Review Article

Is surgery still the best management option for early stage NSCLC?

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Abstract: Under the formidable thrust of alternative management options for early stage lung cancer, the role of surgery in this disease subset has been questioned. Stereotactic body radiotherapy (SBRT) has been advocated as an ideal substitute for surgery not only in high risk patients or for the ones who refuse surgery but also in lieu of sublobar resection in otherwise fit patients. The therapeutic modalities for early stage NSCLC were compared as to warranting local control, enabling adequate tissue sampling for biomolecular studies, and effecting optimal pathologic staging while saving lung parenchyma. As a result, surgery still remains the best management option for early stage lung cancer in 2014.

Keywords: Lung cancer; surgery; stereotactic body radiotherapy (SBRT)

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Introduction

Nowadays, modern clinical outcomes and cost-effectiveness issues mandate careful attention to the process flow governing the diagnostic and therapeutic pathways in lung cancer management (1). Best practice protocols, like Proven Care, are characterized by the focus on the diagnostic and therapeutic value of surgery as the central modality in managing early as well as locally advanced NSCLC (1). Indeed, surgery has been considered for decades the ideal therapeutic option mainly to ensure optimal local control of the disease. The aim of this paper is to demonstrate that minimally invasive thoracic surgery (MITS) remains the best management choice for early NSCLC because, besides continuing to warrant best local control, it is crucial to provide tissue for biomolecular studies and effect the best pathological staging while preserving lung parenchyma (2,3).

Local control

One of the advantages of surgical treatment for early stage NSCLC includes local control of the disease. Recurrent tumors may be present at different sites after initial surgery. In this setting, and unlike many of the series based on other modalities of local control of NSCLC, the surgical series are characterized by a precise definition of the concept of local recurrence (1). In case of local recurrence, tumors may involve adjacent lung parenchyma, the bronchial stump, or the hilum adjacent to the bronchial stump (4). Regional failure means that recurrence is located in the hilum separate from the bronchial stump, mediastinum, chest wall or the ipsilateral pleura (4). When distant failure is present, tumor occurs in the separate lobe of the ipsilateral lung, contralateral thorax, supraclavicular lymph nodes or in a distant organ (4). According to ACOSOG Z0030 trial conducted among 578 pT1 and 440 pT2 patients with recurrent early stage NSCLC, the median overall survival (OS) for pT1 tumors was 9.1 years and 6.5 years for pT2, respectively (4). The 5-year disease free survival was 77% for pT1 and 58% for pT2, respectively whereas the 5-year local disease-free survival was 95% for pT1 and 91% for pT2, respectively (4). When the patterns of recurrence were considered, local recurrence was observed in 1% and 3% of T1 and T2 tumors, respectively (4). Moreover, regional and combined local and regional recurrences were seen in 4% and 0.4% for T1, and, 3% and 0.7%

for T2 subsets, respectively (4). Conversely, randomized trials of stereotactic body radiation treatment like RTOG 0236 do not generally provide a detailed breakdown of the recurrence sites and fail, at this point in time, to prospect 5 year survival figures (4). The fact that stereotactic body radiotherapy (SBRT) remains a promising modality for local control of NSCLC is demonstrated by the 91% and 87% 3-year local and loco-regional recurrence free survival rates observed in RTOG 0236 (4). Even in large retrospective series, the local and regional recurrence rates at 2 years after SBRT were 4.9% and 7.8%, respectively (5). In the same study from the Netherlands, the corresponding local and regional recurrence rates after 5 years were 10.5% and 12.7%, respectively (5). The difference in local and regional relapse compared to the results from ACOSOG Z0030 trial is particularly significant if one considers that 65% (441 patients out of 676) in the SBRT retrospective study did not have a pre-treatment histological diagnosis of lung cancer (5). A direct comparison of the available treatment modalities to attain local control of early stage lung cancer was published by the MD Anderson Cancer Center in 2012 (6). Overall, more than 10,000 patients with stage I NSCLC older than 66 years (median age, 75 years) were considered (6). Among the possible treatment options, lobectomy, sublobar resection, SBRT, conventional radiation, and, observation were evaluated and the main conclusion was that lobectomy yielded the best overall and disease-specific survival rate after 6 months (6). A caveat to the interpretation of the results was suggested by the limited number of SBRT patients in a retrospective series which were nevertheless analyzed with the propensity score method (6). However, SBRT was related to the best mortality rate within 6 months of treatment (6).

Tissue for biomolecular evaluation

One of the most intriguing perspectives of biomolecular medicine is the possibility of diagnosing lung cancer on blood samples (7,8). Recently, Sozzi and coworkers in the MILD lung cancer screening trial have demonstrated that combining screening with low dose CT (LDCT) scan and miRNA signatures the rate of false positives can be reduced fivefold, thus limiting the resort to unnecessary surgery (9). Theoretically, blood-based diagnosis would facilitate targeted treatment especially in patients with lung cancer relapses or convey reluctant or inoperable patients towards non-surgical therapies with the certainty of a histological type. However, the recent reports of increasing resistance to targeted drugs emphasize the concept of multiclonality within the same tumor mass (10). Accordingly, only representative samples from a tumor mass could ensure adequate genomic profiling in the perspective of targeted treatment. The role of surgical biopsies in this context seems obvious especially if tumor resistance is to be ascertained and avoided. Likewise, the question arises as to whether circulating tumor cells or DNA can replace the diagnostic accuracy of surgical specimens in the future (11). In this setting, next generation sequencing (NGS) platforms can be applied to circulating cells as well as free DNA and are already showing promising results (12). However, since most mutations in tumor DNA do not contribute to oncogenesis and are transient, the clinical impact of NGS platforms is yet to be understood (12). Sizeable samples may still be necessary in order to distinguish driver from transient mutation (12). In the meantime, costs and disadvantages of NGS platforms represent the hurdles to be overcome for a more widespread use of this technology (12).

In this setting, the detection of areas in the airways prone to develop recurrences in close contiguity to resected lung parenchyma or after definite time frames from previous pulmonary resection is intriguing because biomolecular studies seem to show the potential to orient the clinical surveillance by analyzing modulation of genetic expression in the bronchial epithelium (13).

Correct staging

Adequate patient selection is crucial to obtain long-term results when any local modality of lung cancer treatment is used. In this context, correct clinical and pathological staging represents a tenet of modern thoracic surgery. Guidelines have proposed to effect standardized protocols for both preoperative and intraoperative staging (14). The quest for the identification of subsets of mediastinal nodal involvement amenable to primary surgery has provided important practical consequences (15). As an example, in Europe, occult as well as single station N2 NSCLC are now increasingly considered a surgical disease given the encouraging survival rates reported in surgical series (15). Minimally invasive techniques, especially VATS, enable surgeons to solve clinical dilemmas with staging procedures which can be performed under locoregional anesthesia (3,16,17). Operations effected via single port (uniportal) VATS are used to distinguish between T2 and T3 or N2 and N3 when EBUS and mediastinoscopy are not helpful or cannot be technically carried out. In the

setting of prethoracotomy exploration of the mediastinum, video assisted mediastinal lymphadenectomy (VAMLA) and trascervical extended mediastinal lymphadenectomy (TEMLA) represent another example of single port surgery which can be used to better select surgical candidates for lung resection (18,19). The whole staging-based prognostic infrastructure of oncologic treatment modalities is the guiding principle for the selection of surgery for early stage lung cancer (20). Without histological confirmation, only clinical stages can be compared between treatment yielding an apparent outcome equipoise (21); this is particularly relevant if one thinks that regional failures after SBRT may account to 15% and mediastinal failures can be found in 7.5% of the patients originally treated with ablative radiation (22). To further complicate this issue, it has been reported that histological confirmation of lung cancer patients treated with SBRT is needed in only 35% of the patient population (5). To justify this paradigm shift not yet supported by conventional collected evidence (i.e., prospective, randomized trials-see above), a theoretical pathway leading to SBRT-led treatment of early stage lung cancer has been put forward which includes ad hoc interpretation of current guidelines, PET driven decision analysis, extremely conservative estimate of patients' preoperative cardio-respiratory reserve or the adoption of somewhat vague and unconventional terminology (i.e., pulmonary insufficiency) when defining operability, and the accidental inattention to thoracic surgical input into tumor boards (5,23,24). However, the quality issues in SBRT administration are partially counterbalanced by similar pitfalls of surgical treatment. Indeed, advocates of SBRT emphasize the non homogeneous quality of surgery outside clinical trials, especially in terms of intraoperative nodal sampling or dissection (25). The thoracic surgical community is taking action and a more rigorous attitude towards mediastinal lymphadenectomy is currently advised (26).

The meaning of minimally invasive thoracic surgery (MITS)

As surgeons, we are concerned with offering the best possible procedure to our patients in order to obtain the longest recurrence free survival (27). In this context, sublobar resections are under scrutiny for their oncologic efficacy compared to SBRT as an alternative to lobectomy for early stage lung cancer (28,29). In particular, wedge resection have been considered by some authors a sort of palliative surgical procedure which should be replaced by anatomical segmentectomy with nodal dissection as the procedure of choice for stage IA NSCLC (27). Again, a matter of quality in surgery has been raised, with regard to the tumor-free margins attainable during non-anatomical segmentectomy, i.e., lung wedge resection (27). Be as it may, correct indications for wedge resection still remain and include CT screened small, subcentimetric nodules and ground glass opacities (GGOs) especially when the solid component is less than 25% compared to the ground glass counterpart (30). In addition, authoritative institutions have reported no differences in survival between sublobar (including wedge resections) and lobectomy for solid nodules classified as clinical stage IA NSCLC (31).

Conclusions

One shared statement that depicts the current surgical philosophy towards lung cancer is expressed in the recent Society of Thoracic Surgeons' recommendations on the role of surgeons in the lung CT screening programs (30). Modern surgery for early stage lung cancer needs to focus on "the least parenchymal resection compatible with current diagnostic and oncologic principles performed through the least invasive surgical approach" (30). By respecting this fundamental principle, surgery remains in 2014 the best management option for early stage lung cancer.

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