Characteristics of and therapeutic strategy for pulmonary typical carcinoid: a population-based study

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To the Editor: Pulmonary carcinoid (PC) is a rare well-differentiated neuroendocrine tumor that accounts for only approximately 2% of all malignant lung tumors.\(^1\) PCs are further divided by malignancy into low- and intermediate-grade malignant tumors, namely typical (TC) and atypical carcinoid (AC). Because of the low morbidity, there is a paucity of data on TC based on a large population or randomized controlled trials. According to recent guidelines and consensus statements, lobectomy or other anatomic resection procedures and mediastinal lymph node dissection or sampling are the standard treatment for stage I-II and resectable stage IIIA disease, and adjuvant therapy is not recommended after complete resection; nevertheless, there is a lack of consensus on the treatment for unresectable stage III and metastatic disease, especially regarding the necessity of surgery and chemotherapy.

We retrospectively analyzed the data of patients with TC (histological code 8240/3) from January 1, 2010 to December 31, 2014 from the Surveillance, Epidemiology, and End Results (SEER) database to explore their characteristics and therapeutic strategy. We were permitted to have Internet access to this database (Username: 10526-Nov2018) after a data-use agreement was approved by the SEER administration. The exclusion criteria included unknown overall survival (OS) or OS <1 month, age younger than 18 years, and other histopathological types. Finally, 2233 records were retrieved. All cases were reclassified by the eighth edition of the tumor-node-metastasis (TNM) staging system. Because of the lack of available data on the number of distant metastases, M1b and M1c tumors were categorized as a group (named M1bc), and stage IVA and IVB were analyzed together (named stage IV).

Compared with other lung cancers, patients with a diagnosis of TC had a tendency to be associated with younger age (≤65 years), women, Caucasian race, lower lobe location, earlier stage (total, T, N, and M stage), less metastases (bone, brain, liver, and lung), more primary site surgery (PrimSurg) and lymph node surgery (LNSurg), and less metastatic site surgery (MetSurg), chemotherapy, and radiation [Supplementary Table 1, http://links.lww.com/CM9/A487]. In terms of treatment, the corresponding 5-year survival rates with and without PrimSurg were 99.0% vs. 80.0% for stage I, 92.0% vs. 71.0% for stage II, 91.0% vs. 61.0% for stage III, and 72.0% vs. 45.0% for stage IV, which were significantly different (\(P < 0.000\)). With regard to LNSurg, patients in stage I–III achieved a longer survival (\(P < 0.000, P = 0.004, \) and \(P < 0.000, \) respectively) rather than those in stage IV (\(P = 0.106\)). Then, we defined stage I–III as early stage and stage IV as late stage to analyze the relationship of chemotherapy and radiation on survival. Although the results showed that chemotherapy and radiation were negatively correlated with survival (\(P = 0.001 \) and \(P = 0.058\) in early stage, \(P < 0.000 \) and \(P = 0.002\) in late stage, respectively), the results may be biased due to the small sample of patients who received chemotherapy (70 patients) and radiation (21 patients). Besides, univariate analysis revealed that factors including age, sex, grade, stage (total, T, N, and M stage), metastases (bone, brain, liver, and lung), surgery (PrimSurg, LNSurg, and MetSurg), chemotherapy, and radiation were statistically correlated with survival [Supplementary Figure 1, http://links.lww.com/CM9/A485]. However, in multivariate analysis, only older age (>65 years), male sex, advanced stage (total, T and M stage), bone and brain metastases, and lack of PrimSurg were significantly associated with poor prognosis [Supplementary Figure 2, http://links.lww.com/CM9/A486].

Our study demonstrated that both PrimSurg and LNSurg presented survival benefits for stage I–III disease; for unresectable and metastatic diseases, patients could still benefit from PrimSurg, but LNSurg, MetSurg, chemotherapy, and radiation did not show a favorable prognosis in the multivariate analysis. Furqan et al\(^{[2]}\) explored the optimal surgery for resectable TCs in 2018 patients and
found that sub-lobar resection was better than no surgery and similar to lobular resection regarding survival. That is, primary site surgery, with both radical and palliative intent, is beneficial for survival. Regarding medical treatments, somatostatin analogs (SSAs) present a classic therapeutic option for locally advanced/metastatic TCs, and chemotherapy is mainly recommended when other treatments are unavailable or patients show rapid progression. From real-world research on locally advanced/metastatic PC that comprised 36 TCs and 47 ACs treated between July 2011 and December 2014, SSAs alone or in combination and cytotoxic chemotherapy were the most common modalities among all treatments; the other treatment options were radiation, liver-directed therapy, and targeted therapies, but surgery was not a choice. The results indicate that chemotherapy plays an important role in advanced TCs and that the actual application of chemotherapy is more frequent than the theoretical suggestions. Besides, some novel options, such as everolimus and 177Lu-DOTATATE peptide receptor radionuclide therapy, show a good survival benefit. Several additional targeted drugs have also been investigated, including vascular endothelial growth factor receptor inhibitors and immunotherapy. But common mutations and programmed cell death ligand 1 (PD-L1) expression are relatively rare in TC cohort; the effect of these drugs remains uncertain in TC.

A limitation of this study is that the small numbers in some subgroups, especially the MetSurg, chemotherapy, and radiation subgroups (31, 70, and 20 cases, respectively), limited the accuracy of our assessment. Additionally, since patients were included from 2010 to 2014, some therapeutic options, such as PD-L1 inhibitors, were not been broadly applied during that period; thus, our results may underestimate the efficacy of medical treatments and radiation.

In conclusion, typical PCs have their own characteristics and a favorable prognosis. PrimSurg was recommended for all patients, including those in stage IV; and LNSurg should be done in stage I–III disease; however, the necessity of MetSurg, chemotherapy, and radiation was unclear, and more studies based on large population are needed to provide convincing evidence of these treatment strategies.

**Declaration of patient consent**

Because the patients were retrieved from the SEER database, the current study was a retrospective analysis. And, we were permitted to have Internet access to this database (Username: 10526-Nov2018) after a data-use agreement was approved by the SEER administration.

**Conflicts of interest**

None.

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