Original Paper

Neuro
endocrinology

Neuroendocrinology
DOI: 10.1159/000480015

Received: December 5, 2016
Accepted after revision: July 21, 2017
Published online: August 3, 2017

Natural History of Localized and Locally Advanced Atypical Lung Carcinoids after Complete Resection: A Joined French-Italian Retrospective Multicenter Study

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Keywords
Atypical carcinoids · Neuroendocrine tumor · Recurrence · Surgery · Survival

Abstract
Background: The natural history and the best modality of follow-up of atypical lung carcinoids (AC) remain ill defined. The aim of this study was to analyze recurrence-free survival (RFS) after complete resection (R0) of stage I–III pulmonary AC. Secondary objectives were prognostic parameters, the location of recurrences, and the modality of follow-up. ***Methods:*** A retrospective review of 540 charts of AC patients treated between 1998 and 2008 at 10 French and Italian centers with experience in lung neuroendocrine tumor management was undertaken. The exclusion criteria were MEN1-related tumor, history of another cancer, referral after tumor relapse, and being lost to follow-up. A central pathological review was performed in each country. ***Results:*** Sixty-two patients were included. After a median follow-up time of 91 months (mean 85, range 6–165), 35% of the patients experi-

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enced recurrence: 16% were regional recurrences and 19% were distant metastases. Median RFS was not reached. The 1-, 3-, and 5-year RFS rate was 90, 79, and 68%, respectively. In univariate analysis, lymph node involvement ($p = 0.0001$), stage ($p = 0.0001$), mitotic count ($p = 0.004$), and type of surgery ($p = 0.043$) were significantly associated with RFS. In multivariate analysis, lymph node involvement was significantly associated with RFS (HR 95% CI: 0.000–0.151; $p = 0.004$). During follow-up, somatostatin receptor scintigraphy, fibroscopy, and abdominal examination results were available for 22, 12, and 25 patients, respectively. The median time interval for imaging follow-up was 10 months. ***Conclusions:*** After complete resection of AC, recurrences were observed mostly within the first 5 years of follow-up, within bronchi, mediastinal nodes, the liver, and bones. In R0 patients, lymph node involvement could help to stratify follow-up intervals. Suboptimal imaging is evidenced.

Introduction

Lung neuroendocrine tumors (NETs) originate from neuroendocrine cells of the bronchoalveolar structures [1]. These tumors represent a broad clinicopathologic spectrum that translates into highly variable outcomes, best stratified according to the WHO classification and TNM staging [2–4]. Based on cell size, mitotic count, and necrosis, the WHO pathological classification recognizes four distinct subgroups that correspond to different outcomes: low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), and high-grade large cell neuroendocrine carcinoma (LCNEC), or small cell lung carcinoma (SCLC). From an epidemiological point of view, primary carcinoid tumors of the lung are rare, accounting for 0.5–3% of resected lung cancers. SCLC constitutes the most prevalent subgroup of lung neuroendocrine neoplasms (NENs) (15–20%), followed by LCNEC (3%), TC (2%), and AC (0.2%) [5, 6]. Based on TNM staging, the four subgroups TC, AC, LCNEC, and SCLC are characterized by an increase in the risk of lymph node or distant metastases at diagnosis [2, 4, 5].

Surgery is the only curative treatment modality for well-differentiated TC and AC. Once complete resection has been achieved, long-term follow-up should be engaged [6, 7]. However, the best modality of surveillance in terms of type and frequency remains ill defined. TC exhibits a good prognosis, as characterized by a 5-year survival rate of >90% in the majority of patients [8–10]. In contrast, AC exhibits a more aggressive course, with 5-year survival rates ranging from 56 to 87% (lower in lymph node-positive tumors, suggesting that this subgroup may benefit from an adjuvant strategy) [9–27].

Several studies, comprising a total number of 960 patients, have analyzed the clinical presentation and prognosis of AC after surgery. However, R status, WHO classification criteria (later than 2004), and/or the modality of follow-up, as well as the rate of recurrence, were reported in three studies only [10, 21, 26].

The aim of this study was to evaluate recurrence-free survival (RFS) from AC of the lung after complete resection (R0) in patients followed up in Italian and French lung NET referral centers. Secondary objectives were to look for prognostic parameters, the location of recurrences, and the modality of follow-up.

Patients and Methods

Study Design

A retrospective review of the files of AC patients treated between 1998 and 2008 was conducted in 4 French (Institute Gustave Roussy, Villejuif; Foch Hospital, Suresnes; Surgical Center, Marie Lannelongue Hospital, Le Plessis-Robinson; University Hospital Rennes Pontchaillou, University of Rennes, Rennes) and 6 Italian centers ("Federico II" University Hospital and "Antonio Cardarelli" Hospital, Naples; "Santa Maria della Misericordia" University Hospital, Udine; "Città della Salute e della Scienza" University Hospital, Turin; Multidisciplinary Group for Diagnosis and Treatment of Neuroendocrine Tumors-Umbria Regional Cancer Network, Perugia; Mediterranean Institute of Oncology, Viagrande). The inclusion criteria were: (1) pathological diagnosis of AC "on site" according to the WHO 2015 classification, as reviewed by a single expert pathologist in each country (J.-Y.S. for the 46 French specimens and M.P. for the 8 Italian specimens) [2]; (2) complete resection of the primary tumor (no microscopic involvement of the margins was found on pathological examination) [28]; and (3) tumor stage I–III according to the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM staging system [3–5]. The exclusion criteria were: (1) MEN1-related tumor, in order to avoid misdiagnosis with mediastinal or abdominal spread from other NET primaries; (2) history of another cancer; (3) referral at the time of tumor relapse; and (4) being lost to follow-up.

All patient charts reporting tumors locally classified as AC were collected and centrally reviewed by one investigator (F.M.) on site. The following parameters were obtained at the time of surgery, as described in Table 1: age, gender, smoking habits (smoker or nonsmoker), presenting symptoms (tumor-related symptoms, hormone-related symptoms, and incidentaloma), tumor location (right or left lung), primary size (expressed in millimeters), and TNM stage (I, II, or III), as well as patient outcome and status as of December 31, 2011.

The pathological specimens were reviewed by two expert pathologists (J.-Y.S. for the French specimens and M.P. for the Italian specimens) to confirm the diagnosis of AC and evaluate the proliferative index. The mitotic count was recorded as defined by

Table 1. Patient characteristics

Patients	62
Gender	
Male	34
Female	28
Mean age ± SD (range), years	56±17 (17–81)
Smoking status	
Nonsmoker	33 (53%)
Smoker	29 (48%)
Symptoms	
Incidentaloma	24 (39%)
Tumor related	36 (58%)
Hormone related	2 (3%)
Preoperative bronchoscopy	
Not done	10 (16%)
Positive	41 (66%)
Negative	11 (18%)
Preoperative somatostatin receptor scintigraphy	
Not done	50 (81%)
Positive	9 (14%)
Negative	3 (5%)
Surgery	
Wedge resection	4 (6.5%)
Lobectomy	47 (76%)
Bilobectomy	9 (14.5%)
Pneumonectomy	2 (3%)
Lymph node dissection	
Not done	1 (1.6%)
Systematic node dissection	39 (62.9%)
Lobe-specific node dissection	14 (22.6%)
Picking	8 (12.9%)
Tumor location	
Left lung	40 (64.5%)
Right lung	22 (35.5%)
TNM classification	
Tx	1 (1.6%)
T1	27 (43.5%)
T2	28 (45.2%)
T3	5 (8.1%)
T4	1 (1.6%)
Nx	1 (1.6%)
N0	40 (64.5%)
N1	15 (24.2%)
N2	6 (9.7%)
Stage I	35 (56%)
Stage II	19 (31%)
Stage III	7 (11%)
Mitosis	
Unknown	7 (11%)
1 mitosis/10 HPF (with necrosis)	4 (6%)
2 mitoses/10 HPF	15 (24%)
3 mitoses/10 HPF	20 (32%)
4 mitoses/10 HPF	3 (5%)
5 mitoses/10 HPF	5 (8%)
6 mitoses/10 HPF	4 (6%)
10 mitoses/10 HPF	1 (2%)
>10 mitoses/10 HPF	3 (5%)
Median number of mitoses/10 HPF	3
Recurrences (first site)	
Total	22 (35%)
Regional	10 (16%)
Bronchial	6 (60%)
Lymph node	4 (40%)
Distant metastasis	12 (19%)
Liver	7 (58%)
Bone	1 (8%)
Brain	1 (8%)
Thyroid	1 (8%)
Lung (contralateral)	1 (8%)
Adrenal gland	1 (8%)

the number of mitoses/10 HPF, which corresponded to a final surface of 2 mm^2. In accordance with recent suggestions showing that in G3 gastroenteropancreatic NETs morphology is a critical determinant of tumor behavior, cases with >10 mitoses/10 HPF but with well-differentiated morphology were not excluded [29–32].

Modality of Follow-Up

The frequency and type of imaging procedures performed before surgery and during follow-up were recorded, including chest and/or abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scans, brain and/or bone MRI, abdominal ultrasound, bronchial fibroscopy, and nuclear medicine imaging including ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), ^{111}In-pentetreotide scintigraphy (somatostatin receptor scintigraphy [SRS]), and bone scintigraphy. The interval of time between each imaging monitoring was also recorded.

Statistical Analysis

The statistical analyses were performed by SPSS for Windows version 20.0 (SPSS, Inc., Chicago, IL, USA). The survival analysis was performed using the Kaplan-Meier method with log-rank testing. RFS was defined from the time of surgery to the time of first evidence of recurrence on imaging or the last imaging follow-up. The following prognostic parameters were considered: tumor size, T status (Tx, T1, T2, T3, or T4), N status (Nx, N0, N1, or N2), TNM stage (I, II, or III), mitotic index (as defined by the median), presence of necrosis (yes or no), type of surgery (lobectomy, bilobectomy, pneumonectomy, or wedge resection), and lymph node dissection (yes or no). The results of the statistical analyses of continuous variables are presented as the mean ± SD or median and 95% CI; the categorical variables are expressed as the number of cases and percentage (%). A statistically significant difference was predetermined to be a p value <0.05. For the multivariate analysis, a Cox regression model with forward stepwise selection of covariates was used. Due to the small sample size, it

was anticipated that the number of events divided by 10 would provide an acceptable number of parameters for the multivariate analysis.

Results

Patient and Tumor Characteristics

The files on 540 patients classified as having lung AC were reviewed. The following exclusion criteria were applied: WHO reclassification (8 patients reclassified as having TC or combined LCNEC/SCLC), MEN1-related tumor (16 patients), distant metastases at the time of diagnosis (194 patients), primary origin other than the lung (27 patients), surgical management in other centers (54 patients), tumor deemed unresectable (86 patients), incomplete resection (Rx, R1, or R2; 81 patients), and lost to follow-up (12 patients).

Therefore, a total of 62 patients formed the basis of this study. The pathological material was centrally reviewed in each country; however, due to difficulties in collecting all pathological specimens, 8 cases underwent local review only. The patient and tumor characteristics are summarized in Table 1. In brief, the male-to-female ratio was 1:1. The mean age at surgery was 56 ± 16 years. Thirty-three patients (53%) were nonsmokers. The most common presentation was associated with tumor-related symptoms (58%) or was incidental (39%). The surgical procedure used most often was lobectomy (76%); lymph node dissection was performed on 98% of the patients, including systematic node dissection (resection of hilar, intrapulmonary, and mediastinal lymph nodes) in 63% of the cases. Three patients underwent neoadjuvant treatment, since they had initially been classified as having a high-grade tumor by the biopsy specimen but were finally classified and confirmed as having AC by the surgical specimen. No surgery-related death was observed, whereas postoperative complications (pneumonia, air leak from thoracotomy tubes for >7 days postoperatively, lobar collapse on postoperative chest radiography, myocardial infarction, arrhythmia, and empyema) occurred in 6% of the patients. Primary tumor diameters ranged from 8 to 80 mm (median 30, mean 31.4 ± 16.1). The median mitotic index was 3 mitoses/10 HPF (range 1–26 mitoses/10 HPF).

In 3 cases, the diagnosis of AC was made despite a mitotic index of >10 mitoses/10 HPF but confirmed well-differentiated morphology after review based on the following criteria: organoid architecture; presence of a dense, well-organized vascular network; necrosis absent or only spotty; tumor cells containing nuclei with "salt and pepper" chromatin and small nucleoli; and absence of the nuclear characteristics suggestive of LCNEC (including dispersed chromatin and large nucleoli). In these cases, the mitotic index was between 11 and 26 mitoses/10 HPF. According to the UICC TNM classification, most patients were T1 (27 patients, 44%) or T2 (28 patients, 45%). Nodal involvement was found in 21 patients (34%): 15 (24.2%) were N1 and 6 (9.7%) were N2; 1 patient (1.6%) was Nx. As for the TNM stage, 35 patients (56%) were classified as stage I, 19 patients (31%) as stage II, and 7 patients (11%) as stage III. The median overall survival was not reached. The 1-, 3-, and 5-year survival rate was 95, 92, and 83%, respectively. Twelve patients (19%) died during the follow-up period, due to tumor progression.

Imaging and Follow-Up Procedures

Before surgery, all patients (100%) had undergone thoracic CT; thoracoabdominal CT had been performed on 39 patients (63%). Preoperative SRS had been performed on 11 patients (18%), with positive results for 8 patients (73%), while ^{18}FDG-PET had been performed on 9 patients (14.5%), with positive results for 1 patient (11%). Preoperative bronchial fibroscopy had been performed on 52 patients (84%), with positive results for 41 patients (79%). Of the 23 patients who had not undergone abdominal CT before surgery, 5 had undergone SRS and 16 abdominal ultrasound. The 2 patients who had not had any abdominal preoperative staging remained free of recurrence in the abdomen during follow-up. Follow-up was performed by annual chest CT alone for 37 patients (60%) and by chest plus abdominal CT for 25 patients (40%). Twenty-two patients (36%) underwent at least one SRS during follow-up. Bronchial fibroscopy was repeated in 12 patients (19%) during follow-up. Considering all modalities of follow-up (conventional imaging, SRS, and fibroscopy) according to the current guidelines only, 16% of our patients experienced an appropriate follow-up. The median time between surgery and the first imaging follow-up was 6 months (range 0–13). The median interval of time for imaging follow-up was 10 months (range 1–26).

RFS and Prognostic Parameters

After a median follow-up time of 91 months (mean 85, range 6–165), 22 recurrences (35%) were observed. Regional recurrences occurred in 10 patients (16%), either within the bronchi (6 patients, 60%) or within the lymph nodes (4 patients, 40%); distant metastases occurred in 12 patients (19%), either in the liver (7 patients) or in other organs (5 patients).

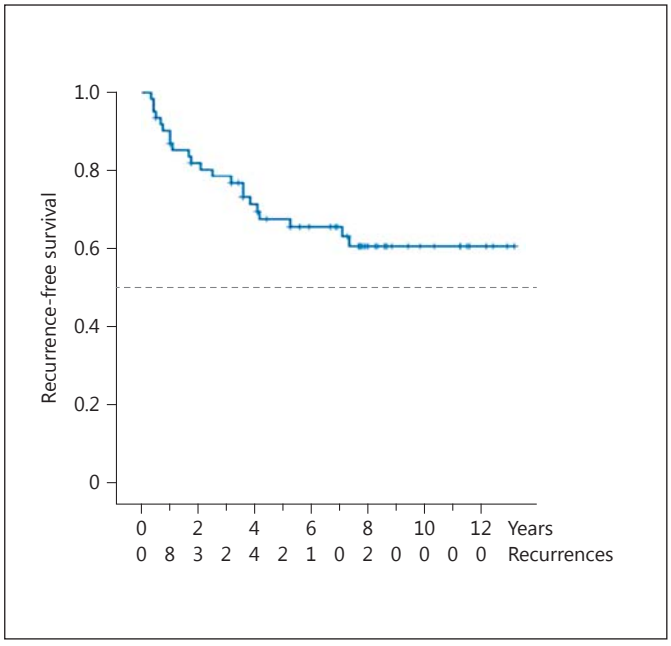

Fig. 1. Cumulative recurrence-free survival among patients with nonmetastatic, completely resected atypical carcinoids of the lung.

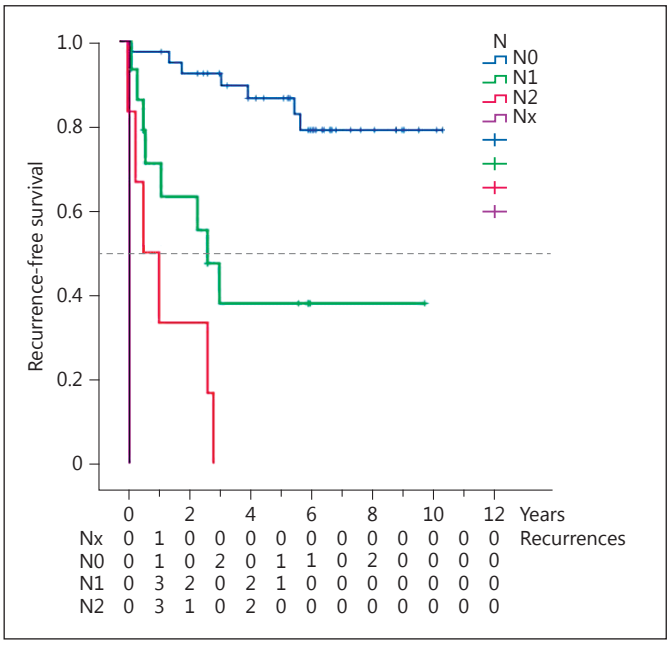

Fig. 2. Recurrence-free survival according to lymph node involvement (N status).

The median time to recurrence from surgery was 23 months (mean 31, range 4–88). Out of 22 patients, 19 (86%) experienced recurrence within 5 years after surgery (8 before 1 year, 5 before 3 years, and 6 before 5 years). Three patients (14%) had distant metastases after 5 years. Median RFS was not reached (Fig. 1). The 1-, 3-, and 5-year RFS rate was 90, 79, and 68%, respectively. With regard to the 8 patients who experienced recurrence within the first year (36% of all recurrences), all had performed preoperative staging by thoracoabdominal CT; 6 underwent lobectomy/bilobectomy, 1 pneumonectomy, and 1 wedge resection. All but 1 had lymph node resection. Seven of the 8 patients had lymph node involvement. All 8 patients had follow-up with thoracoabdominal CT, which detected 4 regional and 4 distant metastases. As regards the 10 patients who experienced regional recurrences, 8 underwent lobectomy/bilobectomy and 9 lymph node resection.

Statistical Analysis

In univariate analysis, the following parameters were found to be significantly associated with RFS: lymph node involvement ($p = 0.0001$), TNM stage ($p = 0.0001$), median mitotic count ($p = 0.004$), and type of surgery ($p = 0.043$) (Table 2).

RFS was significantly higher among N0 patients (rate of recurrence 17.5%; median not reached) than among N1 (rate of recurrence 53%, median 43 months, 95% CI 25.815–60.185) or N2 patients (rate of recurrence 100%, median 12 months, 95% CI 0.000–26.403) (Fig. 2). Median RFS was significantly higher among stage I patients (median not reached) than among stage II (median 85 months) and stage III patients (median 20 months, 95% CI 0.000–40.53).

Median RFS was significantly higher among patients whose tumors had a mitotic count ≤3 mitoses/10 HPF (median not reached) than among those with mitotic counts >3 mitoses/10 HPF (median 49 months, 95% CI 39.529–58.471). Median RFS was significantly ($p = 0.043$) higher among patients who underwent lobectomy and bilobectomy (median not reached) than among those undergoing pneumonectomy (median 5 months) and wedge resection (median 46 months, 95% CI 0.000–107.376).

The 5-year RFS rates among patients with N0, N1, or N2 status and mitotic counts below the median were 93, 53, and 0%, respectively. The 5-year RFS rates among patients with N0, N1, or N2 status and mitotic counts above the median were 71, 27, and 0%, respectively.

In multivariate analysis, lymph node involvement (N status according to TNM classification) was the only pre-

Table 2. Significant prognostic factors for RFS in univariate analysis

Parameters	Patients, *n*	Median RFS, months	95% CI	*p* value
Lymph node involvement				<0.0001
N0	40	not reached	–	
N1	15	43	25.815–60.185	
N2	6	12	0.000–26.403	
Stage				<0.0001
I	35	not reached	–	
II	19	85		
III	7	20	0.000–40.53	
Mitotic count				0.004
≤3 mitoses/10 HPF	39	not reached	–	
>3 mitoses/10 HPF	16	49	39.529–58.471	
Surgery				0.043
Bilobectomy/lobectomy	9/47	not reached	–	
Pneumonectomy	2	5		
Wedge resection	4	46	0.000–107.376	
Lymph node dissection				<0.0001
Not done	1	5		
Systematic	39	not reached	–	
Lobe specific	14	not reached	–	
Picking	8	not reached	–	

RFS, recurrence-free survival.

dictor of RFS (HR 95% CI 0.000–0.151, $p = 0.004$). Table 3 shows the 1-, 3-, and 5-year RFS rates according to the different prognostic parameters.

Discussion

Given the rarity of pulmonary AC, the current data do not allow to precisely define its natural history and the best modality of follow-up according to WHO and TNM classifications of these patients. Our study provides data not only on rates of recurrence, locations, and prognostic factors influencing RFS after complete AC resection, but also on the best modalities of follow-up. Design of adjuvant trials is expected to benefit from these results.

Our patient population showed similarities concerning gender distribution, age, symptoms, and smoking habit to patient populations of previous reports [12, 13, 33–35]. The 5-year survival rate in this study was 83%, and RFS was at the upper end of the range of previous studies (Table 4). This finding may be explained by the R0-based selection of patients and the high rate of routine lymph node dissection [23, 25–27]. The majority of recurrences occurred during the first 5 years of follow-up, but the modalities of follow-up were found to be clearly suboptimal, both in terms of the time interval between control checkups and the type of examinations, suggesting the need to improve both baseline and follow-up imaging modalities.

The population under study benefitted from an optimized surgical approach, as demonstrated by the high frequency of systematic lymph node dissections. In addition, due to the R0 patient selection, most patients were N0 and the median mitotic count was at the low end of the AC spectrum. The first striking result of our study is a suboptimal staging procedure at diagnosis, as well as a suboptimal modality of follow-up. Indeed, at baseline, abdominal CT was performed on 63% of the patients, but liver MRI, the most sensitive modality of detection of liver and bone metastases, not on a single patient and the reference modality (SRS) on 18% of the patients only. Implementation of the recent recommendations (ENETS 2015) for the staging of carcinoids is urgently required at least for patients with preoperative presentation with carcinoid tumors [7].

Recurrences were observed in 35% of the population, which is at the low end of the range of previous studies. Again, the modality of imaging for follow-up was found

Table 3. One-, 3-, and 5-year recurrence free-survival rates according to significant prognostic parameters in univariate analysis

	Recurrence free-survival rate		
	1 year	3 years	5 years
Lymph node involvement			
N0	97%	97%	89.5%
N1	79%	63%	38%
N2	50%	33%	0%
Nx	0%	0%	0%
Stage			
I	94%	91%	88%
II	84%	68%	55%
III	57%	43%	0%
Mitotic count			
≤3 mitoses/10 HPF	92%	87%	81%
>3 mitoses/10 HPF	87%	74%	42.5%
<5 mitoses/10 HPF	90.5%	86%	80%
≥5 mitoses/10 HPF	92%	75.5%	39%
Surgery			
Lobectomy	89%	78.5%	69%
Bilobectomy	89%	89%	76%
Pneumonectomy	0%	0%	0%
Wedge resection	75%	75%	37.5%
Nodal dissection			
Not done	0%	0%	0%
Picking	100%	100%	86%
Systematic	84%	76%	64%
Lobe specific	93%	78%	70%

to be suboptimal for 84% of the patients, considering conventional scintigraphic imaging as well as fibroscopy. First, the median interval of 10 months until the first imaging follow-up is too long in this aggressive-tumor subgroup of patients, and, as stated in recent recommendations, an interval of 3–4 months should be preferred during the first 3–5 years. Second, based on the demonstration that the bronchi, mediastinal lymph nodes, liver, and bone are the major sites of recurrence or spread, imaging workup should include bronchial endoscopy and thoracoabdominal investigation combining both conventional imaging and scintigraphy, which had been routinely performed in only 19, 40, and 8% of the cases, respectively. In addition, the role of SRS in such a setting requires urgent clarification. The ENETS/NANETS recommendations – which advocate a follow-up with CT imaging 3 months after surgery and then every 6 months for 5 years, as well as somatostatin receptor imaging at 1 year and then when a recurrence is suspected, and finally bronchoscopy every 1–3 years – should be rapidly implemented at all centers [7, 36]. Indeed, expression of somatostatin receptors has been demonstrated in lung NET [37, 38]. On this basis, recent series, using ^{68}Ga-DOTANOC-PET and DOTATATE-PET, showed promising results in patients with lung NET [39, 40].

With regard to RFS, WHO classification (AC vs. TC) and pTNM staging are well-known prognostic parameters for bronchial carcinoids [11, 26, 41, 42]. The majority of the studies evaluated heterogeneous series of patients affected by lung NET, without investigating specific prognostic factors for each histotype [9–12, 14–20, 22, 24, 26, 27]. In the few studies that focused on AC populations, prognostic factors for overall survival rather than for recurrence- or disease-free survival have been evaluated [12, 13, 16, 20, 21, 23, 43]. To the best of our knowledge, only Filosso et al. [25] analyzed disease-free survival in a group of exclusively AC patients, finding that the variables influencing disease-free survival in univariate analysis were male gender, age, and pT4 tumors. We confirm the major role of pTNM staging, since in multivariate analysis, lymph node involvement was the most important prognostic factor for RFS in our study. Indeed, the RFS rates at 5 years for N0, N1, and N2 patients were 89.5, 38, and 0%, respectively, suggesting that in R0 N-positive AC, patients may benefit most from future adjuvant therapy. The low RFS of N1 AC patients should be underlined, suggesting that adjuvant therapy should be discussed for both N1- and N2-positive AC patients.

Furthermore, several additional parameters such as mitotic count may help to refine future prognostic subclassification of N1 AC patients who may also benefit from adjuvant therapy. In our study, the 5-year RFS rate among patients with N0 status and a mitotic count of ≤3 mitoses/10 HPF was 93%, but it was 71% when the mitotic count was >3 mitoses/10 HPF, suggesting that the mitotic count – or, more generally, the proliferative index – is a useful adjunct to pTNM staging to further stratify the outcomes of these patients. The low number of patients, as well as the selection criterion of R0 AC, probably explains the absence of statistically significant results for the mitotic count in our study.

The recommended surgery in AC is lobectomy with systemic node dissection, since lymph node metastases are found in >30% of cases. In the current study, pneumonectomy and wedge resection were associated with a worse RFS than lobectomy/bilobectomy, which may be related to a more advanced tumor stage. In all patients, pulmonary function should be spared.

One limitation of our study is due to the fact that a few patients with well-differentiated tumors and mitotic

Table 4. AC recurrence-free survival rates in previous studies

First author, year [Ref.]	Patients, *n*		Follow-up range	5-year survival rate	10-year survival rate	N status (in AC patients)	Recurrence rate (in AC patients only)
	total	AC					
Filosso, 2002 [9]	126	44	6–282 months	77%	52%	7 N1; 7 N2	19.5% (distant)
Srirajaskanthan, 2009 [10]	45	9	6–360 months[a]	62%	–	–	100%[b] (75% regional; 25% both)
Ferguson, 2000 [11]	139	26	1–149 months[a]	70%	–	–	20%
García-Yuste, 2000 [12]	304	43	–	72%	43%	6 N1; 4 N2	23% (2% regional; 21% distant)
Fink, 2001 [13]	142	14	–	75%	56%	4 N1; 2 N2; 2 N3	–
Filosso, 2014 [14]	157	35	6.5 years[d]	58%	38%	5 N1; 8 N2	57% (8.6% regional; 48.6% distant)
Mezzetti, 2003 [15]	98	10	–	71%	60%	3 N1; 2 N1	–
Cardillo, 2004 [16]	163	42	6–150 months	70%	–	18 N1; 9 N2	–
Asamura, 2006 [17]	318	9	2–129 months[a]	78%	–	2 N1; 2 N2	33% (11% regional; 22% distant)
Rea, 2007 [18]	252	78	6–432 months[a]	–	64%	13 N1; 9 N2	18%
Ferolla, 2009 [19]	123	23	6–276 months	72%	57%	3 N+	26% (distant)
Machuca, 2010 [20]	126	16	3–396 months[a]	56%	47%	4 N1; 3 N2	20%
Pusceddu, 2010 [21]	91	25	–	76%	18%	–	65%[c]
Aydin, 2011 [22]	104	20	6–190 months[a]	73%	46%	11 N+	20%
Daddi, 2014 [23]	247	247	25–64 months	87%	72%	36 N1; 27 N2; 1 N3	25%
Correia, 2014 [24]	59	6	0–144 months[a]	67%	–	3 N+	–
Filosso, 2015 [25]	261	126	1–304 months	77%	–	4 Nx; 24 N1; 16 N2[d]	–
Maurizi, 2014 [26]	65	10	2–121 months[a]	87%	–	–	–
Stolz, 2015 [27]	137	42	–	71%	62%	8 N1; 8 N2	–
Present series	**62**	**62**	**6–165 months**	**83%**	**60%**	**15 N1; 6 N2**	**35% (16% regional; 19% distant)**

AC, atypical carcinoid. [a] Cumulative data by different histotypes. [b] Out 9 patients, 4 underwent surgery; all these patients experienced relapse. [c] 13 of 20 patients who underwent surgery. [d] Median.

counts >10 mitoses/10 HPF were classified as having AC even if they did not strictly adhere to the WHO definition. As previously shown by us and other teams in G3 gastroenteropancreatic NENs, patients with high proliferative indices express different tumor behavior according to its morphology [29–32]. Heetfeld et al. [29] reported for a large retrospective, well-characterized cohort of G3 gastroenteropancreatic NEN patients that morphology was more informative than proliferative activity (expressed as Ki-67 index) for stratifying patient outcomes. Moreover, Basturk et al. [30] recognized that patients with grade-discordant, well-differentiated G2 pancreatic NET (mitotic count G2/Ki-67 index G3) showed no statistically significant difference in survival time from patients with grade-concordant pancreatic NET (both mitotic count and Ki-67 index G2) but had significantly longer survival than patients with poorly differentiated NEC. Formerly, Vélayoudom-Céphise et al. [31] proposed a new classification for G3 NEN according to morphological differentiation on the basis of their study, which showed, also with thoracic NEN, a significantly better overall survival with well-differentiated G3 NET than with poorly differentiated LCNEC. More recently, Milione et al. [32] performed a study on mitotic count and showed that the cutoff of 30 mitoses was the best predictor of overall survival in G3 gastroenteropancreatic NEN, and that a well-differentiated tumor morphology is an independent prognostic factor for GEP NEN with a Ki-67 index between 20 and 55%.

Another limitation of our study is that all lung NENs could not be pathologically reviewed on site. Therefore, we cannot affirm the completeness of our study regarding the AC case collection. In addition, due to the retrospective design of our study, we could not achieve a pathological review of all AC cases. Indeed, 8 AC cases were not centrally analyzed. It should be noted that few cases were reclassified into another pathological lung neoplasm category during the review process. For that reason and due to the extreme scarcity of AC, we have not excluded these cases.

In conclusion, we found that following complete resection of AC, 35% of the patients experienced recurrences, both at regional and distant sites, after a median follow-up of 91 months. Also, the utilization of imaging procedures during follow-up was suboptimal. Finally, lymph node-positive patients should be the targeted population for future adjuvant protocols.

Acknowledgements

The study was supported by a grant from Ipsen; however, the authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. F.M. was also supported by the Associazione Italiana Tumori Neuroendocrini (A.I.NET). We are thankful to our colleagues who provided expertise that greatly assisted our research; in particular, we thank Dr. Lucia Beneduce, Dr. Giusi Blanco, and Dr. Valeria Ramundo for their support in data collection. We are also grateful to Prof. Philippe Dartevelle and Prof. Guglielmo Monaco for sharing their invaluable wisdom and experience with us during the course of this work.

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