Editorial

Pulmonary metastectomy: impact of tumor histology and size

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Resection of isolated pulmonary metastases from extrapulmonary primary malignancies has been shown to prolong survival (1,2). Although there are no randomized trials to date validating pulmonary metastectomy, retrospective data (3) support resection for isolated lung involvement. A large series from Memorial Sloan Kettering Cancer Center consisting of 539 patients undergoing pulmonary metastectomy for sarcoma revealed 5- and 7-year survival rates of 34% and 23%, respectively (4). An older analysis of 5,206 patients from the International Registry of Lung Metastases similarly revealed 5- and 10-year survival rates of 36% and 26%, respectively, in patients undergoing pulmonary metastectomy for various histologies (1). Survival outcomes appear to be better in patients with fewer metastases and a longer disease-free survival from the time of treatment of the primary tumor to the identification of metastasis.

The decision to operate on patients with pulmonary metastases is complex consisting of a multi-disciplinary approach involving the surgeon, medical oncologist, radiation oncologist and pathologist. Although there are few consensus guidelines for the treatment of isolated pulmonary metastases (5), patients who are operative candidates with a controlled primary tumor and resectable metastasis should be considered for metastectomy. Most experts favor a parenchymal-sparing approach with the goal of attaining negative margins (6,7). Resection of pulmonary metastases is accomplished optimally via the VATS approach. When thoracotomy is anticipated for resection, the expected survival benefit of metastectomy versus morbidity should be carefully considered and discussed with the patient. Patients in whom a complete resection is not feasible should be palliated by non-surgical measures. Mediastinal lymph node involvement is considered by most to be a contraindication to metastectomy. Patients who are unsuitable for surgical resection may be candidates for alternative modalities including stereotactic radiation or other ablative techniques. Adjuvant chemotherapy is a topic of debate with the strongest data supporting treatment in patients with isolated metastases from colon cancer. Overall, data supporting post-resection chemotherapy is limited to small series and observational studies.

The survival and recurrence implications of specific histologic characteristics of tumors in patients undergoing pulmonary metastectomy have not been well studied to date (8-10). Primary malignancies such as colon cancer, melanoma and renal cell carcinoma have a propensity for lymphatic spread whereas sarcomas mainly spread hematogenously. These, amongst other differences, likely play a role in the aggressiveness of tumors and recurrence patterns. Whether histo-pathologic factors would impact the optimal surgical approach (i.e., lobectomy *vs.* parenchymal-sparing) in any given patient have not been investigated. In their prospective study, published in *European Journal of Cardiothoracic Surgery*, and entitled "Growth patterns of pulmonary metastases: should we adjust resection techniques to primary histology and size?", Welter *et al.* aim to elucidate the impact of specific histologic characteristics of, growth patterns and size of the metastatic tumor on recurrence and survival (11).

The authors conducted a thorough analysis and detailed histologic assessment of pulmonary metastases.

The authors conducted a prospective analysis of 183 patients undergoing pulmonary metastectomy from 2008 to 2012. Among the 183 patients, there were 203 procedures and 412 lung specimens removed, containing 459 metastases. The specimens were resected via various modalities including electrocautery (51.2%), staples (28.9%), laser (11.7%) and wedge resection between clamps (8.3%). The authors observed different average minimal resection margins between different resection modalities favoring stapled resection. Laser resection was favored when multiple metastases were present or when pulmonary function was marginal. It should be noted that the lack of uniformity in the resection approach may have influenced some of the comparisons and results observed.

The authors analyzed several histologic growth characteristics including a smooth capsule, interstitial growth, satellite nodules, aerogenous spread of floating cancer cell clusters (ASFC), pleural infiltration, hematologic and lymphatic spread, perivascular or peribronchial spread. As per the analysis, the presence of a smooth surface and a fibrous pseudocapsule indicate non-aggressive local growth, whereas pleural infiltration, lymphovascular involvement, interstitial growth microsatellite nodules and ASFCs all portend more aggressive growth patterns. The comparison of specific subtypes regarding the propensity of possessing certain growth patterns is intriguing in that perhaps surgical resection margins should be tailored relative to preoperative histology. Specifically, the authors concluded that melanoma metastases had an increased likelihood of perivascular growth compared to renal cell carcinoma and also had a higher incidence of lymphatic spread compared to sarcoma. Sarcomas had the highest incidence of pleural infiltration and lowest incidence of lymphatic spread. Epithelium-derived metastases such as colorectal cancer more frequently had free-floating tumor cells clusters. Colorectal metastases also had the highest rate of interstitial spread. In consideration of the correlation between growth patterns and tumor size, the authors conclude that pleural invasion, interstitial growth, perivascular and peribronchial growth were associated with increasing size of metastases. It is interesting to note that free-floating tumor cell clusters and satellite nodules do not appear to correlate with tumor size. Given the number of subtypes and various characteristics analyzed, one must ask whether or not the study is adequately powered to show significant differences amongst all the subtypes.

The implications of growth patterns relative to lymph node involvement remain unclear. At this time, there is no substantial data to support lymphadenectomy at time of metastectomy. Given that there is intrathoracic lymph node involvement in up to 46% of renal cell carcinomas and 44% of colorectal carcinomas, perhaps these principles should be reconsidered. In their analyses, the authors shed light on growth patterns of specific histologic subtype and found that certain lesions such as renal cell carcinoma have a higher propensity for lymphangitic spread. With this information in mind, it can be surmised that certain types of metastatic lesions may warrant a mediastinal lymphadenectomy in addition to the metastectomy. Data to support the survival benefit or recurrence reduction as a result of this approach are lacking and can be explored with further research efforts.

In the survival analysis, the authors were successful in collecting follow-up data on 82% of the patients. Features such as local intrapulmonary recurrence could be evaluated in 74.5% of resection sites. Local recurrence was observed in 21.2% of the resection sites. Factors correlating with recurrence included pleural infiltration, interstitial growth, safety margins <7 mm. Interestingly, lymphovascular growth, free-floating tumor cell clusters, satellite nodules and non-smooth surface were not shown to have a statistically significant influence on the likelihood of local recurrence. The median survival and 5-year survival for the entire group were 37 months and 37.6%, respectively. Although the authors acknowledge their limitations in the completeness of follow-up data, it would be intriguing to analyze disease-free versus overall survival as well as to compare recurrence patterns relative to specific cancer subtypes, modes of resection and neoadjuvant therapy. The sample size of the study limits these analyses to some degree.

Significant limitations include lack of prospectively obtained follow-up CT scans. The authors do not comment of the characteristics of patients regarding neoadjuvant chemotherapy and/or radiotherapy and their influence of metastatic patterns, nor do they mention the completeness of resection of the index tumors. Further, some of the stage classification was incomplete and there was a lack of data regarding chemotherapy. These factors may have influenced their observed recurrence rates and survival implications. Such limitations result in less granular data and comparisons.

Studies correlating clinical and radiographic factors with microscopic infiltration are particularly informative to

radiation oncologists designing target volumes. Although Welter *et al.* do not specifically address this correlation in their study, their results do have some implications for radiation oncology. For Stage I NSCLC, several studies have demonstrated a several-millimeter microscopic disease extent, generally being more extensive with adenocarcinoma compared to squamous cell carcinoma (12,13). A 2012 study, correlating CT and PET characteristics with microscopic disease extension, accounted for tissue deformations between in-vivo imaging and ex-vivo pathologic lung specimens. From that study, the extent of microscopic disease extent with NSCLC was appreciably greater than shown in prior studies, on the order of >2 cm in some patients and <2.6 cm in 90% of patients (14).

In radiation therapy planning, the 'gross target volume' (GTV) and (when accounting for internal motion) the "internal GTV" (iGTV) are defined from planar imaging. GTV and iGTV do not account for microscopic extension of tumor, which is included in the clinical target volume (CTV), or when accounting for internal motion 'internal target volume' (ITV). While radiation oncologists are well aware of the microscopic extension of lung tumors, it is generally not incorporated into stereotactic body radiotherapy (SBRT) target volumes, including recent and ongoing Radiation Therapy Oncology Group/ NRG cooperative group studies. Perhaps this practice is acceptable, as the penumbra dose of radiation around the target volume may be therapeutic for microscopic disease. Although, for the case of >2 cm microscopic extension of NSCLC described above, the practice of not accounting for subclinical disease extent in target volumes may increase recurrence risks.

For lung oligometastases, data on microscopic extension of disease beyond the gross tumor have been lacking. While Welter and colleagues did not systemically quantify the extent of microscopic tumor infiltration, their analyses of histology-specific growth patterns are potentially helpful not only to the surgeon deciding on the extent of resection, but also to the radiation oncologist delineating target volumes. Clearly more research is needed to more accurately quantify the extent of infiltration in lung oligometastases, as well as to correlate clinical and radiologic factors that might better predict microscopic disease extent. Such analyses will facilitate radiation treatment planning in those patients who will not undergo a resection.

Despite the limitations of the study, the authors are to be applauded for their thorough prospective analysis of the impact of histology on pulmonary metastectomy. Based on the results, it can be concluded that the frequency of local recurrence increased with smaller negative margins, increasing diameter of the tumor >5mm and was associated with certain aggressive growth patterns including pleural invasion and interstitial growth. The authors recommend incrementally increasing resection margins with increasing size of the metastases. This study helps guide not only surgical decision making, but also has implications for radiation therapy planning.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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