Integration of Stereotactic Ablative Radiotherapy in the Management of Pulmonary Metastases from Salivary Adenoid Cystic Carcinoma

George Rodrigues, Tyler Kaster

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Corresponding author: George Rodrigues, george.rodrigues@lhsc.on.ca

Abstract
In this teaching case, we use the example of a woman with pulmonary metastases from a parotid gland adenoid cystic carcinoma (ACC) to illustrate the optimal use of stereotactic ablative body radiotherapy (SABR) in the context of other aggressive treatment options.

Introduction
Adenoid cystic carcinoma (ACC) is a rare salivary gland tumor that comprises only 1% of all malignant oral and maxillofacial region tumors [1]. It predominantly metastasizes via hematogenous spread, while lymphatic spread to the neck is rare [2]. Metastases frequently occur to the lung, with one retrospective study reporting lung involvement in 91% of patients with distant metastases [3]. Other metastatic sites, such as bone, viscera, or brain, are found to occur less frequently. This same study reported that 54% of patients expired within the first three years of distant metastases, but that 10% survived for longer than 10 years, up to a maximum of 16 [3].

With regards to the specific management of pulmonary metastases in ACC, surgery has traditionally been the treatment of choice [4]. These patients are typically good surgical candidates in terms of operative risk and tumor resectability. Additionally, the typical ACC patient is a woman in her 50’s or 60’s, although other presentations can occur [5]. Unfortunately, ACC pulmonary metastases have a tendency to recur, both locally and elsewhere in the lung [6]. Each metastatectomy can have a negative impact on a patient’s lung function and health-related quality-of-life, which can make the management of pulmonary metastatic ACC with repeated metastatectomies increasingly challenging [7].

New advances in stereotactic ablative body radiotherapy (SABR) and other minimally invasive ablative techniques, such as radiofrequency ablation (RFA) and microwave ablation (MWA), offer new management options for patients with metastatic ACC [8-9]. In this teaching case, we use the example of a woman with pulmonary metastases from parotid gland ACC to illustrate the optimal use of SABR in the context of other aggressive treatment options.

Case Presentation
A 49-year-old woman was originally diagnosed in 1997 with Stage 3 ACC of the right parotid gland. The primary tumor was initially treated with a right parotidectomy and modified radical neck dissection, followed by adjuvant radiotherapy of 60Gy in 30 fractions to a postoperative high-risk volume. She initially did well; however, she has subsequently had multiple pulmonary metastases recurrences from 2005 to 2013, which are summarized in Figure 1.
Specifically, she developed a lung metastasis in 2005 in the right lower lobe (RLL) that was treated surgically with a video-assisted thoracic surgery (VATS) wedge resection. This same lesion recurred in 2007 where it was retreated surgically with another wedge resection, this time via an open thoracotomy. As a result of these surgeries, the patient developed significant chronic pain requiring long-term narcotics and analgesics. Therefore, when she developed a new lung lesion in the left lower lobe (LLL) in 2009, the patient wanted to avoid further surgical complications. Thus, she elected to be treated with SABR delivered in 60 Gy in 12 fractions at that time. In 2011, she had a new central lesion in the left upper lobe (LUL). Because definitive surgical management would have required a pneumonectomy, she elected to proceed with an additional course of SABR with a total dose of 60 Gy in eight fractions (Figure 2).

In 2013, she developed a new right peripheral upper lobe (RUL) lesion that was surgically treated with a VATS wedge resection (Figure 3).
FIGURE 3: CT thorax of right upper lung nodule as identified by arrow (a) before surgery and (b) after surgery.

Follow-up CT scan in 2015 demonstrated an enlarging peripheral lung lesion in the medial section of LLL that was treated with MWA (Figure 4).

FIGURE 4: CT thorax of left lower lobe nodule as identified by arrow (a) before microwave ablation and (b) one month after microwave ablation.

This lesion was distinct from the 2009 lesion that was treated by SABR.

At the time of this case report, the patient is alive and continues to be asymptomatic with respect to pulmonary function. No other active lesions are present in the lung parenchyma.

Informed patient consent was obtained for all procedures.

**Discussion**

Pulmonary metastases from ACC pose a unique management challenge. These patients can often live many years with asymptomatic pulmonary metastases in the absence of other sites of disease. They are often good surgical candidates who often wish to be treated with aggressive intent to control active areas of metastatic disease. Unfortunately, the nature of metastatic ACC is such that these patients can experience multiple additional recurrences in the lungs, often occurring in central locations that can be technically challenging for surgical or non-radiotherapy ablative techniques, such as radio-frequency ablation (RFA) or microwave ablation (MWA). Furthermore, robust prospective evidence to help guide the management of this patient population is lacking due to the relative rarity of this disease entity.

SABR can have an important role in the management of these patients because it can be employed to treat centrally-located tumors using a risk-adapted fractionation scheme \[8\]. Other advantages of SABR treatment include the non-invasive nature of the treatment as well as excellent local control associated with its appropriate use. However, the main limitation of SABR is that current safety data currently exists for only up to three pulmonary metastases \[10\]. The safety profile of SABR for more than three metastatic lesions (particularly in the context of patients that have received other pulmonary surgical and ablative procedures)
is currently unknown [10].

The management challenge illustrated by this case is how to best maximize local control while respecting cumulative lung tolerance. We suggest that in patients with serially progressive pulmonary metastases from ACC, SABR should be integrated with other techniques to maximize its utility. Ideally, this treatment should be considered for more technically challenging lesions that may be inaccessible to ablative therapies or may require large surgical procedures (i.e. lobectomy, pneumonectomy). For example, in the patient described above, she had a new LLL lesion near her descending thoracic aorta in 2013 after having already had two other lesions treated with SABR. As such, if she were to receive SABR for this lesion, the currently available safety data would not support her receiving any further radiation to her lungs for the management of additional lesions. Therefore, the patient was advised not to proceed with SABR until she had exhausted her other treatment options.

ACC is a rare cancer that behaves uniquely with slow-growing pulmonary metastases. Information on ACC pulmonary metastases management is often extrapolated from other studies, given the rare nature of this disease entity. These results may not always be applicable to patients with ACC because of its long-term indolent course. This case illustrates the challenging nature of managing these patients, as the treating oncologist often must often think two or three lesions ahead when planning current treatment with surgery, ablative therapy, SABR, or continued observation. Continued research should be performed on the identification of the true total number of lung metastases lesions that can be safely treated with SABR in order to assist decision making for this challenging patient population.

Conclusions

SABR can be an effective tool in conjunction with other techniques for the treatment of pulmonary metastases in ACC; however, its use should be ideally directed to tumors not amenable to other techniques (i.e. central lesions or high-risk surgical cases) given the limited safety data in using SABR for more than three pulmonary lesions.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References