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
Hishida. Surgical candidates for oligometastatic NSCLC

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

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