Evaluation of Lymph Nodes Adequacy in Patients with Colorectal Cancer: Results from a Referral Center in Iran

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Abstract

Background

the presence of lymph node metastases is one of the most important prognostic factors for long-term survival of patients with colorectal cancer. So, thorough pathologic examination of at least 12 lymph nodes is essential for accurate staging this disease, as well as choosing the best adjuvant treatment. The aim of this study is to assess the adequacy of lymph node harvest in patients with colorectal cancer.

Methods

This observational cross-sectional study was performed on 584 patients with colorectal adenocarcinoma who had undergone surgery from 2012 to 2017. Thereafter, the relevant demographic, pathological, and surgical data were extracted from the patients' medical records and a relationship between the number of evaluated lymph nodes and other variables was also assessed.

Results

Among 584 studies cases in this study, 336 (57.5%) subjects had less than 12 evaluated lymph nodes. Mean and median number of the evaluated lymph nodes were calculated as 10.7 (± 5.6) and 10, respectively. The patients aged 60 years old and older and the cases with tumors located in descending colon and rectum were observed to have higher chances of inadequate lymph node retrieval. After an average follow-up for a 60-month period, 63% of the patients were alive. In the patients for whom less than 12 lymph nodes had been assessed, the median survival was estimated as 48 months. As well, in the patients for whom the number of the evaluated lymph nodes was ≥ 12, median survival was calculated as 54 months.

Conclusion

The number of the evaluated lymph nodes in our study was less than the standard number in more than half of the patients. Among various factors, older age, and tumor location in descending colon and rectum are found to be associated with sub-optimal assessment of lymph nodes. The number of lymph nodes dissected is also associated with survival.

Background

Colorectal cancer is one of the leading causes of cancer-related mortality worldwide. Accordingly, its incidence rate in Iran has been increasing over the last 25 years. Based on the cancer registry data reported in 2014, colorectal cancer is the third most common cancer following breast and stomach cancers, in Iranian people with the annual incidence of more than 7100 cases. At the same year, the age-

standardized incidence rate of this disease per 100,000 population was found to be 15.18 and 11.12% for men and women, respectively (1).

It is well-known that the presence of lymph node metastases is one of the most important prognostic factors effective on long-term survival of patients with colorectal cancer (2).

Therefore, thorough pathologic examination of adequate number of lymph nodes is essential for accurate staging this disease as well as choosing the best adjuvant treatment. Currently, adequate lymphadenectomy is defined as the presence of at least 12 lymph nodes in the surgical specimen. In this regard, previous studies have shown that the higher number of harvested lymph nodes is associated with the increased survival rate (3).

However, achieving the standard number of 12 resected lymph nodes is not always possible and many studies have previously demonstrated that inadequate retrievals are still present in a considerable number of patients with this disease (4).

There are many factors affecting the count and the quality of harvested lymph nodes during the surgery of colon cancer, including surgeon's expertise, extent of surgical resection, and experience of the pathology department and the pathologist, as well as some patient-related factors such as obesity, age, gender, and site of tumor (5, 6).

Inadequate number of the resected lymph nodes may result in a worse prognosis. Accordingly, patients with les number of the examined lymph nodes might be falsely down-staged and as a result, they might not receive the necessary adjuvant treatments (7).

Objective:

This study aimed to assess the adequacy of lymph node harvest in patients with colorectal cancer treated in a referral public hospital.

Methods

This observational cross-sectional study included 584 patients with colorectal adenocarcinoma who had undergone surgery (Open or Laparotomy Surgery) between 2012 and 2017. As well, the patients with incomplete records and missing necessary data (related to the objectives of our study) were excluded from the study. The surgical team working on the included patients were all colorectal surgeons specialized in colorectal cancer.

Relevant demographic, pathological, and surgical data were extracted from the patients' medical records and then inserted into a check list consisting of several items, including age, gender, tumor site, pathology stage, grade, number of the dissected lymph nodes, tumor size, and number of the involved lymph nodes.

3.1. Statistical Analysis

This descriptive analysis was performed on all variables of the dataset, including gender, age, tumor location, tumor size, T-stage, and grade and number of the evaluated lymph nodes. Logistic regression was used to assess the association between the number of the evaluated lymph nodes and other variables. In order to measure the adjusted odds ratio, all the variables were added to the model and for crude odds ratio, only one variable was considered in the model. In addition, 95% confidence interval (CI) for all ORs was reported. P-values ≤ 0.05 were considered as statistically significant. SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was finally used for statistical analyses.

Results

We obtained 584 records of the included patients in this study (350 men and 234 women) who had undergone surgery for colorectal cancer from 2012 to 2017. Among them, 257 (40%) patients were elective and 327 (56%) were emergency patients. The mean age of the patients was 59.4 (±13.3) years old ranged from 23 to 87 years old.

In the current study, the majority of the cases (50%) had T3 disease followed by T4 (34.1%), T2 (12.5%), and T1 (1.4%) tumor stages. Staging was recorded using TNM scoring system (Tumor size, Lymph Nodes affected, Metastases) based on the 7th edition of American Joint Committee on Cancer staging system (AJCC 7th Edition).

Accordingly, demographic and clinical characteristics of the studied patients are shown in Table 1.

The obtained data showed that in 336 (57.5%) patients, less than 12 lymph nodes had been assessed. Thereafter, the mean and median of the evaluated lymph nodes were calculated as 10.7 (±5.6) and 10, respectively.

Among various studied parameters, age and tumor site were found to be associated with the number of the retrieved lymph nodes. In this study, we found that the odds of having less than optimal assessed lymph nodes was higher in the patients aged 60 years old and above compared to the patients aged 40 years old and younger (OR = 2.42; 95% CI = 1.29-4.53).

Age can be considered as an important factor in the survival rate of patients, in a way that in the studied patients, it was found that the older the patients, the lower the survival rate. Moreover, the patients over the age of 50 years old died and their survival rates were lower than those of other younger patients. Therefore, age can be considered as a predictor for number of lymph node and a statistical significance also exists for survival difference.

In addition, our results show that patients with tumors located in descending colon or rectum had higher odds of having lower number of the evaluated lymph nodes compared to the patients with tumors

located in ascending or transverse colon (OR = 2.47; 95% CI 1.49 - 4.09 and OR = 2.37; 95% CI 1.42 - 3.94, respectively). It should be noted that all the patients with rectal involvement enrolled in this study were treated in terms of the NCCN (National Comprehensive Cancer Network) guidelines by neoadjuvant therapy.

As well, none of the patients received neoadjuvant-based treatments except those with rectal involvement.

We observed no relationship between other variables such as gender, tumor size, T-stage, and grade and the number of the dissected lymph nodes (Table 2).

After an average follow-up of 60 months (ranged from 36 to 96 months), 369 (63%) patients with colorectal cancer were alive. Median survival time of all the cases (584) was 49 months. Of all the patients, less than 12 lymph nodes had been assessed in 57.5% of them and their median survival time was48 months. Additionally, in 39.4% of the patients, number of the evaluated lymph nodes was ≥12 and median survival time was 54 months (Table 3). As shown in the table, survival was assessed by considering neoadjuvant treatments. Therefore, it was indicated that neoadjuvant theoretical complementary therapies can affect patient's survival.

Discussion

Adequate lymphadenectomy in colorectal cancer is essential to define the stage as well as planning the adjuvant therapy, especially for cases at stage III (8). Furthermore, several studies have demonstrated that adequate lymph node retrieval might be associated with the reduced risk of death and the improved survival rate (3, 9).

Results of our study show that in more than half of the patients (57.5%), the number of the evaluated lymph nodes was below the current standard number of 12, with the mean and median of 10.7 (± 5.6) and 10 in the examined lymph nodes, respectively. Age and tumor site in our study were found to be associated with the adequacy of the evaluated lymph nodes. As well, the odds of low number of the evaluated lymph nodes in the patients aged 60 years old and above was higher than that of the patients aged 40 years old and younger (OR = 2.42; 95% CI = 1.29–4.53) (Table 2).

A systematic review in 2007 analyzed 17 studies that included 61,371 patients. As a result, it concluded that the number of the examined lymph nodes was positively associated with survival of patients at stages II and III of colon cancer (10). Moreover, several other studies have demonstrated that the number of the resected lymph nodes is an independent prognostic factor, particularly in patients at stage II of the disease (8).

One explanation for this finding is that inadequate lymph node rerieval and its assessmant may incorrectly understage a node-positive patient as a node-negative one, which consequently results in inappropriate under-treatment (8, 11).

However, some experts believe that extensive lymphadenectomy might play therapeutic roles in improving tumor clearance and reducing the chance of metastatic spread through lymphatic system, especially in patients at advanced stages of the disease(8). On the other hand, many authors disagree with this latter mechanism, since a number of studies have failed to indicate that higher number of lymph node removal is associated with a better overall survival in patients with advanced-stage disease. Furthermore, a large study have previously examined the relationship between lymph node evaluation and node positivity using SEER (Surveillance, Epidemiology, and End Results) data from 1988 to 2008, and concluded that despite a significant increase in the number of the evaluated lymph nodes in the past decades, this does not result in an overall shift towards higher-staged cancers (11). This finding has questioned the role of “upstaging” in improving the survival of the patients undergoing extensive lymphadenectomy.

Nonetheless, in terms of the majority of currently used guidelines, retrieval of a minimum of twelve lymph nodes is necessary for an accurate pathologic staging. However, this recommended number of 12 is not always achievable. In fact, although the number of inadequate retrievals have significantly decreased over recent decades, they are still present in a consederable number of surgical cases (11).

The published reports in the United Stated between 2005 and 2010 showed that despite all effeorts and recommendations in this regard, lymphadenectomy was still inadequate in 48–63% of surgical cases (12). A similar trend was also reported from many European centers. For instance, a report from Germany showed that in 73% of colon cancer and 58% of rectum cancer cases, the number of examined lymph nodes was less than 10 (13). In addition, there are reports from England showing that the lymphadenectomy was inadequate in 33–50% of colorectal cancer cases (14, 15).

It was observed that several factors might affect the adequacy of lymph node retrieval or its assessment, including expertise of the surgeon and the pathologist as well as some patient-related factors such as various distribution of lymph nodes, colon, and rectum. Other clinical and demographic charectersitics such as age, gender, race, body mass index, tumor T-stage, and type of surgery have also been reported in some previous studies to play roles in this regard (5, 6, 8, 16, 17).

Although many studies have found no relationship between age and the number of evaluated lymph nodes (5), our results are in agreement to the findings of some other studies, showing that older patients have a greater probability of having less optimal lymph node retrieval (8, 17, 18). In this regard, one explanation could be the fact that extensive and time-consuming operations might not be feasible in older individuals due to the presence of comorbidities.

In our study, the patients with the primary tumor locations in descending colon and rectum had higher odds of having a report with a low number of lymph nodes compared to the patients with tumor locations in ascending and transverse colon. (OR = 2.47; 95% CI 1.49–4.09 and OR = 2.37; 95% CI = 1.42–3.94, respectively) (Table 2).

Accordingly, this is in agreement with the results of several other studies (5, 18–20). As well, many experts believe that lymph node retrieval is more difficult in rectal tumors, which may possibly be due to smaller size of the lymph nodes (8). However, some studies have shown that patients with left colon tumors have a greater chance of optimal lymph node removal compared to patients with right colon tumors (21).

Our results show that more than 12 dissected lymph nodes are associated with the increased survival rate, and on the other hand, less than 12 dissected lymph nodes are correlated to the decreased survival in colorectal cancer patients.

In this study, we found no relationship between the number of the evaluated lymph nodes and different stage groups, T-stage, gender, tumor grade, and tumor size.

Conclusion

In this study, we aimed to evaluate the adequacy of lymph node harvest in the patients with colorectal cancer who had been treated in a public referral center. Our results show that the number of the evaluated lymph nodes was less than the standard number in more than half of the studied patients. Among various factors, older age and tumor locations in descending colon and rectum were found to be associated with sub-optimal assessment of lymph nodes.

Abbreviations

Confidence interval
(CI)
American Joint Committee on Cancer staging system
(AJCC)
SEER
(Surveillance, Epidemiology, and End Results)

Declarations

Funding:

This project has been funded by Milad General Hospital.

Conflict of Interest:

Not applicable.

Ethics Approval and Consent to Participate:

This study was approved by the ethics committee on 18 October 2018 in Milad General Hospital, with number: [24906].Informed consent was obtained from all the included participants, their parents or legal guardian. The patients' confirmation and consent in writing were taken from the patients before entering the operating room. In patients under 16 years of age, written and oral consent was obtained from their family or legal guardian before entering the operating room.

Consent for Publication:

Not Applicable.

Availability of Data and Material:

All information is available and accessible at the hospital where the samples were collected.

Code Availability:

Not Applicable.

Authors' Contributions:

SVT and ARM; conceived of the presented idea, developed the theory and performed the computations, verified the analytical methods. HY; supervised the findings of this work, discussed the results and contributed to the final manuscript. MB and AG; contributed to the design and implementation of the research, analysis of the results and to the writing of the manuscript. AA; collected the samples and patients. All authors have read and approved the manuscript.

Tables

Table 1: Demographic and clinical characteristics of the patients.

Variables		Number	Percent
Age (years)	< 40	50	8.6
	40-60	233	39.9
	≥60	301	51.5
Gender	Male	350	59.9
	Female	234	40.1
T stage	T1	8	1.4
	T2	73	12.5
	T3	292	50.0
	T4	201	34.4
	Missing	10	1.7
N stage	N0	315	53.9
	N1	155	26.5
	N2	88	15.0
	Missing	26	4.5
TNM stage	stage I	62	10.6
	stage II	250	42.8
	stage III	248	42.5
	Missing	24	4.1
Grade	grade I	259	44.3
	grade II	266	45.5
	grade III	43	7.4
	Missing	16	2.7
Tumor size	< 5 cm	267	45.7
	≥ 5cm	277	47.4
	Missing	40	6.8
Tumor site	Right colon	159	27.2
	Transverse colon	58	9.9
	Left colon	178	30.5
	Rectum	189	32.3
Number of evaluated lymph nodes	<12	336	57.5
	≥12	230	39.4
	Missing	18	3.1
Mean number of evaluated lymph nodes		10.7 (± 5.6)	
Median number of evaluated lymph nodes		10.0	

Table 2: Relationship between demographic and clinical characteristics of patients and number of evaluated lymph nodes (<12 versus ≥12)

Variables		Odd Ratio (95% CI)	
		Crude	Adjusted
Gender	Female	Reference	Reference
	Male	0.88 (0.61 - 1.26)	0.849 (0.61 - 1.31)
Age (Year)	<40	Reference	Reference
	40-60	1.48 (0.82 - 2.65)	1.17 (0.63 - 2.2)
	60<	2.31 (1.29 - 4.15)	2.42 (1.29 - 4.53)
Tumor Location	Right colon	Reference	Reference
	Transverse colon	1.18 (0.64 - 2.17)	1.21 (0.62 - 2.33)
	Left colon	2.15 (1.36 - 3.4)	2.47 (1.49 - 4.09)
	Rectum	2.41 (1.52 - 3.8)	2.37 (1.42 - 3.94)
Tumor Size	< 5 cm	Reference	Reference
	> 5 cm	0.6 (0.41 - 0.86)	0.72 (0.48 - 1.08)
T Stage	T2	Reference	Reference
	T3	0.71 (0.4 - 1.25)	0.93 (0.5 - 1.73)
	T4	0.97 (0.54 - 1.77)	1.62 (0.83 - 3.15)
	T1	***	***
Grade	Grade I	Reference	Reference
	Grade II	0.79 (0.54 - 1.14)	0.8 (0.53 - 1.19)
	Grade III	0.74 (0.37 - 1.46)	0.84 (0.4 - 1.74)

Table 3: Median survival in participants

Participants	Median Survival (months)
<12 lymph node dissected	48
≥12 lymph node dissected	54
Total	49

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