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EDITORIAL – THORACIC ONCOLOGY

The Increasing Role of Surgery in Comprehensive Treatment of Advanced Non-small Cell Lung Cancer with Targetable Mutations

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In recent years, there has been an increased appreciation for the heterogeneity of stage IV non-small cell lung cancer (NSCLC). It is no longer appropriate to group stage IV patients into a single cohort with a uniform treatment approach. Many of the treatment change center around a new classes of systemic therapies and personalized approach based on tumor genomics, but there is also growing appreciation for the survival benefit associated with the use of local therapies for select populations with stage IV disease. Patients most likely to benefit from this aggressive approach include those with: oligometastatic disease, an excellent and sustained response to systemic therapies, and a good performance status.

Oligometastasis was initially defined by Hellman and Weichselbaum 50 years ago[1] but remained somewhat irrelevant in NSCLC until the last decade. Now oligometastatic NSCLC is recognized as a unique subset of stage IV patients with improved survival compared to widely metastatic disease. It received a unique stage designation in the 8th edition of the American Joint Committee on Cancer Lung Cancer staging system (M1b),[2] and should be considered for more aggressive treatment strategies. The significant benefit of local therapy for oligometastic NSCLC was reported in the "Oligomez" trial, a small prospective phase II trial that which closed early due to the significant progression-free survival (PFS) improvement with the addition of local therapy to chemotherapy alone.[3] Local consolidative therapy to all disease sites significantly improved PFS (14.2 vs. 4.4 months) and overall survival (41.2 vs. 17.0 months). Furthermore, local consolidative therapy could be surgery or stereotactic body radiotherapy (SBRT). A key trial inclusion criteria was lack of disease progression during front-line systemic therapy, highlighting the importance of improvements in systemic therapies in increasing the opportunity for local therapies to have a meaningful impact in the treatment of metastatic NSCLC. Systemic therapies that are effective and well tolerated have greater potential to leave patients with small volume disease for prolonged periods, creating opportunity for local interventions.

NSCLC patients with tumors harboring epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS1 mutations epitomize the clinical setting where local therapy for the primary tumor can have a major impact in stage IV treatment. Patients with these mutations are often quite fit, less likely to have smoked and have fewer smoking related co-morbidities. The second- and third-generation targeted tyrosine kinase inhibitors are highly effective and well tolerated. They can induce dramatic responses and patients can remain on them for prolonged periods, but it is rare to see complete eradication of the intrathoracic disease. It is also known that residual tumor cells will eventually develop resistance to these agents, therefore local consolidative therapy is being used with greater frequency to eradicate the residual disease following initial therapy. This is a significant evolution in treatment, but SBRT has dominated the much of the recent enthusiasm despite surgery having a long history in this setting. Two small prospective SBRT trials[4,5] are overshadowing four decades of retrospective surgical data. Wide spread acceptance of surgery for oligometastatic diseases has been hindered by two main factors: (1) the

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retrospective nature of the data, and (2) the designation of survival advantage to selection bias alone. The work from Kuo et al. is important because it examines surgical resection of residual intrathoracic disease in a highly focused population, stage IV EGFR-mutated patients after initial EGFR targeted therapy and uses a large institutional cohort with propensity matching.[6] Prospective comparisons between surgical and non-surgical therapies are challenging therefore insights from highly focused and well-controlled cohorts are essential in this setting. Kuo and colleagues demonstrate a doubling of PFS from 13 to 29 months with the addition of primary tumor resection. The majority of resections were minimally invasive (87.5%) and R0 (84%) and complications were rare (12% > Gr2).[6]

Most believe that favorable biology is the primary driver of improved prognosis in the oligometastatic NSCLC, and question if retrospective data and small phase II trials are enough to prove a true survival benefit for the addition of local therapies for stage IV NSCLC. We are at a time when these interventions carry minimal morbidity and mortality, and the lack of a randomized phase III evidence should not result in denial of local intervention in well-selected patients. Cure should be the goal for healthy patients with limited metastatic disease. Surgical resection of the primary tumor should be considered as an important aspect of oligometastatic NSCLC treatment because of the exceptional local control and tissue acquisition provided by resection and in EGFR-mutated tumors the ability to remove the greatest source for acquired resistance.

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