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META-ANALYSIS

Meta-analysis of lymph node metastasis in Siewert type Ⅰ and Ⅱ T1 adenocarcinomas

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Abstract

AIM

To evaluate the incidence of lymph node metastasis (LNM) and its risk factors in patients with Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas.

METHODS

We enrolled 85 patients [69 men, 16 women; median age (range), 67 (38-84) years] who had undergone esophagectomy or proximal gastrectomy for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas. Predictive risk factors of LNM included age, sex, location of the tumor center, confirmed Barrett's esophageal adenocarcinoma, tumor size, macroscopic tumor type, pathology, invasion depth, presence of ulceration, and lymphovascular invasion. Multivariate logistic regression analysis was used to identify factors predicting LNM. We also evaluated the frequencies of LNM for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas in meta-data analysis.

RESULTS

LNMs were found in 11 out of 85 patients (12.9%, 95%CI: 5.8-20.0). Only 1 of the 15 patients (6.6%, 95%CI: 0.0-19.2) who had a final diagnosis of pT1a adenocarcinoma had a positive LNM, whereas 10 of

the 70 patients (14.2%, 95%CI: 6.0-22.4) with a final diagnosis of pT1b adenocarcinoma had positive LNM. Furthermore, only one of the 30 patients (3.3%, 95%CI: 0.0-9.7) with a tumor invasion depth within 500 μm from muscularis mucosae had positive LNM. Poor differentiation and lymphovascular invasion were independently associated with a risk of LNM. In meta-data analysis, 12 of the 355 patients (3.3%, 95%CI: 1.5-5.2) who had a final diagnosis of pT1a adenocarcinoma had a positive LNM, whereas 91 of the 438 patients (20.7%, 95%CI: 16.9-24.5) with a final diagnosis of pT1b adenocarcinoma had positive LNM.

CONCLUSION

We consider endoscopic submucosal dissection (ESD) is suitable for patients with Siewert type Ⅰ and type Ⅱ T1a adenocarcinomas. For patients with T1b adenocarcinoma, especially invasion depth is within 500 μm from muscularis mucosae with no other risk factor for LNM, diagnostic ESD could be a treatment option according to the overall status of patients and the presence of comorbidities.

Key words: Siewert type Ⅰ and type Ⅱ adenocarcinomas; Lymph node metastasis

Core tip: We evaluated meta-analysis of the incidence of lymph node metastasis (LNM) in patients with Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas. Of previous 5 reports and our study, 12 of the 355 patients (3.38%, 95%CI: 1.5-5.2) in pT1a adenocarcinoma had LNM, whereas 91 of the 438 patients (20.7%, 95%CI: 16.9-24.5) in pT1b adenocarcinoma had LNM. We consider endoscopic submucosal dissection (ESD) to be a reasonable for patients that have well differentiated, limited to the mucosa, and within 30 mm in diameter with no lymphovascular invasion. For patients with T1b adenocarcinoma, especially invasion depth within 500 μm from muscularis mucosae with no other risk factor for LNM, diagnostic ESD could be a treatment option.

Osumi H, Fujisaki J, Omae M, Shimizu T, Yoshio T, Ishiyama A, Hirasawa T, Tsuchida T, Yamamoto Y, Kawachi H, Yamamoto N, Igarashi M. Meta-analysis of lymph node metastasis in Siewert type Ⅰ and Ⅱ T1 adenocarcinomas. *World J Meta-Anal* 2016; 4(6): 118-123 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i6/118.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i6.118

INTRODUCTION

Barrett's esophagus is most often diagnosed in people who have long term gastroesophageal reflux disease (GERD), which is a chronic regurgitation of acid from the stomach into the lower esophagus. It is associated with an increased risk of developing esophageal adenocarcinoma. The frequency of Barrett's esophageal adenocarcinoma (BEA) from Barrett's esophagus is about 0.5% per year[1]. However, the frequency of BEA is thought to be increasing because of the Westernization of dietary habits, obesity, and increased frequency of GERD associated with a decreasing frequency of *Helicobacter pylori* (*H. pylori*) infection in Japan.

Endoscopic submucosal dissection (ESD) for esophageal and gastric cancer is limited by the possible incidence of regional lymph node metastasis (LNM). There is robust data about the frequencies of LNM of squamous cell carcinoma or esophageal adenocarcinoma over the full length of esophagus. In contrast, there is a few data about the frequency of LNM for Siewert type Ⅰ and type Ⅱ pathological T1 (pT1) adenocarcinomas. Especially, there is only one report about the frequency of LNM for Siewert type Ⅱ pT1 adenocarcinomas from 2005 to 2015 in the PubMed database[2]. Siewert type Ⅰ was defined as adenocarcinoma of the distal esophagus, which usually arises from an area with Barrett's esophagus and may infiltrate the esophagogastric junction (EGJ) from above[3]. On the other hand, Siewert type Ⅱ was defined true carcinoma of the cardia arising immediately at the EGJ[3]. In this range, there are two types of adenocarcinomas: BEA from short or long segment Barret's esophagus develops from inflammation caused by exposure of the esophagus to gastric acid and bile; and gastric adenocarcinoma develops from mucosal atrophy and intestinal metaplasia, mainly caused by *H. pylori* infection[4].

If the frequency of LNM and the risk factors driving this process in this range can be determined, then patient treatment can be stratified: ESD can be offered to patients with tumors that have a low frequency of LNM; and surgical resection can be offered to patients with tumors that have a high frequency of LNM. The aim of this study was to evaluate the frequency of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas and its risk factors of LNM.

MATERIALS AND METHODS

Study population

There were 85 patients who received esophagectomy or proximal gastrectomy or additional surgery after ESD in Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas between January 2006 and December 2014 in our hospital. Our selection criteria were: (1) the center of the tumor was within 2 cm of the EGJ at the gastric side or within 5 cm of the EGJ at the oral side; (2) invasion depth was intramucosal or submucosal and was not reached the muscularis propria; and (3) patients had received primary surgery or additional surgery after ESD. Pathological evaluation was performed by two experienced pathologists (Kawachi H and Yamamoto N).

Tumor classifications

Differentiated pathology included papillary adenocarcinoma and tubular adenocarcinoma. Undifferentiated pathology included poorly differentiated adenocarcinoma, signet-

Table 1 Characteristics of patients with Siewert type I and II pT1 adenocarcinomas

Characteristic	Data
n	85
Median age (range), yr	67 (38-84)
Male sex, *n* (%)	69 (81.1)
Depth, *n* (%)	
T1a	22 (25.9)
T1b	63 (74.1)
Differentiation, *n* (%)	
Differentiated	72 (84.7)
Undifferentiated	13 (15.3)
Median size, (SD), mm	26 (± 14.6)
Lymphovascular invasion, *n* (%)	50 (58.8)
Underlying Barrett's esophagus, *n* (%)	43 (50.5)
Lymph node metastasis, *n* (%)	11 (12.9)

ring cell carcinoma, and mucinous adenocarcinoma. For the condition to be considered Barrett's esophagus, one of the following criteria must have been met: We could identify these pathologic findings in anal side of the tumor; esophageal glands, squamous island, and double layer of muscularis mucosae. Or we could find palisade vessels around the tumor endoscopically. Invasion depth was divided into T1a (Tumor confined to the mucosa) and T1b (Tumor confined to the submucosa) groups. T1b lesions were subclassified as: SM1 (tumor invasion is within 500 μm of the muscularis mucosae) or SM2 (tumor invasion is 500 μm or more deep into the muscularis mucosae). Assessment of the depth of tumor infiltration into the SM layer was based on the Japanese Classification of Gastric Carcinoma[5].

Meta-data analysis of the frequencies of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas

We searched for articles which were mentioned about the frequency of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas in the PubMed database from 2005 to 2015 using following terms: "T1," "esophagogastric junction adenocarcinoma", "esophageal adenocarcinoma", "lymph node metastasis", "early", "superficial". Terms were combined with "and/or" and asterisks. The main reasons of initial exclusion were as follows; squamous cell carcinoma was also included, esophageal adenocarcinoma of over the full length of esophagus, non-English literature, case reports, reviews and double publications.

This study was performed in accordance with the Declaration of Helsinki and approved by our Institutional Review Board (Registry number: 2015-1143).

Statistical analysis

Predictive risk factors included age, sex, location of tumor center (Siewert type Ⅰ or Ⅱ), presence of confirmed BEA (yes or no), tumor size (< 30 mm or ≥ 30 mm), macroscopic tumor type (elevated or depressed), pathology (undifferentiated or differentiated), depth of invasion (mucosal or SM, ≥ 500 μm or < 500 μm), presence of ulceration (yes or no), and presence of lymphovascular invasion (yes or no). All *P* values were the result of two-sided tests, and a *P* value of < 0.05 was considered statistically significant. Prognostic factors with a *P* value of < 0.2 in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing).

RESULTS

Clinical characteristics

Patient characteristics are shown in Table 1. This cohort included 85 patients (81.1% men and 18.9% women). The median age of patients at the time of surgery was 67 years (38-84). In total, 22 patients had pT1a tumors (25.9%) and 63 patients had pT1b tumors (74.1%). Median tumor size was 26 mm (± 14.6 mm). 72 patients (84.7%) had differentiated type tumor pathology and 13 patients (15.3%) had undifferentiated type tumor pathology. A total of 50 patients (58.8%) had lymphovascular invasion and 43 patients (50.5%) had underlying Barrett's esophagus.

Clinical outcomes and incidence of LNM

Overall, 11 out of 85 patients (12.9%, 95%CI: 5.8-20) had LNM. Table 2 shows the rate of LNM for each depth of invasion. There was a higher incidence of LNM in patients with pT1b compared with pT1a disease; however, this was not significant [14.2% (10/70) *vs* 6.6% (1/15), OR = 2.3, 95%CI: 0.28-108.3, *P* = 0.67]. Furthermore, for the actual depth of invasion, the frequencies of LNM were: < 500 μm, 3.3% (1/30, 95%CI: 0-9.7); < 1000 μm, 4.3% (2/46 95%CI: 0-10.2) (Table 3).

Univariate and multivariate logistic regression of risk factors of LNM

In the univariate analysis, poor differentiation (OR 6.6, 95%CI: 1.29-33.7, *P* = 0.01), and lymphovascular invasion (OR = 5.1, 95%CI: 1.04-25.1, *P* = 0.02) were risk factors for LNM; tumor size > 30 mm showed a tendency to be a risk factor (OR = 3.1, 95%CI: 0.72-14.8, *P* = 0.08). Multivariate logistic regression analysis identified poor tumor differentiation (OR = 6.08, 95%CI: 1.4-26.4, *P* = 0.01) and lymphovascular invasion (OR = 4.66, 95%CI: 1.09-19.9, *P* = 0.03) as independent predictors of a positive lymph node status (Table 4).

Meta-data analysis of the frequencies of LNM for Siewert types Ⅰ and Ⅱ pT1 adenocarcinomas

In total, we could find only 5 articles except for our study that were mentioned about the frequency of LNM for Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas in the PubMed database from 2005 to 2015. The overall frequency of LNM was 3.38% (12/355, 95%CI: 1.5-5.2) for pT1a tumors and 20.7% (91/438, 95%CI: 16.9-24.5) for pT1b tumors. Furthermore, the frequencies of LNM

Table 2 Studies of patients who underwent surgery for Siewert type I and II pT1 adenocarcinomas with lymph node status

Ref.	*n*	Siewert classification	TNM classification		SM subdivision		
			T1a, *n* (%)	T1b, *n* (%)	SM1, *n* (%)	SM2, *n* (%)	SM3, *n* (%)
Westerterp *et al*[6]	120	Ⅰ, Ⅱ	1/54 (1.8)	18/66 (27.2)	0/25 (0)	6/23 (20)	12/18 (56)
Barbour *et al*[7]	85	Ⅰ, Ⅱ	0/35 (0)	9/50 (18)	-	-	-
Lees *et al*[8]	126	Ⅰ, Ⅱ	1/75 (1.3)	11/51 (21.6)	4/19 (21)	1/9 (11.1)	6/23 (26.1)
Griffin *et al*[9]	119	Ⅰ, Ⅱ	0/54 (0)	8/65 (12.3)	-	-	-
Lee *et al*[10]	258	Ⅰ, Ⅱ	9/122 (7.3)	35/136 (25.7)	-	-	-
Present study	85	Ⅰ, Ⅱ	1/15 (6.6)	10/70 (14.2)	0/7 (0)	4/43 (9.3)	6/20 (30)
Total	793	Ⅰ, Ⅱ	12/355 (3.4%, 95%CI: 1.5-5.2)	91/438 (20.7%, 95%CI: 16.9-24.5)			

TNM: Tumor-node-metastasis; SM: Submucosal; SM: Subdivision defines 3 sections of equivalent thickness of submucosa: Superficial (SM1), middle (SM2) and deep (SM3).

Table 3 Frequencies of lymph node metastasis and lymphovascular invasion per depth of invasion in this study

Invasion depth (μm)	Lymphatic invasion frequency	Venous invasion frequency	Frequency of lymph node metastasis
SM < 500, *n* (%, 95%CI)	7/30 (23.3, 8.1-38.4)	2/30 (6.6, 0-15.5)	1/30 (3.3, 0-9.7)
SM < 1000, *n* (%, 95%CI)	11/46 (23.9, 11.5-36.2)	7/46 (15.2, 4.5-25.5)	2/46 (4.3, 0-10.2)

SM: Submucosal.

Table 4 Univariate and multivariate analysis of potential risk factors for lymph node metastasis

Statistical test	OR	Lower 95%CI	Upper 95%CI	*P* value
Univariate analysis				
Age (< 70 or ≥ 70 yr)	0.32	0.03	1.75	0.19
Sex (male or female)	1.04	0.18	11	1
Location of tumor center (Siewert type Ⅰ or Ⅱ)	2.1	0.31	10.8	0.37
Depth of invasion (M or SM)	2.3	0.28	108.3	0.67
Depth of invasion (≥ 500 μm or < 500 μm)	4.89	0.58	40.8	0.14
Differentiation (undifferentiated or differentiated)	6.6	1.29	33.7	0.01
Tumor size (< 30 mm or ≥ 30 mm)	3.1	0.72	14.8	0.08
Macroscopic tumor type (elevated or depressed)	1.43	0.31	9.1	0.74
Ulceration (yes or no)	1.91	0.44	8.7	0.33
Barrett's esophageal adenocarcinoma (yes or no)	0.79	0.17	3.42	0.75
Lymphovascular invasion (yes or no)	5.1	1.04	25.1	0.02
Multivariate analysis				
Differentiation (undifferentiated or differentiated)	6.08	1.4	26.4	0.01
Lymphovascular invasion (yes or no)	4.66	1.09	19.9	0.03

M: Mucosal; SM: Submucosal; OR: Odds ratio.

were 9.1% (4/44, 95%CI: 0.5-17.5) for SM1, 22.5% (7/31, 95%CI: 7.8-37.2) for SM2, and 43.9% (18/41, 95%CI: 27-59) for SM3 (Table 2).

DISCUSSION

Our date showed that the frequency of LNM was 14.2% (10/70, 95%CI: 6-22.4) for pT1b and 6.6% (1/15, 95%CI: 0-19.2) for pT1a disease. The frequencies of LNM were 3.3% (1/30, 95%CI: 0-9.7) and 4.3% (2/46, 95%CI: 0-10.2) for invasion depths of < 500 μm and < 1000 μm, respectively. Logistic regression multivariate analysis identified poor differentiation and lymphovascular invasion as independent risk factors of LNM. The overall frequency of LNM was 3.38% (12/355, 95%CI: 1.5-5.2) for pT1a tumors and 20.7% (91/438, 95%CI: 16.9-24.5) for pT1b tumors in meta-analysis.

As I mentioned before, fewer data of LNM are available for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas. Especially, we could find only one report which mentioned the frequency of LNM for Siewert type Ⅱ pT1 adenocarcinoma using pubmed data base from 2005 to 2015[2]. The study included 453 patients: The incidence of LNM was 9.5% (16/173, 95%CI: 4.9-13.5) for pT1a tumors and 22.9% (61/280, 95%CI: 16.6-28.1) for pT1b tumors. Infiltration of the submucosa, tumor size of over 10 mm, and poor tumor differentiation were independently associated with a risk of LNM. On the other hand, when the search was restricted to patients with Siewert type Ⅰ and Ⅱ pT1 adenocarcinomas (as in the present study), there were five reports that reviewed the frequency of LNM[6-10]. Table 2 and 3 shows summary data

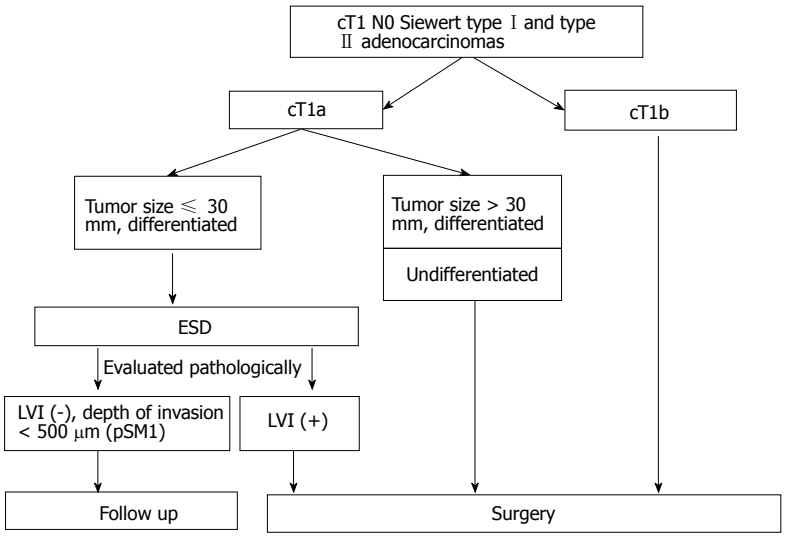

Figure 1 Our strategy of endoscopic submucosal dissection for T1 Siewert type Ⅰ and type Ⅱ adenocarcinomas. ESD: Endoscopic submucosal dissection.

from those studies. There was an increase in the rate of LNM with increasing SM category. In a study of the risk factors for LNM, Lees *et al*[10] described the features of LNM of a pT1a adenocarcinoma with lymphovascular invasion: a tumor size of 22 mm and poor differentiation. Barbour *et al*[7] recommended that patients with lymphovascular invasion or poorly differentiated adenocarcinomas should undergo adjuvant chemotherapy after surgery.

Thus far we described published data on each site of adenocarcinomas and then evaluated the frequency of LNM for each invasion depth category for both BEA and gastric adenocarcinoma. Dunbar and Spechler reported the frequency of LNM in Barrett's esophagus patients with high grade dysplasia (HGD) and pT1a adenocarcinoma in a systematic review[11]. In a total of 70 relevant reports, there were 1874 Barrett's esophagus patients who had undergone esophagectomy for HGD or pT1a adenocarcinoma. LNM were found in 26 patients (1.4%, 95%CI: 0.9-1.9). There were no metastases in the 524 patients with a final pathology diagnosis of HGD; in contrast, 26 (1.9%, 95%CI: 1.2-2.7) of the 1350 patients with a final diagnosis of pT1a adenocarcinoma had LNM. Gotoda *et al*[12] reported the frequency of LNM of pT1a gastric cancer. Of the 3016 pT1a cancers; only 65 (2.2%, 95%CI: 1.6-2.6) patients were associated with regional LNM. Depressed or ulcerated lesions of over 30 mm diameter, undifferentiated histology and invasion into lymph nodes or venules were associated with an increased risk of LNM. Therefore, the risk of unexpected LNM in both intramucosal BEA and gastric adenocarcinoma patients is in the range of 1%-2%.

On the other hand, Gockel *et al*[13] reported the risk of LNM in pT1b esophageal adenocarcinoma patients in a systematic review. The pooled outcomes for 7645 patients with esophageal adenocarcinoma involving tumor infiltration to the submucosal level were analyzed. Esophageal adenocarcinoma patients with SM1 lesions had the lowest incidence of LNM, and there was an increasing rate of LNM with increasing depth of SM invasion: 6% (4/65, 95%CI: 0.3-11.9) for SM1, 23% (10/44, 95%CI: 10.3-35.1) for SM2, and 58% (33/57, 95%CI: 45-70.7) for SM3. In gastric pT1b adenocarcinoma, Gotoda *et al*[12] also reported that 2249 tumors had penetrated the SM and 402 tumors invading the SM (17.9%, 95%CI: 16.2-19.4) were associated with LNM. There was a significant correlation of both tumor size over 30 mm and lymphovascular involvement with an increased risk of LNM. In addition, cancers that penetrated deep into the SM were the most likely to be associated with regional LNM.

Based on these results, we currently consider ESD to be a reasonable treatment for Siewert types Ⅰ and Ⅱ T1a adenocarcinomas that is well differentiated, limited to the mucosa, and within 30 mm in diameter with no lymphovascular invasion (Figure 1). In this study, although only one patient with LNM had pT1a adenocarcinoma, this patient had other risk factors for LNM (tumor size was 82 mm. Pathology was mixed type of tubular adenocarcinoma and signet cell adenocarcinoma. Vascular invasion was positive). On the other hand, the frequency of LNM was high in previous report on pT1b tumors, therefore we think T1b tumors are not appropriate for ESD. Indeed, However, the frequency of LNM was relatively low for tumors of within 500 μm from muscularis mucosae in this study (3.3%; 1/30, 95%CI: 0-9.7). Gotoda *et al*[12] reported that 145 patients with a tumor size of under 30 mm, differentiated histology, no lymphovascular invasion, and submucosal penetration of under 500 μm were entirely free of nodal metastasis (95%CI: 0-2.5%). Furthermore, although the 5-year survival rate for pT1b gastric cancer patients (except for death caused other disease) was 96.7%[14], and esophagectomy has a mortality rate that is 2%-11% higher than that of gastrectomy[3,15,16]. Therefore, diagnostic ESD could be a treatment option for patients with T1b tumors, especially those within 500 μm from muscularis mucosae without other risk factors of LNM, according to the patient's overall status and the presence of comorbidities (Figure 1). Even so, it is difficult to diagnose invasion depth correctly before ESD in this range. More patients undergoing surgery should be

persuaded to accept ESD.

COMMENTS

Background

Barrett's esophagus is most often diagnosed in people who have long term gastroesophageal reflux disease (GERD), which is a chronic regurgitation of acid from the stomach into the lower esophagus. It is associated with an increased risk of developing esophageal adenocarcinoma. The frequency of Barrett's esophageal adenocarcinoma (BEA) from Barrett's esophagus is about 0.5% per year. However, the frequency of BEA is thought to be increasing because of the Westernization of dietary habits, obesity, and increased frequency of GERD associated with a decreasing frequency of *Helicobacter pylori* (*H. pylori*) infection in Japan.

Research frontiers

If the frequency of lymph node metastasis (LNM) and the risk factors driving this process in this range can be determined, then patient treatment can be stratified: ESD can be offered to patients with tumors that have a low frequency of LNM; and surgical resection can be offered to patients with tumors that have a high frequency of LNM.

Innovations and breakthroughs

These date showed that the frequency of LNM was 14.2% (10/70, 95%CI: 6-22.4) for pT1b and 6.6% (1/15, 95%CI: 0-19.2) for pT1a disease. The frequencies of LNM were 3.3% (1/30, 95%CI: 0-9.7) and 4.3% (2/46, 95%CI: 0-10.2) for invasion depths of < 500 μm and < 1000 μm, respectively. Logistic regression multivariate analysis identified poor differentiation and lymphovascular invasion as independent risk factors of LNM. The overall frequency of LNM was 3.38% (12/355, 95%CI: 1.5-5.2) for pT1a tumors and 20.7% (91/438, 95%CI: 16.9-24.5) for pT1b tumors in meta-analysis.

Applications

The authors evaluated the frequencies of LNM for Siewert type Ⅰ and type Ⅱ pT1 adenocarcinomas in meta-data analysis.

Peer-review

This paper has shown accurate incidence of lymph nodes metastasis of esophageal adenocarcinomas. Their study provides us important information related to treatment of esophageal adenocarcinomas.

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