Ann Surg Oncol (2022) 29:4039–4040
https://doi.org/10.1245/s10434-022-11659-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – THORACIC ONCOLOGY

Surgery for Lobar Bronchial Adenoid Cystic Carcinoma: It is R0, Not Location

Shamus R. Carr, MD, FACS

Thoracic Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Adenoid cystic carcinoma (ACC) is a rare tumor that over half the time arises in the oral cavity, salivary glands, or pharynx. A Surveillance, Epidemiology, and End Results (SEER) database study found that of all ACC cases, only about 6% were primarily of either trachea, bronchial, or lung origin.[1] To put this into perspective, annually in the US there are only about 100 cases, and of these, only about 15–20% are of bronchial or lobar origin.[2] The rarity of this tumor limits large-scale studies unless large databases are utilized. Nonetheless, most studies combine pulmonary ACC regardless of location.

Management of ACC patients has been evaluated over the past few decades and surgical resection is consistently shown to be the first-line treatment.[3] However, microscopically positive margins (R1 resection) are not uncommon as the tumor is known to have submucosal progression and perineural invasion along the airways. Fortunately, these tumors do show high sensitivity to radiation.[4] Thus, the standard treatment involves primary surgical resection with negative surgical margins, but in the event of an R1 resection, the addition of radiation therapy is recommended.

Prior series have tried to tease out lobar and bronchial origin ACC patients and compare them with those of tracheal origin. A report of 82 patients from Shanghai over 11 years compared 29 patients with bronchial or lobar origin ACC with 53 patients with tracheal ACC.[2] The conclusion was that ACC of bronchial origin has a significantly worse disease-free survival, but careful evaluation of overall survival (OS) demonstrates no significant difference between bronchial and tracheal tumors ($p = 0.148$). While bronchial or lobar tumors did have worse DFS, 50% of the patients in the bronchial group and 83% in the tracheal group who had follow-up had R1 resection. Additionally, the criteria for the use of adjuvant radiation in this study were unclear and likely carried selection bias as to whom it was delivered. Therefore, we still remain unsure whether ACC of lobar or bronchial origin is a worse actor than its tracheal cousin.

The paper by Zhao et al.[5] published in this issue of Annals of Surgical Oncology is a contemporary collection of 35 patients that focuses solely on ACC of lobar and bronchial origin over 20 years. While it does not have a comparative cohort of tracheal tumors, real-world results are well known to surgeons who encounter this disease. Since tracheal tumors account for 80%, the lack of these patients in the paper by Zhao et al. does not distract but adds solid data to the literature to date for the question 'does location matter'?

All patients were treated using the same practices that have become standard of care for these rare, slow-growing tumors. The 5-year OS was 81.4% as these patients were followed for a median of 61 months. An R0 resection was performed in 57.1% of patients, with the remaining 42.9% undergoing R1 resection. In those patients who had an R0 resection, the OS was 94.4% at both 5 and 10 years. These results further highlight the fact that negative margins are clearly the most important factor for OS (hazard ratio [HR] 9.020, $p = 0.014$). This result adds to many other studies that all reach the same conclusion, that margins do matter.

Further analysis of those patients who underwent R1 resection ($n = 15$) indicated that nine patients received adjuvant radiation while the remainder did not. There was

First Received: 1 March 2022
Accepted: 11 March 2022;
Published Online: 5 April 2022

S. R. Carr, MD, FACS
e-mail: shamus.carr@nih.gov

no demonstrated improvement when comparing these two groups of patients. Comparing these two cohorts with the R0 patients revealed no statistical difference in OS between R0 patients and R1 patients who received adjuvant radiation (94.4% vs. 66.7%, $p = 0.173$); however, there was a difference in OS when comparing R0 patients with R1 patients who did not receive adjuvant radiation (94.4% vs. 62.5%, $p = 0.007$). While this is not conclusive for recommending the addition of adjuvant radiation, it further tips the scales towards offering it.

While margins status has a significant role on OS, it made no difference in local recurrence-free survival (HR 1.157, $p = 0.830$). This remains whether radiation was administered to R1 patients or not ($p = 0.805$). The local recurrence-free survival of the various groups was reported to be 77–100% at 5-years. Additionally, both univariate and multivariable analysis did not reveal any prognostic factors for either local recurrence-free or disease-free survivals. While recurrence does occur, it has a limited role on 5-year survival. As ACC is a slow-growing tumor, a median follow-up of 61 months may not be long enough to see when recurrence does impact survival.

The question of lymph node involvement has previously been raised as a poor prognostic variable as it has been shown that ACC of bronchial and lobar origin has higher rates of lymph node involvement than tracheal tumors.[2,6] This finding has led some to conclude that bronchial and lobar tumors are more aggressive. While Zhao and colleagues[5] also have a high rate of lymph node involvement (48.6%), which is in line with other publications, this was not significant on multivariable analysis. This differs from other published reports that the statement of increasing lymph node involvement corresponds to increased aggressiveness may be more the correlative and not causal relationship. This is highlighted in only 25.7% of patients who developed distant recurrence compared with the nearly 50% that is usually reported for ACC of tracheal origin.[7] However, due to the limited sample size of a rare tumor, this question has still not yet been put to rest.

ACC of either tracheal, bronchial, or lobar origin is rare and all published reports, including the report by Zhao et al.[5], are hampered by being retrospective and either from a single institution or two, which results in a small number of patients for a contemporary study or the same database with patients stretched over scores of years where treatment paradigms have shifted over the decades. Results may also be from a national database (e.g. National Cancer Database [NCDB] or SEER) that may not track all the variables that are unique to an individual disease. In patients who, at final pathology, are found to have microscopically positive margins, there should be a very strong consideration for adjuvant radiation. The opportunity exists for an advanced genomic analysis of tumors that separates them by site of origin. This may show a distinct difference, however it may not relate to outcomes. Until that point in time, we can fall back on the surgical dictum that has served us well, regardless of tumor type—negative margins.

REFERENCES

1. Li N, Xu L, Zhao H, et al. A comparison of the demographics, clinical features, and survival of patients with adenoid cystic carcinoma of major and minor salivary glands versus less common sites within the Surveillance, Epidemiology, and End Results registry. *Cancer*. 2012;118:3945–53.
2. Zhao Y, Zhao H, Fan L, et al. Adenoid Cystic Carcinoma in the bronchus behaves more aggressively than its tracheal counterpart. *Ann Thorac Surg*. 2013;96:1998–2004.
3. Kanematsu T, Yohena T, Uehara T, et al. Treatment outcome of resected and nonresected primary adenoid cystic carcinoma of the lung. *Ann Thorac Cardiovasc Surg*. 2002;8:74–7.
4. Grillo HC, Mathisen DJ. Primary tracheal tumors: treatment and results. *Ann Thorac Surg*. 1990;49:69–77.
5. Zhao Y, He G, Zhai Y, et al. Adenoid cystic carcinoma of lobar bronchial origin: 20-year experience at a single institution. *Ann Surg Oncol*. 2022. https://doi.org/10.1245/s10434-022-11590-5
6. Resio BJ, Chiu AS, Hoag J, et al. Primary salivary type lung cancers in the national cancer database. *Ann Thorac Surg*. 2018;105:1633–9.
7. Je HU, Song SY, Kim DK, et al. A 10-year clinical outcome of radiotherapy as an adjuvant or definitive treatment for primary tracheal adenoid cystic carcinoma. *Radiat Oncol*. 2017;12:196.