ORIGINAL ARTICLE

Preoperative Biopsy Diagnosis in Pulmonary Carcinoids, a Shot in the Dark

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ABSTRACT

Introduction: The preferred treatment for pulmonary carcinoids (PCs) is lobectomy, and parenchyma-sparing approaches might be considered for typical carcinoids (TCs). Treatment decisions are based on a preoperative biopsy diagnosis. Following the WHO criteria (2015), definitive diagnosis is only feasible postoperatively, thereby hampering preoperative treatment decisions. Here, we determined whether the final carcinoid classification on a resection specimen can be predicted by a preoperative biopsy.

Methods: We searched all stage I to III patients with a final carcinoid diagnosis who underwent a curative resection and of whom both a preoperative biopsy and paired resection specimen were available (2003-2012) using the Dutch Pathology Registry (PALGA) and the Netherlands Cancer Registry (IKNL). Pathology report conclusions of the biopsy-resection specimen were compared.

Results: Paired biopsy-resection specimens in combination with clinical data were available from 330 patients. 57% (189 of 330) of the patients exhibited discordance between the preoperative biopsy and paired resection diagnosis, including 36% (44 of 121) preoperatively diagnosed TC, 40% (six of 15) atypical carcinoid (AC), and 65% (103 of 158) not-otherwise-specified (NOS) carcinoids. A quarter of preoperatively diagnosed TC and NOS was reclassified as AC on the resection specimen. Preoperatively diagnosed ACs exhibited the highest relapse rates (40%, 6 of 15). Preoperatively diagnosed TC and NOS patients who were reclassified as ACs exhibited higher relapse rates as compared to nonreclassified TCs and NOS (3% versus 1%, and 16% versus 6%).

Conclusions: We provide evidence that carcinoid classification on preoperative biopsies is imprecise, as is also stated by the current WHO classification. We advise

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clinicians to interpret the preoperative biopsy diagnosis with caution in deciding the extent of surgery (e.g., parenchyma-sparing versus non–parenchyma-sparing).

Keywords: Pulmonary; Neuroendocrine; Carcinoid; Biopsy; Classification

Introduction

Pulmonary carcinoids (PCs) represent a subgroup of lung cancer that, together with large cell neuroendocrine (NE) carcinoma and small cell lung cancer, are referred to as pulmonary NE neoplasms.[1] Following the WHO 2015 classification, PCs can be classified into low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) on the basis of the mitotic count (TC 0–1 and AC $\geq$2–10 mitoses per 2 mm^2) and the presence of necrosis (AC).[1] Although carcinoids have a relatively indolent behavior, they may invade and metastasize. In general, ACs are characterized by a more aggressive disease course as compared with TCs because they more often exhibit local disease relapse and have a higher propensity to metastasize.[2] The preferred treatment for local-regional carcinoid disease is surgery.[2] Parenchyma-sparing strategies, such as sublobar or endobronchial resection, may be considered for TC, whereas lobectomy is advised for AC.[3–13] These treatment decisions are based on a pathological diagnosis obtained from a preoperative tumor biopsy. WHO 2015 criteria have provided new criteria for the diagnosis of lung cancer on the basis of small biopsies and cytology, notwithstanding criteria for PCs are still lacking. It is advised to use the Ki67 labeling index to avoid misdiagnosing carcinoid tumors as high-grade NE tumors. However, the use of this marker to discriminate TC from AC or to predict prognosis within the individual carcinoid tumor categories is not yet established.[1,14] Therefore, definitive diagnosis of TC or AC is only feasible postoperatively, which hampers preoperative treatment decisions on the basis of histologic subtypes. Even though PCs are often diagnosed on a biopsy specimen in current practice, the diagnostic accuracy of pulmonary biopsies has not been thoroughly investigated. Hence, we analyzed all carcinoid diagnoses established in the Netherlands between January 2003 and December 2012, using both the Dutch Pathology Registry (PALGA) and the Netherlands Cancer Registry (IKNL), and we compared the postoperative diagnoses with the diagnoses determined on the preoperative biopsy specimens.

Methods

Selection of Cases

All data for this study were retrospectively retrieved from PALGA,[15] the nationwide network and registry of the histopathologic and cytopathologic specimen in the Netherlands, and the IKNL. The study protocol was approved by the medical ethical committee of Maastricht University Medical Centre (METC 16-4-106) and was performed according to the Dutch Federa Human Tissue and Medical Research: Code of Conduct for Responsible Use 2011 regulations not requiring patient informed consent. Written pathology report conclusions describing PC, TC, or AC diagnosed between January 1, 2003 and December 31, 2012 were retrieved.

All nationwide available pathologic diagnoses for each individual patient were gathered by searching PALGA from less than or equal to 15 years after and before the first carcinoid diagnosis updated until January 1, 2017. Subsequently, all pathology report conclusions were screened by two researchers (Drs. Bunnik and Derks). Cases without a definitive PC diagnosis were excluded (such as high-grade NE carcinoma, non-NE tumor, NE tumor of nonpulmonary origin). PALGA data were coupled to clinical data from the IKNL, and only patients with stage I to III carcinoid tumor who underwent curative resection were selected. Subsequently, patients with both a pathology conclusion on the preoperative biopsy (transbronchial, endobronchial, or needle) and the resection specimen available were selected and included in this study (Fig. 1).

Assessment of Pathologic Diagnosis

Diagnoses based on the prevailing WHO criteria, without central pathological review, of both the biopsy specimen and resection specimen from the included patients, were clustered into subgroups by applying the criteria listed in Table 1 (TC, AC, not-otherwise-specified [NOS]), high-grade NE carcinoma (HGNEC), and other. Patients with carcinoid or NE tumor (NET) and grade 1 or typical were included in the TCs cluster. Patients with carcinoid or NET and grade 2 or atypical were allocated to the AC group. All other patients with carcinoid or NET but no or unclear further differentiation were grouped as carcinoid NOS. All cases with NE carcinoma (small cell or large cell), high-grade or poorly differentiated, were allocated to the HGNEC group. All other cases were allocated to the other cluster (Table 1). In case a revision of the initial diagnosis was performed (i.e., a second opinion was provided), the revised diagnosis was used in the analysis.

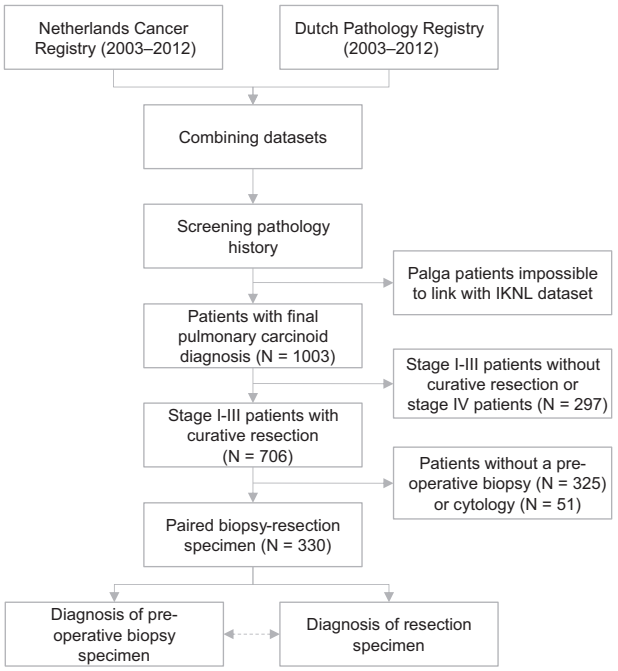

Figure 1. Flowchart presenting an overview of the selection procedure of conclusions from pathology reports leaving 330 combined biopsy resection specimens.

Pathological and Clinical Data

The following data were extracted from PALGA: tumor sampling location (e.g., lung, liver, lymph node), diagnosis recorded in conclusion, the origin of the sample (e.g., primary tumor versus metastasis), location of the primary tumor, sampling method, time between biopsy, and resection in days. After extracting information on the sampling method, cases were further subdivided into nonsurgically obtained biopsy specimens (endobronchial and needle) and resection specimens (any surgical resection).

Pathologically confirmed disease relapse was subtracted from the PALGA database. Relapse was defined as any diagnostic report mentioning a carcinoid tumor metastasis (local and distant). Data was last updated for all included patients on January 1, 2017.

Clinical data from IKNL included the year of diagnosis, TNM classification ($\geq$2010 according to the TNM-7 and $\leq$2009 according to the TNM-6 classification), first-line treatment modality, time from biopsy specimen diagnosis to date of resection, disease relapse, and time from date of resection till the relapse date, date of last follow-up, date of second primary cancer with distant metastasis, or death. Clinical follow-up was updated, using the IKNL database, until February 1, 2019.

Data Analysis

The diagnosis of the preoperative biopsy was compared with the diagnosis established on the resection specimen of the paired biopsy and resection specimen for each patient. The resection diagnosis was regarded as the accepted standard. Percentages of correct diagnoses and percentages and nature of false diagnoses on preoperative biopsy are presented. Cases in which the resection diagnosis did not match the biopsy diagnosis were evaluated for the type of biopsy taken and the extent of surgery performed. In addition, we investigated if carcinoid relapse was related to the type of surgical resection. Relapse-free survival (RFS) was defined as the time from initial surgical treatment until disease relapse. Censoring for RFS occurred on the last day of follow-up, death (without evidence of disease based on IKNL and PALGA database), or date of second primary cancer with distant metastases as from this moment onward, further assessment of carcinoid tumor progression was not possible anymore.

Statistical Analysis

Data were analyzed using the descriptive statistics function of IBM SPSS software for Mac version 26 (SPSS, Inc., Chicago, IL). The chi-square test and Fisher's exact test were used to compare categorical data. RFS was

Table 1. Nomenclature Used to Cluster Carcinoid Diagnoses Retrieved From Pathology Conclusions

Clustered Diagnosis	Words Required for Clustering	
	Word 1 (Any of the Following)	And Word 2 (Any of the Following)
Typical carcinoid	Carcinoid, neuroendocrine tumor	Typical, grade I
Atypical carcinoid	Carcinoid, neuroendocrine tumor	Atypical, grade II
Carcinoid NOS	Carcinoid, neuroendocrine tumor	Unsure if typical or atypical, well differentiated, low grade, not otherwise specified
HGNEC[a]	Neuroendocrine (large/non-small cell) Ca, Combined large/small cell Ca	High-grade, Poorly differentiated, intermediate cell type
Other[a]	Ca (large/non-small cell), Adenocarcinoma, Squamous cell carcinoma, Unclear whether Ca or carcinoid, All conclusions with uncertainty (i.e., more than 2 possible differential diagnosis)	(IHC) neuroendocrine features, (IHC) neuroendocrine differentiation, endocrine features

[a]Additional clinical data of both the HGNEC and Other group are provided (see Table 1, Supplementary Data).
Ca, carcinoma; HGNEC, High grade neuroendocrine carcinoma; IHC, Immunohistochemical; NOS, not otherwise specified.

estimated according to the Kaplan-Meier method and tested using the log-rank test. As the median RFS was not reached, we calculated the percentage of patients without disease relapse at 3, 5, and 10 years after surgery. Kaplan-Meier was drawn using R package survminer (version 0.4.2). Two-sided p values less than 0.05 were considered significant.

Results

Selection of Cases

After combining and screening the PALGA and IKNL databases, 1003 unique patients with a final carcinoid diagnosis were retrieved (Fig. 1). Paired biopsy and resection specimens were available for 330 patients. The final diagnosis, based on the resection specimen, was TC in 160 (48.5%) patients, AC in 88 (26.7%) patients, and carcinoid NOS in 82 (24.8%) patients. The median time between the biopsy and resection procedure was 41 days (interquartile range, 27–65 d). Most (94.5%) preoperative biopsy specimens were endobronchial biopsy specimens.

Preoperative Biopsy Diagnosis Versus Resection Diagnosis

Preoperative biopsy diagnoses included TC (36.6%, n =121 of 330), AC (4.5%, n =15 of 330), carcinoid NOS (47.9%, n =158 of 330); furthermore, this cohort of 330 patients included 36 patients with a final carcinoid diagnosis who were preoperatively diagnosed as HGNEC (1.8%, n = 6 of 330) and other (9.1%, n = 30 of 330). In 57% (n = 189 of 330) of the patients the preoperative biopsy specimen diagnosis did not match the paired final diagnosis. This was the case in 36% (n = 44 of 121) of the patients with a preoperative TC diagnosis, 40% (n = 6 of 15) with AC, and 65% (n = 103 of 158) with carcinoid NOS, respectively (Fig. 2*A*). In 24% (n = 29 of 121) of patients with a preoperative TC diagnosis, the final diagnoses on the resection specimen revealed an AC (Fig. 2*A*). In biopsy-diagnosed AC, 40% (n = 6 of 15) were eventually diagnosed as TC on the resection specimen (Fig. 2*A*). From the patients with a preoperative diagnosis of carcinoid NOS, the resection specimen diagnoses revealed TC in 41.8% (n = 66 of 158) of the patients, AC in 23.4% (n = 37 of 158), and 34.8% (n = 55 of 158) remained carcinoid NOS, respectively (Fig. 2*A*). All patients preoperatively diagnosed as HGNEC (n = 6) or other (n = 30) were downgraded to TC (33% [n = 2 of 6], 30% [n = 9 of 30]), AC (67% [n = 4 of 6], 30% [n = 9 of 30]), and carcinoid NOS (40% [n = 12 of 30]) on the resection specimen (Fig. 2*A*).

Type of Treatment

To investigate whether the preoperative biopsy diagnosis may have influenced the extent of surgical treatment, we evaluated the initial surgical treatment per type of preoperative biopsy diagnosis (e.g., TC, AC, carcinoid NOS, HGNEC, other). In 92% (n = 304 of 330) of patients a (bi)lobectomy or pneumonectomy was performed (Table 2). Lobectomy represents a cluster of patients treated with a lobectomy (n = 176 of 274), bilobectomy (n = 60 of 274), and sleeve lobectomy (n = 38 of 274) (Table 2). Wedge or segment resections were performed infrequently in 5% (n = 15 of 330) of the patients, all with a preoperative non-AC diagnosis (TC [n = 7] or carcinoid NOS [n = 8]). In two of these cases, the final diagnosis was AC, whereas four remained carcinoid NOS. In the case of a preoperative AC, HGNEC, or other diagnosis, the treatment was lobectomy or pneumectomy (Table 2).

Relapse of Disease

The median follow-up was 88.6 months (95% confidence interval [CI]: 82.0–95.3). During follow-up, 8% (25 of 330) of the patients revealed relapse of disease (Table 3). This was the case in 3% (n = 5 of 160) of patients with TC, in 19% (n = 17 of 88) of patients with AC, and in 4% (n = 3 of 82) of carcinoid NOS patients, as assessed in the resection specimen (Table 3). 16% (n = 4 of 25) of the patients revealed local relapse whereas 80% (n = 20 of 25) revealed distant relapse. In addition, one patient revealed both local and distant relapse. All patients with preoperatively diagnosed AC who relapsed (n = 6) revealed distant disease relapse, whereas local disease relapse was observed in preoperatively diagnosed TC (n = 2 of 4), NOS (n = 1 of 11), and other (n = 1 of 4). The highest relapse rates were observed in patients with preoperatively diagnosed AC (40%, n = 6 of 15). Preoperatively TCs and NOS patients who were reclassified as ACs revealed higher relapse rates as compared with nonreclassified TCs and NOS (3% versus 1%, and 16% versus 6%, respectively). A total of 88% (22 of 25) of the relapses were observed in patients who underwent lobectomy (Table 3). Nevertheless, no association was observed between lobectomy and relapse of disease ($p = 0.550$).

Relapse Free Survival

Data on RFS were available in 322 patients. A total of 25 patients progressed, and 55 patients died during the study period. An overview of the RFS is provided in Table 4. Patients preoperatively diagnosed with AC revealed a significantly worse RFS compared with patients preoperatively diagnosed with non-AC (e.g., TC

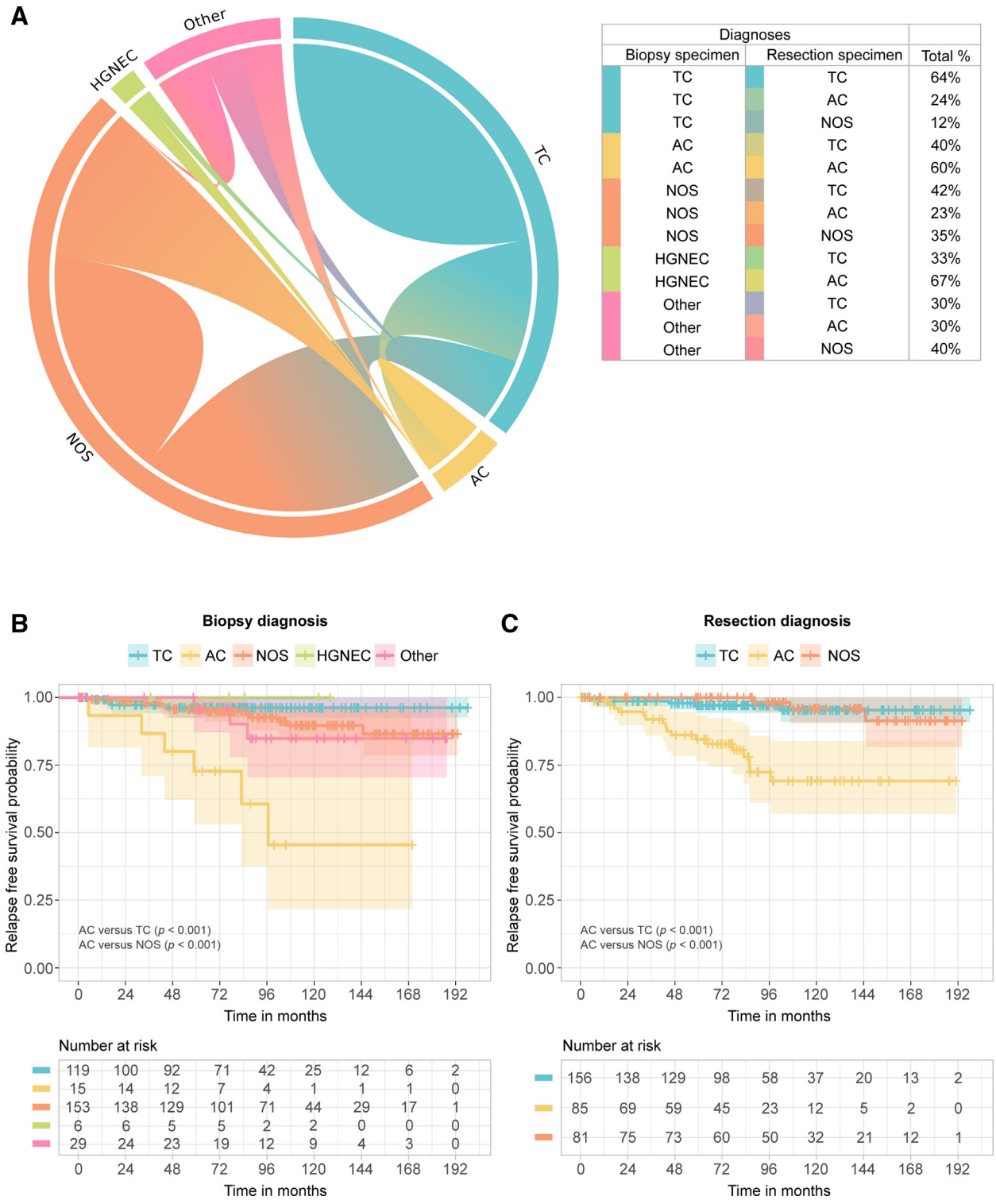

Figure 2. (*A*) Chord diagram illustrating concordance and discordance between the preoperative diagnosis (outer ring) and the corresponding resection specimen diagnosis (inner flows). *(B)* Biopsy specimen diagnosis; Relapse-free survival probability. *(C)* Resection specimen diagnosis; Relapse-free survival probability. AC, atypical carcinoid; HGNEC, high-grade neuroendocrine carcinoma; NOS, not-otherwise-specified; TC, typical carcinoid.

and NOS) (p = 2.02E-7) (Table 4, Fig. 2*B*). Patients postoperatively diagnosed with TC and NOS revealed no significant difference in RFS (p = 0.821), whereas patients postoperatively diagnosed with AC revealed a significantly worse RFS as compared with TC (p = 0.3E-6) and NOS (p = 3.7E-5) patients (Fig. 2*C*).

Table 2. Overview Presenting the Preoperative Diagnosis With the Combined Postoperative Diagnosis and the Corresponding Type of Surgery Performed

Diagnosis		Type of Surgery, N (%)						
Preoperative	Postoperative	Total	Wedge	Segment	Bisegment	Lobectomy[a]	Pneumectomy	Unknown
TC	TC	77 (100)	4 (5)	2 (3)	0 (0)	63 (82)	6 (8)	2 (3)
TC	AC	29 (100)	0 (0)	0 (0)	0 (0)	25 (86)	3 (10)	1 (3)
TC	NOS	15 (100)	0 (0)	1 (7)	0 (0)	13 (87)	1 (7)	0 (0)
AC	TC	6 (100)	0 (0)	0 (0)	0 (0)	6 (100)	0 (0)	0 (0)
AC	AC	9 (100)	0 (0)	0 (0)	0 (0)	8 (89)	1 (11)	0 (0)
NOS	TC	66 (100)	1 (2)	2 (3)	0 (0)	52 (79)	9 (14)	2 (3)
NOS	AC	37 (100)	1 (3)	1 (3)	0 (0)	31 (84)	0 (0)	4 (11)
NOS	NOS	55 (100)	3 (5)	0 (0)	1 (2)	47 (85)	4 (7)	0 (0)
HGNEC	TC	2 (100)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)
HGNEC	AC	4 (100)	0 (0)	0 (0)	0 (0)	2 (50)	2 (50)	0 (0)
Other	TC	9 (100)	0 (0)	0 (0)	0 (0)	7 (78)	2 (22)	0 (0)
Other	AC	9 (100)	0 (0)	0 (0)	0 (0)	8 (89)	1 (11)	0 (0)
Other	NOS	12 (100)	0 (0)	0 (0)	0 (0)	10 (83)	1 (8)	1 (8)
Total		330 (10)	9 (3)	6 (2)	1 (0)	274 (83)	30 (9)	10 (3)

[a]Lobectomy represents a cluster of lobectomy, bilobectomy, and sleeve lobectomy as surgical procedures.
AC, atypical carcinoid; HGNEC, high-grade NE carcinoma; NOS, not-otherwise-specified; TC, typical carcinoid.

Discussion

The WHO 2015 classification of pulmonary NE neoplasms discourages a diagnosis of TC or AC on a biopsy specimen. However, until now, this advice has not been supported by solid clinical data. In this study, we found that, in daily clinical practice, in approximately half of the carcinoid patients (i.e., 57%), a discordance exists between the diagnosis obtained on a preoperative biopsy specimen and the corresponding resection specimen diagnosis. Up to 24% of preoperatively diagnosed (typical) carcinoids were revised to AC on the resection specimen and these patients showed higher relapse rates. These data confirm that the classification of PC tumors on biopsy specimens is challenging in daily practice and that one should be cautious in deciding the extent of surgical resection (e.g., parenchyma-sparing versus lobectomy) on the basis of a preoperatively established carcinoid diagnosis.

Carcinoid diagnosis (i.e., TC versus AC) is currently based on the mitotic index and the presence of necrosis. The assessment of these morphologic features can already be challenging on correctly handled and optimally fixed surgical resection specimens, which makes it considerably harder on small biopsy specimens.[16] In

Table 3. Overview Presenting the Number of Relapses on the Basis of the Preoperative Diagnosis Stratified by Type of Treatment

Diagnosis		Total Cohort	Relapse Cases Per Type of Surgery, N (%)			
Preoperative	Postoperative	Total Cases, N	Lobectomy[a]	Pneumectomy	Unknown	Total Relapses
TC	TC	77	1 (1)	0 (0)	0 (0)	1 (1)
TC	AC	29	1 (3)	1 (3)	1 (3)	3 (10)
TC	NOS	15	0 (0)	0 (0)	0 (0)	0 (0)
AC	TC	6	1 (17)	0 (0)	0 (0)	1 (17)
AC	AC	9	5 (56)	0 (0)	0 (0)	5 (56)
NOS	TC	66	2 (3)	1 (2)	0 (0)	3 (5)
NOS	AC	37	6 (16)	0 (0)	0 (0)	6 (16)
NOS	NOS	55	3(5)	0 (0)	0 (0)	3 (5)
HGNEC	TC	2	0 (0)	0 (0)	0 (0)	0 (0)
HGNEC	AC	4	0 (0)	0 (0)	0 (0)	0 (0)
Other	TC	9	0 (0)	0 (0)	0 (0)	0 (0)
Other	AC	9	3 (33)	0 (0)	0 (0)	3 (33)
Other	NOS	12	0 (0)	0 (0)	0 (0)	0 (0)
Total		330	22 (7)	2 (1)	1 (0)	25 (8)

[a]Lobectomy represents a cluster of lobectomy, bilobectomy, and sleeve lobectomy as surgical procedures.
AC, atypical carcinoid; HGNEC, high-grade NE carcinoma; NOS, not-otherwise-specified; TC, typical carcinoid.

Table 4. Overview Presenting the Percentage 3-, 5-, and 10-Year RFS Stratified by the Preoperative and Postoperative Diagnosis

	Preoperative Diagnosis (N)					Postoperative Diagnosis (N)		
RFS	TC (119)	AC (15)	NOS (153)	HGNEC (6)	Other (29)	TC (156)	AC (85)	NOS (81)
3-y (%)	97.5	86.7	98.0	100	100	98.7	92.9	100
5-y (%)	96.6	73.3	96.1	100	96.6	97.4	87.1	100
10-y (%)	96.6	60.0	92.8	100	89.7	96.8	80.0	97.5

AC, atypical carcinoid; HGNEC, high-grade neuroendocrineE carcinoma; RPS, relapse-free survival; TC, typical carcinoid; NOS, not-otherwise-specified.

addition, inadequate handling, fixation, and processing have more impact on biopsies than resection specimens and may lead to morphologic changes such as nuclear chromatin condensation and shrinking, thereby increasing the risk of preoperative diagnostic misinterpretations.[17] Indeed, other technical issues such as the relatively large microscopic area containing a rather small number of mitoses, the disparate distribution of mitoses within the tissue section, the fact that a mitotic figure may be misinterpreted as an apoptotic cell, a crushed cell, or a granulocyte nucleus, and the heterogeneity of pulmonary tumors, may also be of influence.[18] Overall, it has to be questioned whether a small biopsy specimen is a representative reflection of the tumor and whether it is reliable in preoperative PC diagnosis given the consequences it may entail.

In addition to technical issues, we investigated whether the type of preoperative biopsy (e.g., endobronchial, needle, or excision) was of influence on the diagnostic discordance. However, as our results revealed that most preoperative biopsy specimens were endobronchial biopsies as compared with excision and needle biopsies (95% versus 1% and 4%), no conclusions could be drawn on the influence of the type of biopsy on the correctness of the preoperative diagnosis.

Although the preferred treatment for carcinoid tumors, whether TC or AC, is anatomical lobectomy, several recent retrospective studies have reported the noninferiority of parenchyma-sparing resections (e.g., wedge resection and segmentectomy) compared with the traditionally advised lobectomy for TC.[6,8,10,12,13] On the basis of these studies, the European Neuroendocrine Tumor Society guidelines propose to consider segmental resection (rather than wedge resection) in patients with limited pulmonary function.[2] Furthermore, the European Neuroendocrine Tumor Society recommends performing parenchyma-sparing surgery for patients with central airway tumors. These tumors are almost exclusively TC and are, thus, characterized by a low recurrence potential.[2] However, the National Comprehensive Cancer Network guidelines still advise lobectomy or another anatomical resection for TC, and the European Society for Medical Oncology guidelines prefer lobectomy.[19,20] Furthermore, other studies have suggested endobronchial treatment for centrally-located TC with high success rates and limited recurrences.[3–5,9,11] None of the guidelines advise parenchyma-sparing resection for AC, which is in line with our data illustrating that no parenchyma-sparing strategies were applied to AC. Indeed, the frequent relapse of the disease in postoperatively diagnosed AC (19%, n = 17 of 88) underscores that traditional oncologic anatomical surgery is required in these patients. These findings are also supported by a study of Filosso et al.[7] (n = 126) reporting a sublobar resection (e.g., wedge resection or segmentectomy) as an independent negative prognostic factor for AC.[7] In addition, it needs to be emphasized that a sublobar resection requires a dedicated lymph node dissection to minimize the risk of incomplete resection.

Thus, the different treatment options for TC and AC and the limited concordance between the preoperative and postoperative diagnosis emphasize a serious clinical dilemma when it comes to treatment management on the basis of a preoperative biopsy diagnosis. We did not observe a difference in patient outcomes with regard to disease relapse. However, we did observe a significantly lower RFS for patients diagnosed with AC as compared with both TC ($p = 0.3E\text{-}6$) and NOS ($p = 3.7E\text{-}5$).

Accurate histopathologic diagnosis and prediction of malignancy of lung NET biopsies may require additional analyses besides assessment of morphologic characteristics. A potential marker of additive value is the Ki67 immunohistochemical proliferation index, also known as Mib-1. Evaluation of manual counting of Ki67 stained lung NET biopsies and their paired resection specimens revealed a strong correlation, independent of tumor type, biopsy size, tumor sampling method, and heterogeneity in the distribution.[21] Others have already reported the diagnostic use of Ki67 to separate low-grade NETs (i.e., TC and AC) from small cell carcinoma.[17,21] Furthermore, the Ki67 labeling index has potential diagnostic, prognostic, and grading implications in surgically resected lung NETs.[22] However, in the current literature, cutoff values for Ki67 proliferation index to

subclassify carcinoids are contradictory and therefore not yet advised by the WHO classification.

Additional immunohistochemical markers, known to be able to predict a favorable prognosis in PCs, are the nuclear expression of OTP and membranous expression of CD44.[16,23–26] The combination of OTP and CD44 has recently been proposed to identify patients at risk for disease relapse after surgery.[24] Another marker that correlates with prognosis in multiple endocrine neoplasia type 1 (MEN1). Several studies have reported that MEN1 mutation, which correlates with low gene expression, is related to poor prognosis in carcinoids.[27–30] Hence it is tempting to speculate that a panel of multiple (immunohistochemical) markers (Ki-67, OTP, CD44, and MEN1) in addition to the current morphologic WHO classification may be used in future clinical practice to preoperatively identify patients who are at (very) low risk for disease relapse. For these patients, parenchyma-sparing surgery and a less intense follow-up period could be considered, especially in patients who have high cardiovascular comorbidity or a limited lung capacity.

This study has several limitations. First, it is a retrospective study relying on pathology report conclusions of diagnoses that have not been additionally confirmed by other pathologists. This reflects daily practice in which not all diagnoses are double-read by other pathologists yet are used by clinicians to determine treatment. Second, our data revealed that a large proportion (35%, n = 55 of 158) of the preoperatively diagnosed carcinoid NOS remained carcinoid NOS on the paired resection specimen. This diagnosis is insufficient because subclassification into TC versus AC is essential for, among others, treatment decisions and prognosis.[31] Nevertheless, these carcinoid NOS cases likely represent TC as their RFS was similar. Third, our data revealed that only a small proportion of the patients (5%, n = 15 of 330) underwent parenchyma-sparing surgery. This might be owing to the time frame of our cohort (2003–2012) in which limited literature regarding parenchyma-sparing strategies was available. It might be possible that parenchyma-sparing strategies are currently more frequently performed. This is confirmed in a recent study of Cattoni et al.,[32] analyzing 510 patients who underwent lung resection for a primary NET between 2000 and 2015. Results revealed that 22% (n = 110 of 510) of the patients underwent either a wedge (n = 77) or segmentectomy (n = 33). The wedge resections were performed in 59 patients with TC, nine patients with AC, and nine patients with large cell NE carcinoma.

Conclusions

Our data reveal that carcinoid diagnosis on a histologic biopsy specimen is imprecise; in half of the patients with a carcinoid tumor, the preoperative diagnosis does not match the accepted standard resection specimen diagnosis in current clinical practice. More importantly, this frequently includes "upgrading" from preoperative non-AC to a postoperative AC diagnosis. We advise clinicians to interpret the preoperative biopsy diagnosis with caution in deciding the extent of surgery (e.g., parenchyma-sparing versus non–parenchyma-sparing). Future studies to improve the diagnostic and prognostic accuracy of preoperative PC biopsy specimens are urgently required.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.12.004.

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