Ablative Approaches for Pulmonary Metastases

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KEYWORDS

• Pulmonary metastases • Ablative therapy • Radiotherapy • Oligometastases

KEY POINTS

- Directed treatment of pulmonary metastases was traditionally limited to surgical resection in appropriately selected patients.
- More recently, for patients who are not surgical candidates, non-invasive approaches such as radiotherapy or radiofrequency or microwave ablation have been developed.
- These techniques can provide local control and survival benefit similar to that seen with surgery in well selected patients, such as those with oligometastatic disease.
- Further studies are needed to define the role of ablative therapies compared to surgical management and the integration of these techniques with systemic treatments.

INTRODUCTION

Pulmonary metastases are a common event in patients with cancer. Approximately 50% of patients with malignancy-related deaths were found to have metastases in their lungs at autopsy.[1] This proclivity seems to involve tumor intrinsic factors including epidermal growth factor receptor (EGFR) signaling and matrix metalloproteinase expression, and unidentified factors present in the lung microenvironment.[2] Traditionally, systemic therapies including cytotoxic chemotherapy, hormonal therapies, immunemodulating therapy, monoclonal antibodies, and other "targeted" agents have been used to treat lung metastases. The role of ablative treatments directed at clinically evident metastases has been primarily limited to surgical resection in medically fit patients with long disease-free intervals and a minimal burden of systemic disease.[3] Based on the long history of surgical removal of pulmonary metastases,[4] and the combined diagnostic and therapeutic nature of the procedure, surgery is considered the standard approach for these patients. However, a significant number of patients are not candidates for metastasectomy, whether because of technically unresectable tumors, medical comorbidity rendering them unfit for surgery, a shorter disease-free interval, or extensive extrathoracic disease. For these patients, noninvasive or minimally invasive approaches to ablate pulmonary metastases are potential treatment strategies. This article discusses the data behind nonsurgical ablative approaches, namely ablative radiotherapy (stereotactic body radiation therapy [SBRT]) or thermal ablation via radiofrequency ablation (RFA) or microwave ablation (MWA), for pulmonary metastases.

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BACKGROUND

Surgical resection of pulmonary metastases was described as early as the mid to late nineteenth century, likely because of advances in anesthesia and aseptic techniques.[4] The use of other metastasis-directed therapies, such as radiotherapy and invasive ablative techniques, has been developed more recently.[5] The use of metastasis-directed therapy techniques including surgery,[6] radiotherapy,[7] and invasive ablative strategies[8] has been increasing, likely mirroring the increasing use and availability of advanced imaging, such as high-resolution computed tomography (CT), MRI, and PET-CT to detect metastases when they are few in number and clinically asymptomatic. Furthermore, the increasing availability of advanced CT simulation techniques including multiplanar CT simulation, tumor-associated respiratory motion assessment, and respiratory motion management, and linear accelerators with associated image guidance, rapid dose delivery, and conformal therapy, make these techniques increasingly attractive tools for physicians and patients.

Additionally, a greater acceptance of the philosophic underpinnings of the use of metastasis-directed therapies is also contributing to their increasing use. The oligometastatic state was proposed by Hellman and Weichselbaum[9] as a distinct biologic state between locoregionally confined tumors and widespread metastatic disease. Based on the spectrum theory of cancer metastases,[10] oligometastases are metastases limited in number and destination organ, which in certain circumstances could represent disease unlikely to spread further. In this situation, metastasis-directed ablative therapies could improve the disease-free survival of patients by rendering them without evidence of cancer. Multiple studies consistently report about 25% long-term survival following metastasis-directed therapy to pulmonary (and other) metastases.[3,11,12]

Recent studies are beginning to describe the biology of the oligometastatic state. MicroRNA analyses of primary tumors and metastases undergoing ablative radiotherapy[13] and surgically resected pulmonary metastases[14] have demonstrated that specific microRNA expression patterns are associated with long-term disease control. Furthermore, when these microRNAs are overexpressed in murine models, a change in phenotype from oligometastasis to polymetastasis is observed. Regulation of oligometastases has been proposed to be controlled at some level by microRNA found on chromosome 14q32. These microRNAs suppressed cellular adhesion and invasion and inhibited metastasis development in an animal model of breast cancer lung colonization. Their target genes, including TGFBR2 and ROCK2, are thought to be key mediators of these effects.[15]

Greater biologic understanding of oligometastases raises some interesting questions regarding the use of ablative therapies. If biology truly governs the ability of these tumors to spread, then perhaps patients with oligometastases are destined to do well, and metastasis-directed ablative therapies might not be needed. Although analyses of patients with oligometastases who undergo ablative therapies for pulmonary metastases report better than expected outcomes, few reports have control groups of similar patients who have not received metastasis-directed therapy. Of the few that do, often no difference in overall survival is seen.[16] Ongoing randomized studies will help to determine if survival, or progression-free survival, is improved in patients receiving ablative therapies.

Role of Ablative Therapies

Although most attention has focused on the use of ablative techniques to improve survival in patients with pulmonary oligometastases, there are other clinical situations where these techniques are useful management strategies. In patients who are not candidates for or are unwilling to undergo systemic therapy, ablative therapies can be used as noninvasive or minimally invasive methods to halt the growth of metastases. This is also true for patients who have been on systemic therapy, but are not able to continue based on cumulative toxicity. Furthermore, in patients with polymetastases, a limited number of metastases may be growing while others lesions in the same patient may be stable on systemic therapy. This phenomenon, termed oligoprogression, has been described most clearly in patients with non–small cell lung cancer (NSCLC) with driver mutations treated with targeted therapies to EGFR mutations or ALK and ROS mutations. In oligoprogressive patients, the use of ablative techniques directed toward the few metastases, both intracranial and extracranial, that were progressing through targeted therapy prolonged the time that patients were able to stay on therapy and this directly improved survival because patients on targeted therapy longer than 2 years lived longer than those who were not.[17,18]

General Principles of Ablative Therapies

There are some common themes that permeate the literature regarding ablative therapies for