Editorial

Stereotactic body radiation therapy and surgery for early lung cancer "two sides of the same coin"

Giuseppe Parisi[1], Tino Ceschia[1], Alessandro Parisi[2]

[1]Department of Radiation Oncology, University Hospital S. Maria della Misericordia of Udine, Udine, Italy; [2]Department of Radiation Oncology, Veneto Institute of Oncology IOV-IRCCS Comprehensive Cancer Centre, Padova, Italy

Correspondence to: Giuseppe Parisi, MD. SOC Radioterapia Oncologica AOUD S Maria della Misericordia, P.le S Maria della Misericordia, 15 33100 Udine, UD, Italy. Email: giuseppe.parisi@asuiud.sanita.fvg.it.

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Lung cancer is one of the main leading cause of cancer related death worldwide, and is responsible of one quarter of all deaths, with approximately 234,000 new cases/year and 154,000 deaths in USA (1,2).

The median age at diagnosis is 70 years and the overall survival rates are heterogeneous. Approximately 15% of patients are early stage lung cancer T1 or T2N0M0 at presentation, and are candidates for a radical surgical therapy, with a 5 years survival of about 60–70% (3).

The clinical outcome depends both on patient–and tumor-related characteristics, i.e., gender, age, performance status, TNM stage, tumor grade, and molecular tumor profiling. Therefore, the different roles of these prognostic factors make it difficult to properly define the patients' prognosis and the therapeutic strategy. In a systematic review Brundage *et al.* analyzed 887 publications and identified more than 150 possible prognostic or predictive factors (4).

In 1995, a randomized controlled trial of *The Lung Cancer Study Group* established lobectomy as the standard of care for T1N0 non-small cell lung cancer (NSCLC). This landmark trial demonstrated increased local recurrence and decreased survival in patients treated with a more limited resection compared to those treated with lobectomy (5).

Twenty years later, the standard treatment for early-stage non-small-cell lung cancer remains the removal of the entire lobe of the lung affected, rather than a less extensive operation or radiation treatment. In this setting, the American Society for Radiation Oncology (ASTRO) Guidelines emphasize how thoracic surgeons should decide on operability and offer a pulmonary resection in patients with "standard operative risk" (i.e., with anticipated operative mortality of <1.5%) (6).

However, it is estimated that a quarter of these patients aren't able to undergo a surgical procedure, due to medical comorbidities, older age, or refusal of surgery. These patients are candidates for radiotherapy.

In the last years, parallel to the progressive spread of linear accelerators equipped for stereotactic body radiation therapy (SBRT), the number of patients treated with stereotactic radiotherapy has gradually increased. SBRT has become a viable alternative to surgery as a valid and accepted treatment option for patients in early stages who aren't candidates for lobectomy.

In the retrospective, multicenter analysis on 187 clinical-stage T1a-T2bN0MO NSCLC patients by Scotti *et al.* (7), showed SBRT to be a valid therapeutic approach in this clinical scenario. In this analysis, patients underwent lobectomy (LOB) or SBRT; those undergoing SBRT were sub-classified as surgical candidates and nonsurgical candidates. The univariate analysis showed no significant difference in local control between SBRT and LOB patients, with a trend in favor of surgery. OS was significantly better in LOB patients [3-year OS of 73.4% *vs.* 65.2% 3 y OS for

surgery *vs.* SBRT (P<0.01)].

From the Radiation Oncologist's point of view, some considerations can be made.

The first consideration is on the clinical evaluation of the patient. The patient-related characteristics in the preoperative decision-making process are well coded and are based on the evaluation of perioperative and postoperative lung function. This assessment is based on: respiratory pulmonary scintigraphy (ventilation/perfusion ratio), on PFR and on the general condition and comorbidity of patients that conditions the anesthetic risk (8). In the context of radiotherapy, the treatment should be the result of an equilibrium that balances the need for local control and risk of side effects.

The goal is to ensure the maximum possible dose, with acceptable risk of toxicity. Along with this exquisitely technical aspect, clinical evaluation of the patient plays a fundamental role in common clinical practice. In the current scientific literature, the comparison is reduced to "Hamletic doubt": is the patient a candidate for surgery or not, and, the evaluated parameter is however only "the surgical parameter". Therefore, for this reason, patients who are candidates for SBRT are not "those selected for SBRT", but "those excluded from surgery"!

On the other hand, decision making process of SBRT still appears rather discretionary. Vaguely defined criteria related to "pulmonary and cardiac insufficiency" are used to rule out surgery, without any specific quantitative cut-off values. This led to an extreme variability strictly related to single experiences (9,10). The paradigm is that patients who were medically operable generally received surgery and patients who had been medically inoperable, due to surgical factors, were treated by SBRT. This could be a plausible explanation, for example, for the large survival differences observed in a recent article by Yerokun and colleagues, suggesting a great survival advantage also with wedge resection over SBRT for clinical stage IA NSCLC (11).

For the evaluation of the efficacy of the two treatments, given the retrospective observational nature of almost all published studies, there is an intrinsic prejudice in published investigations, caused by the difficult comparison of heterogeneous patients for age cardiac or pulmonary function and above all, much less healthy patients in the SBRT group than surgical candidates.

Another element, often not much considered, and that could represent an important bias, is that even at the same stage, we compare two deeply different approaches (comparing apples and oranges?).

In the radiotherapy procedure only the lung cancer node is treated, while in the surgical procedure, the complete lobectomy with sampling or radical mediastinal nodes dissection is performed. This often leads to a discrepancy in obtaining a definition of local tumor control.

In surgically treated patients, loco-regional control is defined as the lack of tumor recurrence within the lung parenchyma or mediastinal lymph nodes. In contrast, SBRT treated patients' local control is defined as the lack of radiographic tumor progression in the primary lobe, according to the following assumption: primary tumor control = local control. SBRT reported local control rate is often higher than >90% (12-15).

But what kind/type of local control do we refer to? It is a priority to find an agreement on the concept of local control even if this, as previously mentioned, is often difficult to establish because if a lesion on the residual lung after surgery is easily detectable, a local recurrence after SBRT may be difficult to distinguish clearly from SBRT-related inflammatory changes (16).

The second consideration can be done about the importance of pathological examination and the impact of staging on local and regional control. Surgery, obviously, allows a better definition of these aspects. With surgery it is possible to perform the definitive histological exam and it is possible to find the pathological lymph nodes. We know that the tumor response depends to the tumor subtype population. The definition of the histological specimen, squamous cell versus adenocarcinoma, amend the determination for the molecular marker and are important not only for medical therapy but also for the local failure. The EGFR mutation, the presence of the squamous cell cytologic features or micropapillary subtype in the adenocarcinoma specimen is correlating with higher rates of loco-regional relapse and distant failure (17).

About the impact of staging on local and regional control, in a retrospective analysis published from Crabtree *et al.* in the surgery group, the final pathology upstaged 35% of patients. Totally, 13.8% of patients were found to have N1 disease in the final pathologic analysis and an additional 3.5% were found to have pathologic N2 disease. All patients among each treatment group were clinically staged with CT and PET imaging (18).

Similarly, Bott *et al.* on data of patients with clinical stage I NSCLC undergoing resection, report that approximately 20% of surgical patients are upstaged on pathology review of surgical specimens owing to previously unrecognized mediastinal disease (19). Two Japanese reports found that

OS rates were significantly better for lobectomy than for SBRT (20,21). No significant difference between sublobar resection and SBRT have been demonstrated (22).

However, because mediastinal lymph node dissection or sampling is usually performed during lobectomy, concerns remain about the risk of local or nodal recurrence after SBRT, which could lead to poorer OS than after lobectomy. This data will inevitably have an impact on both prognosis and potential adjuvant treatment and they can determine global survival data. For this reason, the Radiation Oncology Consensus Recommendations Presented at ASTRO 2017, underlined that for patients with standard operative risk lobectomy with adequate, and systematic mediastinal lymph node evaluation is (and remains) the standard of care for early-stage lung cancer, SBRT should be viewed as an additional tool to be utilized by the physician treating NSCLC in inoperable and potentially high-risk patients.

The need for prospective randomized trials that quantify the magnitude of the differences in both survival and recurrence in the treatment of early-stage lung cancer patients and are not subject to the biases that underlie decisions to deliver surgery (either lobectomy, wedge resection and segmentectomy) or SBRT in this setting is preeminent.

In order to answer this question effectively, three important analyses were performed.

The STARS randomized trial (Cyberknife *vs.* surgical resection in stage I NSCLC: NCT00840749), the ROSEL trial (Surgery or stereotactic radiotherapy for early stage IA lung cancer: NCT00687986) and randomized clinical trials RTOG 1021 (surgery *vs.* SBRT for early stage lung cancer), early closed due to a poor accrual. Although they don't reach the expected accrual, the 58 patients included in the ROSEL and STARS phase 3 trials were analyzed. The radiation dose delivered for the peripheral tumors was 54 in 3 fractions in both studies while for central tumors was 60 Gy in 5 fractions in the ROSEL trial and 50 in 4 fractions in the second study, were delivered.

All patients included in the STAR trial performed histological diagnosis by surgical procedure, while in the ROSEL study, the histological diagnosis was not mandatory.

The pooled analysis of these studies shows a good result with a local control about 97.6%, a loco regional control rate of 82.7% and an overall survival rate about 95% at 3 years. The survival rate in the surgery group was only 79% (23).

The authors concluded that the analysis of these two studies allows to deduce that surgery or SBRT are equally effective, and the lower survival rate in the surgery group was due worse comorbidities. However, to date, it is not possible to answer to the question SBRT or surgery in early stage lung cancer using the date of a pooled analysis of these two studies. Despite these limitations, pooled analysis suggests better results in stage T1a or T1b because the small tumor volume is associated with a lower risk of metastatic regional lymph nodes. Moreover, although all patients performed a staging PET, this procedure should not replace the histological confirmation of the lesion, since different histologies have different behaviors.

However, SBRT is a valid alternative to surgery in patients with early lung cancer (T1a-b) especially if we compare the RT treatment either wedge or segmentectomy resection, but further studies are needed to better define patients who are candidates for radiotherapy approach. Today two randomized studies comparing surgical resection and SBRT in early stage lung cancer [VALOR Trial (NCT02984761)] and [STABLEMATES trial (NCT02468024)]—will hopefully accrue, and provide a more unbiased answer to this question.

In real clinical practice, actually, SBRT patients are patients who were not offered surgical treatment. These patients only have the alternative to be treated with SBRT or not to be treated at all. We must change, at least formally, the idea (or philosophy) in a multidisciplinary setting, identifying a priori the best treatment for the patient.

This assessment must be carried out not on the basis of an exclusion criterion, but with the logic of identifying the best opportunity for patient care, moving from the "two-faced herm" logic to the consideration of Surgery and SBRT as "two sides of the same coin".

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Footnote

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

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