

Surgery for mediastinal lymph node and early stage lung cancer: individualized practice based on clinical database

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The increased availability of computed tomography (CT) scan contributes to the early detection of lung cancer. Surgical resection has been proved to be the single curative treatment for patients with early stage non-small cell lung cancer (NSCLC), and lobectomy with mediastinal lymph node dissection has been regarded as the standard procedure for early stage lung cancer. With the increased incidence of early stage lung cancer manifesting as ground-glass opacity or subsolid nodule, the extent and the necessity of mediastinal lymph node dissection or resection become debatable. Furthermore, the oncologic therapeutic effect of lobectomy or sublobar resection has also been under investigation. A recent retrospective analysis using the database of the diagnosed cases of NSCLC as a result of CT screening in the International Early Lung Cancer Action Program (I-ELCAP) cohort was performed by Flores *et al.* (1). Based on their data, the authors concluded that it is not mandatory to perform mediastinal lymph node resection (MLNR) when screen-diagnosed NSCLC manifest as subsolid nodules and are less than 30 mm in diameter. Sublobar resection should also be considered. Peripherally located cancers manifesting as a solid nodule less than 20 mm in diameter should be considered for sublobar resection without MLNR.

Flores and colleagues analyzed 627 surgical patients from 664 patients with cT1aN0M0 clinical stage IA NSCLC, and enrolled 607 after excluding 20 patients whose pathologic

tumor size was more than 30 mm. Of the 404 patients with solid nodule, 311 with MLNR more frequently had a college education and had lobectomy/bilobectomy than 93 without MLNR. Fifteen had pathologic N1 disease and 17 had N2 disease of the 311 with MLNR. Of the 93 patients with solid nodules who did not have MLNR, 44 underwent hilar lymph node resection only, and 3 had intrapulmonary or hilar lymph node metastases. The necessity of systemic lymph node dissection has become a debatable topic under the circumstances of increased chest CT screening and consequently discovery of early stage lung cancer. The rate of occult N2 metastasis in clinical stage I NSCLC was reported 0.4% in lobe-specific lymph node dissection and 0.8% in systematic lymph node dissection, with a substantial rate of postoperative complication (2). Nonetheless, complete and accurate staging for adjuvant therapy and clearance of potential micrometastasis remain the major advantage, supporting the need for lymph node dissection. Previous studies focusing on the predictor of lymph node metastasis concluded that large tumor size, invasive or poorly differentiated histology, the absence of ground-glass opacity, and elevated serum carcinoembryonic antigen indicated systematic mediastinal lymph node dissection (3-5). Haruki *et al.* revealed that in a cohort of 876 patients who underwent complete resection for clinical stage I NSCLC, no cases with hilar and mediastinal lymph node metastasis were identified in ground-glass opacity (GGO)-predominant tumors. Preoperative elevated serum

carcinoembryonic antigen level was significantly associated with mediastinal lymph node metastasis.

Flores *et al.* presented the lung cancer-specific survival rate was 100% regardless of whether they had MLNR or not, and the risk of dying in patients with solid nodule was 70% higher for patients with MLNR using Cox survival analysis. Age, centrally located tumor, tumor size 21 to 30 mm, and invasion beyond the stroma were responsible for the significantly lower cancer-specific survival. These factors contribute to the staging migration in 15 confirmed N1 and 17 N2 disease among those who underwent MLNR and their inferior lung cancer-specific survival. With the advancement in technology, while detection of early stage of lung cancer has been facilitated by CT screening, the utilization of PET for preoperative N staging might not be as pivotal as it used to be in patients with solid lung tumor of substantial size. Preoperative and intraoperative lymph node detection and modification of systemic lymph node dissection has been advocated, such as lymph node sampling, selective lymph node dissection, and sentinel lymph node resection (6-9). Further clinical trial is mandatory to consolidate the indication for not performing lymph node dissection in patients with early stage lung cancer.

Comparison of MLNR with no MLNR in 203 patients with subsolid nodule revealed that the 151 undergoing MLNR more frequently were current smokers, had a centrally located cancer, and lobectomy. There was one patient who had single ipsilateral station 6 lymph node metastasis and was thus pathologic N2. The lung cancer-specific survival rate was 100% regardless of whether they had MLNR, indicating that sublobar resection without MLNR provides equivalent oncologic outcome for NSCLC manifesting as a subsolid nodule. Sublobar resection, including wedge resection and segmentectomy, preserves pulmonary function more than lobectomy, and has historically been considered the surgical procedure for lung cancer in patients with significant comorbidities or compromised cardiopulmonary reserve. Recently, numbers of studies has suggested that sublobar resection yielded equivalent oncologic outcome in patient with stage I NSCLC (10-14). Although sublobar resection is used to describe both approaches, the extent of wedge resection is determined by the location of target lesion and the pulmonary hilum remains intact. Therefore, surgical techniques for segmentectomy are much more demanding and hence more time-consuming than wedge resection. The comparison between segmentectomy and wedge resection

for early stage lung cancer is still under investigation, although studies have demonstrated that wedge resection provided equivalent oncologic outcome given the patients were of older age, the tumor was peripherally located and no more than 2 cm, predominantly lepidic in histopathologic and ground-glass in radiographic feature (15-17). While segmentectomy clears venous and lymphatic drainage in the intersegmental plane, wedge resection has been reported as a risk factor for locoregional recurrence and inferior survival (18-20). Data shown by Flores *et al.* implied that sublobar resection without MLNR yielded equivalent oncologic outcome as lobectomy with MLNR in NSCLC manifesting as a subsolid nodule. Until the results of randomized controlled trials are available, the optimal surgery of early-stage NSCLC remains an issue of debate. Surgeons need to take into account the individual patient's status and clinical evidence when the treatment is planned.

It is always inspiring yet intriguing that we exam the therapeutic effect and necessity of mediastinal lymph node dissection via the big data, try to balance between the curability and unnecessary surgery, and at the same time certain target therapeutic agents are still under developing despite the small proportion of patients. In the era with advanced technology and instruments facilitating surgical procedure, the adverse event or complication resulting from MLNR could be avoided. As the only two studies comparing MLNR with no MLNR based on the surveillance, epidemiology, and end results program (SEER) data revealed the 5-year lung cancer survival rates for those with stage I disease and MLNR was 5% higher (21,22), performing MLNR would benefit the patients more when the complication rate reaches less than 5% (23). Besides, as preoperative 3D reconstruction is gradually available for pulmonary segmentectomy and even subsegmentectomy, overcoming the technical demand may facilitate limited, anatomical resection of the nodule, and specific lymph node resection, not only for individual patient but also for individual nodule.

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Footnote

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