Surgery or stereotactic ablative radiation therapy: how will be treated operable patients with early stage not small cell lung cancer in the next future?

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Abstract: Lung neoplasm is the most influent cause of death for cancer. With the increasing of life expectancy in elderly patients and with the intensification of lung cancer screening by low-dose computed tomography, a further rise of the number of new non-small cell lung cancer (NSCLC) cases has been shown. Standard of care of early stage NSCLC patients is lobectomy but approximately 20% of them are not fit for surgery for comorbidities. Due to the high local control rates and the little adverse effects, stereotactic body radiation therapy (SBRT) also called stereotactic ablative radiation therapy (SABR), has rapidly replaced the conventional radiotherapy in not operable patients with stage I NSCLC. We review the evidence for use of SABR in medically inoperable patients with stage I NSCLC, and its possible extension of use to operable patients, from the perspectives of radiation oncologists and thoracic surgeons. Until the results of large randomized trials will be available, the multidisciplinary management, balancing during discussion the advantages/disadvantages of each treatment modality, could be the coming soon best approach for medically operable early-stage NSCLC. As a result, the minimally invasive thoracic surgery advantages and the SABR innovations will be translated into real clinical benefits.

Keywords: Early stage non-small cell lung cancer (NSCLC); video-assisted thoracic surgery (VATS); stereotactic ablative radiation therapy (SABR)

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Primary malignant lung disease represents the most influent cause of death for cancer in US. With the increasing of life expectancy in elderly patients and with the intensification of lung cancer screening by low-dose computed tomography, a further rise of the number of new non-small cell lung cancer (NSCLC) cases has been shown as continuous and consistent (1,2). Stereotactic body radiation therapy (SBRT), also called stereotactic ablative radiation therapy (SABR) has been developed as an innovative therapy for stage I NSCLC and has now emerged as a standard treatment option for medically inoperable patients. We review the evidence of SABR in medically inoperable patients with stage I NSCLC, and the possible extension to operable patients, from the perspectives of radiation oncologists and thoracic surgeons.

Pro stereotactic ablative radiation therapy (SABR)

Standard of care of early stage NSCLC patients is lobar resections but approximately 20% of them are not suitable for surgery resection for severe cardiac and/or respiratory comorbidities. If untreated, the 5 years mortality lung cancer related is dramatically high, around 90% (3). Radiation therapy has been traditionally indicated in these cases. Using conventional external beam radiation doses, survival has been influenced only with an extension of 7 months in median survival compared to patients submitted only to observation (2,3). In fact, doses of 60-70 Gy, prescribed in conventional fractionated 3D-conformal radiotherapy, lead to

disappointing local control rates of only 30-50% for stage I disease and therefore could not meet the demand to replace surgery.

SBRT was born in the 1990s, as an extracranial application of the well-known radiosurgery approach that uses spatial coordinates to define the position to irradiate target with massive radiation doses. Today, the concept is rapidly changing and with the term SBRT, we identify a "philosophy" for treating cancer in the body not necessarily with spatial coordinates, but essentially prescribing high focused doses in one or few sessions. Over the last few decades, more sophisticated stereotactic, intensity-modulated (IMRT) and image-guided techniques (IGRT) of delivering radiation have allowed clinicians to safely prescribe higher doses than in the past, frequently with hypofractionated schedules (high dose per fraction in few fractions) (4) in several settings. "Dose sculpting" on lung tumor with IMRT is a helpful approach to minimize the radiation dose to healthy surrounding tissues. IGRT reduces repositioning errors and is used to monitor the treatment region and/or to adapt dose distribution to the possibly changing target and organs at risk during radiation (5). Nowadays, four-dimensional CT (4DCT) for planning, active breath control during delivery, tracking the lesion and delivery the dose following respiratory motion, are some of the more common strategies to manage the uncertainties of the movement of the target, especially in the thorax. Recent clinical data has shown that SBRT for peripheral lesions of inoperable patients with early stage NSCLC is able to achieve outcomes comparable to that of surgery (6,7). For early stages of NSCLC, using biological effective doses (BED) greater than 100 Gy, 5-year controls are approximately 85-90% (6,7).

Thus, in the range of 8-20 Gy per fraction, SBRT effect becomes disruptive and it has been defined as SABR. Prevalent phenomena such as endothelium apoptosis and stoma damage has been involved to justify the impressive improvement in local control when ablative doses were prescribed (8,9). According to several international guidelines, SABR is now recommended as the standard curative treatment for medically inoperable patients with early stage NSCLC (10-12). The impact of introducing SABR in the therapeutic scenario was estimated: a significant cost savings and survival gains was found for stage I NSCLC in Canadian patients (13). While SABR is a well defined curative treatment option in medically inoperable patients, its role in the patient suitable for curative surgery is yet to be defined. To date, the large amount of data of SABR for early stage NSCLC regards populations of patients excluded from surgery. Although the local control rates in these patients have been optimal, 3-year overall survival rates remain limited in several series, between 43% and 60%, probably due to deaths related to intercurrent illness (14,15). The absence of randomized trials in this setting does not imply the absence of potential evidence on efficacy of SABR as well as surgery in early stage operable NSCLC patients. A meta-analysis was performed by Zheng *et al*. (16) including forty SABR studies (4,850 patients) and 23 surgery studies (7,071 patients), published in the same period. Population profiles differed between SABR and surgery patients about comorbidities and age. Better treatment outcomes were provided by surgery. Nevertheless, adjusting patient profile differences, extrapolative analysis shows that SABR produced non-inferior survival outcomes in comparison to surgery, especially in patients with operable stage I NSCLC. When SABR is compared with surgery, a consideration concerning the type of resection seems to be also crucial. Recently, 9,093 early-stage, node-negative NSCLC patients who underwent definitive treatment including lobectomy, sublobar resection, and SABR were evaluated for a propensity score-matching well-matched analysis. Compared to lobectomy, sublobar resection was associated with worse overall survival rate; SABR and lobectomy cohorts' demonstrated similar overall survival in both groups. Being sublobar resection suboptimal when compared to lobar surgery, and being SBRT equivalent to the last one, it could be indirectly assumed that SABR is superior to sublobar resection (17). It was confirmed by Port in a propensity-matched analysis of wedge resection and SABR proposed to 164 early stage NSCLC patients poor candidates for lobar resection. In patients treated by SABR, higher overall, disease recurrence rate was shown compared to those treated by wedge Resection. Nevertheless, no difference between the two groups in disease-free 3-year survival was found (18). Several criticisms remain about a comparison between surgery and SABR because of the different definitions of local recurrence, and heterogeneity in the type of SABR across different centers (19). However, where data are available, the impact of SABR in operable setting is certainly not negligible. In a Japan Group study, nearly 100 stage I patients who refused surgery were evaluated: the 5-year overall survival rate achieved prescribing a BED of at least 100 Gy was 70.8% (20). Starting to these backgrounds, two randomized phase III trials (21) have been initiated to randomize stage I NSCLC medically

operable patients to receive SBRT or the gold standard of surgical resection. The results of these trials could modify radically the treatment strategy for these patients. A report regarding operable NSCLC patient's interviews clearly shown how patients averse to taking risks involving the possibility of immediate death (22). Undoubtedly, if the SBRT and surgical resection result as similarly effective, patients may be hesitant to be submitted to a treatment procedure that involves an upfront mortality risk. Thus, the decision between SABR and surgery will be defined patient per patient, based on the relative merits and pitfalls of each treatment approach. The results of SABR are promising and other data in this direction will certainly arrive from ongoing studies. However, follow-up of lobectomy series are longer and these solid data should not be ignored. Conversely, the relative high surgical mortality rate could be crucial in decision-making strategy for patients who are averse to have any kind of risk of operative-related death. Multidisciplinary management, balancing during discussion the advantages/disadvantages of each treatment modality, could be the coming soon best approach for medically operable early-stage NSCLC (23).

Pro surgery

Due to the high local control rates and the little adverse effects, SABR has rapidly replaced the conventional radiotherapy in not operable patients with stage I NSCLC (24). A few well-designed prospective studies have proven that SABR is safe and effective for medically inoperable NSCLC patients (13). After that, some authors reported a short/medium term local control comparable to surgery in series of NSCLC patients who refused surgery, and others reported no differences in overall survival, disease-specific survival, and local control (20,25). Senan *et al*. further reported that SABR achieves similar control rates of surgery without the risks associated to surgery (26). Due to these provocative results, a few authors evidenced that these studies were retrospective and uncontrolled, and subject to some biases (19,27). First, the local control rate favorable for SABR is only referred to the primary tumor site. Second, the residual parenchymal scar after SABR is difficult to differentiate from cancer (17). On the contrary, the local failure rate of surgical series included not only recurrences within the same lobe away from the primary site, but also recurrence in ipsilateral lung (16); therefore, the controversial finding could be a result of differences in the definition of local tumor control (17). Actually, only a few studies (24-27) compare the clinical outcomes of surgery and SABR in early stage NSCLC, using a case-matched analysis, while others were based on non-randomized data or observational series (28). Another unresolved issue of SABR is the lack of pathological confirmation of the tumor and the resected lymph nodes that are mandatory to correctly stage the disease and to pose the indication of adjuvant chemotherapy. Therefore, to compare either retrospective or prospective series, only patients with biopsy-proven cancers should be included. Furthermore, these issues have to be investigated through long-term follow-up of previous clinical trials (29). Randomized phase III trials or large population cohort studies have not been completed; several randomized trials were initiated but they were stopped due to poor accrual (30). Lastly, regarding the little adverse effects from SABR for early stage NSCLC, various serious complications have been reported in numerous studies (31).

Nowadays, thoracic surgery remains the treatment of choice for the early stage NSCLC patients. The wider and wider adoption of the video-assisted thoracic surgery (VATS) techniques has reduced the postoperative morbidity and has led to a decreased hospital length of stay. The increased ability to identify small NSCLC by low dose computed tomography-screening programs arose the question whether or not lobectomy is appropriate in this subset of patients with small size early stage NSCLC (32). Sublobar resections have demonstrated the safety of their perioperative course, the effectiveness of preservation of pulmonary function (in comparison with lobectomy), and the comparable oncologic outcomes (32). To date, sublobar resection is performed most often as an alternative to lobectomy in patients with peripheral tumors with limited pulmonary reserve or other comorbidities (32,33). The medical community is still searching a spirometric cut-off value that could suggest the indication to SABR approach instead of surgery. The thresholds for radical treatment of patients with lung cancer are rapidly changing; therefore, the exclusively use of FEV1 and DLCO may no longer be sufficient and the current guidelines suggest standardized protocols for risk assessment (34).

Conclusions

Until the results of large randomized trials will be available, the multidisciplinary management, balancing during discussion the advantages/disadvantages of each treatment modality, could be the coming soon best approach for

medically operable early-stage NSCLC. Multidisciplinary teams should include experienced thoracic surgeons, radiation oncologists, and medical oncologists. As a result, the VATS advantages and the SABR innovations will be translated into real clinical benefits.

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