Original Article

Prognostic impact of surgical treatment for high-grade neuroendocrine carcinoma of the lung: a multi-institutional retrospective study

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Background: High-grade neuroendocrine carcinoma (HGNEC) of the lung, which includes small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC), is an aggressive form of lung cancer. Although lobectomy followed by adjuvant chemotherapy is regarded as the standard therapy for this disease, it would be an uphill struggle for HGNEC patients to receive that multidisciplinary therapy perfectly. This study aimed to examine recurrence and survival outcomes in surgically treated patients with HGNEC of the lung.

Methods: The medical records of 104 HGNEC patients who underwent surgical treatment in five institutions were retrospectively analyzed. Standard treatment (ST) was defined as lobectomy, bilobectomy, or pneumonectomy with mediastinal lymph node dissection followed by adjuvant platinum-doublet chemotherapy with more than two cycles.

Results: Patients in the ST group (n=31; 30%) were younger and had fewer respiratory complications than those in the non-standard treatment (NST) group (n=73; 70%). A significantly higher proportion of patients in the NST group developed ipsilateral lymph node recurrence (21% *vs.* 3%; P=0.035) and ipsilateral or contralateral lung recurrence (15% *vs.* 0%; P=0.031). Five-year overall survival (OS) was 64.2% in the ST group and 38.3% in the NST group (P=0.038). NST was independently associated with worse OS in multivariate analysis (hazard ratio, 2.044; 95% confidence interval, 1.016–4.113; P=0.045).

Conclusions: Surgically treated HGNEC patients who received ST had a more favorable outcome than those who received NST. Patients who receive NST may require additional treatment.

Keywords: High-grade neuroendocrine carcinoma (HGNEC) of the lung; surgery; standard therapy; survival

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Introduction

Small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) are high-grade neuroendocrine carcinomas (HGNEC) of the lung that behave aggressively and have a poor prognosis. Although the vast majority of HGNEC patients have metastatic disease at diagnosis, cure can be expected in patients with early-stage or locally advanced disease who undergo surgical treatment and adjuvant chemotherapy (1). Lobectomy with mediastinal lymph node dissection followed by adjuvant chemotherapy with platinum-doublet agents is standard treatment (ST) for resectable HGNEC. Limited surgery and omission of postoperative chemotherapy are associated with worse survival (2-5). In real-world clinical practice, not all HGNEC patients can receive multimodality treatment because of heavy smoking, respiratory comorbidities, or reduced organ function. Despite the many studies of surgical treatment in HGNEC patients, the differences in rates of recurrence and survival between ST and non-standard treatment (NST) remain unclear. We conducted a multi-institutional retrospective cohort study using a prospectively maintained clinical database to compare clinicopathological characteristics, postoperative recurrence, and survival outcomes between surgically treated HGNEC patients who received ST and those who received NST. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1938/rc).

Methods

Patient selection

The database records of 104 patients diagnosed with primary HGNEC of the lung (including combined SCLC and LCNEC) who underwent surgical treatment with curative intent at Tottori University Hospital and its four affiliated hospitals (Tottori Prefectural Central Hospital, Tottori Prefectural Kousei Hospital, Yonago Medical Center, and Matsue Medical Center) between January 2005 and December 2020 were retrospectively reviewed and analyzed. Patients who underwent induction therapy, incomplete resection were excluded from this study. Patients who received surgical biopsy of extensive disease small-cell lung cancer for histological diagnosis were also excluded. Surgical resection was categorized as sublobar resection (wedge resection or segmentectomy), lobectomy, or greater than lobectomy (bilobectomy or pneumonectomy). The

following clinicopathological factors were examined: age, sex, smoking status, body mass index, serum pro-gastrin releasing peptide (pro-GRP) concentration, cardiovascular and respiratory comorbidities, percent vital capacity (%VC), forced expiratory volume in one second ($FEV_{1.0}$%), laterality and lobe of primary tumor, surgical procedure, mediastinal lymph node dissection, adjuvant chemotherapy, pathological stage, and histology.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the institutional review board of Tottori University Hospital (No. 20A002) in May 2020. The requirement for written informed consent was waived because of the study's retrospective design.

Histological evaluation

Surgical specimens were fixed with 10% formalin and embedded in paraffin. Serial sections were stained using hematoxylin-eosin (HE) and histopathologically examined. Additional immunohistochemical analysis of neuroendocrine markers (Synaptophysin, Chromogranin A, and CD56) was performed if HGNEC was highly suspected. Histological specimens were reviewed by a qualified pathologist (Y.U.) and certified thoracic surgeons (S.M. and Y.O.) at the time of diagnosis. Combined SCLC (C-SCLC) and combined LCNEC (C-LCNEC) were defined according to the World Health Organization classification as SCLC or LCNEC combined with additional components consisting of other histological non-small cell lung carcinoma (NSCLC) types (usually adenocarcinoma, squamous cell carcinoma, or less common histological types) (6). Tumors in the early study period were initially staged according to the 6th and 7th editions of the TNM classification; these were later restaged according to the 8th edition prior to analysis.

Group classification and definition of each recurrence

Patients were grouped according to treatment (ST or NST). ST was defined as lobectomy, bilobectomy, or pneumonectomy with mediastinal lymph node dissection followed by adjuvant platinum-doublet chemotherapy with more than two cycles. NST was defined as limited resection, surgery without mediastinal lymph node dissection, or less than two cycles of adjuvant chemotherapy. Locoregional recurrence was defined as recurrence in the (I) bronchial stump or staple line of the lung parenchyma, (II) ipsilateral

pleura and/or chest wall, or (III) ipsilateral hilar and/or mediastinal lymph nodes, as described in our previous study (7). Recurrence was defined as distant if it was located in a different lobe of the ipsilateral lung, contralateral thorax, lymph nodes other than ipsilateral hilar and/or mediastinal, or an organ such as the liver, adrenal gland, brain, bone, or other sites. Median follow-up for censored cases was 30 months (range, 1–129 months), and minimum follow-up of living patients was 3 months.

Statistical analysis

Statistical analyses were performed using SPSS software version 22 (IBM Corp., Armonk, NY, USA), BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and GraphPad prism 8.4.1 for Windows (GraphPad Software, La Jolla, CA, USA). Group comparisons were performed using Fisher's exact probability test, Pearson's chi-square test, or the Mann-Whitney U test as appropriate. Recurrence free survival (RFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression was used to identify clinicopathological factors associated with survival outcomes. Variables with P<0.2 in the univariate analyses were included in the multivariate model. P<0.05 (two-sided) was considered significant.

Results

Clinicopathological characteristics

Patient demographics and clinicopathological characteristics are shown in *Table 1*. Patients in the ST group were significantly younger than those in the NST group (P=0.01) and had significantly fewer respiratory complications (P=0.03). Pulmonary function (%VC and $FEV_{1.0}$%) did not significantly differ between the groups. Among the patients in the NST group, 47% underwent limited resection, mediastinal lymph node dissection was omitted in 67%, and 75% did not receive adjuvant chemotherapy. Pathological stage and histology were not significantly different between the groups.

Incidence of recurrence and distribution of initial recurrence sites

Table 2 shows the incidence of postoperative recurrence

and distribution of initial recurrence sites in both groups. During follow-up, 50 patients (48.1%) developed recurrence. The proportion of patients who developed recurrence did not significantly differ between the ST and NST groups (35% *vs.* 53%; P=0.133). No patient developed local recurrence at the bronchial stump or lung staple line in either group. Ipsilateral lymph node recurrence occurred in 1 ST group patient (3%) and 15 NST group patients (21%). Distant recurrence occurred in 9 ST group patients (29%) and 31 NST group patients (42%). A significantly higher proportion of patients in the NST group developed ipsilateral lymph node recurrence (21% *vs.* 3%; P=0.035) and ipsilateral or contralateral lung recurrence (15% *vs.* 0%; P=0.031).

Survival analysis

Figure 1 shows Kaplan-Meier survival curves of the ST and NST groups. Five-year RFS was 58.2% in the ST group and 29.3% in the NST group (P=0.013). The 5-year OS rates were 64.2% and 38.3%, respectively (P=0.038). In ST group subanalysis, 5-year RFS and OS were higher in patients with pathological stage I disease than those with higher stage disease (P=0.046 and 0.053, respectively; Figure S1). Multivariate Cox proportional hazards regression showed that NST was independently associated with worse RFS (hazard ratio, 1.965; 95% confidence interval, 1.038–3.719; P=0.038) and OS (hazard ratio, 2.044; 95% confidence interval, 1.016–4.113; P=0.045; *Table 3*).

Discussion

This study evaluated clinicopathological features and survival outcomes in patients with HGNEC of the lung who underwent surgical resection using data obtained from a prospectively maintained regional multi-institutional database. Our findings show that lobectomy and mediastinal lymph node dissection followed by at least two cycles of adjuvant chemotherapy with platinum-doublet agents can provide a better survival outcome than other more limited treatments.

SCLC is more malignant than other types of lung cancer because of its rapid growth and metastatic spread early in the disease course. For early-stage SCLC, treatment with surgery and adjuvant chemotherapy are generally recommended. A recent large-scale cohort study showed that lobectomy with adjuvant chemotherapy in stage I/II SCLC patients was associated with significantly longer

Table 1 Patient demographics and clinicopathological characteristics

	Standard therapy (n=31)		Non-standard therapy (n=73)		P value
	N or Median [IQR]	% or range	N or Median [IQR]	% or range	
Age	69 [10]	50–80	72 [10]	54–90	0.010
Sex					1.000
Men	28	90	65	89	
Women	3	10	8	11	
Smoking status					0.087
Ever	29	94	73	100	
Never	2	6	0	0	
BMI	22.4 [3.4]	16.0- 27.7	21.6 [4.2]	16.4–31.0	0.599
Pro-GRP	63.9 [64.5]	17.1–908.0	56.5 [52.0]	19.0–854.0	0.515
Cardiovascular comorbidities					0.823
Yes	10	32	27	36	
No	21	68	46	64	
Respiratory comorbidities					0.030
Yes	8	26	37	51	
No	23	74	36	49	
%VC	96.0 [22.5]	68.3–137.2	95.6 [23.5]	31.3–137.3	0.201
$FEV_{1.0}$%	73.7 [9.9]	44.6–91.3	69.6 [14.6]	35.2–100.0	0.133
Primary tumor laterality					0.080
Right	14	45	48	66	
Left	17	55	25	34	
Primary tumor lobe					0.664
Upper & Middle lobe	20	65	43	59	
Lower lobe	11	35	30	41	
Surgical procedure					<0.001
Limited resection	0	0	34	47	
Lobectomy or more	31	100	39	53	
Mediastinal lymph node dissection					<0.001
Yes	31	100	27	37	
No	0	0	46	63	
Adjuvant chemotherapy					<0.001
Yes	31	100	18	25	
No	0	0	55	75	

Table 1 (*continued*)

Table 1 (*continued*)

	Standard therapy (n=31)		Non-standard therapy (n=73)		P value
	N or Median [IQR]	% or range	N or Median [IQR]	% or range	
Pathological stage					0.183
Stage IA	11	35	26	36	
Stage IB	7	23	28	38	
Stage II or more	13	42	19	26	
Histology					0.133
SCLC	15	48	31	42	
LCNEC	5	16	23	32	
Combined SCLC	2	7	9	12	
Combined LCNEC	9	29	10	14	

IQR, interquartile range; BMI, body mass index; Pro-GRP, pro-gastrin releasing peptide; VC, vital capacity; FEV, forced expiratory volume; SCLC, small cell lung cancer; LCNEC, large cell neuroendocrine carcinoma.

Table 2 Incidence and patterns of postoperative recurrence

|	Standard therapy		Non-standard therapy		P value
	N=31	%	N=73	%	
Postoperative recurrence					
No	20	65	34	47	0.133
Yes	11	35	39	53	
Locoregional recurrence	2	6	8	11	0.282
Locoregional and distant recurrences	0	0	8	11	
Distant recurrence	9	29	23	31	
Sites of initial recurrence					
Ipsilateral pleura	1	3	5	7	0.667
Ipsilateral lymph nodes	1	3	15	21	0.035
Other lymph nodes	0	0	3	4	0.553
Lung	0	0	11	15	0.031
Liver	2	6	8	11	1.000
Brain	4	13	7	10	0.729
Bone	2	6	5	7	1.000
Adrenal gland	2	6	2	3	0.581
Other sites	2	6	5	7	1.000
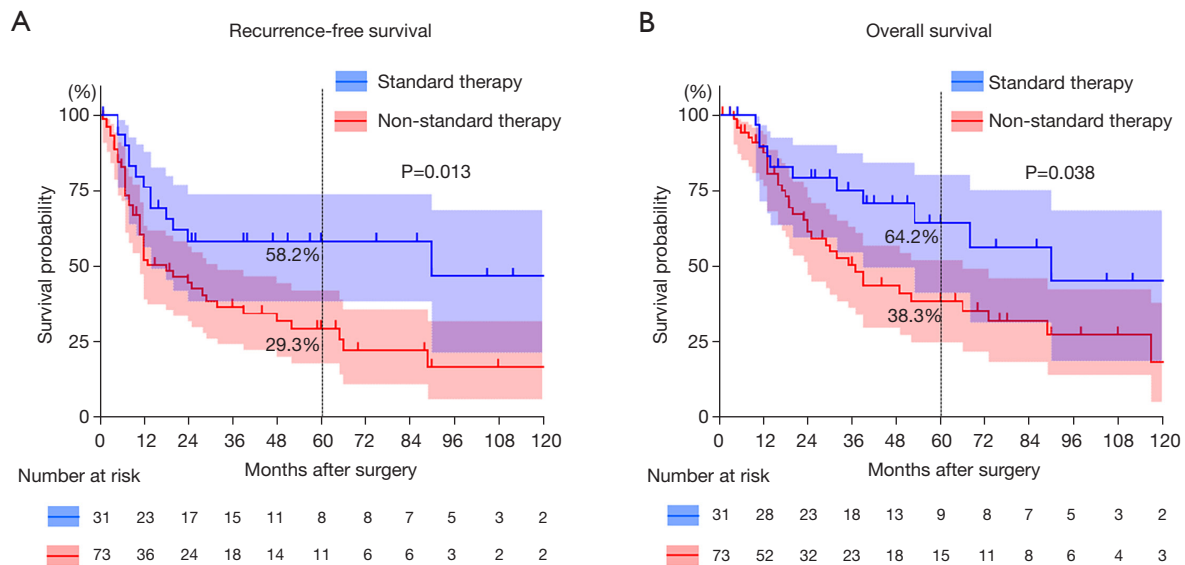
Figure 1 Kaplan-Meier curves for (A) recurrence-free survival and (B) overall survival in patients with high-grade neuroendocrine carcinoma stratified by treatment (standard *vs.* non-standard).

median OS than concurrent chemoradiation therapy (48.6 *vs.* 28.7 months; P<0.0001) (8). LCNEC is a rare neoplasm that was classified with high-grade neuroendocrine tumors of the lung in 2015 (9) and behaves more aggressively than other types of lung cancer. Five-year OS is approximately 50% even in patients who receive curative-intent surgery (10,11). Previous retrospective and prospective studies of adjuvant chemotherapy for LCNEC have shown better survival in patients who receive a SCLC regimen such as cisplatin and etoposide (12,13). Although the differences between LCNEC and SCLC in terms of pathogenesis and detailed molecular and pathological features remain controversial, they are commonly addressed together in clinical practice as HGNEC.

Lobectomy is a standard surgical procedure for primary lung cancer and is generally performed in patients with early to locally advanced HGNEC. Several studies have reported that lobectomy for HGNEC achieves better long-term outcomes than limited surgery such as wedge resection or segmentectomy (2,3,14). In our study, 34 of 104 patients (33%) received limited resection rather than standard resection because of advanced age, respiratory and/or other organ dysfunction, or presence of multiple lung tumors. In addition, most limited resection procedures did not include hilar or mediastinal lymph node sampling or dissection. Considering that 21% of the patients in our study experienced local recurrence in the ipsilateral lymph

nodes after NST, we hypothesize that omitting lymph node dissection can contribute to poor outcome. Regardless of the type of lung resection, sampling or dissection of the hilar and mediastinal lymph nodes should be performed when possible to allow proper pathological staging and avoid regional lymph node recurrence when treating HGNEC.

Postoperative systemic chemotherapy is important when treating HGNEC even in early-stage disease because of its high degree of biological malignancy. Yang *et al.* reported that adjuvant chemotherapy was associated with significantly improved survival in patients with pT1-2N0M0 SCLC (4). Raman *et al.* reported that adjuvant chemotherapy appeared to confer an additional OS advantage in patients with completely resected stage IB LCNEC (5). Kenmotsu *et al.* conducted a large randomized phase III study in patients with completely resected stage I–IIIA HGNEC of the lung to compare postoperative adjuvant chemotherapy regimens (JCOG1205/1206) (15). They demonstrated that irinotecan plus cisplatin was not superior to etoposide plus cisplatin for improving RFS. Therefore, etoposide plus cisplatin remains the standard. In theory, all HGNEC patients should be given etoposide and cisplatin as adjuvant chemotherapy after complete resection; however, this is difficult to implement in real-world clinical practice. In our study population, approximately half of the patients could not receive adjuvant chemotherapy because of advanced age, decreased activities of daily living after surgery, and

Table 3 Univariate and multivariate analyses for recurrence-free survival and overall survival

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	(95% confidence interval)	P value	Hazard ratio	(95% confidence interval)	P value
Univariate and multivariate analysis for RFS						
Age >70 y.o.	1.375	(0.812–2.329)	0.236			
Male	0.856	(0.388–1.892)	0.701			
Cardiovascular complications	0.901	(0.516–1.574)	0.715			
Respiratory complications	1.486	(0.885–2.494)	0.134	1.110	(0.641–1.921)	0.710
Left side	1.066	(0.629–1.805)	0.813			
Lower lobe	1.806	(1.076–3.030)	0.025	1.659	(0.970–2.838)	0.065
Pathological stage II or more	1.325	(0.768–2.284)	0.312			
SCLC/C-SCLC histology	1.299	(0.767–2.201)	0.331			
Non-standard therapy	2.127	(1.143–3.959)	0.017	1.965	(1.038–3.719)	0.038
Univariate and multivariate analysis for OS						
Age >70 y.o.	1.818	(1.005–3.289)	0.048	2.015	(1.090–3.723)	0.025
Male	0.660	(0.294–1.483)	0.314			
Cardiovascular complications	1.263	(0.687–2.322)	0.452			
Respiratory complications	1.373	(0.770–2.447)	0.283			
Left side	1.461	(0.814–2.622)	0.204			
Lower lobe	1.631	(0.918–2.899)	0.095	2.142	(1.144–4.012)	0.017
Pathological stage II or more	1.830	(1.016–3.294)	0.044	2.883	(1.496–5.559)	0.002
SCLC/C-SCLC histology	1.091	(0.610–1.951)	0.769			
Non-standard therapy	2.010	(1.021–3.958)	0.043	2.044	(1.016–4.113)	0.045

RFS, recurrence free survival; OS, overall survival; y.o., years old; SCLC, small cell lung cancer; C-SCLC, combined SCLC.

concurrent respiratory or other systemic comorbidities. The use of immune-checkpoint inhibitors or molecular-targeted therapeutic agents for NSCLC adjuvant therapy has been investigated in recent years (16,17). Moreover, recent advances in molecular pathology have led to the discovery of new potential HGNEC therapeutic targets (18,19). Hopefully, effective and well-tolerated adjuvant therapies with few side effects will be developed for treating HGNEC in the future.

Other additional treatments for surgically resected HGNEC remain controversial. Wakeam *et al.* investigated the effect of postoperative radiation therapy (PORT) on survival outcomes in SCLC patients and concluded that it was associated with longer survival in node-positive patients and those undergoing sublobar resection (20).

Zhou *et al.* conducted a large multi-institutional cohort study to examine survival and recurrence patterns in patients with limited-stage SCLC who underwent surgical resection followed by various adjuvant therapies and reported that mediastinal PORT did not improve OS or reduce locoregional recurrence (21). Survival benefit of prophylactic cranial irradiation (PCI) after surgery in patients with HGNEC is also unclear. Although Zhou *et al.* reported that PCI did not reduce the incidence of brain metastasis or improve OS (21), Yang *et al.* suggested that PCI might be associated with a favorable survival advantage and lower risk of brain metastasis in their meta-analysis of PCI in patients with resected SCLC (22). In our study, only three patients received PORT and/or PCI because these treatments are not commonly utilized in

HGNEC patients in Japan. Large-scale prospective studies are needed to determine their benefit in patients with surgically resected HGNEC.

There are several limitations of this study. Its retrospective nature and differences in surgeons, hospital equipment, and treatment decisions among the participating institutions might have introduced bias. Another limitation is the time-duration of the data collection from 2005–2020. During this time period much has changed in the treatment of lung cancer in terms of diagnosis, staging, surgical, and radiation techniques. Furthermore, its sample size was small because of the relative rarity of HGNEC patients undergoing resection; therefore, our findings cannot be considered definitive.

Conclusions

In conclusion, lobectomy and mediastinal lymph node dissection followed by at least two cycles of adjuvant chemotherapy with platinum-doublet agents provided better outcomes than more limited treatment in patients with HGNEC of the lung undergoing resection. Patients who received more limited treatment experienced worse RFS, worse OS, and more frequent recurrence in the regional lymph nodes and lungs. Lymph node dissection should be performed when possible to avoid regional lymph node recurrence. Patients who receive more limited treatment upfront may require additional treatment.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1938/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1938/dss

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1938/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the word in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Institutional Review Board of Tottori University Hospital (No. 20A002, date: May 1, 2020). The requirement for written informed consent was waived because of the study's retrospective design.

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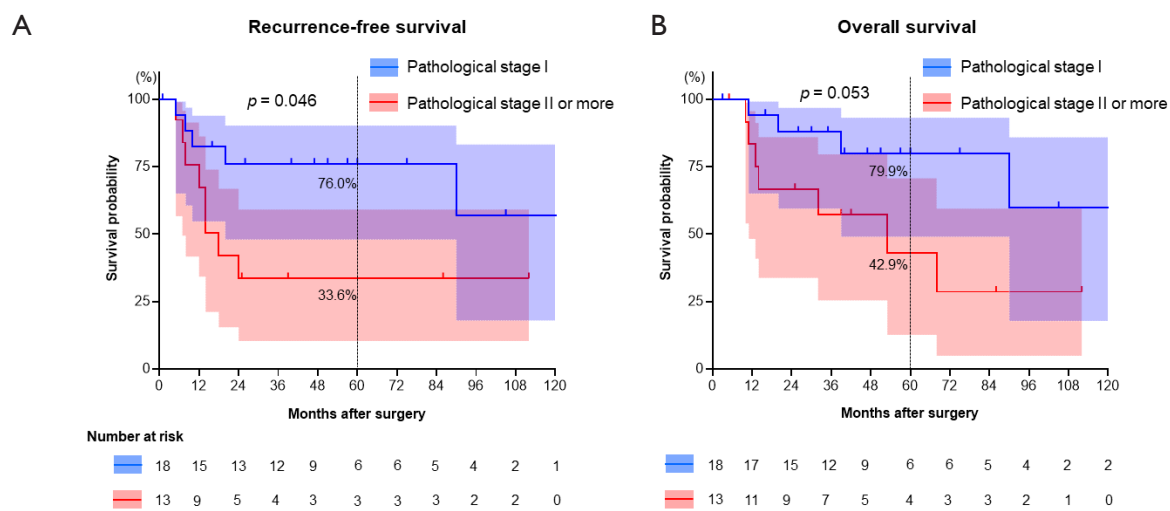
Figure S1 Kaplan-Meier curves for (A) recurrence-free survival and (B) overall survival in patients with high-grade neuroendocrine carcinoma who received standard treatment stratified by pathological stage (stage I *vs.* stage II or higher).