

# Clinical significance of the depth of invasion in superficial Barrett's esophageal adenocarcinoma

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## Article Info

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### Keywords

Superficial Barrett's esophageal adenocarcinoma

Depth of invasion

Lymph node metastasis

Duplication of muscularis mucosae

## ABSTRACT

Superficial Barrett's esophageal adenocarcinoma limited to the lamina propria, like other superficial cancers, is associated with almost no risk of lymph node metastasis. However, lymph node metastasis has been observed in patients with Barrett's esophageal adenocarcinoma invading the muscularis mucosae. The duplication of the muscularis mucosae is a pathological characteristic of Barrett's esophagus; however, the rate of lymph node metastasis might not differ according to the depth of invasion within the muscularis mucosae. Submucosal invasion is considered to be a risk factor for lymph node metastasis; however, many reports have suggested that submucosal invasion alone is not a risk factor but that the likelihood of lymph node metastasis increases as the number of risk factors increases. Generally, lymphovascular invasion, pathological differentiation and tumor size are also considered to be risk factors for lymph node metastasis. Previous reports have suggested that patients with superficial Barrett's esophageal adenocarcinoma limited to T1b-SM1 may have a lower risk of lymph node metastasis and might be candidates for endoscopic resection if other risk factors are negative.

## Introduction

The incidence of adenocarcinoma arising from Barrett's esophagus is increasing because of the increased incidence of gastroesophageal reflux disease caused by obesity or aging<sup>1,2</sup>. Recently, surveillance<sup>3-6</sup> and endoscopic resection (ER)<sup>7-10</sup> for Barrett's esophageal adenocarcinoma (BEA) have been actively investigated; however, only a few published studies have focused on the clinicopathological features of superficial BEA, and the differences between superficial BEA and superficial squamous cell carcinoma in the esophagus remain unclear. Generally, an investigation of the relationship between the depth of invasion and the prevalence of lymph node metastasis in superficial BEA has been very important for deciding the indications for ER or for additional treatments after ER<sup>11,12</sup>.

The aim of the present review was to evaluate previous reports investigating the relationship between the depth of invasion and the prevalence of lymph node metastasis in a large number of cases with superficial BEA and to consider future directions.

## Clinicopathological features of superficial adenocarcinoma invading muscularis mucosae in Barrett's esophagus

There is almost no risk of lymphovascular invasion (LVI) and

lymph node metastasis for superficial BEA limited to the lamina propria, similar to other superficial cancer. However, lymph node metastasis has been found in patients with BEA invading the muscularis mucosae (MM)<sup>13</sup>. Duplication of the MM is a pathological characteristic of Barrett's esophagus<sup>14-16</sup>. Abraham et al. classified 30 resected cases with BEA confined to regions of duplicated MM into three subgroups according to depth of invasion: inner MM (n = 10), between MM (n = 12) and outer MM (n = 8). No differences in the rates of LVI and lymph node metastasis were observed among these three groups<sup>17</sup>. In our review, the rate of lymph node metastasis in patients with BEA invading the MM was 6% (Table 1). This rate tended to be lower than that in patients with esophageal squamous cell carcinoma invading the MM<sup>11,17-20</sup>.

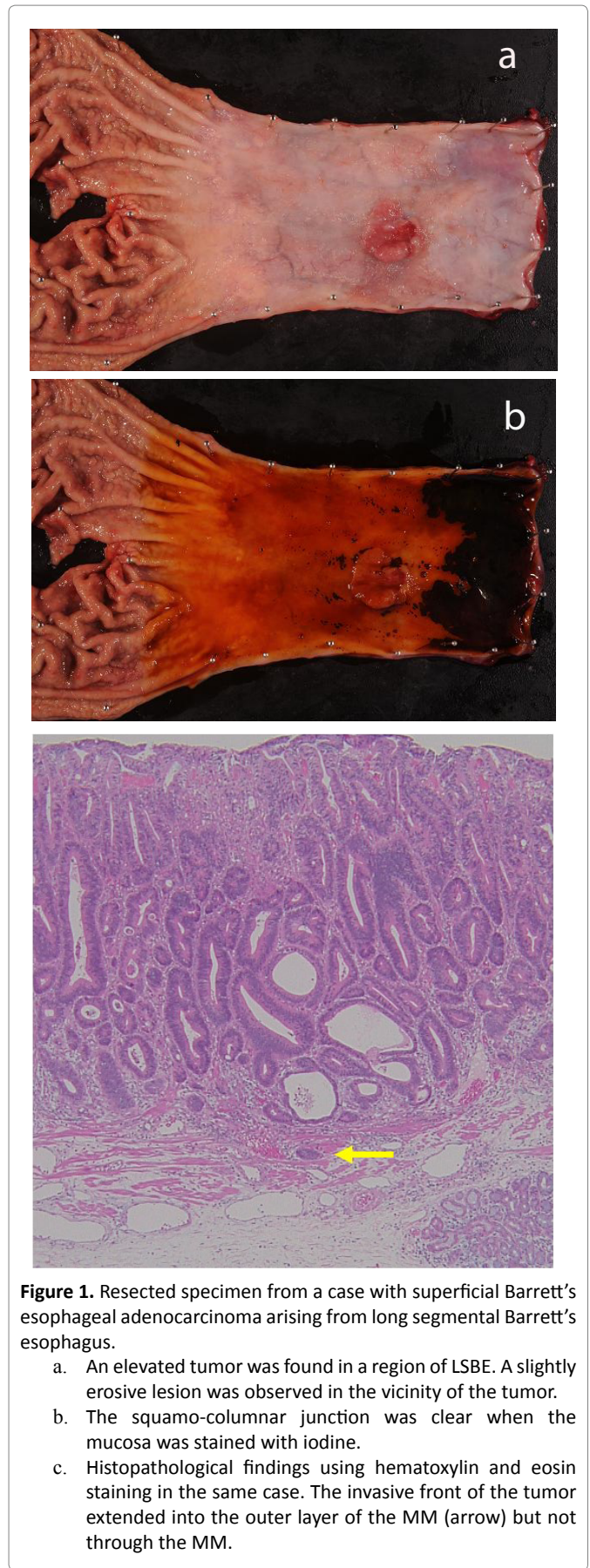
We previously reported a resected case with superficial BEA arising from long segmental Barrett's esophagus (LSBE). The tumor had invaded the deep layer of the MM pathologically. An erosive lesion in LSBE was initially found, and the lesion had developed into a superficial BEA with deep invasion of the MM two years later. An esophagectomy was performed (Figure 1) and no signs of LVI or lymph node metastasis were observed<sup>21</sup>. Sakaguchi et al. also reported a resected case with superficial BEA that had invaded deep into the MM. LVI was not observed pathologically, but a single metastatic lymph node was found in the lower mediastinum. The histopathological results for the resected specimen showed a poorly differentiated adenocarcinoma at the invasive front of this tumor<sup>22</sup>.

### Risk factors for lymph node metastasis in superficial BEA

Some reports have suggested that invasion to the submucosa is a risk factor for lymph node metastasis<sup>18,23,24</sup>, while other reports have suggested that submucosal

**Table 1.** Summary of previous reports which had shown the rate of lymph node metastasis in patients with resected superficial BEA.

Author (year)	Depth of invasion (LN metastasis / Total cases)				Ref
	T1a-DMM	T1b-SM1	T1b-SM2	T1b-SM3	
Liu (2005)	2/17 (12%)	1/12 (8%)	-	9/25 (36%)	18
Westerterp (2005)	1/23 (4%)	0/25 (0%)	6/23 (26%)	12/18 (67%)	19
Abraham (2007)	3/30 (10%)	-	-	-	17
Kaneshiro (2011)	0/30 (0%)	3/35 (9%)	-	-	20
Badreddine (2011)	-	4/31 (13%)	10/49 (20%)	-	11
Total	6/100 (6%)	8/103 (8%)	16/72 (22%)	21/46 (46%)	



**Figure 1.** Resected specimen from a case with superficial Barrett's esophageal adenocarcinoma arising from long segmental Barrett's esophagus.

- An elevated tumor was found in a region of LSBE. A slightly erosive lesion was observed in the vicinity of the tumor.
- The squamo-columnar junction was clear when the mucosa was stained with iodine.
- Histopathological findings using hematoxylin and eosin staining in the same case. The invasive front of the tumor extended into the outer layer of the MM (arrow) but not through the MM.

invasion alone is not a risk factor<sup>19,25,26</sup>. Previous reports describing the rate of lymph node metastasis in patients with resected superficial BEA are summarized in Table 1. This table shows that the rate of lymph node metastasis in patients with T1b-SM1 was similar to that in patients with T1a-MM, while it was clearly lower than that in patients with T1b-SM2 or SM3. The rate of lymph node metastasis in patients with esophageal squamous cell carcinoma (SCC) confined to T1b-SM1 was approximately 20%<sup>27</sup>, and this rate was clearly higher than that for BEA. Although the relationship between lymph node metastasis and other risk factors, such as pathological differentiation and LVI, should be evaluated, the clinicopathological features of T1b-SM1 seem to differ between BEA and SCC. Consequently, it has been suggested that the treatment strategies should also differ for each cancer. Other risk factors of lymph node metastasis are LVI, pathological differentiation and tumor size<sup>26,28</sup>. Boy et al. suggested that the likelihood of lymph node metastasis increases as the number of these risk factors in a patient increases<sup>26</sup>.

An international consensus on the classification of submucosal subgroups does not yet exist. In the Japanese classification of esophageal cancer, T1b-SM1 in surgical specimens is defined as the upper-third of the submucosal layer, while T1b-SM1 in ER specimens is defined as submucosal invasion to a depth of up to 200  $\mu$ m. Thus, the definition of T1b-SM1 differs between surgical and ER specimens<sup>29</sup>. On the other hand, T1b-SM1 is defined as submucosal invasion to a depth of up to 500  $\mu$ m in some European countries' guidelines<sup>30,31</sup>. Caution to avoid confusing these definitions of T1b-SM1 is needed.

Although the further investigation of a larger number of cases with superficial BEA is needed, previous reports suggest that patients with superficial BEA limited to the T1b-SM1 may have a lower risk of lymph node metastasis and might be candidates for ER if other risk factors are negative.

### Conclusions and future directions

According to the present review of previous reports on superficial BEA, there was no relationship between the depth of invasion and lymph node metastasis in patients with superficial BEA confined to duplicated MM in BE. Patients with superficial BEA limited to T1b-SM1 have a lower risk of lymph node metastasis and might be candidates for ER if other risk factors, such as pathological differentiation and LVI, are all negative. However, the number of previously reported cases was not sufficient to perform a statistically significant analysis. Moreover, the definition of the depth of invasion in superficial BEA remains controversial. These problems should be recognized and novel evidence should be collected from a large number of cases to ensure the development of optimal treatment strategies.

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