Research Article

Advances in Hematology and Oncology Research

Factors Associated with Lymphovascular Invasion in Colorectal Adenocarcinoma at Dr. Cipto Mangunkusumo General Hospital, Jakarta: A Preliminary Report

Febiansyah Ibrahim*, Wifanto Saditya Jeo, Ridho Ardhi Syaiful

Division of Digestive Surgery, Department of Surgery, Dr. Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universities Indonesia, Jakarta, Indonesia, 10430.

***Corresponding author**
Febiansyah Ibrahim, Division of Digestive Surgery, Department of Surgery, Dr. Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universities Indonesia, Jakarta, Indonesia.

Submitted: 23 Jun 2020; **Accepted:** 01 July 2020; **Published:** 11 July 2020

Abstract

Background: *Lymph node metastasis is a prognostic factor in colorectal adenocarcinoma. Besides, lymphovascular invasion is one of the factors to indicate the lymph node metastasis. This study aimed to investigate factors associated with lymphovascular invasion in our hospital.*

Methods: *This preliminary report was a cross−sectional study of patients with colorectal adenocarcinoma in Cipto Manungkusumo General Hospital, Jakarta, Indonesia between 2012 and 2016. Our focus of interest was the association between lymphovascular invasion and variables of patient's characteristics, including age, gender, location of the tumor, tumor differentiation, pathological stage of tumor infiltration, and lymph node metastasis.*

Results: *We found 70% of the 68 subjects had lymphovascular invasions. Among all the variables analyzed for association with lymphovascular invasion, there is no factor with significant association. However, lymph node metastasis was found to have significant association with lymphovascular invasion (odd ratio [OR] = 6.69, 95% confidence interval [CI] = 2.09–21.38, p−value =0.001).*

Conclusion: *Although lymphovascular invasion was significantly associated with lymph node metastasis in colorectal adenocarcinoma, there is no factor significantly associated with lymphovascular invasion in this study.*

Keywords: Lymphovascular Invasion, Colorectal Adenocarcinoma, Gastrointestinal Malignancies, Lymph Node Metastasis.

Background

Colorectal cancer is the third most commonly diagnosed cancer, 95% of which comprised of adenocarcinoma [1-3]. In recent years, lymph node metastasis has been identified as a prognostic factor associated with metastasis as well as survival [4-6]. However, lymph node involvement is difficult to assess before surgery. Thus, factors that can predict lymph node involvement before surgery may lead to better management [6].

A previous study had shown that tumor size and colloid histologic characteristics were not correlated with lymph node metastasis [7]. On the other hand, identification of lymphovascular invasion has the potential to be an indicator for lymph node metastasis; thus it may serve as a prognostic factor [8,9]. Any information regarding lymphovascular invasion may help surgeons in deciding treatment modality for local non-metastatic diseases. We investigated the factors associated with lymphovascular invasion in colorectal carcinoma in dr. Cipto Mangunkusumo General Hospital, Indonesia.

Methods

This was a cross-sectional study performed in August to October 2017. Data was taken from medical records, retrospectively enrolling patients diagnosed with colorectal adenocarcinoma in the Division of Digestive Surgery, Department of Surgery, dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia from January 2012 to December 2016, using the total sampling method. We excluded patients who had received chemotherapy or radiotherapy (neo-adjuvants), subjects with signet ring cell or mucinous adenocarcinoma, and subjects with incomplete data. Due to the study being a preliminary study, the small sample size was deemed sufficient. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Universities Indonesia (approval number 843/UN2.F1/ETIK/2017 and protocol number 17-09-0901).

We collected data on the presence of lymphovascular invasion, which was defined as the presence of tumor spread in the blood vessels or lymphatic vessels. Hence, subjects were categorized into two groups: negative lymphovascular invasion group and positive lymphovascular invasion group. Besides, we recorded baseline characteristics data such as age, gender, and the location of the tumor, tumor differentiation, pathological staging of tumor infiltration (pT), and lymph node metastasis. We categorized the patients by age with a cut-off of 50 years old. The location of the tumor, based on colonoscopy/rectoscope investigation or the intestine resected part, was classified into two areas, the right colon

(the cecum, ascending, and transverse colon) and the left colon (the descending colon, sigmoid, and rectum). The differentiation of colorectal adenocarcinoma was determined based on the Borders criteria (well–, moderate–, and poorly differentiated).

Statistical analysis was performed using IBM© SPSS® version 20 to investigate odd ratios (OR). Categorical data were analyzed using the Chi–Square test. Differences with p-values of less than 0.05 were considered statistically significant.

Results

From 183 included subjects, complete data eligible for this lymphovascular invasion study were only available on 68 subjects. Eighteen subjects were predominantly males and aged over 50 years. Seventy-two percent showed a well-differentiated colorectal adenocarcinoma. Seventy-two percent showed positive lymphovascular invasion, and sixty-seven percent showed positive lymph node metastasis. Detailed baseline characteristics of the study subjects are shown in Table 1.

Table 1: Subjects baseline characteristics

Variables	**n**	**%**
Age (yrs)		
<50	25	36.76
≥50	43	63.24
Gender		
Females	27	39.71
Males	41	60.29
Tumor differentiation		
Well–differentiated	49	72.06
Moderately–differentiated	14	20.59
Poorly–differentiated	5	7.35
Tumor location		
Right colon	35	51.47
Left colon	33	48.53
pT		
T1	1	1.47
T2	8	11.76
T3	44	64.71
T4	15	22.06
Lymph node metastasis		
Negative	19	32.40
Positive	49	67.60
Lymphovascular invasion		
Negative	22	27.94
Positive	46	72.06

pT: pathological staging of tumor infiltration

Bivariate analysis showed no significant associations between identified factors (tumor differentiation, age, location of the tumor, gender, and pT staging) with lymphovascular invasion. Further details of associations between factors and lymphovascular invasion are shown in Table 2.

Table 2. Bivariate analysis of identified factors with lymphovascular invasion.

Variable		Lymphovascular invasion				Crude OR	p–value	95% CI
		Negative		Positive				
		n	%	n	%			
Age (yrs)	<50	6	24.0	19	76.0	1.00	0.74	0.23–2.80
	> 50	13	30.2	30	69.8	0.81		
Gender	Females	4	14.8	23	23.0	1.00	0.06	0.08–1.04
	Males	15	36.6	26	63.4	0.29		
Tumor differentiation	Well	16	32.7	33	67.3	1.00	0.17	0.58–18.67
	Moderate	2	14.3	12	85.7	3.31		
	Poor	1	20.0	4	80.0	1.28	0.84	0.12–14.02
Location	Right colon	8	22.9	27	77.1	1.00	0.78	0.25–2.79
	Left colon	11	33.3	22	66.7	0.84		
pT	T1 and T2	4	44.4	5	55.6	1.00	0.26	0.52–11.24
	T3 and T4	15	25.4	54	72.1	2.43		

pT: pathological staging of tumor infiltration, OR = odds ratio, CI confidence interval

However, we found a statistically significant association between lymphovascular invasion and the presence of lymph node metastasis in the bivariate analysis. The detailed analysis is provided in Table 3.

Table 3. Bivariate analysis between lymphovascular invasion and lymph node metastasis.

Variable		Lymph node metastasis				Crude OR	p–value	95% CI
		Positive		Negative				
		n	%	n	%			
Lymphovascular Invasion	Positive	39	57.4	10	14.7	6.69	0.001	2.09– 21.38
	Negtive	7	10.3	12	17.6			

OR = odds ratio, CI confidence interval

Discussion

In this study, we found more than 70% of subjects had positive lymphovascular invasion and it was associated with lymph node metastasis. As expected, we found that subjects with positive lymphovascular invasion were significantly more likely to have lymph node metastasis (OR = 6.69). This finding is in line with a meta-analysis by Choi et al., which showed that lymphatic invasion (OR = 6.91) and vascular invasion (OR = 2.70) were associated with the presence of lymph node metastasis [10]. Another study also showed that lymphovascular invasion was a risk factor for lymph node metastasis [11]. Furthermore, Lim et al. reported that lymphovascular invasion was a prognostic factor for 5–year overall (p <0.001) and 5–year disease–free survival (p <0.001) of colorectal cancer patients [12]. In the study, we found lymphovascular invasion denoting those with aggressive and sporadic primary colorectal cancer and indicates a poor prognosis. Most subjects with moderately and poorly differentiated tumors had positive lymphovascular invasion, showing a higher likelihood of lymphovascular invasion for patients with worse degrees of tumor differentiation. A study by Okabe et al showed that subjects with lymphovascular invasion with moderate and poor colorectal adenocarcinoma differentiation, males gender, and pT2–3 had a risk of lymph node metastasis [13].

We found no significant association between gender and lymphovascular invasion. Colorectal adenocarcinoma is mostly found in

males with a ratio of 1.5: 1 to females. A previous study showed a ratio of 19.4 and 15.3 per 100.00 population for colorectal adenocarcinoma cases [14]. Seventy–two percent of our subjects were over 50 years old, but no association was seen between age and lymphovascular invasion. Like cancers in general, the incidence of colorectal adenocarcinoma increases sharply after 50 years of age [15]. The phenomenon is a natural one following long–term exposure to a carcinogen and the aging process. We also found that lymphovascular invasion was not significantly associated with the location of the tumor, in contrast with a study by Nascimbeni et al, which describe colorectal adenocarcinoma T1 pT3 invasion, and the lower 1/3 location showing a high risk of lymph node metastases [16]. Tumor size was not associated with lymphovascular invasion, although we observe a tendency for subjects with pT3 and pT4 tumors to have a positive lymphovascular invasion. A study of Aktekin et al showed that lymphovascular invasion was influenced by pT [6].

Nevertheless, the total of subjects observed in the research is considered less than enough. Hence, this might be the cause of the analysis results in this study. We suggest any further research to conduct with more subjects in a multi-centered study design.

Age above 50, male gender, pT3-4 stage, and moderate tumor differentiation is more associated with lymphovascular invasion in this study. However, in this preliminary study we concluded that although lymphovascular invasion is significantly associated with lymph node metastasis in colorectal adenocarcinoma, there is no factor proven significantly associated with lymphovascular invasion.

Acknowledgment

The authors would like to thank Dr. Cita Resti A. Putri and Dr. Kevin Varian M. for assisting the publication of this study.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66: 7-30.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.
3. Thrumurthy SG, Thrumurthy SS, Gilbert CE, Ross P, Haji A (2016) Colorectal adenocarcinoma: Risks, prevention, and diagnosis. BMJ 354: 1-12.
4. Kim HJ, Choi GS (2019) Coloproctology Clinical Implications of Lymph Node Metastasis in Colorectal Cancer: Current Status and Future Perspectives. Ann Coloproctol 35: 109-117.
5. Fortea-sanchis C, Martínez-ramos D, Escrig-sos J (2018) The lymph node status as a prognostic factor in colon cancer: Comparative population study of classifications using the logarithm of the ratio between metastatic and nonmetastatic nodes (LODDS) versus the pN–TNM classification and ganglion ratio systems. BMC Cancer 18: 1208.
6. Aktekin A, Özkara S, Gürleyik G, Odabaşi M, Müftüoğlu T, et al. (2015) The Factors Effecting Lymphovascular Invasion in Adenocarcinoma of the Colon and Rectum. Indian J Surg 77: 314-318.
7. Brodsky JT, Richard GK, Cohen AM, Minsky BD (1992) Variables correlated with the risk of lymph node metastasis in early rectal cancer. Cancer 69: 322-326.
8. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, et al. (2000) Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 124: 979-994.
9. Ross A, Rusnak C, Weinerman B, Kuechler P, Hayashi A, et al. (1999) Recurrence and survival after surgical management of rectal cancer. Am J Surg 177: 392-395.
10. Choi JY, Jung SA, Shim KN, Cho WY, Keum B, et al. (2015) Meta-analysis of Predictive Clinicopathologic Factors for Lymph Node Metastasis in Patients with Early Colorectal Carcinoma. J Korean Med Sci 30: 398-406.
11. Choi PW, Yu CS, Jang SJ, Jung SH, Kim HC, et al. (2008) Risk factors for lymph node metastasis in submucosal invasive colorectal cancer. World J Surg 32: 2089-2094.
12. Lim SB, Yu CS, Jang SJ, Kim TW, Kim JH, et al. (2010) Prognostic significance of lymphovascular invasion in sporadic colorectal cancer. Dis Colon Rectum 53: 377-384.
13. Okabe S, Shia J, Nash G, Wong WD, Guillem JG, et al. (2004) Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. J Gastrointest Surg 8: 1032-1040.
14. Boyle P, Langman JS (2000) ABC of Colorectal Cancer-Epidemiology. BMJ 321: 805-808.
15. American Cancer Society (2002) Cancer Facts & Figures, 2002. New York: American Cancer Society Inc. Surv Res 02-250M No 508.02: 20-26.
16. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR (2002) Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Col Rectum 45: 200-206.