sciendo
ПРИЛОЗИ. Одд. за мед. науки, XLIV 3, 2023 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XLIV 3, 2023 MASA

10.2478/prilozi-2023-0049 ISSN 1857-9345

THE INCIDENCE OF LYMPHOVASCULAR AND PERINEURAL INVASION AND THEIR IMPACT ON SURVIVAL IN PATIENTS WITH RECTAL CANCER

Shqipe Misimi[1], Dajana Cako[1], Ali İlbey Demirel[2], Andrej Nikolovski[3], Cemal Ulusoy[2], Mehmet Güray Duman[2]

[1] Medical Faculty in Skopje, Ss. Cyril and Methodius University in Skopje, RN Macedonia

[2] Department of General Surgery, Prof. Dr. Cemil Taşçıoğlu Şehir Hastanesi, Istanbul, Turkey

[3] Department of Visceral Surgery, University Surgery Clinic "St. Naum Ohridski", Skopje, Ss. Cyril and Methodius University in Skopje, RN Macedonia

Corresponding author: Shqipe Misimi, E-mail: misimishqipe99@gmail.com

ABSTRACT

Aim: Lymphovascular Invasion (LVI) and Perineural Invasion (PNI) represent undesirable but still realistic pathological features of rectal cancer, associated with poor prognosis and worse survival. The aim of this study is to assess the incidence of LVI and PNI in patients treated for rectal cancer and the impact of LVI and PNI on patient survival.

Material and Methods: This retrospective single center observational study, conducted in the period of 2016-2019, includes patients with rectal cancer treated with/without long-course neoadjuvant chemoradiotherapy (nCRT). Data collection encompassed demographics, tumor characteristics, type of surgery (abdominal perineal rectal resection - APR and low anterior rectal resection - LAR), and LVI/PNI presence. Survival during follow-up was estimated and compared for patients with/without LVI and PNI involvement.

Results: A total number of 234 patients (77 females and 157 males) with mean age of 61.3 enrolled in the study. Neoadjuvant CRT was conducted in 170 patients. APR procedure was performed in 67 of them and LAR in 167. LVI presence was noted in 55 (24.4%) and PNI in 77 (34.2%) patients. Mean survival during follow-up was 42.07 months. The use of nCRT influenced on survival ($p < 0.033$). Patients treated with LAR had better survival outcomes ($p = 0.001$). Presence of LVI and PNI was associated with a worse prognosis ($p < 0.001$).

Conclusion: PNI was more frequent than the LVI in this study. Patients with nCRT conduction had better overall survival. LVI and PNI presence was associated with poor prognosis in terms of overall survival in patients with rectal cancer.

Keywords: Rectal cancer, lymphovascular invasion, perineural invasion, survival, prognosis

INTRODUCTION

Lymphovascular invasion (LVI) defines the presence of cancer cells in the blood and lymphatic vessels. Perineural invasion (PNI) describes the invasion of cancer cells of the nerve fiber of at least 33% of its circumference [1]. Both PNI and LVI are reliable independent prognostic predictors in rectal cancer, the presence of which has a worsening effect on the outcome [2]. LVI is described to be the main route for lymphatic spread and distant metastasis occurrence [3]. Tumor involvement of the rectal nerves is considered to be another important pathway for metastasis occurrence and decreased survival in patients [4]. This is a retrospective single center observational

study in which LVI and PNI presence are assessed in patients with rectal cancer and their impact on the estimation of survival is observed.

MATERIAL AND METHODS

This retrospective study was conducted in a single center tertiary institution, in the period from 2016-2019. It included patients treated for rectal cancer with low anterior resection (LAR) surgery, abdominal perineal rectal resection (APR) with\ without protective ileostomy and neoadjuvant chemoradiotherapy (nCRT) in part of them. The decision for nCRT conduction was brought by the oncology board of the institution. Data collection encompassed demographics, tumor characteristics, type of surgery and LVI/PNI presence. Survival during follow-up was estimated and compared for patients with/without LVI and PNI involvement. The study was approved by the local ethical committee of the Prof. Dr. Cemil Taşçıoğlu Şehir Hospital, Istanbul, Turkey. IBM SPSS, version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Kaplan–Meier method and the log rank test were used to compare differences between the groups in terms of overall survival. P value of less than 0.05 was considered statistically significant.

RESULTS

This study enrolled a total number of 234 patients operated on for rectal cancer, of whom 157 were male and 77 were female. The mean age of the patients was 61.3 years. In the majority of them (170), a long course nCRT was conducted. Low anterior rectal resection was performed in 167 patients, while in the rest 67, abdominoperineal rectal resection was employed (Table 1).

Table 1. *Patient demographics and treatment features*

Variable	N	%
Mean age (years)	61.3	n.a.
Gender		
Male	157	67.1
Female	77	32.9
nCRT conduction		
Yes	170	72.6
No	64	27.4
Type of surgery		
LAR	167	71.4
APR	67	28.6

Footnote: n.a. – not applicable, nCRT – neoadjuvant chemoradiotherapy, LAR – low anterior rectal resection, APR – abdominoperineal rectal resection

The mean number of harvested lymph nodes in the resected specimens was 18.2. Lymph node metastases were present in 168 patients (71.8%). Data on the LVI and PNI presence was provided in total number of 225 patients. LVI presence was detected in 55 (24.4%) patients, while PNI positivity was noted in 77 (34.2%) of them (Table 2).

Table 2. *Pathology and tumor data*

Variable	N	%
Mean number of harvested lymph nodes (mean)	18.2	n.a.
Metastatic lymph nodes		
Yes	168	71.8
No	66	28.2
LVI		
Yes	55	24.4
No	161	71.6
Missing	9	4
PNI		
Yes	77	34.2
No	139	61.8
Missing	9	4

Footnote: n.a. – not applicable, LVI – lymphovascular invasion, PNI – perineural invasion

The two groups of patients (with/without the use of nCRT) compared for the patient age, harvested lymph nodes and survival presented with statistical significance ($p = 0.027$, $p = 0.004$ and $p = 0.04$, respectively) according to the 2-sided Pearson Chi-Square test.

The mean survival for all patients during the follow-up period (3.5 years) was 42.1 months. Estimated survival for the patients whether nCRT was used or not presented with statistical significance (77.2 months without nCRT vs. 86.7 months with nCRT; $p = 0.003$). Survival estimation according to the performed procedure also presented with statistical significance (74.3 months for APR vs. 91.4 months for LAR; $p = 0.001$).

Survival rates for the use of nCRT, LVI and PNI presence were different. Those patients with nCRT conduction and with negative LVI and PNI had higher survival rates (Table 3).

Table 3. *Survival rates during follow-up (3.5 years) according to nCRT conduction, type of surgery performed and LVI and PNI presence.*

Variable	%
nCRT conduction	
Yes	83.5
No	71.9
Type of surgery	
LAR	85.6
APR	67.2
LVI	
Yes	60
No	87.1
PNI	
Yes	59.7
No	90.5

Footnote: nCRT – neoadjuvant chemoradiotherapy, LAR – low anterior rectal resection, APR – abdominoperineal rectal resection, LVI – lymphovascular invasion, PNI – perineural invasion

Patients with the presence of LVI had statistically significant worse survival rates. The estimated survival rate for LVI presence was 57.2 months (95% CI: 46.5 – 67.9). In patients with negative LVI status survival estimation was 93.3 months (95% CI: 88.2 – 98.4). This difference was with high statistical significance ($p < 0.001$) (Figure 1).

Worse survival was also statistically significant for the presence of PNI. Survival estimation for PNI positive patients was 58.7 months (95% CI: 49.9 – 67.4). PNI absence resulted in longer survival estimation of 96.4 months (95% CI: 91.4 – 101.4). The difference presented with statistical significance ($p < 0.001$), (Figure 2).

DISCUSSION

In this study, the incidence of the LVI and PNI in patients with rectal cancer subsided for curative resection was examined. A comparison of survival rates between the groups of patients with/without LVI and PNI was performed. Additionally, estimation of survival differences was calculated for the presence/absence of LVI and PNI.

Since it is questionable to distinguish vascular from lymphatic vessels, LVI is defined with the presence of tumor cells in any of these vessels [5]. The phenomenon of tumor invasion of peripheral nerves and spread along the nerve sheets is defined as PNI [6]. In order for the pathologist to confirm tumor PNI positivity, at least one third of the nerve circumference should be involved by the tumor [7]. Yet, there are disagreements when a tumor should be reported as PNI-positive. The dedication of the pathologist is expected to raise the reported incidence in order to properly define the PNI status of the given tumor specimen [8].

Previously reported incidences of LVI vary in ranges between 2 – 50% [9-12]. In the Swedish

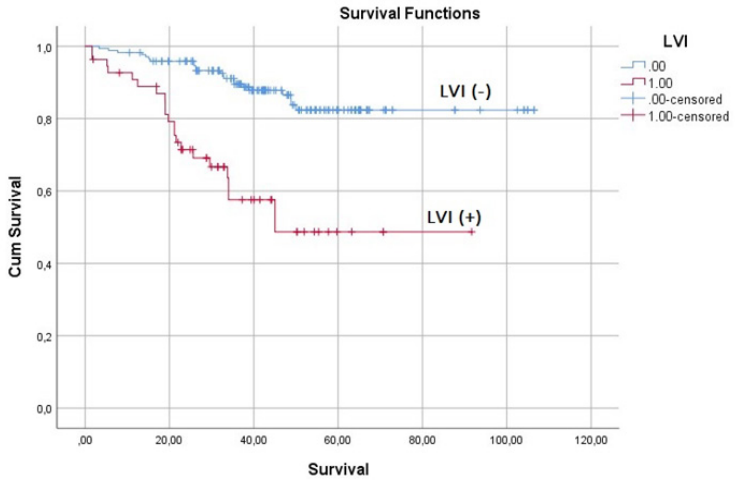


Figure 1. *Kaplan-Meier curve for overall survival according to LVI status (Log rank $p < 0.001$)*

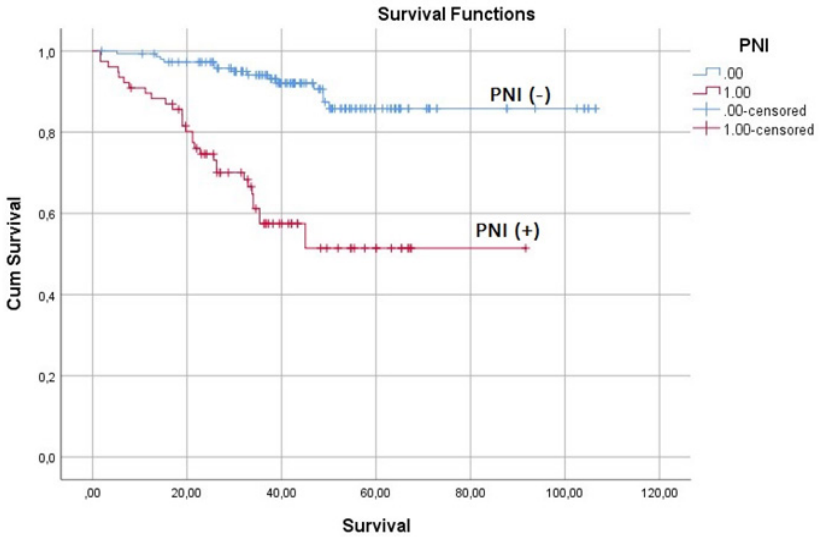


Figure 2. *Kaplan-Meier curve for overall survival according to PNI status (Log rank p < 0.001)*

colorectal cancer registry of Nikberg et al. report, conducted on 2649 patients, LVI was detected in 15% of them [13]. In the observational study of Chen et al., among 330 patients with rectal cancer, LVI was detected in 32.1% [14]. In the cohort study of Sun et al., conducted on 181 patients with locally advanced rectal cancer, positive LVI status was noted in 26 (14.4%) [15]. The reported incidence of LVI status in this study is within the reported ranges.

The reported PNI incidence is described to be from 4.3 – 50% [3,4,11,15,16]. In the observational study of Kim et al., of the analyzed 1411 patients, PNI was confirmed in 28.8% [2]. In the single-center study of Kinugasa et al., among 363 patients treated with upfront-surgery approach for rectal cancer (Dukes' stage B and C), PNI was detected in 22.9% [17]. The study of Qin et al. encompassed a total number of 1470 patients with surgically treated stage I–IV colorectal cancer. Of them, 281 were with rectal cancer. Positive PNI status was presented in 137 (50%) [16]. In the retrospective study of Kamalı et al., conducted on 496 patients with colorectal cancer, the reported incidence of PNI was 24.6%. However, the authors did not separate the patients with rectal cancer from those with tumors located in other parts of the colon when reporting the PNI status [18]. This study shows PNI frequency occurrence within the reported literature.

It is well established that the LVI and/or PNI positivity are indicators for poor prognosis in patients with rectal cancer [13–15,19,20], although some authors question the prognostic value of the LVI [21]. A worse prognosis for LVI and PNI positive patients was also shown in the current study.

Another reported feature of PNI positivity is the absence of influence by the conducted nCRT. Therefore, Kim et al. suggest more intensive adjuvant chemotherapy in rectal cancer patients with positive PNI status [2]. Sun et al. have shown that the use of adjuvant chemotherapy in PNI-positive patients significantly improved the 3-year overall survival [15]. In the meta-analysis of Yang et al., it has been recommended that adjuvant therapy should be considered for patients with postoperative Stage II and PNI (+) as in Stage III [22]. Nikberg et al. emphasize the need for possible adjuvant chemotherapy inclusion in Stage II rectal cancer patients with LVI (+) and PNI (+) [13].

Although, the presence of LVI and PNI (separately or both) do not change the final tumor stage, they certainly influence survival and it is recommended both to be taken into account when the estimation for the prognosis is performed [9].

STUDY LIMITATIONS

This is a single-center retrospective study. The investigated group of patients was heterogeneous regarding whether nCRT was used or not.

CONCLUSION

This study shows that the presence of LVI and PNI significantly influenced the survival rates and the survival estimation in patients with rectal cancer. The LVI and PNI status of rectal cancer should always be taken into account when adjuvant oncological treatment is considered with the final goal of achieving prolonged survival rates.

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Резиме

ИНЦИДЕНЦИЈА НА ЛИМФОВАСКУЛАРНАТА И ПЕРИНЕВРАЛНАТА ИНВАЗИЈА И НИВНОТО ВЛИЈАНИЕ НА ПРЕЖИВУВАЊЕТО КАЈ ПАЦИЕНТИ СО РЕКТАЛЕН КАРЦИНОМ

Шќипе Мисими[1], Дајана Цако[1], Али Илбеј Демирел[2], Андреј Николовски[3], Џемал Улусој[2], Мехмет Гурај Думан[2]

[1] Медицински факултет во Скопје, Универзитет „Св Кирил и Методиј“ во Скопје, РС Македонија

[2] Одделение за општа хирургија, општа болница „Проф. д-р Џемил Ташчиоглу“, Истанбул, Турција

[3] Одделение за висцерална хирургија, Универзитетска хируршка клиника „Св. Наум Охридски“, Универзитет „Св. Кирил и Методиј“ во Скопје, РС Македонија

Цел: Лимфоваскуларната и периневрална инвазија се непожелни, но сепак, реални патолошки карактеристики на ректалниот карцином, кои се асоцирани со лоша прогноза и исход. Целта на оваа студија е да се процени инциденцата на лимфоваскуларната и периневрална инвазија кај пациенти третирани поради ректален карцином и нивното влијание на преживувањето.

Материјал и методи: Оваа ретроспективна опсервациска студија од еден центар спроведена во период од 2016 до 2019 година опфаќа пациенти со ректален карцином третирани со/без долг курс на неоадјувантна хеморадиотерапија. Собирани се демографски податоци на пациентите, карактеристики на туморот, типот на оперативната интервенција (абдомино-перинеала ресекција на ректум и ниска предна ресекција на ректум) и присуството на лимфоваскуларна и периневрална инвазија. Процена на преживувањето за време на следењето е компарирано кај пациентите со/без присуство на лимфоваскуларна и периневрална инвазија.

Резултати: Вкупно беа вклучени 234 пациенти (77 жени и 157 мажи) со средна возраст од 61,3 години. Неоадјувантна хеморадиотерпија беше спроведена кај 170. Абдоминоперинеална ресекција на ректум се изведе кај 67, а ниска предна ресекција на ректунот кај 167 пациенти. Присуство на лимфоваскуларна инвазија се потврди кај 55 (24,4 %), додека периневрална инвазија кај 77 (34,2 %) пациенти. Средното преживување изнесуваше 42,07 месеци. Користењето на неоадјувантна хеморадио терапија влијаеше на преживувањето ($p < 0,033$). Пациентите оперирани со ниска предна ресекција имаа подобро преживување ($p = 0,001$). Присуството на лимфоваскуларна и периневрална инвазија беше асоцирано со полоша прогноза ($p < 0,001$).

Заклучок: Периневралата инвазија беше позастапена од лимфоваскуларната. Пациентите со спроведена неоадјувантна хеморадиотерапија имаа подобро преживување. Присуството на лимфоваскуларната и периневрална инвазија беше асоцирано со полоша прогноза во поглед на севкупното преживување кај пациентите со ректален карцином.

Клучни зборови: ректален канцер, лимфоваскуларна инвазија, периневрална инвазија, преживување, прогноза