World J Surg (2019) 43:1997–2005
https://doi.org/10.1007/s00268-019-05004-z

ORIGINAL SCIENTIFIC REPORT

Significance of Intramural Metastasis in Patients with Esophageal Squamous Cell Carcinoma: An Indicator of Aggressive Cancer Behavior

Akihiko Okamura[1] · Masayuki Watanabe[1] · Ryotaro Kozuki[1] · Tasuku Toihata[1] · Keita Takahashi[1] · Yu Imamura[1] · Shinji Mine[1]

Published online: 16 April 2019

Abstract

Background Intramural metastasis (IM) is occasionally noted in patients with esophageal squamous cell carcinoma (ESCC). However, few recent studies have investigated the clinicopathological characteristics of IM and its survival impact. The present study aimed to clarify the clinicopathological and prognostic significance of IM in patients with ESCC.

Methods We retrospectively examined 918 consecutive patients who underwent curative intent esophagectomy for ESCC. IM was defined as a pathologically confirmed metastatic lesion, which was clearly separate from the primary tumor and located within the esophageal or gastric wall. The clinicopathological characteristics and survival impact of IM were evaluated. A propensity score-matched analysis was performed to further elucidate the prognostic impact of IM.

Results Among 918 patients, 46 (5.0%) had IM. Advanced tumors were significantly more frequent in patients with IM than in those without IM. The curative resection rate was lower in patients with IM ($P = 0.001$). Overall survival (OS) and disease-specific survival (DSS) were worse in patients with IM (both $P < 0.001$). In multivariate Cox proportional hazard analysis, IM presence was an independent poor prognostic indicator for OS and DSS (both $P < 0.001$). After propensity score matching, advanced tumors according to pathological N stage and lymphatic invasion were more frequent in patients with IM ($P = 0.015$ and 0.004, respectively). Additionally, OS and DSS were different between patients with and those without IM (both $P = 0.002$).

Conclusions IM from ESCC is a local indicator of lymphatic invasion and advanced cancer, as well as an independent factor for poor prognosis.

Introduction

Intramural metastasis (IM) from the primary cancer lesion is occasionally noted in patients with digestive tract cancers, such as esophageal and gastric cancers. This type of metastasis is considered as cancer spreading from the primary lesion through the intramural lymphatic system. The presence of IM has been reported to be one of the important poor prognostic indicators [1–8].

IM of esophageal squamous cell carcinoma (ESCC) has been reported in 5.5% to 16.6% of cases [1–4, 6, 8] and suggested to be associated with large tumor size and

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00268-019-05004-z) contains supplementary material, which is available to authorized users.

✉ Masayuki Watanabe
masayuki.watanabe@jfcr.or.jp

[1] Department of Gastroenterological Surgery, Gastroenterology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135–8550, Japan

advanced T and N stages. In addition, it is considered a local indicator of advanced esophageal cancer. However, in this decade which is the era of multidisciplinary treatment comprising of surgery, chemotherapy, and radiotherapy, few studies have investigated the clinicopathological characteristics of IM in detail, and it is unclear whether the presence of IM is correlated with cancer progression or biological behavior. In the present study, we comprehensively analyzed the correlations between clinicopathological variables and the presence of pathologically confirmed IM in order to clarify the clinicopathological and prognostic significance of IM in patients with ESCC.

Patients and methods

Patients

We retrospectively examined consecutive patients who underwent curative intent surgery for ESCC at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (Tokyo, Japan) between 2005 and 2016. Patients without data regarding the pathological evaluation of IM were excluded from this study. We reviewed the medical records of 918 patients who fulfilled the criteria and collected data, including clinical characteristics, pathological findings, and patient survival rates. The study protocol was approved by our institutional review board.

Treatment for ESCC

All patients had undergone routine preoperative evaluations including esophagogastroduodenoscopy and computed tomography (CT). In patients with T2 or higher tumors or with possible metastatic nodes on CT, positron emission tomography was also performed. We do not perform endoscopic ultrasound and endobronchial ultrasound routinely to evaluate the preoperative clinical nodal staging and the invasiveness to adjacent structures. Each patient was treated in accordance with the JES guidelines as follows [9]: stage I, surgery alone or definitive chemoradiotherapy (CRT); stage II or III, neoadjuvant chemotherapy (NAC) followed by surgery; T4 tumor or surgery refusal irrespective of the stage, definitive CRT; CRT failure, salvage surgery. NAC involved two courses of cisplatin and 5-fluorouracil (CF), as adopted in the randomized trial JCOG 9907 [10]. However, it should be noted that NAC was not available before 2009 [11, 12]. Surgery involved resection of the esophagus along with the periesophageal tissue using the open or minimally invasive approach.

Pathological evaluation and definition of IM

Each specimen was usually reviewed by two experienced pathologists. In the pathological evaluation, the histological tumor type, histological tumor grade, depth of tumor invasion, presence of lymphatic invasion, presence of venous invasion, presence of IM, and resection margin were assessed. In addition, all dissected lymph nodes were explored, and the nodal status was recorded. IM was defined as metastasis that was clearly separate from the primary tumor and located within the esophageal or gastric wall. To distinguish residual tumor nests after preoperative treatment from IM, we referred to the existence of histological therapeutic changes such as fibrosis, granulation tissue, necrosis, or degenerated tumors. In cases after neoadjuvant therapy, we diagnosed the isolated tumor nests which lacked apparent therapeutic changes as IM. The tumor stage was determined according to the Union for International Cancer Control *TNM Classification of Malignant Tumours*, eighth edition [13]. Regarding IM within the gastric wall which was defined as distant metastasis (M1), it was evaluated in the en bloc resected esophagus and proximal stomach.

Patient follow-up

Patients were followed up every 4 months for 1 year postoperatively and every 6 months thereafter. At each visit, physical examination and computed tomography were performed and serum SCC antigen levels were assessed. In addition, upper endoscopy was performed annually. Patient follow-up was planned for at least 5 years postoperatively.

Statistical analysis

All data are presented as median (range) or number (%). The Mann–Whitney *U* test and Fisher's exact test were performed for statistical comparisons between groups, as appropriate. In addition, survival analysis was performed using the Kaplan–Meier method and log-rank test. A Cox proportional hazard model was used to assess the impact of variables on survival, and the hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. In the multivariate analysis, we considered potential confounders, including sex (female or male), age (continuous), body mass index (BMI; continuous), preoperative treatment (none, NAC, or CRT), pathological T stage (pT0–1, pT2, pT3, or pT4), pathological N stage (pN0, pN1, or pN2–3), pathological M stage (pM0 or pM1), resection margin (R0, R1, or R2), and IM (presence or absence). Additionally, survival analysis was performed using a propensity score-matched (PSM) analysis to minimize the impact of possible

confounders and treatment-related bias. PSM analysis was performed using a logistic regression model with the following covariates: sex (female or male), age (continuous), BMI (continuous), initial clinical T stage (cT1, cT2, cT3, or cT4), initial clinical N stage (cN0, cN1, or cN2–3), initial clinical M stage (cM0 or cM1), and preoperative treatment (none, NAC, or CRT). Patients without IM were matched to those with IM in a 1:1 ratio according to propensity scores (precision: ±0.01), and their characteristics and survivals were compared. All statistical analyses were performed using the SPSS software package (version 23.0; IBM Corp., Armonk, NY, USA). A P value < 0.05 was considered statistically significant.

Results

Patient characteristics and pathological findings

Among the 918 patients, 46 (5.0%) had IM. Table 1 summarizes the comparisons of patient characteristics and pathological findings between patients with IM and those without IM. Clinically and pathologically advanced tumors were significantly more frequent in patients with IM than in those without IM. In addition, the curative resection rate was significantly lower in patients with IM ($P = 0.001$). Although no significant difference was observed in the histological tumor grade, both lymphatic invasion and venous invasion were more frequent in patients with IM than in those without IM (both $P < 0.001$). Regarding surgical outcomes, the 30- and 90-day mortality rates in this study were 0.3% ($n = 3$) and 0.9% ($n = 8$), respectively, and there were no significant differences between the groups.

Details of IM

The details of IM in this study are presented in Table 2. Of the 46 patients with IM, 27 (58.7%) had clinically apparent IM, which was diagnosed during preoperative endoscopy, and 19 (41.3%) had latent IM, which was diagnosed by pathological evaluation after surgery. Additionally, 10 (21.7%) had IM on the oral side of the primary tumor, 31 (67.4%) had IM on the anal side, and 5 (10.9%) had IM on both sides. IM within the gastric wall was noted in 17 (36.9%) patients. The median number of IMs was 1 (range 1–11), and multiple IMs were detected in seven patients (15.2%).

Prognostic significance of IM with regard to patient survival

Of all patients, disease-specific mortality was 26.9% ($n = 247$), other cause mortality was 14.5% ($n = 133$), completion follow-up was 32.6% ($n = 299$), and lost to follow-up was 26.0% ($n = 239$). Kaplan–Meier curves for overall survival (OS) and disease-specific survival (DSS) were calculated (Fig. 1). OS and DSS were significantly worse in patients with IM than in those without IM (both $P < 0.001$). OS and DSS in patients with IM were worse regardless of pStage category (Supplementary Figs. 1 and 2). We calculated the HRs of IM presence for OS and DSS using univariate and multivariate Cox proportional hazard analyses (Supplementary Tables 1 and 2) and found that IM presence was one of the independent poor prognostic indicators for OS (HR 2.04, 95% CI 1.41–2.96, $P < 0.001$) and DSS (HR 2.07, 95% CI 1.37–3.15, $P = 0.001$).

Differences between patients with and those without IM in the PSM cohort

We performed a PSM analysis to further elucidate the significance of IM. After propensity score matching, 45 well-balanced pairs of patients with regard to the preoperative status were identified (Table 3). In the PSM cohort, although the preoperative status was comparable between the patient groups, the number of metastatic lymph nodes, frequency of advanced pathological N stage, and frequency of lymphatic invasion were significantly greater in patients with IM than in those without IM (Table 4; $P = 0.002$, $P = 0.015$, and $P = 0.004$, respectively). In addition, OS and DSS were significantly different between patients with IM and those without IM (Fig. 2; both $P = 0.002$).

Recurrence pattern in R0 resected patients

There were 250 patients who experienced disease recurrence in R0 resected 841 patients. Comparisons of the recurrence patterns between the groups are described in Table 5. The incidence of locoregional recurrence and distant metastasis were significantly different between patients with and without IM. However, in the PSM cohort, there was no difference in recurrence pattern.

Relationships between the characteristics of IM and survival in patients with IM

We investigated the relationships between the clinical characteristics of IM and survival in patients with IM. Although there were no survival differences between groups stratified according to the direction of IM, the presence of gastric IM, and the presence of multiple IMs,

Table 1 Patient characteristics, surgical outcomes, and pathological findings

Variables		Patients without IM (n = 872)	Patients with IM (n = 46)	P value
Age, years		65 (32–88)	65 (31–80)	0.898
BMI, kg/m^2		21.5 (12.9–31.6)	21.3 (13.5–30.6)	0.761
Sex	Male	729 (83.6)	40 (87.0)	0.683
	Female	143 (16.4)	6 (13.0)	
Main tumor location	Ce, Ut	175 (20.1)	8 (17.4)	0.838
	Mt	418 (47.9)	24 (52.2)	
	Lt, Ae	279 (32.0)	14 (30.4)	
Initial clinical T stage	cT1	328 (37.6)	4 (8.7)	<0.001*
	cT2	161 (18.5)	7 (15.2)	
	cT3	340 (39.0)	31 (67.4)	
	cT4	43 (4.9)	4 (8.7)	
Initial clinical N stage	cN0	427 (49.0)	11 (23.9)	0.001*
	cN1	331 (38.0)	22 (47.8)	
	cN2–3	114 (13.1)	13 (28.3)	
Initial clinical M stage	cM0	831 (95.3)	41 (91.3)	0.227
	cM1	42 (4.7)	4 (8.7)	
Preoperative treatment	None	472 (54.1)	23 (50)	0.234
	NAC	334 (38.3)	22 (47.8)	
	CRT	66 (7.6)	1 (2.2)	
Type of surgery	Subtotal esophagectomy	788 (90.4)	40 (87.0)	0.559
	TPLE	52 (6.0)	4 (8.7)	
	Distal esophagectomy	28 (3.2)	2 (4.3)	
	Others	4 (0.5)	0 (0.0)	
No. of harvested lymph nodes		50 (0–131)	46 (4–92)	0.179
Postoperative morbidities		575 (65.9)	32 (69.6)	0.749
30-day mortality		3 (0.3)	0 (0.0)	1.000
90-day mortality		7 (0.8)	1 (2.2)	0.338
Pathological T stage	pT0–1	433 (49.7)	8 (17.4)	<0.001*
	pT2	112 (12.8)	6 (13.0)	
	pT3	279 (32.0)	29 (63.0)	
	pT4	48 (5.5)	3 (6.5)	
Pathological N stage	pN0	409 (46.9)	9 (19.6)	<0.001*
	pN1	258 (29.6)	7 (15.2)	
	pN2–3	205 (23.5)	30 (65.2)	
Pathological M stage	pM0	812 (93.1)	39 (84.8)	0.071
	pM1	60 (6.9)	7 (15.2)	
No. of metastatic lymph nodes		1 (0–39)	4 (0–20)	<0.001*
Resection margin	R0	807 (92.5)	34 (73.9)	0.001*
	R1	40 (4.6)	10 (21.7)	
	R2	25 (2.9)	2 (4.3)	
Histological tumor grade	Well differentiated	220 (27.3)	14 (30.4)	0.892
	Moderately differentiated	457 (56.8)	25 (54.4)	
	Poorly differentiated	128 (15.9)	7 (15.2)	
	Not available	67	0	
Lymphatic invasion	Negative	381 (43.7)	5 (10.9)	<0.001*
	Positive	490 (56.3)	41 (89.1)	
	Not available	1	0	

Table 1 continued

Variables		Patients without IM (n = 872)	Patients with IM (n = 46)	P value
Vascular invasion	Negative	415 (47.6)	9 (19.6)	<0.001*
	Positive	457 (52.4)	37 (80.4)	

IM intramural metastasis, *BMI* body mass index, *Ce* cervical, *Ut* upper thoracic, *Mt* middle thoracic, *Lt* lower thoracic, *Ae* abdominal, *NAC* neoadjuvant chemotherapy, *CRT* chemoradiotherapy, *TPLE* total pharyngolaryngoesophagectomy, *No.* number

Data are presented as median (range) or n (%). *$P < 0.05$

Table 2 Details of IM

Variables		Value
Diagnosis type	Preoperative (clinically apparent)	27 (58.7)
	Pathological (latent)	19 (41.3)
IM location	Oral side	10 (21.7)
	Anal side	31 (67.4)
	Both sides	5 (10.9)
Gastric IM (pM1)		17 (36.9)
No. of IMs		1 (1–11)
	Single	39 (84.8)
	Multiple	7 (15.2)

IM intramural metastasis, *No.* number

Data are presented as median (range) or n (%)

DSS tended to be worse in patients with clinically apparent IM than in those with latent IM (Fig. 3; $P = 0.075$).

Discussion

In this study, we evaluated the clinical characteristics of IM from ESCC, as well as the relationship between IM and prognosis following curative intent surgery for ESCC. We observed that advanced tumors were significantly more frequent, and OS and DSS were significantly worse in patients with IM than in those without IM. IM from ESCC independently increased the risk of poor OS and DSS following surgery. Moreover, it was significantly associated with lymphatic invasion and poor prognosis even after adjusting the preoperative status with PSM analysis. Notably, the prognosis of patients with clinically apparent IM was extremely poor.

In 1993, IM from esophageal cancer was first reported by Watson [14]. This type of metastasis is considered to be cancer spreading through the submucosal lymphatic system and to be one of the important factors for predicting poor prognosis [1–4, 6, 8]. In this study, we demonstrated that IM from ESCC was significantly associated with lymphatic invasion and poor prognosis, and was a local indicator of advanced tumor stage. These results confirmed that ESCC with IM has highly aggressive biological behavior when compared with ESCC without IM.

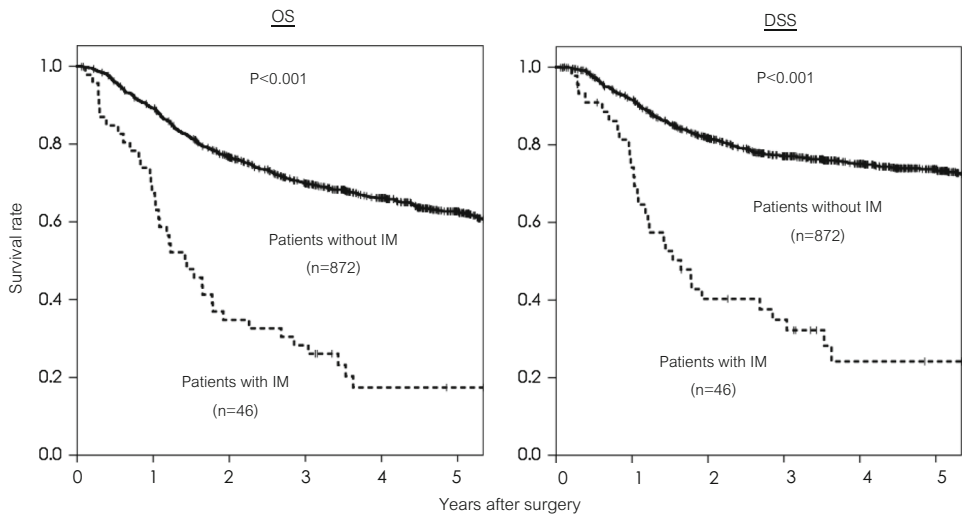

Fig. 1 Kaplan–Meier curves for the overall survival (OS) and disease-specific survival (DSS) of patients with intramural metastasis (IM) and those without IM

Table 3 Patient characteristics in the propensity score-matched cohort

Variable		Patients without IM (n = 45)	Patients with IM (n = 45)	P value
Age, years		66 (42–76)	65 (31–80)	1.000
BMI, kg/m^2		21.9 (15.8–29.4)	21.1 (13.5–30.6)	0.271
Sex	Male	42 (93.3)	39 (86.7)	0.485
	Female	3 (6.7)	6 (13.3)	
Main tumor location	Ce, Ut	8 (17.8)	8 (17.8)	0.786
	Mt	21 (46.7)	24 (53.3)	
	Lt, Ae	16 (35.6)	13 (28.9)	
Initial clinical T stage	cT1	4 (8.9)	4 (8.9)	0.663
	cT2	9 (20.0)	7 (15.6)	
	cT3	26 (57.8)	31 (68.9)	
	cT4	6 (13.3)	3 (6.7)	
Initial clinical N stage	cN0	10 (22.2)	11 (24.4)	0.852
	cN1	25 (55.6)	22 (48.9)	
	cN2–3	10 (22.2)	12 (26.7)	
Initial clinical M stage	cM0	41 (91.1)	41 (91.1)	1.000
	cM1	4 (8.9)	4 (8.9)	
Preoperative treatment	None	23 (51.1)	22 (48.9)	1.000
	NAC	21 (46.7)	22 (48.9)	
	CRT	1 (2.2)	1 (2.2)	

IM intramural metastasis, *BMI* body mass index, *Ce* cervical, *Ut* upper thoracic, *Mt* middle thoracic, *Lt* lower thoracic, *Ae* abdominal, *NAC* neoadjuvant chemotherapy, *CRT* chemoradiotherapy

Data are presented as median (range) or n (%). *$P < 0.05$

Although the prognosis of patients with IM was undoubtedly poor, nearly 40% of patients whose IM was not detected preoperatively had relatively good survival in our study. On the other hand, the prognosis of patients with clinically apparent IM was extremely poor. Therefore, clinically apparent IM should be considered as a systemic disease. Previously, Nishimaki et al. compared the survival difference between extended radical esophagectomy and less radical esophagectomy for ESCC patients with IM in a setting without preoperative treatment and found that there was no significant difference in survival between the two types of surgeries, suggesting that ESCC with IM is mainly beyond the scope of radical esophagectomy [4]. Therefore, surgery alone is not an appropriate choice and powerful systemic therapy is required. However, there is no evidence to deny the implication of surgery for patients with clinically apparent IM. Currently, we consider that surgical resection should be performed for locoregional control only when the induction therapy was effective.

However, there has been no consensus on the multimodal treatment of ESCC with IM. With regard to NAC, Hokamura et al. reported no apparent improvement in the survival of ESCC patients with IM when using NAC with CF [5]. In addition, we previously reported that IM is significantly associated with inoperableness because of disease progression during NAC with CF and incomplete resection even after NAC with CF [15]. Therefore, NAC with CF might be insufficient in these patients, although data on the efficacy of regimens other than CF are unavailable. In the future, alternative strategies, such as triplet chemotherapy with strong antitumor activity, should be evaluated, and it has been reported that docetaxel plus CF (DCF) is one of the most promising regimens for ESCC [16–18].

Recently, a randomized clinical trial showed that neoadjuvant CRT for advanced ESCC is associated with improved survival and curative resection rates when compared with the findings using surgery alone [19]. However, there is no information indicating the efficacy of neoadjuvant CRT in ESCC patients with IM. We assumed that adding radiotherapy to chemotherapy as neoadjuvant therapy might not be effective, because CRT is more likely to be useful for local disease control, and clinically apparent IM appears to be an indicator of systemic disease.

The present study has several limitations. First, this was a retrospective observational study performed in a single institution during a relatively long study period. As mentioned above, NAC was not available before 2009, and it

Table 4 Surgical outcomes and pathologic findings in the propensity score-matched cohort

Variable		Patients without IM (n = 45)	Patients with IM (n = 45)	P value
Type of surgery	Subtotal esophagectomy	41 (91.1)	40 (88.9)	1.000
	TPLE	4 (8.9)	4 (8.9)	
	Distal esophagectomy	0 (0.0)	1 (2.2)	
No. of harvested lymph nodes		58 (10–131)	46 (4–92)	0.074
Postoperative morbidities		33 (73.3)	32 (71.1)	1.000
30-day mortality		1 (2.2)	0 (0.0)	1.000
90-day mortality		2 (4.4)	1 (2.2)	1.000
Pathological T stage	pT0–1	10 (22.2)	7 (15.6)	0.654
	pT2	8 (17.8)	6 (13.3)	
	pT3	23 (51.1)	29 (64.4)	
	pT4	4 (8.9)	3 (6.7)	
Pathological N stage	pN0	17 (37.8)	9 (20.0)	0.015*
	pN1	13 (28.9)	7 (15.6)	
	pN2–3	15 (33.3)	29 (64.4)	
Pathological M stage	pM0	40 (88.9)	38 (84.4)	0.758
	pM1	5 (11.1)	7 (15.6)	
No. of metastatic lymph nodes		1 (0–17)	4 (0–20)	0.002*
Resection margin	R0	38 (84.4)	33 (73.3)	0.343
	R1	5 (11.1)	10 (22.2)	
	R2	2 (4.4)	2 (4.4)	
Histological tumor grade	Well differentiated	12 (26.7)	14 (31.1)	0.915
	Moderately differentiated	26 (57.8)	25 (55.6)	
	Poorly differentiated	7 (15.6)	6 (13.3)	
Lymphatic invasion	Negative	16 (35.6)	4 (8.9)	0.004*
	Positive	29 (64.4)	41 (91.1)	
Vascular invasion	Negative	14 (31.1)	9 (20.0)	0.333
	Positive	31 (68.9)	36 (80.0)	

TPLE total pharyngolaryngoesophagectomy, *No.* number

Data are presented as median (range) or n (%). *$P < 0.05$

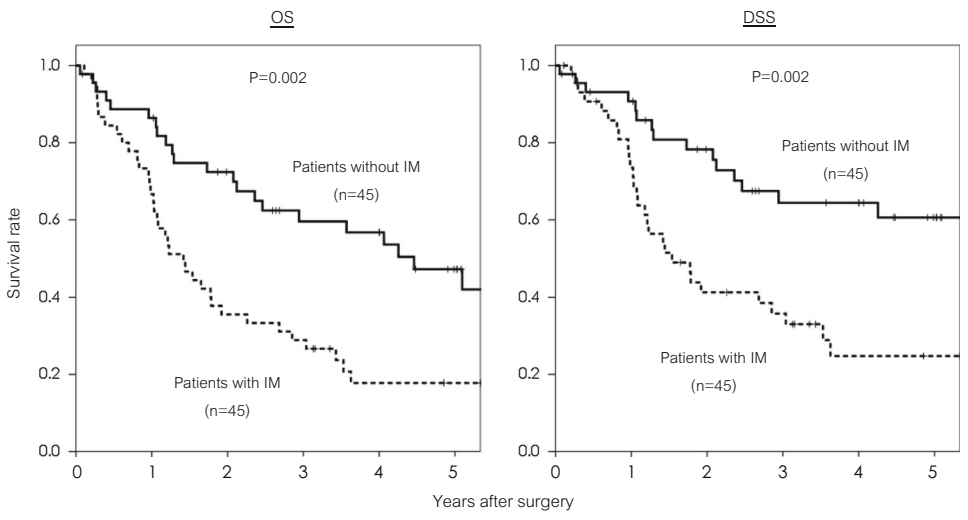

Fig. 2 Kaplan–Meier curves for the overall survival (OS) and disease-specific survival (DSS) of patients with intramural metastasis (IM) and those without IM in the propensity score-matched (PSM) cohort

Table 5 Recurrence pattern in R0 resected patients

Variables	Unmatched cohort			Matched cohort		
	Patients without IM (n = 807)	Patients with IM (n = 34)	P value	Patients without IM (n = 38)	Patients with IM (n = 33)	P value
Locoregional	106 (13.3)	9 (27.3)	0.035*	7 (19.4)	9 (28.1)	0.568
Distant	146 (18.3)	13 (39.4)	0.005*	8 (22.2)	12 (37.5)	0.192
Not available	7	1		2	1	

IM Intramural metastasis

Data are presented as median (range) or n (%). *$P < 0.05$

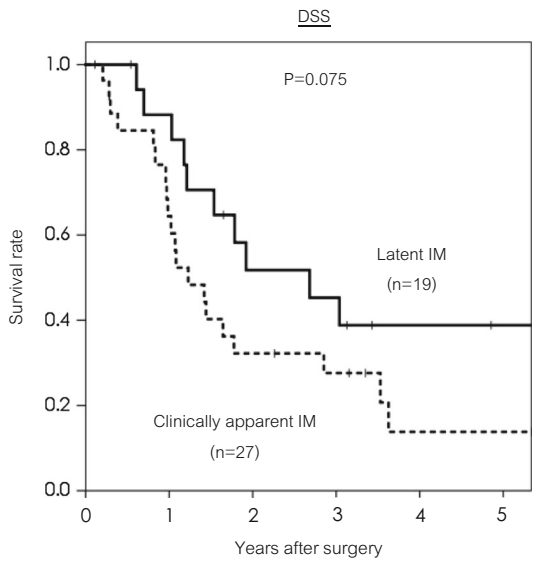

Fig. 3 Kaplan–Meier curves for the disease-specific survival (DSS) of patients with clinically apparent intramural metastasis (IM) and those with latent IM

was introduced after 2009 based on the results of the JCOG 9907 study [10]. This change in protocol may have affected the results. In addition, the statistical power might have been limited as the number of patients with IM was relatively small. Therefore, a more extensive multicenter cohort study is warranted to validate our findings. Second, this study was based on pathological diagnosis rather than clinical diagnosis, and decisions about management were only made with knowledge about clinical diagnosis prior to treatment. However, among patients without any preoperative treatment, 2 of 16 patients (12.5%) who were diagnosed as having IM preoperatively did not have IM pathologically, and the clinical diagnostic accuracy was not sufficient. Therefore, accurate knowledge of IM prior to treatment is required to obtain important clinical information.

In conclusion, IM from ESCC is a local indicator of lymphatic invasion and advanced cancer, as well as an independent prognostic factor for poor prognosis. Furthermore, the prognosis of patients with clinically apparent IM is extremely poor. To improve outcomes, multimodal treatment with chemotherapy showing strong antitumor activity should be considered.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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