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Lymph node ratio, an independent prognostic factor for patients with stage II-III rectal carcinoma

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ABSTRACT

Background: Identification of the proper surgical method and the most reliable prognostic parameters of rectal carcinomas is a challenging issue. The aim of this paper was to determine the possible prognostic role of the number of harvested lymph nodes versus lymph node ratio (LNR) in patients with rectal carcinomas, and the proper value of LNR that can be used as prognostic parameter.

Materials and methods: A retrospective study was performed in 186 consecutive patients with rectal carcinomas that underwent surgical resection. The LNR was calculated for cases from stage II-III, and was correlated with classic prognostic parameters and overall survival (OS).

Results: A statistically significant difference was found between LNR of 0.15 and OS ($p = 0.03$), respectively LNR > 0.15 and TNM stage ($p < 0.0001$), but also tumor infiltration level ($p < 0.05$). The number of harvested lymph nodes was not correlated with the tumor stage ($r = 0.148$, $p = 0.06$) and this parameter did not influence the OS, when the number of 12 or 14 lymph nodes was used as the ideal value ($p = 0.6$ and $p = 0.66$, respectively).

Conclusion: In patients with rectal carcinomas that underwent preoperative chemoradiotherapy, a LNR of 0.15 is a parameter with independent prognostic value, comparing with the number of harvested lymph nodes. The specific LNR should be calculated in larger cohorts.

1. Introduction

Colorectal cancer represents the second cause of cancer-related death in both males and females [1,2]. It is the third most common cancer in men, respectively the second most common cancer among women [2,3].

One-third of the cases are reported to involve the rectum [4,5] but carcinomas of the anal canal show a progressively increased incidence [5–7]. For early rectal cancers (stage II), the aim of preoperative chemoradiation is sphincter saving surgery. For the locally advanced (stage III) rectal carcinomas, the gold standard management consists on preoperative neoadjuvant chemoradiotherapy [8] and the Total Mesorectal Excision (TME) surgery technique [4]. A proper management of the cases leads to decreasing of local recurrence rates from 30 to 40% to 5–15% [4]. As regarding surgery, open versus laparoscopic intervention is still debated.

Along the years, it was proved that the main important factor included in the tumor staging refers to the lymph node (LN) status [9]. The nodal status is essential for including the case in stage II or III [10,11]. Many systems were proposed to define accurately the lymph node status. The mostly used system is those developed by the American Joint Committee on Cancer (AJCC), which was recently modified and included in the 8th edition of the AJCC Cancer Staging Manual [12]. It is based on the depth of invasion (T stage) and total number of positive lymph nodes (N stage) [12]. There are also proposals regarding the total number of harvested lymph nodes [1,10].

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Another proposal refers to the lymph node ratio (LNR). It is defined as the number of positive lymph nodes reported to the total number of harvested nodes (TNLN) and seems to be an independent prognostic factor [1,13,14]. The LNR was proved to have a better prognostic value, compared with N stage [15]. However, although this concept is accepted, it is not yet included in the colorectal cancer guidelines and a specific LNR value is not defined.

The aim of this paper was to emphasize the possible prognostic role of LNR in rectal carcinomas (RC), in patients that underwent open or laparoscopic surgery. As preoperative chemoradiotherapy is administrated for patients with stage II (T2N0-early cancer) and III (T1-4N1) [8,12], only these cases were used to calculate the prognostic impact of LNR.

As the ideal number of TNLN is controversial (12 vs. 14), we have calculated the LNR for both groups (below versus over 12 and below versus over 14) and a value of LNR that might be used as prognostic parameter. Similar studies were published in the Medline database, and were based on the 7th edition of the AJCC Cancer Staging Manual [13,14,16]. This is the first study in literature that analyzed the specific LNR value in rectal carcinomas classified based on the 8th edition of the AJCC Cancer Staging Manual [12].

2. Material and methods

After obtaining the Ethical Committee approval, a 5-year retrospective study (First of April 2013-March 31, 2018) was performed in a university hospital from Transylvania, Romania. Consecutive adult patients with rectal carcinomas diagnosed in stages II-III, that underwent open or laparoscopic surgical resection, were included. All patients underwent surgery in a single institution, reducing surgical and pathological variability.

As the preoperative chemotherapy was done in other oncologic institutions, no data about the chemoradiotherapy regimen was obtained. However, the currently recommendation of the National Comprehensive Cancer Network (NCCN) were used [8].

The exclusion criteria consisted on biopsic specimens, patients that died in first two weeks after surgery, patients below 18 years old, patients with tumors of the colon and the anal canal, and patients with rectal carcinomas diagnosed in stages I or IV. In all of the cases the tumor was located at 4 to 15 cm from the anal verge.

Besides the demographic data (age, gender), the survival rate and classic prognostic factors (anatomic localization, TNM stage, histologic type) were analyzed. Tumor staging was re-evaluated using the criteria of the 8th edition of the AJCC - TNM staging system [12].

Under microscope, the tumors were categorized in the following histologic subtypes: adenocarcinoma (G1-3, with/without mucinous component), mucinous adenocarcinoma, signet ring cell carcinoma and other rare types (neuroendocrine carcinoma, clear cell adenocarcinoma, and serous papillary adenocarcinoma). The resection margins (proximal, distal and radial/circumferential) were also evaluated, same as maximum tumor thickness and the presence of perineural and angiolymphatic invasion.

The LNR was calculated based on the TNLN. For statistical purposes, the TNLN was calculated for two groups: lower versus at least 12 harvested nodes and lower versus at least 14 retrieved lymph nodes. Based on the LNR value, two classes were taken into account: ≤ and over 0.15, based on the previous similar studies [13,14].

For statistical assessment, specific data sheets in the Microsoft Office Excel software were created. Data analysis was performed using Graph Pad Prism 7 software. A p value < 0.05 was considered statistically significant, with 95% confidence interval. For correlation analysis Spearmen correlation test was used. Survival rate analysis was performed using the Kaplan Meier estimator. Patients were followed until July 2018.

Table 1
The clinicopathological characteristics of patients with rectal carcinomas diagnosed in stages II-III.

Characteristics	Number (n = 186)	Percentage (%)
Gender		
Male	119	63.98
Female	67	36.02
Age (years old)		
< 50	12	6.45
≥50	174	93.55
Type of the procedure		
Open surgery	180	96.77
Low anterior resection of the rectum	*66*	36.66
Hartmann procedure	*52*	28.88
Miles' procedure	*41*	22.77
Laparoscopic resection	6	3.22
Depth of tumor invasion		
T1	3	1.61
T2	11	5.92
T3	139	74.73
T4	33	17.74
TNM staging		
II	69	42.33
III	94	57.67

3. Results

3.1. Clinico-pathological parameters

During 2013–2018, 186 patients with rectal cancer diagnosed in stages II-III underwent surgical resection in our Surgery Clinic, with a M:F ratio of 1.77:1 (Table 1). The mean age was 66.46 ± 12.5 (ranging 21–89) years, without differences among males and females (p = 0.36).

The average hospitalization time was 11 ± 4.5 days (ranging between 4–31 days). Most of the patients (55.36%) were hospitalized between 4–10 days, followed by 11–15 days (32.14%). The other patients (12.5%) required more than 15 days of hospitalization, as result of postoperative complications.

Regarding the type of surgical procedure, laparoscopic resection was performed in only 6 of the 186 cases (3.22%). Low anterior resection of the rectum was the most often used technique (35.48%), followed by Hartmann procedure (27.96%) and Miles' surgery or rectal amputation with definitive left iliac anus (22.04%) (Table 1).

Tumor recurrence was observed in 29 patients (15.59%), with a median age of 65.52 ± 15.12 years and M:F ratio of 1.63:1.

3.2. Histopathological parameters

The sampling time of surgical specimens in pathology averaged 3–4 days. To verify and to release the pathological outcome after surgical specimen sampling requested a mean time of 12.4 ± 2.40 days.

The median value of the maximum tumor thickness was 15.65 ± 5.34 mm (ranging 3–60 mm). In most of the cases (50.69%) the maximum thickness was of 10–19 mm, followed by tumors of ≥20 mm (29.17%) and rarely < 10 mm (20.14%).

During surgery, invasion of the peritumoral tissue was suspected in 50 (26.88%) cases, with multiple penetration sites in 17 of these cases. The most frequent penetration site was the bladder, with a rate of 42%. Under microscope, crossing of the circumferential resection margin was confirmed in only 24 (12.9%) cases (Table 2).

The histological diagnosis was dominated by adenocarcinoma and mucinous adenocarcinoma (Table 2). Adenocarcinoma was diagnosed in patients with a median age of 65.82 ± 12.50 years, whereas mucinous adenocarcinoma affected older patients, with a median age of 75.74 ± 11.35 years (p = 0.02). From all adenocarcinomas, tendency for diagnosis in elderly patients was seen for those cases that showed

Table 2
The histopathological characteristics of rectal carcinomas diagnosed in stages II-III.

Characteristics	Number (n = 186)	Percentage (%)
Histological type		
Adenocarcinoma	153	82.26
G1	7	
G2	136	
G3	10	
Mucinous adenocarcinoma	23	12.37
Signet ring cell carcinoma	7	3.76
Neuroendocrine carcinomas	2	1.07
Serous papillary adenocarcinoma	1	0.54
Invasion of the resection margins (R1)		
Proximal resection margin	6	3.22
Distal resection margin	25	13.44
Circumferential resection margin	24	12.9
Angiolymphatic invasion	28	15.05
Perineural invasion	43	23.12

mucinous component (< 50%); they occurred in patients with median age of 71.86 ± 15.67 years. In contrast, signet ring cell carcinoma, which affected only males, presented the lowest mean age at the time of diagnosis (60.85 ± 12.11 years). In 5 patients (2.68%), synchronous carcinomas were diagnosed.

The depth of infiltration (pT) was directly correlated with the resection margin invasion ($r = 0.410$, $p < 0.0001$). Resection margin invasion showed a significant correlation with TNM stage ($r = 0.246$, $p < 0.005$). The tumor stage presented a correlation with the presence of perineural and angiolymphatic invasion ($r = 0.533$, $p = 0.03$). Presence of perineural and angiolymphatic invasion was also correlated with the LNR value ($r = 0.499$, $p < 0.01$), respectively it presented a very weak negative correlation with the OS ($r = -0.078$, $P < 0.05$).

3.3. Lymph node ratio and its prognostic role

A strong correlation was found between the LNR value and pTNM stage ($r = 0.8$, $p < 0.0001$) (Fig. 1). A negative correlation between LNR and survival rate was also observed ($r = 0.306$, $p < 0.001$). LNR was directly correlated with the resection margin invasion ($r = 0.155$, $p < 0.05$).

The TNLN was of at least 14 lymph nodes in 53.73% of patients from stage II and 59.14% of patients diagnosed in stage III. The tumor stage proved to be an independent prognostic factor (Fig. 2).

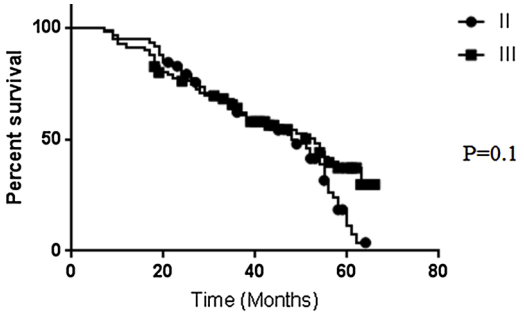

Fig. 2. The 5 year overall survival correlated with the tumor stage.

No significant statistical correlation was found between the TNM stage and the TNLN, in neither of the two groups: those that assumed a sampling of at least 12 lymph nodes ($r = 0.148$, $p = 0.06$) and those with 14 lymph nodes ($r = 0.135$, $p = 0.08$). Examining the prognostic role of the TNLN, the number of harvested nodes did not influence the overall survival rate (OS). Lack of influence was seen for both groups: with at least 12 ($p = 0.6$), or at least 14 harvested lymph nodes ($p = 0.66$) (Fig. 3).

The OS was significantly influenced by the LNR, when was calculated for ≤ or over 0.15 ($p = 0.03$) (Fig. 4).

4. Discussion

In patients with rectal tumors, the main goals of surgery are free resection margins, TME and high number of TNLN [17]. In these cases, it is a challenging decision for surgeon that should decide for open, transanal, or laparoscopic surgery. The optimal technique depends on the surgical team experience, the tissue quality after preoperative chemoradiotherapy, tumor location, and other patient-related parameters.

Appropriate low anterior resection is difficult for rectal cancer, due to the anatomical characteristics of the pelvis [18]. There is also a challenging decision regarding sphincter-saving operations versus abdominal perineal resection [19]. The laparoscopic instruments seem to make the intervention more accurate and reduce the time of hospitalization [20]. However, for tumors of the inferior rectum laparoscopic procedure is not always the gold choice [21]. The narrow pelvis, especially in men, low rectal tumors and bulky mesorectal cases can cause difficulties in the adequate traction of the rectum [18].

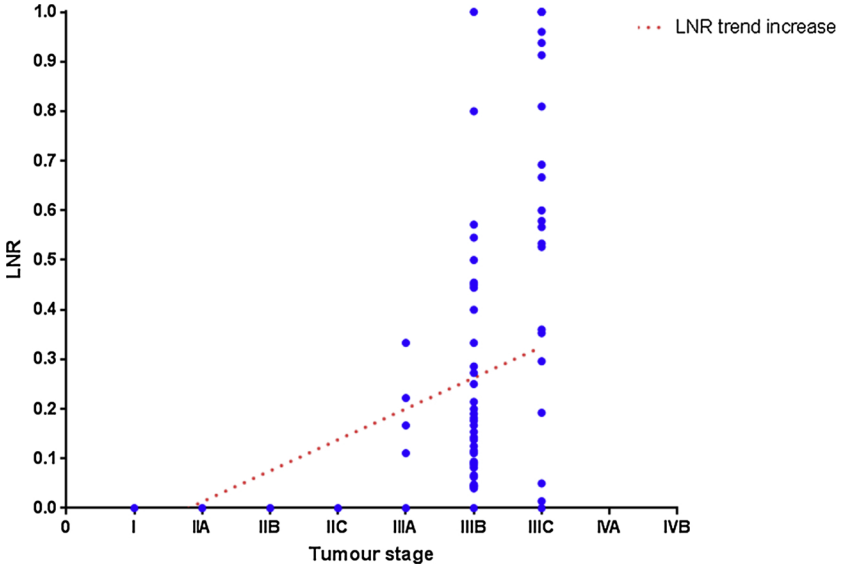

Fig. 1. Correlation between the lymph node ratio (LNR) and tumor stage.

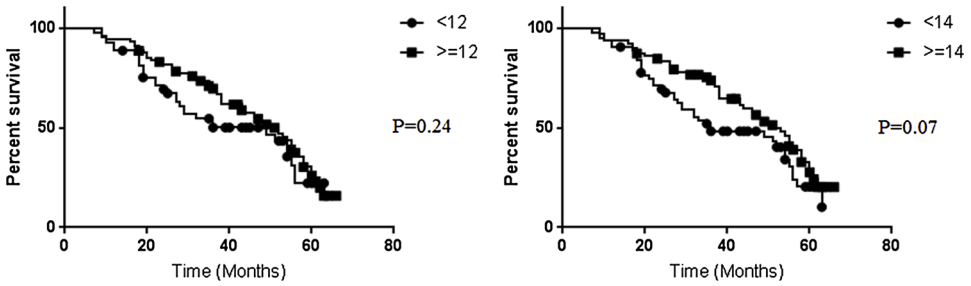

Fig. 3. The 5 year overall survival correlated with the number of retrieved lymph nodes.

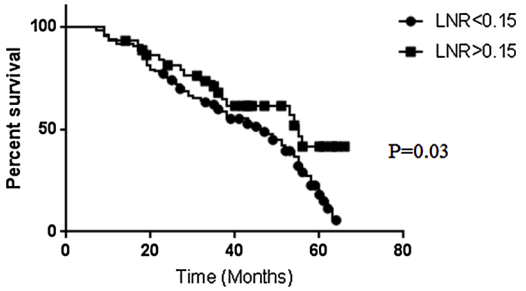

Fig. 4. The 5 year overall survival correlated with lymph node ratio cut-off.

Surgeons continue to debate the advantage of laparoscopic technique compared to the open method, because local recurrence rates do not show always-significant differences between these two approaches. The recurrence rate form our study was similar to those reported after laparoscopic procedure.

In this study, we mainly used open surgery, performed by a surgery team with experience and the results were comparable with literature data. As in the present study the median time of histopathological assessment was 16 days, although the recommendation of the College of American Pathologists' (CAP) is of two-five days [22,23], the delays were related to the tumor size, tissue-related factors but also to the number of cases per pathologist. The recurrence rate in this study was 15.59%, being comparable with other studies that reported a risk of recurrence of 12.9% [24].

This study was mainly focused on the prognostic role of LNR, a parameter that was not intensely examined in literature for patients with rectal tumors. According to our knowledge this is the first study in literature which analyzed the specific LNR value in rectal carcinomas, which were classified based on the 8th edition of the AJCC Cancer Staging Manual. Regarding the differences between the 7th [16] and 8th edition of the AJCC Cancer Staging Manual classifications [12], based on the rectal cancer, the only novelty consists of the introduction of a third sub stage within stage IV, namely IVC, regarding metastasis to the peritoneal surface, which is identified alone or with other site or organ metastases. Although we excluded all patients who presented stage IV cancer, namely 43 cases, restaging was necessary in 11 cases from IVB to IVC.

The currently recommendation of the NCCN rather refers to the TNLN, being required, for a proper diagnosis, harvesting of a minimum number of 12 lymph nodes [8,14]. This number is, however, debatable and 14 or 15 removed nodes were proposed by other authors, especially for considering a node-negative case [10,25]. The number of retrieved lymph nodes has a substantial diversity, which is dominated by surgical, pathological and patient-related characteristics [15,26]. In cases where the harvested LN number is low, stage evaluation might be inadeqate [15]. In these cases, LNR might have significant prognostic value [15]. In this study, the TNLN (below or over 12 vs. below or over 14) did not prove to have prognostic importance.

A valuable results of this study regards the strongly correlation that was observed between LNR, TNM stage and the angiolymphatic and perineural invasion, but also negative correlation with OS. The angiolymphatic invasion was reported in literature in over 14% of cases [27], similar to our data. The prognostic value of LNR is also sustained by other previous studies [1,13,14].

Based on these results and the fact that, after chemoradiotherapy, is difficult to retrieve more than 12 lymph nodes [8,10], we consider that LNR should be used as a valuable prognostic parameter. It is known that in rectal cancer patients the long-course neoadjuvant chemoradiotherapy has a negative effect on the LN retrieval [28]. Only 20% of the cases that benefited by preoperative neoadjuvant therapy have an adequate number of retrieved lymph nodes ($\geq$12), which are required to accurately specify stage II tumor [8]. Moreover grade and site of the tumor, respectively patients' age and gender can influence the number of retrieved lymph nodes [8].

Based on the LNR ($>$ 0.25), physicians may be able to identify cases with aggressive behaviour and select patients that should receive a more aggressive chemotherapy regimen [26]. LNR, N2 nodal status and over presence of LN metastases in four or more lymph nodes were defined as significant prognostic factors of patients with colorectal cancer [26,29]. Moreover, in cases diagnosed in stage III, LNR allows a prognostic stratification of patients [28]. In these patients, it was demonstrated that it is a more accurate predictor regarding 5-year disease-free survival, comapred with the N stage [15].

LNR was also proved having a major importance in other gastrointestinal cancers. In patients with esophageal cancer, it was demonstrated to be an independent factor of disease-free - and overall survival [30]. In squamous cell carcinoma of esophagus, LNR could be used to predict the risk of angiolymphatic invasion and patients' outcome [31]. In patients with gastroesophageal cancer who underwent radical resection, LNR serves as a negative prognostic factor [32]. In patients with gastric cancer who underwent radical gastrectomy, LNR also serves as a valuable independent prognostic factor [33,34]. In gastric cancer, it was proved that a LNR $>$ 0.25 is an indicator of resistance to postoperative chemoradiotherapy [35]. LNR could be able to predict patients survival more accurately, compared to the current TNM staging system, in patients with gastrectomy and few resected lymph nodes [36].

As prognostic parameter a LNR of 0.15-0.20 represents the standard value which can be taken into account and which was used also in the other two similar studies [13,14]. We have obtained statistical correlation regarding OS with a value of 0.15. A LNR $>$ 0.12 resulted in 70% reduction in overall survival [13].

In conclusion, in patients with rectal carcinomas that underwent preoperative chemoradiotherapy, LNR is a parameter with stronger independent prognostic value, comparing with TNLN. A LNR value of 0.15 is a positive prognostic factor for patients with rectal carcinomas diagnosed in stages II and III.

Study limitations consist on the retrospective observation and a relatively short time follow-up. Another limitation is, due to low number of cases, examination of carcinomas in stages II (T2N0) and III (T1-4N1) and not a separate delineation between LNR value in each of these two stages. For more accurate and complex data, further studies are needed, with a high number of cases and longer follow-up.

Multicenter research studies can be also taken into consideration.

Conflict of interest

None declared.

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References

[1] F. Shen, J. Cui, K. Cai, H. Pan, H. Bu, F. Yu, Prognostic accuracy of different lymph node staging systems in rectal adenocarcinoma with or without preoperative radiation, Jpn. J. Clin. Oncol. 48 (2018) 1–8.
[2] O.V. Bochis, Fekete Zs, C. Vlad, B. Fetica, D.C. Leucuta, C.I. Busuioc, A. Irimie, The importance of a multidisciplinary team in rectal cancer management, Clujul Med. 90 (2017) 279–285.
[3] L. Liu, K. Zhu, W. Yu, S. Zhang, G. Teng, J. Guo, Detection rate, anatomic sites, and pathologic types of colorectal cancer during colonoscopy procedures, Surg. Laparosc. Endosc. Percutan. Technol. 27 (2017) 394–399.
[4] R. Vernet, J.M. Borras, L. Aliste, M. Antonio, A. Guarga, P. Manchon-Walsh, Influence of age on variation in patterns of care in patients with rectal cancer in Catalonia (Spain), Clin. Transl. Oncol. (2018), https://doi.org/10.1007/s12094-018-1882-8.
[5] D. Leonard, D. Beddy, E.J. Dozois, Neoplasms of anal canal and perianal skin, Clin. Colon Rectal Surg. 24 (2011) 54–63.
[6] J.J. Mazeron, E.V. van Limbergen, Anorectal cancer, in: A. Gerbaulet, R. Potter, J. Mazeron, H. Meertens, E. VanLimbergen (Eds.), The GECESTROH and Book of Brachytherapy, ESTRO, Brussels, 2000, pp. 505–514.
[7] S.A. Salati, A.A. Kadi, Anal cancer – a review, Int. J. Health Sci. (Qassim) 6 (2012) 206–230.
[8] National Comprehensive Cancer Network (NCCN), NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer Version 3.2018, National Comprehensive Cancer Network, 2018.
[9] F.L. Obrocea, M. Sajin, E.C. Marinescu, D. Stoica, Colorectal cancer and the 7th revision of the TNM staging system: review of changes and suggestions for uniform pathologic reporting, Rom. J. Morphol. Embryol. 52 (2011) 537–544.
[10] P.C. Chandrasinghe, D.S. Ediriweera, J. Hewavisenthi, S. Kumarage, K.I. Deen, The total number of lymph nodes harvested is associated with better survival in stages II and III colorectal cancer, Indian J. Gastroenterol. 33 (2014) 249–253.
[11] C. Russu, C. Molnar, S. Gurzu, I. Jung, S. Voidazan, C. Copotoiu, The role of clinical and pathological assessment in choosing the best therapeutic management to improve survival in rectal cancer, Rom. J. Morphol. Embryol. 57 (2016) 1253–1259.
[12] J.M. Jessup, R.M. Goldberg, E.A. Asare, I.I.I.A.B. Benson, J.D. Brierley, G.J. Chang, et al., Colon and rectum, in: M.B. Amin (Ed.), AJCC Cancer Staging Manual, eight edition, Springer Nature, 2017, pp. 251–269.
[13] A.B. Bhatti, A. Akbar, A. Hafeez, A.A. Syed, S. Khattak, A. Jamshed, A.S. Kazmi, Impact of lymph node ratio and number on survival in patients with rectal adenocarcinoma after preoperative chemo-radiation, Int. J. Surg. 13 (2015) 65–70.
[14] Z.G. Zuo, X.F. Zhang, H. Wang, Q.Z. Liu, X.Z. Ye, C. Xu, X.B. Wu, J.H. Cai, Z.H. Zhou, J.L. Li, H.Y. Song, Z.Q. Luo, P. Li, S.C. Ni, L. Jiang, Prognostic value of lymph node ratio in locally advanced rectal cancer patients after preoperative chemoradiotherapy followed by total mesorectal excision, Medicine (Baltimore) 95 (2016) e2988.
[15] C.C. Chin, J.Y. Wang, C.Y. Yeh, Y.H. Kuo, W.S. Huang, C.H. Yeh, Metastatic lymph node ratio is a more precise predictor of prognosis than number of lymph node metastases in stage III colon cancer, Int. J. Colorectal Dis. 24 (11) (2009) 1297–1302.
[16] S.B. Edge, D.R. Byrd, C.C. Compton, A.G. Fritz, F.L. Greene, A. Trotti, Colon and Rectum, M.B. Amin, et al. (Eds.), AJCC Cancer Staging Handbook, seventh edition, Springer Nature, 2010, pp. 173–207.
[17] P. Videhult, K. Smedh, P. Lundin, W. Kraaz, Magnetic resonance imaging for preoperative staging of rectal cancer in clinical practice: high accuracy in predicting circumferencial margin with clinical benefit, Colorectal Dis. 9 (2007) 412–419.
[18] R. Persiani, A. Biondi, F. Pennestrì, V. Fico, V. De Simone, F. Tirelli, F. Santullo, D. D'Ugo, Transanal total mesorectal excision vs laparoscopic total mesorectal excision in the treatment of low and middle rectal cancer: A propensity score matching analysis, Dis. Colon Rectum 61 (2018) 809–816.
[19] M. Muresan, S. Bancu, T. Bara, L. Bancu, M. Turcu, S. Muresan, Local recurrence after the sphincter–saving operation and abdominal perineal resection in rectal cancer, Chirurgia 104 (2009) 415–418.
[20] S.K. Burgdorf, J. Rosenberg, Short hospital stay after laparoscopic colorectal surgery without fast track, Minim. Invasive Surg. 2012 (2012) 260273.
[21] K. Hida, R. Okamura, Y. Sakai, T. Konishi, T. Akagi, T. Yamaguchi, T. Akiyoshi, M. Fukuda, S. Yamamoto, M. Yamamoto, T. Nishigori, K. Kawada, S. Hasegawa, S. Morita, M. Watanabe, Japan Society of Laparoscopic Colorectal Surgery. Open versus laparoscopic surgery for advanced low rectal cancer, Ann. Surg. 268 (2018) 318–324.
[22] S. Alshieban, K. Al-Surimi, Reducing turnaround time of surgical pathology reports in pathology and laboratory medicine departments, BMJ Qual. Improv. Rep. (2015) 4 pii: u209223.w3773.
[23] A.T. Atanda, I. Yusuf, M.S. Haruna, Perceived and real histopathology turnaround time: a teaching hospital experience, Niger. J. Surg. 23 (2017) 98–101.
[24] R.V. Rodrigues, J. Pereira da Silva, I. Rosa, I. Santos, N. Pereira, C. Soares, A.D. Pereira, Intensive follow-up after curative surgery for colorectal cancer, Acta Med. Port. 30 (2017) 633–641.
[25] M.I. Rivadulla-Serrano, D. Martínez-Ramos, M. Armengol-Carrasco, J. Escrig-Sos, G.A. Paiva-Coronel, C. Fortea-Sanchís, J.L. Salvador-Sanchís, Impactof the total number of harvested lymph nodes after colon cancer resections on survival in patients without involved lymph node, Rev. Esp. Enferm. Dig. 102 (2010) 296–301.
[26] P.D. Ainsworth, M.A. Johnson, The prognostic significance of the metastatic lymph node ratio in Dukes stage C colorectal cancer in a district general hospital, Colorectal Dis. 12 (2010) 1219–1222.
[27] M. Linter Kapisinska, E. Hovorkova, V. Zavalova, Z. Subrt, M. Kunes, A. Ferko, Distribution of metastases in mesorectum is unpredictable: metastases do not respect tumor location even in small non-circumferential rectal cancers, Eur. J. Surg. Oncol. 44 (2018) 87–92.
[28] W. Ceelen, Y. Van Nieuwenhove, P. Pattyn, Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review, Ann. Surg. Oncol. 17 (2010) 2847–2855.
[29] S. Gurzu, I. Jung, L. Azamfirei, T. Mezei, A.M. Cimpean, Z. Szentirmay, The angiogenesis in colorectal carcinomas with and without lymph node metastases, Rom. J. Morphol. Embryol. 49 (2008) 149–152.
[30] N. Wang, Y. Jia, J. Wang, X. Wang, C. Bao, Q. Song, B. Tan, Y. Cheng, Prognostic significance of lymph node ratio in esophageal cancer, Tumour Biol. 36 (2015) 2335–2341.
[31] Z. Tan, G. Ma, H. Yang, L. Zhang, T. Rong, P. Lin, Can lymph node ratio replace pn categories in the tumor-node-metastasis classification system for esophageal cancer? J. Thorac. Oncol. 9 (2014) 1214–1221.
[32] M. Melis, A. Masi, A. Pinna, S. Cohen, I. Hatzaras, R. Berman, L.H. Pachter, E. Newman, Does lymph node ratio affect prognosis in gastroesophageal cancer? Am. J. Surg. 210 (2015) 443–450.
[33] K. Bouliaris, G. Rachiotis, A. Diamantis, G. Christodoulidis, E. Polychronopoulou, K. Tepetes, Lymph node ratio as a prognostic factor in gastric cancer patients following D1 resection. Comparison with the current TNM staging system, Eur. J. Surg. Oncol. 43 (2017) 1350–1356.
[34] A. Guevara Jabiles, E. Ruiz Figueroa, F. Berrospi Espinoza, I. Chávez Passiuri, F. Young Tabusso, C. Luque Vásquez, E. Poquioma Rojas, R. Mantilla, E. Payet Meza, Prognostic value of lymph node ratio (LNR) in patients who underwent radical gastrectomy, Rev. Gastroenterol. Peru 38 (2018) 253–260.
[35] Y. Kim, Y. Kim, M.H. Squires, G.A. Poultsides, R.C. Fields, S.M. Weber, K.I. Votanopoulos, D.A. Kooby, D.J. Worhunsky, L.X. Jin, W.G. Hawkins, A.W. Acher, C.S. Cho, N. Saunders, E.A. Levine, C.R. Schmidt, S.K. Maithel, T.M. Pawlik, Impact of lymph node ratio in selecting patients with resected gastric cancer for adjuvant therapy, Surgery 162 (2017) 285–294.
[36] K. Yamashita, K. Hosoda, A. Ema, M. Watanabe, Lymph node ratio as a novel and simple prognostic factor in advanced gastric cancer, Eur. J. Surg. Oncol. 42 (2016) 1253–1260.