Retrospective analysis for the LNM risk factors and effect of chemotherapy for the early colorectal cancer: A Chinese multicenter study

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Research article

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Abstract

Background Estimating the risk of lymph node metastasis (LNM) is crucial for determining subsequent treatments following curative resection of early colorectal cancer (ECC). This multicenter study analyzed the risk factors of LNM and the effectiveness of postoperative chemotherapy in patients with ECC.

Methods We retrospectively analyzed the data of 473 patients with ECC who underwent general surgery in five hospitals between January 2007 and October 2018. The correlations between LNM and sex, age, tumor size, tumor location, endoscopic morphology, pathology, depth of invasion and tumor budding (TB) were directly estimated based on postoperative pathological analysis. We also observed the overall survival (OS) and recurrence in ECC patients with and without LNM after matching according to baseline measures.

Results In total, 473 ECC patients were observed, 288 patients were enrolled, and 17 patients had LNM (5.90%). The univariate analysis revealed that tumor size, pathology, and lymphovascular invasion were associated with LNM in ECC (P=0.026, 0.000, and 0.000, respectively), and the multivariate logistic regression confirmed that tumor size, pathology, and lymphovascular invasion were risk factors for LNM (P=0.021, 0.023, and 0.001, respectively). There were no significant differences in OS and recurrence between the ECC patients with and without LNM after matching based on baseline measures (P=0.158 and 0.346, respectively), and no significant difference was observed between chemotherapy and no chemotherapy in ECC patients without LNM after surgery (P=0.729 and 0.052).

Conclusion Tumor size, pathology, and lymphovascular invasion are risk factors for predicting LNM in ECC patients. Adjuvant chemotherapy could improve OS and recurrence in patients with LNM but not always in ECC patients without LNM.

Background

Recently, as a result of the advocacy for endoscopic screening projects, the number of documented cases of early colorectal cancer (ECC) has increased [1]. ECC is defined as cancer located in the mucosa or submucosa with or without lymph node involvement (T1 TNM stage). Endoscopic treatment is absolutely the best choice of treatment for intramucosal ECC patients with no lymph node metastasis (LNM) and vascular invasion [2-4]. However, it has been reported that the LNM rate is as high as 7%-15% in T1 colorectal cancer [5-8].

Therefore, endoscopic treatment can accomplish local primary tumor resection but not lymphadenectomy, and using this procedure for the radical excision of ECC with LNM undoubtedly must increase the postoperative recurrence rate and unfavorable prognosis. Moreover, preoperatively determining whether ECC is associated with lymph node metastasis is critical for selecting a surgical approach and the extent of resection. Although previous studies have reported that poor differentiation, the submucosal invasion depth, lymphovascular invasion, and tumor budding (TB) are risk factors for LNM, sufficient evidence suggesting that a particular risk factor affects long-term prognosis and the

efficiency of postoperative chemotherapy is lacking. Thus, more evidence derived from long-term surveillance is needed. Furthermore, there is no consensus regarding the survival benefit of postoperative chemotherapy in early colon cancer [9].

In this study, our aim is to further analyze the risk factors in ECC patients with LNM in relation to various clinicopathologic characteristics. Moreover, we evaluate the effect of adjuvant chemotherapy following curative surgery.

1. Methods

1.1 Patient Selection and Data Collection

The demographic and clinical data of 473 individuals who underwent endoscopic treatment and general surgery in our hospital and other four affiliated hospitals were retrospectively collected between January 2007 and August 2018. Inclusion criteria were as follows: all cases diagnosed with ECC by postoperative pathological analysis after surgery. Exclusion criteria were as follows: recurrence after surgical resection, advanced colorectal cancer, presence of other primary malignant tumors, patients undergoing perioperative radiotherapy and preoperative chemotherapy, endoscopic resection of ECC and patients with familial adenomatous polyposis. Finally, all of the patients (288 patients after surgery) in the Jiangxi Province region were followed until November 30th, 2018 (Fig. 1). Moreover, the following data associated with chemotherapy were recorded: regimens, drugs, and times of treatment. The indications for chemotherapy were the presence of LNM or risk factors for LNM in ECC patients, such as poorly differentiated carcinomas, submucosal invasion, lympho-vascular invasion, or TB (tumor budding). We established a collaborative study group including five hospitals from two cities of Jiangxi province in China. The study group confirmed that the design and data collection of this retrospective research was performed in accordance with relevant guidelines and regulations. Informed consent was not required because this was a retrospective study. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Nanchang University.

1.2 Clinicopathological parameters

The following demographic and clinicopathological data were recorded: gender, age, tumor size (in maximum diameter), tumor location, endoscopic morphological type, depth of invasion, pathology, lympho-vascular invasion, tumor budding and LNM. Tumor differentiation is based on the 2010 WHO colorectal cancer pathology grading standard: colorectal cancer is divided into highly differentiated, moderately differentiated, poorly differentiated, and undifferentiated carcinoma. According to the morphology of the tumor under endoscopy, the ECC are divided into the uplift type (Ip, Isp, Is), the flat type (IIa, IIb, IIa + dep, non-granular type LST, granular LST), and the concave type (IIc, IIc + IIa, Is + IIc).

1.3 Statistical Analysis

IBM SPSS statistics (version 20.0) was applied for statistical analysis. The chi-squared test or T test were used to analyze the relations between the clinicopathological data and LNM in ECC. Logistic regression was used for multivariate analysis of the factors that were identified as significant in univariate analysis. The log-rank test was used for tumor recurrence and overall survival analysis. $P < 0.05$ was considered to indicate statistical significance.

2. Results

2.1 Clinicopathological parameters (Table 1)

Table 1
Univariate analysis of risk factors and occurrence of lymph node metastasis

Factors	**N**	**LNM(-),n(%)**	**LNM(+),n(%)**	***P-value***
N	288	271	17	
Gender				0.431
Male	162	154(53.47)	8(47.06)	
Female	126	117(46.53)	9(52.94)	
Age,χ ± SD(years old)	59.5 + 11.6	59.7 + 11.7	56.8 + 11.2	0.316
Smoking				0.084
Positive	68	67(23.26)	1(5.88)	
Negative	220	204(76.74)	16(94.12)	
Alcohol				0.520
Positive	43	41(15.13)	2(11.76)	
Negative	245	230(84.87)	15(88.24)	
Family history				0.557
Positive	10	10(3.69)	(0.00)	
Negative	278	261(96.31)	17(100.00)	
Tumor size, χ ± SD(mm)	30.0 ± 15.6	29.2 ± 15.4	38.3 ± 17.3	**0.026***
Tumor location				0.115
Rectum	186	171(63.10)	15(88.24)	
Sigmoid colon	68	68(25.09)	0	
Ascending colon	19	17(6.27)	2(11.76)	
Descending colon	10	10(3.69)	0	
Transverse colon	5	5(1.85)	0	
Endoscopic morphology				0.703
I (the uplift type)	248	232(85.61)	16(94.12)	
II (the flat type)	7	7(2.58)	0(0.00)	
III (the concave type)	25	24(8.86)	1(5.88)	
Uncertain	8	8(2.95)	0(0.00)	

Note: * *P < 0.05, ** P < 0.01.* LNM(-):No lymph node metastasis, LNM(+):Lymph node metastasis.

Factors	N	LNM(-),n(%)	LNM(+),n(%)	*P-value*
Pathology				**<0.001****
Highly differentiated	78	78(28.78)	0(0.00)	
Moderately differentiated	202	189(69.74)	13(76.47)	
Poorly differentiated	8	4(1.48)	4(23.53)	
Depth of invasion				0.255
Mucosal layer	76	74(27.31)	2(11.76)	
Submucosal layer	212	197(72.69)	15(88.24)	
Lympho-vascular invasion				**<0.001****
Positive	6	2(0.74)	4(23.53)	
Negative	282	269(99.26)	13(76.47)	
Tumor budding				0.833
Positive	3	3(1.11)	0(0.00)	
Negative	285	268(98.89)	17(100.00)	
Note: * *P < 0.05, ** P < 0.01.* LNM(-):No lymph node metastasis, LNM(+):Lymph node metastasis.				

Two hundred and eighty-eight patients who underwent surgery and lymph node dissection were enrolled (male: female = 162 :126). The age of the patients ranged from 27 to 82 years old. The cancer was located in the rectum in 186 patients, sigmoid colon in 68 patients, in the ascending colon in 16 patients, in the descending colon in 10 cases, and in the transverse colon in 4 cases. In the endoscopic morphological classification, there were 248 cases of the type I (including the uplift type, Ip, Isp, Is), 7 cases of type II (including the flat type, IIa, IIb, IIa + dep, non-granular type LST, granular LST), and 25 cases of type III(including the concave type, IIc, IIc + IIa, Is + IIc). The diameter of the mass ranged from 7-120 mm (30.0 ± 15.6 mm). For pathological grading, 78 cases were highly differentiated, 202 cases were moderately differentiated, 8 cases were poorly differentiated. With regard to the depth of invasion, 76 cases infiltrated the mucosal layer, while 212 cases infiltrated the submucosal layer. A total of 6 patients patients had lymphovascular invasion, and 3 cases had tumor budding.

2.2 Univariate analysis of factors associated with LNM in ECC

LNM was more prevalent in patients with larger tumor size ($P = 0.026 < 0.05$). Further, the rate of LNM was also highest for the uplift type than for other endoscopic types in all the patients. For the LNM group, there were 4 cases with poorly differentiated type (23.53% VS 1.48%, LNM VS no LNM group), the others presented with moderately differentiated type (76.47% VS 69.74%, LNM VS no LNM group) ($P < 0.01$).With respect to the depth of invasion, there were no significant difference ($P > 0.05$) between LNM and no LNM

group(88.24% vs 72.69%). Furthermore, the rate of lympho-vascular invasion was higher in cases with LNM than in those without LNM (23.53% vs 0.74%, $P < 0.001$). Details of the comparisons with *P*-values were shown in Table 1.

Univariate analysis of the clinicopathological factors assessed in patients with LNM and without LNM revealed a significant relationship between LNM and Tumor size (t=-2.234, $P = 0.026 < 0.05$), Pathology differentiation, lymphovascular invasion ($X^2 = 23.593$, 40.734, both $P < 0.001$). LNM rates were higher in patients with poorly differentiated carcinomas, tumor in large diameter, lympho-vascular invasion. However, gender, age, tumor location, endoscopic morphology, depth of invasion and tumor budding did not have a statistically significant association with LNM ($P = 0.431$, 0.316, 0.115, 0.703, 0.255 and 0.833 respectively; Table 1).

2.3 Multivariate logistic regression analysis of factors associated with LNM in ECC

Multivariate logistic regression analysis was used for multivariate analysis of the following factors that were identified as significant during univariate analysis: tumor size, pathology differentiation and lympho-vascular invasion. The analysis showed that tumor size, pathology differentiation and lympho-vascular invasion were the risk factors for LNM in ECC (OR = 1.036, and $P = 0.021$; OR = 8.877, and $P = 0.023$; OR = 0.039, and $P = 0.001$; Table 2).

Table 2
Multivariate logistic regression analysis of ECC lymph node metastasis

Factors	OR	*P*-value	95% CI
Tumor size	1.036	**0.021 ***	1.005–1.068
Pathology differentiation	8.877	**0.023 ***	1.357–58.050
Lympho-vascular invasion	0.039	**0.001 ***	0.005–0.285
Note: * *P < 0.05*			

2.4 Kaplan-Meier estimates of overall survivals and recurrence rates associated with chemotherapy in no-LNM ECC patients

The overall survival and recurrence rate of no-LNM ECC patients was determined by Kaplan–Meier analysis between chemotherapy (20 cases included) and no- chemotherapy (251 cases included) groups. The 11-year overall survival rates and recurrence rates were 95.94% (260/271) and 3.32% (9/271) individually in all 271 followed up no-LNM ECC patients after surgery. Furtherly, 20 patients received chemo-therapy after resection of the tumor, and 2 of those patients had recurrences, including 1 death. The main chemotherapy regimen included CapeOX (L-OHP + Cap) and FLOX (L-OHP + CF + 5-FU), and periods of treatment ranged from 4 to 12 weeks. In this study, the patients treated with chemotherapy after surgery had no difference in overall survival rates (95.0% vs. 96.02%, $P = 0.729 > 0.05$). For the ECC

patients without LNM, there were no significant differences between the chemotherapy and non-chemotherapy groups in overall survivals and recurrence rates (Fig. 2).

2.5 Kaplan-Meier estimates of overall survivals and recurrence rates in matched LNM and no-LNM ECC patients according to the base-line

Seventeen ECC patients with LNM were matched with no LNM patients. The base line was showed in the Table 3. But more patients in the LNM group received chemotherapy therapy ($P = 0.034 < 0.05$) and got lymphovascular invasion ($P = 0.033 < 0.05$) than the ECC patients with negative LNM. Kaplan-Meier analysis showed that there were no significant differences of overall survivals and recurrence rates between the ECC patients with LNM and without LNM (Fig. 3).

Table 3
Base-line of the ECC patients with and without LNM after matching

Factors	**N**	**LNM(-)**	**LNM(+)**	***P-value***
	n = 34	**n = 17**	**N = 17**	
Gender				0.730
Male	15	7	8	
Female	19	10	9	
Age (years old)	57.1 ± 11.4	57.5 ± 12.3	56.8 ± 11.2	0.851
Chemotherapy				**0.034***
Negative	27	16	11	
Positive	7	1	6	
Smoking				0.287
Negative	30	14	16	
Positive	4	3	1	
Alcohol				0.628
Negative	29	14	15	
Positive	5	3	2	
Family history				0.628
Negative	31	15	16	
Positive	3	2	1	
Tumor size	38.3 ± 17.3	38.3 ± 17.3	38.3 ± 17.3	1.000
Tumor location				1.000
Rectum	30	15	15	
Colon	4	2	2	
Endoscopic morphology				0.480
I (the uplift type)	30	14	16	
II (the flat type)	1	1	0	
III (the concave type)	3	2	1	
Pathology				0.504

Note: * *P < 0.05*, LNM(-):No lymph node metastasis, LNM(+):Lymph node metastasis.

Factors	N n = 34	LNM(-) n = 17	LNM(+) N = 17	*P-value*
Highly differentiated	3	2	1	
Medium differentiated	27	14	13	
Poorly differentiated	4	1	3	
Depth of invasion				1.000
Mucosal layer	4	2	2	
Submucosal layer	30	15	15	
Negative	30	17	13	
Positive	4	0	4	
Note: * $P < 0.05$, LNM(-):No lymph node metastasis, LNM(+):Lymph node metastasis.				

Discussion

Early colorectal cancer is defined as an invasive adenocarcinoma of any size invading into, but not beyond, the submucosa, with or without LNM. According to the cancer classification criteria of 2000 from the WHO, when the tumor only invades the submucosa (pT1), it is defined as ECC. However, carcinoma in situ (Tis) and intramucosal carcinoma are customarily classified as ECC in China and Japan due to their different characteristics from the Western countries. A total of 19 carcinomas in Epithelial layer, 57 in Mucosal layer and 212 Submucosal carcinoma cases were included in our study. In our study, the rate of LNM occurrence among the ECC cases was 5.90% (17/288). The rate of LNM has been previously reported to range from 7–15% [5–8], which is higher than our findings. Previously, it has been established that LNM may be highly correlated with lympho-vascular invasion[10–11], tumor size[12–17], TB[18] ,tumor invading in submucosa[19–24] and pathological differentiation[25–27]. In our study, lympho-vascular invasion was identified to be an independent risk factor for LNM in ECC. Moreover, the incidence of lympho-vascular invasion in ECC patients with LNM was 23.53% as opposed to 0.74% in those without LNM ($P < 0.001$). And the poor differentiated cases accounted for 2.78% (8/288) of all cases. Our study confirmed that lympho-vascular invasion, tumor size and pathological differentiation were the risk factors for LNM in ECC patients by multivariate logistic regression analysis. While the pathological differentiation of the tumor is the most reliable predictor for LNM, which is supported by a meta-analysis for ECC [27]. As other studies [28, 29] showed that we found that the depth of tumor invasion in ECC patients was not related to LNM($P = 0.255 > 0.05$)

Currently, it is still unclear whether chemotherapy is needed for the ECC patients after the resection of tumor. The NCCN(National Comprehensive Cancer Network)and JSCCR(Japanese Society for Cancer of the Colon and Rectum) guidelines recommend that local removal and regular follow-up are the standard

treatment for selected ECC patients at TisN0M0 and T1N0M0 stage[30–32], while the ECC patients with LNM are suggested to receive the adjuvant chemotherapy after curative surgery. As for the ECC patients without LNM, chemotherapy seemed not to be beneficial for improving the overall survival and recurrence rates (Fig. 2).

However, Seyed Reza, et al [33] found that the current guidelines for chemotherapy in T1N1M0 might not be necessary. Furtherly, we matched the LNM-ECC patients to another no-LNM patients according to the base-line (Table 3). More patients in the LNM group (64.71%) chose adjuvant chemotherapy than the no-LNM group (5.88%, $P = 0.034 < 0.05$). For the two groups, chemotherapy was the only difference. Moreover, we found that there were no significant differences of overall survival and recurrence rates between the matched LNM and no LNM groups (Fig. 3). Thus, our study proved that adjuvant chemotherapy could improve the overall survival or reduce the recurrence rate of the ECC patients with LNM.

In conclusion, this study showed that tumor size, pathological differentiation and lympho-vascular invasion are the main risk factors for LNM in patients with ECC. Whether the ECC patients should choose surgery or endoscopic resection, might make the decision after considering the potential risks of LNM. Although the suggestion that the ECC patients with LNM should receive adjuvant chemotherapy is still controversial. Our results verify that the postoperative chemotherapy is necessary for the ECC patients with LNM, but might not be helpful for the ECC patients without LNM.

Conclusion

In summary, tumor size, pathology, lympho-vascular invasion were risk factors for predicting LNM in early colorectal cancer (ECC) patients. It's no necessary for the ECC patients to receive chemotherapy after resection of tumor, while adjuvant chemotherapy could improve the overall survival and recurrence in patients with LNM after resection.

Abbreviations

LNM: lymph node metastasis; ECC: early colorectal cancer; TB: tumor budding; NCCN: National Comprehensive Cancer Network; L-OHP: Oxaliplatin; CAP: Capecitabine; CF: Calcium folinate; 5-FU: 5-fluorouracil; Chemo: chemotherapy.

Declarations

Ethics approval and consent to participate

Not applicable. All data in this study are publicly available.

Consent for publication

Not applicable.

Declarations

None.

Availability of data and material

All analyzed data are included in this published article. The original data are available upon reasonable request to the corresponding author.

Competing interests

The authors have no conflicts of interest to declare.

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Author contributions

CZ, DX and FC contributed equally to this work; CZ and DX designed the study and drafted the manuscript; FC,DX, QL, QW and JH collected the data; CZ, GL and HZ analyzed the data; CZ and YC revised the manuscript for important intellectual content; CZ and YC made substantial contributions to conception, design, and coordination of the study and gave final approval of the version to be published. All authors have read and approved the final manuscript.

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None.

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Tables

Table 1 Univariate analysis of risk factors and occurrence of lymph node metastasis

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Age,χ±SD(years old)	59.5+11.6	59.7+11.7	56.8+11.2	0.316
Smoking				0.084
Positive	68	67(23.26)	1(5.88)	
Negative	220	204(76.74)	16(94.12)	
Alcohol				0.520
Positive	43	41(15.13)	2(11.76)	
Negative	245	230(84.87)	15(88.24)	
Family history				0.557
Positive	10	10(3.69)	(0.00)	
Negative	278	261(96.31)	17(100.00)	
Tumor size, χ±SD(mm)	30.0 ±15.6	29.2 ±15.4	38.3 ±17.3	**0.026***
Tumor location				0.115
Rectum	186	171(63.10)	15(88.24)	
Sigmoid colon	68	68(25.09)	0	
Ascending colon	19	17(6.27)	2(11.76)	
Descending colon	10	10(3.69)	0	
Transverse colon	5	5(1.85)	0	
Endoscopic morphology				0.703
I (the uplift type)	248	232(85.61)	16(94.12)	
II (the flat type)	7	7(2.58)	0(0.00)	
III (the concave type)	25	24(8.86)	1(5.88)	
Uncertain	8	8(2.95)	0(0.00)	
Pathology				**<0.001****
Highly differentiated	78	78(28.78)	0(0.00)	
Moderately differentiated	202	189(69.74)	13(76.47)	
Poorly differentiated	8	4(1.48)	4(23.53)	
Depth of invasion				0.255
Mucosal layer	76	74(27.31)	2(11.76)	
Submucosal layer	212	197(72.69)	15(88.24)	
Lympho-vascular invasion				**<0.001****
Positive	6	2(0.74)	4(23.53)	
Negative	282	269(99.26)	13(76.47)	
Tumor budding				0.833
Positive	3	3(1.11)	0(0.00)	
Negative	285	268(98.89)	17(100.00)	

Note: * *P<0.05, ** P<0.01.* LNM(-):No lymph node metastasis, LNM(+):Lymph node metastasis.

Table 2 Multivariate logistic regression analysis of ECC lymph node metastasis

Factors	OR	*P*-value	95% CI
Tumor size	1.036	**0.021 ***	1.005-1.068
Pathology differentiation	8.877	**0.023 ***	1.357-58.050
Lympho-vascular invasion	0.039	**0.001 ***	0.005-0.285

Note: * *P<0.05*

Table 3 Base-line of the ECC patients with and without LNM after matching

Factors	N n=34	LNM(-) n=17	LNM(+) N=17	*P-value*
Gender				0.730
Male	15	7	8	
Female	19	10	9	
Age (years old)	57.1±11.4	57.5±12.3	56.8±11.2	0.851
Chemotherapy				**0.034***
Negative	27	16	11	
Positive	7	1	6	
Smoking				0.287
Negative	30	14	16	
Positive	4	3	1	
Alcohol				0.628
Negative	29	14	15	
Positive	5	3	2	
Family history				0.628
Negative	31	15	16	
Positive	3	2	1	
Tumor size	38.3±17.3	38.3±17.3	38.3±17.3	1.000
Tumor location				1.000
Rectum	30	15	15	
Colon	4	2	2	
Endoscopic morphology				0.480
I (the uplift type)	30	14	16	
II (the flat type)	1	1	0	
III (the concave type)	3	2	1	
Pathology				0.504
Highly differentiated	3	2	1	
Medium differentiated	27	14	13	
Poorly differentiated	4	1	3	
Depth of invasion				1.000
Mucosal layer	4	2	2	
Submucosal layer	30	15	15	
Negative	30	17	13	
Positive	4	0	4	

Note: * *P<0.05,* LNM(-):No lymph node metastasis, LNM(+):Lymph node metastasis.

Figures

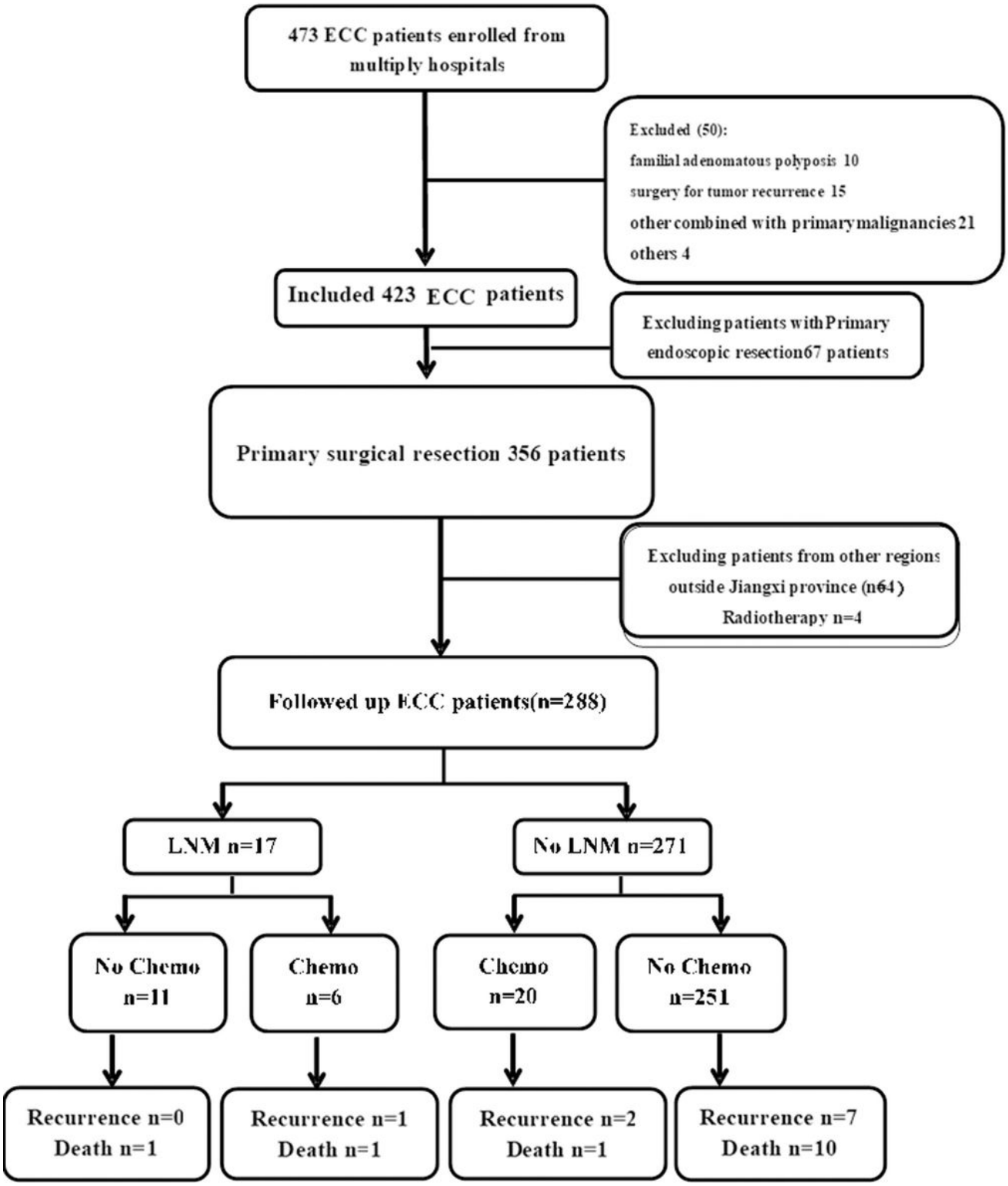

Figure 1

Flowchart of enrolled patients. Abbreviations: ECC, early colorectal cancer; LNM, lymph node metastasis; Chemo, chemotherapy.

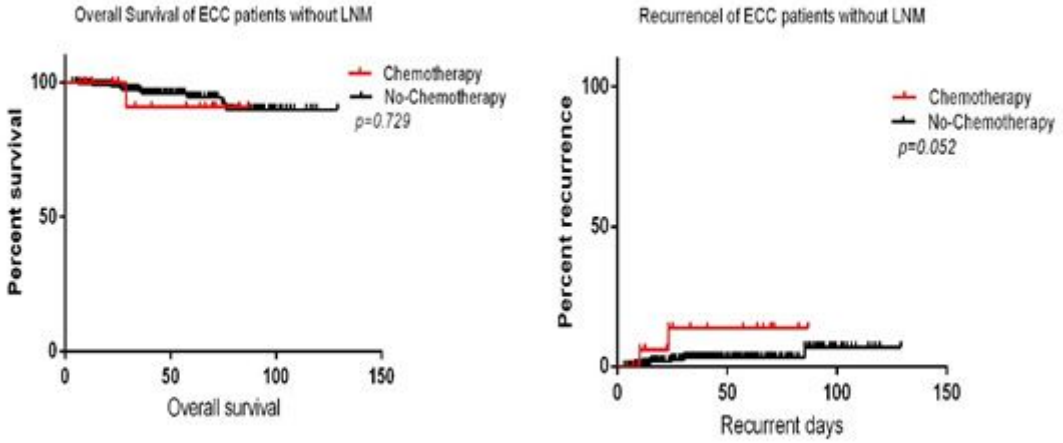

Figure 2

Overall survivals and recurrence rate in followed-up ECC patients without LNM.

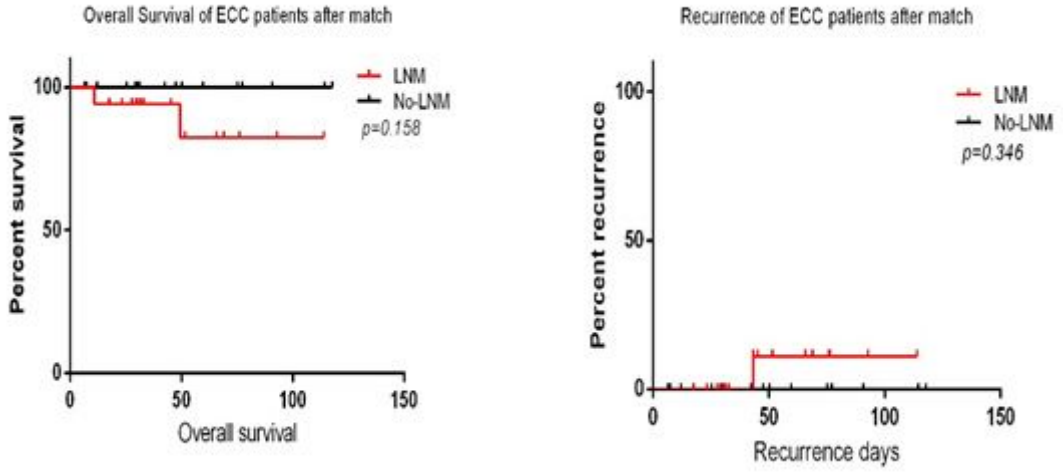

Figure 3

Overall survivals and recurrence rate in followed-up ECC patients with LNM and without LNM after match.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- DataAvailabilitystatement.pdf
- statementInstitutionalReviewBoard.pdf