Review Article

Impact of lymph node involvement in pulmonary carcinoids: a narrative review

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Background and Objective: Pulmonary carcinoids (PCs) represent a rare subset of neuroendocrine tumors (NETs) within the respiratory tract that exhibit unique characteristics and clinical behaviors. These tumors are currently staged according to the tumor-nodules-metastases (TNM) classification of non-small cell lung cancer (NSCLC), which brings their reliability into question. The aim of this study was to assess reliability of the current TNM staging of PCs and explore other relevant prognostic factors of patient outcomes.

Methods: From January 2023 to October 2023, the PubMed and Embase databases were searched according to predefined keywords. Studies focusing on PCs, TNM classification, surgical management, and lymph node involvement were included. The search included meta-analyses, retrospective studies, and case reports. Pediatric cases and articles written in languages other than English were excluded.

Key Content and Findings: This review identified several retrospective cohort studies investigating the correlation between TNM staging, lymph node involvement, and survival outcomes in PC patients. Inconsistencies in survival rates across TNM stages were observed, highlighting the limitations of the current TNM classification as a main predictor of patient outcomes. Lymph node involvement emerged as a significant predictor of survival, with higher nodal stages associated with a poorer prognosis, especially for patients with atypical carcinoid tumors.

Conclusions: Excluding PCs from TNM staging of NSCLC and implementing new staging methods based on histological subtype and lymph node involvement may provide a better classification of this type of tumor, which could lead to more effective care for patients in the future.

Keywords: Pulmonary carcinoids (PCs); lymph node involvement; tumor-nodules-metastases staging (TNM staging)

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Introduction

Pulmonary carcinoids (PCs) are rare oncological malignancies with an occurrence rate as low as 0.5% of all malignancies. These tumors fall within the category of neuroendocrine tumors (NETs), which are responsible for up to 25% of all lung cancers. The respiratory tract is the second most prevalent site of origin for these tumors, following the gastrointestinal tract (1,2). NETs are recognized by common morphological, immunohistochemical, and cellular structures, with differences varying in type, and are divided according to the World Health Organization classification into PC, large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC). PCs can later be subclassified into typical and atypical carcinoids (ACs), both of which present less malignant potential than LCNEC and SCLC (3). Typical carcinoids (TCs) are identified by their low mitotic activity (<2 mitoses per 2 mm^2) and the absence of necrosis. In contrast, ACs may present with greater mitotic activity (2–10 mitoses per 2 mm^2) and the potential for necrosis (2,4,5). ACs tend to be more aggressive and have greater distant metastasis rates and poorer outcomes than TCs (6,7). The typical clinical presentations of central tumors include dyspnea, cough, hemoptysis, and reoccurring pulmonary infections. However, peripheral malignancies can be clinically unrecognizable, with shortness of breath as the only symptom, and can usually be detected only after a CT scan (8-11). PCs rarely result in greater hormonal imbalance, manifesting as a carcinoid or Cushing syndrome with a much greater number of non-specific symptoms (11-13). Unlike in NSCLC, tobacco use is not clearly correlated with a greater chance of PC occurrence; however, it is more likely to be associated with ACs than with TCs (2,14,15). Women are more prone to PC tumors than men are. PCs are diagnosed at an earlier age than other lung cancers (11,15).

Current recommendations, proposed by the International Association for the Study of Lung Cancer (IASLC) and supported by the American Joint Committee on Cancer (AJCC), were constructed based on NSCLC management, with pulmonary NETs being unrecognized. The 7th edition of the tumor-nodules-metastases (TNM) classification excluded any NETs from having separated staging, which has been corrected in the 8th edition with Pancreatic and Gastrointestinal NETs recognized. Overall, the number of patients diagnosed with NETs has been growing for the past 30 years, with a great number of articles being published each year and population-based studies being performed (9,11,16-18). It is well documented that the recommended staging method is not suitable for a large number of patients, especially those with lymph node involvement, as it was constructed for non-small cell lung cancer (NSCLC) progression and treatment. The initial search yielded a substantial number of studies, of which a selected subset met the inclusion criteria. This review identified trends in the reliability of TNM staging for PCs, emphasizing variations in staging accuracy across different tumor subtypes, populations, and study methodologies. This review also explored the accuracy of TNM staging and the feasibility of using the pN descriptor as an independent prognostic factor for survival. Thus, in this study, we present a narrative review of pN descriptors in PCs. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-446/rc).

Methods

The PubMed and Embase databases were searched from January 2023 to October 2023 with the following search terms to identify papers of interest: “pulmonary carcinoids”, “TNM classification of pulmonary carcinoids”, “intrabronchial carcinoids”, “surgical management of pulmonary carcinoids” and “lymph node involvement in pulmonary carcinoids”. We reviewed meta-analyses, retrospective studies, and review articles as well as case reports and case series. To support ourselves with data sourced from cutting-edge imaging, we excluded studies published before the year 2000. Moreover, papers written in a non-English language or describing pediatric patients were also excluded. In this study, we used the nomenclature Caplin and Travis to refer to PC, TC, AC, and NSCLC tumors. The search strategy is summarized in *Table 1*.

Current and past TNM staging

For the year 2023, the 8th edition of the TNM classification is considered a fundamental guide for lung cancer management (19-21). Since the introduction of the 8th edition in 2017, numerous retrospective studies and case series aiming to correlate TNM staging with patient outcomes, measured as 5- or 10-year survival rates, have been published. Currently, the primary treatment for well-differentiated NETs is surgery, supported by a high number of studies reporting positive survival outcomes. Additionally, adjuvant chemotherapy or somatostatin

Table 1 The search strategy summary

Items	Specification
Date of search	23th of January 2023
Database searched	PubMed, Embase
Search terms used	"pulmonary carcinoids", "TNM classification of pulmonary carcinoids", "intrabronchial carcinoids", "surgical management of pulmonary carcinoids" and "lymph node involvement in pulmonary carcinoids"
Timeframe	2000–2023
Inclusion and exclusion criteria	Inclusion criteria: articles published in years 2000–2023, articles written in English language, articles describing reliability of TNM staging in pulmonary carcinoids, articles describing lymph node involvement in pulmonary carcinoid patients. Exclusion criteria: articles published before year 2000, articles written in non-English language, articles describing pediatric patients
Selection process	Selection process was conducted independently by the following authors: M.D., M.C., M.P., Z.G. and K.G. The consensus was obtained after a discussion conjointly with all the authors

analog therapy may be beneficial for patients, especially those with ACs, as described in the latest guidelines of The National Comprehensive Cancer Network (NCCN) and the European Neuroendocrine Tumor Society (ENETS). The European Society for Medical Oncology (ESMO) guidelines suggest octreotide-labeled analogs for patients who are positive for somatostatin receptors as a possible adjuvant therapy. However, the current data are not sufficient to determine the long-term effectiveness of the aforementioned therapy. Currently, TNM staging of PCs is crucial for the organization of patient-centered, multimodal therapy, including adjuvant therapy, but controversies may arise (22-25). Jackson *et al.* conducted a large study based on 12,415 patients with PCs. After histological grading, the results were as follows: 7,524, grade 1 (TC); 1,211, grade 2 (AC); and 3,680, grade 3 (LCNEC). Throughout grades 1 and 2, stages IA and IB were more common in grade 1 than in grade 2 (65.3% *vs.* 41.4% and 10.9% *vs.* 10.7%, respectively). However, stages IIA, IIB, III, and IV were staged more often in G2 (4.1% *vs.* 3.2%, 20.4% *vs.* 11.9%, 19.2% *vs.* 6.9%, and 4.2% *vs.* 1.8%, respectively). No nodal involvement (N0) was observed in a total of 10,122 (81.5%) patients, with a greater percentage in G1 (88.6% compared to 64.9% in G2). In contrast, stages N1–N3 showed a higher percentage in G2, with 19.8% *vs.* 7.7% for N1, and 15.3% *vs.* 3.8% for N2 and N3 combined. Based on these criteria, higher 5-year survival rates were observed for stages IB *vs.* IIA (92% *vs.* 96%) and IIIB *vs.* IV (85% *vs.* 88%) for TC tumors. For AC tumors, the survival rates were 73% *vs.* 80% for stage IB *vs.* IIA, and 55% *vs.* 59% *vs.* 64% for stages IIIA, IIIB, and IV, respectively. In both histological types, for stage IIIB patients, it was impossible to determine the 5-year survival rate. Overall, a 5-year survival rate was calculated and showed inconsistencies for stages IB *vs.* IIA (71% *vs.* 76%) (25). Travis *et al.* created a study cohort from patients included in the Surveillance, Epidemiology and End Results (SEER) database (n=1,437). Patients in this study were staged according to the 7th edition of the TNM. The difference between TC and AC tumors was not detected. The total number of patients with nodal involvement was significantly lower than that of patients without nodal involvement (184 *vs.* 1,243). There were 124, 56, and 4 patients in stages N1, N2, and N3, respectively. Among all patients, 56%, 22%, 9%, 3%, and 6% had stage IA, IB, IIA, IIB, IIIA, and IV disease, respectively. Based on the pN stage, significant differences in the 5-year survival rate were observed. For stages N1, N2, and N3, decreased survival rates of 81%, 74%, and 67%, respectively. No nodal involvement resulted in a 93% survival rate (26). Yoon *et al.* conducted research based on the SEER database. After implementing all the inclusion and exclusion criteria, the clinical cohort included 4,645 patients diagnosed with PCs who were staged using the 8th edition of the TNM. The most commonly diagnosed carcinoid was TC rather than AC (4,254 *vs.* 391 patients). Stages IA1–3 accounted for 51% of patients, and stage 1B accounted for 14%, accounting for 65% of all patients. Patients with other stages (IIA, IIB, IIIA + B, and IV) accounted for 35% and accounted for 3%, 9%, 13%, and 2%, respectively. A 10-year disease-specific survival (DSS) analysis was conducted, which revealed the following results. Overall DSS was greater for all stages of TC cancer except for stage IIA (83.7% *vs.* 87.5%) and was as follows: IA1 (97.7% *vs.* 83.1%), IA2 (97.1% *vs.* 91.1%), IB (94.1% *vs.* 85.5%), IIB (85.7% *vs.* 73.0%), IIIA (85.3%

vs. 57.7%), IIIB + C (48.8% *vs.* 24.0%), and IV (58.8% *vs.* 18.5%). For stage IA3 patients, the survival rate could not be compared due to a lack of incidence. The survival rates for the combined stage of TC and AC tumors decreased gradually with increasing stage (from I–IV) and were 96.3% *vs.* 87.8%, 85.3% *vs.* 75.5%, 80.7% *vs.* 47.5%, and 58.8% *vs.* 18.5%, respectively (27).

Lymph node involvement as a predictor of survival

The assessment of lymph node involvement has long been recognized as a crucial determinant of the prognosis of patients with lung cancer, especially NSCLC. In the context of PCs, the interplay between lymph node status and survival outcomes remains a subject of ongoing research. Current guidelines for the preoperative work-up of NSCLC patients and PC patients include endobronchial ultrasonography (EBUS), endoscopic ultrasonography (EUS), respiratory function tests, and, in some cases, mediastinoscopy. Data collected by Kneuertz *et al.* and later used by Baudin *et al.* for creating guidelines on behalf of the ESMO show a higher mean percentage of lymph node metastases for atypical than for TCs (46% *vs.* 17%), with more advanced stages being more frequently observed in ACs (23% *vs.* 6%). The differences in the frequency and advancement of lymph node involvement between patients with NSCLC and patients with PC suggest that EBUS and EUS may not be mandatory tests for the preoperative work-up of patients with PC, leaving positron emission tomography/computed tomography (PET/CT) and CT as sufficient diagnostic tools for lymph node staging. Mediastinoscopy has a small diagnostic yield for lymph node diagnosis for most types of lung cancer and therefore may not be the first-line procedure for NSCLC or PC diagnosis. However, inconsistencies in the correlation of the survival rate with the current TNM stage have been reported in many studies. Decreasing survival rates combined with increasing stages have been reported in most lung cancers; however, in PCs, a consistent survival rate with increasing TNM stages is often not observed, and lymph node involvement is sometimes considered a reliable outcome predictor, especially for ACs (28-30). Research conducted by Mineo *et al.* on micrometastases of lymph nodes revealed that 55 patients were diagnosed with PC tumors and treated surgically. Most of these patients had TCs (85.5% *vs.* 14.5%) and lacked lymph node involvement after the first biopsy (78%), 43 patients, 4 of whom were diagnosed with ACs. pN1 stage was identified in 12 patients and was more common in patients with TC rather than AC tumors (8 *vs.* 4) (P=0.002). After a second examination of previously pN0 patients, micrometastases were found in a total of 8 patients, of which 6 had N1mi and 2 had N2mi, increasing the number of patients with nodal involvement to 20 (36.4%, P=0.01). The reoccurrence rate was 9.1%, which was greater for pN1 than for pN1mi (2 *vs.* 1, P=0.001). Distant recurrence was found in 2 pN2mi patients, and stage pN0 patients did not experience any recurrence. The disease-free survival rates for patients with stages pN1 and pN1mi were 83.3% and 100%, respectively, lower than those for patients with pN0, and 55.6% and 100%, respectively, for 5 and 10 years. Overall, the 5- and 10-year survival rates for patients with nodal involvement (pN1 and pN1mi) were significantly lower than those for patients without nodal involvement (66.7% *vs.* 96.6%, P<0.001). Statistical analysis revealed that both lymph node involvement and tumor type were significant predictors of overall survival (P<0.001 and P=0.02, respectively) (31). In a retrospective study conducted by Cardillo *et al.* (14), the results of treatment of 163 patients were presented. The most commonly found tumor was a TC (121 *vs.* 42 patients), and in 98 patients, the tumor was centrally localized, which was confirmed by bronchoscopy. Patients without lymph node involvement were more common (123 *vs.* 41) and mostly associated with TC rather than ACs (107 *vs.* 15). Of the 41 patients, 32 were staged as pN1, 9 as pN2, and none as pN3. Stage pN1 was slightly more common in atypical patients (18 *vs.* 14), and pN2 was absent in patients with TC tumors (9 *vs.* 0). Overall, the 5-year survival rate was 90.3%, and for TCs and ACs, the 5-year survival rates were 98.6% and 70.1%, respectively, with pN0 status resulting in a 100% survival rate for both histological types. The survival rate for patients with N1-stage disease was 84.2%, and that for patients with atypical disease was lower (90% *vs.* 78.8%). For stage N2 patients, a 22.2% 5-year survival rate was observed. Filosso *et al.* performed a retrospective study with a significant collection of data and long-term follow-up of patients. The study group was created based on a 20-year observation (1977–1997) and consisted of 126 patients who were diagnosed with bronchial carcinoid tumors and who underwent surgical treatment. Eighty-two (65%) patients presented with TC tumors, and 44 (35%) presented with atypical tumors. Bronchoscopic biopsy was conducted for all patients; however, only 98 patients were classified as having carcinoid tumors, 70 of whom had TC tumors and 28 of whom had

AC tumors. Among 126 surgically treated patients, 113 underwent lymphadenectomy and were subsequently staged postoperatively. Pathological staging through stages I, II, III, and IV included 90, 6, 15, and 2 patients, respectively. A greater number of patients in stages II and III were found in the atypical group (2 *vs.* 4 and 3 *vs.* 12), with stage I being more common (70 *vs.* 20) and stage IV (0 *vs.* 2) being absent in the typical group. No nodal involvement was observed in 93 patients with more TC tumors. Among all postoperative patients, 75 had TC and 38 had AC tumors. Overall, nodal involvement percentages were greater in patients with ACs (36.8% *vs.* 8%), and surprisingly, most patients had stage N2 disease. Stages pN1, pN2, and pN3 were observed in 9, 11, and 0 consecutive patients, respectively, with pN1 being more common in atypical patients and pN2 being the same in both histological types. The overall survival rates at 5, 10, and 15 years for patients treated with PCs were 89%, 79% and 74%, respectively. Both nodal status and histological subtype are important factors related to long-term survival. Patients with AC tumors had worse prognoses than those with TC tumors, with 5-, 10-, and 15-year survival rates of 77% *vs.* 97%, 52% *vs.* 93%, and 84% *vs.* 52%, respectively. Compared with patients with positive lymph node status, patients with no nodal involvement had better 5-, 10-, and 15-year survival rates (92% *vs.* 85%, 87% *vs.* 52%, and 80% *vs.* 52%, respectively) (10). After 15 years, another important study was conducted by Filosso. As a member of the European Society of Thoracic Surgeons (ESTS), he conducted research with his colleagues as a part of the Neuroendocrine Tumors Working Group (NET-WG) based on a respectable database collected in the years 2012–2014. The number of patients diagnosed with pulmonary NETs was 2,051, of which 1,440 had PC tumors. The most common carcinoid was a TC, with 1,212 reported cases (vs. 228 for atypical cases). After TNM staging, stages II, III, and IV were more common among patients with AC tumors (28% *vs.* 10%, 16% *vs.* 5%, 4% *vs.* 1%), in contrast to stage I, which was present in a larger number of patients with TC tumors (84% *vs.* 52%). No nodal involvement was observed more commonly than in stages N1, N2, or N3, with a greater percentage in TCs (90% *vs.* 60%). Stages N1 and N2 were both more common in ACs (24% *vs.* 6% and 15% *vs.* 3%, respectively), and stage N3 was absent in both histological types. Nodal involvement could not be acknowledged in approximately 1% of patients with either TCs or ACs. Multivariate analysis revealed significant differences in survival rates based on lymph node involvement [hazard ratio (HR) 1.33; 95% confidence interval (CI): 1.17–1.53; P<0.001 for typical tumors; HR 1.29; 95% CI: 1.04–1.60; P=0.01 for atypical tumors]. Lymph node involvement was also described as a predictor of local and distant metastases (32). Kneuertz *et al.* conducted research based on The National Cancer Database (NCDB), supported by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. After applying the exclusion criteria, 3,335 patients were included in the study cohort, with a greater percentage of patients with TC tumors than atypical tumors (87% *vs.* 13%), all of whom had at least 10 resected lymph node samples. The most common pT stages were T1 and T2 (93.4%), which were more common in patients with TCs (94.3% *vs.* 90.7%). Lymph node involvement was found in 21% of patients, with stages N1 and N2 being more common in patients with AC tumors (11% *vs.* 23% and 6% *vs.* 23%, respectively). Lymph node metastasis correlated positively with tumor size and was significantly greater overall in patients with AC tumors. The median 5-year survival rate for patients with lymph node involvement was greater for those with TC tumors (88% *vs.* 58%) than for those with AC tumors, and the overall survival rate was lower than that for patients without lymph node involvement (93% *vs.* 88%, TC *vs.* AC, respectively) (29). In contrast, the pN descriptor did not significantly predict the survival rate in a study conducted by Johnson *et al.* A total of 52 out of 123 patients were included in the study after the exclusion criteria were applied. More commonly diagnosed by far were TC rather than ACs (43 *vs.* 9 patients), with a lower mean size of the tumor (2.3 *vs.* 3.2 cm, P=0.046). Lymph node involvement was found in 10 patients, with a greater percentage of AC tumors (22% *vs.* 19%), and consisted of N1 and N2 stages. More commonly, N1 and N3 were absent. The 5- and 10-year survival rates were both significantly greater for TC than for ACs (97% *vs.* 35% and 72% *vs.* 0%, respectively). The 5-year survival rates based on node metastases were 100% and 97%, respectively, with and without lymph node involvement for TCs and 50% and 28%, respectively, for ACs. Overall survival was not significantly different between patients with and without lymph node involvement, and histological type was the main outcome predictor (15). All of the data is presented in *Table 2*.

Discussion

NETs are neoplasms originating from neuroendocrine cells. They occur in the gastrointestinal tract being the

Table 2 Summary table

Study	Type of study	Patient group, type of pulmonary carcinoid	Age (years), mean [range]	Survival rate based on TNM	Survival rate based on lymph node involvement
Jackson *et al.*, 2020 (25)	Retrospective cohort study	12,415 patients identified from National Cancer Database from 2004–2014: 7,524 presented with TC, 1,211 with AC and 3,680 with LCNEC	63 [18–90]	5-year survival rate: (I) TC: IA 92%, IB 92%, IIA 96%, IIB 90%, IIIA 86%, IIIB 85%, IIIC 0%, IV 88%; (II) AC: IA 80%, IB 73%, IIA 80%, IIB 70%, IIIA 55%, IIIB 59%, IIIC no record, IV 64%	Not given
Travis *et al.*, 2008 (26)	Retrospective cohort study	Case series from the Surveillance Epidemiology and End Results database from 1990–2002: 1,437 surgically treated patients, TC and AC were not distinguished	55 [12–91]	5-year survival rate: IA (93%), IB (91%), IIA (85%), IIB (86%), IIIA (78%), IIIB (47%), IV (57%)	5-year survival rate: N0 (92%), N1 (81%), N2 (74%), N3 (67%)
Yoon *et al.*, 2019 (27)	Retrospective cohort study	4,645 patients between the year 2000 and 2013 were identified from the Surveillance, Epidemiology and End Results database: 4,254 were diagnosed with TC, 391 with AC	58	10-year survival rate: (I) TC: IA1 (97.7%), IA2 (97.1%), IA3 (96.1%), IB (94.1%), IIA (84.7%), IIB (85.7%), IIIA (85.3%), IIIB + C (48.8%), IV (58.8%); (II) AC: IA1 (83.1%), IA2 (91.1%), IA3 (100.0%), IB (85.5%), IIA (87.5%), IIB (73.0%), IIIA (57.7%), IIIB + C (24.0%), IV (18.5%)	10-year survival rate: (I) TC: N0 (94.3%), N1 (76.2%), N2 (55.6%), N3 (0%); (II) AC: N0 (83.4%), N1 (57.3%), N2 (28%), N3 (32.9%)
Cardillo *et al.*, 2004 (14)	Retrospective cohort study	A retrospective single center review of 163 patients surgically treated from 1990 to 2002: 74% presented with TC, 26% with AC	54 [16–80]	5-year survival rate: T1 (98.6%), T2–4 (70.1%)	TC: N0 (100%), N1 (90%); AC: N0 (100%), N1 (78.8%), N2 (22.2%)
Filosso *et al.*, 2002 (10)	Retrospective cohort study	A retrospective single center review of 126 surgically treated patients observed for 20 years (1977–1999); 65% of patients presented with TC, 35% with AC	47 [11–77]	Not given	5-, 10-, and 15-year survival rates for pulmonary carcinoid without nodal involvement were: 92%, 87%, 80%; 5-, 10-, and 15-year survival rates for pulmonary carcinoid with nodal involvement were 85%, 52%, 52%
Kneuertz *et al.*, 2018 (29)	Retrospective cohort study	3,335 cases of surgically treated patients in The National Cancer Database from 2004 to 2014 were reviewed; 87% of patients presented with TC, 13% with AC; all had resected at least 10 lymph nodes samples	60	Not given	Median 5-year survival rate with lymph node involvement: TC (88%), AC (58%); median 5-year survival rate without: TC (93%), AC (88%)
Johnson *et al.*, 2011 (15)	Retrospective cohort study	A retrospective single center study of all patients with bronchogenic carcinoid tumor from 1985 to 2009, 52 of which were included in this study; 83% presented of them with TC, 17% with AC	–	Not given	5-year survival rate with lymph node involvement: TC (100%), AC (50%); 5-year survival rate without lymph node involvement: TC (97%), AC (28%)

LCNEC, large-cell neuroendocrine cancer; TNM, tumor-nodules-metastases; AC, atypical carcinoid; TC, typical carcinoid.

most common site, followed by the respiratory tract. The World Health Organization (WHO) differentiates them into PCs, LCNEC, and SCLC tumors, with differences in morphology and immunohistochemistry. PCs can be located centrally or peripherally, which results in important changes in clinical presentation with changes in the survival rate, which is high for both TCs and ACs, resulting in low- and intermediate-grade tumors, respectively (15). PCs, which have a lower metastatic rate and lymph node involvement, are less malignant than other types of lung cancer in the NSCLC group. The TNM staging system, based on NSCLC progression and management, represents a framework that suits other lung cancers; however, it has not evolved enough to encompass the unique characteristics of these NETs, thus making it often unreliable for clinicians (4,12). In studies conducted by Jackson, Travis, and Yoon *et al.* (25-27), many inconsistencies were found in the survival rate for the assigned stage. In a comprehensive study by Jackson *et al.* (25) involving 12,415 patients with PCs, histopathological grading revealed 7,524 cases of grade 1 (TC), 1,211 cases of grade 2 (AC), and 3,680 cases of grade 3 (LCNEC) tumors. In TC patients, the most common stages were IA and IB, with percentages of 65.3% *vs.* 41.4% and 10.9% *vs.* 10.7%, respectively. Conversely, stages IIA, IIB, III, and IV were more frequently staged in ACs, with percentages of 4.1% *vs.* 3.2%, 20.4% *vs.* 11.9%, 19.2% *vs.* 6.9%, and 4.2% *vs.* 1.8%, respectively. After determining the 5-year survival rate for both histological grades, inconsistencies were found, particularly for stages IB *vs.* IIA (92% *vs.* 96%) and IIIB *vs.* IV (85% *vs.* 88%) for TCs and for IB *vs.* IIA (73% *vs.* 80%) and IIIA *vs.* IIIB *vs.* IV (55% *vs.* 59% *vs.* 64%) for ACs. Disparities between tumor stage and 5-year survival rate could have resulted from inadequate TNM staging as well as from a low number of patients throughout stages IB–IV. The overall 5-year survival rate also exhibited inconsistencies, especially for IB *vs.* IIA (71% *vs.* 76%) stages (25). Yoon *et al.* utilized the SEER database and identified 4,656 patients eligible for the study who met the inclusion criteria. The tumors were staged according to the TNM 8th edition and histopathologically classified accordingly. The results demonstrated higher 10-year survival rates for patients with TCs in most stages. The combined stage of TC and AC tumors was constant, and the survival rate decreased with decreasing stage. Nevertheless, inconsistencies were found in TNM staging for both TCs and ACs. Differences included stages IIA *vs.* IIB (84.7% *vs.* 85.7%), IIIB + C *vs.* IV (48.8% *vs.* 58.8%) for TC tumors and stages IA1 *vs.* IA2 (83.1% *vs.* 91.1%) and IB *vs.* IIA (65.5% *vs.* 87.5%) for AC tumors (27). Similarly, Travis and his colleagues published a study cohort gathered from the SEER database that included 1,437 patients treated surgically for PCs. All patients were staged according to the 7th edition of the TNM system; however, differences between TC and AC tumors were not detected. Inconsistencies in survival were found in patients with stage IIIA *vs.* IV disease (3% *vs.* 6%) (26). Since the current TNM staging system is often unreliable, the histological type of the tumor and lymph node involvement have emerged as the main independent prognostic factors for patient outcomes. Several studies conducted by Mineo, Cardillo, Filosso, and Kneuertz *et al.* (10,14,29,31) have shown that lymph node involvement and/or histological type are significant predictors. Most of the patients analyzed by Mineo *et al.* were diagnosed with TC tumors without lymph node involvement. The statistical analysis revealed that both lymph node involvement and tumor histology type were significant predictors of patient outcomes, with P values <0.001 and 0.02, respectively (31). In a retrospective study by Cardillo *et al.* involving 163 patients, TC tumors were more prevalent than atypical tumors (121 *vs.* 42). Lymph node involvement was not acknowledged in 123 patients, and among the 41 patients with lymph node involvement, 32 were staged as pN1, 9 as pN2, and none as pN3. pN1 stage was slightly more common in patients with ACs (18 *vs.* 14), and pN2 stage was absent in patients with TCs (9 *vs.* 0). Overall, the 5-year survival rate was 90.3% (98.6% and 70.1% for TCs and ACs, respectively) (14). Filosso *et al.* conducted two large studies, one spanning 20 years (1977–1997) and the second spanning 2012–2014. In the first study, the patient group consisted of 126 patients, 65% of whom had TC tumors. Pathological staging revealed differences in stages among the two histological types, with ACs showing a greater prevalence in stages II and III. Nodal involvement was more frequent in ACs (36.8% *vs.* 8%), mainly throughout the N2 stage. Patients with ACs had a worse prognosis than patients with TCs (77% *vs.* 97%, 52% *vs.* 93%, and 52% *vs.* 84%, respectively) (P=0.0014), as did patients with nodal involvement (92% *vs.* 85%, 87% *vs.* 52% and 80% *vs.* 52%, respectively) for 5-, 10- and 15-year survival rates (10). In another study conducted by Filosso *et al.* on behalf of the NET-WG, 1,440 patients with PCs were included. TNM staging revealed that stages II, III, and IV were more common for ACs than for stage I, which was more frequent for TCs (84% *vs.* 52%). Similar to an earlier study, statistical analysis revealed significant differences in survival rates between patients with and without lymph

node involvement, with HRs of 1.33 (95% CI: 1.17–1.53, P<0.001) for TCs and 1.29 (95% CI: 1.04–1.60, P=0.01) for ACs (32). Lymph node involvement as a predictor of survival rates for patients treated with PCs was also investigated in a study conducted by Kneuertz *et al.* (29). The 5-year survival rate for patients with lymph node involvement was greater for those with TCs (88% *vs.* 58%) but lower overall than for those without (93% *vs.* 88%) (29). A comprehensive understanding of TNM staging is crucial for clinicians, enabling accurate prognostication and tailored therapeutic interventions for patients with PCs. Surgical resection remains the primary curative approach for localized disease, but advanced disease may necessitate multimodal therapies, including systemic treatments and novel targeted agents (11,12,33). As diagnostic and therapeutic strategies continue to advance, ongoing refinements to the staging system should occur, similar to those for NETs of the gastrointestinal tract (GI tract), which are described in the latest 8th edition of the TNM for pancreatic, stomach and other (jejunum, duodenum and ampulla of Vater, jejunum and ileum, appendix, colon and rectum) GI NETs, with separate staging (3). Despite in NSCLC, where one of the most evident prognostic factors of patients' outcome, is the pathological TNM it seems that in patients with pulmonary NETs other factors play a more important role. Grading, Ki67 expression and others are being discussed to be responsible for the inconsistencies related to vague survival of patients in different stages. Some researchers also suggest that factors such as tumor location, immunohistochemical markers, and the distinct morphology of these tumors may be linked to an overall better prognosis compared to other NSCLC tumors. Based on the presented research, more adequate and reliable staging could be achieved by implementing lymph node status and/or histological type as a part of the staging process; however, additional studies and case series are still needed.

Conclusions

In conclusion, PCs present unique clinical challenges due to their distinct morphology and clinical presentation than NSCLC. Studies have shown significant inconsistencies between current TNM stages and survival rates, highlighting the need for more tailored staging criteria that account for histological type and lymph node involvement, which have emerged as more reliable prognostic factors. Excluding PCs from NSCLC TNM staging and incorporating the mentioned factors may increase reliability of the new staging, which will benefit the patients.

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Footnote

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