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Surgery Versus Stereotactic Body Radiotherapy for Resectable Lung Cancer

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Abstract
Purpose of Review Radiotherapy has been considered in the past an option for local control of resectable lung cancer only in cases of patients considered unfit or declining surgical treatment.
Recent Findings Recent technological improvements allow radiation oncologists to deliver precisely targeted radiation at much higher doses compared to traditional radiation therapy, in one single or few sessions, minimizing damage to the surrounding healthy tissue. In this review, we discuss the advantages and inconveniences of surgery and stereotactic body radiotherapy (SBRT) for the treatment of resectable non-small cell lung cancer.
Summary Although the use of modern surgical techniques has decreased the overall rate of adverse effects and mortality of lung resection, surgery-related morbidity is not comparable to that recorded after SBRT. This advantage has to be balanced against, in some cases, lack of definite cyto-histological diagnosis and non-accurate definitive pathological staging. In the absence of high-quality randomized trials comparing surgery and SBRT, the published 1- and 3-year survival rates after SBRT seem to be comparable to lung resection. Nevertheless, we have to be cautious in recommending non-surgical therapy for operable patients having resectable tumours due to the aforementioned limitations biasing the results.

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Keywords Non-small cell lung cancer · Lung surgery · Pulmonary lobectomy · Radiotherapy · Stereotactic body radiation therapy · High-dose radiotherapy

Introduction

Surgical resection has been considered the gold standard for local control in resectable non-small cell lung cancer (NSCLC), in spite of the fact that its superiority over other local therapeutic alternatives has never been tested by randomized clinical trials (RCT) [1]. The use of modern mini-invasive techniques in surgery and improved perioperative care has contributed to a dramatic decrease of the rate of postoperative adverse effects and 30-day mortality for NSCLC patients treated surgically [2••].

On the other hand, technological improvements in radiation equipment (optimal planning, target delineation, image guidance and patient immobilization and synchrony with respiratory movements) allow for high radiation delivery even to small tumours with very precise margins (1–2 millimetres), avoiding damage to healthy surrounding tissues. Basically, SBRT delivers radiation at much higher doses, compared to previous techniques, in very short periods of time: usually no more than 1–2 weeks and, in some protocols, in only 1–2 fractions [2••].

Although initially SBRT was restricted to non-operable patients—or those refusing surgery—the lack of sound evidences on the superiority of surgery and the publication of promising results in early NSCLC treated with SBRT [3] have made the hypothesis of non-superiority of surgery compared to SBRT worthy to be tested.

Although anatomical resection can be safely performed today by minimally invasive techniques preserving pulmonary function [4] and with good long-term survival in

selected cases [5], this review has been written from the understanding that lobectomy plus mediastinal lymph node dissection still has to be considered the treatment of choice for early stage NSCLC [6, 7], and the surgical techniques against SBRT have to be compared.

To our mind, the most relevant questions to be answered to facilitate decision-making in daily practice are the following:

Question 1: Who Should be Considered a Non-operable Patient?

Some recently published papers reporting experiences where SBRT was used as definitive therapy for resectable tumours only include "medical inoperability" or similar terms as major criteria for patients' selection [8, 9]. The concept "medical inoperability" can be understood in different ways, depending on the local protocols and practices. In our settings, we have adopted the recommendations published in 2013 to evaluate functional operability, with some modifications to adapt to our local practices (Fig. 1).

Basically, the Thoracic Revised Cardiac Risk Index for lung resection [10] is calculated first. If the patient is considered as having high risk of major cardiac postoperative complication, cardiac consultation is advisable and the surgical decision is postponed. In all cases, FEV1 % and DLCO % are measured and postoperative values estimated [10]. Surgery is indicated straightforward if both values are over 60 %. In case one of those values is under 30 %, no surgical treatment is recommended. Between 31 and 60 %, exercise tests with estimation of VO2max are indicated, and surgery is not recommended if the value is 10 ml/(kg min) or lower.

Patient's age per se is never considered a contraindication for surgery, but the advantages and risks of surgery are carefully discussed with patients over 85. Of course, all therapeutic decisions in NSCLC patients are adopted after discussion in a multidisciplinary team (MDT). MDT management has become the standard of care in some countries, after some advantages to both the patient and the clinicians have been demonstrated [11]. In our practice, we noticed a slight decrease in lung resection-related mortality after implementing internationally accepted guidelines and MDT agreement before indicating surgical therapy for lung cancer patients [12].

Question 2: How to Define as "Resectable" a Case of NSCLC?

Lung cancer can be successfully and completely resected using different techniques according to the local extent of the disease. On the other hand, the agreement with the type

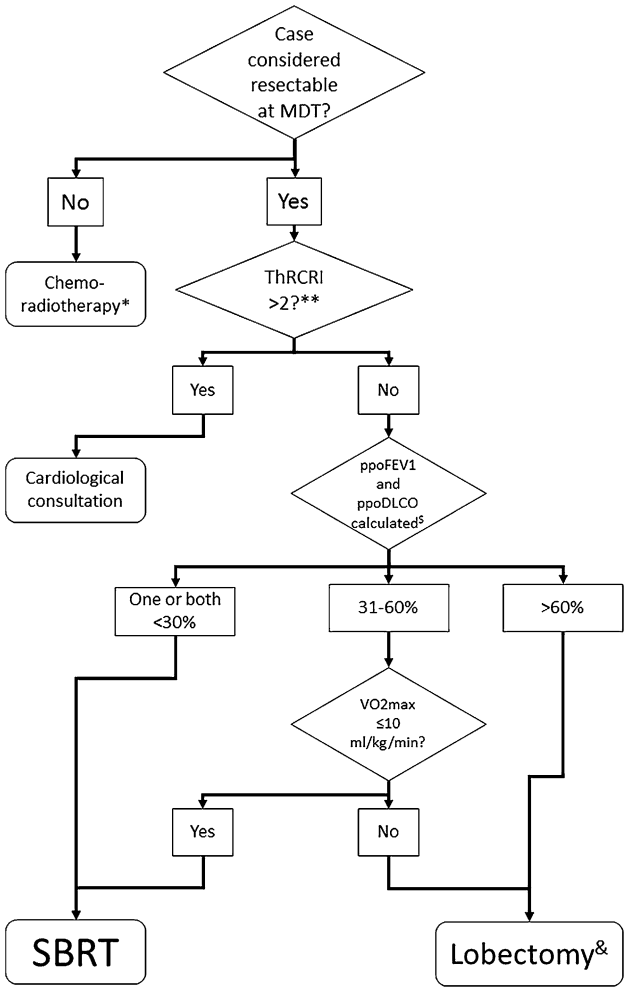

Fig. 1 Recommended flow chart to facilitate decision-making in our settings. *Asterisk* in some instances, clinical N2 disease can be judged to be resectable (see text) but SBRT is usually not considered in such cases. *Double asterisk* the Revised Thoracic Cardiac Risk Index for Preoperative Risk estimates the risk of cardiac complications after surgery. See reference 10. *Dollar* Estimated postoperative FEV1 % and DLCO %. See reference 10. *Ampersand* VATS lobectomy plus systematic mediastinal lymph node dissection

of resection originally planned and the one finally performed is not 100 % due to intraoperative findings forcing the surgical team to a more extended resection [13]. Obviously, the higher the clinical T status, the bigger the rate of discordance between planned and performed surgery due to local invasion of mediastinal tissues. Although some reported experiences on SBRT for T3 and T4 tumours can be found in the literature [14], the technique is usually reserved to peripheral small tumours [2••]. Thus, when comparing the effectiveness of surgery and SBRT, only comparable cases—in terms of clinical staging—can be selected to avoid biasing the conclusions. Only well organized and managed MDTs where surgeons are actively involved guarantee the accurate selection of cases to avoid exploratory operations or incomplete resections.

The N factor represents a more debatable aspect to be considered when discussing case selection and survival of patients treated with SBRT or surgery, as we are commenting below. To note is the fact that, even in completely clinically staged patients, the rate of intraoperatively found N2 disease is not negligible, representing more than 5 % of the cases, as we are discussing below [15]. While in Europe there is a current trend to consider limited N2 as a resectable disease, due to favourable outcomes with surgery [15–17], it is not the same in most centres in the U.S. [18].

Question 3: Are Patients Treated by SBRT Correctly Staged?

Before dealing with the staging issue, we have to underline that even high-quality papers reporting retrospective analysis of series of early stage NSCLC patients treated with SBRT [19, 20] included cases having no histologic diagnosis, potentially biasing the survival analysis.

As we have commented above, the finding of unsuspected N2 after mediastinal dissection is not rare, hence the relevance of thorough mediastinal evaluation before recommending SBRT in supposed early stage NSCLC. In the previously quoted study from Obiols and colleagues [15] on unsuspected N2 disease after mediastinal staging according to ESTS guidelines [21], 406 of 540 patients underwent surgical exploration of the mediastinum before resection, whereas the remaining 134 underwent up-front surgery. After surgical staging of the mediastinum, unsuspected N2 disease was identified in 9 % of patients, of whom 80 % had single-station N2 disease and 90 % of these received adjuvant chemotherapy or chemoradiotherapy. Importantly, the 3- and 5-year survival rates for these patients with unsuspected N2 disease were 80 and 40 %, respectively. In the aforementioned publication by Rocco et al. [18], the reported rate of unsuspected N2 after lobectomy was 8 % in the STS database and 14 % in the European registry. There is no reason to think that in SBRT patients these rates are different. Furthermore, there is vast evidence that some patients with lymph node metastases detected at the time of surgery could have an overall survival benefit from adjuvant therapies [22].

The accuracy of combined positron emission tomography and computed tomography(FDG-PET/CT) in detecting mediastinal metastases is around 80 %, with positive and negative predictive values of 56.3 and 87.7 %, respectively. [23] Low maximum standardized uptake value (SUVmax) of the tumour, diagnosis of adenocarcinoma and small tumour size have been associated to false-negative results.

In case of positive mediastinal lymph nodes at FDG-PET, the ESTS guidelines for preoperative mediastinal lymph node staging for NSCLC recommend invasive tissue confirmation [24]. Fine-needle aspiration guided by endosonography—endobronchial ultrasonography (EBUS) and esophageal ultrasonography (EUS)—is the first choice, due to its high negative predictive value [25]. Surgical staging with nodal dissection or biopsy would be indicated only if endosonography is negative. The combined use of endoscopic and surgical staging results in the highest accuracy [24]. FDG-PET/CT underestimates the spread of cancer into N1 lymph nodes; thus, candidates to SBRT may benefit from increased pathologic evaluation of N1 nodal stations in addition to N2 nodes [26].

The inferiority of the clinical staging performed in patients treated by SBRT compared to surgically treated cases is demonstrated by the higher rates of mediastinal relapse after SBRT [8].

Based on the previous data, invasive nodal staging procedures should be indicated in early stage NSCLC patients, when SBRT is considered, to rule out mediastinal spread in spite of negative mediastinal images.

Question 4: Is the Rate of Adverse Events After Surgery Comparable to SBRT?

Data about morbidity and mortality after lung cancer resection are widely available and can be easily quoted. According to the ESTS Data Base Annual Report [27], the current European 30-day mortality rate for lobectomy in lung cancer patients is 1.9 %, with a trend to decrease especially in VATS cases (Fig. 2). Cardio-pulmonary morbidity (including any kind of adverse event) is over 17 % after lobectomy [27].

Contrary to what happens in surgery, papers aimed to systematically describe complications after SBRT are not easy to find [28••]. Even well-documented reviews [29] comparing SBRT and surgery omit any reference to early or late morbidity after SBRT, while providing thorough data on local control rates and survival. Additionally, some confusion is connected to the fact that SBRT-related morbidity is graded differently depending on the target organ [30–32]. Patient death has also been correlated to SBRT, if indicated for centrally located tumours. A phase II trial from the Indiana University of 70 patients reported that SBRT was a possible contributing factor in 6 patient deaths [33]. In five cases, death resulted from pulmonary infection in patients with delayed radiation pneumonitis. Severe radiation pneumonitis is rarely reported after SBRT, and its occurrence is mostly related to central location of the tumour and neoplasms with gross tumour volume of more than 10 mL [32]. A deleterious delayed effect of

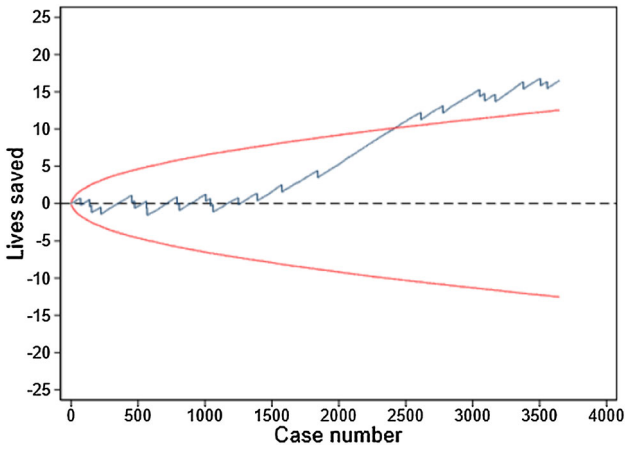

Fig. 2 Hospital mortality after VATS lobectomy represented in CUSUM plot. To note is a continuous decrease in the occurrence of mortality in the last period of time (after around case 250). SBRT, being the best and up-to-date therapy, has to be compared to modern surgical techniques. Data from the ESTS Database (see reference [27])

SBRT on pulmonary volumes has been rarely reported after treating peripheral nodules. In some published experiences, [34, 35] no impairment is found on the values of FEV1 % and FVC % 3–4 months after completing the treatment and, in some instances, a slight increase is reported in pulmonary volumes.

In the majority of cases after SBRT, only grade 1 or 2 toxicity [36] is published and it is resolved a few months after SBRT. It has been estimated that the risk of developing rib fractures within 2 years of SBRT can be as high as 42 % with a median time of 17 months [30, 31].

Question 5: Do Patients Treated by Surgery Survive Longer?

This question has been addressed in two randomized trials whose results have been pooled and published together [3]. Although the authors of the pooled analysis concluded that SABR can be considered a treatment option in operable patients fit for lobectomy, both trials were considerably biased and their conclusions arguable as we have reported elsewhere [37].

In the absence of high-quality randomized trials, some quasi-experimental retrospective analyses on the subject have been published. In the study by Matsue et al. [38], the authors retrospectively reviewed all patients unfit for lobectomy treated either by SBRT or sub-lobar resection. Cases were conveniently matched according to clinical characteristics. The cumulative incidence of cancer-specific death was comparable between both groups. In a similar study [39], the authors found that the overall recurrence (local and distant) was significantly higher after SBRT, but no statistically significant difference between the two groups in disease-free 3-year survival was found. Previously published articles comparing SBRT versus sub-lobar resection have been systematically reviewed by Mahmood et al. [40••]. The authors collected 18 papers representing the best evidence to the date of publication, and concluded that 1-year survival was similar between patients treated with SABR (around 85 %) and sub-lobar resection (92 %); however, overall 3-year survival was higher following surgical treatment (87.1 vs. 45–57 %). There was no statistically significant difference in local recurrence in patients treated with SABR compared with surgery (3.5–14.5 vs. 4.8–20 %).

According to another recently published review [29], surgery remains the treatment of choice for patients with operable early stage NSCLC, since there is insufficient evidence to establish that SBRT is equivalent to surgery. Among the recommendations, the authors state that for medically operable patients with stage T1-2 N0M0 NSCLC, surgery remains the standard treatment due to the lack of high-quality comparative analysis. However, for medically inoperable patients or those with stage T1-2N0M0 NSCLC refusing surgery, SBRT should be preferred.

Zang and colleagues [41••] conducted a systematic review and meta-analysis on six studies containing 864 matched patients. Surgical treatment was associated with a better long-term survival in patients with early stage NSCLC. However, the difference in 1- and 3-year cancer-specific survival, disease-free survival and local and distant control rates were not statistically different.

As we can see from different reviews, the available evidence is not enough to conclude that surgery (sub-lobar resection) can be replaced by SBRT in operable patients. On the contrary, it seems that in high-risk cases, similar or even better long-term survival can be achieved with SBRT. Unfortunately, conclusions from most published experiences and reviews are biased by case selection and technical confounders.

Conclusions and Recommendations

Currently, there is not enough evidence to recommend non-surgical treatment by SBRT in patients considered fit for VATS lobectomy and mediastinal lymph node dissection. In high-risk cases, SBRT is a good option compared to wedge resection, but anatomical segmentectomy plus mediastinal lymphadenectomy can be an option to be discussed at MDT meetings. If SBRT is considered indicated, complete mediastinal staging by image techniques (FDG-PET/CT) plus fine-needle mediastinal lymph node

puncture guided by endosonography (EUS and EBUS) is a must in order to decrease the rate of mediastinal relapsing and allow for adjuvant chemotherapy when indicated.

Compliance with Ethics Guidelines

Conflict of Interest Drs. Jimenez, Novoa, and Varela declare no conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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