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Role of nodal skip metastasis in patients with mid-thoracic oesophageal squamous cell carcinoma: a propensity score matching study

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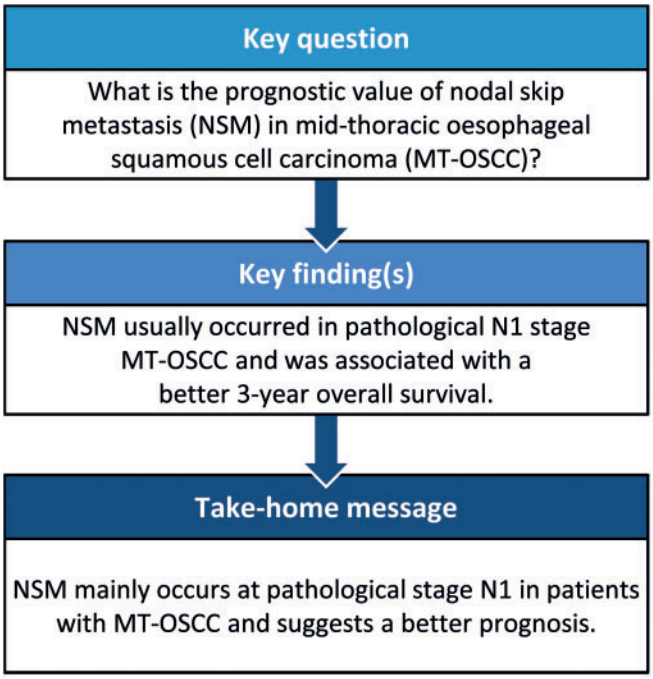

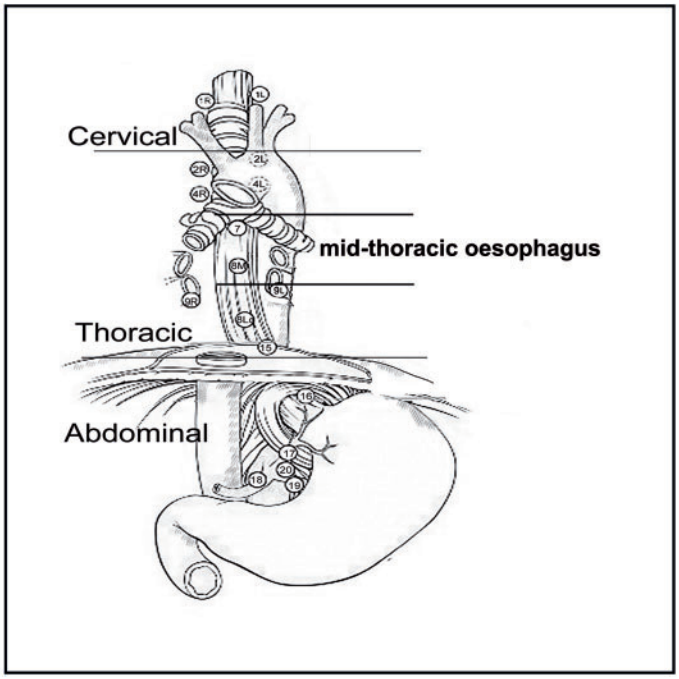

Abstract

OBJECTIVES: Nodal skip metastasis (NSM) is a common phenomenon in mid-thoracic oesophageal squamous cell carcinoma (MT-OSCC); however, the prognostic implications of NSM in patients with MT-OSCC remain unclear.

METHODS: This retrospective study enrolled 300 patients with MT-OSCC who underwent radical oesophagectomy and who had pathologically confirmed lymph node metastasis from January 2014 to December 2016. The patients were divided into 2 groups according to the presence or absence of NSM. Propensity score matching was applied to minimize patient selection bias. The impact of NSM on overall survival (OS) was assessed by Kaplan–Meier and multiple Cox proportional hazards analyses. The median follow-up time was 57 months.

RESULTS: The NSM rate in the entire cohort was 22.0% (66/300). Pathological N (pN) stage ($P < 0.001$) and sex ($P = 0.001$) were identified as significant independent risk factors for NSM. NSM was more frequent in pN1 compared with pN2 patients (87.9% vs 12.1%, $P < 0.001$) and no NSM was found in pN3. NSM(+) patients had better prognoses than NSM(-) patients (Kaplan–Meier; 3-year OS, 62.1% vs 34.1%, $P < 0.001$). Propensity score matching produced 51 matched pairs, and the 3-year OS was still better in the NSM(+) compared with the

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NSM(-) group (66.7% vs 40.0%, $P = 0.025$). Multivariable Cox analysis confirmed NSM(+) as an independent factor favouring OS in patients with MT-OSCC.

CONCLUSIONS: NSM usually occurs at pN1 stage in patients with MT-OSCC, and is associated with a favourable prognosis.

Keywords: Nodal skip metastasis • Mid-thoracic oesophageal squamous cell carcinoma • Prognosis • Propensity score matching

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
JES	Japan Esophageal Society
LNM	Lymph node metastasis
LNs	Lymph nodes
MT-OSCC	Mid-thoracic oesophageal squamous cell carcinoma
NSM	Nodal skip metastasis
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
pN	Pathological N category
PSM	Propensity score matching
pT	Pathological T category

INTRODUCTION

Oesophageal cancer is one of the most common causes of cancer-related deaths worldwide [1], and was responsible for 11.0% of all cancer-related deaths among Chinese men in 2018 [2]. In contrast to the predominance of oesophageal adenocarcinoma in Western countries, >90% of oesophageal cancers in China are oesophageal squamous cell carcinomas (OSCCs), of which mid-thoracic OSCC (MT-OSCC) accounts for nearly 60% of the total cases [3].

The 8th edition of the American Joint Committee on Cancer (AJCC) staging system for oesophageal cancer currently provides the main basis for treatment planning, but only focuses on the number of metastatic nodes [4], without considering their distribution, which was confirmed to be associated with prognosis by the Japan Esophageal Society (JES) [5]. Nodal skip metastasis (NSM) is a specific pattern of lymph node metastasis (LNM) referring to the involvement of distant lymph nodes (LNs) without prior involvement of adjacent LNs. Although NSM is common in oesophageal cancer due to the complex lymphatic drainage networks [6, 7], its role in OSCC, in terms of prognosis, is still controversial [8–16]. Notably, all previous studies showed that MT-OSCC had the highest incidence of NSM among patients with OSCC, possibly due to the absence of intermuscular transverse lymphatic vessels in the mid-thoracic oesophagus [17]. In this study, we investigated the clinical features and prognostic value of NSM with a focus on patients with MT-OSCC.

PATIENTS AND METHODS

Ethics statement

This study was approved by the Ethics Committee of West China Hospital, which waived the need for informed consent from individual patients because of the retrospective nature of the study.

Patient selection

The medical records of patients with MT-OSCC who underwent oesophagectomy in Department of Thoracic Surgery, West China Hospital, Sichuan University, from January 2014 to December 2016 were reviewed retrospectively. The criterion for MT-OSCC location was an oesophageal tumour with an epicentre between the lower border of the azygos vein and lower border of the inferior pulmonary vein, according to the eighth edition AJCC staging system for oesophageal cancer [4]. We excluded patients with a permanent residence outside Sichuan province to reduce the potential influence of socio-geographical confounders. Patients with the following characteristics were also excluded: (i) a history of other cancers or human immunodeficiency virus, (ii) neoadjuvant therapy, (iii) <12 LNs resected, (iv) non-R0 resection, (v) no LNM, (vi) incomplete clinical data and (vii) operative death, defined as death within 30 days of operation or death at any time after surgery but before discharge. A total of 300 patients were finally included in the study and their pathological characteristics were re-evaluated according to the eighth edition AJCC staging system [4].

Surgical procedure and adjuvant treatment

Prior to 2016, patients in our hospital with MT-OSCC and no cervical LNM detected by preoperative ultrasound generally underwent the Sweet procedure (oesophagectomy and two-field lymphadenectomy via left thoracotomy). However, Sweet oesophagectomy has gradually been replaced by the minimally invasive McKeown procedure combined with three-field lymphadenectomy, while some surgeons preferred the Ivor-Lewis operation combined with two-field lymphadenectomy.

Patients with LNM received different postoperative adjuvant treatments, according to their individual characteristics.

Evaluation of lymph node metastasis and nodal skip metastasis

The LNs were divided into cervical, thoracic and abdominal LNs, based on their anatomic location (Table 1). NSM in patients with MT-OSCC was defined as LNM in the abdominal or cervical region with no LNM in the thoracic region. Patients with NSM were included in the NSM(+) group, and patients with thoracic LNM (with or without abdominal and cervical LNM) were included in the NSM(-) group (Fig. 1).

Follow-up

After surgery, patients received outpatient follow-up every 3 months for the first 2 years, every 6 months for the next 3–5 years, and once a year thereafter. Patients who could not attend regular outpatient visits received telephone follow-ups. Follow-up information was available up to December 2019 or the date

Table 1: Regional grouping of lymph nodes and the metastatic rate of each lymph node station

Region	Station	Name	Metastatic rate (%)
Cervical	1R/1L	Right/left lower cervical paratracheal nodes	2.3
Thoracic	2R/2L	Right/left upper paratracheal nodes	20.3
	4R/4LL	Right/left lower paratracheal nodes	7.0
	7	Subcarinal nodes	31.0
	8U	Upper thoracic paraoesophageal lymph nodes	5.7
	8M	Middle thoracic paraoesophageal lymph nodes	33.3
	8Lo	Lower thoracic paraoesophageal lymph nodes	18.3
	9R/9L	Right/left pulmonary ligament nodes	5.0
	15	Diaphragmatic nodes	8.3
Abdominal	16	Paracardial nodes	30.7
	17	Left gastric nodes	36.7
	18	Common hepatic nodes	4.3
	19	Splenic nodes	1.7
	20	Celiac nodes	0.7

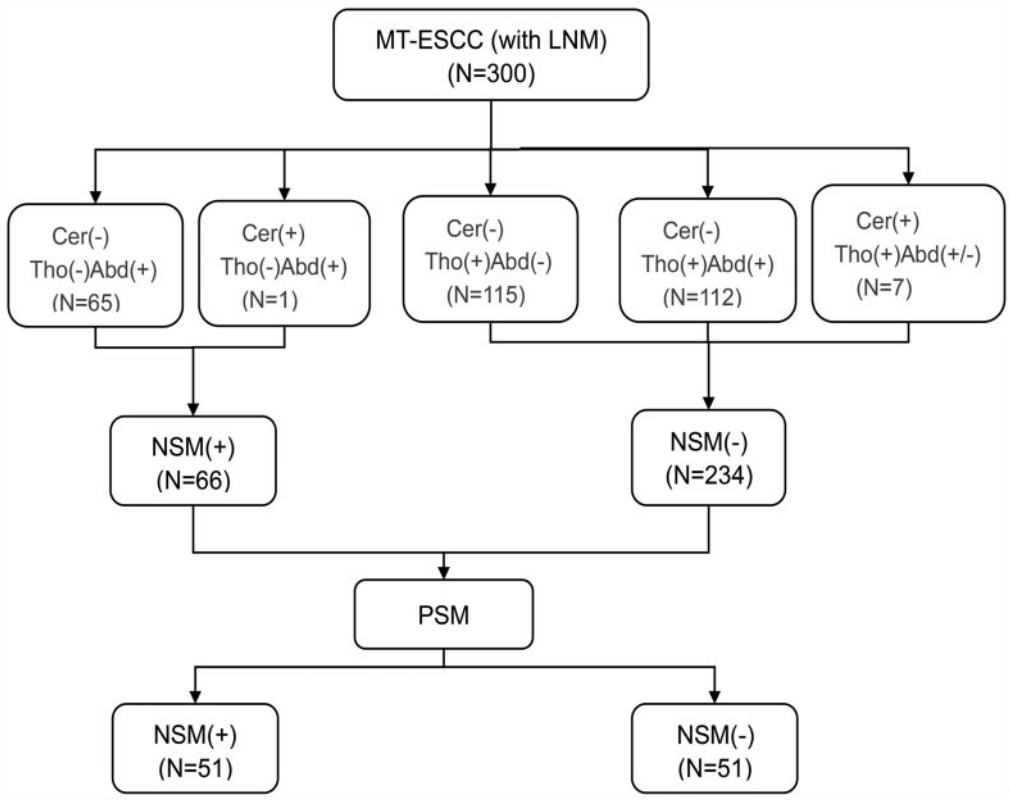

Figure 1: Overview of patient selection and grouping. Abd: abdominal; Cer: cervical; LNM: lymph node metastasis; MT-OSCC: mid-thoracic oesophageal squamous cell cancer; NSM: nodal skip metastasis; PSM: propensity score matching; Tho: thoracic.

of death. Survival time was measured from the date of operation to the date of death. Patients who survived were censored at the last follow-up date. No patients were lost to follow-up, and the median follow-up time was 57 months.

Statistical analysis

Normally distributed continuous variables were compared between the 2 groups using Student's *t*-tests, and non-normally distributed continuous variables and ordinal variables were compared by Mann–Whitney *U*-tests. The sample size was >40, and categorical variables were therefore compared using Pearson's χ^2 test, continuity correction or Fisher's exact test, according to the minimum expected count (*T*). For 2×2 grids, Pearson's χ^2 was used when $T \geq 5$, continuity correction was used when $T \geq 1$ and <5, and Fisher's exact test when $T < 1$. For 2×3 and 2×4 grids, Pearson's χ^2 was used when $T \geq 1$ and the number of grids with $T < 5$ was $\leq 1/5$ of the total, and Fisher's exact test was used in other cases. Binary logistic regression analysis was performed to determine predictors for NSM. The Kaplan–Meier method with the log-rank test was used to compare overall survival (OS) curves between the groups. Cox proportional hazards regression was used to identify independent prognostic factors

Table 2: General clinicopathological characteristics of MT-OSCC before and after PSM in the entire cohort

Variables	Before PSM (*N* = 300)			After PSM		
	NSM(+) (*N* = 66)	NSM(-) (*N* = 234)	*P*-value	NSM(+) (N = 51)	NSM(-) (N = 51)	*P*-value
Gender, *n* (%)			**<0.001**[a]			0.807[a]
Male	44 (66.7)	206 (88.0)		41 (80.4)	40 (78.4)	
Female	22 (33.3)	28 (12.0)		10 (10.5)	11 (21.6)	
Age (years)						
≤60, *n* (%)	29 (43.9)	95 (40.8)	0.626[a]	25 (49.0)	23 (45.1)	0.692[a]
>60, *n* (%)	37 (56.1)	139 (59.4)		26 (51.0)	28 (54.9)	
Mean ± SD	61.94 ± 7.921	61.76 ± 8.154	0.874[b]	61.10 ± 7.908	62.39 ± 7.534	0.399[b]
Median (min–max)	61.00 (46–77)	62.00 (34–81)		61.00 (46–77)	61.00 (49–80)	
BMI, *n* (%)			0.131[c]			0.737[c]
<18.5	3 (4.5)	18 (7.7)		3 (5.9)	1 (2.0)	
18.5–23.9	44 (66.7)	167 (71.4)		36 (70.6)	38 (74.5)	
≥24	19 (28.8)	49 (20.9)		12 (23.5)	12 (23.5)	
Surgical style, *n* (%)			0.629[a]			0.822[a]
Thoracotomy	51 (77.3)	174 (74.4)		38 (74.5)	37 (72.5)	
MIE	15 (22.7)	60 (25.6)		13 (25.5)	14 (27.5)	
Surgical procedure, *n* (%)			0.508[a]			0.786[d]
Sweet	45 (68.2)	145 (62.0)		32 (62.7)	32 (62.7)	
McKeown	16 (24.2)	74 (31.6)		14 (27.5)	16 (31.4)	
Ivor-Lewis	5 (7.6)	15 (6.4)		5 (9.8)	3 (5.9)	
Anastomotic method, *n* (%)			0.978[a]			0.689[a]
Stapler	32 (48.5)	113 (48.3)		21 (41.2)	23 (45.1)	
Handsewn	34 (51.5)	121 (51.7)		30 (58.8)	28 (54.9)	
Anastomotic location, *n* (%)			0.275[a]			0.664[a]
Cervical	16 (24.2)	73 (31.2)		14 (27.5)	16 (31.4)	
Intrathoracic	50 (75.8)	161 (68.8)		37 (72.5)	35 (68.6)	
Number of resected LNs						
≤21, *n* (%)	44 (66.7)	118 (50.4)	**0.019**[a]	31 (60.8)	29 (56.9)	0.687[a]
≥22, *n* (%)	22 (33.3)	116 (49.6)		20 (39.2)	22 (43.1)	
Mean	20.86 ± 6.825	23.19 ± 8.027	**0.024**[c]	21.69 ± 7.716	22.20 ± 7.071	0.690[c]
Median (min–max)	19.00 (12–46)	21.00 (12–58)		20.00 (12–46)	21.00 (13–44)	
Fistula, *n* (%)			0.187[e]			1.000[a]
Yes	0 (0.0)	10 (4.3)		0 (0.0)	1 (2.0)	
No	66 (100)	224 (95.7)		51 (100.0)	50 (98.0)	
Pathological T category, *n* (%)			**0.032**[c]			0.797[c]
I	7 (10.6)	23 (9.8)		3 (5.9)	7 (13.7)	
II	13 (19.7)	35 (15.0)		9 (17.6)	6 (11.8)	
III	32 (48.5)	85 (36.3)		28 (54.9)	23 (45.1)	
IVA	14 (21.2)	91 (38.9)		11 (21.6)	15 (29.4)	
Pathological N category, *n* (%)			**<0.001**[c]			0.485[e]
1	58 (87.9)	111 (47.4)		45 (88.2)	48 (94.1)	
2	8 (12.1)	90 (38.5)		6 (11.8)	3 (5.9)	
3	0 (0.0)	33 (14.1)		0 (0.0)	0 (0.0)	
Histologic grade, *n* (%)			0.338[c]			0.552[a]
Poor	35 (53.0)	140 (59.8)		28 (54.9)	25 (49.0)	
Moderate	31 (47.0)	93 (39.7)		23 (45.1)	26 (51.0)	
Well	0 (0.0)	1 (0.4)		0 (0.0)	0 (0.0)	
Regions of LNM involved, *n* (%)			**<0.001**[c]			
1 region	65 (98.5)	115 (49.1)		50 (98.0)	51 (100.0)	1.000[d]
2 regions	1 (1.5)	114 (48.7)		1 (2.0)	0 (0.0)	
3 regions	0 (0.0)	5 (2.1)		0 (0.0)	0 (0.0)	
Adjuvant treatment, *n* (%)			**0.013**[a]			0.687[a]
None	10 (15.2)	73 (31.2)		9 (17.6)	12 (23.5)	
Chemotherapy	21 (31.8)	42 (17.9)		16 (31.4)	14 (27.5)	
Radiotherapy	8 (12.1)	18 (7.7)		7 (13.7)	4 (7.8)	
Chemoradiotherapy	27 (40.9)	101 (43.2)		19 (37.3)	21 (41.2)	

[a]Pearson's χ^2 test.
[b]Student's *t*-test.
[c]Mann–Whitney *U*-test.
[d]Fisher's exact test.
[e]Continuity correction.

BMI: body mass index; LNM: lymph node metastasis; LNs: lymph nodes; MIE: minimally invasive oesophagectomy; MT-OSCC: mid-thoracic oesophageal squamous cell carcinoma; NSM: nodal skip metastasis; PSM: propensity score matching.
P values in boldface represent $P < 0.05$.

impacting OS. All statistical analyses were performed using IBM SPSS Statistics (version 26.0, IBM Corporation, Armonk, NY, USA). A two-sided *P*-value <0.05 was considered statistically significant.

We performed propensity score matching (PSM) to exclude bias resulting from potential confounding factors. Propensity scores were calculated by logistic regression, including sex, age, body mass index (BMI), surgical type, surgical procedure, anastomotic method, postoperative anastomotic fistula, pathological T category (pT), pathological N category (pN), adjuvant treatment, histologic grade, number of resected LNs and involved regions of LNM, with a matching ratio of 1:1 and caliper value set at 0.02.

RESULTS

Patient characteristics

A total of 300 patients with MT-OSCC were enrolled in this study, including 66 (22.0%) with NSM and 234 (78.0%) without NSM (Fig. 1). NSM to the abdominal region accounted for most cases (65/66, 98.5%). Only 1 patient had NSM to the cervical region, and this patient also had abdominal LNM. The metastatic rate of each LN station is listed in Table 1. The patient characteristics are listed in Table 2. There was no difference in age, BMI, surgical type, surgical procedure, anastomotic method, anastomotic location or histological grade between the 2 groups. Patients with NSM were more likely to be female ($P < 0.001$) and to have fewer resected LNs (20.86 ± 6.825 vs 23.19 ± 8.027, $P = 0.024$). The pT stage and pN stage were both significantly earlier in patients with NSM ($P = 0.032$ and $P < 0.001$, respectively). NSM was significantly more frequent in pN1 compared with pN2 patients (87.9% vs 12.1%, $P < 0.001$), and no NSM was found in pN3 patients. LNM was mostly limited to 1 region (abdominal) in patients with NSM, and only 1 patient had LNM in 2 regions (abdominal and cervical). In contrast, >50% of patients without NSM had 2 (thoracic and abdominal) or 3 (cervical, thoracic and abdominal) involved regions. Multivariable logistic regression analysis identified pN ($P < 0.001$) and sex ($P = 0.001$) as independent risk factors for NSM (Table 3). In this study, adjuvant treatment was performed more frequently in patients with NSM, but we did not include adjuvant therapy in the multivariable logistic regression analysis because we considered postoperative adjuvant therapy to be unassociated with LNM.

The clinicopathological characteristics in the 51 PSM pairs were well balanced between the 2 groups (Table 2).

Table 3: Multivariable analysis of predictors of NSM in the unmatched cohort

Variables	HR	95% CI	*P*-value
Gender			
Male	Reference		
Female	3.547	1.698–7.411	**0.001**
Number of resected LNs			
≤21	Reference		
≥22	0.586	0.308–1.114	0.103
Pathological T category			
I	Reference		
II	1.636	0.495–5.415	0.420
III	1.922	0.653–5.659	0.236
IVA	0.830	0.266–2.594	0.749
pN category[b]			
1	Reference		
2	0.173	0.076–0.392	**<0.001**
3	[a]	[a]	

[a]Number of eligible patients was insufficient.
[b]Regions of LNM involved not included in multivariable analysis because of association with pN stage.
CI: confidence interval; HR: hazard ratio; LNM: Lymph node metastasis; LNs: lymph nodes; NSM: nodal skip metastasis; pN: pathological N.
P values in boldface represent $P < 0.05$.

Survival analysis

Before PSM, the NSM(+) group had a better prognosis than the NSM(-) group according to Kaplan–Meier survival curves ($P < 0.001$) (Fig. 2A). The mean survival time in the NSM(+) group was 47.3 months, with a 3-year OS of 62.1%, compared with 32.5 months and 34.1%, respectively, in the NSM(-) group. The 3-year OS in the NSM(+) group remained better than that in the NSM(-) group after PSM (66.7% vs 40.0%, $P = 0.025$) (Fig. 2B). Multivariable Cox analysis confirmed that NSM(+) was an independent factor favouring OS before PSM [hazard ratio (HR) 0.626, 95% confidence interval (CI) 0.403–0.972; $P = 0.037$, Table 4] and after PSM (HR 0.476, 95% CI 0.267–0.851; $P = 0.012$) (Table 4) in patients with MT-OSCC.

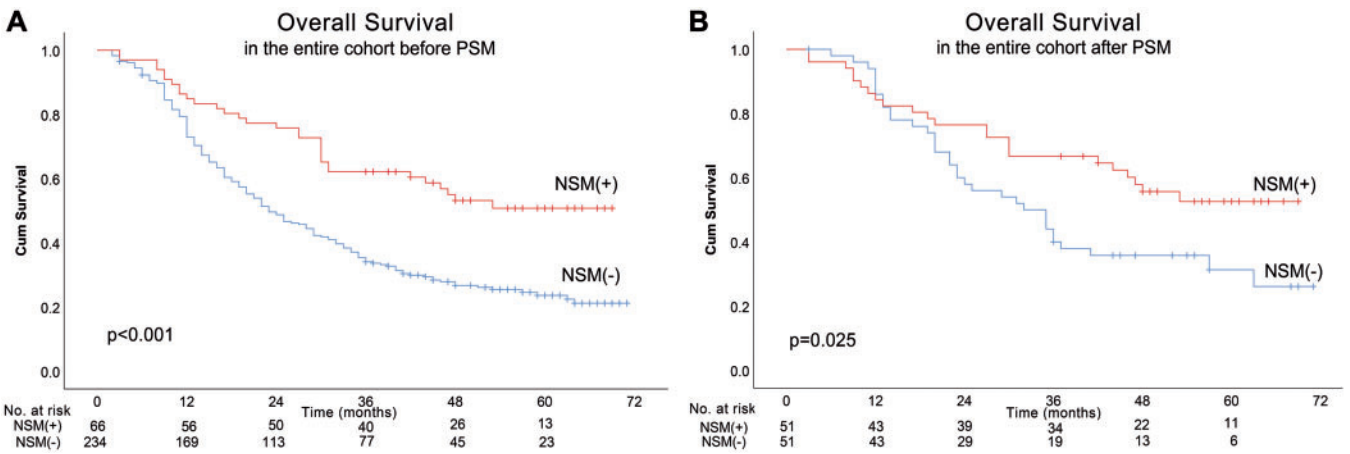

Figure 2: Overall survival in patients with and without NSM. (**A**) Before PSM ($P < 0.001$); (**B**) after PSM ($P = 0.025$). NSM: nodal skip metastasis; PSM: propensity score matching.

Table 4: Multivariable Cox regression analyses for prognostic factors before and after PSM in the entire cohort

Variables	Entire cohort (n = 300)		After PSM (n = 102)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Male	Reference		Reference	
Female	0.725 (0.474–1.108)	0.058	0.390 (0.171–0.892)	**0.026**
Age (years)				
≤60	Reference		Reference	
>60	1.087 (0.804–1.469)	0.588	1.869 (1.020–3.422)	**0.043**
Surgical style				
Thoracotomy	Reference		Reference	
MIE	1.357 (0.701–2.624)	0.365	1.092 (0.242–4.926)	0.909
Surgical procedure				
Sweet	References		Reference	
McKeown	0.781 (0.411–1.486)	0.452	1.350 (0.299–6.085)	0.696
Ivor-Lewis	0.806 (0.414–1.568)	0.525	0.248 (0.051–1.217)	0.086
Anastomotic method				
Stapler	Reference		Reference	
Handsewn	0.907 (0.654–1.257)	0.558	1.126 (0.574–2.213)	0.730
Number of resected LNs				
≤21	Reference		Reference	
≥22	0.681 (0.506–0.916)	**0.011**	0.788 (0.439–1.417)	0.427
BMI				
<18.5	Reference		Reference	
18.5–23.9	0.773 (0.453–1.322)	0.347	0.362 (0.065–2.002)	0.244
≥24	0.687 (0.378–1.249)	0.218	0.297 (0.052–1.707)	0.174
P for trend		0.539		0.292
Pathologic T category				
I	Reference		Reference	
II	2.162 (1.086–4.303)	**0.028**	1.127 (0.332–3.825)	0.848
III	2.298 (1.232–4.286)	**0.009**	2.377 (0.841–6.716)	0.102
IVA	2.673 (1.423–5.023)	**0.002**	3.423 (1.127–10.401)	**0.030**
P for trend		**0.005**		**0.010**
Pathologic N category				
1	Reference		Reference	
2	1.365 (0.927–2.011)	0.115	3.709 (1.394–9.864)	**0.009**
3	2.248 (1.276–3.961)	**0.005**	[a]	[a]
P for trend		**0.013**		
Histologic grade				
Poor	Reference		Reference	
Moderate	0.856 (0.634–1.157)	0.313	0.729 (0.394–1.348)	0.313
Well	[a]	[a]	[a]	[a]
NSM				
No	Reference		Reference	
Yes	0.626 (0.403–0.972)	**0.037**	0.476 (0.267–0.851)	**0.012**
Fistula				
No	Reference			
Yes	0.540 (0.208–1.399)	0.204	[a]	[a]
Regions of LNM involved				
1 region	Reference		Reference	
2 regions	1.164 (0.783–1.731)	0.244	[a]	[a]
3 regions	2.394 (0.742–7.724)	0.144	[a]	[a]
P for trend		0.241		
Adjuvant treatment				
No	Reference		Reference	
Yes	0.676 (0.488–0.931)	**0.019**	0.353 (0.163–0.763)	**0.008**

[a]Number of eligible patients was not sufficient.

BMI: body mass index; CI: confidence interval; HR: hazard ratio; LNM: lymph node metastasis; LNs: lymph nodes; MIE: minimally invasive oesophagectomy; NSM: nodal skip metastasis; PSM: propensity score matching.

P values in boldface represent $P < 0.05$.

DISCUSSION

NSM, indicating the metastatic infiltration of distant LNs without prior involvement of the nodes adjacent to the primary tumour, has been found in a variety of tumours [18–20]. However, there is currently no consensus regarding the definition of NSM in oesophageal cancer. Definitions based on anatomical regions are commonly used in clinical practice [6, 10, 14–16], and previous studies adopting the same anatomical regional criterion to the current study showed an incidence of NSM ranging from 18.2% to 26.0% [14–16], similar to the 22.0% found in this study. NSM in oesophageal cancer may also be defined based on the JES criterion, which divides LNs into 4 groups (N1–N4) in relation to the primary oesophageal lesion. NSM was thus defined as LNM in

N2–N4 without N1, with a corresponding incidence of NSM according to JES of 32.3–64.0% [9, 11–13]. Notably, a consistent finding of these previous studies was that MT-OSCC had the highest incidence of NSM among patients with OSCC, irrespective of the criterion used [8–16].

Numerous studies have explored the anatomic mechanism responsible for the high incidence of NSM in MT-OSCC. Kuge *et al.* [21] found abundant longitudinal lymphatic networks in the oesophageal submucosa at autopsy. Another anatomical cadaver study by Kumakura *et al.* [17] found fewer intermuscular transverse lymphatic vessels in the mid-thoracic oesophagus compared with other oesophageal sites, suggesting that lymphatic flow in the mid-thoracic oesophagus was more likely to drain through submucosal longitudinal lymphatic ducts to distant LNs than to the adjacent LNs, potentially providing an anatomical basis for the high probability of NSM in MT-OSCC.

In light of the high incidence of NSM in MT-OSCC, the current study focused exclusively on patients with MT-OSCC. The incidence of NSM in patients with MT-OSCC in this study was 22.0% according to the anatomical region criterion, which was lower than in previous studies using other criteria [6, 9–13], mainly because this criterion was more stringent. We considered that this strict criterion could reflect more precise characteristics of NSM, and LN categories based on anatomical regions have been proved to be an independent prognostic factor in patients with OSCC [22]. In addition, the LN map for oesophageal cancer according to the 11th JES was more sophisticated for MT-OSCC, with the lesser curvature LNs along the branches of the left gastric artery (No. 3a) and the right and left paracardial LNs (Nos 1 and 2) classified as N1 [5], which was too complicated to be fully adopted in clinical practice [11]. In contrast, the anatomical region criteria are simpler and more practical.

In this study, pN stage was an independent risk factor for NSM. NSM was significantly more frequent in pN1 compared with pN2 patients (87.9% vs 12.1%, $P < 0.001$), and no NSM was found in pN3 patients, possibly because the probability of adjacent LN involvement increased with the progression of pN stage. Furthermore, the involved LNMs in patients with NSM were mostly limited to 1 region, and only 1 patient had involvement of 2 regions (abdominal and cervical). pT stage was also significantly earlier in the NSM(+) compared with the NSM(-) group. Overall, these results indicated that NSM mostly occurred in early rather than advanced MT-OSCC, consistent with the results of previous studies [8–16]. We also found that NSM was more common in female patients; however, further studies with more female patients are needed to confirm this relationship between NSM and sex because only 16.7% (50/300) of patients in the current study were female.

The pN2 with NSM has been included in the eighth edition of the AJCC staging system for non-small-cell lung cancer, as a separate subgroup with a relatively better prognosis [23]. However, the prognostic significance of NSM in OSCC is still controversial. Several studies using the JES criterion to define NSM have produced conflicting results, suggesting either a favourable or a poor prognosis [9, 11–13]. Three other studies adopting the same criterion to define NSM as the current study all concluded that NSM was not associated with prognosis [14–16]. However, these conclusions remain debatable because of possible differences in baseline characteristics between the NSM(+) and NSM(-) groups. For example, He *et al.* [10] found that NSM was associated with worse OS in pN2 stage using univariable analysis, without consideration of other confounders, including pT stage.

In the present study, MT-OSCC patients with NSM showed significantly longer OS than patients without NSM. However, pT stage and pN stage, as established independent prognostic factors for OSCC, were both significantly less advanced in the NSM(+) compared with the NSM(-) group. In addition, other factors, including adjuvant treatment, number of resected LNs and sex might have affected the prognosis. We therefore used PSM to balance these potential confounding factors between the 2 groups, and showed that the presence of NSM still had a favourable impact on OS, even after PSM, and this positive impact was further confirmed by multiple Cox regression. This result suggested that NSM might be an earlier mode of lymphatic metastasis, compared with adjacent LNM, consistent with the fact that NSM usually occurred in early rather than late MT-OSCC.

Limitations

This study had some limitations. First, the retrospective nature of the analysis and the limited number of cases from a single centre should be noted. Second, most patients with MT-OSCC without cervical LNM at preoperative examination underwent two-field lymphadenectomy, and only 30.0% (90/300) of patients underwent three-field lymphadenectomy. It is possible that some patients with NSM to the cervical region were not detected and were excluded as patients with negative LNs. Third, information on recurrence in the database was incomplete, making it impossible to evaluate disease-free survival. Further multicentre, prospective clinical studies and basic research on the biological mechanism of NSM are warranted to clarify the characteristics and clinical significance of NSM in MT-OSCC.

CONCLUSIONS

Among patients with MT-OSCC, NSM mainly occurs in pN1 patients and is associated with a favourable prognosis. MT-OSCC may thus be classified into 2 subgroups according to the presence or absence of NSM in future AJCC staging systems for OSCC.

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Author contributions

Zhi-Jie Xu: Conceptualization; Formal analysis; Methodology; Software; Supervision; Writing—original draft. **Ze-Guo Zhuo:** Investigation; Project administration. **Tie-Niu Song:** Data curation; Resources. **Gu-Ha Alai:** Data curation; Methodology. **Xu Shen:** Data curation. **Peng-Yao:** Methodology; Software. **Yi-Dan Lin:** Conceptualization; Funding acquisition; Project administration; Visualization; Writing—review & editing.

Reviewer information

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