Commentary

Who are appropriate surgical candidates among patients with oligometastatic non-small cell lung cancer?

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Metastasis of cancer should be microscopically present in the systemic circulation, which justifies the need for systemic chemotherapy. Although systemic chemotherapy can improve survival relative to supportive care, for the vast majority of patients, disease progression occurs and a cure cannot be achieved. Patients with a limited number of cancer metastases may represent an exception to this general rule, and efforts to eradicate all metastases with ablative therapy (such as surgery or radiotherapy) with the goal of cure were reported as early as the 1930s (1). This paradigm was formalized in 1995 by Hellman and Weichselbaum using the term "oligometastases", which refers to a state of limited metastatic burden. This concept has recently attracted considerable attention from thoracic multidisciplinary teams in cases where the patient may be amenable to cure if both the primary and all known metastatic lesions can be radically ablated (2). It is important to understand how to select appropriate candidates for radical local therapy. What criteria are useful for selecting the proper radical local therapy for both primary and oligometastatic lesions? Do these criteria include the location and number of metastases, the stage of intrathoracic tumor (T- and N-factors), histology, and molecular characteristics?

The article "*Outcomes of a Highly Selective Surgical Approach to Oligometastatic Lung Cancer Recently*", which was recently published in the *Annals of Thoracic Surgery* by Johnson and colleagues (Department of Thoracic Surgery, Yale University School of Medicine, New Haven, CT, USA) described the outcomes of synchronous oligometastatic stage IV non-small cell lung cancer (NSCLC) treated by local therapy with curative intent, including surgery, radiation, or both, at all sites of disease (primary and metastatic tumors) (3). Since 2005, the authors conducted definitive local therapy as a first-line treatment in oligometastatic NSCLC patients who were confirmed to be free of N2 disease by pretreatment invasive mediastinal staging including mediastinoscopy, endobronchial ultrasonography (EBUS), or endoscopic ultrasonography (EUS), in addition to a positron emission tomography (PET) scan. In this study, oligometastases were defined as ≤5 metastases in a single organ other than lung, as proposed previously, although a universal definition has not been established (4-6). Until 2014, a total of 22 patients were diagnosed mainly by mediastinoscopy (n=21) as negative N2 disease and underwent local treatment for both primary and metastatic lesions. The brain was the most common location for oligometastases (n=16), although the actual number of metastatic lesions was not described. Local treatment of the primary tumor included 21 pulmonary resections, mainly by lobectomy (n=19), and one stereotactic radiosurgery. The local treatment of metastasis included 12 surgical resection and 10 gamma knife/linear acceleration/stereotactic radiosurgery. The pathological (p) N stage of patients who underwent lung resection (n=21) included only one pN2

disease (pN0: 16, pN1: 4). On the other hand, during the same period, 13 oligometastatic NSCLC patients with confirmed N2 disease by invasive mediastinal staging were excluded from local therapy with curative intent, and were treated palliatively. The N2-negative patients treated by local therapy with curative intent had a superior 5-year overall survival (OS) compared with N2-positive patients who were treated palliatively (58% *vs.* 0%, respectively; P=0.028), although the follow-up period for the N2-negative population was fairly short (29.3 months). The authors strongly suggested the importance of excluding patients with N2 disease from among candidates for local therapy with curative intent for synchronous oligometastatic NSCLC.

Even with the support of only low-level evidence, international clinical guidelines recommend local therapy for patients with a single or a few metastases and a good performance status. The National Comprehensive Cancer Network (NCCN) guidelines recommend local therapy for both primary and a few brain/solitary adrenal metastases only if the thoracic lesion is T1-2N0-1 or T3N0 disease (7). The most recent version of the NCCN guidelines (version 4, 2017) extends the indication for definitive local therapy to limited metastases other than in the brain and adrenal gland. Furthermore, definitive therapy for thoracic lesions is indicated even for N2 disease (chemoradiation), but surgical resection is still not indicated for thoracic lesions with N2 disease (8). The American College of Chest Physicians (ACCP) guidelines also recommend surgery for primary lesions and radical local therapy for 1–3 brain or solitary adrenal metastasis if N2 is excluded by PET scan or EBUS (9). The current study by Johnson *et al.* clearly confirmed the importance of excluding N2 if we perform radical local therapy including surgery for both primary and synchronous oligometastatic lesions. However, further studies will be needed to determine whether routine invasive staging is necessary for all cN0-1 patients based on the results of CT and PET scan.

In Johnson's study, the survival curve of the N2-negative population decreased until 20 months after treatment, similar to that of the N2-positive population, suggesting that the N2-negative population was heterogeneous and a negative N2 status itself does not identify proper candidates for initial local therapy for oligometastatic stage IV NSCLC. How can we select patients for whom we can expect long-term survival and even cure? The forthcoming 8th edition of the tumor, node, and metastasis (TNM) classification for lung cancer is proposed based on the International Association for the Study of Lung Cancer (IASLC) database created from 94,708 lung cancer patients between 1999 and 2010 (10,11). When M1b (distant metastases outside the chest cavity) was assessed according to the number of metastases, tumors with a single metastasis in a single organ had a significantly better prognosis than those with multiple metastases in one or several organs [median survival: 11.4 months (95% CI 9.6–13.7) *vs.* 6.3 (4.8–7.0)] (10). The 8th edition of the TNM classification recommends that single metastatic lesions in a single distant organ should be newly designated as M1b, and multiple lesions in a single organ or multiple lesions in multiple organs should be reclassified as M1c. The IASLC database does not indicate the detailed treatments for metastases, but in terms of survival outcome, local therapy including surgery might be particularly ideal as a first-line treatment for new M1b (a single metastasis in a single organ) without cN2 disease.

Oligometastatic disease is essentially stage IV disease regardless of the number of metastases and systemic chemotherapy is theoretically considered to be a standard first-line treatment. Therefore, the clinical efficacy of a first-line local therapy for both the primary lesion and oligometastatic lesions should be evaluated in comparison to first-line systemic treatment, except for symptomatic or symptom-expecting oligometastases such as brain metastases. For patients with brain oligometastases, systemic therapy plus local therapy for brain oligometastases seems to be an appropriate control arm for local therapy for both the primary lesion and brain oligometastases.

Recently, a multicenter randomized phase 2 study was conducted to assess the effect of local consolidation therapy versus maintenance chemotherapy for patients with oligometastatic (three or fewer metastatic sites) stage IV NSCLC after standard first-line chemotherapy (12). The recruited patients had received standard first-line systemic therapy, defined as four or more cycles of platinum doublet chemotherapy, erlotinib or another approved first-line epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), for 3 months or longer for an EGFR mutation-positive population, or crizotinib for 3 months or longer for an ALK rearrangement-positive population. Patients had no disease progression before randomization. From November 2012 to January 2016, 74 patients were enrolled either during or at the completion of first-line systemic therapy, and 49 patients were allocated to local therapy for residual primary and oligometastatic lesions (n=25) and maintenance chemotherapy (n=24). The primary

endpoint was progression-free survival (PFS), and at a median follow-up time of 12.39 months for all randomized patients, the median PFS in the local consolidative therapy group was 11.9 *vs.* 3.9 months in the maintenance treatment group [hazard ratio 0.35 (90% CI 0.18–0.66)]. Although OS data are not currently available, this study suggested that aggressive local therapy should be further explored in phase 3 trials.

Although randomized studies of a first-line local therapy including surgery versus a first-line systemic therapy for synchronous oligometastatic NSCLC are difficult to perform, the clinical efficacy and appropriate candidates for first-line local therapy including surgery should be evaluated by a well-designed clinical trial in the near future.

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Footnote

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

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