Impact of Lymphovascular Invasion in Patients With Stage II Colorectal Cancer: A Propensity Score-matched Study

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Abstract. *Background/Aim:* Whether lymphovascular invasion (LVI) is a high-degree risk factor in stage II colorectal cancer has not been fully clarified, as different results have been reported in the literature. If LVI is a risk factor, postoperative chemotherapy may be recommended. The purpose of this study was to evaluate the impact of lymphovascular invasion on disease recurrence and patient prognosis in conjunction with stage II colorectal cancer (CRC). *Patients and Methods:* A total of 636 patients with stage II CRC, each undergoing radical resection between April 2007 and December 2015, were selected for the study. Subjects with or without venous or lymphatic invasion were assigned to positive and negative groups, respectively. We then compared overall survival (OS) and disease-free survival (DFS) using propensity score matching. *Results:* After matching ($n=226$, each group), OS and DFS were found to be significantly lower (OS: $p=0.047$; DFS: $p=0.004$) in patients positive (vs. negative) for venous invasion. However, the same was not true of lymphatic invasion. After matching, positive and negative groups ($n=92$, each) did not significantly differ in terms of OS ($p=0.951$) or DFS ($p=0.258$). *Conclusion:* In patients with stage II CRC, venous invasion proved to be a significant high-degree risk factor that may warrant adjuvant chemotherapy.

The Union for International Cancer Control (UICC) stipulates that infiltration of colorectal cancer (CRC) beyond

muscularis propria in the absence of lymph node metastasis qualifies as stage II disease. This is insufficient basis for routine postoperative adjuvant chemotherapy in Japan (1). Although both the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) guidelines advise such treatment if there are high-degree risk factors for recurrence (2, 3), the definitions of high recurrence risk patently differ. Lymphovascular invasion (LVI), signified by tumor cells within endothelial-lined spaces, is considered a high-risk factor for stage II CRC recurrence by ESMO, but not by ASCO guidelines.

LVI encompasses lymphatic as well as venous invasion. At present, it is unclear whether the full spectrum of LVI carries a poor prognosis in the setting of stage II CRC (4-7). It would be of immense value to determine whether each component separately confers an ominous prognosis, thus allowing more selective administration of adjuvant chemotherapy. This study was conducted to evaluate the respective effects of venous and lymphatic invasion on overall survival (OS) and disease-free survival (DFS) rates in patients with radically resected stage II CRC, using propensity score matching.

Patients and Methods

As a retrospective effort, we reviewed data on 652 patients undergoing surgical resections for stage II CRC between April 2007 and December 2015 at the Saitama Medical University International Medical Center. Those with recurrent CRC, synchronous malignancy, or squamous cell carcinoma were excluded, leaving 636 for analysis. Written informed consent was granted by all subjects, and the Ethics Committee at the center approved our study protocol. Two pathologists evaluated all CRC specimens. Resected tumors were classified using the UICC (8th edition) TNM system and discretionary immunohistochemistry.

All statistical computations were powered by the EZR freeware (R Foundation for Statistical Computing, Vienna, Austria). We used propensity score matching to overcome bias in differing group distributions. A 1:1 match without replacement was performed through nearest available matching, with caliper set at 0.2. Each patient was propensity scored, based on a logistic regression model

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Key Words: Lymphovascular invasion, high-risk factor, stage II colorectal cancer, adjuvant chemotherapy.

Figure 1. Algorithm for analysis of venous invasion.

Figure 2. Overall survival in patients with stage II CRC, positive (+) or negative (-) for venous invasion.

Figure 3. Disease-free survival in patients with stage II CRC, positive (+) or negative (-) for venous invasion.

addressing the following eight covariates: sex, age, American Society of Anesthesiologists physical status (ASA-PS), tumor location, tumor histotype, lymphatic or venous invasion, infiltrative depth, and adjuvant chemotherapy. After matching, logistic regression analysis was invoked to determine survival differences of groups positive and negative for venous or lymphatic invasion. Differences in categorical variables were tested by Chi-squared or Fisher's exact test, and survival rates (OS, DFS) were estimated via Kaplan-Meier method. Significance was set at $p<0.05$.

Results

A total of 636 patients with stage II CRC patients were selected for the study. Venous invasion was detected in 390 (61.3%) patients, and lymphatic invasion was evident in 94 (17.3%).

Initially, a single-factor analysis of patients with (n=390) and without (n=246) venous invasion was performed. In

Table I. Clinicopathologic parameters of stage II CRC pertaining to venous invasion.

Variable	Before PSM			After PSM		
	Venous invasion (+)	Venous invasion (–)	<i>p</i> -Value	Venous invasion (+)	Venous invasion (–)	<i>p</i> -Value
Gender, n	390	246		226	226	
Male	237 (60.8%)	143 (58.1%)		141 (62.4)	137 (60.6)	
Female	153 (39.2%)	103 (41.9%)	0.561	85 (37.6)	89 (39.4)	0.772
Age, years	67.96±10.48	68.35±10.89	0.654	69.01±10.58	68.35±10.91	0.509
ASA-PS						
1	130 (33.3%)	86 (35.0%)		78 (34.5%)	80 (35.4%)	
2	229 (58.7%)	138 (56.1%)		132 (58.4%)	125 (55.3%)	
3	30 (7.7%)	22 (8.9%)		15 (6.6%)	21 (9.3%)	
4	1 (0.3%)	0 (0.0%)	0.838	1 (0.4%)	0 (0.0%)	0.550
Tumor location						
Colon	236 (60.5%)	162 (65.9%)		148 (65.5%)	147 (65.0%)	
Rectum	154 (39.5%)	84 (34.1%)	0.180	78 (34.5%)	79 (35.0%)	1.000
Tumor histotype						
Well-, moderately differentiated	368 (94.4%)	207 (84.1%)		205 (90.7%)	207 (91.6%)	
Other	22 (5.6%)	39 (15.9%)	<0.001	21 (9.3%)	19 (8.4%)	0.869
Lymphatic invasion						
No	327 (83.8%)	215 (87.4%)		188 (83.2%)	199 (88.1%)	
Yes	63 (16.2%)	31 (12.6%)	0.252	38 (16.8%)	27 (11.9%)	0.180
Infiltrative depth						
T3	351 (90.0%)	222 (90.2%)		210 (92.9%)	206 (91.2%)	
T4	39 (10.0%)	24 (9.8%)	1.000	16 (7.1%)	20 (8.8)	0.603
Adjuvant chemotherapy						
No	382 (97.9%)	237 (96.3%)		222 (98.2%)	222 (98.2%)	
Yes	8 (2.1%)	9 (3.7%)	0.312	4 (1.8%)	4 (1.8%)	1.000

CRC, Colorectal cancer; PSM, propensity score matching; ASA-PS, American Society of Anesthesiologists physical status.

patients positive (*vs.* negative) for venous invasion, the percentage of well- or moderately differentiated tubular adenocarcinoma was significantly greater (94.4% *vs.* 84.1%; $p<0.001$). Otherwise, no significant differences were observed with respect to male sex (60.8% *vs.* 58.1%; $p=0.561$), age (67.96±10.48 *vs.* 68.35±10.89; $p=0.654$), ASA-PS ($p=0.838$), tumor location (colon: 60.5% *vs.* 65.9%; $p=0.180$), incidence of lymphatic invasion (16.2% *vs.* 12.6%; $p=0.252$), deep infiltration (T4: 10.0% *vs.* 9.8%; $p=1.000$), or adjuvant chemotherapy (2.1% *vs.* 3.7%; $p=0.312$).

The two groups were then matched by propensity scores (1:1 ratio), each yielding 229 patients (Figure 1) with similarities of gender, age, ASA-PS, tumor location, tumor histotype, lymphatic invasion, infiltrative depth, and adjuvant chemotherapy (Table I).

Five-year OS rates in groups positive and negative for venous invasion were 86.3% (95% CI=81.0-90.3) and 91.8% (95% CI=86.5-95.1), respectively ($p=0.047$) (Figure 2). Corresponding 5-year DFS rates were 79.3% (95% CI=73.4-84.1) and 88.0% (95% CI=82.4-92.0), respectively ($p=0.004$) (Figure 3). Patient prognosis was thus poorer in the in the presence of venous invasion.

We then subjected patients with (n=94) and without (n=542) lymphatic invasion to single-factor analysis. In those showing lymphatic invasion, tumors more often involved the colon rather than rectum (72.3% *vs.* 60.9%; $p<0.038$). No significant differences were encountered with respect to male sex (57.4% *vs.* 60.1%; $p=0.649$), age (69.69±10.05 *vs.* 67.83±10.72; $p=0.118$), ASA-PS ($p=0.359$), tumor histotype (well- or moderately differentiated: 88.3% *vs.* 90.8%; $p=0.449$), incidence of venous invasion (67.0% *vs.* 60.3%; $p=0.252$), deep infiltration (T4: 14.9% *vs.* 9.0%; $p=0.092$), or adjuvant chemotherapy (5.3% *vs.* 2.2%; $p=0.091$). The two groups were also matched by propensity scores (1:1 ratio), each comprised of 92 patients (Figure 4). All paired covariates were well balanced, showing no significant differences (Table II).

Five-year OS rates in groups positive and negative for lymphatic invasion were 82.6% (95% CI=71.0-89.9) and 84.7% (95% CI=74.5-91.1), respectively ($p=0.951$) (Figure 5). Corresponding 5-year DFS rates were 70.3% (95% CI=58.2-79.5) and 78.3% (95% CI=67.5-85.8), respectively ($p=0.258$) (Figure 6). On the basis of lymphatic invasion, OS and DFS did not differ significantly.

Figure 4. Disease-free survival in patients with stage II CRC, positive (+) or negative (-) for venous invasion.

Table II. Clinicopathological parameters of stage II CRC pertaining to lymphatic invasion.

Variable	Before PSM			After PSM		
	Lymphatic invasion (+)	Lymphatic invasion (-)	p-Value	Lymphatic invasion (+)	Lymphatic invasion (-)	p-Value
Gender, n	94	542		92	92	
Male	54 (57.4%)	326 (60.1%)	0.649	54 (58.7%)	56 (60.9%)	0.881
Female	40 (42.6%)	216 (39.9%)		38 (41.3%)	36 (39.1%)	
Age, yr	69.69±10.05	67.83±10.72	0.118	69.46±9.93	70.21±9.89	0.608
ASA-PS						
1	25 (26.6%)	191 (35.2%)	0.359	24 (26.1%)	26 (28.3%)	0.898
2	61 (64.9%)	306 (56.5%)		60 (65.2%)	57 (62.0%)	
3	8 (8.5%)	44 (8.1%)		8 (8.7%)	9 (9.8%)	
4	0 (0.0%)	1 (0.2%)		0 (0.0%)	0 (0.0%)	
Tumor location						
Colon	68 (72.3%)	330 (60.9%)	0.038	66 (71.7%)	69 (75.0%)	0.739
Rectum	26 (27.7%)	212 (39.1%)		26 (28.3%)	23 (25.0%)	
Tumor histotype						
Well-, moderately differentiated	83 (88.3%)	492 (90.8%)	0.449	81 (88.0%)	82 (89.1%)	1.000
Other	11 (11.7%)	50 (9.2%)		11 (12.0%)	10 (10.9%)	
Venous invasion						
No	31 (33.0%)	215 (39.7%)	0.252	31 (33.7%)	29 (31.5%)	0.875
Yes	63 (67.0%)	327 (60.3%)		61 (66.3%)	63 (68.5%)	
Infiltrative depth						
T3	80 (85.1%)	493 (91.0%)	0.092	80 (87.0%)	82 (89.1%)	0.821
T4	14 (14.9%)	49 (9.0%)		12 (13.0%)	10 (10.9%)	
Adjuvant chemotherapy						
No	89 (94.7%)	530 (97.8%)	0.091	88 (95.7%)	90 (97.8%)	0.682
Yes	5 (5.3%)	12 (2.2%)		4 (4.3%)	2 (2.2%)	

CRC, Colorectal cancer; PSM, propensity score matching; ASA-PS, American Society of Anesthesiologists physical status.

Figure 5. Overall survival in patients with stage II CRC, positive (+) or negative (-) for lymphatic invasion.

Figure 6. Disease-free survival in patients with stage II CRC, positive (+) or negative (-) for lymphatic invasion.

Discussion

In early-stage CRC, particularly at stage II, postoperative administration of adjuvant chemotherapy is controversial (4, 5). Results from clinical trials have shown no significant differences in recurrence or survival rates recorded for surgically treated stage II CRC, with or without adjuvant chemotherapy (4, 6, 7). Thus, adjuvant chemotherapy is not routinely given in this setting unless the risk of recurrence is heightened.

ASCO and ESMO guidelines suggest that patients with stage II CRC be stratified, reserving adjuvant chemotherapy to those at high risk (2, 3). High-degree risk factors for recurrence of stage II CRC are stipulated by ASCO as <12 dissected lymph nodes, T4 staging, instances of perforation, poorly differentiated adenocarcinoma, and signet ring cell or mucinous carcinoma. However, ESMO guidelines specify T4 staging; poorly differentiated adenocarcinoma or undifferentiated carcinoma; venous, lymphatic, or perineural invasion; initial symptoms of intestinal obstruction or bowel perforation; and <12 dissected lymph nodes as high-degree risk factors. In Japan, patients with these risk factors generally receive adjuvant chemotherapy postoperatively.

LVI is marked by freely existing malignant cells that seed lymphatic vessels or small veins, having escaped the primary tumor (8). While linked to tumor metastasis/recurrence (and perhaps worse prognosis) and cited as a prognostic factor in various cancers, including those of breast (9) and prostate (10), the impact of LVI on CRC recurrence or prognosis remains unclear. Some researchers have determined that vascular invasion confers a poor prognosis (11, 12), whereas

others have failed to identify any bearing on prognosis (13, 14). Such differences may be due to disparate population samplings or methods of analysis. Herein, we used propensity score matching to minimize the potential for confounding in group analyses. Because venous and lymphatic invasion are seldom differentiated, the potential differences are not fully appreciated. A previous study suggested that in CRC, positive venous invasion significantly worsened 5-year DFS, but lymphatic invasion did not affect prognosis (15). In this study, we focused on lymphatic invasion and venous invasion respectively limited in stage II CRC patients to explore the possibility of omitting postoperative adjuvant chemotherapy.

Our data have shown that OS and DFS in patients with stage II CRC are significantly influenced by venous invasion. Recurrent disease, and thus a poorer prognosis, is therefore more likely in the presence (vs. absence) of venous invasion. Postoperative adjuvant chemotherapy may then be appropriate under these circumstances to improve patient outcomes. On the other hand, lymphatic invasion had no significant impact on disease recurrence or prognosis in this clinical context.

By immunohistochemical means, Liang P. *et al.* have established distinct associations linking lymphatic invasion to nodal metastasis and venous invasion to distant metastasis (16). In patients with venous invasion, elimination of intravascular cancer cells with adjuvant chemotherapy may reduce postoperative distant metastases. We routinely performed D3 nodal dissections for stage II CRC, so any potential lymphatic spread (including lymphatic seeding) is apt to be resected and controlled. Ultimately, lymphatic

invasion had no significant impact on recurrence or prognosis of stage II CRC in our patients. For patients with stage II CRC who have had adequate lymph node dissection, a lymphatic invasion result alone suggests that there is little need for adjuvant chemotherapy, which may be omitted.

The incidence of LVI in previously published studies of stage II CRC ranges from 5.2-30.3% (12, 14, 17-19). We documented venous invasion in 61.3% of our cohort and lymphatic invasion in only 14.8%. This sizeable disparity, relative to other reported data, may be explained by differences in targeted groups and tumors, criteria for determining vascular invasion, and immunohistochemical support. In addition to routine histopathological assessments by hematoxylin and eosin (H&E) stain, immunohistochemistry was an added discretionary measure, enabling more accurate diagnosis of vascular invasion (16, 20). This helped distinguish between venous and lymphatic invasion, which is often difficult in H&E-stained sections (21), no doubt bolstering the diagnostic rate at our institution.

There were certain limitations to this study, the first being the ability to discern venous and lymphatic invasion in histological preparations. The retrospective nature of this study was yet another issue. Although propensity score matching served to minimize bias, complete randomization was lacking. The premise that adjuvant chemotherapy may benefit patients with proven vascular invasion of stage II CRC must be fully tested in randomized, controlled clinical trials.

Conclusion

In patients with stage II CRC, venous invasion bodes poorly for prognosis, so adjuvant chemotherapy should be considered. After curative lymph node dissection, lymphatic invasion assumes no prognostic influence, so adjuvant chemotherapy may not be necessary with lymphatic invasion alone.

Conflicts of Interest

The Authors have no competing interests to declare with regard to this study.

Author's Contributions

MK drafted the manuscript. YH and SY supervised and reviewed its content. TI, HK, MA, SI, AK, TF, and SS reviewed the content as well. All authors have read and approved the final deliverable.

Consent for Publication

All patients have agreed to the use of their personal medical data for research and publication.

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