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Prognostic factors in atypical carcinoid tumors

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ABSTRACT

Objectives: Carcinoid tumors are rare neuroendocrine neoplasms of the lung. Although typical and atypical carcinoids have different clinical courses, most studies in the literature evaluate them together. Therefore, we aimed to investigate prognostic factors in patients with atypical carcinoids, excluding typical carcinoids.

Methods: We included 32 patients with atypical carcinoids according to WHO 2021 criteria admitted to Uludag University Hospital. We retrospectively extracted the clinicopathological characteristics from electronic medical records. The log-rank tests were used to determine the prognostic factors on survival.

Results: Median age was 57 (24-71) years. Pathological stages were as follows: stage I in 41%, II in 9%, III in 34%, and IV in 16%. Median Ki-67 index was 11% (1-50). Median follow-up time was 46.2 (0.7-184.2) months. 12-month and 48-month disease-free survival (DFS) rates were 92.3% and 79.2%, respectively. 12-month and 48-month overall survival (OS) rates were 93.8% and 86.2, respectively. Receiver operating characteristic curve analysis determined the Ki-67 cut-off as 12.5%. The log-rank test indicated that Ki-67 and stage were statistically significant prognostic factors for DFS and OS. The patients with a Ki-67 index lower than 12.5% had longer DFS and OS ($p = 0.007$ and $p = 0.020$, respectively).

Conclusions: The Ki-67 index and 8th TNM staging have prognostic value on DFS and OS in patients with atypical carcinoids. Large-scale studies are needed to define the optimal cut-off value of Ki-67.

Keywords: Lung carcinoid, atypical carcinoid, ki-67 index, stage, survival

Carcinoid tumors are a component of a heterogeneous group of pulmonary neuroendocrine neoplasms [1]. Although twenty percent of neuroendocrine tumors of all body sites are carcinoid and their incidence is reported to be increasing, carcinoid tumors constitute less than 2% of all lung malignancies [2, 3]. The World Health Organization has classified carcinoid tumors into two histological types according to histopathological criteria: typical (well-differentiated, low grade) and atypical carcinoid tumors (well-differentiated, intermediate grade) [4]. Atypical carcinoid tumors constitute approximately one-quarter of lung carcinoids [5].

Carcinoid tumors have better survival than other neuroendocrine neoplasms of the lung, small-cell lung cancer, and large-cell neuroendocrine carcinoma [6].

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Histological type is the most crucial factor in determining survival. In addendum to histological type, many factors affecting the survival of carcinoid tumors, such as stage, Ki-67 index, gender, tumor size, lymph node metastasis, and treatment modalities, were investigated [7-12]. In most of these studies, patients with typical and atypical carcinoid tumors were evaluated together. However, the survival, recurrence sites, and rates of typical and atypical carcinoid tumors were reported to differ [13-16]. Therefore, in the present study, we aimed to investigate the clinicopathological factors affecting the survival of patients with atypical.

METHODS

We included the patients admitted to Bursa Uludag University Hospital between January 2007 and December 2021 for atypical carcinoid tumors according to the criteria determined in the WHO 2021 classification of lung tumors [4]. We retrospectively reviewed the electronic medical records and extracted the demographic and clinical features of all the participants: age, gender, imaging modalities, tumor side, tumor localization, clinical manifestation, clinical stage, treatment modalities, site of recurrences, and areas of metastasis. We obtained histopathological features from the patients' pathology reports, including pathological T and N stage, tumor size, lymphovascular invasion, Ki-67 index, mitotic count, and necrosis. We excluded patients younger than 18 and those with a history of other sites' malignancy and incomplete clinicopathological data.

Ethical Statement

The study was per the 1964 Declaration of Helsinki and approved by the clinical research ethics committee of Bursa Uludag University Faculty of Medicine (Approval number: 2020-19/19).

Statistical Analysis

We defined overall survival (OS) as the time from diagnosis until death from any cause. Disease-free survival (DFS) was specified to the time from surgery until disease recurrence, confirmed by histological examination or imaging modalities, or death for any reason, whichever occurred first. The optimal cut-off points for the Ki-67 index and tumor size were deter-

Table 1. Clinicopathological characteristics of the patients

	Data (n = 32)
Age (years)	57.0 (24.6-71.3)
Gender	
Female	17 (53.1)
Male	15 (46.9)
Symptoms at diagnosis	
Cough	15 (46.9)
Dyspnea	7 (21.9)
Hemoptysis	3 (9.4)
Carcinoid Syndrome	2 (6.3)
Absent (asymptomatic)	5 (15.6)
Imaging at diagnosis	
Computed tomography	32 (100.0)
FDG PET/CT	21 (65.6)
Ga68-Dotatate PET/CT	9 (28.1)
Tumor side	
Right	18 (56.3)
Left	14 (43.7)
Localization	
Central	18 (56.3)
Peripheral	14 (43.7)
Surgery	
Lobectomy	21 (65.6)
Sublobar Resection	6 (18.8)
None	5 (15.6)
Stage at diagnosis	
I	13 (40.6)
II	3 (9.4)
III	11 (34.4)
IV	5 (15.6)
Tumor size (mm)	31 (5-75)
Ki-67 index (%)	11 (1-50)
Necrosis	
Absent	19 (59.4)
Present	13 (40.6)
Mitosis	
< 2	8 (25.0)
2-10	24 (75.0)
(Neo)Adjuvant Therapy	
Chemotherapy	11 (34.4)
Radiotherapy	6 (18.8)

Data are show as median (minimum-maximum or number (percent). FDG PET/CT = fluorodeoxyglucose positron emission tomography-computed tomography, Ga68-Dotatate PET/CT = Gallium-68 Dotatate positron emission tomography-computed tomography

mined using receiver operating characteristic (ROC) curve analysis, taking the DFS event as the endpoint of interest. Statistical analyses were performed using IBM SPSS version 28 software. Continuous and categorical variables were represented as median (minimum-maximum) and frequency, respectively. Kaplan–Meier analysis was operated for survival rates. The log-rank tests were used to compare the patient groups. Statistical significance was indicated by *p* - values less than 0.05.

RESULTS

Our study comprised thirty-two patients. Table 1 displays the clinicopathological characteristics of the patients included. The median age was 57.0 (24.6-71.3) years. Nearly half of the patients had a cough at presentation. Carcinoid syndrome was observed in only two patients. All patients had computed tomography (CT) scans during evaluation, and Ga68-Dotatate positron emission tomography-computed tomography (PET/CT) was performed in 28% of them at the initial diagnosis. Eighteen patients had centrally located tumors. Of the patients, 84% had nonmetastatic disease at presentation. Pathological stages were as follows: stage I in 41%, II in 9%, III in 34%, and IV in 16%. The median tumor size was 31 (5-75) mm, and the median Ki-67 index was 11% (1-50). Necrosis was present in 41% of the patients. (Neo)Adjuvant chemotherapy and radiotherapy were performed in 43% and 19%, respectively. All patients received a somatostatin analog and cytotoxic chemotherapy in the metastatic stage.

In ROC curve analysis, the cut-off values for the Ki-67 index and tumor size were determined as ≥ 12.5% (AUC:0.771, sensivity:100%, specificity: 75%), and ≥ 34.5 mm (AUC:0.604, sensivity:71%, specificity: 60%), respectively.

The median follow-up time was 46.2 (0.7-184.2) months. 6 (8.3%) patients had recurrences, 83% representing distant metastasis. 6 patients died, and five deaths were attributed to the disease. 12-month, and 48-month DFS rates were 92.3%, and 79.2%, respectively. 12-month and 48-month OS rates were 93.8%, and 86.2, respectively. Fig. 1 demonstrates the Kaplan Meier DFS (A) and OS (B) curves.

Table 2 represents the results of the log-rank test analyses set for DFS and OS. The log-rank test revealed that Ki-67 and stage were statistically significant prognostic factors for DFS and OS. The patients with a low Ki-67 index (≤ 12.5) had longer DFS and OS ($p = 0.007$ and $p = 0.020$, respectively). Figs. 2 and 3 show the Kaplan-Meier curves of DFS and OS according to the Ki-67 index (A) and the pathological stage (A).

DISCUSSION

In the current retrospective study, we analyzed the prognostic factors impacting survival in patients with atypical carcinoids, excluding typical carcinoids. We observed that the Ki-67 index and stage were statistically significant factors in both DFS and OS in this population.

Ki-67 is a non-histone DNA binding nucleolar protein first identified in 1993 [17]. Ki-67 protein is a component of the perichromosomal layer functioning as a platform during nucleolar assembly [18]. The lev-

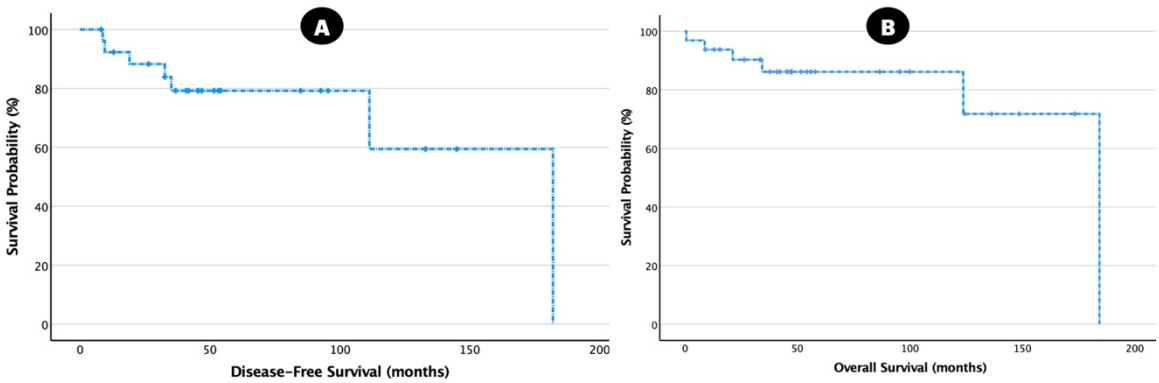

Fig. 1. Kaplan Meier curves of disease-free survival (A) and overall survival (B) of all patients.

Table 2. Results of the Log-rank test: factors affecting disease-free survival and overall survival

Factor	Disease-free survival			Overall survival		
	12-month (%)	48-month (%)	*p* value	12-month (%)	48-month (%)	*p* value
Age (years)						0.624
< 65	91.3	76.2	0.289	96.4	87.5	
≥ 65	100	100		75.0	75.0	
Gender						0.589
Female	86.7	86.7	0.897	94.1	87.8	
Male	90.9	72.7		93.3	84.8	
Tumor side						0.343
Right	93.8	79.1	0.533	94.4	81.7	
Left	90.0	80.0		92.9	92.9	
Tumor localization						0.951
Central	91.7	83.3	0.851	88.9	82.5	
Peripheral	92.9	73.1		100	92.3	
Surgery						0.289
Sublobar resection	100	80.0	0.822	100	95.0	
Lobectomy	90.0	79.3		100	100	
Tumor Size						0.529
< 34.5 mm	92.9	92.9	0.060	100	86.5	
≥ 34.5 mm	91.7	62.9		87.5	87.5	
Ki-67 index						**0.020**
< 12.5	100	100	0.007	100	100	
≥ 12.5	83.3	58.3		86.7	72.7	
Necrosis						0.089
Absent	100	87.5	0.266	100	83.0	
Present	86.7	72.2		89.5	77.1	
Mitosis						0.262
< 2	87.5	87.5	0.842	100	100	
2-10	94.7	77.9		91.7	82.2	
Pathological stage						**0.007**
I	100	90	0.034	100	100	
II	100	100		100	100	
III	80	58.3		100	90.0	
IV	-	-		60.0	30.0	
(Neo)Adjuvant treatment						0.819
No	100	82.5	0.233	100	100	
Yes	81.8	72.7		100	90.9	

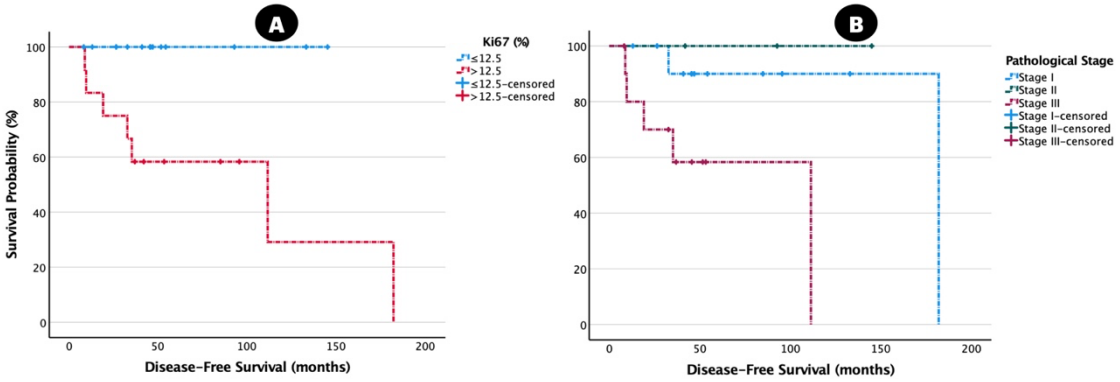

Fig. 2. Kaplan Meier curves of disease-free survival according to the Ki-67 index (A) and stage (B).

els of Ki-67 were reported to increase from the late G1 phase to the S phase and peak at mitosis [19]; therefore, it is widely used as a proliferative marker. The diagnostic, prognostic, and predictive values have been extensively studied in neuroendocrine neoplasms and other solid organ malignancies [14, 20-24].

Ki-67 is mandatory to grade gastroenteropancreatic neuroendocrine neoplasms [14, 25], but in lung carcinoid tumors, necrosis and mitotic count are recommended to grade rather than the Ki-67 index [4]. The Ki-67 index is recommended as a complementary tool to help to differentiate atypical carcinoids from lung neuroendocrine carcinomas (small cell carcinoma and large cell neuroendocrine carcinoma); a Ki-67 index below 30% is in favor of atypical carcinoids rather than high-grade neuroendocrine carcinomas [4, 10, 26-28]. In complement to this diagnostic value, studies on the prognostic value of Ki-67 level, particularly in lung carcinoid tumors, are increasing in the literature [11, 26, 29].

In 2018, Kasajima *et al*. [26] reported an evaluation of a multi-center retrospective study of 244 lung neuroendocrine neoplasms, of which 20 atypical carcinoids, and stated that patients with atypical carcinoids with a Ki-67 ≥ 20% had a worse prognosis compared to those with pulmonary carcinoid with a Ki-67 < %20, consistent with our findings. In 2020, Dermavan *et al*. [11] conducted the results of a retrospective cohort of 176 pulmonary carcinoids (11 atypical carcinoids). They found that Ki-67 is an independent prognostic factor in lung carcinoids, and integrating the Ki-67 index to histological grade and TNM staging is superior in predicting recurrence compared to TNM alone. Recently, Centonze *et al*. [29] reported that Ki-67 has a substantial predictive value in post-surgical recurrence in lung carcinoid tumors. Although the Ki-67 cut-off values in the studies mentioned above were reported to be lower than our study since atypical and typical carcinoids were assessed together, these studies also support our study's findings, indicating the prognostic value of the Ki-67 index.

Although scientific evidence concerning the diagnostic and prognostic value of the Ki-67 index in carcinoid tumors has expanded recently, there are some

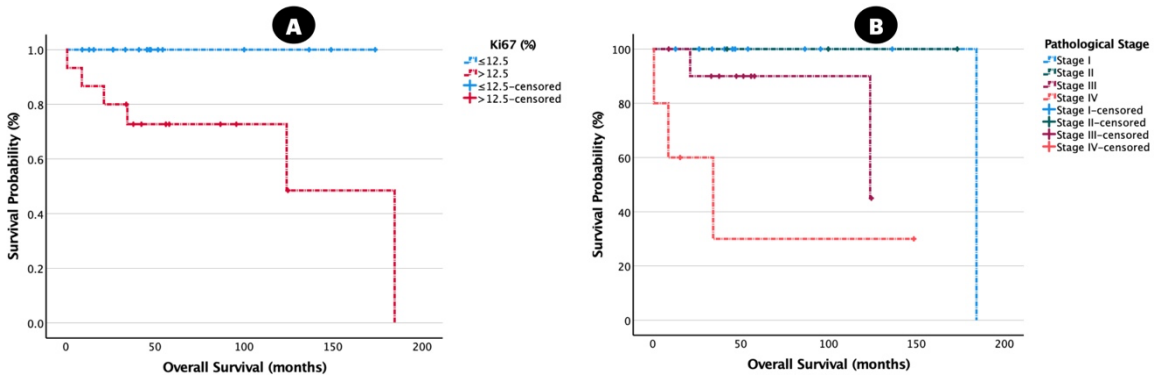

Fig. 3. Kaplan Meier curves of overall survival according to the Ki-67 index (A) and stage (B).

limitations regarding its clinical use: interobserver variability, intratumoral heterogeneity, and interlaboratory variability caused by various reasons such as fixation and tissue processing [30-32]. In addition, a substantial limitation is the lack of internationally accepted cut-off values in carcinoid tumors, in contrast to gastroenteropancreatic neuroendocrine neoplasms.

Several limitations to using TNM staging in lung carcinoids are reported [7, 13]. Although new staging recommendations have been proposed by incorporating prognostic parameters such as histological grade and ki-67, international guidelines recommend the 8th TNM edition [14, 16]. TNM staging is the most noteworthy prognostic parameter after histological grade [14]. Numerous reports support the prognostic value of TNM staging in the literature, consistent with our results [33, 34].

Limitations

Our study has several limitations, such as its retrospective design and limited number of patients due to the rarity of the disease. In addition, a multivariate analysis could not be performed due to the low number of cases and DFS events.

CONCLUSION

In conclusion, the Ki-67 index and 8th TNM staging have prognostic value on DFS and OS in patients with atypical carcinoids. Embodying Ki-67 into the TNM staging system may improve its prognostic value. Large-scale studies are needed to determine the optimal cut-off value.

Authors' Contribution

Study Conception: ABS, BO, EC; Study Design: TE, EC, ABS; Supervision: TE, EC, HM, ASB; Funding: N/A; Materials: N/A; Data Collection and/or Processing: BE, BC, BO, HM, EUA; Statistical Analysis and/or Data Interpretation: ABS, ASB, AD; Literature Review: BE, BC, BO, HM, EUA; Manuscript Preparation: ABS, BE, BC, AD and Critical Review: ASB, TE, EUA, AD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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