Extended Abstract

Radiation strategy and techniques for metastatic pleural disease from thymic malignancies: extended abstract

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Although thymic tumors are the most common tumor originating from the anterior mediastinum, they are relatively rare with an incidence in the United States of 0.13–0.15 per 100,000 population at risk (1). Patients who present with pleural metastases are considered to have stage IVA disease according to the Masaoka-Koga and tumor-node-metastasis (TNM) 8th edition staging systems (2). Despite the advanced stage of presentation, due to the indolent nature of the disease, survival rates can still be favorable with 5-year overall survival rates up to 80–90% for patients with stage IVA thymoma (3,4). Pleural and pericardial metastases are common sites for recurrence and progression in patients who present with earlier stage disease (5,6). In a study of 156 newly-diagnosed Stage II–IV thymoma patients treated with resection and postoperative radiotherapy (PORT), the majority (85%) of local-regional failures occurred in the pleura (6).

The management of pleural metastases typically requires a multidisciplinary approach and treatment recommendations depend on the patient's performance status and co-morbidities, the extent of disease and how quickly the disease appears to be progressing. Options include systemic therapy, surgical resection, radiotherapy, and close monitoring with interval imaging. If there is a limited extent of indolent, resectable pleural disease in a fit patient, surgical resection is usually considered as a primary treatment. After surgical resection of pleural metastasis, progression can occur with a 2-year progression-free survival (PFS) rate estimated at 60–70% (7,8). Upon progression, patients may undergo repeat surgery until further surgical resection is no longer recommended.

Radiotherapy can be considered as a local treatment modality in cases where surgical resection is not recommended. Radiotherapy is standardly used in the management of locally-advanced thymic malignancies. In cases with high-risk pathologic features after surgical resection, PORT is used to target the thymic bed. Multiple studies have demonstrated an improvement in disease-specific and overall survival rates with PORT in these settings (9-16).

For pleural metastases, the typical indications for radiotherapy include the palliation of symptoms caused by the tumor, prevention of impending symptoms when pleural metastases are radiologically encroaching upon critical structures and the treatment of oligometastatic/oligoprogressive disease. Examples of symptoms that can be caused by pleural metastases include chest wall or back pain when the tumor is invading the chest wall or vertebral body, respectively, superior vena cava (SVC) syndrome caused by compression of the SVC, brachial plexopathy from compression of the neural plexus, or neurologic deficits caused by neural foramen involvement or spinal cord compression. Additionally, compression of the bronchial airway or vasculature can cause shortness of breath, palpitations, or chest pain. In these cases, radiotherapy can shrink the metastases away from the critical structures to alleviate symptoms and prevent future local progression.

Highly-effective local therapies, such as surgical resection or stereotactic body radiation therapy (SBRT), for the treatment of oligometastases (limited number of metastatic sites of disease) or oligoprogression (limited number of progressive sites of disease) is a relatively newer treatment approach for metastatic disease. For patients with small metastases, SBRT can deliver high doses of

radiation in a few treatments using a highly conformal approach to maximize the dose of radiation delivered to the target and avoid sensitive organs. Data from other disease sites, such as lung cancer, have demonstrated improvements in progression-free and overall survival with this aggressive treatment approach (17-21). In these studies, oligometastases/oligoprogression was defined as either 5 or fewer or 3 or fewer sites. While the data for definitively treating thymic-specific patients with oligometastatic/oligoprogressive disease is lacking, the ability of highly-effective local therapies to eradicate all macroscopically-appreciable disease make this an attractive approach as an alternative or adjunct to systemic therapy. The optimal management strategy for how to combine SBRT with systemic therapy regimens is not known.

The radiation approach for the palliation of symptoms varies based on the prognosis of the patient, the size of the radiation target and the location of the target. For patients with poor prognoses, conventional radiation techniques that deliver low doses of radiation using comprehensive, non-conformal fields, may be adequate to provide palliation for a short duration of time. Patients with thymic malignancies, however, tend to have more favorable prognoses, which underscores the need to achieve long-term local tumor control with higher biologically effective doses of radiation.

More extensive radiation targets and targets abutting critical organs may not be appropriate for SBRT. In these cases, spreading the radiation treatment out over a longer period of time with alternative highly-conformal techniques such as intensity-modulated radiation therapy (IMRT) or proton beam therapy may be appropriate.

For patients with extensive pleural involvement, there is a need for therapy that delays the progression of pleural metastases. A recent Phase II study by Wang *et al.* treated patients with unresectable pleural metastases that progressed on chemotherapy with IMRT to 30–50 Gy in 2 Gy/fractions (22). This regimen was safe when 1 course of radiation was delivered and the control rates were optimal with 50 Gy. Unfortunately, 93.5% of patients developed out-of-field failures, indicating that only targeting areas of known pleural metastases is not sufficient in preventing future progression. With advancing radiation technologies, such as IMRT with photons and pencil beam scanning with proton therapy, it is now feasible to safely deliver higher radiation doses to the hemithoracic pleura with 2 intact lungs. Hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) is a radiation technique currently used to treat malignant pleural mesothelioma and may be an option in select thymic patients to delay or prevent progression of pleural metastases from thymic malignancies (23-25). The technique targets the entire pleural space and could eradicate microscopic pleural disease prior to developing into an out-of-field failure when targeting only known sites of disease. Hemithoracic IMPRINT is currently under investigation as a treatment for patients with pleural metastases from thymic malignancies (ClinicalTrials.gov identifier: NCT05354570).

In summary, radiotherapy should be considered as part of a multidisciplinary approach to the management of pleural metastases from thymic malignancies. Radiotherapy can be used to palliate symptoms, as well as to maximize disease control, particularly in patients with limited sites of disease. Additionally, hemithoracic IMPRINT is a radiotherapy technique that may benefit thymic patients with pleural involvement. While this technique has been established to be safe in patients with malignant pleural mesothelioma, at centers of excellence with significant experience, the safety and efficacy data of IMPRINT in thymic patients needs to be established.

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