variables and the one-way analysis of variance (ANOVA) for continuous variables. Survival analysis was performed using the Kaplan-Meier estimation method.

Overall survival (OS) was defined as the interval between the diagnosis date and time of death for any reason or the last follow-up. Disease-free survival (DFS) was defined as the time from the radical surgery to disease relapse or death. The overall survival (OS) and disease-free survival (DFS) of these groups were compared with the log-rank test. The univariate analysis of the various clinical and pathological parameters, using the survival results as a dependent factor, was performed with the Cox-Mantel log-rank test. A risk ratio greater than 1 means poorer survival. Significant parameters, $p < 0.05$, were included in the multivariate analysis using Cox regression analysis in a step-by-step method.

Ethical Considerations

All patients had written informed consent for inclusion before enrolling in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Local Ethics Committee of University Emergency Hospital of Bucharest.

RESULTS

Baseline Characteristics of the Patients

The study included patients aged between 37 years to 80 years. The median age was 62 years. Patients were divided into two groups, one treated with surgery alone (group A) and another one with surgery plus chemotherapy (group B).

In our study, from 130 patients totally, 54.61% were represented by men (71 patients) and 45.38% by women (59 patients). The location of the tumour was in 57.69% of cases reported on the left side (75 patients), with G2 being the most frequent histological grade in 62.3% of cases (81 patients) and stage T4a reported on 50.76% of histological results (66 patients). Most patients, 59.23% (77 patients) had more than 12 lymph nodes resected; vascular and perineural invasion were described in 23.07% of pathological reports (30 patients). Baseline characteristics of the patients are summarised in Table 1.

The majority of patients (50.76%) included in the study were diagnosed with T4a tumour stage, 57.57% (38 patients) were in the group B and 42.42% (28 patients) were in group B (Table 2).

TABLE 1. The clinical and pathological characteristics of patients in various lymph node yield groups at the baseline

Patients characteristics	Number of patients Group A (%)	Number of patients Group B (%)	Total of patients (No) (%)	P value
Sex				
Men	31 (43.66%)	40 (56.3%)	71 (54.61%)	p= 0.883
Women	25 (42.37%)	34 (57.62%)	59 (45.38%)	
Tumor localization				
Right colon	24 (43.63%)	31 (56.36%)	55 (42.3%)	p= 0.912
Left colon	32 (42.66%)	43 (57.33%)	75 (57.69%)	
Histologic grade				
G1	12 (52.17%)	11 (47.82%)	23 (17.69%)	p= 0.409
G2	31 (38.27%)	50 (61.72%)	81 (62.3%)	
G3	4 (23.52%)	13 (76.47%)	17 (13.07%)	
T stage				
T3	16 (43.24%)	21 (56.75%)	37 (28.46%)	p= 0.984
T4a	28 (42.42%)	38 (57.57%)	66 (50.76%)	
T4b	12 (44.44%)	15 (55.55%)	27 (20.76%)	
Number of lymph nodes				
<12 lymph nodes	24 (45.28%)	29 (54.71%)	53 (40.76%)	p= 0.673
≥12 lymph nodes	32 (41.55%)	45 (58.44%)	77 (59.23%)	
Vascular and perineurial invasion				
Yes	13 (43.33%)	17 (56.66%)	30 (23.07%)	p=0.794
No	43 (43%)	57 (57%)	100 (76.92%)	

Patients were divided into two groups according to the number of lymph nodes examined. In group A, 41.55% of patient were included (32 patients), and 58.44% (45 patients) were included in group B. The number of lymph nodes present in the pathological reports varied from 2 to 38 (Table 3). Recurrence of the disease was present in 31.54% (41 patients) of all patients included in the study. During follow-up, local or distant recurrence of the disease was higher in group A alone 33.93% (19 patients) compared to 29.73% (22 patients) in group B (Table 4).

TABLE 2. Correlation of colon cancer staging with therapeutic regimen

Tumor stage	Group A		Group B		Total number (percent)	
	No	%	No	%	No	%
T3	16	28.57	21	28.38	37	28.46
T4a	28	42.43%	38	57.57%	66	50.77
T4b	12	21.43	15	20.27	27	20.77
Total number	56	43.08	74	56.98	130	100

Chi2 – P test = 0.984

TABLE 3. Number of resected lymph nodes correlated with therapeutic regimens groups

No of lymph nodes	Group A		Group B		Total No	
	N	%	N	%	N	%
< 12	24	42.86	29	39.19	53	40.77
≥ 12	32	57.14	45	60.81	77	59.23
Total no	56	43.08	74	56.98	130	100

Chi2 – P test = 0.673

Table 4. Recurrence of the disease in both groups

Recurrence	Group A		Group B		Total	
	No	%	No	%	N	%
No	37	66.07	52	70.27	89	68.46
Yes	19	33.93	22	29.73	41	31.54
Total no	56	43.08	74	56.98	130	100

Chi2 – P test = 0.610

Survival data of patients with stage II colon cancer

Disease free survival of patients without recurrence. Disease-free survival (DFS) of patients from both groups was analysed, and the patients from group B were found to have similar survival to those in group A, 28.54 months vs. 27.96 months (p=0.2548).

Regarding the overall survival analysis, during the 3 years of monitoring, out of 130 patients, 21% of patients from group B died (15 patients) and 28.57% of patients from group A died (16 patients). The analysis of the whole group showed that those patients who, in addition to surgical treatment, benefit from chemotherapy, have a superior survival (OS) (p = 0.4314).

In group B, from 74 patients enrolled, 39.19 % (29 patients) had less than 12 lymph node reported on pathologic report and 51.72% (15 patients) of them experienced recurrence of disease.

In group A, from 56 patients, 26.78% (15 patients) had less than 12 lymph nodes reported on pathologic report and 60% of them (9 patients) had disease recurrence.

Patients with T3 tumor stage colon cancer presented a higher survival rate according long-rank

TABLE 5. Hazard ratio of risk factors associated with relapse (n = 130)

Patients	Parameters	HR (IC95%)	P
	Chemotherapy Patients vs Surgery	0.76(0.38-1.52)	0.435
Group B	T stage	4.81(2.09-11.06)	< 0.0001
Group A	T stage	3.5(1.6-7.64)	0.002
Group B	Lymphovascular invasion	2.97(1.1-7.99)	0.031
Group A	Lymphovascular invasion	9.84(3.51-27.62)	< 0.0001
Group B	No of lymph nodes (>12 vs < 12)	0.25(0.09-0.73)	0.011
Group A	Left-sided vs. right- sided localization	2.0(0.75-5.38)	0.169

test for equality of disease-free survival (DFS) ($p < 0.0001$) and also OS ($p < 0.0001$).

Patients DFS was also analysed according to the degree of differentiation, and patients with G1 histological grade had better 3 years DFS results compared to those patients with G3 tumors ($p = 0.0353$).

The 3-year survival data of patients according to histological grade also showed superior outcome for those with G1 compared to G3 ($p = 0.0321$).

Depending on the number of lymph nodes excised, statistical analysis revealed a superior disease-free survival for those patients who received resection of ≥ 12 lymph nodes ($p = 0.0090$). In terms of overall survival, patients with resection of ≥ 12 lymph nodes showed better survival if they also benefited from adjuvant chemotherapy ($p = 0.0292$).

The survival of stage II colon cancer patients was also influenced by lymphovascular and perineural invasion. Statistical analyses revealed better disease-free survival ($p < 0.0001$) and overall survival ($p < 0.0001$) respectively for those patients without lymphovascular and perineural invasion.

In the multivariate Cox proportional risk analysis, a relapse for those patients treated with chemotherapy regimens was associated independently with the stage of the disease (T stage) ($p < 0.0001$), lymph invasion ($p = 0.031$) and the number of resected lymph nodes ($p = 0.011$) (Table 5).

DISCUSSIONS

Stage II colon cancer chemotherapy has been under debate for many years. The recommendations for stage II colorectal cancer staging system are pathological T3 or T4 tumor stage without lymph node involvement [4, 11]. If lymph node dissemination is found, tumor stage will upgrade to stage III, which influences the long-term survival of patients [4, 11]. Proper surgical resection of the lymph nodes is vital for staging, accurate prognosis, and the need for adjuvant treatment in stage II colon cancer patients and could influence long-term prognosis for those patients [4,11]. Thus, in patients with less than 12 resected lymph nodes, according to the recommendations of the American Society of Clinical Oncology (ASCO), it is important to analyse the need for adjuvant chemotherapy [4].

Since 1990, it has been demonstrated that appropriate number of resected lymph nodes is important due to its crucial role as oncological indicator, but also in the quality of surgery [4-6,11,12]. Even so, lymphatic resection is dependent on the presence of several factors, some unconstrained to surgeon performing the intervention [13]. The literature has highlighted factors such as the patient's young age, advanced stages of the disease (stages T and N), large tumour size, and right hemicolectomy [4-6].

Over the years, the average number of lymph nodes examined in colorectal cancer patients has steadily increased, so it has been established that maybe 12 lymph nodes may not be enough [3]. It is important to know that resection of the lymph nodes takes time since the lymph nodes are small (<5 mm in diameter) [3]. Examination by the pathologist is difficult because the lymph nodes are in the mesenteric fat, and the diligence and skills of the pathologist are extremely important during the examination [3].

In recent years, studies have shown that patients with stage II colon cancer have a better survival when the number of resected lymph nodes is higher [4]. There are also studies that contradict the above, so a study based on the Canadian population showed that high lymph node performance is not associated with better survival [6].

So, it is yet to be discussed what the real stage of the disease is, if an un-appropriate number of lymph nodes are resected. Parson and van Erning consider that a higher number of lymph nodes resected is crucial for correct disease staging [4].

Current guidelines recommend microsatellite instability testing and the evaluation for the presence of certain risk factors for treatment decision planning [4]. With these steps, a minority of patients with stage II colon cancer that may benefit from chemotherapy can be identified. Taking into considerations the current recommendations regarding risk factors analysis, we evaluated the importance of the number of resected lymph nodes as a prognostic factor for patients with stage II colon cancer.

The current study aimed to demonstrate that number of lymph nodes resected was significantly correlated with improved OS and DFS in stage II colon cancer. In our study, the number of lymph nodes

presented in the pathological reports varied from 2 to 38. Patients included in this study were analysed according to the number of resected lymph nodes and patients with more than 12 lymph nodes were divided into two groups according to the chosen therapeutic option. 60.81% of patients were assigned to surgery and chemotherapy group (group B) and 57.81% of patients to the surgery treated group (group A). Recurrence of the disease was registered in 31.54% (41 patients) of all patients included in the study. During follow-up, local or distant recurrence of the disease was noted in 31.54% (41 patients) of all patients included in the study; those patients from group a - 33.93% (19 patients) had a higher recurrence compared to group B - 29.73% (22 patients). Statistical analysis of disease-free survival (DFS) in patients included in the study revealed a similar survival rate for the two groups of patients.

Following statistical analysis, both overall and disease-free survival were influenced by tumour stage, tumour differentiation, number of resected lymph nodes, and the presence of perivascular and perineural invasion.

CONCLUSIONS

Our study suggests that resection of ≥ 12 lymph nodes for stage II colon cancer patients would be

Conflict of interest: none declared

Financial support: none declared

REFERENCES

- West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol*. 2010 Jan 10;28(2):272-8. doi: 10.1200/JCO.2009.24.1448. Pub 2009 Nov 30. PMID: 19949013.
- Miller KD, Sauer AG, Fedewa SA. Colorectal Cancer Statistics. *A Cancer Journal for Clinicians*. 2020;70(3):145-164. <https://doi.org/10.3322/caac.21601>.
- Wu W, Li D, Ma W, et al. Examining More Lymph Nodes May Improve the Prognosis of Patients With Right Colon Cancer : Determining the Optimal Minimum Lymph Node Count. 2021;28:1-14. doi:10.1177/10732748211064034
- Foo CC, Ku C, Wei R, et al. How does lymph node yield affect survival outcomes of stage I and II colon cancer?. *World J Surg Onc*. 2020 Jan 29;18(1):22. doi.org/10.1186/s12957-020-1802-6
- Wu Q, Zhang Z, Chen Y, Chang J, Jiang Y. Impact of Inadequate Number of Lymph Nodes Examined on Survival in Stage II Colon Cancer. *Front Oncol*. 2021;11:1-6. doi:10.3389/fonc.2021.736678
- Bui L, Rempel E, Reeson D, Simunovic M. Lymph node counts, rates of positive lymph nodes, and patient survival for colon cancer surgery in Ontario, Canada: a population-based study. *J Surg Oncol*. 2006 May 1;93(6):439-45. doi: 10.1002/jso.20499. PMID: 16615148.
- Swanson RS, Bland KI. The Prognosis of T3N0 Colon Cancer Is Dependent on the Number of Lymph Nodes Examined. *Annals of Surgical Oncology*. 2003;10(1):65-71.
- Tang X, Huang M, Han S, et al. *The Circumferential Resection Margin Is a Prognostic Predictor in Colon Cancer*. 2020;10:1-10. doi:10.3389/fonc.2020.00927
- Lykke J, Rosenberg J, Jess P, Roikjaer O, Colorectal D, Group C. Lymph node yield and tumour subsite are associated with survival in stage I–III colon cancer : results from a national cohort study. 2019:1-8. doi:10.1111/codi.13798/abstract
- Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature. *Acta Oncol*. 2015 Jan;54(1):5-16. doi: 10.3109/0284186X.2014.975839. Epub 2014 Nov 28. PMID: 25430983.
- Lei P, Ruan Y, Liu J, Zhang Q, Tang X, Wu J. Prognostic Impact of the Number of Examined Lymph Nodes in Stage II Colorectal Adenocarcinoma: A Retrospective Study. *Gastroenterol Res Pract*. 2020 Jun 24;2020:8065972. <https://doi.org/10.1155/2020/8065972>
- Vergara-Fernandez O, Navarro-Navarro A, Rangel-Ríos HA, Salgado-Nesme N, Reyes-Monroy JA, Velázquez-Fernández D. Oncological Implications of Lymph Nodes Retrieval and Perineural Invasion in Colorectal Cancer: Outcomes from a Referral Center. *Rev Invest Clin*. 2018;70(6):291-300. doi:10.24875/RIC.18002505
- Kim HJ, Choi GS. Coloproctology Clinical Implications of Lymph Node Metastasis in Colorectal Cancer : Current Status and Future Perspectives. 2019;35(3):109-117.

beneficial for their survival, especially if combined with adjuvant chemotherapy. The survival of those patients also depends on the size of the tumor, the degree of differentiation and the presence of perineural and lymphovascular invasion.

Conflicts of Interest: We undersign and certificate that we do not have any financial or personal relationships that might bias the content of this work.

Statement on human and animal rights: We undersign and certificate that the research conducted complied with the ethical standards in accordance with the Helsinki Declaration (of 1975, revised in 2013) as well as national regulations in the field

Statement on informed consent: We understand and certificate that we have obtained the written consent of the identified persons or their legal guardians for the presentation of the cases within the present scientific paper

Funding: No external funding was received.

Declaration of Originality and Transfer of Copyright: We warrant that the information provided by us in this article is true, complete and accurate