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Original Article

Wedge resection versus anatomic resection for long-term survival outcomes of stage IA pulmonary atypical carcinoids: a SEER population-based study

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Abstract: Background: This study aims to compare the long-term survival of patients with stage IA atypical carcinoids (ACs) who underwent wedge resection versus those who underwent anatomic resection. Methods: Patients with pathological stage IA AC from the Surveillance, Epidemiology, and End Results (SEER) database diagnosed between 2004 and 2015 were included. Cox regression analyses were used to assess the association of overall survival (OS) and type of surgery. Subgroup analyses were conducted to further validate the robustness of our findings. Results: Among the 299 eligible patients, 168 (73.4%) patients underwent anatomic resection, and 61 (26.6%) patients underwent wedge resection. A multivariate Cox analysis demonstrated that age at diagnosis (HR: 5.935, P < 0.001) and surgical resection (HR: 0.409, P = 0.004) were independent prognostic factors for predicting long-term OS. In the subgroup analysis, the patients who had anatomic resections were significantly associated with better clinical outcomes than those who underwent wedge resections when the tumor size was between 20 mm and 30 mm (HR: 0.178, P = 0.006). We also found that anatomic resection tended to have a benefit for the prognosis among tumors ranging from 10 mm to 20 mm, but without statistical significance (P = 0.058). There was no significant difference when tumor size ≤ 10 mm (P = 0.006). Conclusions: Anatomic resection showed superior long-term survival compared with wedge resection in patients with stage IA ACs and with a tumor size between 10 mm and 30 mm. For patients with a tumor size ≤ 10 mm, wedge resection showed acceptable clinical outcomes.

Keywords: Pulmonary atypical carcinoids, SEER database, wedge resection, anatomic resection, survival, tumor size, lung cancer, surgery, mortality, prognosis

Introduction

Pulmonary carcinoids (PCs) are rare tumors with an age-adjusted incidence rate ranging from 0.2 to 2/100,000 population/year in both United States and Europe, accounting for 1-2% of all invasive lung malignancies [1, 2], the second most common site of carcinoid tumors [3]. PCs are classified into typical carcinoids (TCs, about 90%) and atypical carcinoids (ACs, about 10%) based on histologic features according to the widely accepted WHO 2004 scheme [4, 5]. Compared with TCs, ACs are more uncommon and most ACs are usually peripheral [6-8]. More importantly, ACs characterized by increased mitotic activity, cellular atypia or necrosis in pathology show a tendency for a higher rate of nodal involvement and metastasis and have a worse long-term survival rate [5, 9-11].

In recent years, the diagnostic rate of early-stage ACs has been rising with the extensive application of cross-sectional imaging and the increased use of special immunohistochemistry (IHC) stains [12]. The evaluation of the treatment and prognosis of early-stage ACs deserves more serious attention. According to different established guidelines, surgical resection in localized pulmonary ACs is endorsed, but the optimal surgical extent for early stage ACs is still debated [1, 13]. Previous studies seem to be unsatisfactory, and they were mainly carried out as follows [14, 15]: at first, given the rarity

and the resulting paucity of data, detailed independent analyses for the prognosis of early stage ACs, though necessary, were scarce or small-scale. In addition, due to the lack of prospective studies, the long-term survival outcomes of anatomic resection (lobectomy/segmentectomy) versus wedge resection (WR) for patients with stage IA ACs remains unknown [16]. It was widely accepted that surgical resection represents the cornerstone of AC treatment [1]. Nevertheless, most prior retrospective studies for surgical treatment only included small-sample, single-institution cases series of entire ACs [17-20], and they did not emphasize early-stage tumors.

In this study, we used the population-based Surveillance, Epidemiology, and End Results (SEER) registry to evaluate the prognostic factors and assess the equivalency of wedge resection versus anatomic resection among patients with pulmonary ACs ≤ 30 mm in size.

Materials and methods

Patient identification and data extraction

The data used in this study was extracted from the SEER registry program of the National Cancer Institute. Since 1973, SEER has been collecting data regarding the cancer incidence and survival of approximately 28% of the US population and providing national leadership in the science of cancer surveillance [21]. The tumor locations and histology were identified according to the International Classification of Diseases for Oncology, Version 3 (ICD-O-3) in the SEER database. The tumor stages were coded according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system [22]. Information about the latest eighth TNM staging has not been provided in the SEER database. The patients selected in the analyses were cases with histologically confirmed stage IA (AJCC 7th edition) atypical pulmonary carcinoid tumors (ICD-O-3 site code C34; ICD-O-3 morphology code 8249) recorded between January 2004 and December 2015. The exclusion criteria were as follows: multiple primaries; patients aged < 18 years old; patients who were not given a histologically confirmed diagnosis; carcinoma in situ; patients with missing or insufficient data on tumor size, extent of the surgery, TNM staging, survival status, and cause of death; survival time ≤ 1 month.

The following variables were obtained for each included patient from the SEER database: patient demographics (patient ID, year of birth, year of diagnosis, age at diagnosis, sex, race, marital status, and normalized cost-of-living index); clinicopathological characteristics of the tumors (diagnostic confirmation, location of the lesion, laterality, tumor size, tumor differentiation, and TNM staging); therapy information (surgical approach, lymph node surgery, and radiation) and survival information (vital status, cause of death, and survival months). It was noted that the stages of the patients were then updated in line with the 8th edition of the AJCC criteria [23].

Surgical procedure and lymphadenectomy

In the SEER database, the surgery codes for the patients diagnosed between 2004 and 2015 were included in 'RX Summ-Surg Prim Site', which is defined as the surgical procedure that removed tissue from the primary site performed as part of the first course of therapy. For classifying the extent of the resection, our analysis categorized surgical procedures coded into 2 groups: wedge resection (codes 21) and anatomic resection contains segmenctomy (codes 22) and lobar resection (codes 30-33). And during the initial course of therapy, the resection of lymph nodes coded as 'Scope Reg LN Sur' was used to describe the procedure of dissection or sampling of the regional lymph nodes performed.

Statistical analysis

In the current study, overall survival (OS) was chosen as the primary endpoint of our study. Causes of death were coded using the SEER database according to the information extracted from the death certificate data. OS was defined as the time from diagnosis to all-causes of death. X-tile (Version 3.6.1; Yale university, New Haven, CT, USA), a bio-statistics tool, was used to determine the optimal cut-off of age for survival, similar to the method used in previous publications [24, 25]. In the current study, categorical variables were displayed as count and percentages. Kaplan-Meier (KM) survival analyses were used to estimate the OS and curves for visualizing the survival of vari-

Table 1. Baseline characteristics of the study population

Characteristics	Level	Number	Percentage (%)
Total		229	100
Age at diagnosis[a]	24-66 years	135	59.0
	67-76 years	72	31.4
	77-89 years	22	9.6
Sex	Male	61	26.7
	Female	168	73.4
Race	White	211	92.1
	Black	11	4.8
	Others	7	3.1
Marital status	Single	25	10.9
	Married	130	56.8
	Divorced/Separated	41	17.9
	Others	33	14.4
Household income	Higher than U.S. mean	129	56.3
	lower than U.S. mean	100	43.7
Location	Upper lobe	87	38.0
	Middle lobe	48	21.0
	Lower lobe	87	38.0
	Main bronchus/others	7	3.1
Laterality	Right	140	61.1
	Left	89	38.9
Tumor size (mm)	≤ 10 mm	41	17.9
	10-20 mm	123	53.7
	20-30 mm	65	28.4
Differentiation	Well differentiated	32	14.0
	Moderately differentiated	76	33.2
	Others/unknown	121	52.8
Surgical resection	Wedge resection	61	26.6
	Anatomical resection	168	73.4
Lymph node surgery	No	41	17.9
	Yes	188	82.1
Radiation	No	226	98.7
	Yes	3	1.3

[a]Subgroups identified by two optimal cut-offs of age from the X-tile analysis: 66 years and 76 years.

ables, with log-rank tests used to determine the statistical differences across subgroups stratified by each covariate. The 3-year and 5-year OS rates were also reported in detail.

For the univariate analyses, the relationships between various variables and OS were determined. Those that exhibited $P < 0.100$ and were potentially associated with the clinical prognosis were assembled into a multivariate analysis using the Cox proportional hazards model to determine the effect of each variable, which are described as hazard ratios (HRs) and 95% confidence intervals (CIs). Subgroup analyses of the OS were conducted using Cox proportional hazard analyses based on different variables and presented on the forest plot.

A 2-sided $P < 0.050$ was considered statistically significant. The SEER*Stat software program (version 8.3.5; National Cancer Institute, Bethesda, MD, USA) was used for data extraction. All the statistical analyses were performed using SPSS (Version 24.0; IBM Corporation, Armonk, NY, USA). This study utilized the anonymous data available in the SEER database, hence the requirement for informed consent was waived. This study was approved by the Institutional Review Board of Changzheng Hospital (The Naval Medical University, Shanghai, People's Republic of China).

Results

Patient characteristics

Following the inclusion and exclusion criteria described above, there were 229 patients with stage IA ACs identified in our final analysis (**Table 1**). Of the 229 patients, 135 (59.0%) patients ranged in age from 24 to 66 years old. Female patients comprised 73.4% of the entire cohort. A total of 123 (53.7%) of the patients had tumors between 10 mm and 20 mm in diameter, followed by 65 (28.4%) with tumor sizes between 20 mm and 30 mm in diameter, and 41 (17.9%) with tumors less than 10 mm in size. Regarding the surgical treatment, 168 (73.4%) underwent an anatomic resection, and 61 (26.6%) underwent a wedge resection. All the baseline characteristics of the patients are summarized in **Table 1**. The median follow-up time was 4.08 years (standard deviation [SD], 3.21).

Survival analysis

The 3-year OS and 5-year OS rates for the anatomic resection group were 94.8% and 88.5%, and the 3-year OS and 5-year OS rates for the wedge resection group were 89.4% and 64.5%, respectively. The Kaplan-Meier curves for OS in the whole population and the curves stratified by each variable are shown in **Figure 1**.

In the univariate analysis, age at diagnosis, surgical resection, and lymph node surgery were identified as potential prognostic factors, so they were subsequently entered into the multivariate Cox regression model (**Table 2**).

Our multivariate analysis demonstrated that age at diagnosis (HR: 5.935, 95% CI: 2.656-13.262, P < 0.001) and type of surgery (HR: 0.409, 95% CI: 0.224-0.355, P = 0.004) were independent predictors for long-term OS among stage IA AC patients (**Table 3**). Our results suggests that younger patients treated with anatomic resection are associated with better clinical OS.

Subgroup analyses were conducted to validate the robustness of our findings. The survival results are presented on the forest plot (**Figure 2**). The results demonstrate that the patients who underwent anatomic resection were correlated with better OS than the patients who underwent wedge resection in nearly half of the subgroups including age between 24 years and 66 years (HR: 0.179, 95% CI: 0.064-0.499, P < 0.001), white race (HR: 0.447, 95% CI: 0.237-0.843, P < 0.001), Married status (HR: 0.280, 95% CI: 0.117-0.671, P = 0.004), a lower household income (HR: 0.208, 95% CI: 0.086-0.500, P = 0.001), a lower lobe (HR: 0.337, 95% CI: 0.128-0.889, P = 0.028), right lung (HR: 0.398, 95% CI: 0.186-0.854, P = 0.018), a tumor size between 20 mm and 30 mm (HR: 0.178, 95% CI: 0.052-0.616, P = 0.006), moderately differentiated (HR: 0.346, 95% CI: 0.128-0.936, P = 0.037), lymph node surgery (HR: 0.389, 95% CI: 0.186-0.814, P = 0.012), and without radiation (HR: 0.445, 95% CI: 0.243-0.816, P = 0.009).

Discussion

Pulmonary AC tumors are intermediate-grade malignant tumors and the least common primary pulmonary neuroendocrine tumors (NETs) [1, 2]. There are many studies that evaluate the surgical extent in early-stage non-small cell lung cancer (NSCLC) [26, 27]. However, most of them focus on TCs [9, 28] and lung cancer patients should receive tailored treatment based on the histological subtype because of the disparities in tumor aggressiveness [29]. With the increasing detection of early-stage pulmonary AC tumors in the aging population with limited cardiopulmonary reserve, interest in the optimal surgical approach has been renewed. To this end, large population-based studies are needed to estimate the potential independent prognostic factors for survival and explore the optimal treatment strategy, especially for early-stage ACs.

In our cohort, the age at diagnosis ranged from 67 to 89 years, accounting for 41.0% of the total and associated with a worse OS. Our result was in accordance with previous reports of poor outcomes in older patients [14, 30-33]. Fox et al. [32] identified age as a significantly negative prognostic factor (< 60 vs. > 75; HR 6.062; P < 0.001) among patients with TC tumors (N = 3084) and patients with AC tumors (N = 186) based on another SEER analysis from 2000 to 2007. Wu et al. [30] also found worse survival in patients aged ≥ 56 years at diagnosis compared with those aged < 56 years in their series of 176 pulmonary NETs including ACs (N = 46), which was likely related to the poor immunity to the illness and the higher comorbidities of the elderly patients. In addition, previous studies reported that older patients had the tendency to a more aggressive tumor histology and had a higher rate of metastasis compared with the younger patients [10, 34, 35]. Our study still achieved a similar result in AC tumors without lymph node involvement and metastasis, confirming the negative effect of age on survival again. Tumor size is a known prognostic factor and is important for planning the surgical treatment in NSCLC [36, 37]. In our study, however, tumor size was not a prognostic factor in either the univariate or multivariate analysis. Similar to our study, a retrospective analysis including 96 patients with TCs and 25 patients with ACs showed that tumor size was not associated with either the recurrence rate or the survival [38]. Furthermore, there was no sex or race predilection related to OS in our analyses. In the current study, it was observed that ACs are

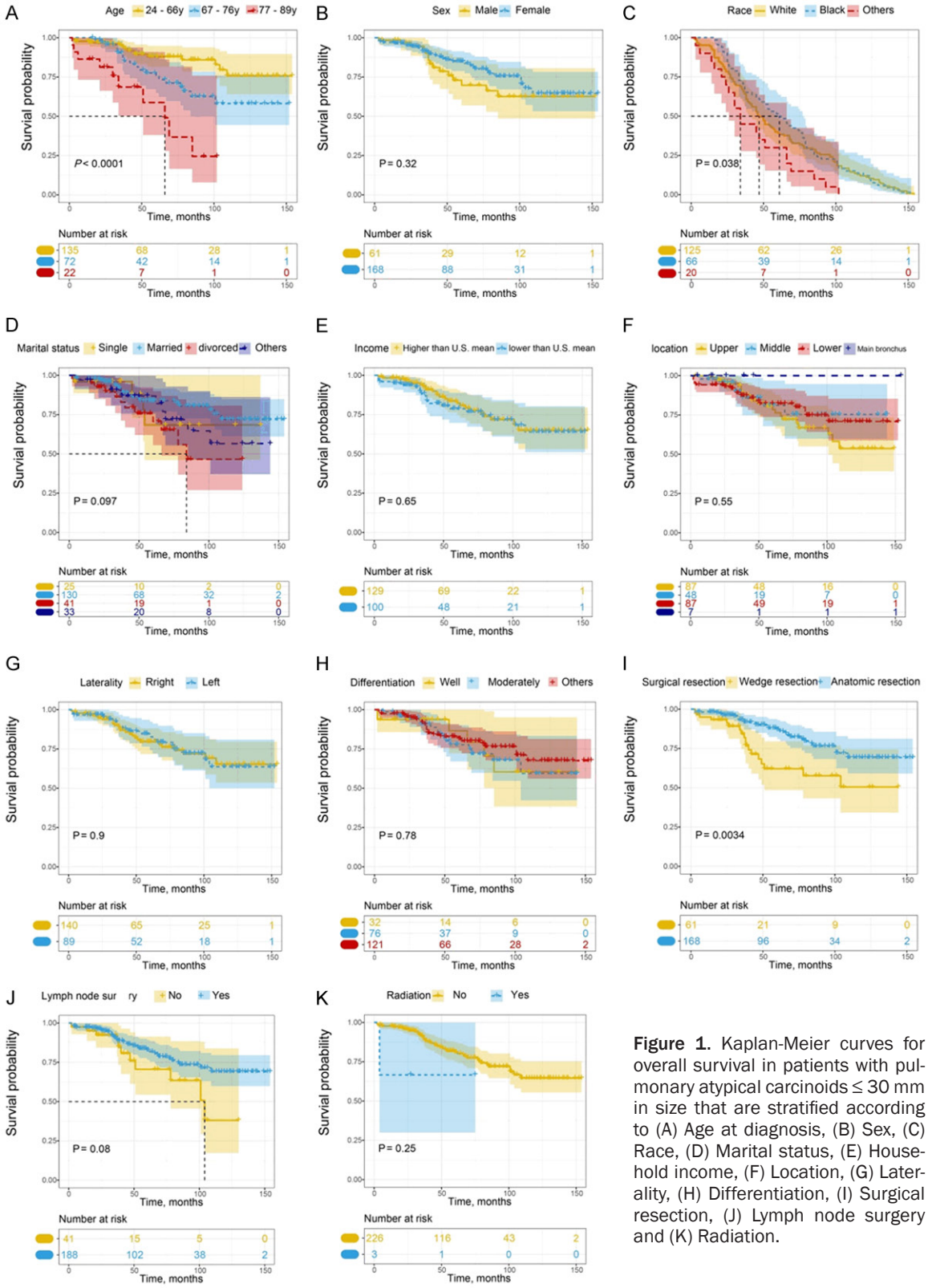


Figure 1. Kaplan-Meier curves for overall survival in patients with pulmonary atypical carcinoids ≤ 30 mm in size that are stratified according to (A) Age at diagnosis, (B) Sex, (C) Race, (D) Marital status, (E) Household income, (F) Location, (G) Laterality, (H) Differentiation, (I) Surgical resection, (J) Lymph node surgery and (K) Radiation.

more prevalent in women (N = 168; 73.4%), and this is similar to observations in previous publications [3, 31]. However, two previous studies reported that women constituted about 46% and 50% of the population [14]. This difference might reflect the fact that the data col-

Table 2. Univariate analysis of the risk factors for OS

Characteristics	Level	HR	95% CI	*P* value
Total				
Age at diagnosis[a]	24-66 years	Reference		-
	67-76 years	2.184	1.131-4.218	0.020
	77-89 years	6.100	2.740-13.580	< 0.001
Sex	Male	Reference		
	Female	0.734	0.396-1.360	0.326
Race	White	Reference		
	Black	1.009	0.244-4.185	0.990
	Others	1.277	0.308-5.288	0.736
Marital status	Single	Reference		
	Married	0.723	0.24-2.113	0.553
	Divorced/Separated	1.754	0.565-5.448	0.331
	Others	1.174	0.361-3.821	0.790
Household income	Higher than U.S. mean	Reference		
	lower than U.S. mean	1.145	0.640-2.047	0.648
Location				0.503
	Upper lobe	Reference		
	Middle lobe	0.701	0.299-1.643	0.414
	Lower lobe	0.735	0.390-1.384	0.340
	Main bronchus/others	0.000	0.000-Inf	0.996
Laterality	Right	Reference		
	Left	0.963	0.535-1.733	0.899
Tumor size				0.991
	≤ 10 mm	Reference		
	10-20 mm	0.970	0.440-2.139	0.940
	20-30 mm	0.701	0.281-1.744	0.445
Differentiation				0.949
	Well differentiated	Reference		
	Moderately differentiated	1.085	0.424-2.775	0.865
	Others/unknown	0.869	0.355-2.127	0.759
Surgical resection	Wedge resection	Reference		
	Anatomic resection	0.423	0.233-0.767	0.005
Lymph node surgery	No	Reference		
	Yes	0.550	0.278-1.086	0.085
Radiation	No	Reference		
	Yes	3.046	0.417-22.257	0.272

[a]Subgroups identified by two optimal cut-offs of age from the X-tile analysis: 66 years and 76 years. Abbreviations: OS, overall survival; HR, Hazard ratio; CI, confidence interval.

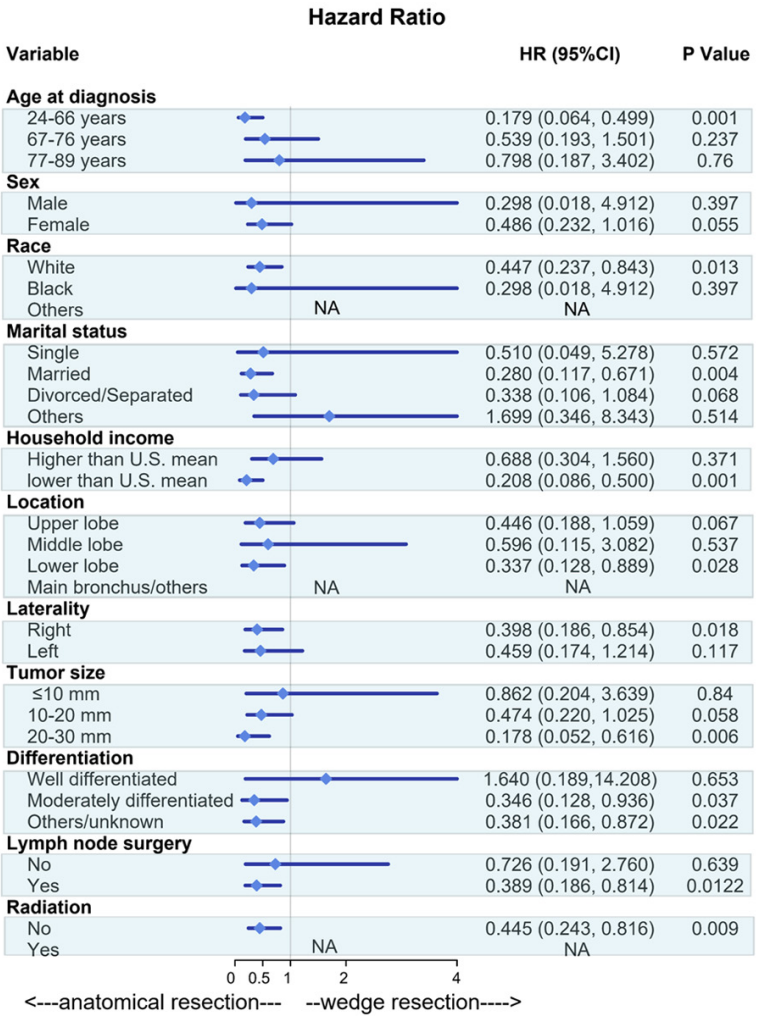
lected from the SEER 18 registries were more representative.

Surgical resection, the only curative approach, remains the cornerstone of various therapies, especially in the early stage carcinoids [1, 39]. In our study, anatomic resection (N = 168, 73.4%) was the most common surgical approach, similar to previous studies [31, 32]. Raz et al. [40] observed that patients with TC tumors may have excellent long-term survival without surgical resection with a high 5-year disease-specific survival (DSS) rate of 88.0%. DSS might overestimate true DSS in indolent and slowly growing diseases such as TCs. However, ACs had an aggressive biological behavior and a higher incidence of nodal involvement and metastasis compared with

Table 3. Multivariate analysis of the risk factors for OS

Characteristics	Level	HR	95% CI	*P* value
Total				
Age at diagnosis[a]	24-66 years	Reference		
	67-76 years	2.391	1.233-4.636	0.010
	77-89 years	5.935	2.656-13.262	< 0.001
Surgical resection	Wedge resection	Reference		
	Anatomic resection	0.409	0.224-0.355	0.004

[a]Subgroups identified by two optimal cut-off of age from the X-tile analysis: 66 years and 76 years. Abbreviations: OS, overall survival; HR, Hazard ratio; CI, confidence interval.



TCs [41, 42]. Therefore, it should be emphasized that patients with early stage ACs who are fit for surgery should still undergo surgical resection.

The optimal extent of the surgical approaches for this disease is still controversial. Our comprehensive analyses showed the superiority of anatomic resection to wedge resection in OS among patients with tumors between 20 mm and 30 mm. We also found that anatomic resection tended to have a benefit for the prognosis among patients with tumors ranging from 10 mm to 20 mm, but without statistical significance. In the subgroups of tumor size ≤ 10 mm, however, there was an equivalence in survival between the two types of surgery.

The European Neuroendocrine Tumor Society (ENETS) guidelines [1] indicated that complete anatomic resection should be recommended for peripheral ACs with a lower local recurrence rate. Cañizares et al. [15] concluded that wedge resection is an independent negative prognostic factor for ACs. Rahouma and his colleagues [43] reported that anatomical resections are superior to wedge resections for DSS in patients with T1a AC tumors (≤ 20 mm). The limitations of their study included the fact that only 68 T1a patients were enrolled in the cohort and the inferior OS of the wedge resection cohort was also influenced by confounders such as N stage and M stage, which were not restricted during the population selection process. Different from the AC tumors, Rahouma [43] and Filosso [44] reported that wedge resection had an equivalent DSS to anatomic resection in patients with early stage

typical carcinoids after a propensity score matching (PSM) analysis, which indicated that tumor histology is the important determinant of the extent of surgical resections among patients with pulmonary carcinoids. It is suggested that preoperative needle biopsies and intraoperative frozen section examinations should be performed to try to differentiate between the TCs and ACs.

Several previous studies based on the SEER database and the National Cancer Data Base (NCDB) came to a similar conclusion that sublobar resection compared with lobectomy is associated with noninferior survival in patients with early stage typical carcinoid of the lungs [16, 32, 45, 46]. The major limitation of these studies was that the authors grouped wedge and segmental resections together, which was incorrect from an oncological point of view. Survival is similar between lobectomy and segmentectomy for clinical T1N0 and unsuspected pathological N1/N2 nodal metastases [47].

Although atypical carcinoid tumors are considered intermediate-grade tumors with relatively indolent biological behavior, they might be locally aggressive and have higher rates of lymph node involvement at diagnosis (36.6%) [11, 48]. Given the involvement of the adjacent lymph nodes in locally advanced pulmonary carcinoids, the North American Neuroendocrine Tumor Society (NANETS), the National Comprehensive Cancer Network (NCCN), and the ENETS guidelines recommend that either sampling or lymph node dissection should be performed during the local resection [13, 39, 49]. Considering the risk of missing possible N1 nodes located between the site of the wedge resection and the dissected mediastinal lymph nodes, a wedge resection alone is not recommended by some surgeons. In our study, lymph nodal resection during surgery was not an independent factor for stage IA patients. However, lymph node assessment should be performed to accurately stage patients [50].

For early stage resectable ACs, adjuvant therapy has not been well studied, and its implementation is still in dispute. The NCCN guidelines don't support the utility of adjuvant therapy for stage I and II pulmonary NETs [39]. The ENETS [1] guidelines indicate that adjuvant treatment may be considered in patients with ACs with positive lymph nodes. However, Anderson et al. [51] conducted a retrospective study of pathologically node-negative (pN0) and node-positive (pN+) patients who either had an operation alone or who received adjuvant treatment postoperatively. They concluded that adjuvant therapy didn't confer superior survival in the pN0 and pN+ patients with atypical carcinoid tumors. In our univariate analysis, radiation or chemotherapy had a worse overall survival in the node-negative patients. However, our results were limited due to some missing data and the lack of exact chemotherapies or radiation schedules, so further studies with larger cohorts are needed. For patients with advanced or metastatic tumors, a multidisciplinary approach should be used. An optimal management approach (observation, surgery, and systemic therapy) should be identified after the discussion within the multidisciplinary tumor board [48, 52].

Limitations

The study has some limitations. One of them includes the lack of detailed information about smoking history, tumor location (central vs. peripheral), comorbidities, the completeness of the resection (R0, R1, or R2), the extent of the lymphadenectomy, the radiation schedules, and the recurrence development. In addition, this study is a retrospective analysis and they almost always have bias caused by an imbalance of the prognostic factors, though statistical adjustment methods are used. Randomized trials or prospective registries could provide more definitive answers about the optimal surgical management; however, such efforts would be challenging to organize for this rare disease.

Conclusion

To the best of our knowledge, this study is the largest study of stage IA atypical carcinoids reported to date. In summary, the extent of surgical resections and the patients' ages were independent predictors for OS. Wedge resection showed acceptable oncologic outcomes in patients with a tumor size ≤ 10 mm and should be considered an alternative for patients who are unable to endure a more extensive and complex resection. For patients with a tumor size between 10 mm and 30 mm, anatomic resection leads to a better prognosis and is the optimal therapeutic strategy.

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Disclosure of conflict of interest

None.

Abbreviations

PCs, Pulmonary carcinoids; TCs, Typical carcinoids; ACs, Atypical carcinoids; IHC, Immunohistochemistry; SEER, Surveillance Epidemiology and End Results; ICD-O-3, International Classification of Diseases for Oncology, Version 3; AJCC, American Joint Committee on Cancer; OS, Overall survival; KM, Kaplan-Meier; HRs, Hazard ratios; Cis, Confidence intervals; NETs, Neuroendocrine tumors; NSCLC, Non-small cell lung cancer; DSS, Disease-specific survival; ENETS, European Neuroendocrine Tumor Society; PSM, propensity score matching, NCDB, National Cancer Data Base; NANETS, North American Neuroendocrine Tumor Society; NCCN, National Comprehensive Cancer Network; pN0, Pathologically node-negative; pN+, Pathologically node-negative.

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