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Lung metastasectomy in adenoid cystic cancer: Is it worth it?

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ABSTRACT

Background and purpose: Adenoid cystic carcinoma (ACC) of salivary glands is characterized by long-term distant metastasis, most commonly in lungs. No agreement has been reached about the role of surgical treatment of pulmonary lesions. We evaluated the long-term results of lung metastasectomy for ACC in order to identify factors that should be taken into account in selecting patients eligible for surgery and treatment planning.

Patients and methods: A retrospective study was conducted on 109 patients selected from our institutional experience and from the International Registry of Lung Metastases. Survival was calculated by Kaplan-Meier estimate and prognostic factors endowed with a predictive power for most other metastatic cancers were investigated.

Results: The cumulative survival was 66.8% at 5 years and 40.5% at 10 years. In patients with a disease-free interval (DFI) greater than 36 months, the overall survival was 76.5% at 5 years. Survival in case of complete surgical resection was 69.5% at 5 years. Multivariate analysis confirmed DFI and completeness of resection resulted in the best prognostic variables.

Discussion: Lung metastasectomy should be considered as a therapeutic option to achieve local control of disease when 2 conditions are met: (1) complete surgical resection is feasible and (2) the time to pulmonary relapse after primary tumor treatment is greater than 36 months. Symptomatic benefits of an incomplete lung resection in slow-growing tumors such as ACC remain uncertain. The turning point in the management of disseminated cancers will be clarified with biological profiling of ACC and the development of targeted therapies.

Background and purpose

Adenoid cystic carcinoma (ACC), a rare malignant tumor with an incidence of 3–4.5 cases per million, represents 1% of all head and neck malignancies [1]. Adenoid cystic carcinoma typically affects minor and major salivary glands, such as parotid, submandibular, and sublingual salivary glands. Less frequently, it can also affect the lacrimal and serous glands or respiratory mucosa. Altogether, it represents about 10% of all tumors of the salivary glands [2]. The clinical behavior of this tumor usually has been described as indolent; however, it has been shown that ACC is correlated with an inauspicious prognosis when it invades perineural tissues. Adenoid cystic carcinoma aggressiveness is linked to its ability to produce local recurrences and long-term distant metastases [1].

Adenoid cystic carcinoma is rarely associated with regional lymph node involvement, but delayed hematogenous metastases occur in 25–50% of patients. Such metastases have been most commonly reported in lungs and bones [3,4]. Even with metastatic disease, patients with ACC have a natural history of long-term survival [4]. Pulmonary metastases are associated with more favorable prognosis as compared with disseminated disease [5]. The literature reports that pulmonary metastasectomy is widely considered a safe and potentially curative procedure in other types of disseminated cancers, with low morbidity and mortality. It is the standard therapy for a number of different metastatic malignancies [6,7]. However, the role of radical surgery in metastatic ACC has been difficult to evaluate. This is due to the relative rarity of ACC and its tendency to relapse late, with the consequence of losing many patients at follow-up evaluation. For this reason, evidence

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of the effectiveness of lung metastasectomy in the treatment of ACC at stage VI has to be proved.

Few works in the literature have presented limited series of patients selected for ACC histology [3,8,9]. Patients with ACC typically have been included in larger series with different neoplasms of salivary glands or head and neck cancers [2,10–13]. In such studies, different prognostic factors have been investigated to identify metastatic patients who could take advantage of lung resection in terms of survival, but no consensus has been reached about the role of surgery in ACC. Current opinion states that the best option for patients with metastatic ACC is supportive care, palliative chemotherapy, or inclusion in clinical trials to prove the effectiveness of new treatment strategies [1]. However, no agreement has been reached on the role of surgical treatment of lung metastases in the management of ACC and its potential in improving survival of a selected group of patients. On the other hand, consensus has been reached on the importance of improving systemic therapies to ameliorate ACC prognosis.

In order to evaluate the efficacy of prognostic factors in determining the survival of patients undergoing lung metastasectomies for ACC of salivary glands, we performed a retrospective analysis of 109 cases. To our knowledge, this is the largest series ever described.

We identified 2 long-term survival factors that should be taken into account when selecting patients eligible for surgery as well as in planning therapy.

Patients and methods

We performed a retrospective analysis of all patients who underwent pulmonary metastasectomy for ACC of the salivary glands at the Unit of Thoracic Surgery of the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan (INT) between 1991 and 2014. Data were reviewed and collected from our archives according to the method described by the International Registry of Lung Metastases (IRLM) [7].

The dataset employed comprised clinical, radiologic, and surgical evaluations. The number, size, and localization of metastases were reported, together with the surgical approaches used and the related oncologic outcomes.

Patients were selected for surgery by considering the technical feasibility of the procedure and the absence of other sites of metastatic dissemination. Patients with local recurrence at the time of metastasis detection were treated surgically on pulmonary nodules and with local treatment on the primary site.

The number and size of metastases, as indicators of the tumor burden, were not considered discriminating criteria for surgery.

All patients were scanned using computed tomography preoperatively at their thorax. Respiratory volumes and performance status were also evaluated before confirming surgery. The typical surgical approach employed was thoracotomy in case of ipsilateral lesions and median sternotomy or 2-stage thoracotomy when both lungs were involved. Wedge or precision resections were performed for small peripheral nodules, in order to preserve pulmonary parenchyma. However, in case of central lesions, more extensive anatomical resections, such as lobectomy or segmentectomy, were performed. Histologic results were always discussed with medical oncologists, and patients were sent to their attention for further treatment.

Our database also incorporates patients with ACC from the IRLM (1971–1991) according to the previously published methodology of data collection [7].

We considered disease-free interval (DFI), IRLM staging classification, number of lung metastases, and completeness of resection and evaluated their relation to overall survival (OS). The OS was calculated from the date of first metastasectomy to the date of death or last follow-up (censored). The DFI was defined as the interval between the initial treatment of primary tumor and the occurrence of lung metastases. Patients were classified according to the IRLM staging system [7] into 4 prognostic groups: I (complete resection, DFS >36 months and single metastasis); II (complete resection, DFS < 36 months or multiple metastases); III (complete resection, DFS < 36 months and multiple metastases); IV (incomplete metastasectomy) (Table 1).

Survival curves were estimated using Kaplan-Meier method and were compared by the log-rank test. Confidence intervals (CIs) for the estimated survival probabilities were calculated using the Greenwood method. Hazard ratio (HR) and the corresponding 95% CIs were estimated using multivariate Cox proportional and hazard models. In particular, a first model included a term for age (<50, 50–<60, ⩾60 years) and sex, and a second one for resection (complete, incomplete), DFI (<36 vs ⩾36 months), IRLM stage (1–2 vs 3–4), and number of total metastases (1 vs >1). All tests were 2-sided; a p value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

The main clinical characteristics of all patients are summarized in Table 2. This series includes 42 (38.5%) patients with metastatic ACC of salivary glands who underwent surgery at our institution (INT), and 67 (61.5%) patients from IRLM archives. A total of 51 (46.8%) of those were women and 58 (53.2%) were men; median age at the time of metastasectomy was 48 years (interquartile range 17). Median DFI was 50 months, and most patients showed a DFI greater than 36 months (65.1%). A single metastasis was found in 29 (26.6%) patients, and multiple lesions in 80 (73.4%) cases. In 91 patients (83.5%), a complete metastatic resection was achieved, while incomplete resections were performed in 18 (16.5%) patients. Out of these 18 patients, 2 presented microscopic positive margins at the histopathologic analysis, due to marginal resection; 16 patients had macroscopic residual tumor. In our practice, we perform incomplete resections for the diagnostic assessment of pleural or parenchymal dissemination found intraoperatively. According to IRLM staging, 13 patients were stage I (12%), 60 stage II (55%), 24 stage III (22%), and 12 stage IV (11%). The median follow-up was 52 months; one patient was lost immediately after surgery.

In a first stage, patients deriving from the IRLM database and our own patients were considered separately. However, given that the 2 populations showed similar cumulative survival curves (p for comparison = 0.88 log-rank test; Fig. 1), we decided to consider them as a whole. For all 109 patients, the cumulative 5-year survival was 66.8% (95% CI 55.9–75.6%) and the 10-year survival was 40.5% (95% CI 28.5–52.1%), with a median survival of 90.9 months (95% CI 70.4–123.9; data not shown).

Table 1
International registry of lung metastases.

Group	Characteristics
I	Resectable disease, no risk factors (DFI ⩾ 36 months and single metastases)
II	Resectable disease, 1 risk factor (DFI < 36 months or multiple metastases)
III	Resectable disease, 2 risk factors (DFI < 36 months and multiple metastases)
IV	Unresectable disease

DFI = disease-free interval.