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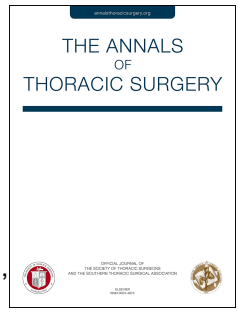

Results of Surgical Resection of Locally Advanced Pulmonary Neuroendocrine Tumors

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Results of Surgical Resection of Locally Advanced Pulmonary Neuroendocrine Tumors

Running head: Surgery in Locally Advanced pNETs

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Abstract

Background: Pulmonary neuroendocrine tumors (pNETs) include well-differentiated and poorly differentiated histology for which cell type has proved to be a determinant of survival in many studies. In patients diagnosed with Bronchial Carcinoid (BC) and Large Cell Neuroendocrine Carcinoma (LCNEC), surgery is the treatment of choice even in the case of locally advanced disease with lymph node involvement.

Methods: We retrospectively analyzed patients undergoing anatomical lung resection for BC or LCNEC with lymph node involvement (N1/N2) at the final pathological examination (pN+). Characteristics of patients and differences in overall survival (OS) and Disease Free Survival (DFS) are presented according to tumor type. Overall survival (OS) of distinct histological groups was compared with survival in our institutional experience in stage I-patients, without nodal involvement (pN0).

Results: 325 patients underwent surgical resection forneuroendocrine tumors ; 89 patients had nodal involvement. 5-year survival was 89% in pN+ BCs both for typical (TC) and atypical carcinoid (AC) but worse in pN+ LCNEC (47%). Cell type did not influence the prognosis in N0-disease, and no differences in survival were evident between N0 and N+ in BC group. In the group of LCNEC, 5-year OS was much worse for pN+ LCNEC (47%) compared with pN0 LCNEC (91%).

Conclusions: BCs have the best prognosis, and surgery remains the treatment of choice both for early and locally advanced disease. On the contrary, aggressive forms (LCNEC) with lymph nodal metastasis have a poor prognosis, and they need to be treated with an aggressive multidisciplinary approach.

Word count: 244

Abbreviations

Abbreviations	Explanations
AC	atypical carcinoids
CI	confidence interval
CT	chemotherapy
CT/RT	chemo-radiotherapy
DFS	disease free survival
HR	hazard ratio
ICU	intensive care unit
LCNEC	large-cell neuroendocrine carcinoma
OS	overall survival
PO	post-operative
pNETs	pulmonary neuroendocrine tumors
RT	radiotherapy
SCLC	small cell lung cancer
TC	typical carcinoids
WHO	world health organization

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The 2015 World Health Organization (WHO) classification of pulmonary neuroendocrine neoplasms divides well-differentiated and poorly differentiated tumors into 4 different groups.

Typical Carcinoid (TC) and Atypical carcinoid (AC) are respectively low-grade and intermediate grade tumors, while aggressive and poorly differentiated neoplasms are represented by large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC).These neoplasms account for approximately 20% of all primary lung cancers (1-3).

Typical and atypical carcinoids are also generally called Bronchial Carcinoids (BC) and do not share common traits with SCLC.

The patterns of pulmonary neuroendocrine tumors (pNETs) have been mainly investigated by multi-center analysis due to the rarity of these pathological entities, underlining the good prognosis of BCs and the biological aggressiveness of LCNEC (2,4).

Many studies have confirmed that cell type has proved to be the major determinant of survival in these tumors (2,4-7). In fact, survival in patients with AC is intermediate between the 'indolent' behavior of TCs and the more aggressive nature of LCNECs (2). Unlike SCLC, usually treated with chemotherapy (CT), BCs and LCNEC can be managed with different therapeutic strategies.

Surgery is the treatment of choice for localized disease in patients diagnosed with BC and LCNEC, and is deemed feasible even in loco-regional nodal diffusion, defined as N1 or N2 disease, even if LCNEC requires aggressive multimodal treatment (2,4-7). The aim of this paper was to investigate prognostic factors and survival outcomes in patients affected by locally advanced pNETs (pN1-N2) treated by complete anatomical surgical resection. We considered patients with N0 disease in our institutional experience for a comparison on overall survival (OS), since their clinical behavior and prognostic factors have already been described in previous papers (2,4-7).

Patients and Methods

This is a retrospective study based on a large single institution's experience on patients who underwent anatomical lung resection for a BCs or LCNEC at our Division, from January 1998 to December 2016.

We included patients with BC and LCNEC, since these subtypes usually undergo surgical treatment, on the contrary to SCLC. In addition, only patients with loco-regional lymph-node involvement at the final pathological exam were included.

Clinical charts were retrospectively reviewed and all patients signed a consent form prior to surgery; the Institutional Review Board approved the study.

All patients were studied preoperatively with a total body computed tomography scan, and from 2003 all patients received positron emission tomography with fluorodeoxyglucose. Mediastinal lymph node involvement, if suspected, was verified with EBUS-TBNA (from 2011), mediastinoscopy or Video-assisted thoracoscopy.

Demographic and clinic-pathological characteristics included age, gender, smoking habit, previous malignancies, side, site and type of surgery, tumor size (pT), number of lymph nodes dissected and pathological nodal stations, neoadjuvant and adjuvant treatments. Patient outcome was analyzed by means of postoperative complications, intensive care unit (ICU) stay and in-hospital stay. Post-operative mortality was defined as deaths occurring within 30 days after surgery or during hospital stay.

Statistical Methods

Characteristics of patients are presented according to tumor type (AC/TC, LCNEC). Differences in the distribution of patient characteristics across tumor types was assessed using the Fisher exact test for categorical variables and the Kruskal Wallis test for continuous variables.

OS was defined from the date of surgery to the date of last contact or death. Disease free survival (DFS) was defined from the date of surgery to the date of recurrence, death or last contact. OS and DFS curves were plotted using the Kaplan Meier method and the log-rank test was used to assess differences in survival between groups. Additionally, OS and DFS of distinct histological groups was compared with survival of our institutional experience of stage-I patients without nodal involvement.

Cox proportional hazard regression was used to assess the association between clinical and pathological characteristics and OS. Hazards Ratios (HRs) and 95% confidence intervals (CIs) were adjusted according to tumor type. Separate analyses were conducted for patients with carcinoid and large cell neuroendocrine

tumors. Analyses were performed with SAS software version 9.4 (Cary, NC). All p-values were two-sided.

Results

A total of 325 patients underwent complete surgical resection for pNETs; 236 patients were pN0 while 89 were pN+. The characteristics of the 89 enrolled patients (pN+) are detailed in Table 1. Twenty-one patients (23.6%) had TC, 35 (39.3%) AC and 33 (37.1%) LCNEC. Lobectomy was the most common operation performed (52; 58.4%) followed by pneumonectomy (19; 21.3%). Tumor median size was 27.5 mm (range 11-130 mm). Fifty-two patients (58.4%) had pathological N1 whereas N2 lymph node involvement was confirmed in 37 (41.6%) cases. Twenty-one patients received preoperative CT (23.6%), and 5 patients received preoperative chemo-radiotherapy (CT/RT) (5.6%). Adjuvant CT was given to 7 patients (7.9%), RT to 9 patients (10.1%), and CT/RT to 2 patients (2.2%).

On average, hospitalization was 6 days (range 4-15). Post-operative complications are listed in table 2.

After a median follow-up of 4.0 years contributing to 474 person-years of observation, 24 patients died resulting in a crude annual mortality rate of 5.1%. Follow-up was significantly shorter for patients with LCNEC, as an effect of the worse prognosis of this group of patients (P=0.003)

Mortality was significantly higher in patients with LCNEC (14.8 per 100-year) than in patients with TC (1.3 per 100-year) or AC (2.8 per 100-year).

Overall survival was 89% both for AC and TC N+ at 5 years (95% CI 76-95) and 78% at 10 years (95% CI 58-89); on the other hand, the OS was significantly worse in LCNEC: 47% at 5 years (95% CI 28-64) and 41% at 10 years (95% CI 21-60;P=0.001; Figure 1).

Patients with N0-disease had a good prognosis: 94% (95% CI 89-96) of OS at 5 years and 82% (95% CI 73-88) at 10 years, without significant differences per tumor type (P=0.41;Figure 2).

Focusing on survival of BC according to nodal status, no differences were detected comparing N0 patients with N+: 94% (95% CI 89-95) for N0 TC/AC and 89% (95% CI 76-95) for N+ TC/AC at 5 years (P=0.57) respectively (Figure 3).

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Finally, LCNEC showed a significant worsening in 5-year OS in patients with nodal disease: 5-year OS rate was 47% (95% CI 28-64) for pN+ LCNEC compared with 95% (95% CI 67-98) for pN0 (P=0.002) (Figure 4).

Similar results for disease free survival are provided in supplementary figures 1-4. N+ TC and AC showed a similar DFS (75% at 5 years; 95%CI 60-86), whilst the N+ LCNEC group had a significantly lower DFS (45% at 5 years; 95%CI 26-62; P=0.0002). For the BC group there was no difference in DFS for nodal staging, while for LCNEC histology, nodal involvement was related to a worse DFS (N+ LCNE DFS=45% at 5 years, 95%CI 26-62 vs N0 LCNEC DFS=66%, 95%CI 43-81; P=0.05).No difference in survival was evident comparing N1 and N2 involvement for all histological groups.

All investigated factors are reported in Table 3. Factors significantly associated with the OS analyzed for all patients included tumor type (P=0.005), age (P=0.003), previous malignancies (P=0.05) and need for ICU stay (P=0.0004). For the BC group, neoadjuvant and adjuvant treatment influenced the survival (neoadjuvant CT +/- RT, P=0.04; adjuvant CT and/or RT, P=0.046). Finally for the LCNEC group, age (P=0.003) and need for ICU stay (P=0.007) were significant. Some factors were then evaluated according to postoperative complications, which proved to be influenced by tumor type and number of N2 lymph nodes resected (LCNEC: HR 21.2, 95% CI 2.55-177, P=0.005; N2 lymph nodes resected: HR 1.11, 95% CI 1.00-1.22, P=0.05) (Table 4).

Comment

According to the WHO classification (1), the differences in survival between AC/TC and LCNEC are: TCs are diseases with favorable clinical behavior, ACs are intermediate-grade tumors with an aggressive biological behavior with a better survival if compared with LCNECs.

In our study, the survival of pNET pN+ was mostly influenced by the histology and the differentiation grade with significant differences between low grade BC and high grade LCNEC. Besides cell-type, the pN+ was always one of the most important prognostic factors (8-11). Lim et al. retrospectively reviewed 177 cases of resected pulmonary neuroendocrine tumors, including SCLC, assessing the association of

both cell-type and nodal disease with survival (12). As a result of this study, cell type was the strongest determinant of prognosis, revealing a close association between stage progression and more undifferentiated types. The authors therefore considered surgical resection the main option for TC, but not for the other categories.

The OS of pN+ TCs and ACs in our cohort was similar (89%) at 5 years and the trend reflected the pattern of pN0 disease OS. In fact, in both categories of BCs with lymph node involvement, the prognosis was still optimal and complete surgery played the main role in their treatment even in the case of locally advanced disease. Despite the good prognosis, even radically resected BCs could relapse, particularly in the case of pN2 AC, confirming the importance of radical lymphadenectomy and of a multidisciplinary discussion for post-operative treatments (13).

Regarding LCNEC patients, there was a difference in survival between patients with N0 disease and patients with mediastinal involvement who showed a worse outcome (p=0.0018). Whereas the 5-year OS of LCNEC was poorer with less than 50% of patients, with pN+ as the most important factor for prognosis, the OS for N0 disease was not influenced by cell type in our cohort. Indeed, the absence of nodal involvement was related to a better prognosis also in LCNEC, confirming surgery as the first treatment option also for these patients with limited disease, and the importance of systematic lymphadenectomy, which seemed to counteract the impact of a more aggressive histology.

In the case of lymph node involvement, LCNEC had the most aggressive histology in the pNET group of patients, with a survival closer to SCLC, suggesting a more careful and aggressive approach both in terms of surgery and of peri-operative treatments.

Previous studies on LCNEC had already recommended aggressive multimodal treatments, like SCLC, especially in advanced lymph nodal stage (9,11). Veronesi et al. retrospectively analyzed a series of 144 patients with a diagnosis of LCNEC, showing that early stages treated with surgery combined with adjuvant or induction chemotherapy (p=0.077) had better outcomes if compared to surgery alone (11). Lo Russo et al. (14) confirmed that radical surgery should always be performed when technically feasible, and patients with nodal involvement should always be treated with adjuvant chemotherapy. However, in

our cohort of LCNEC, no CT strategy influenced patient OS (neoadjuvant p=0.89; adjuvant p=0.19).

Considering neoadjuvant chemotherapy, its role is not yet established in the literature, and is still not recommended. Nevertheless, in our study, resected locally advanced LCNEC seemed to have an improved prognosis after neoadjuvant treatments, even if not statistically significant, showing a similar survival to BC (supplementary Figure 5). This should be considered in future studies to better understand the impact of neoadjuvant therapy on downstaging and on OS.

In the management of BCs (TCs and ACs), for which surgery remains the mainstay of treatment, the adjuvant regimens are usually administered in N(+) atypical carcinoids (16), whereas in typical carcinoids pN+ the use of post-operative CT is associated with a worse OS (17-19). In fact, current guidelines suggest observation alone after surgery for TC (13), whereas patients affected by AC with positive lymph nodes and high proliferative index should be considered for adjuvant therapy (13). However, although advanced AC is more aggressive than TC at the same stage (12-14), as is widely known, there are still no studies about the role of neoadjuvant chemotherapy in these locally advanced diseases because in both cases surgery is performed first as the gold standard treatment.

In our analysis, the OS of BCs proved to be influenced by both neoadjuvant and adjuvant treatments (neoadjuvant P=0.03;adjuvant P=0.002) with a worse survival for patients who underwent systemic treatments (supplementary Figure 5 and 6). However, we cannot consider these findings as clinically relevant, also because of the small number of patients treated and the heterogeneity of the treatments performed, even though this could be a hypothesis for future prospective studies in specific clinical settings.

A potential limitation of this study refers to a selection bias as in all retrospective analyses. However, our Institute is a referral Center for neuroendocrine neoplasms, and this large single center cohort of rare subtype (N+ only) tumors provides homogeneity in terms of surgical approach, pathology examination and multidisciplinary management.

Conclusions

In our study, BCs were confirmed to have the best prognosis, while locally advanced LCNECs showed a poor prognosis if compared with early stages. TCs N0 and TCs N+ presented the same good prognosis and we can speculate that surgery should be considered the treatment option , avoiding adjuvant therapy, even in the case of N+ disease. Similarly, nodal involvement in our AC patients did not influence their survival, but according to international guidelines we would rather discuss the benefit of an adjuvant therapy. LCNECs with lymph nodal metastasis are the most difficult cases to treat, thus, while waiting for a definitive randomized trial, and considering our results and literature, we choose a multidisciplinary approach based on case-by-case discussion.

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Table 1: Patient characteristics.

	All	TC	AC	LCNEC	P-value
All patients	89	21(23.6%)	35(39.3%)	33(37.1%)	
Age					
Median (range)	59(15-79)	59(15-76)	59(20-77)	62(35-79)	0.39
<50 years	26	8(30.8%)	14(53.8%)	4(15.4%)	
50-59 years	21	4(19.0%)	5(23.8%)	12(57.1%)	
60-69 years	20	4(20.0%)	8(40.0%)	8(40.0%)	
≥70 years	22	5(22.7%)	8(36.4%)	9(40.9%)	0.14
Sex					
Men	49	6(12.2%)	13(26.5%)	30(61.2%)	
Women	40	15(37.5%)	22(55.0%)	3(7.5%)	<0.0001
Smoker					
No	28	12(42.9%)	15(53.6%)	1(3.6%)	
Yes	55	9(16.4%)	14(25.5%)	32(58.2%)	<0.0001
Missing	6	-	6(100%)	-	
Previous malignancy					
No	73	19(26.0%)	26(35.6%)	28(38.4%)	
Yes	16	2(12.5%)	9(56.3%)	5(31.3%)	0.29
Side					
Right	51	16(31.4%)	17(33.3%)	18(35.3%)	
Left	38	5(13.2%)	18(47.4%)	15(39.5%)	0.12
Access					
Thoracotomy	81	18(22.2%)	33(40.7%)	30(37.0%)	
Other access*	8	3(37.5%)	2(25.0%)	3(37.5%)	0.51
Intervention					
Bilobectomy	9	2(22.2%)	6(66.7%)	1(11.1%)	
Lobectomy	52	15(28.8%)	20(38.5%)	17(32.7%)	
Lobectomy+wedge	6	1(16.7%)	3(50.0%)	2(33.3%)	
Pneumonectomy	19	1(5.3%)	5(26.3%)	13(68.4%)	
Segmentectomy	3	2(66.7%)	1(33.3%)	-	0.02
Tumor size (mm)					
Median (range)	27.5(11-130)	20.0(11-75)	27.0(11-67)	48.5(13-130)	<0.0001
pT					
pT1	31	13(41.9%)	13(41.9%)	5(16.1%)	
pT2	30	3(10.0%)	9(30.0%)	18(60.0%)	
pT3	10	2(20.0%)	2(20.0%)	6(60.0%)	
pT4	3	-	1(33.3%)	2(66.7%)	0.003
Missing	15	3(20.0%)	10(66.7%)	2(13.3%)	
Lymph nodes					
Median N1 resected (range)	9.0(2-27)	8.5(4-13)	11.0(2-27)	9.0(2-20)	0.47
Median N1 positive	2.0(0-12)	1.0(0-11)	2.0(0-12)	2.0(0- 7)	0.85

(range)					
Median N2 resected (range)	7.0(1-33)	5.0(1-19)	6.0(1-33)	9.5(2-27)	0.20
Median N2 positive (range)	0.0(0- 9)	0.5(0- 2)	1.0(0- 9)	0.0(0- 3)	0.27
pN					
pN1	52	14(26.9%)	17(32.7%)	21(40.4%)	
pN2	37	7(18.9%)	18(48.6%)	12(32.4%)	0.32
Neoadjuvant treatment					
None	61	18(29.5%)	28(45.9%)	15(24.6%)	
CT	21	1(4.8%)	4(19.0%)	16(76.2%)	
CT/RT	5	2(40.0%)	1(20.0%)	2(40.0%)	0.0003
Missing	2	-	2(100%)	-	
Adjuvant treatment					
None	65	21(32.3%)	27(41.5%)	17(26.2%)	
CT	7	-	-	7(100%)	
RT	9	-	3(33.3%)	6(66.7%)	
CT/RT	2	-	-	2(100%)	0.0002
Missing	6	-	5(83.3%)	1(16.7%)	

P-values calculated omitting the unknown category and using the Fisher exact test for categorical variables and the Kruskal-Wallis test for continuous variables
AC= atypical carcinoid CT= chemotherapy CT/RT= chemo-radiotherapy LCNEC= large-cell neuroendocrine carcinoma
RT= radiotherapy TC= typical carcinoids

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Table 2: Patient outcome

	All	TC	AC	LCNEC	P-value
All patients	89	21(23.6%)	35(39.3%)	33(37.1%)	
PO complications					
No	64	20(31.3%)	28(43.8%)	16(25.0%)	
Yes	25	1(4.0%)	7(28.0%)	17(68.0%)	0.0004
ICU (days)					
Median (range)	0(0-3)	0(0-1)	0(0-3)	0(0-2)	0.54
Hospital stay (days)					
Median (range)	6(4-15)	5(4-14)	6(4-13)	7(5-15)	0.0001
Follow-up					
Median (range)	4.0(0-18.1)	6.6(0.1-18.1)	5.9(0.1-14.4)	2.0(0.0-10.3)	0.003
Person-years	474	150	215	108	
Deaths	24	2	6	16	
Death rate/100-year	5.1	1.3	2.8	14.8	0.0001

P-values calculated using the Fisher exact test for categorical variables, the Kruskal-Wallis test for continuous variables and the Log-rank test for survival (death rate).
AC= atypical carcinoids ICU= intensive care unit LCNEC= large-cell neuroendocrine carcinoma PO= post-operative TC= typical carcinoids

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Table 3: Analysis of factors associated with OS

	All HR (95% CI)*	P-value	AC/TC HR (95% CI)	P-value	LCNEC HR (95% CI)	P-value
Tumor type						
TC	1.00		1.00		-	
AC	1.79 (0.36-8.86)	0.48	1.87 (0.38-9.28)	0.44	-	
LCNEC	**8.35 (1.89-36.9)**	**0.005**	-		-	
Age						
<60 years	1.00		1.00		1.00	
≥60 years	**3.82 (1.56-9.35)**	**0.003**	1.06 (0.25-4.54)	0.94	**7.23 (1.96-26.7)**	**0.003**
Sex						
Men	1.00		1.00		1.00	
Women	1.94 (0.53-7.09)	0.32	1.88 (0.38-9.32)	0.44	1.78 (0.23-14.0)	0.58
Smoker						
No	1.00		1.00		1.00	
Yes	1.71 (0.44-6.64)	0.44	0.97 (0.19-4.81)	0.97	-	
Missing	2.82 (0.42-19.0)	0.29	1.96 (0.29-13.2)	0.49	-	
Previous malignancy						
No	1.00		1.00		1.00	
Yes	**2.41 (0.99-5.90)**	**0.05**	2.86 (0.68-12.1)	0.15	2.13 (0.68-6.63)	0.19
Side						
Right	1.00		1.00		1.00	
Left	1.02 (0.45-2.31)	0.96	1.10 (0.26-4.65)	0.90	0.98 (0.37-2.63)	0.97
Intervention						
Lobectomy	1.00		1.00		1.00	
Bilobectomy	0.90 (0.11-7.24)	0.92	1.49 (0.16-13.6)	0.72	-	
Lobectomy+wedge	0.77 (0.10-5.91)	0.80	-		1.23 (0.15-9.93)	0.85
Pneumonectomy	1.79 (0.74-4.36)	0.20	2.37 (0.42-13.4)	0.33	1.71 (0.61-4.77)	0.31
Segmentectomy	3.21 (0.34-30.7)	0.31	3.93 (0.35-43.5)	0.27	-	
Tumor size (mm)			-			
Per 10mm	1.13 (0.94-1.35)	0.18	0.92 (0.48-1.76)	0.80	1.11 (0.92-1.34)	0.27

pT						
pT1	1.00		1.00		1.00	
pT2	3.16 (0.97-10.3)	0.06	3.28 (0.52-20.8)	0.21	2.52 (0.54-11.8)	0.24
pT3/pT4	0.82 (0.17-3.98)	0.81	-		0.80 (0.13-4.81)	0.81
Missing	2.31 (0.56-9.55)	0.25	2.56 (0.41-16.1)	0.32	1.71 (0.15-19.2)	0.66
Lymph nodes						
N1 resected	0.99 (0.89-1.09)	0.80	0.91 (0.70-1.18)	0.48	1.05 (0.92-1.20)	0.48
N1 positive	1.05 (0.85-1.30)	0.63	1.14 (0.86-1.52)	0.37	1.09 (0.76-1.57)	0.64
N2 resected	0.99 (0.91-1.07)	0.73	0.82 (0.59-1.15)	0.25	1.00 (0.92-1.09)	0.99
N2 positive	0.80 (0.50-1.29)	0.36	0.77 (0.33-1.79)	0.54	0.92 (0.51-1.67)	0.79
pN						
pN1	1.00		1.00		1.00	
pN2	1.14 (0.49-2.61)	0.77	0.98 (0.24-4.07)	0.98	1.24 (0.45-3.42)	0.68
Neoadjuvant treatment						
None	1.00		1.00		1.00	
CT and/or RT	1.66 (0.69-3.99)	0.26	**4.82 (1.06-21.9)**	**0.04**	1.07 (0.40-2.87)	0.89
Missing	3.12 (0.36-27.1)	0.30	4.52 (0.48-42.9)	0.19	-	
Adjuvant treatment						
None	1.00		1.00		1.00	
CT and/or RT	2.24 (0.86-5.85)	0.10	**11.1 (1.05-117)**	**0.046**	1.91 (0.71-5.16)	0.20
Missing	1.15 (0.13-9.86)	0.90	1.27 (0.14-11.4)	0.83	-	
Postoperative complications						
No	1.00		1.00		1.00	
Yes	1.34 (0.55-3.30)	0.52	1.13 (0.13-9.76)	0.91	1.45 (0.53-4.00)	0.47
Need for ICU						
No	1.00		1.00		1.00	
Yes	**4.36 (1.93-9.82)**	**0.0004**	3.64 (0.90-14.8)	0.07	**3.94 (1.46-10.7)**	**0.007**

* Adjusted for tumor type. AC= atypical carcinoids CI= confidence interval CT= chemotherapy CT/RT= chemo-radiotherapy ICU= intensive care unit HR=hazard ratio LCNEC= large-cell neuroendocrine carcinoma PO= post-operative RT= radiotherapy TC= typical carcinoids

Table 4: Analysis of factors associated with post-operative complications.

	Patients	PO complications	OR (95% CI)*	P-value
All patients	89	25(28.1%)		
Tumor type				
TC	21	1(4.8%)	1.00	
AC	35	7(20.0%)	5.00(0.57-43.9)	0.15
LCNEC	33	17(51.5%)	**21.2(2.55-177)**	**0.005**
Age				
<60 years	47	9(19.2%)	1.00	
≥60 years	42	16(38.1%)	2.72(0.94-7.82)	0.06
Sex				
Men	49	18(36.7%)	1.00	
Women	40	7(17.5%)	1.17(0.31-4.49)	0.82
Smoker				
No	28	5(17.9%)	1.00	
Yes	55	19(34.6%)	0.61(0.13-2.90)	0.53
Missing	6	-	0.61(0.05-6.88)	0.69
Previous malignancy				
No	73	19(26.0%)	1.00	
Yes	16	6(37.5%)	1.95(0.54-7.05)	0.31
Side				
Right	51	12(23.5%)	1.00	
Left	38	13(34.2%)	1.49(0.53-4.19)	0.45
Intervention				
Lobectomy	52	12(23.1%)	1.00	
Bilobectomy	9	2(22.2%)	1.41(0.22-9.02)	0.72
Lobectomy+wedge	6	3(50.0%)	3.83(0.55-26.5)	0.17
Pneumonectomy	19	8(42.1%)	1.28(0.38-4.40)	0.69
Segmentectomy	3	0(0.0%)	-	
Tumor size (mm)				
Per 10mm			1.04(0.83-1.30)	0.74

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pT				
pT1	31	7(19.2%)	1.00	
pT2	30	10(33.3%)	0.64(0.16-2.49)	0.52
pT3/pT4	13	7(53.8%)	1.81(0.37-9.01)	0.47
Missing	15	1(6.7%)	0.17(0.02-1.71)	0.13
Lymph nodes				
N1 resected			1.06(0.95-1.19)	0.31
N1 positive			0.90(0.63-1.28)	0.55
N2 resected			**1.11(1.00-1.22)**	**0.05**
N2 positive			1.05(0.69-1.59)	0.82
pN				
pN1	52	14(26.9%)	1.00	
pN2	37	11(29.7%)	1.29(0.45-3.67)	0.64
Neoadjuvant treatment				
None	61	15(24.6%)	1.00	
CT and/or RT	26	10(38.5%)	0.85(0.26-2.73)	0.78
Missing	2	0(0.0%)	-	
Adjuvant treatment				
None	65	15(23.1%)	1.00	
CT and/or RT	18	8(44.4%)	0.91(0.26-3.21)	0.88
Missing	6	2(25.0%)	1.60(0.23-11.1)	0.63

* Adjusted for tumor type. AC= atypical carcinoids CI= confidence interval CT= chemotherapy CT/RT= chemo-radiotherapy
HR=hazard ratio ICU= intensive care unit LCNEC= large-cell neuroendocrine carcinoma PO= post-operative
RT= radiotherapy TC= typical carcinoids

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Figure Legends

Figure 1: Overall survival of TC(N+), AC(N+) and LCNEC(N+).

AC=atypical carcinoid; LCNEC= and large cell neuroendocrine carcinoma; OS=overall survival; TC=typical carcinoid

Figure 2: Overall survival of TC(N0), AC(N0) and LCNEC(N0).

AC=atypical carcinoid; LCNEC= and large cell neuroendocrine carcinoma; OS=overall survival; TC=typical carcinoid

Figure 3: Overall survival of TC or AC according to nodal status.

AC=atypical carcinoid; OS=overall survival; TC=typical carcinoid

Figure 4: Overall survival of LCNEC (N0) and LCNEC (N+).

LCNEC=large cell neuroendocrine carcinoma; OS=overall survival

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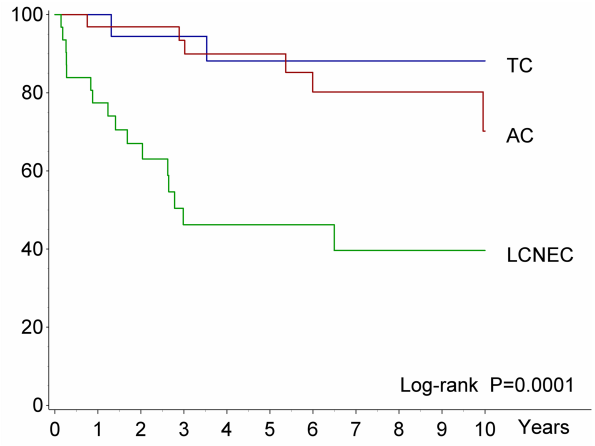

N° at risk											
TC	21	19	15	15	13	13	11	8	6	6	6
AC	35	31	30	27	22	19	16	15	13	9	7
LCNEC	33	24	17	11	10	10	8	6	4	2	1

OS (95% CI)	1-year	2-year	3-year	5-year	10-year
TC/AC	98 (88-100)	96 (85-99)	94 (82-98)	89 (76-95)	78 (58-89)
LCNEC	78 (60-89)	68 (48-81)	47 (28-64)	47 (28-64)	41 (21-60)

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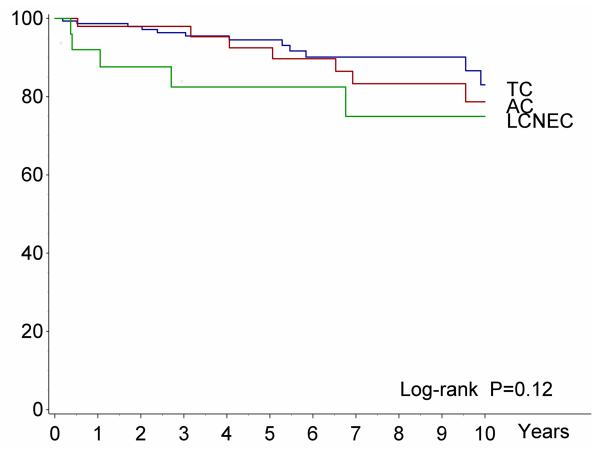

Nº at risk											
TC	155	141	128	115	98	75	54	42	36	31	23
AC	51	47	40	39	34	33	29	26	23	20	14
LCNEC	27	21	20	16	15	15	12	10	9	7	7

OS (95% CI)	1-year	2-year	3-year	5-year	10-year
TC/AC	99 (95-100)	98 (95-99)	97 (93-99)	94 (89-97)	82 (72-89)
LCNEC	92 (72-98)	88 (66-96)	83 (60-93)	83 (60-93)	76 (50-90)

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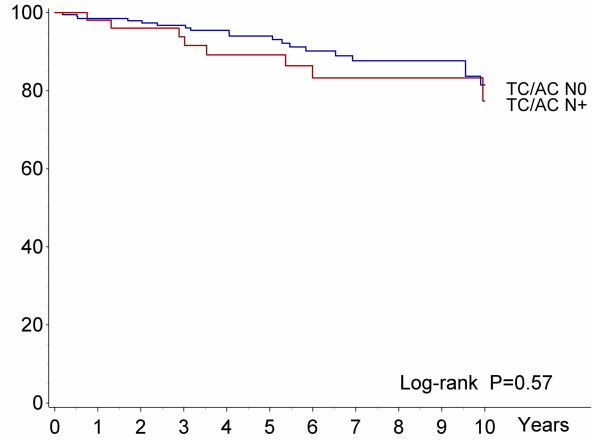

N° at risk											
TC/AC N0	206	188	168	153	132	108	83	68	59	51	37
TC/AC N+	56	50	45	42	35	32	27	23	19	15	13

OS (95% CI)	1-year	2-year	3-year	5-year	10-year
TC/AC N0	99 (95-100)	98 (95-99)	97 (93-99)	94 (89-97)	82 (72-89)
TC/AC N+	98 (88-100)	96 (85-99)	94 (82-98)	89 (76-95)	78 (58-89)

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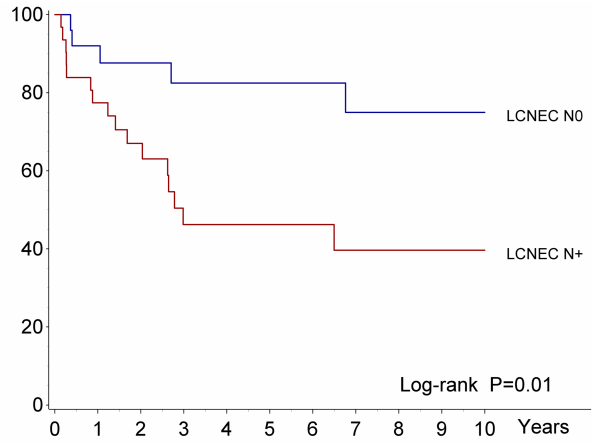

N° at risk											
LCNEC N0	27	21	20	16	15	15	12	10	9	7	7
LCNEC N+	33	24	17	11	10	10	8	6	4	2	1

OS (95% CI)	1-year	2-year	3-year	5-year	10-year
LCNEC N0	92 (72-98)	88 (66-96)	83 (60-93)	83 (60-93)	76 (50-90)
LCNEC N+	78 (60-89)	68 (48-81)	47 (28-64)	47 (28-64)	41 (22-60)

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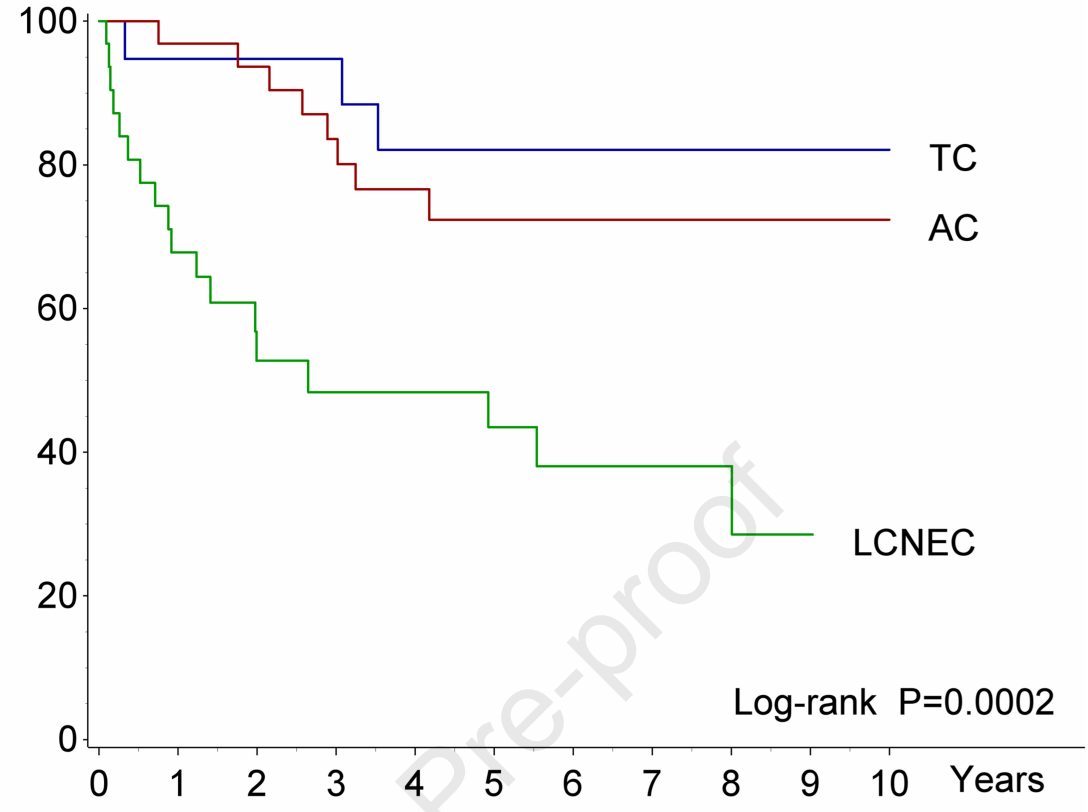

N° at risk											
TC	21	17	15	15	12	12	11	8	6	6	6
AC	35	31	29	24	19	15	14	13	11	8	7
LCNEC	33	21	13	11	10	9	6	5	4	1	0

DFS (95% CI)	1-year	2-year	3-year	5-year	10-year
TC/AC	96 (86-99)	94 (83-98)	88 (74-94)	75 (60-86)	75 (60-86)
LCNEC	69 (50-82)	54 (35-70)	50 (31-66)	45 (26-62)	26 (7-52)

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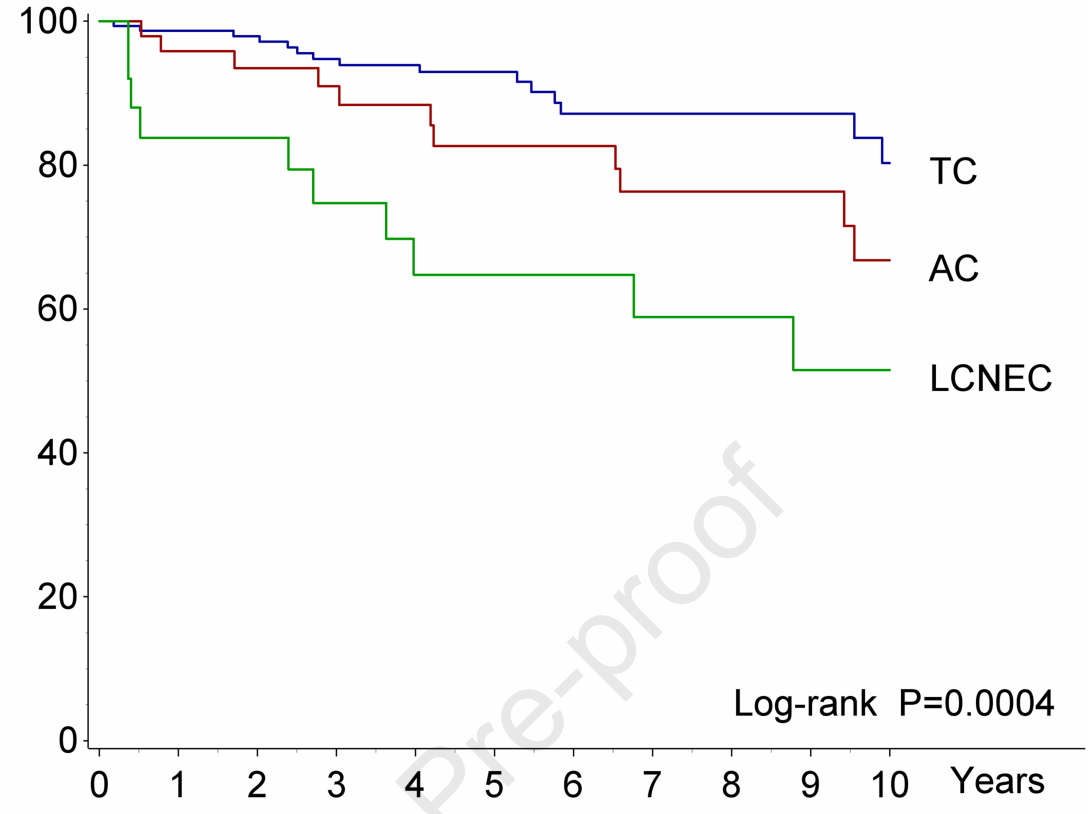

N° at risk											
TC	155	141	128	114	98	75	54	42	36	31	23
AC	51	46	38	35	31	29	27	24	21	18	11
LCNEC	27	20	20	16	13	13	12	10	9	6	6

DFS (95% CI)	1-year	2-year	3-year	5-year	10-year
TC	99 (95-100)	98 (94-99)	95 (89-98)	93 (86-96)	81 (68-89)
AC	96 (85-99)	94 (82-98)	91 (78-97)	83 (67-92)	67 (46-81)
LCNEC	84 (63-94)	84 (63-94)	75 (53-88)	66 (43-81)	53 (28-72)

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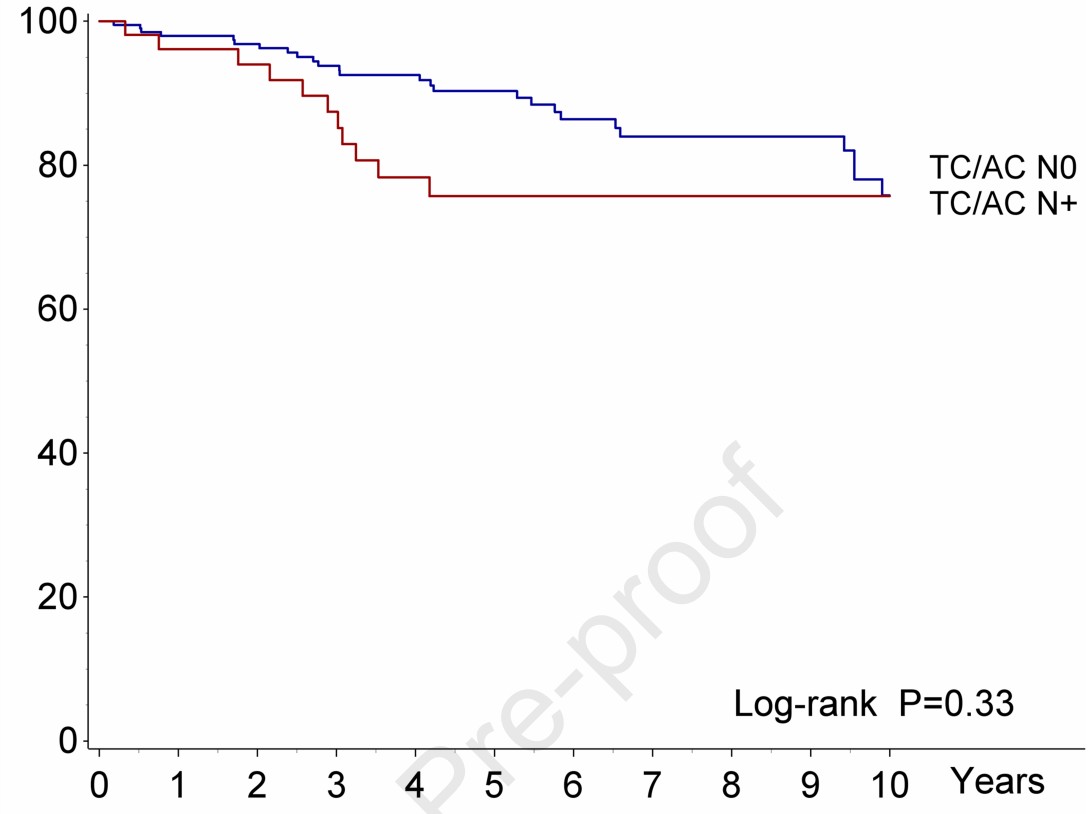

N° at risk											
TC/AC N0	206	187	166	149	129	104	81	66	57	49	34
TC/AC N+	56	48	44	39	31	27	25	21	17	14	13

DFS (95% CI)	1-year	2-year	3-year	5-year	10-year
TC/AC N0	98 (95-100)	97 (93-99)	94 (89-97)	90 (84-94)	76 (65-84)
TC/AC N+	96 (86-99)	94 (83-98)	88 (74-94)	75 (60-86)	75 (60-86)

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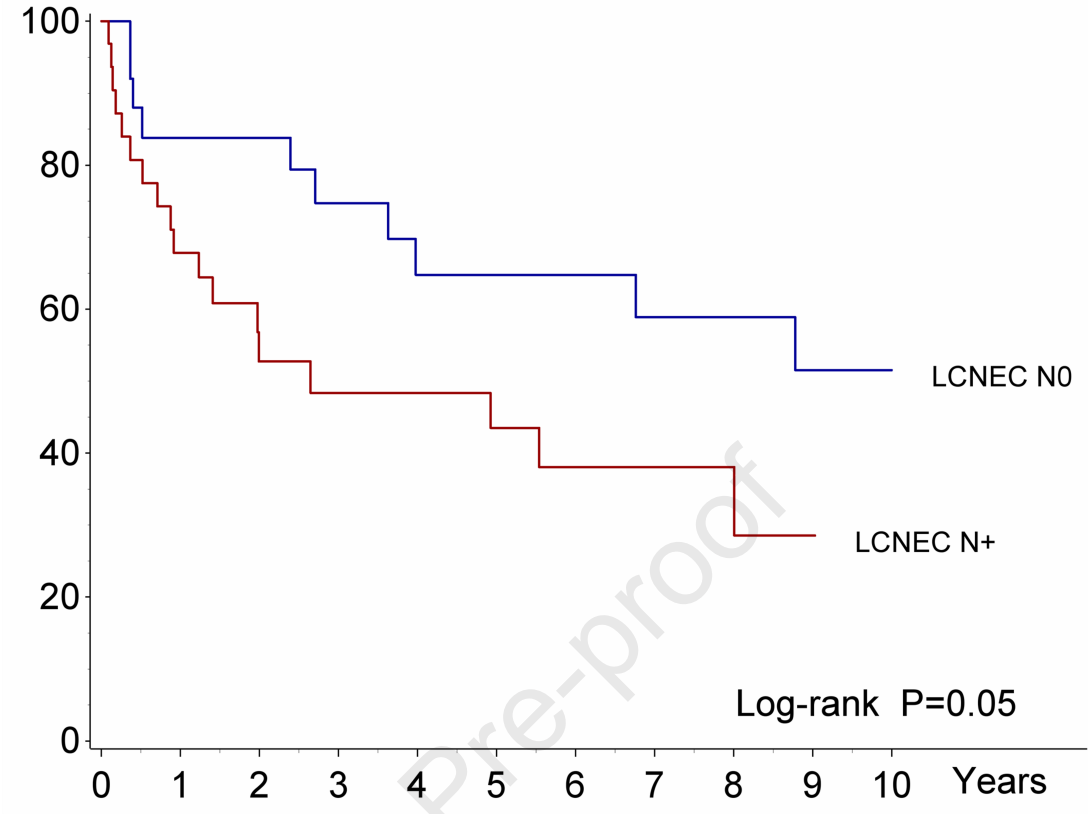

N° at risk											
LCNEC N0	27	20	20	16	13	13	12	10	9	6	6
LCNEC N+	33	21	13	11	10	9	6	5	4	1	0

DFS (95% CI)	1-year	2-year	3-year	5-year	10-year
LCNEC N0	84 (63-94)	84 (63-94)	75 (53-88)	66 (43-81)	53 (28-72)
LCNEC N+	69 (50-82)	54 (35-70)	50 (31-66)	45 (26-62)	26 (7-52)

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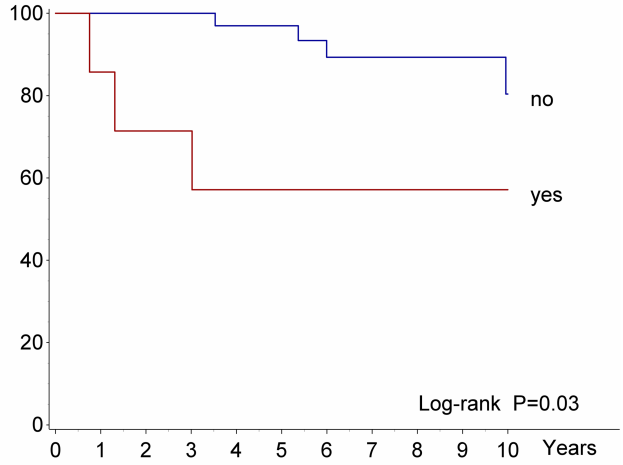

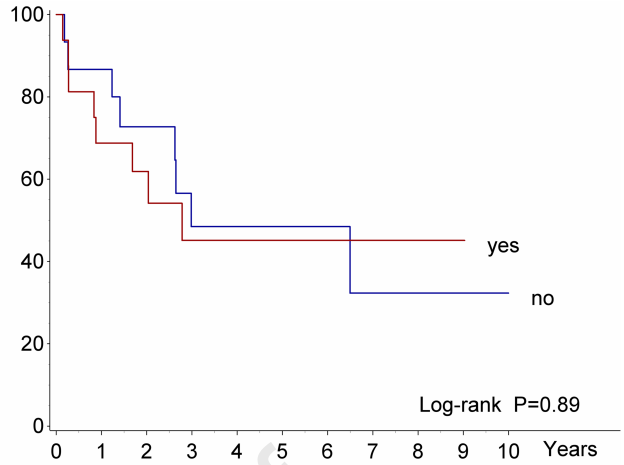

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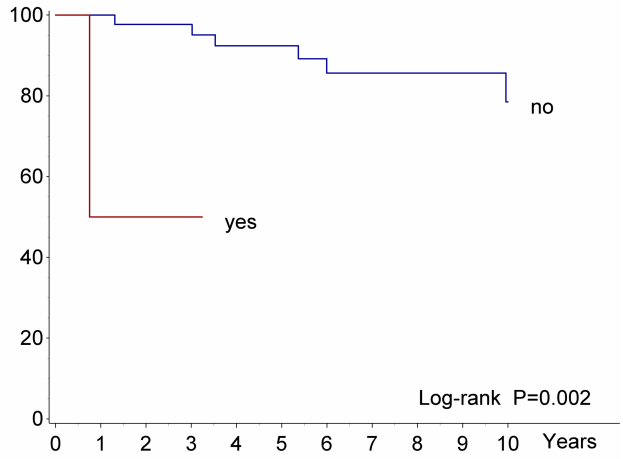

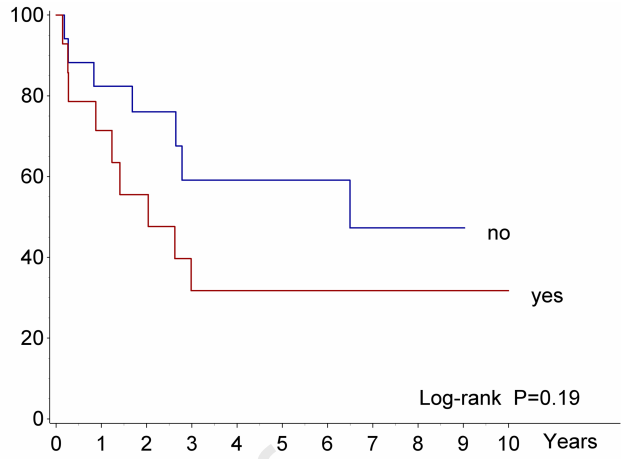

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