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ASSOCIATION BETWEEN TUMOR GRADE AND LYMPHOVASCULAR INVASION IN COLORECTAL CANCER PATIENTS

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ABSTRACT

Background: Colorectal cancer (CRC) is the third most common malignant tumor with high post-operative recurrence and metastasis rate. Lymphovascular invasion (LVI) is one of the most important predictors of CRC metastasis. Several factors have been linked to the development of LVI including matrix remodeling, epithelial mesenchymal transition, and tumor aggressiveness. **Purpose:** In this retrospective study, we aim to investigate the effect of CRC grade on the presence of LVI and surgical outcomes in a population of CRC Jordanian patients who underwent surgical resection. **Methods:** We will collect patients' data retrospectively using hospital records from King Hussein Medical Center (KHMC), Amman, Jordan between the period 2016 to 2024. Demographic variables will include patients' hospital ID, national number, age, and sex. Clinical data will include tumor site, mode of surgery (laparoscopic or open), tumor grade, presence of LVI, perineural invasion, lymph node ratio (LNR), and post-operative outcomes. Continuous data will be described using mean (standard deviation, (SD)) and analyzed using the student's t-test for normally distributed variables, and as median (range) with the Mann-Whitney U test for non-normally distributed variables. Categorical variables will be presented as frequencies and percentages and analyzed with the Chi-square test. A logistic regression model will be developed to evaluate the association between Lymphovascular invasion and tumor grade adjusted for age and sex. All analyses will be performed using R statistical software.

KEYWORDS: Colorectal cancer, Lymphovascular invasion, Tumor grade, Jordan, Metastasis.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths worldwide, with many patients presenting at late stages. The first line management for non-metastatic CRC is surgery with adjuvant chemotherapy, showing a 30% reduction in cancer recurrence.[1,2] In Jordan and the middle east, the incidence of CRC is increasing, in contrast to the western world where CRC incidence is decreasing, which can be attributed to lifestyle and bad dietary habits, in addition to lack of awareness on CRC screening.[3,4]

Histopathological staging determines the use of adjuvant chemotherapy. However, the use of adjuvant chemotherapy in stage III CRC is still controversial, showing a need for robust biomarkers evaluating the prognostic response in those patients.[5] When tumor cells are present inside the lymphatics or blood vessels this is called lymphovascular invasion (LVI). Detecting LVI is done routinely through hematoxylin and eosin (H&E) staining.[6] The importance of LVI presence comes from its strong association with distant metastasis through an unclear mechanism.[7]

Precisely evaluating the pathological stage and tumor grade and differentiation is a crucial step in predicting patients' prognostic and oncological outcomes, in addition to assessing the use of adjuvant or neoadjuvant therapy for a personalized treatment approach.[8] The presence of poorly differentiated CRC clusters has been shown to be an important factor in predicting patients' prognosis with significantly worse outcomes, therefore, it can be useful to stratify patients' risk and guide treatment approach.[9]

In breast and esophageal carcinoma, LVI showed a significant association with lymph node metastasis, and worse recurrence-free survival rates.[10,11] However, in CRC, the association between LVI and tumor grade and histopathological characteristics is not very well

understood. Therefore, in this retrospective observational study, we aim to investigate the clinicopathological characteristics in CRC patients with and without LVI and determine the applicability of using LVI as a diagnostic and prognostic biomarker in CRC.

Methods

Study design

A single-center, retrospective study was carried out at King Hussien Medical Center (KHMC) in Jordan between the period of May 2014 to April 2024. Patients with non-metastatic CRC and who underwent surgical resection followed by adjuvant chemotherapy were included in this study. The primary outcome of this study was the association between lymphovascular invasion and tumor grade.

We collected the data retrospectively through accessing the patients' medical records between the period May 2014 to April 2024 for the following demographic and clinical variables: patient's hospital ID, national ID, age, sex, American Society of Anesthesiologists (ASA) score, surgical approach (laparoscopic, or open resection), tumor grade (poorly differentiated, moderately differentiated, invasive moderately differentiated (IMDA), or well differentiated), presence or absence of LVI, perineural invasion (PNI), post-operative complications, length of hospitalization in days, the number of positive lymph nodes (LNs), the total number of collected LN, and LN ratio (LNR) which was calculated as the ratio between the number of positive LNs and total number of collected LNs.

Ethical approval

This study received ethical approval from the Institutional Review Board at King Hussein Medical Center. As it was a retrospective study utilizing de-identified data from existing medical records, the requirement for informed consent was waived in accordance with the Declaration of Helsinki. All procedures followed relevant ethical standards and institutional guidelines.

Statistical analysis

Continuous data will be summarized as mean (Standard deviation) and analyzed using the Student's t-test for normally distributed variables, while median (Range) and the Wilcoxon rank-sum test will be used for non-normally distributed variables. Categorical data will be reported as frequencies and percentages and analyzed using the Chi-square test. A logistic regression model will be developed to assess the association between lymphovascular invasion and tumor grade. A P-value of <0.05 will be considered statistically significant. All analyses will be conducted using R statistical software.

RESULTS

Baseline demographic characteristics of included patients

We included a total of 591 CRC patients who underwent surgical resection with a mean age of 59.0 (13.0) years, and 325 (55%) were males. Preoperative ASA score showed that the majority (59%) of patients were in good health (ASA score = 1), while 200 (34%) patients had mild systemic diseases (ASA score = 2) as shown in **Table 1**. The majority of the cohort (84%) were non-smokers, while 81 (14%) were current smokers, and 13 (2.2%) were former smokers.

Clinical and Pathological characteristics

Laparoscopic resection was performed in 318 (54%) of patients, 235 (40%) patients underwent open resection, while 38 (6.4%) patients had laparoscopy but converted to open resection. Postoperative complications occurred in 85 (14%) of patients, with a mean of hospitalization period of 4.41 (3.17) days. Histological grade showed moderately differentiated tumors in 413 (70%) of patients, 68 (12%) patients had invasive moderately differentiated tumors, 66 (11%) had well-differentiated tumors, and 44 (7.4%) had poorly differentiated tumors. Pathological assessment showed a mean positive LNs of 2.5 (5.4), with a mean LNR of 0.19 (2.14) (**Table 1**).

Clinical and Pathological characteristics with lymphovascular invasion (LVI)

A total of 220 (37.2%) samples showed LVI, while 371 (62.8%) did not have LVI. There was a significant difference in the ASA score and presence of LVI, in which samples with no LVI had an overall better ASA score compared to samples with LVI (p-value=0.024). Histological grade also differed significantly with the presence of LVI, in which 28 (13%) of samples with LVI exhibited poorly differentiated histology compared to 16 (4.3%) of samples with absence of LVI (p-value<0.001), in addition, 54 (15%) of samples with LVI absence had well-differentiated tumors compared to 12 (5.5%) of samples with LVI (**Table 1**). Perineural invasion was significantly higher in samples with LVI (54% vs. 11%, p-value<0.001), and the number of positive LNs and LNR was also significantly higher in samples with LVI (means: 4.7 (5.9), and 0.21 (0.27) vs. 1.3 (4.6), and 0.19 (2.7), respectively).

Clinical and Pathological characteristics with perineural invasion (PNI)

Perineural invasion was seen in 159 (27%) of samples, while 432 (73%) did not have PNI (**Table 2**). There was a significant difference in tumor grade with the presence of PNI, in which 25 (16%) of samples with PNI had poorly differentiated tumors compared to 19 (4.4%) samples with no PNI (p-value<0.001). While 57 (13%) of samples without PNI had well-differentiated tumors compared to 9 (5.7%) of samples with PNI (**Table 2**). Positive LNs and LNR were significantly higher in samples with PNI (means: 4.9 (6.0), and 0.21 (0.25) vs. 1.7 (4.9), and 0.19 (2.5), respectively). The rate of

postoperative complications was significantly higher in samples with PNI (20% vs. 12%, p-value=0.016).

Association of tumor grade with clinical and pathological characteristics

The multinomial logistic regression model for tumor grade showed a significant association with ASA score in moderately differentiated tumors and ASA scores (2-4) compared to patients with ASA score of 1 (p-value<0.001) as shown in **Table 3**. In addition, males showed a lower risk of having poorly differentiated tumors compared to females (OR: 0.4, 95% CI: 0.2-0.8, p-value=0.015), and patients with high ASA scores with mild to severe systemic diseases were also associated with higher likelihood of having poorly differentiated tumors (p-value<0.001). Samples with LVI had a significantly higher odds of having poorly differentiated tumors (OR: 3.5, 95% CI: 1.6-8.0, p-value=0.002).

DISCUSSION

The occurrence of poor surgical outcomes in colorectal cancer (CRC) surgery is linked to a wide range of clinical and histopathological factors. Poorly differentiated histology in CRC is one of the most important factors associated with worse prognostic outcomes.[12,13] This can be attributed to intracellular and extracellular changes within the tumor and the tumor microenvironment.[14] Previous studies suggest that lymphovascular invasion (LVI) can be used as an early predictor of tumor metastasis, which can guide the treatment approach.[15] In this retrospective study from Jordan, we investigated the association between tumor histological grade and presence or absence of LVI or perineural invasion (PNI), to understand the possible mechanisms driving tumor aggressiveness and metastasis.

In our cohort, the majority of tumor samples showed moderately differentiated histology (70%), and only 7.4% had poorly differentiated tumors. Tumor pathological stage based on the American Joint Committee on Cancer (AJCC TNM) is not solely adequate in the prediction of prognostic outcomes in CRC and treatment response.[16,17] Whereas the histological grade showed to be a significant predictor of CRC prognosis independent of tumor stage, with worse prognostic outcomes in high-grade tumors.[18] In a retrospective study by Ji et al. investigate the prognostic value of poorly differentiated CRC clusters with T1 stage showing to be an independent prognostic predictor for LN metastasis with poorer overall and disease-free survival rates (adjusted HR: 4.3, and 6.6, respectively).[19] Additionally, histological diagnosis of CRC also influence tumor grade, with the majority (70%) of CRC with adenocarcinoma histology having moderately differentiated tumor grade, while only 10-20% of adenocarcinomas having well and poor tumor differentiation.[20]

Our findings showed that LVI was associated with poorly differentiated histology. Similarly, a study by Jiang et al. showed that LVI was present in 12.3% of sample, with a significant association with poor histology and high tumor stage. In addition, they showed a high mortality risk associated with presence of LVI 1.8 times higher than absence of LVI.[21] Additionally, our results showed that presence of PNI was associated with poor tumor differentiation. PNI was shown to be an important factor in cancer metastasis and poorer treatment outcomes.[22] Highly-innervated organs such as the colon, making neuronal invasion in CRC a very crucial marker for oncological outcomes. The presence of PNI in CRC was reported to be between 9-33%, however, the presence of PNI is enough to predict poor outcomes.[23,24]

Our study provides several strong points. First, we presented a large sample of 591 CRC patients from Jordan, adding to the literature valuable clinical and pathological characteristics of CRC in Jordan. In addition, we investigated various clinical and histopathological characteristics in an underrepresented sample of CRC patients. However, our study have some limitations. Our study was limited to a single center, which may reduce the generalizability of the results to other populations or healthcare settings. Additionally, we did not include long-term follow-up data on patient outcomes, which limits the ability to assess the impact of LVI and PNI on survival rates and recurrence. Future study designs should consider prospective multi-center approach to confirm the findings and overcome the limitations associated with retrospective data. Also, exploring the role of molecular markers alongside LVI and PNI is needed to better understand the mechanisms driving tumor aggressiveness and to identify potential therapeutic targets.

In conclusion, our study showed significant associations between presence of LVI and PNI with poorly differentiated tumors in CRC patients. These findings highlight the role of these pathological features in predicting tumor aggressiveness and patient outcomes and suggesting that LVI and PNI are crucial factors linked to poorer histological grades and increased risk of post-operative complications. These results underscore the importance of incorporating LVI and PNI assessment into routine pathological evaluation to better stratify patients' risk and guide personalized treatment strategies. Further prospective, multi-center studies are warranted to validate these findings and explore their implications for long-term patient management and outcomes.

Table 1: Patients' demographics and clinical characteristics based on the presence of LVI.

Characteristic	LVI, N[1] = 220	No LVI, N[1] = 371	p-value[2]	Overall, N[1] = 591
Gender			0.9	
Male	122 (55%)	203 (55%)		325 (55%)
Female	98 (45%)	168 (45%)		266 (45%)
Age	59 (13)	59 (13)	0.9	59 (13)
ASA			**0.024**	
1	129 (59%)	222 (60%)		351 (59%)
2	68 (31%)	132 (36%)		200 (34%)
3	22 (10%)	17 (4.6%)		39 (6.6%)
4	1 (0.5%)	0 (0%)		1 (0.2%)
Smoking			0.8	
Non-Smoker	188 (85%)	309 (83%)		497 (84%)
Smoker	28 (13%)	53 (14%)		81 (14%)
Ex-Smoker	4 (1.8%)	9 (2.4%)		13 (2.2%)
Mode of surgery			0.8	
Laparoscopy	116 (53%)	202 (54%)		318 (54%)
Open	88 (40%)	147 (40%)		235 (40%)
Laparoscopy converted to open	16 (7.3%)	22 (5.9%)		38 (6.4%)
Tumour grade			**<0.001**	
Moderately differentiated	157 (71%)	256 (69%)		413 (70%)
IMDA	23 (10%)	45 (12%)		68 (12%)
Well differentiated	12 (5.5%)	54 (15%)		66 (11%)
Poorly differentiated	28 (13%)	16 (4.3%)		44 (7.4%)
PNI	118 (54%)	41 (11%)	**<0.001**	159 (27%)
Positive LNs	4.7 (5.9)	1.3 (4.6)	**<0.001**	2.5 (5.4)
Total LNs	26 (16)	24 (19)	**0.04**	24 (18)
LNR	0.21 (0.27)	0.19 (2.70)	**<0.001**	0.19 (2.14)
Hospital stay (Days)	4.61 (3.46)	4.29 (2.98)	0.4	4.41 (3.17)
Postoperative complications	32 (15%)	53 (14%)	>0.9	85 (14%)

[1] n (%); Mean (SD)

[2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Table 2: Patients' demographics and clinical characteristics based on the presence of PNI.

Characteristic	PNI, N[1] = 159	No PNI, N[1] = 432	p-value[2]	Overall, N[1] = 591
Gender			0.6	
Male	90 (57%)	235 (54%)		325 (55%)
Female	69 (43%)	197 (46%)		266 (45%)
Age	59 (13)	59 (13)	0.7	59 (13)
ASA			0.3	
1	91 (57%)	260 (60%)		351 (59%)
2	54 (34%)	146 (34%)		200 (34%)
3	13 (8.2%)	26 (6.0%)		39 (6.6%)
4	1 (0.6%)	0 (0%)		1 (0.2%)
Smoking			0.8	
Non-Smoker	137 (86%)	360 (83%)		497 (84%)
Smoker	19 (12%)	62 (14%)		81 (14%)
Ex-Smoker	3 (1.9%)	10 (2.3%)		13 (2.2%)
Mode of surgery			>0.9	
Laparoscopy	86 (54%)	232 (54%)		318 (54%)
Open	62 (39%)	173 (40%)		235 (40%)
Laparoscopy converted to open	11 (6.9%)	27 (6.3%)		38 (6.4%)
Tumour grade			**<0.001**	
Moderately differentiated	107 (67%)	306 (71%)		413 (70%)
IMDA	18 (11%)	50 (12%)		68 (12%)
Well differentiated	9 (5.7%)	57 (13%)		66 (11%)
Poorly differentiated	25 (16%)	19 (4.4%)		44 (7.4%)

LV invasion	118 (74%)	102 (24%)	**<0.001**	220 (37%)
Positive LNs	4.9 (6.0)	1.7 (4.9)	**<0.001**	2.5 (5.4)
Total LNs	25 (15)	24 (19)	0.2	24 (18)
LNR	0.21 (0.25)	0.19 (2.50)	**<0.001**	0.19 (2.14)
Hospital stay (Days)	4.32 (2.69)	4.45 (3.33)	0.8	4.41 (3.17)
Postoperative complications	32 (20%)	53 (12%)	**0.016**	85 (14%)
[1] n (%); Mean (SD) [2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test				

Table 3: Logistic regression model.

Tumour grade	Predictor	Odds ratio	95% CI		p-value
			Lower	Upper	
Moderately differentiated - IMDA					
	Gender:				
	Male – Female	0.79633	0.45821	1.3839	0.419
	Age	0.97807	0.95627	1.0004	0.054
	ASA:				
	2 – 1	12.10099	4.59944	31.8373	**<.001**
	3 – 1	1.96E+07	1.01E+07	3.81E+07	**<.001**
	4 – 1	248230.3822	248230.3366	248230.4277	**<.001**
	Smoking:				
	Non-Smoker – Ex-Smoker	6.78E-06	3.41E-06	1.35E-05	**<.001**
	Smoker – Ex-Smoker	3.62E-05	1.27E-05	1.03E-04	**<.001**
	LV invasion:				
	Yes – No	1.25175	0.70584	2.2199	0.442
	LNR	1.07342	0.77366	1.4893	0.672
Poorly differentiated - IMDA					
	Gender:				
	Male – Female	0.35328	0.15248	0.8185	**0.015**
	Age	0.96635	0.93512	0.9986	**0.041**
	ASA:				
	2 – 1	4.58684	1.31034	16.0563	**0.017**
	3 – 1	2.72E+07	1.13E+07	6.53E+07	**<.001**
	4 – 1	0.01052	0.01052	0.0105	**<.001**
	Smoking:				
	Non-Smoker – Ex-Smoker	26.18722	10.5894	64.7601	**<.001**
	Smoker – Ex-Smoker	142.26804	39.18552	516.5223	**<.001**
	LV invasion:				
	Yes – No	3.5481	1.5676	8.0308	**0.002**
	LNR	1.09512	0.77557	1.5463	0.606
Well differentiated - IMDA					
	Gender:				
	Male – Female	0.50236	0.24332	1.0372	0.063
	Age	1.01144	0.98166	1.0421	0.456
	ASA:				
	2 – 1	4.57709	1.51694	13.8106	**0.007**
	3 – 1	4.81E+06	1.66E+06	1.39E+07	**<.001**
	4 – 1	0.12624	0.12624	0.1262	**<.001**
	Smoking:				
	Non-Smoker – Ex-Smoker	83.28782	35.99679	192.7078	**<.001**
	Smoker – Ex-Smoker	786.63097	246.64058	2508.8665	**<.001**
	LV invasion:				
	Yes – No	0.4508	0.19894	1.0215	0.056
	LNR	1.02879	0.70216	1.5074	0.884

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