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The Metastatic Lymph Node Ratio is a Crucial Criterion in Colorectal Cancer Therapy Management and Prognosis

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Abstract

Objective: Every year, 1.8 million people are diagnosed with colon cancer. The presence of lymph node (LN) metastases is a key prognostic factor in adjuvant treatment planning and follow-up. The tumor-node-metastasis (TNM) classification can be used to assist in prognostic cancer staging. However, TNM-classification may not always compromise the necessary prognostic information. Therefore, guidelines are updated regarding prognostic value and new prognostic parameters are investigated. One of these parameters is metastatic lymph node ratio (mLNR), which is calculated by dividing the number of metastatic lymph nodes (mLNs) by the total number of lymph nodes excised. Similar publications have already reported on the prognostic value of the mLNR in gastric, pancreatic, and bladder cancer.

Methods: Pathology reports of 496 stage II and stage III patients treated for colorectal cancer (CRC) in our hospital in the last decade were retrospectively reviewed. Factors such as age, gender, tumor location, tumor size, T stage, lymphovascular invasion, perineural invasion, tumor budding, tumor deposit, total and mLN count were evaluated for overall survival.

Results: The mean tumor size was 53.8 mm. The patients who had an average of 2 LN involvement among those who had 23 lymph nodes excised were followed up for an average of 66.8 months. Receiver operating characteristic test presented the cut-off value of mLNR on overall survival was 0.028, with a sensitivity of 42% and a specificity of 71%. Gender, tumor's localization, and size of ≥6 cm had no significant impact on survival. However, survival was related to age >60, lymphovascular, and perineural invasion, tumor deposit/budding, and mLNR >0.028 ($p \leq 0.05$). Furthermore, multivariate analysis revealed that only mLNR ($p=0.034$) affected overall survival independently.

Conclusion: We believe that mLNR that does not require additional costs will gain more value in diagnosis and treatment. Based on our results, mLNR may be a useful to assess prognosis in CRC patients.

Keywords: Metastatic lymph node ratio, colorectal cancer, prognostic factor

INTRODUCTION

Over 1.8 million new colorectal cancer (CRC) cases and 881,000 deaths were observed in 2018 worldwide, accounting for almost one-tenth of all cancer cases and deaths (1). The mortality rate varies depending on tumor stage and/or the treatment availability (2).

Accurate staging is essential for managing the disease. According to the 8th American Joint Committee on Cancer (AJCC) cancer staging guideline, the assessment for lymph node (LN) metastases in CRC is conducted via involved regional lymph nodes. This guideline is updated over time due to evolving needs and technical developments. Although the basic structure was preserved in the evaluation in AJCC 8, some new parameters such as status for micrometastasis and isolated tumor cells were added (3). For evaluating LN metastasis, a minimum of 12 lymph nodes must be removed (4,5). Less than this number of removed lymph nodes may cause false LN negativity or a lower N grade (5).

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CRC is defined as stage III in the current staging method when there are regional LN metastases. Additional treatment alternatives, such as adjuvant chemotherapy, should be used at this stage (6). Although tumor staging according to the AJCC guide helps assess prognosis, prognosis estimation for IIIA and II stages cannot be performed precisely. According to the current staging method, the prognosis of stage IIIA can be better than that of the lower stages. According to several authors, stage IIIA has a better prognosis than stages IIB and IIC (2,4,6,7).

As a result, a more specific and thorough technique for assessing nodal metastasis would be beneficial. It has been discovered that the metastatic lymph node ratio (mLNR), defined as the ratio of the number of metastatic lymph nodes (mLNs) to the number of inspected lymph nodes (LNs) and not included in the AJCC guidance, is crucial in assessing prognosis in gastric and pancreatic tumors (8,9).

Considering this information, we retrospectively investigated parameters such as age, gender and tumor size, stage, location, LN status, perivascular-perineural involvement, tumor deposit and tumor budding such as mLNR from pathology reports that may impact the overall survival of CRC patients without distant metastasis.

METHODS

Patients' data was collected from the archives of the department of pathology from 01/01/2011 to 01/01/2021. Approval was obtained on 24.11.2021 from the Local Ethics Committee of University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital with the number E-48670771-514.99. Retrospectively 496 patients with stage II and III were included with the following criteria: ≥ age 18, male/female, surgery due to CRC, adequate clinical record and follow-up, excision of at least 12 lymph nodes. Stage I and IV patients, as well as those with postoperative mortality of at least one month or patients with multiple primary tumors and rectum cancer treated with neo-adjuvant therapies were excluded. Patient staging was made after 8th AJCC cancer staging guideline and tumor budding in CRC was reported accordingly to The International Tumor Budding Consensus Conference (ITBCC) (10).

Statistical Analysis

Data are presented as the mean with interquartile range and minima and maxima, if not as stated in the figure legend. Categorical variables were compared using Fisher's Exact test. Survival analysis was performed using the Kaplan-Meier method and Cox proportional hazards regression modeling.

The area under the receiver operating characteristic curve (ROC) was generated to define diagnostic test's accuracy and a cut-off point of age, tumor size, mLNR for survival. The log-rank test as a non-parametric test was used for comparing survival curves. Missing data were omitted when clinical records were not complete. An overall alpha value of $p<0.05$ was applied to reject the null hypothesis. SPSS [version 18.0, SPSS Inc, Chicago (IL), United States)] for Windows was used for statistical analysis.

RESULTS

Totally 496 patients are included in the study. The mean age of 197 (39.7%) female and 299 (60.3%) male patients was 61.5. For each patient, a mean of 23 LN was excised, on average 2 LN were metastatic. The mean tumor diameter was found to be 53.8 mm in patients with a mean follow-up of 66.8 months (Table 1). Of the total CRC, 171 (34.5%) were detected in the rectum, 129 (26%) in the right colon, 98 (19.8%) in the sigmoid colon, 68 (13.7%) in the left colon and 9 (1.8%) in the transverse colon. Multiple foci were detected in 21 (4.2%) patients (Table 2). It was observed that 403 (81.3%) patients were in T3 stage, 81 (16.3%) patients were in T4 and 12 (2.4%) patients were in T2 (Table 3). It was observed that 310 (62.5%) patients did not show a LN involvement, therefore rated stage II. The remaining 186 (37.5%)

Table 1. General characteristics of patients

	n	Minimum	Maximum	Mean	Standard deviation
Age/years	496	21.7	89.8	61.51	13.27
Longest diameter/mm	496	10	200	53.79	23.91
Survey/month	496	1	179	66.80	46.21
Total excised lymph node	496	12	73	23.09	11.48
Metastatic lymph node	496	0	66	2.14	5.73

Table 2. Tumor anatomical localization

Location	Frequency (n)	Percentage (%)
Right colon	129	26.0
Transverse colon	9	1.8
Left colon	68	13.7
Sigmoid colon	98	19.8
Rectum	171	34.5
Multifocal	21	4.2
Total	496	100

Table 3. T stage distribution

	T2	T3	T4	Total
Frequency (n)	12	403	81	496
Percentage (%)	2.4	81.3	16.3	100

patients showed a LN involvement and reported as stage III.

While 355 (71.6%) patients showed lymphovascular invasion (LVI), 374 (75.4%) individuals exhibited perineural invasion. Out of 130 patients evaluated for extranodal tumor deposits, which was not addressed as a prognostic factor in the 8th AJCC despite its negative impact on overall survival and disease-free survival (11), 28 (21.5%) were positive. Another important prognostic factor tumor budding was reported in 35 patients via the scoring system according to ITBCC and 11 (31.4%) patients were positive for budding.

Since there is no consensus on the cut-off values including the age of the patient, the largest tumor size and the mLNR of the patients we determined these cut-off values for patients admitted to our hospital with a ROC test. These values were reported as 60.2 years for age (sensitivity: 0.66; specificity: 0.56), 57.8 mm (sensitivity: 0.4; specificity: 0.63) for the largest tumor size and 0.028 (sensitivity: 0.42; specificity: 0.71) for mLNR (Figure 1).

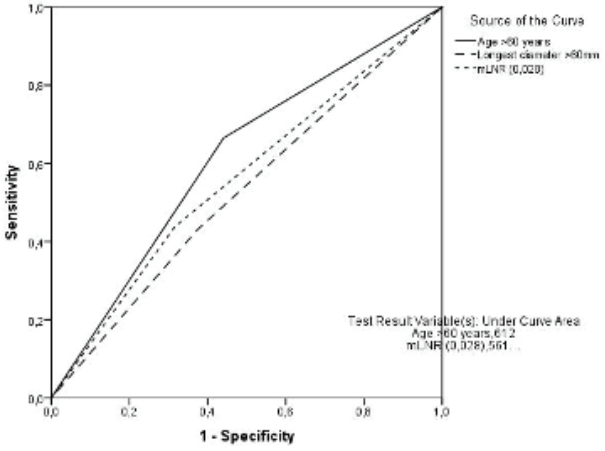

Figure 1. Cut-off values for age, diameter and mLNR
mLNR: Metastatic lymph node ratio

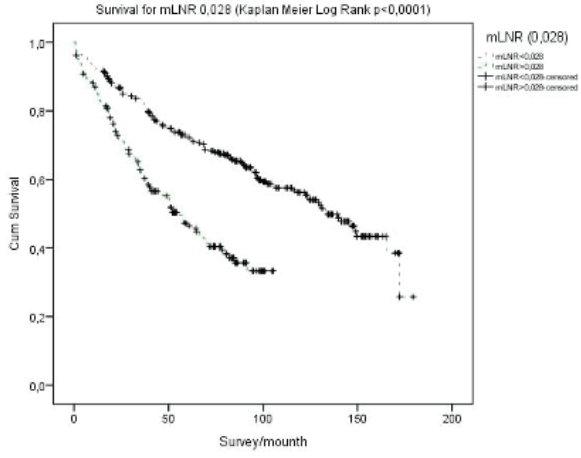

Figure 2. Survival mLNR stages
mLNR: Metastatic lymph node ratio

When survival analysis was performed for these factors; there was no statistically significant difference in overall survival in terms of gender, tumor diameter, tumor localization and tumor perforation (p>0.05). For patient age (60/year), tumor stage, LN metastasis, mLNR (0.028) (Figure 2), LVI, perineural invasion (p<0.0001), tumor deposit (p<0.001) and tumor budding (p=0.016) significant survival difference was detected (Table 4). There was a survival difference between stage IIIA and IIB and IIC, but it could not be statistically proven (p=0.078) (Figure 3). When multivariate analysis was performed for survival, only mLNR (p=0.034) was found to be an independent prognostic factor (Table 5).

DISCUSSION

In a study with 1.837 patients diagnosed with CRC it was reported that there is no difference in survival rate in different sexes when the other causes of death than cancer are excluded. The same finding was also discovered in our study (12).

Table 4. Factors affecting survival with results of univariate analysis

Parameters (n)	Negative (%)	Positive (%)	Log rank (Mantel-Cox) p
Age >60 years (496)	225 (45.4)	271 (54.6)	p<0.0001
Longest diameter >60 mm (496)	298 (60.1)	198 (39.9)	p=0.120
Lymph node (496)	310 (62.5)	186 (37.5)	p<0.0001
Lymphovascular invasion (496)	355 (71.6)	141 (28.4)	p<0.0001
Perineural invasion (496)	374 (75.4)	122 (24.6)	p<0.0001
Tumor deposit (130)	102 (78.5)	28 (21.5)	p=0.001
Tumor budding (36)	24 (66.7)	12 (33.3)	p=0.016
mLNR >0.028 (496)	311 (62.7)	185 (37.3)	p<0.0001
mLNR: Metastatic lymph node ratio			

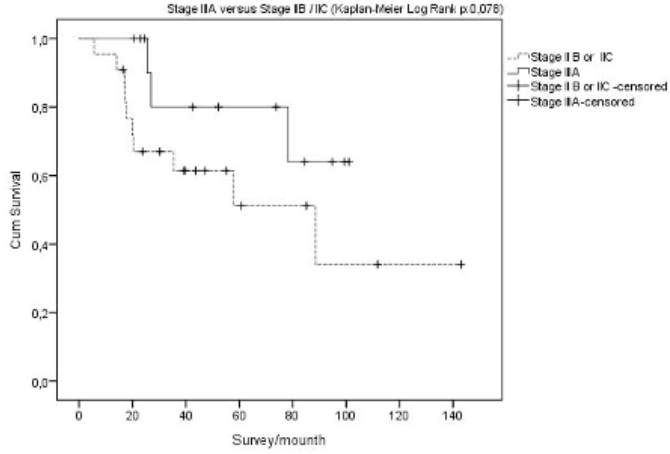

Figure 3. Survival stage IIIA versus stage IIB-IIC

Table 5. Factors affecting survival analysis via multivariate analysis/Cox regression)								
	B	SE	Wald	df	Sig.	Exp (B)	95.0% Cl for Exp (B)	
							Lower	Upper
Age >60 years	-1.117	1.237	0.815	1	0.367	0.327	0.029	3.697
T stage	-	-	1.948	2	0.378	-	-	-
T stage (1)	-2.311	194.926	0.000	1	0.991	0.099	0.000	8.277E+164
T stage (2)	-4.019	194.931	0.000	1	0.984	0.018	0.000	1.513E+164
Lymph node positive	-12.508	86.834	0.021	1	0.885	0.000	0.000	3.026E+68
Lymphovascuar invasion	16.167	86.834	0.035	1	0.852	10499330.74	0.000	8.940E+80
Perineural invasion	0.457	1.219	0.141	1	0.708	1.580	0.145	17.226
Tumor deposit	-	-	2.559	2	0.278	-	-	-
Tumor deposit (1)	-21.781	115.592	0.036	1	0.851	0.000	0.000	8.559E+88
Tumor deposit (2)	2.566	1.614	2.527	1	0.112	13.016	0.550	308.031
Tumor budding	-11.707	86.825	0.018	1	0.893	0.000	0.000	6.628E+68
mLNR (0.028)	-3.376	1.595	4.479	1	0.034	0.034	0.002	0.779
mLNR: Metastatic lymph node ratio, CI: Confidence interval								

In a study from Kornprat et al. (13) with 369 patients, tumor size proved to be an independent prognostic parameter for patients with CRC. In this study it was also reported that the cut-off points differed among the colon locations. However, there was no certain coherence found between the tumor size and prognosis in other studies (14-16).

Our cut-off value was found at 60 mm and at this level there was no difference in survival in our patients.

Some studies showed, that a cancer in the left colon had a worse prognosis than in the right colon, yet other studies could not support the same effect of tumor location on the prognosis (17). In a study from 2020, the general differences among survival rate was compared between the right and left colon cancers. Right and left colon cancers showed differences in microbiom, clinical presentation and molecular features. Separate therapy regimes were recommended (18). We did not see the effect of tumor location on the survival.

Assessing the relationship between perforation and the survival rate did not show any significant difference in multivariate analysis, even if a tendency was inspected in univariate analysis (19-21). Our univariate analysis did not show a relationship between perforation and survival either.

Patients of higher age are admitted and operated most of the time as emergency cases, hence they show a higher mortality (22). In a study from Steele et al. (23) in 2014 with 7.948 patients, the effect of age on overall survival was conducted and younger patients showed at the time of diagnosis higher grades of the cancer and higher recurrence, meanwhile no significant difference in survival compared to the older patients. In our study we observed a lower survival rate in patients older than 60 (based on ROC analysis)

Staging is vital in the assessment of the prognosis and the therapeutic goals in CRC. Progress in the grade shows bad prognosis (24). A study of Zielinski et al. (20) proved higher age, advanced T stage and high American Society of Anesthesiologists score effected the survival independently. In our study the T stage showed significant effects on survival in univariate analysis.

AJCC staging system is also essentially adopted by World Health Organization and updated regularly with the AJCC-8 version being the most up-to-date. A novelty in the latest edition is the detailed description of Tis dysplasia. It is lesions penetrating lamina propria with probable invasion of muscularis mucosa are defined as intramucosal carcinoma. While in other malignant entities only the basal membrane penetration is assessed as invasive, in CRCs even lesions advanced into the submucosa have the potential of metastasizing (3).

In a study from 2016, the survival rate differed between the patients in stages IIB-IIC and IIIA, in favor of IIIA, where the older AJCC-7 system was used for the staging (25). Isolated tumor cells, which had not been mentioned in the N grading of the colorectal tumors in the earlier editions, are also available in the AJCC-8. Isolated tumor cells in subcapsular or marginal sinus lymph nodes (<20 cells or <0.2 mm tumor cell group) and micro-metastasis (20 cells or more and metastasis diameter between 0.2-2 mm) are being described in detail. LN containing isolated tumor cells are being registered as N0 (or N0i) and these cells do not upstage the disease to stage III. Patients with micro-

metastasis are registered as N1, as they show a worse prognosis. Since we did not have a patient diagnosed with micrometastasis and isolated tumor cell, these findings were not taken into account in our study.

Tumor deposits, being one of the important histopathological factors, are seen in 20% of the CRCs and are related to worse prognosis. The discussion of their consideration in the TNM staging is still not concluded (26). We found in our study that patients with tumor deposits showed lower survival rates.

The definition of tumor deposit in AJCC-7 is a tumor forming a prominent nodule, independent of lymphatic tissue finding. AJCC-8 clarified the interpretation of the tumor nodules found in lymphatic drainage field of primary CRCs. Nodules not containing prominent lymph nodes or vascular/neural constructs are being defined as tumor deposit (N1c). Nodules shape, borders and size are not being taken into consideration. Tumor cells covered by smooth muscle or endothelial cells in contact with erythrocytes are being accepted as vascular invasion. If tumor nodules are seen in the proximity of neural constructs, it is being classified as perineural invasion (11,27-29).

Studies describe a vascular invasion in 65% of the CRC cases. LVI is a significant indicator of advanced stage and is remarkably correlated with worse prognosis in CRC patients (30). LVI was an indicator of more aggressive biological behavior and poor prognosis in patients with stage III CRC (31). Vascular invasion showed a difference in survival in our univariate analysis.

Perineural invasion is a sign of worse prognosis, progress of the disease and are seen in 22% of CRC cases. Studies show independently of other factors a positive perineural invasion reduced the 5-year survival from 75% to 25% (32).

In a meta-analysis of 38 studies and 12,661 patients from 2015 perineural invasion lead to lower survival rates in CRC. Patients in grade 2 and 3 showed the perineural invasion independently an effect on the survival rate. In our study, perineural invasion reduced the survival rate as well (33).

N1c elevates disease to stage III, even in the absence of nodal metastases. The number of tumor deposits is recorded with site-specific factors but does not influence the designation (i.e. a patient with one tumor deposit and a patient with four tumor deposits are both staged as N1c). The number of tumor deposits is not added to the number of positive lymph nodes (34).

Among 20 patients we recruited in our study since 2018, none had the finding of a N1c grade. In this period 4 patients passed away, 2 of them without any lymphatic invasion (in IIA stage). Most our patients were assessed according to the AJCC-7 system. We also found that the prognosis of IIIA stage being better than the II stage, yet showing no statistical significance. Limited invasion depth and early regional LN metastasis show the indecisive character of the stage IIIA colon cancer. These tumors are rather superficial and their mLNs are mostly in the proximity of their main lesion, making them treatable with surgical resection and show good prognosis. However, the fact that they show metastasis although being superficial shows how aggressive their biological character is (25). Hence, there are further parameters in need, in addition to the LN metastasis and tumor invasion depth, to describe their character properly.

Tumor budding is the tumor infiltration in form of single cells or a small cell cluster (<5 cells) in the invasive tumor border and is not being considered by AJCC but required by the College of American Pathologists in the pathological findings. It is accepted as a sign of advanced mobility, invasive phenotype transformation and tumor progression. It is also being considered because of epithelial/mesenchymal transformation of neoplastic cells and a special type of apoptotic escape (35). A multi-center prospective study with 991 patients from 2019 tumor budding correlated with the tumor stage, size and the lymphatic invasion and lowered the survival significantly (36). In a review and meta-analysis from 2016 the value of tumor budding as a prognostic factor was studied. Out of 2.728 studies 34 were included and it was shown that the tumor budding affected the LN metastasis and local recurrence (37).

In the previous studies factors such as surgeons' experience, disease's stage, sample size, tumor size, individual immune response and the pathologist's ability to dissect lymph nodes causing a wide margin of dissected lymph nodes between 6 to 40.

The number of positive lymph nodes has a strong influence on the prognosis of CRC patients. LN assessment in CRC will ensure accurate patient staging. LN metastasis rate was increased in poorly differentiated tumors. It was also shown that higher number of mLNs and their localization in the stems of major vessels reduced the survival rate (38). Another study described the number of harvested mLNs correlated with the possibility of LN metastasis (39). Since the number of minimum harvested lymph nodes plays a defining role in the staging, we only included patients with at least 12 lymph nodes in our study. We speculate that this might be lowering our LNR values sensitivity

LNR is recommended as an additional staging to the pN stage for cancer patients. It is defined as the ratio of positive nodes to LNH and is based on the observation that LNH can affect positive node count and survival. The LNR has been shown in multiple retrospective studies to be an independent prognostic factor in cancer (gastric, pancreatic, euosophagus, bladder) patients (5).

Deployment of LNR can help prevent an over- or understaging. However, the most significant discussion on LNR is the cut-off point. Different authors agree on different cut-off values and a it has not been come to a consensus.

However, both univariate and multivariate analysis (p=0.034) showed LNR efficient. We believe with more upcoming studies on LNR in colorectal and other cancers, LNR will receive an important place among the prognostic factors.

In our study, we found that patient age (more than 60 years); tumor, T stage, N stage, LVI, perineural invasion, deposits, budding and LNR were the factors that influenced prognosis of patients according to the univariate analysis. Patients with a better young age and earlier stage of T staging, N staging and absence of perineural-LVI, tumor deposit-budding, and a lower LNR have improved survival rates.

However, when all eight factors are entered into the Cox proportional-hazards model, the multivariable analysis showed that only LNR showed statistical significance. LNR still had statistical significance in both the univariate and multivariable analysis. Neo-adjuvant therapies used especially in rectum cancer notably reduced the LN invasion. Therefore patients with rectum cancer treated with neo-adjuvant therapies are excluded in our studies and patients with stage II and III are being considered in the same group. Further research is required on only stage III or rectum cancer patients treated with neo-adjuvant therapies and its influence on the LNR should be regarded.

CONCLUSION

Currently, as in other malignities, the personalized approaches of diagnostics and therapies (consideration of somatic and germline mutations leading to microsatellite instabilities, RAS pathway (KRAS, BRAF, NRAS) mutations) come into prominence. We believe that prognostic factors, which do not require further expenses, such as LNR, peritoneal metastasis, tumor budding and tumor deposit are to gain further clinical value in diagnostics and therapy beside the innovative genetic analysis, mentioned earlier. Hence, with the upcoming publications, the mLNR, used already in other malignant diseases, will also become one of the indispensable prognostic factors.

Ethics

Ethics Committee Approval: Approval was obtained on 24.11.2021 from the Local Ethics Committee of University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital with the number E-48670771-514.99.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.H.K., Concept: G.H.K., Design: G.H.K., S.K., Data Collection or Processing: G.H.K., S.K., Analysis or Interpretation: G.H.K., S.K., Literature Search: G.H.K., S.K., Writing: G.H.K.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Pei JP, Zhang CD, Fu X, Ba Y, Yue S, Zhao ZM, et al. A Novel TNM classification for colorectal cancers based on the metro-ticket Paradigm. J Cancer 2021;12:3299-306.
3. Weiser MR. AJCC 8th Edition: Colorectal cancer. Ann Surg Oncol 2018;25:1454-5.
4. Horne J, Bateman AC, Carr NJ, Ryder I. Lymph node revealing solutions in colorectal: should they be used routinely? J Clin Pathol 2014;67:383-8.
5. Walker R, Wood T, LeSouder E, Cleghorn M, Maganti M, MacNeill A, et al. Comparison of two novel staging systems with the TNM system in predicting stage III colon cancer survival. J Surg Oncol 2018;117:1049-57.
6. Pyo JS, Kim JH, Lee SY, Baek TH, Kang DW. Metastatic lymph node ratio (mLNR) is a useful parameter in the prognosis of colorectal cancer; a meta-analysis for the prognostic role of mLNR. Medicina 2019;55:673.
7. Kim MJ, Jeong SY, Choi SJ, Ryoo SB, Park JW, Park KJ, et al. Survival paradox between stage IIB/C (T4N0) and stage IIIA (T1-2N1) colon cancer. Ann Surg Oncol 2015;22:505-12.
8. Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, et al. The clinical impact of the lymph node ratio as a prognostic factor after resection of pancreatic cancer. Anticancer Res 2014;34:2389-94.
9. Hou Y, Wang X, Chen J. Prognostic significance of metastatic lymph node ratio: the lymph node ratio could be a prognostic indicator for patients with gastric cancer. World J Surg Oncol 2018;16:198.
10. Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017;30:1299-311.
11. Lord AC, D'Souza N, Pucher PH, Moran BJ, Abulafi AM, Wotherspoon A, et al. Significance of extranodal tumour deposits in colorectal cancer: a systematic review and meta-analysis. Eur J Cancer 2017;82:92-102.
12. Samawi HH, Yin Y, Speers CH, Cheung WY. Sex disparities in outcomes of early stage colorectal cancer: a population-based study. Clinical Colorectal Cancer 2018;17:e711-7.
13. Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P, Langner C. Value of tumor size as a prognostic variable in colorectal cancer: a critical reappraisal. Am J Clin Oncol 2011;34:43-9.

14. Kamphues C, Andreatos N, Kruppa J, Buettner S, Wang J, Sasaki K, et al. The optimal cut-off values for tumor size, number of lesions, and CEA levels in patients with surgically treated colorectal cancer liver metastases: an international, multi-institutional study. J Surg Oncol 2021;123:939-48.

15. Crozier JE, McMillan DC, McArdle CS, Angerson WJ, Anderson JH, Horgan PG, et al. Tumor size is associated with the systemic inflammatory response but not survival in patients with primary operable colorectal cancer. J Gastroenterol and Hepatol 2007;22:2288-91.

16. Li X, An B, Ma J, He B, Qi J, Wang W, et al. Prognostic value of the tumor size in resectable colorectal cancer with different primary locations: a retrospective study with the propensity score matching. J Cancer 2019;10:313-22.

17. Brouwer NPM, Bos ACRK, Lemmens VEPP, Tanis PJ, Hugen N, Nagtegaal ID, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer 2018;143:2758-66.

18. Stintzing S, Tejpar S, Gibbs P, Thiebach L, Lenz HJ. Understanding the role of primary tumour localization in colorectal cancer treatment and outcomes. Eur J Cancer 2017;84:69-80.

19. Banaszkiewicz Z, Woda Ł, Tojek K, Jarmocik P, Jawień A. Colorectal cancer with intestinal perforation - a retrospective analysis of treatment outcomes. Contemp Oncol (Pozn) 2014;18:414-8.

20. Zielinski MD, Merchea A, Heller SF, You YN. Emergency management of perforated colon cancers: how aggressive should we be? J Gastrointest Surg 2011;15:2232-8.

21. Kim MS, Lim SW, Park SJ, Gwak G, Yang KH, Bae BN, et al. Survival rate and prognostic factors in perforated colorectal cancer patients: a case-control study. J Korean Soc of Coloproctol 2010;26:69-75.

22. Limam M, Matthes KL, Pestoni G, Michalopoulou E, Held L, Dehler S, et al. Are there sex differences among colorectal cancer patients in treatment and survival? a swiss cohort study. J Cancer Res Clin Oncol 2021;147:1407-19.

23. Steele SR, Park GE, Johnson EK, Martin MJ, Stojadinovic A, Maykel JA, et al. The impact of age on colorectal cancer incidence, treatment, and outcomes in an equal-access health care system. Dis Colon Rectum 2014;57:303-10.

24. van den Berg I, Coebergh van den Braak RRJ, van Vugt JLA, Ijzermans JNM, Buettner S. Actual survival after resection of primary colorectal cancer: results from a prospective multicenter study. World J Surg Oncol 2021;19:96.

25. Huang B, Feng Y, Ni M, Chen C, Cai G. Heterogeneous survival between stage IIA and stage IIIA colon cancer when different numbers of lymph nodes are harvested. ANZ J Surg 2018;88:316-21.

26. Delattre JF, Selcen Oguz Erdogan A, Cohen R, Shi Q, Emile JF, Taieb J, et al. A comprehensive overview of tumour deposits in colorectal cancer: towards a next TNM classification. Cancer Treat Rev 2022;103:102325.

27. Lin Q, Wei Y, Ren L, Zhong Y, Qin C, Zheng P, et al. Tumor deposit is a poor prognostic indicator in patients who underwent simultaneous resection for synchronous colorectal liver metastases. Onco Targets Ther 2015;8:233-40.

28. Nagayoshi K, Ueki T, Nishioka Y, Manabe T, Mizuuchi Y, Hiranashi M, et al. Tumor deposit is a poor prognostic indicator for patients who have stage II and III colorectal cancer with fewer than 4 lymph node metastases but not for those with 4 or more. Dis Colon Rectum 2014;57:467-74.

29. Ueno H, Hashiguchi Y, Shimazaki H, Shinto E, Kajiwara Y, Nakanishi K, et al. Peritumoral deposits as an adverse prognostic indicator of colorectal cancer. Am J Surg 2014;207:70-7.

30. Wang X, Cao Y, Ding M, Liu J, Zuo X, Li H, et al. Oncological and prognostic impact of lymphovascular invasion in Colorectal Cancer patients. Int J Med Sci 2021;18:1721-29.

31. Zhong JW, Yang SX, Chen RP, Zhou YH, Ye MS, Miao L, et al. Prognostic value of lymphovascular invasion in patients with stage III colorectal cancer: a retrospective study. Med Sci Monit: Med Sci Monit 2019;25:6043-50.

32. Liebig C, Ayala G, Wilks J, Verstovsek G, Liu H, Agarwal N, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol 2009;27:5131-7.

33. Yang Y, Huang X, Sun J, Gao P, Song Y, Chen X, et al. Prognostic value of perineural invasion in colorectal cancer: a meta-analysis. J Gastrointest Surg 2015;19:1113-22.

34. Dursun N, Paşaoğlu E. Changes and updates in staging colorectal carcinomas at American joint of cancer commitee and cancer reporting protocol of College of American Pathologists. J Curr Pathol 2018;2:78-84.

35. Liotta LA, Kohn E. Anoikis: cancer and the homeless cell. Nature 2004 26;430:973-4.

36. Ueno H, Ishiguro M, Nakatani E, Ishikawa T, Uetake H, Matsuda C, et al. Prospective multicenter study on the prognostic and predictive impact of tumor budding in stage II colon cancer: results from the SACURA trial. J Clin Oncol 2019;37:1886-94.

37. Rogers AC, Winter DC, Heeney A, Gibbons D, Lugli A, Puppa G, et al. Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. Br J Cancer 2016;115:831-40.

38. Faerden AE, Sjo OH, Bukholm IR, Andersen SN, Svindland A, Nesbakken A, et al. Lymph node micrometastases and isolated tumor cells influence survival in stage I and II colon cancer. Dis Colon Rectum 2011;54:200-6.

39. Ogino S, Nosho K, Irahara N, Meyerhardt JA, Baba Y, Shima K, et al. Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, microsatellite instability, and CpG island methylator phenotype. Clin Cancer Res 2009;15:6412-20.