Prognostic significance of lymph node dissection on stage-specific survival for patients with primary small intestine tumor treated with enterectomy: A population-based study, 2004-2015

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Research article

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Abstract

Background: The positive rate of lymph node detection(LND) can be used as a predictor of prognosis for patients undergoing radical resection of small bowel tumors; thorough local LND may be crucial for the accurate staging and management of the disease.The purpose of our study was to determine the effect of the LND in specific stages.

Methods: This study included 5413 patients with primary small intestine tumors after enterectomy within SEER database from 2004-2015. A multivariable COX model and Kaplan-Meier plots survival curves were used to analyze survival.

Results: Of the 5413 patients, 4675(86.4%) underwent lymphadenectomy, and 3896(72.0%) were moved 4 or more than 4 lymph nodes. LND was performed in 67.8%, 83.3%, 87.9%, 89.3% in pT1/2/3/4 disease. In multivariable Cox regression analyses, LND was associated with OS and CSS, and the extended LND are better than limited LND (all P<0.05 except pT2). Kaplan-Meier plots survival curves showed that LND can benefit patients.

Conclusions: The removal of LND with 4 or more lymph nodes in pT1/3/4 patients has relatively obvious benefits for survival. The effect of LND with more lymph nodes is significantly better than limited LND. For pT1, pT3 and pT4, LND can be considered.

Introduction

Primary malignant small intestine tumor is a very rare gastrointestinal tumor. Due to its rarity, we still do not know enough about small intestine tumors. The most frequent small bowel tumors are adenocarcinoma (30-40%), neuroendocrine tumors (35-44%), lymphomas (10-20%) and gastrointestinal stromal tumors (12-18%)[1-3]. Even with the advances in therapeutic methods, surgery is still the main method of curing small bowel tumor patients[4].

Lymph node status is one of the most important prognostic indicators for solid organ malignancies. As tumors develop, they acquire increased genetic heterogeneity, which is associated with tumor progression and subsequent spread. In the AJCC Cancer Staging Manual (7th edition), the TNM classification places patients with regional lymph node metastasis (N1) in stage IIIB disease. Recently, several studies discussed the number of positive lymph node detections used to define the grade of lymph node metastasis in order to obtain a better survival prognosis[5-8], which indicates that lymph node metastasis is a very important prognostic indicator of small intestinal tumors. It has been proved that for patients undergoing radical resection of small bowel tumors, the positive rate of lymph node detection can be used as a predictor of prognosis[7, 9]. A study[10] believe it be used as a predictor of tumor recurrence and distant metastasis after curative surgery. Therefore, thorough local lymph node dissection may be crucial for the accurate staging and management of the disease[5, 6]. However, lymph node dissection will still

bring some controversy, a higher number of positive lymph node detections may be associated with a poorer prognosis[5].

There is no precise conclusion as to whether ample benefits can be obtained from lymph node dissection of various degrees. Although the reports of each stage model are separate, there is still a small amount of them about evaluation and comparison of the effect of LND in patients with small bowel cancer at different T stages. Therefore, We look forward to being able to further judge the role and the usage indicators of lymph node dissection to pursue greater benefits. the purpose of this study is to evaluate the benefits that different degrees of lymph node dissection can bring to patients with small bowel tumors, and to predict cancer specific survival in each specific-stage disease, based on a large population from the Surveillance, Epidemiology, and End Results(SEER) database.

Methods

Patients Selection and Data resource

Data of this study was collected from the US Surveillance, Epidemiology and End Results (SEER) database. SEER data(Incidence- SEER 18 Regs Custom Data with additional treatment fields, Nov 2018 Sub,1975-2016 varying) were obtained via SEER*Stat software(Version 8.4.6; http://seer.cancer.gov/seerstat/). SEER provided population-based data about cancer incidence, feature, treatment and survival status throughout the country covered more than 34% population. We defined the primary small intestinal cancer by the ICD for Oncology, Version 3 (ICD-O-3). Data of lymph node dissection was recorded from 2004 in SEER database so we collected the data from January 1 2004 through November 30 2015.

The patients are between 15 and 90 years with small intestine tumor underwent enterectomy between 2004 and 2015. Patients are included in our study according to the following requirements: (1) primary small intestinal cancer at CS Schema-AJCC 6th Edition, (2) active follow-up at Type of follow-up expected, (3)clear histopathology. We excluded cases: (1) death certificate only or autopsy only, (2)included information deficiency, (3)with follow-up periods of less than 6 months. (Figure 1)A total of 5413 patients with primary small intestine cancer were characterized without important information missing (Table 1). The primary outcome in this study was a measure of cancer-specific death, defined as a death with the specific cancer of interest listed as the primary cause of death in the SEER registries[11].

Variables for analyses

Patients were stratified according to presence or absence of LND. The covariables include age of diagnosis, gender(male, female), race(black, white, other),marital status(married , single , other), grade(□□ □□□, □)□tumor stage(T1, T2, T3, T4), lymph node stage(N0 , N1 , N2 , N3), metastasis(M0, M1), tumor size(□ 5cm , ≥5 cm) and year of surgery categories(2004-2007 , 2008-2011 , 2012-2015)

Statistical Analysis

A description and comparison of the baseline characteristics of the patients from the database (SEER) treated with lymph node dissection or no without lymph node dissection was conducted in which the concomitant variables were compared by the chi-square or Fisher's exact test, as appropriate. Kaplan-Meier plots survival curves and log rank tests were used to compare the overall survival (OS) and the cancer- special survival (CSS). First, Cox proportional hazards models were used to test the effect of the lymph node dissection in small intestine cancer surgery by comparing the LND and no LND group and assumptions of proportionality were verified. All statistical analyses were performed with SPSS version 24.0 (SPSS Inc, Chicago, IL, USA), GraphPad Prism 8.0.4 and R version 3.6.1 (http://www.r-project.org). Statistical significance was set at two-sided P <0.05. The Kaplan-Meier method was used to estimate overall survival rate and cancer-special survival rate in the different stage and the differences were evaluated using the log-rank test with a threshold of P<0.05.

Results

Characteristic of patients

Data of 5413 patients with complete information who underwent small bowel resection was collected from SEER database. Among them, 2943(54.4%) are male and 2470(45.6%) are female. The selection schema for patients in the SEER database is shown in Figure 1. The median patient age was 68 years (range 21~89) and 3518(65.0%) were over 60 years old. According to pathology,1682(31.09%) were well differentiated, 2205(40.74%) were moderately differentiated, 1400(25.9%) were poorly differentiated and 125(2.3%) were undifferentiated. Most of patients were T3(n=2428;44.9%) and T4(n=2029;37.5%). More than half of patients had lymph node metastasis (Nx-N1; n=3018;55.8%) and most patients do not have distant metastasis (M0; n=4134;76.4%). About half of the patients are already married (n=3191;59.0%). Most patients have a tumor diameter less than 5cm (n=3686; 68,1%). The number of people diagnosed with small bowel tumors has risen in recent years, 2004-2007(n=1214;22.4%), 2008-2011(n=1982;36.6%), 2012-2015(n=2217;41.0%) (Table 2).

Comparing the covariables of LND and NO LND groups, we found that age, race, grade, T stage, N stage, Marital status and tumor size were predictive factors. Younger, non-white race, poorly differentiated, higher t-stage, lymph node metastasis, unmarried, and larger tumor size are the determinants of lymph node dissection. (Table 2)

Survival analyses according to LND status

The 3-year ,5-year and 10-year OS CSS rates for all T stages patients grouped by the different LND status were shown in Table 3. For the LND patients and no LND patients, the overall survival rate and cancer-special survival rate were 51.1% vs 38.6% and 68.2% vs 61.4%. For LND and no LND patients, T stage-special 5-year OS rates and CSS rates were as follow: pT1 were 76.2% vs 48.2% and 95.1% vs 78.3%, pT2 were 73.2% vs 64.7% and 89.3% vs 86.5%, pT3 were 54.3% vs 37.4% and 71.6% vs 65.7%, pT4 were 37.9% vs 23.2% and 53.6 v 52.7%.

In patients with limited LND and completed LND, the overall survival rate and cancer-special survival rate were 43.9% vs 52.5% and 65.6% vs 68.6%. In T stage-special patients, the OS rates and CSS rates were as follow: pT1 were 70.4% vs 77.6% and 89.9% vs 94.0%, pT2 were 63.0% vs 74.1% and 85.4% vs 90.0%, pT3 were 50.7% vs 53.6% and 67.0% vs 72.6% and pT4 were 31.8% vs 38.9% and 52.0% vs 53.9%. In patients who had pN0 and pN1-3 tumor, the 5-year OS rate and CSS rates were 50.9% vs 48.2% and 74.0% vs 63.5%.

According to the LND status, extended LND status and neuroendocrine adenoma status, we analyzed the hazard rates of the patients in special T stage. Compared to the patients treated with no LND, the patients who underwent LND had lower hazard rate for OS (HR=0.592, P=0.013), but not CSS (HR=0.981, P=0.809) (Table 4, Table 5).Subdivided according to stage ,LND would provide benefits in different stage except pT2 disease. Patients who accepted limited LND treatment had not enough benefit from LND in specific-stage disease except pT1(HR=0.516;P=0.012).By contrast, patients who treated by extended LND would benefited more from lymph node dissection(HR=0.567;P=0.009) ,but not in pT2 stage(0.716;P=0.114).Similar results appear in the CSS analysis(Table 5).We only find that patients with pT1 tumor could benefit from the limited LND when OS rates were tested(HR=0.516;P=0.012), and we didn’t find any other benefit from limited LND in both OS and CSS tests. Otherwise, the positive and protective effect could only be found in pT1 stage when the N-stage were compared for OS rates. Quite differently, when it comes to CSS rates, with the exception of pT1 and pT2 stage, patients with N0 stage could get more benefit from the extended LND (Table 5).

Discussion

Compared with colorectal cancer, the incidence of small bowel tumors is very low, so we need a larger population sample to determine the benefit of lymph node dissection on patients with small bowel cancer tumors, and to determine that this behavior will not be a burden on patients. According to the research results of Overman MJ et al., adequate nodal assessment is much less common in small bowel malignant tumor than large bowel malignant tumor; and it appears that small bowel malignant tumor, in particular duodenal malignant tumor, is understaged[12].

Lymph node dissection, also called lymphadenectomy, was divided into LND (including limited LND and extended LND) and no LND, which could be essentially relevant with prognostic end of primary small intestinal tumor. Therefore, evaluating lymph node dissection in small bowel tumor surgery is of great significance to prevent negative outcomes. Several studies have demonstrated that LN metastasis is a negative prognostic factor in small bowel adenocarcinoma[6, 13]. Limited by the data in the SEER database, we are unable to clarify the patient's disease choices and indications for surgery, but there are other studies that prove that lymph node dissection can make patients with small bowel tumors get greater benefits in surgery. In our study, LND was performed in 86.4% of all patients treated with enterectomy. According to reports by Wilhelm A et al, as the number of detected lymph nodes increased (>9), the number of positive lymph nodes detected also increased steadily, and the greater number of detected lymph nodes was also associated with a better prognosis, which is also in line with our research trends[14].

According to result, younger age, non-white race, high grade, high T stage, unmarried, bigger tumor size, neuroendocrine adenocarcinoma were important factors to make LND decision.

Surgery is the most commonly used treatment for small bowel tumors[2, 15], and adjuvant chemotherapy has also been shown to play a role in improving the survival outcome of patients [16].Up to now, the therapeutic effect of LND is still discussed controversially. From 2004 to the present, the number of lymph node dissections used in small bowel tumor resection has increased slightly, but the proportion of lymph node dissection and extended lymph node dissection have not changed significantly (Figure S2-3). This may be due to increased physical examination leading to increased detection of small bowel tumors, but lymph node dissection and deep lymph node dissection have not increased. In other cancers, there has been a report that the proportion of LND is gradually increasing[17, 18], and this trend is not obvious in small intestine tumors, which may be caused by the rarity of small intestine tumors. Kaplan-Meier plots illustrated that extended LND with 4 or more regional lymph nodes removed might benefit OS for all T stage, but CSS only for pT1 obviously, and limited LND with 1 to 3 regional lymph nodes removed may benefit OS for all T stage except pT2(Figure 2-3). In multivariable Cox regression analyses, we can see that extended LND may benefit for SBT patients for pT1, pT2 and pT4 stage both for OS and CSS. Compared to limited LND, extended LND can bring obvious benefits, although at pT2 stage, also no obvious difference. Although the phenomenon in the pT2 stage is strange, further research is needed to consider. Doctors may need to be more careful when evaluating the stage of pT2 patients.

When comparing small intestinal neuroendocrine tumors with small intestinal non-neuroendocrine tumors, we can find that they can also obtain significant benefits from LND (Figure S1). In the current clinical research, most researchers focus on primary small intestinal adenocarcinoma and small intestinal neuroendocrine tumors. Considering the rarity of small intestine tumors, we hope that LND can obtain similar benefits in these subtypes. In COX analysis, extended LND has a significant survival rate in all stage diseases except pT2, while restricted LND has not significantly improved the survival outcome of patients, and neither of them has significantly benefited patients in pT2 disease. However, this may also be due to selection bias. In any case, further prospective research is needed to verify. Up to now, there have been several studies supporting the comprehensive and thorough lymph node dissection of small bowel tumors in order to obtain better survival benefits. According to Arnaud Pasquer et al.[19], they suggested that systematic, extensive LN resection may be required to prevent unresectable locoregional recurrence in retropancreatic portion, as a result of skip metastases. Sophie Lardière-Deguelte et al.[20] evaluated the correlation between the length of resected small bowel and the number of removed LNs, and to propose a preoperative morphological classification of siNET-associated LNs. They believe that the best lymph node dissection is not simply a prolonged small bowel resection, but that the classification of mesenteric LNs should be standardized to help standardize the management of NET patients. According to Benjamin M Motz's report[21], about 20% of patients with small bowel cancer resection from The National Cancer Database have not received lymph node dissection, although this can bring some benign effects.

Our research is still subject to some restrictions, which may affect our conclusion to a certain extent. First, we excluded patients with incomplete information from the study, and this selection method may cause selection bias. The region and economic status of the patients in the database, the level of hospitals receiving doctors and the experience of doctors are different. These factors may also lead to bias in the selection of LND. Secondly, our study is an observational study rather than an experimental study, and patients entering each cohort are not random, so the covariates we consider are not sufficient to consider all risk factors of patients. Finally, due to the specificity of small intestine tumors, the area where the tumor is located is very different, so the range of LND is also difficult to determine, and this variable lacks standardization.

Conclusions

LND is performed more frequently in patients with locally advanced primary malignant small bowel tumors. In pT1/3/4 disease, the beneficial effect of LND with 4 or more regional lymph nodes removed on survival is obvious, but pT2 is gone. In addition, we found that a more adequate LND can bring benefits that are significantly better than the restricted LND with only 1-3 lymph nodes removed, which can be observed in neuroendocrine tumors and non-neuroendocrine tumors. For patients with pT1, pT3, and pT4, LND can be considered, and a sufficient LND is recommended. pT2 is still to be observed, which will be verified by further prospective studies.

Abbreviations

CSS: Cancer-specific survival; OS: Overall survival; LNM: lymph node metastasis;

LND: Lymph node dissection; SEER: Surveillance, Epidemiology and End Results database.

Declarations

Consent for publication

No applicable.

Availability of data and materials

The data sets used and analyzed during this current study are available from the corresponding author on reasonable request. The authors have obtained permission from the Surveillance, Epidemiology and End Results database for patient information(not reveal personal privacy).

Ethics approval and consent to participate

For the institutional cohorts, data were extracted from the Surveillance, Epidemiology and End Results database. This article does not include any studies conducted by the authors with human participants. For this type of study,

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YF C carried out most of the conceptualization, data curation, formal analysis and writing-original draft.SX H contributed to the design of the project, writing- review and editing. F H contributed to the visualization. Dan Guo contributed to proofreading. YR L contributed to supervision and editing. RH W and X Z contributed to writing-review.

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Tables

Table 1 The classification of histopathologic subtypes of 5413 small intestine tumor patients in this study

Histopathologic subtypes	Cases(%)
ADENOCARCINOMA, NOS	2582(47.7)
CARCINOID TUMOR, MALIGNANT	1744(32.2)
MUCINOUS ADENOCARCINOMA	322(5.9)
PAPILLARY ADENOCARCINOMA, NOS	305(5.6)
SIGNET RING CELL CARCINOMA	152(2.8)
ENDOCRINOMAS	113(2.1)
CARCINOMA, NOS	83(1.5)
BRONCHIOLO-ALVEOLAR ADENOCA.	40(1.5)
CARCINOMA, UNDIFF., NOS	28(0.5)
ADENOCA. WITH METAPLASIA	16(0.3)
SMALL CELL CARCINOMA, NOS	12(0.2)
PAPILLARY CARCINOMA, NOS	10(0.2)
NEOPLASM	6(0.1)

Table 2 Characteristics for small intestine tumor patients

Characteristic	Total	LND	no-LND	P value
	5413	4675	738	
Age				<0.001
<60	1894	1683	211	
≥60	3518	2991	527	
Sex				0.512
Male	2943	2550	393	
Female	2470	2125	345	
Race				0.006
White	4308	3745	563	
Black	857	711	146	
Other	248	219	29	
Grade				<0.001
	1683	1409	274	
	2205	1906	299	
	1400	1256	144	
	125	104	21	
Stage-T				<0.001
T1	422	286	136	
T2	534	445	89	
T3	2428	2133	295	
T4	2029	1811	218	
Stage-N				<0.001
N0	2395	1714	681	
N1-3	3018	2961	57	
Stage-M				0.904
M0	4134	3658	576	
M1	1179	1017	162	
Marital status				<0.001

Married	3191	2804	387	
Unmarried	1799	1674	125	
Divorced	421	195	226	
Tumor size				<0.001
<50	3686	3148	538	
≥50	1354	1254	100	
Unknown	373	273	100	
year of diagnosis				0.432
2004-2007	1214	1035	179	
2008-2011	1982	1716	266	
2012-2015	2217	1924	293	
Neuroendocrine differentiation				0.132
Neuroendocrine	1733	1479	254	
Non-neuroendocrine	3680	3196	484	

P values are based on Pearson Chi-square test for categorical variables. LND, lymph node dissection.

Table 3 3-year, 5-year and 10-year overall survival and cancer-specific survival rate based on the specific-stage.

		Overall survival rate%		Cancer-specific survival rate%		
	3 years	5 years	10 years	3 years	5 years	10 years
All T stage						
LND status						
LND	60.4	51.1	37.1	74.5	68.2	60.3
no LND	50.9	38.6	25	75	67.4	61.1
LND extent						
no LND	50.9	38.6	25	75	67.4	61.1
limited LND	53.5	43.9	31.1	71.9	65.6	55.6
extended LND	61.8	52.5	38.3	75	68.6	61.2
Lymph node metastasis						
N0	61.3	50.9	35.2	79.8	74	66.7
N1-3	57.3	48.2	36.2	70.5	63.5	55.2
T1						
LND status						
LND	82.2	76.2	61.1	95.8	95.1	93.1
no LND	56.7	48.6	26.2	78.3	78.3	78.3
LND extent						
no LND	56.7	48.6	26.2	78.3	78.3	78.3
limited LND	75.9	70.4	59.7	93.8	89.9	54.6
extended LND	83.6	77.6	61.1	96.3	96.3	95
Lymph node metastasis						
N0	70.1	64.2	43.8	88.3	88.3	86.1
N1-3	83.2	75.1	67	95.5	94	94
T2						
LND status						
LND	79.8	73.2	59.5	91	89.3	87.5
no LND	73.4	64.7	58.2	92.3	86.5	86.5
LND extent						

no LND	73.4	64.7	58.2	92.3	86.5	86.5
limited LND	69.8	63	46.5	85.4	85.4	85.4
extended LND	81.6	74	61.8	91.9	90	87.9
Lymph node metastasis						
N0	77.5	68	53.5	92.6	89.7	87.6
N1-3	80.3	76.2	65.7	89.6	88	87.1
T3						
LND status						
LND	65.5	54.3	38.8	78.8	71.6	62
no LND	54	37.5	24.5	78.3	65.7	59.5
LND extent						
no LND	54	37.5	24.5	78.3	65.7	59.5
limited LND	58.3	45.2	31.1	75.3	67	53.3
extended LND	67.2	56.5	40.7	79.6	72.6	64.1
Lymph node metastasis						
N0	63.5	50.7	36.4	82.1	74.6	67.1
N1-3	64.6	53.6	37.2	76	68.1	56.7
T4						
LND status						
LND	46.1	37.9	26.1	61.2	53.6	45.4
no LND	33.3	23.2	11.9	59.5	52.7	39.2
LND extent						
no LND	33.3	23.2	11.9	59.5	52.7	39.2
limited LND	37.2	31.8	21.9	56.6	52	45.7
extended LND	47.6	38.9	26.8	62	53.9	45.5
Lymph node metastasis						
N0	47.5	38	22.1	66	59.7	49
N1-3	43.3	35	26.6	58.2	50.3	42.8

Table 4 Multivariable Cox regression analyses predicting overall survival

	All stage	pT1	pT2	pT3	pT4
	Multivariable	Multivariable	Multivariable	Multivariable	Multivariable
	HR(95%CI)	Multivariable	Multivariable	Multivariable	Multivariable
LND status					
no LND	ref	ref	ref	ref	ref
LND	0.592(0.391-0.897)*	0.371(0.266-0.516)***	0.771(0.514-1.155)	0.648(0.553-0.760)***	0.644(0.546-0.760)***
LND extent					
no LND	ref	ref	ref	ref	ref
limited LND	0.721(0.412-1.260)	0.516(0.307-0.867)*	1.113(0.651-1.903)	0.837(0.688-1.018)	0.822(0.663-1.018)
extended lnd	0.567(0.371-0.868)**	0.338(0.237-0.483)***	0.716(0.473-1.083)	0.607(0.515-0.714)***	0.619(0.524-0.732)***
Lymph node stage					
pN0	ref	ref	ref	ref	ref
pN1-3	1.229(0.873-1.730)	0.556(0.371-0.833)*	0.726(0.525-1.004)	0.963(0.858-1.081)	1.070(0.952-1.202)

*P<0.05, **P<0.01, ***P<0.001. Adjusted to age, gender, race, tumor grade, tumor size, tumor stage, marital status, year of surgery, distant metastases, neuroendocrine differentiation. HR hazard ratio, 95% CI 95% confidence interval, LND lymph node dissection.

Table 5 Multivariable Cox regression analyses predicting cancer-specific survival

	All stage	pT1	pT2	pT3	pT4
	Multivariable	Multivariable	Multivariable	Multivariable	Multivariable
	HR(95%CI)	Multivariable	Multivariable	Multivariable	Multivariable
LND status					
no LND	ref	ref	ref	ref	ref
LND	0.981(0.838-1.148)	0.232(0.120-0.448)*	0.957(0.449-2.038)	0.897(0.698-1.154)	0.861(0.679-1.093)
LND extent					
no LND	ref	ref	ref	ref	ref
limited LND	1.120(0.920-1.365)	0.462(0.176-1.211)	1.314(0.493-3.502)	1.124(0.834-1.515)	0.976(0.721-1.322)
extended LND	0.855(0.614-1.020)	0.181(0.084-0.391)***	0.899(0.416-1.942)	0.798(0.657-0.947)*	0.805(0.625-0.975)*
Lymph node stage					
pN0	ref	ref	ref	ref	ref
pN1-3	1.528(1.371-1.703)***	0.394(0.165-0.942)*	1.212(0.696-2.111)	1.391(1.177-1.644)***	1.313(1.124-1.535)***

*P<0.05, **P<0.01, ***P<0.001. Adjusted to age, gender, race, tumor grade, tumor size, tumor stage, marital status, year of surgery, distant metastases, neuroendocrine differentiation. HR hazard ratio, 95% CI 95% confidence interval, LND lymph node dissection.

Figures

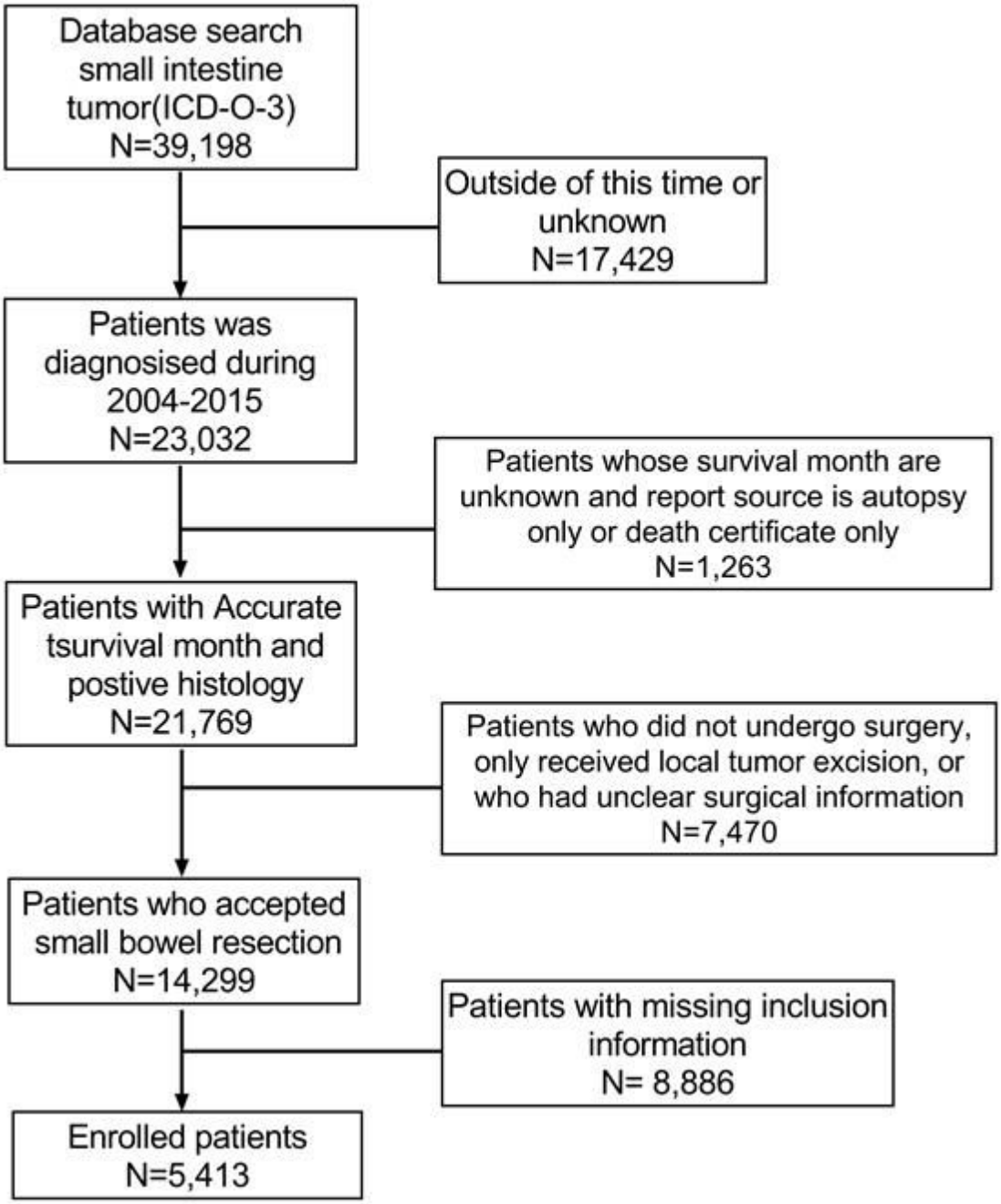

Figure 1

Selection of patients included in the study.

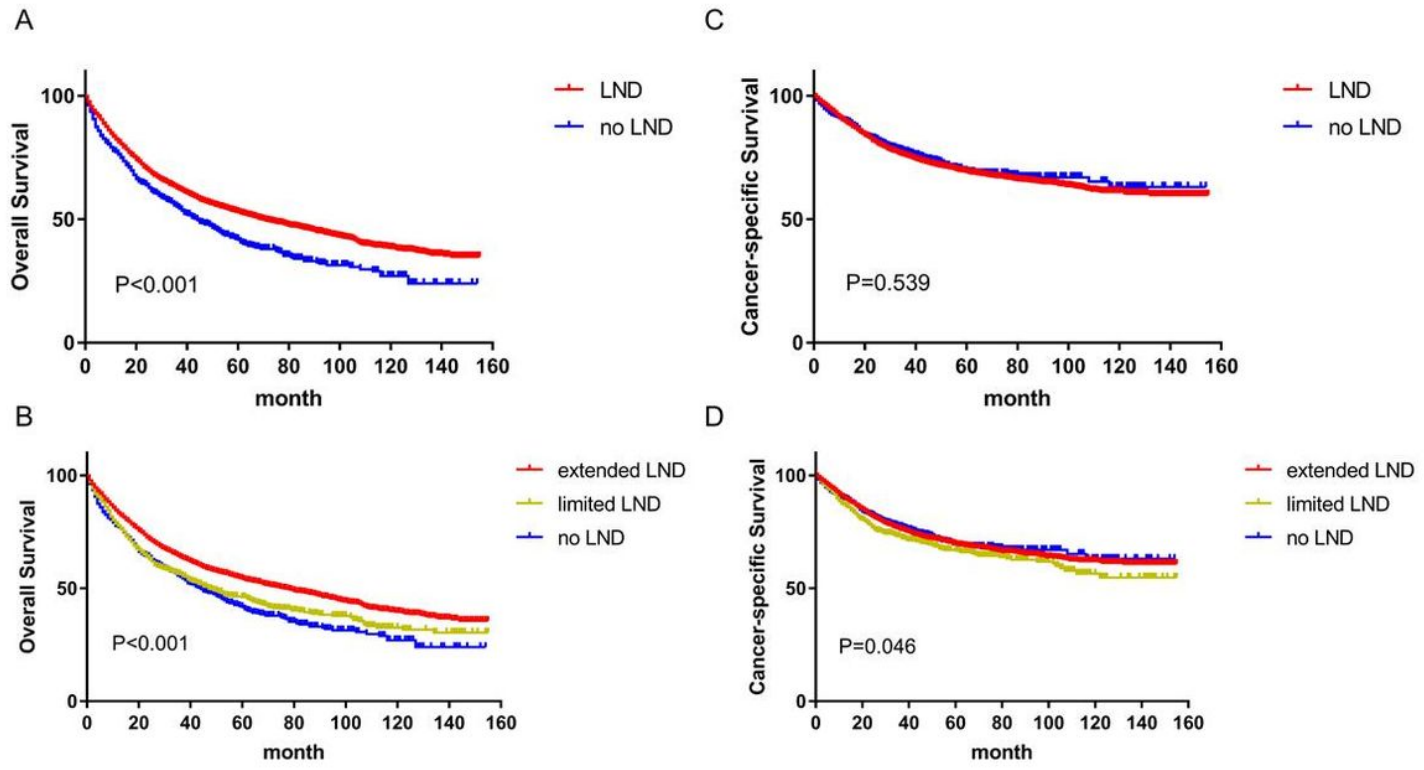

Figure 2

Kaplan-Meier plots depicting overall survival(A) and cancer-specific survival(B) according to LND status, survival(C) and cancer-specific survival(D) according to extended LND status.

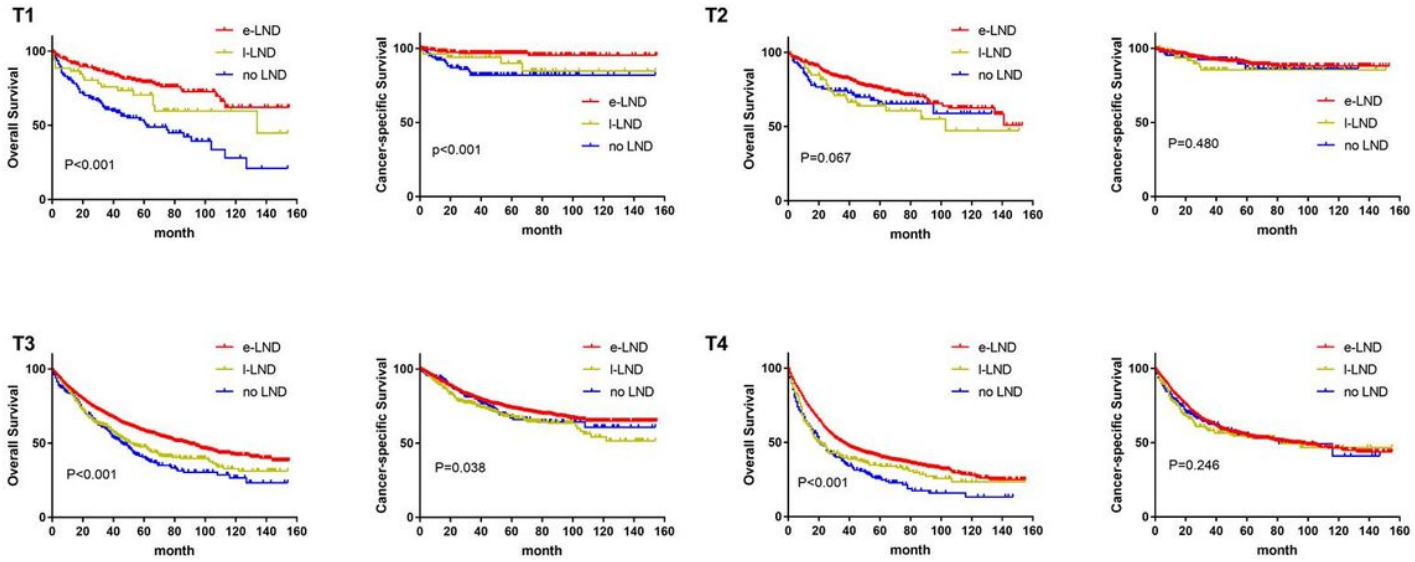

Figure 3

Kaplan-Meier plots depicting overall survival and cancer-specific survival according to LND extent status in specific-stage pT1, pT2, pT3 and pT4 disease.

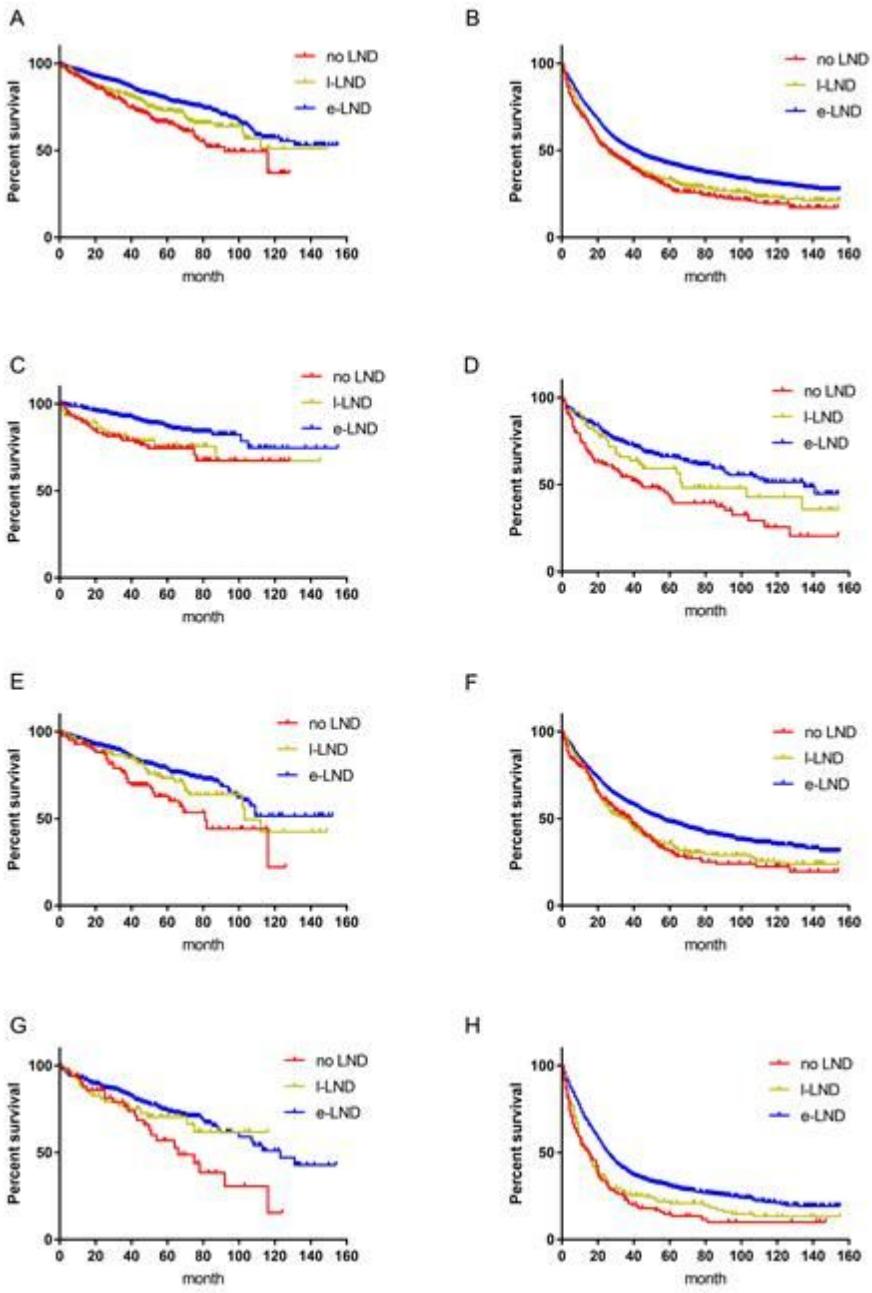

Figure 4

Figure 4

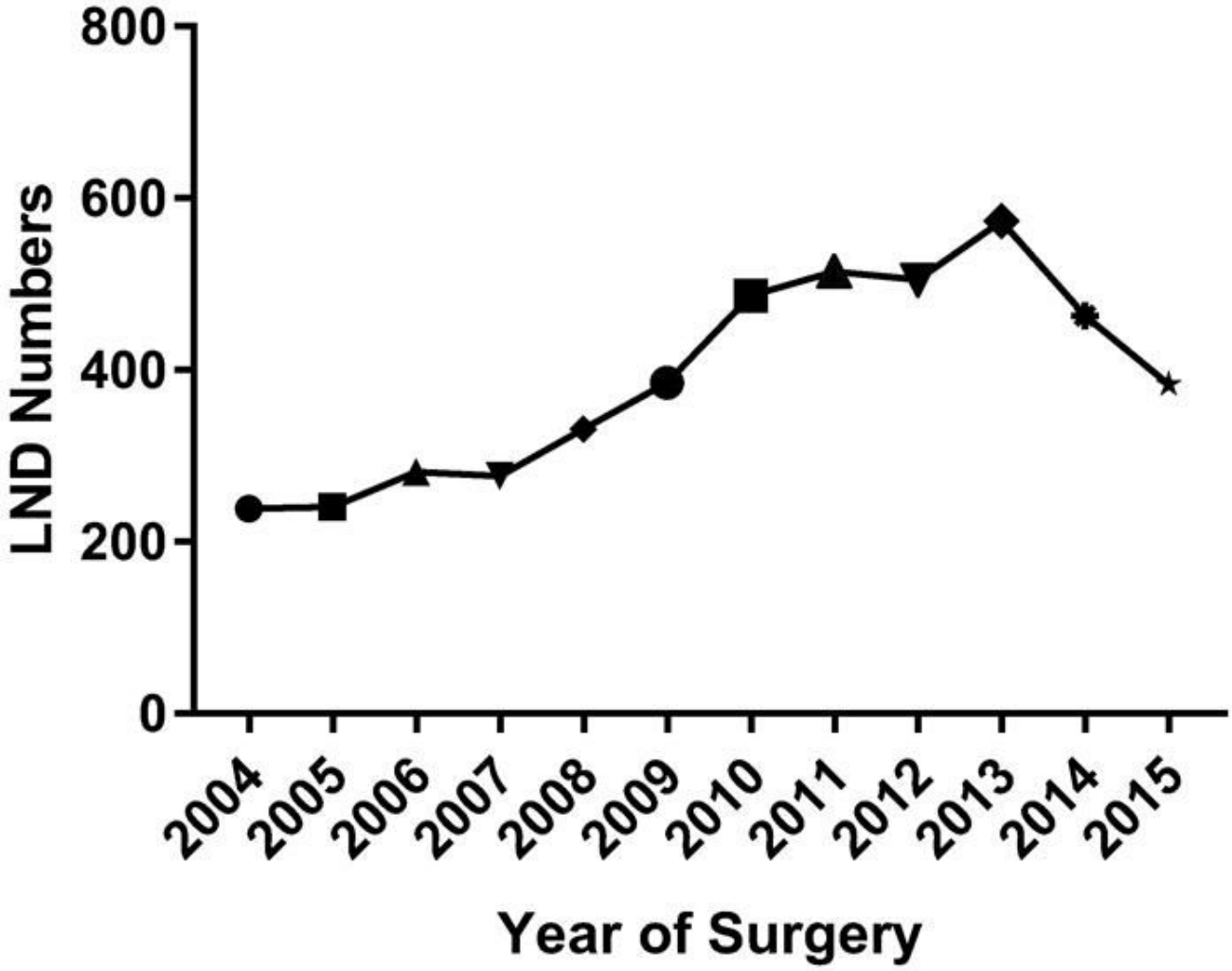

Figure 5

Figure 5

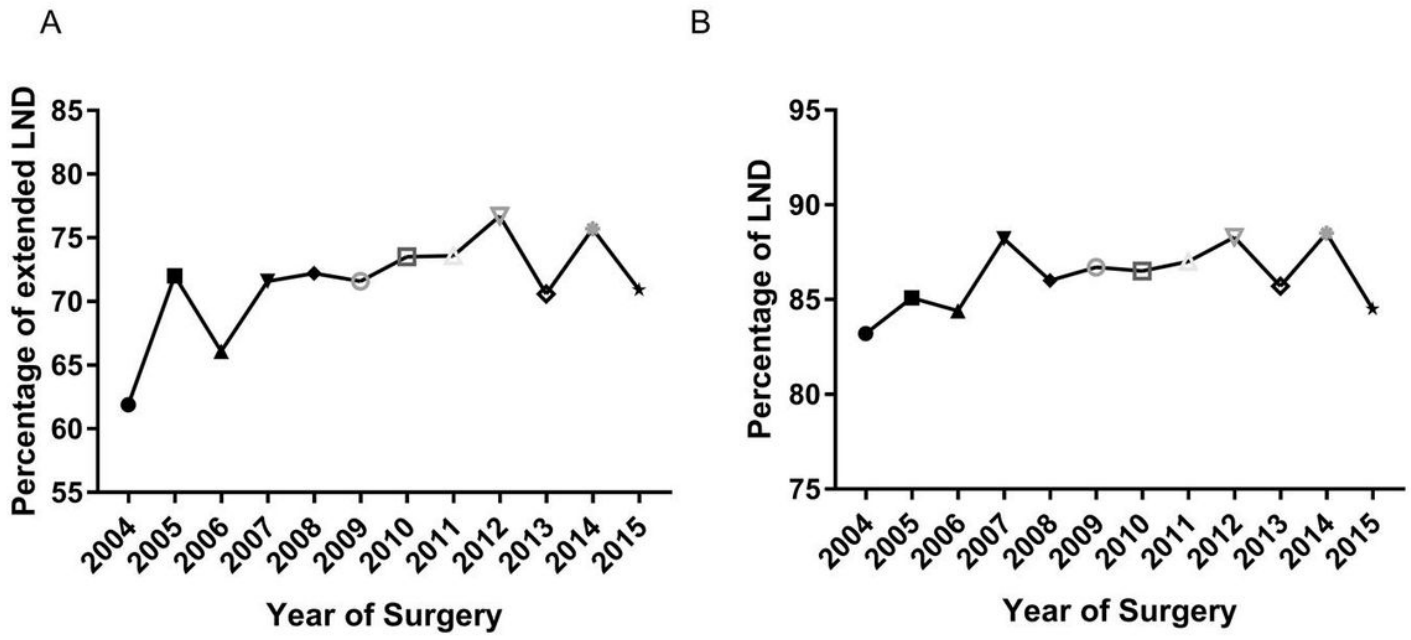

Figure 6

Figure 6

Supplementary Files

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- supplementary.docx