Surgical Endoscopy (2019) 33:2304–2312
https://doi.org/10.1007/s00464-018-6524-2

Comparison of the short-term and long-term outcomes of surgical treatment versus endoscopic treatment for early esophageal squamous cell neoplasia larger than 2 cm: a retrospective study

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Received: 26 June 2018 / Accepted: 11 October 2018 / Published online: 25 October 2018

Abstract

Background NCCN Guidelines of esophageal cancer recommend that endoscopic therapy is considered "preferred" for patients with limited early-stage disease less than or equal to 2 cm. However, there is currently no definite evidence to support either endoscopic therapy or esophagectomy for early esophageal cancer larger than 2 cm. We aimed to explore the optimal treatment for this condition.

Methods From January 2010 to June 2016, 116 patients with early esophageal neoplasia [high-grade dysplasia (HGD), lamina propria and muscularis mucosae (T1a) cancer, selected superficial submucosa (T1b) cancer without lymph node metastases] larger than 2 cm and treated either surgically or endoscopically were included.

Results Endoscopic therapy was performed in 69 patients and esophagectomy in 47 patients, respectively. The median follow-up time was 43.8 months in the endoscopic cohort and 49.4 months in the surgical cohort. The overall survival was similar between the two cohorts (97.1% vs. 91.5%, $P=0.18$). Survival without readmission for treatment-related complicates was also similar. Minor and severe procedure-related complications occurred more often in the surgical cohort than in the endoscopic cohort (63.8% vs. 43.5% and 8.5% vs. 0 respectively, $P<0.05$ for both). Four patients in the endoscopic cohort had to undergo additional esophagectomy and were alive during follow-up. There were no procedure-related deaths in the endoscopic cohort, whereas two deaths occurred in the surgical cohort. Recurrence occurred in nine patients in the endoscopic group (13%): six with local recurrence, one with residual neoplasia and two with metachronous neoplasia. None of them died after repeated endoscopic treatments.

Conclusions Efficacy was similar between endoscopic therapy and esophagectomy in the treatment of early esophageal squamous cell neoplasia larger than 2 cm and endoscopic therapy was associated with fewer and manageable complications. We recommend endoscopic treatment should be preferred selected for early esophageal neoplasia larger than 2 cm.

Keywords Esophagus · Endoscopic therapy · Esophagectomy · Early esophageal cancer · Esophageal dysphagia · Esophageal squamous cell neoplasia

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The increased use of endoscopic surveillance has contributed to an increased proportion of patients with early-stage diseases [1]. Over the past 2 decades, endoscopic treatments, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have been demonstrated to be effective and less invasive for early stage esophageal neoplasia [ie, high-grade dysplasia (HGD) or lamina propria or muscularis mucosae (T1a) cancer, selected superficial submucosa (T1b) cancer without lymph node metastases] [2]. Several studies reported the cure rate of HGD and early mucosal cancer by endoscopy was very high [3–8]. Endoscopic therapies are superior in terms of esophageal preservation, duration of hospital stay and cost. In addition, endoscopic treatment could also serve as a diagnostic procedure for evaluating tumor differentiation and infiltration, especially lymph vessel infiltration, which is important in deciding whether there is a risk for lymph-node metastasis and whether the patient can be treated endoscopically alone. Although endoscopic procedures are increasingly applied in patients with superficial esophageal neoplasia, esophagectomy remains the mainstay treatment for early esophageal cancer.

Indeed, there are several limitations for endoscopic therapy. First, patients treated endoscopically do have a higher recurrence rate [3, 9–11]. However, it does not influence overall survival after being re-treated endoscopically. Second, symptomatic stricture is common after endoscopic therapy. It can be treated with endoscopic balloon dilatation or placement of a recoverable metal stent [8]. Third, endoscopic therapy cannot remove lymph node metastases, which is an important risk factor of recurrence, especially for T1sm cancer. Although metastasis is rare in early-stage disease, it is life-threatening. In a study enrolling 7645 patients with submucosal esophageal cancer, the rate of lymph node metastasis in sm1 esophageal cancers was 27% [12]. Because endoscopic treatment cannot achieve complete resection and systematic lymphadenectomy in early esophageal cancers, esophagectomy is the first choice, although esophagectomy is associated with a high morbidity rate (46%) and post-esophagectomy syndromes might affect patients' quality of life in up to 20% of patients [13].

National Comprehensive Cancer Network (NCCN) Guidelines (Version 4.2017) of esophageal cancer recommend that endoscopic therapy is considered "preferred" for patients with limited early-stage disease (Tis and T1a, less than or equal to 2 cm, and well or moderately differentiated carcinoma) [14]. However, the histopathologic diagnosis is often inconsistent between endoscopic biopsy and endoscopic resection specimen and between endoscopic biopsy and esophagectomy specimen. For example, it was reported that endoscopic biopsy correlated with EMR specimens in only 50% of patients with Barrett's esophagus with high-grade dysplasia and early cancer [15]. Pretreatment assessment of the depth of invasion by endoscopic ultrasound is difficult for early-stage esophageal cancers [16] and it is thus impossible to accurately stage cancer with biopsy specimen and select the optimal treatment between endoscopy and esophagectomy. Due to the fact that lymph node metastases may occurs in superficial submucosal tumors (T1b–sm1), NCCN guidelines do not make a definite recommendation for optimal treatment advice of these lesions.

There are several additional tumor characteristics, such as tumor size greater than 2 cm, presence of lymphovascular invasion, and poor differentiation, that make esophagectomy theoretically better than endoscopic resection. However, there is no consensus on optimal treatment for early esophageal neoplasia with above characteristics among endoscopists and surgeons. In this retrospective study, we addressed this issue by evaluating the short-term and long-term outcomes of surgical and endoscopic management of HGD and early-stage esophageal cancers.

Methods

Patients

Medical records of patients with HGD and early esophageal squamous cell cancer (ESCC) and treated with endoscopy [ESD, endoscopic multiband mucosectomy (EMBM)] or esophagectomy in Jinling Hospital from January 2010 to June 2016 were retrieved. Patients with early esophageal lesions larger than 2 cm were included if they met at least one of the following criteria: superficial submucosal tumors (T1b–sm1), presence of lymphovascular invasion, and poor differentiation. Patients with a lesion < 2 cm, or lymph node and/or organ metastasis were excluded. This study was approved by the Institutional Review Board of Jinling Hospital. Informed consent was waived by the Institutional Review Board.

At admission, the patient received treatment advice from either the endoscopists or surgeons. The endoscopists or surgeons informed the patients the advantages and disadvantages of each treatment approach. The patient made a final decision as to the treatment approach after consultation and discussion with their family members.

Classification of complications

The postoperative complications are classified according to the criteria described by Dindo and colleagues, with five grades and two subgrades [17]. Grade I complication does not require any special medical intervention (e.g., analgesic, antipyretic, and antiemetic); grade II complication needs pharmacologic treatment (e.g., pneumonia, blood transfusion, and tachyarrhythmia); grade III complication

requires surgical, endoscopic, or radiological intervention (grade IIIa: anastomotic leakage requiring drainage of the neck and pleural empyema requiring drainage of the chest; grade IIIb: any reoperation under general anesthesia); grade IV complication is life-threatening, with single organ (grade IVa) or multiorgan (grade IVb) dysfunction, and grade V complication indicates death of patient. Readmission due to complications was recorded.

Histopathology assessment

Two experienced gastrointestinal pathologists independently reviewed the specimens. If an esophageal neoplasia was found, the following parameters were evaluated: differentiation grade, infiltration depth, the radicality of the resection at the deep resection margins, and presence of lymphatic or vascular infiltration. Surgical pathology of all esophagectomy specimens was also reviewed by the same gastrointestinal pathologists.

Follow-up

Follow-up after endoscopic treatment consisted of chromoendoscopy with iodine staining, CT, and positron-emission tomography (PET) if necessary. Endoscopy examinations with Lugol's staining and biopsy were conducted at 4, 12, 24, 36, and 48 weeks and every 6 months thereafter for the first 3 years. Then patients underwent endoscopy examination once a year. CT scans of the neck, chest, and upper abdomen were performed once a year for evaluation of lymph nodes or distant metastases. Recurrence was defined as the presence of squamous cell carcinoma or HGD detected in either biopsy sample or endoscopic resection specimen after complete remission.

Follow-up after surgical treatment was performed with endoscopy, chest and abdominal CT and additional diagnosis when necessary. Follow-up was done every 3 months in the first year, every 6 months in the second year and annually thereafter.

Statistical analysis

Statistical analysis was performed using the Statistical Software Package version 22 (SPSS, Chicago, Illinois, USA) for Windows. The continuous data were compared using the 2-sample *t* test or the Wilcoxon rank sum tests based on the data normality. The categorical data were compared with Fisher exact test. Overall survival was conducted according Kaplan–Meier product limit method. Statistical significance was set at $P < 0.05$.

Results

A total of 116 patients met the inclusion criteria were included in this study: 64 with HGD and 52 with early ESCC. Sixty-nine patients received endoscopic treatment [ESD or endoscopic multiband mucosectomy (EMBM)] and 47 patients received surgery treatment. The characteristics of the patients are shown in Table 1. There were no significant differences between the endoscopic and surgical cohorts in terms of age, gender, alcohol/tobacco use, tumor location, and longitudinal extent of neoplasia. Circumferential extent of neoplasia, length of hospital stays, and cost differed significantly between the two groups.

The pathological results were partially inconsistent in both cohorts before and after treatment. For patients receiving endoscopic treatment or surgical treatment, the original diagnoses corresponded to the final evaluation in 68.1% (47/69) and 44.7% (21/47) of the cases, respectively. In the endoscopic cohort, the original diagnosis was upgraded in 22 cases (31.9%). In the surgery cohort, the original diagnosis was upgraded in 26 (55.3%). Incomplete resection occurred significantly more often in the endoscopic cohort than in the surgery cohort (7.2% vs. 0%, $P < 0.001$). Tumor differentiation and maximum penetration depth of ESCC were similar between the two cohorts. There was one patient with positive vascular invasion in the endoscopic cohort and no vascular invasion was found in the surgical cohort. There was no lymph node metastasis in both cohorts. The histological characteristics of patients were shown in Table 2.

Significantly more minor and severe complications occurred in the surgical cohort than in the endoscopic cohort: 63.8% and 8.5% versus 43.5% and 0%, respectively ($P < 0.05$) (Tables 3, 4). No patient died in the endoscopic cohort due to complications, whereas two died in the surgical cohort due to complications (intestinal infection and renal failure). Four patients (5.8%) in the endoscopic cohort had an additional esophagectomy due to incomplete resection of cancer. Poor differentiation and deeper invasion of ESCC, which were evaluated by post-treatment specimens, were more common in patients receiving additional esophagectomy than those receiving endotherapy only. But the other variables (age, gender, alcohol or tobacco abuse, tumor location, circumferential extent of neoplasia and longitudinal extent of neoplasia) of pretreatment were similar in these two endoscopic subgroups.

The median follow-up time was 43.8 months (range 16–86 months) and 49.4 months (range 1–91 months) for the endoscopic cohort and surgical cohort, respectively. In the endoscopic cohort, local recurrence, residual neoplasia, and synchronous multiple esophageal neoplasia were found in 8.7% (6/69), 1.4% (1/69), and 2.9% (2/69) of the

Table 1 Clinical characteristics of patients

Items	Endotherapy ($n=69$)	Esophagectomy ($n=47$)	P value
Age, median years	63.7 (46–82)	61.1 (43–77)	0.096
Gender (female/male)	18/51	11/36	0.829
Alcohol use			
Yes	21	13	0.837
No	48	34	
Tobacco use			0.185
Yes	25	23	
No	44	24	
Tumor location, *n* (%)			0.582
Cervical/upper (15–24 cm)	9	4	
Middle (24–32 cm)	43	28	
Distal (32–40 cm)	17	15	
Circumferential extent of neoplasia (estimated by endoscopist), *n*			0.037
75–100%	18	23	
50–74%	20	8	
< 50%	31	16	
Longitudinal extent of neoplasia[a] (cm)	4.59 (2.1–11)	4.21 (2.1–10)	0.415
2–3	27	22	
3–4	9	5	
4–5	13	10	
5–6	8	2	
> 6	12	8	
Mean length of hospital stay (day)	10.7 (5–21)	19.2 (9–43)	< 0.001
Cost (Yuan, ¥)	24,781 (12,327–83,841)	72,028 (36,585–83,086)	< 0.001

[a]Estimated by the endoscopist. Circumferential extent was measured in hours and percentage of circumferential extent was calculated as 100/12 (8.3%) per hour

Table 2 Histological characteristics of patients

Parameter	Endotherapy ($n=69$)		Esophagectomy ($n=47$)		P
	Pre-Tx	Post-Tx	Pre-Tx	Post-Tx	
Grade of esophageal neoplasia					0.007*
HGD/Tis	67	44	45	20	
ESCC (T1a)	2	20	2	14	
ESCC (T1b)	0	5	0	13	
Maximum penetration depth of ESCC					0.132
m1		4		1	
m2		4		3	
m3		12		10	
sm1		5		13	
Tumor differentiation					0.214
Well (G1)		11		6	
Moderate (G2)		11		18	
Poor (G3)		3		3	
Complete resection					
Yes		64		47	< 0.001
No		5		0	

HGD high-grade dysplasia, *ESCC* esophageal squamous cell carcinoma, *Tx* treatment

*Endotherapy (post-Tx) versus esophagectomy (post-Tx)

Table 3 Categorization of complications [17]

Category	Examples	Grade	Endotherapy ($n=69$)	Esophagectomy ($n=47$)
Minor complications	Wound infections, urethral catheterization, analgetics, antiemetics, gout	I	24	12
	Hypotension, tachyarrhythmia, pneumonia, urinary tract infection, blood transfusions	II	0	12
	Pleural effusion requiring treatment, pneumothorax, chyle leak observation, chyle leak reoperation, tracheotomy, fiberoptic bronchoscopy suction, anastomotic leaks, endoscopic intervention	IIIa	2	6
	Decubitus surgery, additional esophagectomy	IIIb	4	0
Severe complications	Reintubation, respiratory failure, renal insufficiency	IVa	0	2
	Multiorgan dysfunction	IVb	0	0
	Death	V	0	2
Total			30	34

Table 4 Complications requiring readmission

Adverse events	Endotherapy ($n=69$)	Esophagectomy ($n=47$)
Symptomatic stricture	12	5
Adjuvant chemotherapy	5	
Metastases	1	2
Gastroesophageal reflux disease		3
Live abscess		1
Digestive tract infection		1
Anastomotic leaks		2
Pneumonia		1
Postoperative pain		1
Residual neoplasia	1	
Local recurrence	6	
Synchronous multiple esophageal neoplasia	2	
Total	27	16

patients, respectively, during follow-up. Nine patients who had recurrence, residual, or synchronous esophageal neoplasia received a second endoscopic resection. Among these patients, 3 received a third endoscopic resection, 2 a fourth endoscopic resection, and 1 a sixth endoscopic resection for recurrence. The mean recurrence time was 17.8 months (range 3–43 months). There was no significant correlation between initial lesion size and local recurrence (5.0 ± 1.7 cm vs. 4.5 ± 2.5 cm, local recurrence versus no recurrence $P=0.641$). Five patients (7.2%) in the endoscopic cohort had an additional chemotherapy for poor tumor differentiation, positive vascular invasion, or incomplete resection. One patient with an additional esophagectomy died from abdominal cavity lymph nodes metastases after 16 months in the endoscopic cohort.

The rates of complication-related readmission were 39.1% (27/69) and 34% (16/47) in the endoscopic cohort and the surgical cohort, respectively ($P=0.578$), during follow-up for 80 months. The 1-year, 3-year, and 5-year readmission rates in the endoscopic cohort and surgery cohorts were 21.7% (15/69) versus 27.7% (13/47) ($P=0.464$), 21.7% (15/69) versus 38.3% (18/47) ($P=0.052$), and 23.2% (16/69) versus 38.3% (18/47) ($P=0.079$), respectively. In the endoscopic cohort, the most common reasons for readmission were symptomatic stricture and residual/ recurrence neoplasia requiring endoscopic resection. In the surgery cohort, the most common reason for readmission was symptomatic anastomoses stricture.

The overall survival rates were similar between the surgical cohort (91.5%) and the endoscopic cohort (97.1%) ($P=0.18$). The 1-year, 3-year, and 5-year survival rates in the endoscopic cohort and surgery cohort was 100% versus 95.7% ($P=0.084$), 98.6% versus 93.6% ($P=0.153$), and 97.1% versus 91.5% ($P=0.18$), respectively. Four patients died in the surgery cohort: 2 for distant metastases, 1 for renal failure, and 1 for intestinal infection. Two patients died in the endoscopic surgery cohort due to lymph node metastasis and cerebral infarction, respectively. Overall survival and survival without readmission for treatment-related complicates are shown in Fig. 1.

Discussion

We retrieved medical records of patients with early esophageal neoplasia larger than 2 cm and controversial criterion (T1b–sm1, presence of lymphovascular invasion, and poorly differentiated pathology) and retrospectively compare the safety and efficacy of surgical and endoscopic treatments. The results showed that long-term survival was similar between the endoscopic cohort and the surgical cohort. The

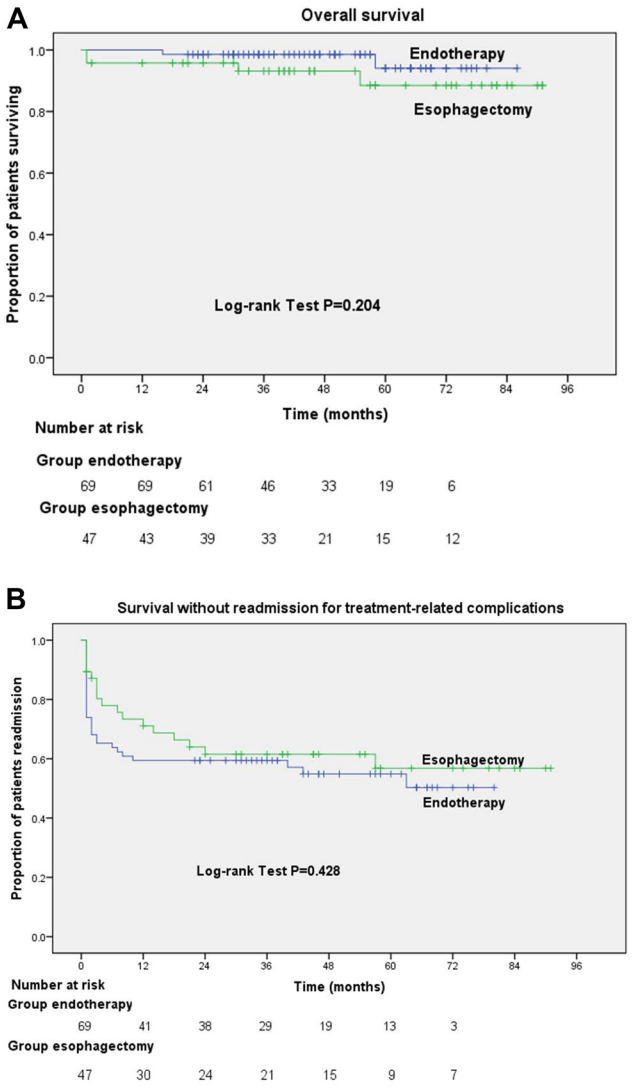

Fig. 1 Kaplan–Meier curves showed overall survival (**A**) and survival without readmission for treatment-related complications (**B**)

rates of readmission for complications were also similar. However, significantly more minor and severe complications occurred in the surgical cohort than in the endoscopic cohort. In addition, patients treated endoscopically had a shorter hospital stay. Although more local recurrences occurred in the endoscopic cohort, they were successfully treated endoscopically.

NCCN guidelines for early esophageal neoplasia have been widely accepted by both endoscopists and surgeons. According to the guidelines, Tis and T1a lesions of esophageal less than 2 cm should be treated by endoscopic resection. However, endoscopic therapy for lesions > 2 cm is associated with a greater risk of complications [14]. Due to potential regional lymph node metastases for superficial submucosal tumors (T1b–sm1), presence of lymphovascular invasion, and poor differentiation, NCCN guidelines recommend a thorough and detailed discussion among surgeons, endoscopists and patients in selecting optimal treatment for these patients and no consensus exists presently. Thus our study shed new light on this controversy issue.

Overall survival is the most important endpoint when different therapeutic modalities are compared. Our results showed that patient treated endoscopically had similar overall survival with patients treated surgically (97.1% vs. 91.5%, $P = 0.18$). Our results are in consistent with reports by others [9, 18–22]. With regards to elderly patients, Cummings et al. [23] revealed that endoscopic treatment was associated with an improved 2-year survival comparing with esophagectomy. A systematic review, excluding the population selection bias, reported associated cancer mortality at 5 years, and pooled data showed worse results with surgical therapies [24]. Published data and our study suggest a favorable long-term survival in patients receiving endoscopic therapies. In the published comparison studies, different size of esophageal neoplasia had been included for comparing the results of two therapies. The size of lesion does not specialize as a key factor in comparing the difference between endoscopic and surgical treatment. The tumor lengths of advanced esophageal cancer were found to be significantly associated with overall and recurrence free survival [25, 26]. However, with regard to early esophageal cancer, our results showed that tumor size greater than 2 cm has a comparable overall survival rates between two therapies. Indeed, in the guidelines issued by the Japan Esophageal Society, the length of lesion is not considered to be a factor for selection of endoscopic or surgical treatment. Endoscopists from China think that most of superficial esophageal neoplasia > 2 cm could be completely and safely resected by endoscopy base on their expert hand and improving protocols. Most of pathological types of esophageal cancers in China and Japan are squamous cell carcinoma. Therefore, both countries adopt similar treatment strategies in clinical practice.

The cost of therapy only covers all expenses during the hospital stay in this study. After esophagectomy, surgical patients are unlikely to have additional cost directly related to the follow-up of esophageal cancer. Endotherapy patients will require long-term surveillance and possibly additional therapy. Theoretically, lifelong cost for endotherapy will likely exceed those of esophagectomy if a patient has long-term survival. These results suggest endoscopic treatment may have no cost advantage. However, esophagogastroduodenoscopy examination is very convenient and relatively inexpensive (¥402 or $58) in China. For surgical patients, post-esophagectomy syndromes may affect quality of life in up to 20% of patients and many of them need additional medication or hospitalization. These complications and related costs need to be considered. Due to the obvious cost difference between these two methods (usually the cost of

esophagectomy is three times as much as endotherpy), endotherapy may have an advantage in total cost.

Thus, due to the well-known advantages of endoscopic treatment in esophageal preservation, lower duration of hospital stays and cost, we think endoscopic therapies for early esophageal cancer larger than 2 cm are superior to esophagectomy.

Esophagectomy is associated with frequent minor complications (32–69%) and some major complications (0–17%) [9, 19, 21–23, 27]. The same tendency was found in our study. These complications will result in longer hospital stays, higher hospital costs and procedure-related death. This may partially explain why endoscopic treatment is superior to surgical treatment in terms of medium and long-term survival. Although the total number of complications was lower in the endotherapy group, the number of complications requiring admission was actually higher in the endotherapy group. Thus preservation of esophagus is a risk factor for local recurrence, synchronous multiple esophageal neoplasia and residual neoplasia. However, most of these complications were successfully treated endoscopically. In a hospital-based cancer registry system that collects data from more than 1500 American hospitals, an analysis of 5390 patients showed the risk of 30-day mortality was lower after endoscopic resection than after surgical resection (0.5% vs. 3.5%) [26]. Although the perioperative mortality rates are reported as low as 2–4.9% at high-volume centers [28–30], surgery-related death should be considered during selection of treatment modality.

Incomplete resection after endoscopic treatment for early esophageal cancer contributes to local recurrence, lymphatic and distant metastasis of the tumor. Four patients (5.8%) (2 with poor differentiation and 2 with ESCC of sm1) in the endoscopic cohort needed an additional esophagectomy due to incomplete resection of esophageal cancer in our study. In these cases, the pathological findings were inconsistent before and after endoscopic treatment. More studies are needed for precise determination of differentiation and invasion status before treatment to help choose optimal treatment. EMR should be routinely used for preoperative staging for multidisciplinary review [31]. Consistent with previous report [32], although esophagectomy was necessary in few patients after endoscopic treatment of stage T1 esophageal cancer, it did not increase the incidence of postoperative complications and did not affect survival after esophagectomy.

The residual, recurrent or metachronous neoplasia occurred in more patients who underwent endotherapy than those underwent esophagectomy [19–21, 26]. These patients usually received repeated endotherapy, chemotherapy, radiotherapy or surgical resection [33, 34]. In our hospital, these patients were treated with repeated endotherapy and all patients survived until the manuscript was prepared. Thus a close follow-up program to monitor recurrence or metachronous neoplastic lesion is mandatory. Some patients with invasion in the endotherapy group need chemotherapy, which will increase the cost of treatment and the time of hospitalization. The endoscopists should consider and inform the patients these.

It should be pointed out that only squamous cell neoplasia (SCC) was included in our study. SCC are common in Japan, Korea and China etc. In the published studies, most patients were diagnosed with early adenocarcinoma and HGD in Barrett's esophagus [11, 18, 26, 18, 26], which have different natural history and treatment outcomes [35]. Our findings are informative for patients with SCC, which accounts for about 87% of all esophageal cancers globally [36].

There are several limitations of the present study. First, the follow-up time was relatively short and the number of patients was small. Second, several types of endotherapy, including ESD, EMBM, and EMR, and several types of esophagectomy were performed in our hospital. The efficacy of these treatments is different [8]. Third, the circumferential extent of tumor is significantly higher in the esophagectomy group, and this factor will have more likely to increase the risk of stricture in the endotherapy group, not the risk of complications in the esophagectomy group. However, most of stricture can be prevented by medications (eg. corticoids) or treated successfully by endotherapy [37].

In conclusion, early esophageal neoplasia larger than 2 cm could be effectively and safely treated by endoscopic therapy. NCCN Guidelines recommendations may make some patients with larger than 2 cm loss opportunities of endoscopic treatment. According to Japan guidelines, we think that focus on the invasion depth (T1b–sm1) and poor differentiation of cancer, instead of consideration of the size of lesion as an indication of endoscopic therapy is acceptable. Endoscopic treatment is associated with equivalent survival and fewer complications, esophageal preservation, lower duration of hospital stays and cost than surgical treatment, and should be a preferred treatment approach. RCT studies are needed to further compare the efficacy and safety of surgical and endoscopic treatments of HGD and superficial esophageal cancer.

Compliance with ethical standards

Disclosures Drs. Baisi Yuan, Leilei Liu, Hairong Huang, Demin Li, Yi Shen, Bo Wu, Jiong Liu, Miaofang Yang, Zhenkai Wang and Heng Lu, Professor Yuxiu Liu, Lianming Liao and Fangyu Wang have no conflicts of interest or financial ties to disclose.

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