

Clinical Impact of Abdominal Versus Mediastinal Metastases as a Prognostic Factor for Poor Outcomes Following Esophageal Cancer Surgery: A Retrospective Study

Yutaka Miyawaki (✉ miyawaki.srg1@tmd.ac.jp)

Saitama Ika Daigaku Kokusai Iryo Center <https://orcid.org/0000-0001-7141-2473>

Hiroshi Sato

Saitama Ika Daigaku Kokusai Iryo Center

Shuichiro Oya

Saitama Ika Daigaku Kokusai Iryo Center

Hirofumi Sugita

Saitama Ika Daigaku Kokusai Iryo Center

Yasumitsu Hirano

Saitama Ika Daigaku Kokusai Iryo Center

Shinichi Sakuramoto

Saitama Ika Daigaku Kokusai Iryo Center

Kojun Okamoto

Saitama Ika Daigaku Kokusai Iryo Center

Shigeki Yamaguchi

Saitama Ika Daigaku Kokusai Iryo Center

Isamu Koyama

Saitama Ika Daigaku Kokusai Iryo Center

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Abstract

Background

Surgery is still the mainstay of radical treatment for resectable esophageal cancer (EC). It is apparent that the presence or spread of lymph node metastasis is a powerful prognostic factor in patients with EC who are eligible for curative treatment. Although the importance and efficacy of lymph node dissection in radical esophagectomy have been reported, the clinical or prognostic relevance of specific metastatic patterns within the mediastinal cavity and abdomen remains unclear.

Methods

We retrospectively analyzed the association between postoperative survival with clinical mediastinal lymph node metastases (cMLNMs) and abdominal lymph node metastases (cALNMs) in 143 patients who underwent radical EC surgery at our hospital between May 2012 and July 2017.

Results

A significant difference in cause-specific survival (CSS) was observed between patients with and without cALNM (log-rank $p=0.000$). A multivariate Cox regression analysis revealed that cALNM and thoracic surgery (mediastinal lymphadenectomy via conventional open right thoracotomy or video-assisted thoracoscopic surgery) independently predicted CSS ($p=0.001$ and 0.037 , respectively). Moreover, a significant difference in systemic recurrence-free survival was observed between those with and without cALNM (log-rank $p=0.000$). Multivariate Cox regression analysis revealed that cALNM and sex independently predicted systemic recurrence-free survival ($p=0.005$ and 0.013 , respectively).

Conclusion

cALNM was an independent poor prognostic factor for CSS after EC surgery. It may also be an independent prognostic factor for postoperative systemic recurrence, which can shorten CSS. For patients with cALNM-positive EC who have a high potential risk of systemic metastases, more extensive treatment besides the conventional perioperative systemic chemotherapy may be necessary.

Background

Surgery is the mainstay of radical treatment for resectable esophageal cancer (EC) worldwide [1, 2]. Many studies have been conducted on factors that affect outcomes following EC surgery, including clinicopathological and surgery-related factors. In particular, the presence of lymph node metastasis (LNM) is a powerful prognostic factor in patients with EC who are eligible for curative treatment.

The extent of LNM associated with EC can anatomically span multiple areas, such as the neck, chest, and abdomen, and the risk of LNM is high even in the early stages [3]. Our previous study on the oncological tolerability of minimally invasive esophagectomy (MIE) suggested that clinical abdominal lymph node metastasis (cALNM) was a poor prognostic factor after EC surgery [4]. The clinical or prognostic relevance of specific metastatic patterns within the mediastinal cavity and abdomen remains unclear, although the importance and efficacy of lymph node dissection in radical esophagectomy have been reported [5, 6].

Here, we performed a detailed study to assess the significance of clinical mediastinal LNM (cMLNM) and cALNM as postoperative prognostic factors in patients with EC.

Methods

Patients

We identified 178 consecutive patients who had undergone radical esophagectomy with two- or three-field lymphadenectomy for thoracic EC at our Department of Gastroenterological Surgery in Saitama Medical University International Medical Center between May 2012 and July 2017. See details regarding the exclusion criteria described below. After application of these criteria, 143 cases were eligible for inclusion. The clinicopathological characteristics and postoperative outcomes were collected from patient records. Table 1 provides details on the patient characteristics.

The exclusion criteria

The exclusion criteria were those with salvage surgery after definitive radiation therapy, those with obvious residual lesions identified intraoperatively, those who underwent a planned two-stage split surgery, and those who underwent esophageal reconstruction using methods other than a gastric tube. In addition, patients with an observation period of less than 180 days were excluded. Moreover, those who received adjuvant chemotherapy (AC) were excluded from the study because AC was received by only some adenocarcinoma patients with pathological multiple LNM. Actually, only 5 patients received AC in our cohort. However, we did not exclude patients with supraclavicular LNM, which is defined in the 8th edition of the International Union Against Cancer guidelines [7] as distant metastasis, because it is a locoregional factor in the Japanese Classification of Esophageal Cancer (11th Edition) [8].

Clinical tumor–node–metastasis staging and follow-up after surgery

Tumor staging was performed according to the 8th edition of the International Union Against Cancer guidelines [7]. Any metastases from the neck to the abdomen were identified using computed tomography (CT) and fluorodeoxyglucose-positron emission tomography. Follow-up CT assessments every 2–4 months and annual esophagogastroduodenoscopy after surgery were performed for 5 years if no recurrence was suspected.

Surgical procedure

For those who underwent thoracic procedures, an esophagectomy with mediastinal lymphadenectomy was performed by conventional open right thoracotomy or video-assisted thoracoscopic surgery (VATS) in a left lateral position while receiving separate lung ventilation. For patients who underwent abdominal procedures, we performed abdominal lymphadenectomy and mobilization of the stomach as a reconstructed organ via conventional open laparotomy or hand-assisted laparoscopic surgery (HALS). Overall, the extent of lymph node dissection was D2 according to the Japanese Classification of Esophageal Cancer (11th Edition) [8].

Neoadjuvant chemotherapy and adjuvant chemotherapy

Neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) were administered in accordance with the Japanese Esophageal Society guidelines [1]. Therefore, in principle, NAC was administered to patients who were indicated for radical surgery, except for patients with clinical stage I disease. If radical resection was confirmed pathologically, AC was not administered to patients with squamous cell carcinoma, but only to a small proportion of patients who had adenocarcinoma with multiple positive pathological LNMs. Only five patients received AC in our cohort, and they were excluded from the study to avoid selection bias.

Postoperative survival and recurrence

The initial recurrence was divided into two types: locoregional and systemic. Locoregional recurrence encompassed resectable mediastinal and abdominal lymph node recurrences, as well as cervical paraesophageal or supraclavicular lymph node recurrence. Systemic recurrence included the following: distant metastases to other organs such as the liver or lungs, unresectable recurrence such as dissemination to the pleura or pericardium, cervical lymph node recurrence other than at the paraesophageal or supraclavicular areas, and recurrence at the para-abdominal aortic lymph nodes. If locoregional and systemic recurrence were observed at the same time, they were treated as systemic recurrence. Locoregional relapse-free survival (L-RFS) was calculated from the date of the esophagectomy until locoregional recurrence was confirmed, and when any systemic recurrences were confirmed as initial recurrence, they were censored. Likewise, systemic recurrence-free survival (S-RFS) was calculated from the date of the esophagectomy until systemic recurrence was confirmed, and when any locoregional recurrences were confirmed as initial recurrence, they were censored.

Statistical analyses

The groups were compared using the Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate. The Kaplan-Meier method and log-rank test were used to evaluate differences in cause-specific survival (CSS) and relapse-free survival (RFS). Univariate and multivariate survival analyses were also performed using a stratified Cox proportional hazards model. In the multivariate analysis, covariates were selected by forced entry. Differences were considered statistically significant at two-tailed p -values of < 0.05 . All statistical analyses were performed using SPSS software (version 24.0; IBM Corp., Armonk, NY).

Results

Associations between clinical mediastinal or abdominal lymph node metastases and clinicopathological factors

As shown in Table 1, the cMLNM-positive group included many patients with NAC, deeper clinical tumor invasion depth, clinical abdominal LNM, and VATS because many of them were at an advanced stage. The same was observed in the cALNM-positive group. In addition, many patients with HALS were included in the cALNM group. The frequency of cALNM was low in patients with upper thoracic EC.

Likewise, as shown in Table 2, both the cMLNM- and cALNM-positive groups consisted of patients with deeper pathological tumor depth invasion and with pathological LNM in both the mediastinum and abdomen. The frequency of vascular invasion was high in the cMLNM-positive group, while lymphatic invasion was high in the cALNM-positive group. The number of harvested abdominal lymph nodes was not significant in both groups, although it was higher in the cALNM-positive group. Intraoperative bleeding was high in both the cMLNM- and cALNM-positive groups, although there was no significant difference between the groups in terms of total operative time and length of postoperative hospital stay.

Associations among clinicopathological factors, surgery-related factors, and postoperative cause-specific survival

The mean postoperative follow-up period was 44.8 months, and 26 cause-specific EC deaths occurred during the entire observational period. A significant difference in CSS was observed between those with and without cALNM ($p = 0.000$), although no such difference was found between those with and without cMLNM ($p = 0.114$), (Fig. 1a, 1b). Additionally, in the univariate analysis, the prognosis was predicted by an absence of VATS ($p = 0.004$). Multivariate Cox regression analysis revealed that cALNM ($p = 0.001$, hazard ratio [HR] = 4.567) and the thoracic procedure ($p = 0.037$, HR = 0.395) independently predicted CSS (Table 3).

Associations among clinicopathological factors, surgery-related factors, and postoperative relapse-free survival

During the entire observational period, there were 48 instances of postoperative recurrence. A significant difference in RFS between those with and without cMLNM and cALNM was observed ($p = 0.005$ and 0.002 , respectively) (Fig. 1c, 1d). Additionally, in the univariate analysis, the prognosis was predicted by an absence of NAC, deeper tumor depth invasion, and VATS ($p = 0.028$, 0.011 , and 0.012 , respectively). The multivariate Cox regression analysis revealed that there were no independent prognostic factors for RFS (Table 3).

Associations among clinicopathological factors, surgery-related factors, and locoregional or systemic relapse-free survival

To verify risk assessment by recurrence pattern, we classified the initial postoperative recurrence into two types: locoregional or systemic. Overall, 28 and 20 patients had locoregional and systemic recurrence, respectively, during the entire observational period. Table 4 shows the initial postoperative recurrence sites in patients with or without clinical mediastinal or abdominal LNM.

Although there was no statistically significant difference between those with and without cMLNM in S-RFS ($p = 0.182$), a significant difference in S-RFS was observed between those with and without cALNM ($p = 0.000$) (Fig. 1e, 1f). Additionally, the univariate analysis revealed that the prognosis was predicted according to sex ($p = 0.004$), and the multivariate Cox regression analysis revealed that cALNM and sex independently predicted S-RFS ($p = 0.005$ and 0.013 , respectively) (Table 5). Significant differences in L-RFS were observed between those with and without cMLNM, NAC, clinical tumor depth invasion, and thoracic procedures ($p = 0.012$, 0.029 , 0.020 , and 0.046 , respectively). However, the multivariate Cox regression analysis also revealed that there were no independent prognostic factors for L-RFS. (Table 5).

Difference in postoperative survival with and without lymph node metastasis in the mediastinal or abdominal fields

To eliminate the bias of including cMLNM- or cALNM-negative patients who had a favorable prognosis in our study population, we performed a subgroup analysis of 62 patients with cMLNM and/or cALNM. A significant difference in CSS between those with and without cALNM was observed ($p = 0.027$), although no such difference was found between those with and without cMLNM ($p = 0.135$) (Fig. 2a, 2b). Additionally, based on the presence or absence of LNM in the mediastinum and abdomen, we classified patients into four groups: cMLNM(-)/cALNM(-), cMLNM(+)/cALNM(-), cMLNM(-)/cALNM(+), and cMLNM(+)/cALNM(+). The Kaplan-Meier analysis revealed significant differences in CSS and RFS among these four groups ($p = 0.000$ and 0.001 , respectively) (Fig. 2c, 2d). Furthermore, in a subgroup analysis of 36 cases with metastasis in only one field, survival rate in CSS was worse in the cALNM-positive group than in the cMLNM-positive group ($p = 0.022$) (Fig. 2c). For RFS, there was no statistically significant difference among the groups ($p = 0.477$) (Fig. 2d).

Discussion

Clinical LNM is a known poor prognostic factor in patients with EC, and the significance of lymph node dissection for postoperative survival after EC surgery has been verified [9]. The effect of dissection on postoperative survival at each lymph node station has also been verified using an efficacy index [10]. However, the significance of metastasis to the mediastinal or abdominal lymph nodes, which are common sites of metastasis in EC, for postoperative survival has not been verified yet. Our study on the postoperative long-term prognosis of clinical LNM in the mediastinal and abdominal fields demonstrated that cALNM was an independent poor prognostic factor for CSS following EC surgery. Additionally, cALNM was an independent poor prognostic factor for postoperative systemic recurrence, although neither cMLNM nor cALNM was found to be associated with RFS. The presence of cALNM was also associated with poor CSS in a subgroup analysis of the cMLNM- and cALNM-positive patient groups.

In addition, among patients with metastasis in the mediastinum or abdomen alone, those with only cALNM had a poorer prognosis than those with only cMLNM. These results suggest that cALNM may be a poorer prognostic factor for postoperative survival, even when compared with cMLNM, due to its association with potential systemic recurrence.

Recurrence after radical surgery for EC is, unfortunately, a major clinical issue [11–13]. There are many reports showing the usefulness of radiotherapy or chemoradiotherapy for localized recurrence after EC surgery, and these are widely used in clinical practice [14]. The usefulness of resecting the lymph nodes, including the cervical lymph nodes, for localized postoperative recurrence has also been reported in a retrospective observational study [15]. Most of the treatments for recurrence affecting organs are not radical treatments; resection has been limited to a small number of patients [16, 17], and its usefulness is unknown [18, 19]. If cALNM is considered to be a risk factor for postoperative systemic concurrence, this may be one reason why it is a poor prognostic factor for CSS in our study. Comparison of cLNM in the mediastinal and abdominal fields alone showed a similar survival curve for RFS; however, for CSS, the survival rate of the cALNM group tended to be lower. This appears to support the above hypothesis. Moreover, if cALNM reflects the potential risk of systemic recurrence in patients with EC after radical surgery, the introduction of a more powerful perioperative adjuvant therapy should be considered as systemic treatment for patients with cALNM.

Interestingly, the number of harvested abdominal lymph nodes was significantly higher in cALNM-positive patients than in cALNM-negative patients. Although the extent of lymphadenectomy was the same regardless of the cALNM status, it is speculated that this is partly due to the surgeon trying to perform more aggressive abdominal lymphadenectomy in cALNM-positive cases. Only nine cases were found to have recurrence limited to the

abdominal field, and locoregional control was performed to some extent. The finding that cALNM-positive patients had a poor prognosis despite some locoregional control secured by aggressive dissection may support our hypothesis that cALNM poses a risk for systemic recurrence.

Even with recent advances in diagnostic modalities, the clinical diagnosis of LNM remains difficult. The presence of numerous micrometastases at early clinical stages may explain discrepancies in pathological LNM assessments [20]. In our study, likewise, it is necessary to fully consider the accuracy of cALNM diagnosis. Because our study suggests that cALNM reflects a potential risk for postoperative systemic recurrence at the stage of curative treatment, cALNM is considered to be an important clinical finding that can complement the inaccuracies in preoperative metastasis diagnosis.

In our study, differences in thoracic procedures were also demonstrated as independent factors associated with CSS after EC surgery. Although it remains unclear whether MIE contributes to improved long-term prognosis in those who undergo EC surgery [21], the superiority of its long-term prognosis has been reported in some retrospective studies, which is similar to our results [22]. The patient's sex was also demonstrated as an independent factor associated with postoperative systemic recurrence, coinciding with some reports where sex was identified as a prognostic factor in patients undergoing EC surgery [23].

Because cALNM associated with upper thoracic EC has a poor prognosis, it is characterized by group-3 lymph nodes in such patients [8]. It is necessary to consider the difference in the effect of cALNM on the prognosis depending on the tumor location. Because the proportion of patients with upper thoracic EC in our cohort was a minority at 9.8%, and only 2.5% of those with upper EC with a poor prognosis in the cALNM-positive group were included, we believe that the impact of this on the results was very small.

One major limitation of the current research is that it was a single-institution retrospective study. In addition, cLNM was inevitably associated with advanced stages which necessitated open surgery over endoscopic surgery; therefore, a selection bias occurred. Furthermore, because those who were cLNM-positive were in more advanced stages, the cMLNM- and cALNM-positive patients included many patients with pathologically advanced stages. It is unclear how this bias affected the results, although in the survival analysis, factors such as cMLNM, cALNM, and thoracic procedure implementation were included in the covariates and carefully examined. Therefore, the results appear to be sufficiently credible. Another limitation is that our treatment system was based on the standard treatment in Japan, which is different from the treatment systems in Europe and the United States, with the latter focusing on NAC and perioperative adjuvant chemotherapy. Of course, in clinical practice with different treatment regimens, re-examining the treatment system may be necessary, although we believe that our results offer universal prognostic factors for predicting poor prognosis in patients with EC.

Conclusion

In conclusion, cALNM is an independent poor prognostic factor for CSS after EC surgery. It may also be an independent prognostic factor for postoperative systemic recurrence, which in turn, may be a mechanism that shortens CSS. For patients with cALNM-positive EC who have a high potential risk of systemic metastasis, a regimen stronger than the conventional perioperative systemic chemotherapy may be necessary to improve the prognosis.

Abbreviations

AC
adjuvant chemotherapy, cALNM:clinical abdominal lymph node metastasis, cMLNM:clinical mediastinal LNM, CSS:cause-specific survival, CT:computed tomography, EC:esophageal cancer, HALS:hand-assisted laparoscopic surgery, LNM:lymph node metastasis, L-RFS:locoregional relapse-free survival, NAC:neoadjuvant chemotherapy, RFS:relapse-free survival, S-RFS:systemic recurrence-free survival, VATS:video-assisted thoracoscopic surgery

Declarations

Ethics approval and consent to participate

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The study's retrospective protocol was approved by the Institutional Review Board of Saitama Medical University International Medical Center (IRB number 19-002); the need for informed consent was waived.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YM, HS, and SS provided the conceptualizing and study design. YM, SO, and HS performed data collection. YM, YH, and KO analyzed the data. YM and SH drafted the manuscript. IK performed supervising the entire study, and all the authors read and approved the final manuscript.

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Authors' information (optional)

None

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Tables

Table 1: Differences in clinical factors between those with and without mediastinal or abdominal lymph node metastases

Factor	Variables	All patients (N=142)	cMLNM ^a			cALNM ^b		
			Absent (N=92)	Present (N=50)	<i>p</i> value	Absent (N=100)	Present (N=42)	<i>p</i> value
Sex	Male	120	77	43	0.811	85	35	0.803
	Female	22	15	7		15	7	
Age (years)	Mean±SD ^c	68.9±7.8	69.2±7.2	68.3±8.8	0.694	69.6±7.1	67.1±9.1	0.110
Body mass index	Mean±SD	21.8±3.0	21.7±3.2	21.8±2.7	0.849	21.8±3.2	21.8±2.7	0.963
Tumor location	Ut ^d	13	6	7	0.288	12	1	0.075
	Mt ^e	53	33	20		41	12	
	Lt ^f	76	53	23		47	29	
Histology	SCC ^g	121	78	43	1.000	86	35	0.796
	non-SCC	21	14	7		14	7	
Neoadjuvant chemotherapy	Absent	69	57	12	0.000*	59	10	0.000*
	Present	73	35	38		41	32	
Adjuvant chemotherapy	Absent	136	89	47	0.665	99	37	0.009*
	Present	6	3	3		1	5	
Clinical mediastinal lymph node metastasis	Absent	92	92	0	0.000*	78	14	0.000*
	Present	50	0	50		22	28	
Clinical abdominal lymph node metastasis	Absent	100	78	22	0.000*	42	0	0.000*
	Present	42	14	28		0	100	
Clinical M factor	M0	138	91	47	0.125	99	39	0.078
(supraclavicular lymph node metastasis)	M1	4	1	3		1	3	
Thoracic procedure	OT ^h	62	30	32	0.000*	35	27	0.002*
	VATS ⁱ	80	62	18		65	15	
Abdominal procedure	OL ^j	65	38	27	0.162	37	28	0.002*
	HALS ^k	77	54	23		63	14	

^a cMLNM: clinical mediastinal lymph node metastasis, ^b cALNM: clinical abdominal lymph node metastasis, ^c SD: standard deviation, ^d Ut: upper thoracic, ^e Mt: middle thoracic, ^f Lt: lower thoracic, ^g SCC: squamous cell carcinoma, ^h OT: open thoracotomy, ⁱ VATS: video-assisted thoracoscopic surgery, ^j OL: open laparotomy, ^k HALS: hand-assisted surgery. **p*<0.05

Table 2: Pathological and surgery-related factors in patients with and without clinical mediastinal/abdominal lymph node metastases

Factor	Variables	All patients (N=142)	cMLNM ^a			cALNM ^b		
			Absent	Present	<i>p</i> value	Absent	Present	<i>p</i> value
			(N=92)	(N=50)		(N=100)	(N=42)	
Pathological T factor	pT0/T1	74	58	16		63	11	
	pT2/3/4a	68	34	34	0.000*	37	31	0.000*
Pathological N factor	pN0	72	60	12		66	6	
	pN1	70	32	38	0.000*	34	36	0.000*
Pathological M factor	pM0	140	92	48		100	40	
	(supraclavicular lymph node metastasis)	2	0	2	0.122	0	2	0.000*
Lymphatic invasion	Absent	90	61	29		71	19	
	Present	52	31	21	0.364	29	23	0.004*
Vascular invasion	Absent	70	52	18		52	18	
	Present	72	40	32	0.023*	48	24	0.361
Intramural metastasis	Absent	131	88	43		95	36	
	Present	11	4	7	0.052	5	6	0.083
Number of harvested mediastinal lymph nodes	Mean±SD ^c	14.3±8.6	14.3±9.4	14.3±6.7	0.678	14.4±9.2	13.9±6.9	0.964
Number of mediastinal lymph node metastases	Mean±SD	0.8±3.9	0.7±4.7	0.9±1.4	0.000*	0.7±4.5	1.0±1.5	0.000*
Number of harvested abdominal lymph nodes	Mean±SD	13.8±7.7	13.3±7.0	14.8±8.8	0.568	12.6±6.8	16.6±8.9	0.009*
Number of abdominal lymph node metastases	Mean±SD	1.3±4.0	1.2±3.4	1.6±4.8	0.019*	0.6±2.5	3.1±5.9	0.000*
Total operative time (min)	Mean±SD	437.4±69.4	433.3±69.8	445.8±68.9	0.331	439.9±67.2	431.5±75.0	0.505

Total intraoperative bleeding (ml)	Mean±SD	267.6±245.3	234.6±229.8	328.4±266.8	0.005*	228.8±183.3	360.0±339.2	0.027*
Length of postoperative hospital stay (days)	Median (range)	16 (8-239)	15 (8-106)	19 (9-239)	0.140	15 (8-239)	18 (9-58)	0.677
^a cMLNM: clinical mediastinal lymph node metastasis, ^b cALNM: clinical abdominal lymph node metastasis, ^c SD: standard deviation. *: $p < 0.05$								

Table 3: Univariate and multivariate analyses of prognostic factors for postoperative survival

Factor	Category	Cause-specific survival				Relapse-free survival			
		Univariate	Multivariate			Univariate	Multivariate		
		<i>p</i> value	<i>p</i> value	HR ^a	(95% CI) ^b	<i>p</i> value	<i>p</i> value	HR	(95% CI)
Age	<70 (vs. ≥70)	0.820				0.631			
Sex	Male (vs. Female)	0.423				0.073	0.057	1.911	(0.982-3.717)
Body mass index	<20 (vs. ≥20)	0.311				0.360			
Tumor location	Ut ^c (vs. Mt ^d or Lt ^e)	0.569				0.606			
Histology	SCC ^f (vs. non-SCC)	0.368				0.277			
Neoadjuvant chemotherapy	Absent (vs. present)	0.871				0.076			
Adjuvant chemotherapy	Absent (vs. present)	0.000*§				0.035*§			
cT factor	cT1 (vs. T2-3)	0.174				0.009*	0.192	1.638	(0.780-3.439)
Clinical mediastinal lymph node metastasis	Absent (vs. present)	0.106	0.449	0.706	(0.286-1.741)	0.003*	0.197	1.567	(0.792-3.101)
Clinical abdominal lymph node metastasis	Absent (vs. present)	0.000*	0.003*	4.149	(1.615-10.656)	0.005*	0.376	1.343	(0.699-2.580)
cM factor (supraclavicular lymph node metastasis)	cM0 (vs. cM1)	0.983				0.625			
Thoracic procedure	OT ^g (vs. VATS ^h)	0.002*§	0.011*	0.269	(0.098-0.739)	0.008*§	0.209	0.670	(0.359-1.251)
Abdominal procedure	OL ⁱ (vs. HALS ^j)	0.116	0.411	1.476	(0.584-3.732)	0.162			
Reconstruction route	Retrosternal (vs. mediastinal or antethoracic)	0.149				0.562			
^a HR: hazard ratio, ^b CI: confidence interval, ^c Ut: Upper thoracic, ^d Mt: Middle thoracic, ^e Lt: Lower thoracic, ^f SCC: squamous cell carcinoma, ^g OT: Open thoracotomy, ^h VATS: Video assisted thoracic surgery, ⁱ OL: Open Laparotomy, ^j HALS: Hand assisted laparoscopic surgery. *: <i>p</i> <0.05. §: HR<1.0									

Table 4: Initial postoperative recurrence site details in patients with or without clinical mediastinal/abdominal lymph node metastases

Initial recurrence pattern	Variables		All patients (N=143)	(Recurrence site ^a)	cMLNM ^b				cALNM ^c			
					Absent (N=95)		Present (N=48)		Absent (N=104)		Present (N=39)	
Locoresional recurrence	Absent		115		82		33		85		30	
	Present	Cervical lymph node	28	(11)	13	(6)	15	(5)	19	(4)	9	(7)
		Mediastinal local or lymph node		(23)		(10)		(13)		(13)		(10)
		Abdominal lymph node		(9)		(6)		(3)		(5)		(4)
Systemic recurrence	Absent		123		84		39		96		27	
	Present	Lung	20	(8)	11	(4)	9	(4)	8	(3)	12	(5)
		Liver		(6)		(3)		(3)		(2)		(4)
		Para-abdominal aortic lymph node		(5)		(4)		(1)		(2)		(3)
		Pleura		(5)		(2)		(3)		(2)		(3)
		Others (Adrenal gland, bone, or ventricle)		(4)		(2)		(2)		(1)		(3)
^a Including duplication, ^b cMLNM: clinical mediastinal lymph node metastasis, ^c cALNM: clinical abdominal lymph node metastasis.												

Table 5: Univariate and multivariate analyses of prognostic factors for locoregional and systemic relapse-free survival

Factor	Category	Locoregional relapse-free survival				Systemic relapse-free survival			
		Univariate	Multivariate			Univariate	Multivariate		
		<i>p</i> value	<i>p</i> value	HR ^a	(95% CI) ^b	<i>p</i> value	<i>p</i> value	HR	(95% CI)
Age	<70 (vs. ≥70)	0.207				0.470			
Sex	Male (vs. Female)	0.919				0.005*	0.007*	3.423	(1.393-8.412)
Body mass index	<20 (vs. ≥20)	0.391				0.684			
Tumor location	Ut ^c (vs. Mt ^d or Lt ^e)	0.247				0.576			
Histology	SCC ^f (vs. non-SCC)	0.835				0.159			
Neoadjuvant chemotherapy	absent (vs. present)	0.028*§	0.586	1.353	(0.456-4.014)	0.868			
Adjuvant chemotherapy	absent (vs. present)	0.842				0.003*§			
cT factor	cT1 (vs. T2-3)	0.013*	0.449	0.706	(0.286-1.741)	0.264			
Clinical mediastinal lymph node metastasis	absent (vs. present)	0.021*	0.339	1.877	(0.516-6.826)	0.057	0.394	1.540	(0.570-4.156)
Clinical abdominal lymph node metastasis	absent (vs. present)	0.303				0.002*	0.040*	2.821	(1.049-7.583)
cM factor (supraclavicular lymph node metastasis)	cM0 (vs. cM1)	0.198				0.437			
Thoracic procedure	OT ^g (vs. VATS ^h)	0.032*§	0.215	0.595	(0.261-1.353)	0.116			
Abdominal procedure	OL ⁱ (vs. HALS ^j)	0.137				0.675			
Reconstruction route	Retrosternal (vs. mediastinal or antethoracic)	0.580				0.132			

^a HR: hazard ratio, ^b CI: confidence interval, ^c Ut: Upper thoracic, ^d Mt: Middle thoracic, ^e Lt: Lower thoracic, ^f SCC: squamous cell carcinoma, ^g OT: Open thoracotomy, ^h VATS: Video assisted thoracic surgery, ⁱ OL: Open Laparotomy, ^j HALS: Hand assisted laparoscopic surgery. *: $p < 0.05$. §: HR < 1.0

Figures

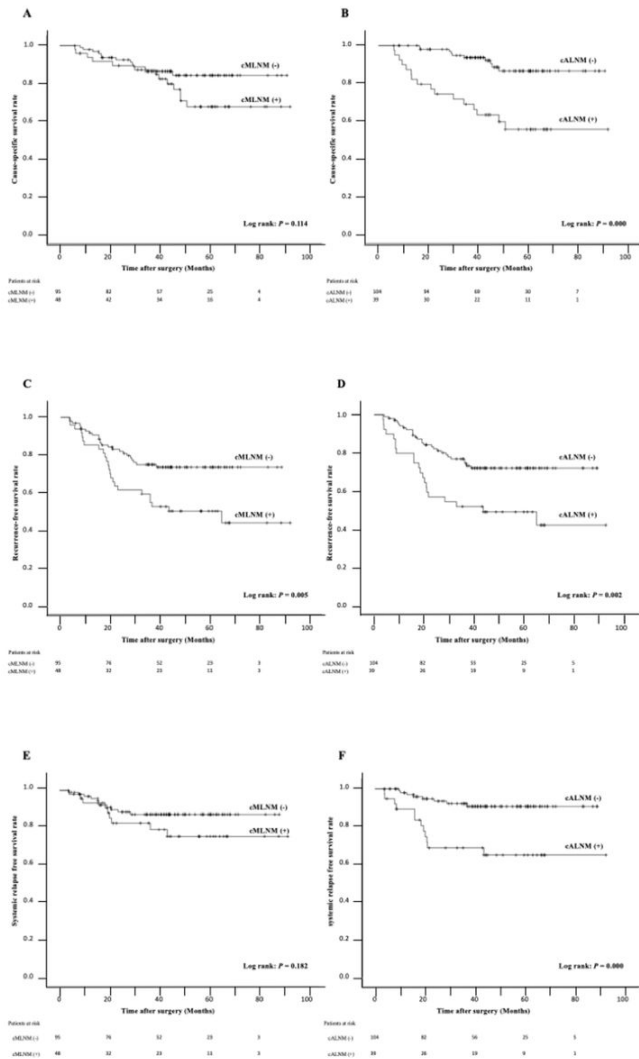


Figure 1

Kaplan-Meier curves for CSS, RFS, and S-RFS in all patients (a) There was no statistically significant difference in CSS between those with and without cMLNM ($p=0.114$). (b) A significant difference in CSS was observed between those with and without cALNM (3-year survival rates: 93.5% and 68.7%, respectively; $p=0.000$). (c) A significant difference in RFS was observed between those with and without cMLNM (3-year survival rates: 74.6% and 58.9%, respectively; $p=0.005$). (d) A significant difference in RFS was also observed between those with and without cALNM (3-year survival rates: 76.5% and 51.3%, respectively; $p=0.002$). (e) There was no statistically significant difference between those with and without cMLNM in terms of S-RFS ($p=0.182$). (f) A significant difference in S-RFS was observed between those with and without cALNM (3-year survival rates: 92.2% and 68.6%, respectively; $p=0.000$). CSS: cause-specific survival, cMLNM: clinical mediastinal lymph node metastasis, cALNM: clinical abdominal lymph node metastasis, RFS: recurrence-free survival, S-RFS: systemic recurrence-free survival

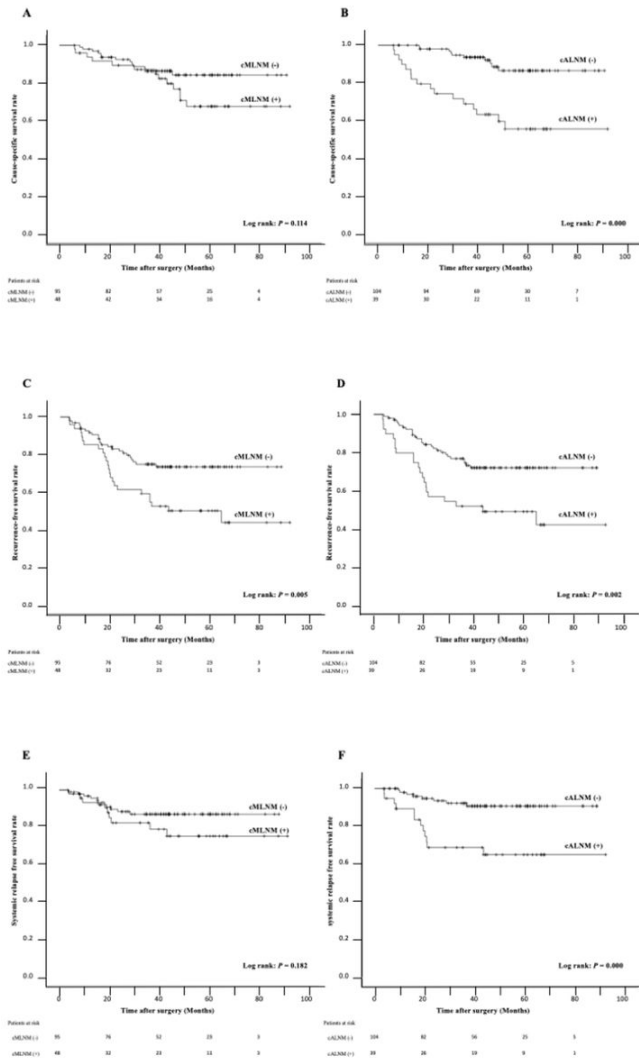


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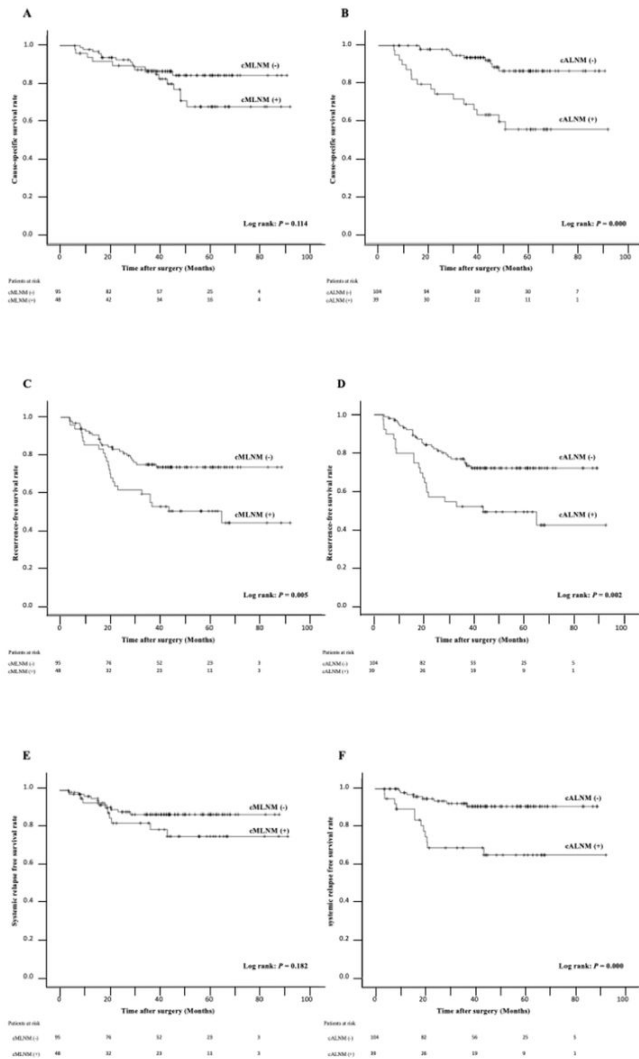


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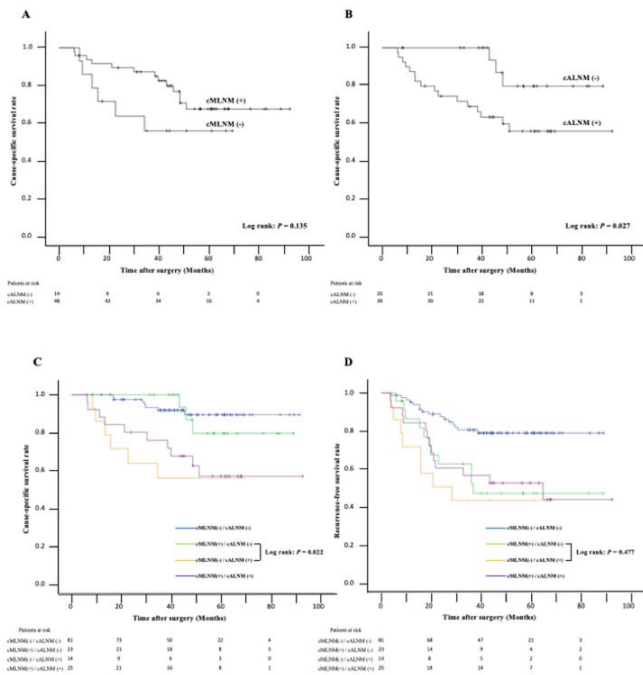


Figure 2

Kaplan-Meier curves for CSS in patients with cALNM/cMLNM, and in the cMLNM(-)/cALNM(-)/+ groups. (a) There was no statistically significant difference in CSS between those with and without cMLNM ($p=0.135$). (b) A significant difference in CSS was observed between those with and without cALNM (3-year survival rates: 100.0% and 65.8%, respectively; $p=0.027$). (c) A significant difference was observed for CSS among the four (cMLNM(-)/cALNM(-)/+) groups ($p=0.000$), as well as between those who were cMLNM(+)/cALNM(-) and those who were cMLNM(-)/cALNM(+) (3-year survival rates: 100.0% and 55.6%, respectively; $p=0.027$). (d) A significant difference in RFS was likewise observed among these four groups ($p=0.001$). There was no statistically significant difference between those who were cMLNM(+)/cALNM(-) and those who were cMLNM(-)/cALNM(+) ($p=0.47$). cALNM: clinical abdominal lymph node metastasis, cMLNM: clinical mediastinal lymph node metastasis, CSS: cause-specific survival, RFS: recurrence-free survival

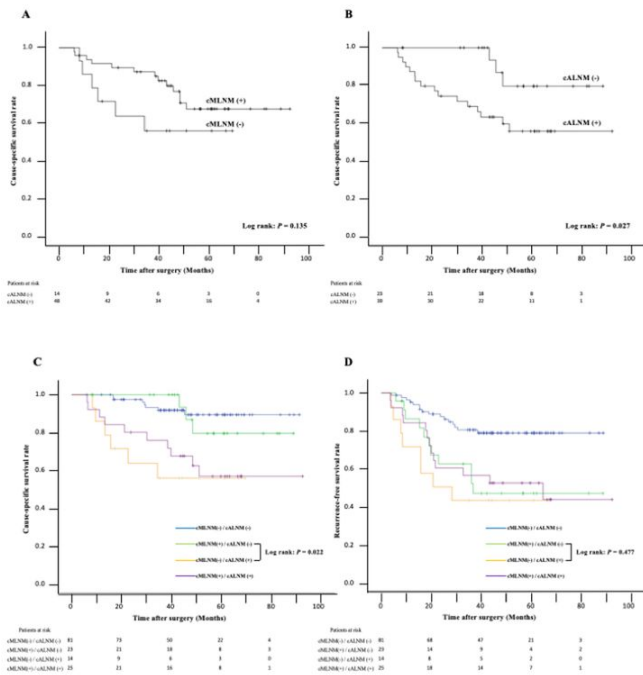


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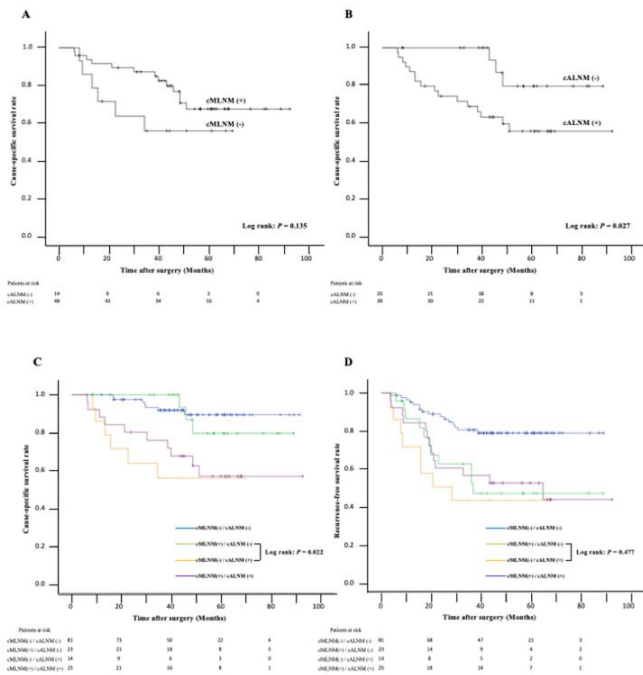


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