Wedge resection is equal to segmental resection for pulmonary typical carcinoid patients at localized stage: a population-based analysis

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ABSTRACT

Background. Medical institutions worldwide have not reached a consensus on what surgery is the most advisable for pulmonary typical carcinoid (TC) patients at the localized stage. This research focuses on exploring whether wedge resection or segmental resection is the superior option.

Methods. The demographic and clinical information of 1,887 TC patients diagnosed at the localized stage from 2004 to 2015 was collected from the Surveillance, Epidemiology, and End Results (SEER) Program. Patient prognosis was evaluated by KM curves. The chi-square test was used to examine the variation between different groups that would be eliminated by propensity score matching (PSM). Univariate and multivariate Cox proportional hazard model analyses were used to evaluate prognostic values of relative factors.

Results. The prognosis of TC was the most favorable for patients suffering from pulmonary squamous cell carcinoma (SCC), adenocarcinoma (ADC), and pulmonary carcinoids (PCs). The choice to have surgery, not the type of surgery chosen, was the most significant independent prognostic factor correlated with overall survival (OS) and lung cancer-special survival (LCSS). The prognostic result of the comparison between wedge resection and segmental resection was not statistically significant before or after PSM. In subgroup analysis, the inference still held.

INTRODUCTION

Typical carcinoid (TC) is one of four major pathological classifications of neuroendocrine tumor (NET) of the lung categorized by the World Health Organization (WHO). The others are atypical carcinoid (AT), large-cell neuroendocrine carcinoma (LCNEC), and small-cell lung cancer (SCLC) (Caplin et al., 2015). Data shows that bronchopulmonary...
or lung NETs constitute approximately 25 percent of carcinoma of the lungs, while the prevalence of primary NETs is 20–25% (Ramirez et al., 2017; Yao et al., 2008). Compared with other types of NET, the incidence of TC and AT is lower and accounts for 1–2% of pulmonary malignant tumor (Chen, Travis & Krug, 2006; Travis, 2010). Another study indicates that there are 10 times more TC than AT patients (Gosain et al., 2018; Rekhtman, 2010). Until now, surgery has been the main treatment for TC, the low-grade lung NET, at the localized stage (Wolin, 2015; Wolin, 2017). The recommendation of adjuvant therapy, especially radiation and chemotherapy, remains controversial (Wolin, 2017).

For early stage patients with operable TC, there is no general agreement on the optimal operation mode (Fox et al., 2013; Mezzetti et al., 2003; Raz et al., 2015; Rea et al., 2007). Lobectomy and sublobectomy (wedge resection and segmental resection) are the major surgical options for localized diseases. Traditionally, anatomic resection (lobectomy and segmental resection) is considered the best option for patients with peripheral lung tumors, while segmentectomy and wedge resection are widely used for patients who have limited pulmonary function (Caplin et al., 2015). Recently, Taher Abu Hejleh et al. (Furqan et al., 2018), after collecting and researching the SEER data, suggested that the prognoses for lobectomy and sublobectomy were comparable. Some studies have shown segmental resection to be superior to wedge resection in liver cancer and non-small cell lung cancer (NSCLC) (El-Sherif et al., 2007; DeMatteo et al., 2000). Other studies found no differences between wedge resection and segmental resection in lung neoplasm (Altorki et al., 2016; Romano & Mark, 1992). However, currently no research compares the two operations, wedge resection and segmental resection, which constitute the sublobectomy, in TC patients. Although both surgeries are sublobectomies, wedge resection causes a smaller operative wound than segmental resection.

Now that surgery is the main choice of treatment for TC patients, and given that other therapeutic methods are not powerful, the smaller operative wound is a major consideration after guaranteeing the survival rate. The objective of this research is to determine if there is a difference between wedge resection and segmental resection for early stage TC patients.

**MATERIALS & METHODS**

**Data source**

We have been given access to the SEER databases in October 2018 with the “numbered” SEER*Stat account(12991-Nov2017). The retrospective research collected the data from the Surveillance, Epidemiology and End Results (SEER) by using SEER*Stat 8.3.5 in December 2018. The inclusion criteria were as follows: (I) TC patients (code 8240) at the localized stage; (II) patients treated via no surgery at the primary site (code 00), wedge resection (code 21), segmentectomy (code 22), or lobectomy (code 33); (III) patients with only one primary tumor. The exclusion criteria included: (I) diagnosis before 2004, (II) survival of less than one month or unknown, (III) lung cancer-special survival (LCSS) missing, (IV) tumor size unknown, (V) scope of regional lymph node surgery unknown, (VI) radiation therapy unknown, and (VII) regional, distant, or unknown summary stage.
Variates
Demographic information for patients included patient ID, age, gender, and race. Age at diagnosis was divided into two groups, under 70 and 70 or older. Race was categorized into white and other. Variables collected for the research included pathological data, treatment, and follow-up information, such as laterality, surgery, procedure used, tumor size, scope of regional lymph node surgery, radiation, chemotherapy, summary stage, differentiation grade, overall survival status, LCSS, and survival month.

Statistical analyses
Unbalanced distribution of variables between groups was evaluated by chi-square test. A KM curve was generated to assess survival and a log-rank test was used to evaluate survival discrepancy. Univariate and multivariate Cox proportional hazards regressions were conducted to evaluate the effects of involved factors on prognosis, acquire hazards ratio, and generate a 95% confidence interval (HR and 95% CI). Propensity score matching (PSM) of 1:1 was used to eliminate the differences of variable components between wedge and segmental resection, and the caliper was 0.01. Statistical analysis was performed with SPSS 24.0 software (SPSS Inc, Chicago, IL). Significance was set at $P$ of less than 0.05.

RESULT
Prognosis for carcinoid, squamous cell cancer (SCC), and adenocarcinoma (ADC) in lung
Presently squamous cell cancer and adenocarcinoma are common forms of lung cancer, accounting for 78% of this disease. Lung carcinoid is composed of typical carcinoid and atypical carcinoid. To acquire general prognosis information about TC patients, we compared the cumulative survival rate for lung carcinoid and its components with SCC and ADC. The clinical information was recorded in Table 1. Obviously, carcinoid has the more favorable prognosis compared with SCC and ADC in overall survival (OS) and lung cancer-specific survival (LCSS) (Fig. 1), as follows: hazard ratio (HR) = 0.149 (0.141–0.519), $P < 0.001$ of carcinoid versus ADC in OS; HR = 0.092 (0.085–0.100), $P < 0.001$ of carcinoid versus ADC in LCSS; HR=1.192 (1.181–1.204), $P < 0.001$ of SCC versus ADC in OS; HR = 1.135 (1.123–1.147), $P < 0.001$ of SCC versus ADC in LCSS.

Furthermore, TC has a better prognosis than AT in OS and LCSS, as follows: HR = 2.105 (1.786–2.480), $P < 0.001$ of AT versus TC in OS; HR=3.768 (3.122–4.549), $P < 0.001$ of AT versus TC in LCSS.

In conclusion, typical carcinoid has a more favorable prognosis than the other three types of lung cancers.

Baseline information of TC patients from SEER database
There were 1,887 TC patients in our cohort: 235 patients with no surgery, 465 undergoing wedge resection, 113 receiving segmental resection, and 1,074 going under the lobectomy. Some demographic and clinical information, such as age, gender, race, etc., was been recorded (Table 2). Notably, 71.8% patients were female and most patients were white. Compared with the no surgery group, the percentages of old patients (age $\geq$ 70 years)
| Race     | Adenocarcinoma | SCC  | Carcinoid | AC  | TC  |
|----------|----------------|------|-----------|-----|-----|
| White    | 133,061        | 66,319| 4,666     | 4,183| 483 |
| Black    | 19,659         | 10,057| 381       | 344 | 37  |
| Others   | 15,546         | 4,311 | 197       | 19  | 178 |
| Gender   |                |      |           |     |     |
| Female   | 87,558         | 29,751| 3,574     | 350 | 3,224|
| Male     | 80,708         | 50,936| 1,670     | 189 | 1,481|
| Primary Site |            |      |           |     |     |
| Main Bronchus | 4,914  | 5,190 | 286       | 30  | 256 |
| Upper Lobe | 84,247        | 42,587| 1,540     | 171 | 1,369|
| Middle Lobe | 8,221         | 2,833 | 897       | 88  | 809 |
| Lower Lobe | 44,029         | 22,265| 2,117     | 201 | 1,916|
| Others   | 26,855         | 7,812 | 404       | 49  | 355 |
| Laterality |             |      |           |     |     |
| Left     | 63,614         | 33,873| 2,065     | 215 | 1,850|
| Right    | 95,605         | 44,602| 3,069     | 314 | 2,755|
| Others   | 9,047          | 2,212 | 110       | 10  | 100 |
| Grade    |                |      |           |     |     |
| I        | 15,316         | 1,642 | 1,767     | 60  | 1,707|
| II       | 32,248         | 21,232| 488       | 175 | 313 |
| III      | 39,710         | 27,415| 39        | 11  | 28  |
| IV       | 1,457          | 574   | 15        | 5   | 10  |
| Others   | 79,535         | 29,824| 2,935     | 288 | 2,647|
| TNM Stage|                |      |           |     |     |
| I        | 33,843         | 17,665| 1,936     | 240 | 1,696|
| II       | 6,339          | 5,573 | 400       | 56  | 344 |
| III      | 34,607         | 24,946| 301       | 112 | 189 |
| IV       | 80,900         | 27,311| 338       | 104 | 234 |
| Others   | 12,577         | 5,192 | 2,269     | 27  | 2,242|
| T        |                |      |           |     |     |
| 0        | 895            | 189   | 0         | 0   | 0   |
| 1        | 34,263         | 11,815| 1,703     | 217 | 1,486|
| 2        | 42,925         | 27,268| 724       | 172 | 552 |
| 3        | 6,797          | 7,486 | 268       | 13  | 255 |
| 4        | 61,538         | 26,729| 259       | 99  | 160 |
| Others   | 21,848         | 7,200 | 2,290     | 38  | 2,252|
| N        |                |      |           |     |     |
| 0        | 63,527         | 31,446| 2,504     | 303 | 2,201|
| 1        | 13,234         | 7,844 | 247       | 72  | 175 |
| 2        | 53,635         | 28,058| 264       | 126 | 138 |
| 3        | 20,096         | 8,247 | 38        | 15  | 23  |
| Others   | 17,774         | 5,092 | 2,191     | 23  | 2,168|

(continued on next page)
Table 1 (continued)

|                        | Adenocarcinoma | SCC    | Carcinoid | AC   | TC   |
|------------------------|----------------|--------|-----------|------|------|
| M                      |                |        |           |      |      |
| 0                      | 77,237         | 50,072 | 2,785     | 418  | 2,367|
| 1                      | 80,900         | 27,311 | 338       | 104  | 234  |
| Others                 | 10,129         | 3,304  | 2,121     | 17   | 2,104|
| Summary Stage          |                |        |           |      |      |
| Localized              | 31,653         | 15,415 | 3,346     | 225  | 3,121|
| Regional               | 33,274         | 25,968 | 1,072     | 178  | 894  |
| Distant                | 99,878         | 37,202 | 675       | 119  | 556  |
| Others                 | 3,461          | 2,102  | 151       | 17   | 134  |
| Surgery                |                |        |           |      |      |
| No                     | 120,379        | 61,452 | 1,052     | 127  | 925  |
| Sublobar Resection     | 9,597          | 3,116  | 1,128     | 95   | 1,033|
| Lobectomy/Bilobectomy  | 35,236         | 12,992 | 2,790     | 280  | 2,510|
| Pneumonectomy          | 1,559          | 2,008  | 186       | 29   | 157  |
| Others                 | 1,495          | 1,119  | 88        | 8    | 80   |
| Chemotherapy           |                |        |           |      |      |
| No/Unknown             | 93,973         | 46,482 | 4,953     | 406  | 4,547|
| Yes                    | 74,293         | 34,205 | 291       | 133  | 158  |
| Radiotherapy           |                |        |           |      |      |
| No/Unknown             | 109,686        | 43,866 | 4,973     | 458  | 4,515|
| Yes                    | 58,580         | 36,821 | 271       | 81   | 190  |
| Overall Survival Rate  |                |        |           |      |      |
| 3-year Survival (%)    | 30.81          | 22.67  | 87.88     | 73.28| 89.38|
| 5-year Survival (%)    | 22.78          | 16.01  | 83.03     | 64.50| 84.84|
| 10-year Survival (%)   | 14.81          | 8.56   | 72.43     | 44.30| 74.49|
| Lung Cancer Specific Survival Rate |        |        |           |      |      |
| 3-year Survival (%)    | 34.29          | 27.55  | 92.03     | 76.70| 93.60|
| 5-year Survival (%)    | 27.01          | 21.92  | 89.89     | 67.84| 92.01|
| 10-year Survival (%)   | 21.16          | 17.01  | 85.70     | 48.14| 88.45|

Notes.
SCC, Squamous lung carcinoma; AC, Atypical Carcinoid; TC, Typical Carcinoid.

are less than 30% of the other three surgery groups: 58.3% in no surgery, 27.1% in wedge resection, 15.9% in segmental resection, and 18.1% in lobectomy. Thus, it can be seen that age may be an important factor in choosing a treatment option. In addition, the number of female patients is much larger than that of male patients no matter what treatment they receive. As for the factor “scope of the lymph node,” wedge resection results in less regional lymph node resection compared to segmental resection or lobectomy: the percentage of no regional lymph node resection is 68.6% in wedge resection and 38.9% in segmental resection.

**Prognosis for TC patients treated with no surgery, wedge resection, segmental resection, and lobectomy**
The influence of surgery and surgery type on overall survival (OS) and lung cancer-specific survival (LCSS) for pulmonary TC patients were evaluated using KM curves (Figs. 2A, 2D).
Figure 1  OS and LCSS for ADC, SCC and carcinoid patients evaluated using KM plots. Overall survival and lung cancer-special survival among adenocarcinoma, squamous lung cancer and carcinoid (A, C). Overall survival and Lung cancer-special survival among adenocarcinoma, squamous lung cancer, typical carcinoid and atypical carcinoid (B, D). HR is from Cox regression analysis. P value is from a log-rank test. HR, hazard ratio; OS, overall survival; LCSS, Lung cancer-special survival.
| Table 2  Baseline characteristics of all TC patients. |
|---------------------------------------------------|
| Characteristic                                    | No surgery (n = 235) | Wedge (n = 465) | Segmental (n = 113) | Lobectomy (n = 1074) | Total (n = 1887) |
| Age                                               |                      |                |                    |                       |                  |
| <70y                                              | 98 (41.7%)           | 339 (72.9%)    | 95 (84.1%)         | 880 (81.9%)           | 1412 (74.8%)     |
| ≥70y                                              | 137 (58.3%)          | 126 (27.1%)    | 18 (15.9%)         | 194 (18.1%)           | 475 (25.2%)      |
| Gender                                            |                       |                |                    |                       |                  |
| Female                                            | 172 (73.2%)          | 355 (76.3%)    | 80 (70.8%)         | 738 (68.7%)           | 1345 (71.3%)     |
| Male                                              | 63 (26.8%)           | 110 (23.7%)    | 33 (29.2%)         | 336 (31.3%)           | 542 (28.7%)      |
| Race                                              |                       |                |                    |                       |                  |
| White                                             | 201 (85.5%)          | 419 (90.1%)    | 102 (90.3%)        | 979 (91.2%)           | 1701 (90.1%)     |
| Black                                             | 25 (10.6%)           | 27 (5.8%)      | 8 (7.1%)           | 54 (5.0%)             | 114 (6.0%)       |
| Others                                            | 9 (3.9%)             | 19 (4.1%)      | 3 (2.6%)           | 41 (3.8%)             | 72 (3.9%)        |
| Grade                                             |                       |                |                    |                       |                  |
| Well/Moderate                                     | 76 (32.3%)           | 194 (41.7%)    | 52 (46.0%)         | 571 (53.2%)           | 893 (47.3%)      |
| Poor/Undifferentiated                             | 1 (0.4%)             | 3 (0.6%)       | 1 (0.9%)           | 3 (0.3%)              | 8 (0.4%)         |
| Unknown                                           | 158 (67.3%)          | 268 (57.7%)    | 60 (53.1%)         | 500 (46.5%)           | 986 (52.3%)      |
| Laterality                                        |                       |                |                    |                       |                  |
| Right                                             | 146 (62.1%)          | 261 (56.1%)    | 43 (38.1%)         | 648 (60.3%)           | 1098 (58.2%)     |
| Left                                              | 89 (37.9%)           | 204 (43.9%)    | 70 (61.9%)         | 426 (39.7%)           | 789 (41.8%)      |
| Tumor size                                        |                       |                |                    |                       |                  |
| T1 (≤3 cm)                                        | 184 (78.3%)          | 453 (97.4%)    | 105 (92.9%)        | 904 (84.2%)           | 1646 (87.2%)     |
| T2 (≤5 cm, <3 cm)                                 | 38 (16.2%)           | 11 (2.4%)      | 7 (6.2%)           | 138 (12.8%)           | 194 (10.3%)      |
| T3 (≤7 cm, >5 cm)                                 | 6 (2.5%)             | --             | 1 (0.9%)           | 20 (1.9%)             | 27 (1.4%)        |
| T4 (>7 cm)                                        | 7 (3.0%)             | 1 (0.2%)       | --                 | 12 (1.1%)             | 20 (1.1%)        |
| Scope of regional lymph node                      |                       |                |                    |                       |                  |
| 0                                                 | 235 (100%)           | 319 (68.6%)    | 44 (38.9%)         | 4 (0.4%)              | 602 (31.9%)      |
| 1–3                                               | --                   | 88 (18.9%)     | 29 (25.7%)         | 166 (15.5%)           | 283 (15.0%)      |
| >3                                                | --                   | 58 (12.5%)     | 40 (35.4%)         | 904 (84.1%)           | 1002 (53.1%)     |
| Radiation                                         |                       |                |                    |                       |                  |
| No                                                | 209 (89.9%)          | 462 (99.4%)    | 112 (99.1%)        | 1068 (99.4%)          | 1851 (98.1%)     |
| Yes                                               | 26 (11.1%)           | 3 (0.6%)       | 1 (0.9%)           | 6 (0.6%)              | 36 (1.9%)        |
| Chemotherapy                                      |                       |                |                    |                       |                  |
| No                                                | 232 (98.7%)          | 464 (99.8%)    | 112 (99.1%)        | 1068 (99.4%)          | 1876 (99.4%)     |
| Yes                                               | 3 (1.3%)             | 1 (0.2%)       | 1 (0.9%)           | 6 (0.6%)              | 11 (0.6%)        |

There were significant differences between the group with no surgery and the other three groups, both in OS and LCSS: The 5-year survival rate of the no surgery, wedge resection, segmental resection, and lobectomy, respectively, were 73%, 90%, 94%, and 94% for OS ($P < 0.001$). There is an even greater gap between patients with no surgery and groups who underwent surgery when the 10-year survival rate is examined.

For further research about the impact of surgery type, the three groups were defined here as pairs to be assessed with KM curves (Fig. 3). Although the comparison between lobectomy and wedge resection indicated that the difference in patient prognoses was statistically significant for OS ($P < 0.001$), the propensity score match (PSM) eliminated
Figure 2  OS and LCSS for pulmonary TC patients evaluated using KM plots. Overall survival (A) and lung cancer-special survival (D) among no surgery (n = 235), wedge resection (n = 465), segmental resection (n = 113) and lobectomy (n = 1,074) TC patients at localized stage form SEER project. Overall survival (B) and lung cancer specific survival (E) in wedge resection versus lobectomy after PSM. Overall survival (C) and lung cancer specific survival (F) in wedge resection versus segmental resection after PSM. The difference of OS between two operations was eliminated after PSM: P = 0.256. P value is from a log-rank test. OS, overall survival; LCSS, Lung cancer-special survival; No., no surgery; Wed., wedge resection; Seg., segmental resection; Lob., lobectomy.

this diversity between those groups for OS (P = 0.256) (Figs. 2B, 2E). The results of other contrast groups showed comparable prognoses for both OS and LCSS (P > 0.05).

Univariate and multivariate COX regression analyses of TC patients in the localized stage

Relative risk factors for OS were analyzed using univariate and multivariate COX regression hazard models (Table 3). The factors whose P < 0.05, both in univariate and multivariate analysis, are: age (P < 0.001 in multivariate analysis), gender (P = 0.037 in multivariate...
Three surgery groups were assessed as pairs with KM curves. Overall survival and lung cancer specific survival in wedge resection versus lobectomy, segmental resection versus lobectomy, wedge resection versus segmental resection. There was no significant difference between two surgical options in OS except wedge versus lobectomy: (A) wedge resection versus lobectomy, $P < 0.001$; (B) segmental resection versus lobectomy, $P = 0.150$; (C) wedge resection versus segmental resection, $P = 0.492$. There was no significant difference between two surgical options in LCSS: (D) wedge resection versus lobectomy, $P = 0.983$; (E) segmental resection versus lobectomy, $P = 0.882$; (F) wedge resection versus segmental resection, $P = 0.912$. OS, overall survival; LCSS, Lung cancer-special survival; No., no surgery; Wed., wedge resection; Seg., segmental resection; Lob., lobectomy.

Analysis), and surgery ($P < 0.001$ in multivariate analysis). For OS, age, gender, and surgery were independent prognostic factors with HR as follows: 3.889 (95% CI [2.536–5.965], $\geq 70$ y versus <70 y), 1.574 (95% CI [1.028–2.410], female versus male), 0.520 (95% CI [0.317–0.853], wedge resection versus no surgery, $P = 0.008$), 0.259 (95%CI [0.095–0.706], segmental resection versus no surgery, $P < 0.001$), 0.159 (95% CI [0.059–0.427], lobectomy versus no surgery, $P < 0.001$).

The hazard study for LCSS was completed in the same way (Table 4). Data showed that age ($P = 0.008$ in multivariate analysis), tumor size ($P = 0.012$ in multivariate analysis), and surgery ($P = 0.004$ in multivariate analysis) are independent prognostic factors whose $P < 0.05$ both in univariate and multivariate analysis. As for LCSS, the HR of independent prognostic factors is as follows: 2.261 (95% CI [1.232–4.149], $\geq 70$ y versus...
Table 3  Univariate and multivariate Cox regression analyses according to OS for TC patients.

| Variables in the equation | Univariate | | | | Multivariate | | | |
|---------------------------|------------|---|---|---|------------|---|---|---|
|                           | P          | Hazard ratio (95% CI) | P          | Hazard ratio (95% CI) | | | |
| Age                       |            | | | | | | |
| <70y                      |            | – | – | – | – | – | – |
| ≥70y                      |            | *<0.001 | 4.553 (3.358–6.173) | *<0.001 | 3.889 (2.536–5.965) | | | |
| Gender                    |            | | | | | | |
| Female                    |            | – | – | – | – | – | – |
| Male                      |            | 0.008 | 1.521 (1.116–2.073) | 0.037 | 1.574 (1.028–2.410) | | | |
| Race                      |            | | | | | | |
| White                     |            | 0.050 | – | 0.056 | – | – | – |
| Black                     |            | 0.033 | 1.753 (1.047–2.936) | 0.056 | 2.058 (0.980–4.321) | | | |
| Others                    |            | 0.272 | 0.527 (0.168–1.652) | 0.166 | 0.247 (0.034–1.782) | | | |
| Grade                     |            | | | | | | |
| Well/Moderate             |            | *<0.001 | – | 0.176 | – | – | – |
| Poor/Undifferentiated     |            | 0.011 | 6.285 (1.522–25.950) | 0.063 | 3.992 (0.930–17.137) | | | |
| Unknown                   |            | *<0.001 | 2.172 (1.449–3.255) | 0.902 | 1.035 (0.600–1.785) | | | |
| Laterality                |            | | | | | | |
| Right                     |            | – | – | – | – | – | – |
| Left                      |            | 0.908 | 0.982 (0.724–1.333) | – | – | – | – |
| Tumor size                |            | | | | | | |
| T1 (≤1 cm)                |            | 0.112 | – | – | – | – | – |
| T2 (≤2 cm, >1 cm)         |            | 0.309 | 0.811 (0.543–1.213) | – | – | – | – |
| T3 (≤3 cm, >2 cm)         |            | 0.092 | 0.660 (0.407–1.070) | – | – | – | – |
| T4 (>3cm)                 |            | 0.533 | 1.168 (0.717–1.902) | – | – | – | – |
| Scope of regional lymph node |            | | | | | | |
| n = 0                     |            | *<0.001 | – | 0.357 | – | – | – |
| n > 0, n ≤ 3              |            | *<0.001 | 0.346 (0.212–0.566) | 0.960 | 0.974 (0.357–2.659) | | | |
| n > 3                     |            | *<0.001 | 0.305 (0.217–0.428) | 0.225 | 1.763 (0.706–4.403) | | | |
| Surgery                   |            | | | | | | |
| No surgery                |            | *<0.001 | – | 0.001 | – | – | – |
| Wedge resection           |            | *<0.001 | 0.281 (0.192–0.412) | 0.008 | 0.520 (0.317–0.853) | | | |
| Segmental resection       |            | *<0.001 | 0.228 (0.117–0.444) | *<0.001 | 0.259 (0.095–0.706) | | | |
| Lobectomy                 |            | *<0.001 | 0.140 (0.097–0.202) | *<0.001 | 0.159 (0.059–0.427) | | | |

Notes.

* p < 0.05, statistically significant.

<70 y), 0.167 (95% CI [0.061–0.461], wedge resection versus no surgery, P = 0.001), 0.197 (95% CI [0.040–0.967], segmental resection versus no surgery, P = 0.045), 0.158 (95% CI [0.026–0.951], lobectomy versus no surgery, P = 0.044). The independent prognostic factors for both OS and LCSS were age and surgery.

**Prognosis of TC patients who underwent wedge resection or segmental resection before and after PSM**

According to the selection criterion, 465 patients in the cohort received wedge resection and 113 underwent segmental resection. A distinctly unequal distribution of factors existed...
Table 4  Univariate and multivariate Cox regression analyses according to LCSS for TC patients.

| Variables in the equation | Univariate | Multivariate |
|--------------------------|------------|--------------|
|                          | P          | Hazard ratio (95% CI) | P          | Hazard ratio (95% CI) |
| Age                      |            |                |            |                |
| <70y                     |            |                |             |                |
| ≥70y                     | *<0.001    | 4.112 (2.341–7.225) | *0.008     | 2.261 (1.232–4.149) |
| Gender                   |            |                |            |                |
| Female                   |            |                |             |                |
| Male                     | 0.362      | 1.315 (0.730–2.368) |            |                |
| Race                     |            |                |            |                |
| White                    | 0.348      |                |             |                |
| Black                    | 0.151      | 1.753 (1.047–2.936) |            |                |
| Others                   | 0.755      | 0.527 (0.168–1.652) |            |                |
| Grade                    |            |                |            |                |
| Well/Moderate            | 0.086      |                |             |                |
| Poor/Undifferentiated    | *0.027     | 9.928 (1.301–75.743) |            |                |
| Unknown                  | 0.756      | 1.143 (0.492–2.655) |            |                |
| Laterality               |            |                |            |                |
| Right                    |            |                |             |                |
| Left                     | 0.641      | 1.143 (0.651–2.007) |            |                |
| Tumor size               |            |                |            |                |
| T1 (≤1 cm)               | *<0.001    |                | *0.012     |                |
| T2 (≤2 cm, >1 cm)        | 0.924      | 0.955 (0.371–2.463) | 0.663      | 0.806 (0.305–2.127) |
| T3 (≤3 cm, >2 cm)        | 0.536      | 1.369 (0.506–3.703) | 0.670      | 1.255 (0.441–3.574) |
| T4 (>3 cm)               | *0.005     | 3.853 (1.519–9.774) | *0.060     | 2.586 (0.960–6.968) |
| Scope of regional lymph node |            |                |            |                |
| n = 0                    | *<0.001    |                | 0.357      |                |
| n > 0, n ≤ 3             | *0.003     | 0.169 (0.052–0.552) | 0.960      | 0.974 (0.357–2.659) |
| n > 3                    | *<0.001    | 0.244 (0.129–0.465) | 0.225      | 1.763 (0.706–4.403) |
| Surgery                  |            |                |            |                |
| No surgery               | *<0.001    |                | *0.004     |                |
| Wedge resection          | *<0.001    | 0.089 (0.037–0.216) | *0.001     | 0.167 (0.061–0.461) |
| Segmental resection      | *0.002     | 0.106 (0.025–0.448) | *0.045     | 0.197 (0.040–0.967) |
| Lobectomy                | *<0.001    | 0.089 (0.047–0.170) | *0.044     | 0.158 (0.026–0.951) |

Notes. *p < 0.05, statistically significant.

between these two groups (Table 5). To reach a more objective conclusion, factors such as age, laterality, tumor size, and scope of regional lymph node must be balanced. Compared with wedge resection, segmental resection was more often offered to people of older age, with larger tumor sizes, who had a larger region of lymph node resected.

To avoid being influenced by factors’ disproportionate distribution and data bias, we used PSM (an analysis function of the software, Statistical Package for the Social Sciences) to acquire an adequate sample set. First, we found the unbalanced variates by t-test. Then we chose the PSM to solve those imbalances by matching analogical cases from two
Table 5  Baseline characteristics for patients whom underwent wedge resection/segmentectomy before and after PSM.

| Characteristic                        | Before PSM |          |          |          |          |          |          |          |          |          |          |
|--------------------------------------|------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                                     |            | Wedge R  | Segmental R |            | Wedge R | Segmental R |            |            | Wedge R | Segmental R |            |
|                                     |            | (n = 465) | (n = 113) |           | (n = 100) | (n = 100) |           |           | (n = 100) | (n = 100) |           |
| Age                                  |            |          |        | 0.015    |          |        | 1.000    |          |          |          |          |
| <70y                                  |            | 339      | 95      |           | 83       | 82      |           |          |          |          |          |
| ≥70y                                  |            | 126      | 18      |           | 17       | 18      |           |          |          |          |          |
| Gender                               |            |          |        | 0.226    |          |        | 0.629    |          |          |          |          |
| Female                               |            | 355      | 80      |           | 76       | 72      |           |          |          |          |          |
| Male                                 |            | 110      | 33      |           | 24       | 28      |           |          |          |          |          |
| Race                                 |            |          |        | 1.000    |          |        | 0.822    |          |          |          |          |
| White                                |            | 419      | 102     |           | 88       | 90      |           |          |          |          |          |
| Others                               |            | 46       | 11      |           | 12       | 10      |           |          |          |          |          |
| Grade                                |            |          |        | 0.611    |          |        | 0.352    |          |          |          |          |
| Well/Moderate                        |            | 172      | 45      |           | 41       | 39      |           |          |          |          |          |
| Poor/Undifferentiated                |            | 25       | 8       |           | 2        | 6       |           |          |          |          |          |
| Unknown                              |            | 268      | 60      |           | 57       | 55      |           |          |          |          |          |
| Laterality                           |            |          |        | <0.001   |          |        | 1.000    |          |          |          |          |
| Right                                |            | 261      | 43      |           | 42       | 41      |           |          |          |          |          |
| Left                                 |            | 204      | 70      |           | 58       | 59      |           |          |          |          |          |
| Tumor size                           |            |          |        | <0.001   |          |        | 0.251    |          |          |          |          |
| T1 (≤1 cm)                           |            | 159      | 30      |           | 41       | 30      |           |          |          |          |          |
| T2 (≤2 cm, >1 cm)                    |            | 253      | 50      |           | 38       | 43      |           |          |          |          |          |
| T3 (>2 cm)                           |            | 53       | 33      |           | 21       | 27      |           |          |          |          |          |
| Scope of regional lymph node         |            |          |        | <0.001   |          |        | 0.845    |          |          |          |          |
| 0                                    |            | 319      | 44      |           | 37       | 41      |           |          |          |          |          |
| 1–3                                  |            | 88       | 29      |           | 31       | 29      |           |          |          |          |          |
| >3                                   |            | 58       | 40      |           | 32       | 30      |           |          |          |          |          |
| Radiation                            |            |          |        | 0.058    |          |        | 1.000    |          |          |          |          |
| No                                   |            | 462      | 112     |           | 100      | 99      |           |          |          |          |          |
| Yes                                  |            | 3        | 1       |           | 0        | 1       |           |          |          |          |          |
| Chemotherapy                         |            |          |        | 0.353    |          |        | 1.000    |          |          |          |          |
| No                                   |            | 464      | 112     |           | 100      | 99      |           |          |          |          |          |
| Yes                                  |            | 1        | 1       |           | 0        | 1       |           |          |          |          |          |

Notes. *p < 0.05, statistically significant.

The prognoses for 100 pairs of patients after exactly matching were evaluated using KM curves (Figs. 2C, 2F). The difference between wedge resection and segmental resection did not achieve statistical significance: for OS, the 5-year survival rates of wedge resection and segmental resection were 90.07% and 94.17% respectively, and the 10-year survival rates of wedge resection and segmental resection were 83.48% and 84.78%, respectively.
Table 6  Univariate Cox regression analyses according to OS and LCSS for TC patients whom underwent wedge and segmental resection.

| Variables in the equation | OS  | LCSS |
|---------------------------|-----|------|
|                           | P   | Hazard ratio (95% CI) | P   | Hazard ratio (95% CI) |
| Age                       |     |                  |     |                  |
| <70y                      | –   | –                | –   | –                |
| ≤70y                      | *<0.001 | 4.141 (2.430–7.058) | *0.021 | 5.428 (1.296–22.728) |
| Gender                    |     |                  |     |                  |
| Male                      | –   | –                | –   | –                |
| Female                    | 0.093 | 1.612 (0.924–2.812) | 0.915 | 1.092 (0.220–5.430) |
| Race                      |     |                  |     |                  |
| White                     | –   | –                | –   | –                |
| Others                    | 0.581 | 0.751 (0.271–2.077) | 0.575 | 0.331 (0.007–15.723) |
| Grade                     |     |                  |     |                  |
| Well/Moderate             | 0.872 | –                | 0.681 | –                |
| Poor/Undifferentiated     | 0.604 | 0.676 (0.154–2.963) | 0.488 | 2.350 (0.210–26.312) |
| Unknown                   | 0.830 | 0.935 (0.508–1.722) | 0.902 | 0.899 (0.167–4.847) |
| Laterality                |     |                  |     |                  |
| Right                     | –   | –                | –   | –                |
| Left                      | 0.812 | 1.066 (0.628–1.810) | 0.143 | 3.311 (0.668–16.417) |
| Tumor size                |     |                  |     |                  |
| T1 (≤1 cm)                | 0.456 | –                | 0.682 | –                |
| T2 (≥2 cm, >1 cm)         | 0.377 | 0.776 (0.443–1.361) | 0.653 | 0.693 (0.140–3.438) |
| T3 (≤2 cm)                | 0.258 | 0.595 (0.242–1.463) | 0.638 | 1.537 (0.257–9.202) |
| Scope of regional lymph node |     |                  |     |                  |
| n ≤ 3                     | –   | –                | –   | –                |
| n > 3                     | 0.698 | 0.845 (0.361–1.979) | 0.297 | 2.366 (0.470–11.917) |
| Surgery                   |     |                  |     |                  |
| Wedge resection           | –   | –                | –   | –                |
| Segmental resection       | 0.493 | 0.786 (0.395–1.564) | 0.912 | 1.096 (0.217–5.541) |

Notes.
*<p>0.05, statistically significant.

(P = 0.320); for LCSS, the 5-year survival rates of wedge resection and segmental resection were 97.89% and 98.75%, respectively, and the 10-year survival rates of wedge resection and segmental resection were 93.67% and 98.75%, respectively (P = 0.342).

Univariate COX regression analyses of TC patients who underwent wedge resection and segmental resection before PSM

Relative risk factors for OS and LCSS were analyzed using a univariate COX regression hazard model (Table 6). The study showed that age was only a prognostic factor for OS and LCSS: HR = 4.141 (95% CI [2.430–7.058], P < 0.001) for OS, and HR = 5.428 (95% CI [1.296–22.728], P = 0.021) for LCSS. Notably, gender (P = 0.093) and tumor size (P = 0.682) no longer independently affected the prognoses for OS and LCSS, respectively.
Figure 4  Prognostic analysis for subgroup of age and sex by KM plots. Overall survival and lung cancer specific survival in subgroups of age (<70 and ≥70) and gender (female and male) between wedge resection and segmental resection. There was no significant difference between two surgical options in OS: (A) age < 70; (B) age ≥ 70; (C) female; (D) male. Besides, there was no significant difference between two surgical options in LCSS: (E) age < 70; (F) age ≥ 70; (G) female; (H) male. OS, overall survival; LCSS, Lung cancer-special survival.

Subgroup analysis of TC patients who received wedge or segmental resection for OS and LCSS before PSM

The results showed no statistically significant difference between wedge and segmental resection in any subgroup of age, race, gender, tumor size, or scope of regional lymph node, which was rendered in KM plots (Figs. 4–6). Cox regression analysis for OS also supported that view (Table 7). The results of Cox regression analysis for LCSS are not shown because death was rare after sectionalization.

DISCUSSION

The study showed that the prognosis of TC patients was best among those suffering from ADC and SCC. Further univariate and multivariate Cox analysis showed that the surgery option was independent of the prognosis for OS and LCSS in TC patients. As for the impact of surgery type (wedge and segmental resection) on survival, the result was not statistically significant either before or after PSM. In conclusion, the important discovery of this report is that wedge resection is likely to be equal to segmental resection for TC patients at the localized stage.

As the low-grade lung NET, TC has a favorable prognosis, where the 5-year and 10-year survival rate for OS and LCSS were highest compared with NSCLC and AC (Table 1). Some studies also showed that 5-year OS of TC was more than 87 percent (Filosso et al., 2013; Gosain et al., 2018). The excellent prognosis for TC may be attributed to a handful of
mitoses, no necrosis, and a low Ki-67 labeling index (Caplin et al., 2015; Rindi et al., 2014). However, other research has indicated that the survival rate for Pulmonary carcinoids (PCs) has dropped for the past 30 years (Gustafsson et al., 2008). In its milder forms, it may still be a major problem increasing mortality and delaying diagnosis. Compared with other lung carcinomas, only 10.4% of primary TC is located in the bronchi, so respiratory symptoms, such as chest infections, cough, hemoptysis, and chest pain are relatively rare (Gustafsson et al., 2008; Caplin et al., 2015). Similarly, lung neoplasms were larger than five cm resected from the TC patients at the localized stage because the symptoms were so mild.

For TC patients who were at the localized stage, age, gender, and surgery option were independent prognostic factors for OS in the multivariate Cox analysis. However, the factor “gender” was replaced by the factor “tumor size” in assessment for LCSS in the multivariate analysis. Same with James W. Vaupel’s finding, Women live longer than men today (Zarulli et al., 2018). Long life span of female may contribute to the cause differences in analysis of OS. Besides, unlike OS, people were classified as having died from LCSS only when the cause was related to lung cancer. Therefore, gender may not influence the progress of death from TC. The significant difference between the group with no surgery and the group who underwent surgery indicated that surgery was essential for the treatment of TC even though it had low malignancy. In a Cox regression model with time dependence, age was statistically significant (data not shown). The HR increases as patients age.
Like the results of Taher Abu Hejleh et al. (Furqan et al., 2018), research on surgery type showed that TC patients at the localized stage would benefit equally from lobectomy or sublobectomy. However, Taher Abu Hejleh et al. overlooked that sublobectomy contained both wedge and segmental resection. Comparisons between sublobectomy and lobectomy respectively were not done. Thus, superiority of lobectomy cannot be proved by being contrasted with sublobectomy, similar anatomy resection (segmentectomy), or wedge resection.

The emphasis of this research is on whether the benefits of wedge resection can equal those of segmentectomy. The raw data indicated that the choice between the two procedures did not influence the prognosis of patients who underwent sublobectomy. Furthermore, after 1:1 PSM, the gaps between the OS and LCSS survival rate of two surgery procedures closed, providing additional evidence for the uniformity of the benefits from treatment, whether treatment consisted of wedge resection or segmentectomy produced in TC therapy. Besides, the Cox analysis of TC patients who underwent those two surgeries before PSM...
Table 7 Subgroup analyses according to OS and LCSS before PSM.

| Variables in the equation       | OS                  |
|---------------------------------|----------------------|
|                                 | P   | Hazard ratio (95% CI) |
| Age                             |     |                     |
| <70y                            | 0.220 | 0.469 (0.140–1.574) |
| ≥70y                            | 0.393 | 1.448 (0.619–3.384) |
| Gender                          |     |                     |
| Female                          | 0.451 | 0.712 (0.295–1.721) |
| Male                            | 0.914 | 0.941 (0.312–2.837) |
| Race                            |     |                     |
| White                           | 0.373 | 0.719 (0.348–1.485) |
| Others                          | 0.686 | 1.601 (0.163–15.704) |
| Tumor size                      |     |                     |
| T1 (≤1 cm)                      | 0.696 | 0.804 (0.269–2.403) |
| T2 (≤2 cm, >1 cm)               | 0.249 | 0.428 (0.101–1.811) |
| T3 (≥2 cm)                      | 0.254 | 2.706 (0.489–14.969) |
| Scope of regional lymph node    |     |                     |
| n ≤ 3                           | 0.692 | 0.857 (0.400–1.837) |
| n > 3                           | 0.546 | 0.592 (0.108–3.245) |

showed that only age was a relevant prognostic factor for OS or LCSS, and surgery type was no exception. The therapeutic effect of sublobectomy eliminated the impact of factors other than age on prognosis and both two operating methods were effective for TC. Furthermore, this held true for many subgroups of TC patients, including groups that were younger or older, or male or female, verified by the subgroup analyses.

A survey that involved 172 institutions worldwide showed that only 11 percent of participants regarded wedge resection as an appropriate surgical option for peripheral PCs (Caplin et al., 2015). However, the results of this research showed that patients did not benefit more from segmental resection than wedge resection. Compared to the anatomic resection, the operation wound from wedge resection was milder and caused less damage to pulmonary function. Therefore, the results proved that wedge resection, as well as anatomic resection, should be considered a conventional treatment for TC patients at the localized stage. Preserving better pulmonary function and leaving a smaller surgical wound will promote better quality of life for patients undergoing the surgery.

Inevitably, there are several limitations similar to those of most retrospective studies based on the SEER database used for this study. First of all, information on patients, such as complications, recurrence, follow-up treatment received, TMN stage, and so on was not complete. This reduced the level of accuracy and detail of the prognoses. Secondly, the number of cases was limited because the disease is rare. The results of the research will be more convincing when additional cases are studied. Third, this research may include more bias than a prospective study or a randomized trial.
CONCLUSION

The wedge resection was a comparable treatment to segmental resection for TC patients at the localized stage.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding
The work was supported by National Natural Science Foundation (81672288), National Natural Science Foundation (81602009) and Natural Science Foundation of Shandong Province of China (ZR2019PH002). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures
The following grant information was disclosed by the authors:
National Natural Science Foundation: 81672288.
National Natural Science Foundation: 81602009.
Natural Science Foundation of Shandong Province of China: ZR2019PH002.

Competing Interests
The authors declare there are no competing interests.

Author Contributions
• Tao Yan conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
• Kai Wang conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.
• Jichang Liu performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
• Yukai Zeng analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, approved the final draft.
• Fenglong Bie contributed reagents/materials/analysis tools, approved the final draft.
• Guanghui Wang contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.
• Jiajun Du conceived and designed the experiments, performed the experiments, approved the final draft.

Data Availability
The following information was supplied regarding data availability:
The raw measurements are available in Table S1, Table S2, and Dataset S1.
Supplemental Information
Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.7519#supplemental-information.

REFERENCES

Altorki NK, Kamel MK, Narula N, Ghaly G, Nasar A, Rahouma M, Lee PC, Port JL, Stiles BM. 2016. Anatomical segmentectomy and wedge resections are associated with comparable outcomes for patients with small cT1N0 non-small cell lung cancer. *Journal of Thoracic Oncology* 11:1984–1992 DOI 10.1016/j.jtho.2016.06.031.

Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, Oberg K, Pelosi G, Perren A, Rossi RE, Travis WD, ENETS consensus conference participants. 2015. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Annals of Oncology* 26:1604–1620 DOI 10.1093/annonc/mdv041.

Chen LC, Travis WD, Krug LM. 2006. Pulmonary neuroendocrine tumors: what (little) do we know? *Journal of the National Comprehensive Cancer Network* 4:623–630 DOI 10.6004/jnccn.2006.0051.

DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. 2000. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *Journal of Gastrointestinal Surgery* 4:178–184 DOI 10.1016/S1091-255X(00)80054-2.

El-Sherif A, Fernando HC, Santos R, Pettiford B, Luketich JD, Close JM, Landreneau RJ. 2007. Margin and local recurrence after sublobar resection of non-small cell lung cancer. *Annals of Surgical Oncology* 14:2400–2405 DOI 10.1245/s10434-007-9421-9.

Filosso PL, Oliaro A, Ruffini E, Bora G, Lyberis P, Aslioni S, Delsedime L, Sandri A, Guerrera F. 2013. Outcome and prognostic factors in bronchial carcinoids: a single-center experience. *Journal of Thoracic Oncology* 8:1282–1288 DOI 10.1097/JTO.0b013e31829f097a.

Fox M, Van Berkel V, Bousamra 2nd M, Sloan S, Martin 2nd RC. 2013. Surgical management of pulmonary carcinoid tumors: sublobar resection versus lobectomy. *American Journal of Surgery* 205:200–208 DOI 10.1016/j.amjsurg.2012.05.008.

Furqan M, Tien YY, Schroeder MC, Parekh KR, Kech J, Allen BG, Thomas A, Zhang J, Clamon G, Abu Hejleh T. 2018. Lobar versus sub-lobar surgery for pulmonary typical carcinoid, a population-based analysis. *Journal of Thoracic Disease* 10:5850–5859 DOI 10.21037/jtd.2018.09.141.

Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM. 2008. Bronchopulmonary neuroendocrine tumors. *Cancer* 113:5–21 DOI 10.1002/cncr.23542.

Gosain R, Mukherjee S, Yendamuri SS, Iyer R. 2018. Management of typical and atypical pulmonary carcinoids based on different established guidelines. *Cancer* 10:510 DOI 10.3390/cancers10120510.
Mezzetti M, Raveglia F, Panigalli T, Giuliani L, Lo Giudice F, Meda S, Conforti S. 2003. Assessment of outcomes in typical and atypical carcinoids according to latest WHO classification. Annals of Thoracic Surgery 76:1838–1842 DOI 10.1016/s0003-4975(03)01194-9.

Rekhtman N. 2010. Neuroendocrine tumors of the lung: an update. Archives of Pathology & Laboratory Medicine 134:1628–1638 DOI 10.1043/2009-0583-RAR.1.

Ramirez RA, Chauhan A, Gimenez J, Thomas KEH, Kokodis I, Voros BA. 2017. Management of pulmonary neuroendocrine tumors. Reviews in Endocrine and Metabolic Disorders 18:433–442 DOI 10.1007/s11154-017-9429-9.

Raz DJ, Nelson RA, Grannis FW, Kim JY. 2015. Natural history of typical pulmonary carcinoid tumors: a comparison of nonsurgical and surgical treatment. Chest 147:1111–1117 DOI 10.1378/chest.14-1960.

Rea F, Rizzardi G, Zuin A, Marulli G, Nicotra S, Bulf R, Schiavon M, Sartori F. 2007. Outcome and surgical strategy in bronchial carcinoid tumors: single institution experience with 252 patients. European Journal of Cardio-Thoracic Surgery 31:186–191 DOI 10.1016/j.ejcts.2006.10.040.

Rindi G, Klersy C, Inzani F, Fellegara G, Ampollini L, Ardizzoni A, Campanini N, Carbognani P, De Pas TM, Galetta D, Granone PL, Righi L, Rusca M, Spaggiari L, Tiseo M, Viale G, Volante M, Papotti M, Pelosi G. 2014. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. Endocrine-Related Cancer 21:1–16 DOI 10.1530/ERC-13-0246.

Romano PS, Mark DH. 1992. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. Chest 101:1332–1337 DOI 10.1378/chest.101.5.1332.

Travis WD. 2010. Advances in neuroendocrine lung tumors. Annals of Oncology 21(Suppl 7):vi65–71 DOI 10.1093/annonc/mdq380.

Zarulli V, Barthold Jones JA, Oksuzyan A, Lindahl-Jacobsen R, Christensen K, Vaupel JW. 2018. Women live longer than men even during severe famines and epidemics. Proceedings of the National Academy of Sciences of the United States of America 115:E832–E840 DOI 10.1073/pnas.1701535115.

Wolin EM. 2015. Challenges in the diagnosis and management of well-differentiated neuroendocrine tumors of the lung (typical and atypical carcinoid): current status and future considerations. Oncologist 20:1123–1131 DOI 10.1634/theoncologist.2015-0198.

Wolin EM. 2017. Advances in the diagnosis and management of well-differentiated and intermediate-differentiated neuroendocrine tumors of the lung. Chest 151:1141–1146 DOI 10.1016/j.chest.2016.06.018.

Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey J-N, Rashid A, Evans DB. 2008. One hundred years after carcinoid: epidemiology of and prognostic factors for neuroendocrine tumors in 35, 825 cases in the United States. Journal of Clinical Oncology 26:3063–3072 DOI 10.1200/jco.2007.15.4377.