

## Stereotactic body radiotherapy in lung cancer: an update\*

Radioterapia estereotáxica extracraniana  
em câncer de pulmão: atualização

Carlos Eduardo Cintra Vita Abreu<sup>1</sup>, Paula Pratti Rodrigues Ferreira<sup>1</sup>,  
Fabio Ynoe de Moraes<sup>1</sup>, Wellington Furtado Pimenta Neves Jr<sup>1</sup>,  
Rafael Gadia<sup>2</sup>, Heloisa de Andrade Carvalho<sup>1,3</sup>

### Abstract

For early-stage lung cancer, the treatment of choice is surgery. In patients who are not surgical candidates or are unwilling to undergo surgery, radiotherapy is the principal treatment option. Here, we review stereotactic body radiotherapy, a technique that has produced quite promising results in such patients and should be the treatment of choice, if available. We also present the major indications, technical aspects, results, and special situations related to the technique.

**Keywords:** Radiation oncology; Lung neoplasms/radiotherapy; Lung neoplasms/surgery; Respiratory function tests.

### Introduction

Lung cancer is the most common type of cancer in males and females worldwide, accounting for the highest number of cancer deaths.<sup>(1)</sup> This is probably due to the fact that many lung cancer patients are diagnosed at advanced stages. Patients who are diagnosed at early stages can undergo surgical resection and account for 20-25% of cases. However, 20-30% of such patients are not surgical candidates or are unwilling to undergo surgery.<sup>(2)</sup> Median survival is 13 months for patients with untreated T1 tumors and 8 months for those with untreated T2 tumors, the 5-year cancer-specific survival rate being 16%.<sup>(3)</sup> Therefore, a therapeutic intervention is warranted in this group of inoperable patients, radiation therapy being the traditional alternative.

Conventional radiation therapy involves fractionated radiation doses of 1.8-2.0 Gy/day for a total radiation dose of 60-70 Gy, corresponding to more than six weeks of treatment. Various techniques can be used, ranging from simple, two-dimensional techniques to sophisticated techniques such as three-dimensional radiation

therapy and intensity-modulated radiation therapy. However, in patients with stage I lung cancer, the results of conventional radiation therapy are markedly inferior to those of surgery, with local recurrence rates of up to 70%.<sup>(4-6)</sup>

In an attempt to improve the results, dose escalation studies involving conventional fractionation have been conducted and have generally involved patients with locally advanced disease, showing controversial results regarding the benefits of dose escalation; however, the results regarding increased toxicity have been consistent.<sup>(7-9)</sup> For the treatment of early-stage lung cancer, another strategy is to combine stereotactic localization techniques with high-dose hypofractionation, and this strategy is the focus of the present review. In general, 1-5 fractions are delivered in a period of less than two weeks.

Initially employed in the treatment of central nervous system tumors, in which context it is popularly known as radiosurgery, stereotactic radiation therapy has yielded promising results

\*Study carried out in the Departamento de Radioterapia, Hospital Sírio-Libanês, São Paulo (SP), in the Departamento de Radioterapia, Hospital Sírio-Libanês, Brasília (DF), and at the Departamento de Radioterapia, Instituto de Radiologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

1. Departamento de Radioterapia, Hospital Sírio-Libanês, São Paulo (SP) Brasil.

2. Departamento de Radioterapia, Hospital Sírio-Libanês, Brasília (DF) Brasil.

3. Serviço de Radioterapia, Departamento de Radiologia e Oncologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

Correspondence to: Heloisa de Andrade Carvalho. Rua Dona Adma Jafet, 91, CEP 01308-050, São Paulo, SP, Brasil.

Tel.: 55 11 3394-5367. E-mail: heloisa.carvalho@hc.fm.usp.br

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since it was first described in 1995<sup>(10)</sup> and, in recent years, has been considered the treatment of choice for medically inoperable patients with early-stage non-small cell lung carcinoma (NSCLC).<sup>(11)</sup>

Although a variety of terms are used in order to describe stereotactic radiation therapy, the principle remains the same. In North America, it is commonly referred to as stereotactic body radiotherapy (SBRT), whereas in Europe it is known as stereotactic ablative radiotherapy. The term radiosurgery continues to be used, especially by patients and the media.

## Biological aspects of high-dose radiation therapy

A key feature of stereotactic radiation therapy is the use of ablative doses of radiation delivered in few fractions and recognized by a biological equivalent dose (BED) > 100 Gy. A mathematical formalism, BED takes into account the radiation dose per fraction, the number of fractions, the total duration of treatment, and the radiosensitivity of tissues. It is used in order to calculate biologically equivalent doses between different fractionation schedules, given that the nominal total dose does not completely reflect the biological effects of radiation therapy on a tumor.

In addition to causing direct and indirect cell damage, delivery of ablative doses of radiation to neoplastic lesions prevents tumor repopulation. Furthermore, ablative radiation therapy causes vascular damage, which results in endothelial apoptosis and remodeling of the microvasculature and probably induces an immune response against the tumor as a result of the use of high radiation doses per fraction.<sup>(12)</sup>

In cases in which SBRT is delivered to lung lesions, local control rates are related to the BED employed. In a secondary analysis of retrospective studies examining the clinical implications of SBRT, local control and survival rates were found to be higher when BED was high ( $\geq 100 \text{ Gy}_{10}$ ) than when BED was  $< 100 \text{ Gy}_{10}$ .<sup>(13,14)</sup>

## Technical aspects of SBRT

According to Timmerman et al.,<sup>(15)</sup> the toxicity of ablative doses of radiation is related to doses within a radius of 0–3 cm around the edges of the target volume. One can thus imagine a “shell” surrounding the tumor and constituting the volume of damaged normal tissue, which

will eventually result in toxicity. Therefore, low rates of SBRT-related toxicity essentially depend on reducing the volume of this shell. This can be achieved with high-dose conformal radiation around the target and a rapid decrease in dose levels around it (defined as high dose gradient).

The use of SBRT requires a high level of accuracy throughout the treatment process. Such accuracy is achieved through the integration of modern imaging, simulation, planning, and dose delivery technologies and is maintained during treatment delivery (Figure 1).

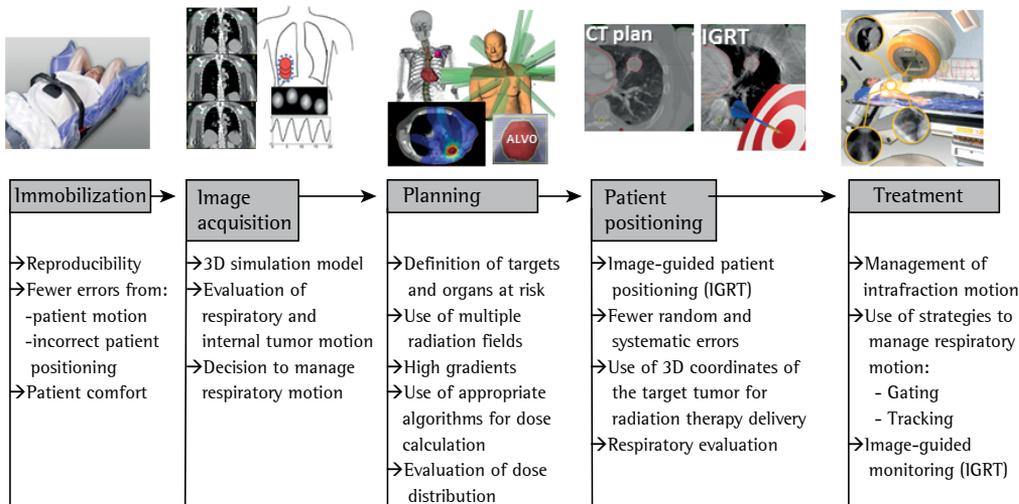
The process begins with the production of an immobilization device aimed at minimizing patient motion during treatment (intrafraction motion). In addition to minimizing intrafraction motion, immobilization aids in reproducing patient positioning throughout the treatment period (interfraction motion).

The next step is the acquisition of a CT image with the patient in the treatment position. The CT image is used in order to create a three-dimensional model on which radiation therapy planning will be based. At this stage of the process, internal tumor motion caused by breathing should be evaluated in order to define the margin of treatment field.

Tumor motion can be studied by four-dimensional CT imaging, which is the current gold standard. However, serial CT imaging can also be used.

If target motion amplitude is large, the inclusion of the entire region in the treatment volume might result in exceedingly high rates of SBRT-related toxicity. Therefore, a decision can be made to manage respiratory motion. Techniques to manage respiratory motion include abdominal compression, synchronization of radiation delivery with a particular stage of the respiratory cycle (gating), and moving the radiation beam so as to follow the tumor motion trajectory in real time (tracking).

During planning, multiple radiation fields and a highly conformal dose distribution around the target volume are obtained after the targets have been defined, and specific objectives are established by protocols such as Radiation Therapy Oncology Group (RTOG) 0236<sup>(16)</sup> and RTOG 0813,<sup>(17)</sup> by means of which these objectives are evaluated, the tolerance of neighboring organs being taken into account.



**Figure 1** – Description of the steps involved in stereotactic body radiation therapy. IGRT: image-guided radiotherapy.

Three-dimensional coordinates of the target tumor are used in order to position patients for radiation therapy delivery (stereotactic concept). This is achieved with the use of image-guided radiation therapy techniques that allow visualization of the tumor or of markers implanted during treatment. This technology allows a significant reduction in geometric errors that are inherent to conventional radiation therapy and are related to patient positioning.

SBRT can be performed with linear accelerators, with tools that allow monitoring of target motion, or with systems specifically designed for it, such as CyberKnife® (Accuray Inc., Sunnyvale, CA, USA), all of which yield similar results.

### Current indications for SBRT and outcomes

Stage I or II NSCLC patients, who have no lymph node involvement and who are medically inoperable, constitute the target population for SBRT. Although there have been reports of SBRT in patients with tumors of up to 10 cm in diameter, mean tumor diameter is 3 cm, and consensus dictates that patients with lesions ≤ 5 cm in diameter can be treated with SBRT. Cases of tumor recurrence and metastatic lesions can also be treated with SBRT.<sup>(13)</sup>

Initially, the most relevant studies evaluating the use of SBRT in patients with lung lesions (early-stage NSCLC) examined the treatment of central and peripheral lesions. However, adverse

event profiles were found to be different across studies, and the data constituted evidence for the use of SBRT in patients with peripheral lesions.<sup>(18-20)</sup>

### Peripheral lesions

Several retrospective studies have shown local control rates > 80% and a low toxicity profile in patients with small (T1 and T2) peripheral tumors (Table 1).<sup>(18,21-26)</sup>

In RTOG 0236 (a multicenter phase II study), 52 patients with medically inoperable T1-3 NSCLC (< 5 cm) were treated with 60 Gy delivered in 3 fractions. Long-term results showed a disease-free survival of 26% and an overall survival of 40% after a median follow-up of 4 years. In addition, only 7% of the patients had primary tumor recurrence; however, 13% experienced locoregional recurrence at 3 years. Grade 3 toxicity was reported in 15 patients, and grade 4 toxicity was reported in 2, with no reports of grade 5 toxicity.<sup>(27)</sup>

In another study (RTOG 0618), 33 operable patients with T1-3NO NSCLC were also treated with 60 Gy delivered in 3 fractions. The 2-year local failure rate was 8%.<sup>(28)</sup>

An interesting observational study conducted in the Netherlands showed that the introduction of SBRT for the elderly increased survival in inoperable stage I NSCLC patients when compared with historical groups of untreated patients.<sup>(29)</sup> In patients with peripheral lesions, there is an increased risk of chest wall toxicity, which manifests as pain or rib fracture.<sup>(30)</sup> In patients

with apical lesions, there is an increased risk of brachial plexopathy.<sup>(31)</sup> A better understanding of tolerance and dose limits has led to a decrease in the risk of chest wall pain and rib fracture.<sup>(32)</sup>

### Central lesions

The use of SBRT to treat patients with central lung lesions (Figure 2) began to be questioned after the publication of results showing severe toxicity rates of 17% and 46% at 3 years for peripheral and central lesions, respectively, 6 deaths having been related to the treatment of central lesions.<sup>(33,34)</sup>

Because of the aforementioned results, it was suggested that it would be safer and more appropriate to use a larger number of fractions (5 or more fractions) and smaller doses per fraction to treat patients with central lesions. It was recommended that the dose limits for adjacent organs and normal structures be rigorously evaluated and that imaging methods that are more consistent be used in order to evaluate tumors and tumor motion during breathing.<sup>(35)</sup>

In studies conducted more recently, central lesions were evaluated separately, and the incidence of toxicity was reported to be low, with excellent clinical outcomes (Table 2).<sup>(36-42)</sup>

In the Netherlands, Haasbeek et al. reported data regarding the use of SBRT delivered in 8 fractions of 7.5 Gy to 63 patients with central lung lesions (hilar lesions, in 37, and lesions abutting the pericardium or mediastinal structures, in 26), comparing those patients with those receiving SBRT for the treatment of peripheral lesions. Median follow-up was 35 months, during which no grade 4/5 toxicity was observed, and late grade 3 toxicity was observed in only 4 patients, 2 of whom had chest pain and 2 of whom had worsening dyspnea. Three-year overall survival and local control rates were better in the group of patients with central lesions than in that of those with peripheral lesions: 64.3% vs. 51.1% ( $p = 0.09$ ) and 92.6% vs. 90.2% ( $p = 0.9$ ), respectively.<sup>(36)</sup>

Because toxicity is always a concern in patients with central lesions, one group of researchers conducted a systematic review of 20 studies and 563 central lung lesions treated with SBRT. Grade 3/4 toxicity was reported in 8.6% of cases, and SBRT-related mortality was 2.7%; albeit low, those rates were higher than those observed in the treatment of peripheral lesions. Three-year local control and overall survival rates were 60-100% and 50-75%, respectively.<sup>(43)</sup>

Table 3<sup>(36-42)</sup> summarizes the data regarding SBRT toxicity in patients with central lesions,

**Table 1** – Studies reporting clinical outcomes in patients with central or peripheral lung lesions treated with stereotactic body radiation therapy.

Study	Number of patients	Dose	Central or peripheral lesion	Local control	Complications
Onishi et al. <sup>(21)</sup>	257	1-14 fractions (30-84 Gy)	both	84% (5 years) BED $\geq$ 100 Gy	$\geq$ grade 3: pulmonary complications, in 5.4%; esophageal complications, in 1.0%; dermatitis, in 1.2%
Nagata et al. <sup>(22)</sup>	104	4 $\times$ 12 Gy	both	3-year progression-free survival, 69%	grade 3: dyspnea, in 9%; pneumonitis, in 7%; intercostal pain, in 2%; cough, in 1% grade 4: dyspnea, in 1%
Baumann et al. <sup>(23)</sup>	57	3 $\times$ 15 Gy	peripheral	92% (3 years)	grade 3: 28% grade 4: 1.7%
Senthi et al. <sup>(24)</sup>	676	3-8 fractions (54-60 Gy)	both	89% (5 years)	-
Timmerman et al. <sup>(18)</sup>	70	3 $\times$ 20-22 Gy	both	95% (2 years)	pneumonitis, in 6%; rib fractures, in 3%
Brown et al. <sup>(25)</sup>	59	1-5 fractions (15.0-67.5 Gy)	both	disease-free survival, 90%	grade 3: pneumonitis, in 7%
Van der Voort et al. <sup>(26)</sup>	70	3 $\times$ 12-15 Gy	peripheral	96% (2 years if dose was = 60 Gy)	late toxicity, in 10%

BED: biological equivalent dose.

and Table 4<sup>(43-49)</sup> presents the treatment regimens used in studies showing no grade 3/4 toxicity.<sup>(36)</sup>

For patients with early-stage NSCLC, SBRT appears to be safe and effective, being the best treatment option for inoperable patients with peripheral or central lesions.

### SBRT in patients with clinical stage I NSCLC and no histological confirmation of cancer

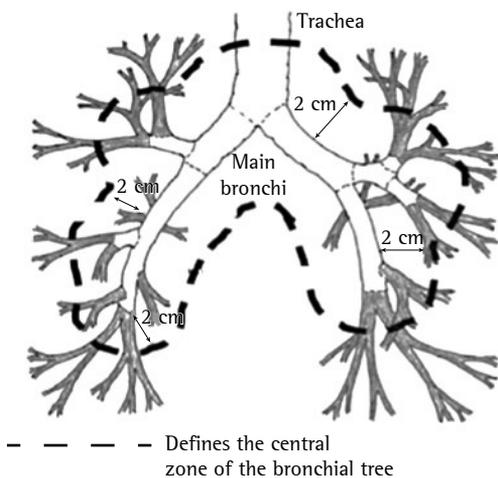
It is common practice that patients with solitary pulmonary nodules are referred for therapeutic

thoracotomy without previous histological confirmation. In a prospective study evaluating the impact of adding positron emission tomography (PET) to conventional staging, thoracotomy was found to have been “futile” (i.e., was performed in patients with benign disease) in less than 10% of cases.<sup>(50)</sup>

The probability of malignancy of a solitary pulmonary nodule can be estimated by age, nodule diameter, smoking history, presence of spiculated margins, affected lobe, and standardized uptake value as assessed by PET.<sup>(51)</sup> According to the American College of Chest Physicians, for patients in whom the probability of malignancy is greater than 60%, surgery is recommended without a histological diagnosis.<sup>(52)</sup>

Although technical difficulties and biopsy-related complications are few, they can be decisive in a population of patients who are not surgical candidates and are referred for SBRT.

One of the most controversial topics in SBRT for the treatment of stage I NSCLC is the fact that some studies conducted in Europe have included a considerable proportion of patients without histological confirmation. In a large study conducted in the Netherlands (n = 676), in which all patients were staged by PET, 65% had no histological diagnosis.<sup>(24)</sup> In a comparison between two cohorts of stage I NSCLC patients (with and without histological confirmation), no differences were found between the two regarding local control or survival, suggesting



**Figure 2** - Definition of central zone: region within a radius of 2 cm around the proximal bronchial tree (within the dashed line). Adapted from the Radiation Therapy Oncology Group.<sup>(16)</sup>

**Table 2** - Clinical outcomes of stereotactic body radiation therapy in central lesions.

Study	Number of patients	Tumor	Dose	Local control	Survival
Haasbeek et al. <sup>(36)</sup>	63	NSCLC (T1-3N0M0)	60 Gy (8 fxs)	92.6% (5 years)	DFS: 71% OS: 49.5% (5 years)
Nuyttens et al. <sup>(37)</sup>	56	NSCLC: 69.6%; metastatic NSCLC: 30.4%	45-60 Gy (5 fxs); 48 Gy (6 fxs)	76% (2 years)	CSS: 80% (3 years) OS: 60% (2 years)
Rowe et al. <sup>(38)</sup>	47	NSCLC: 59%; metastatic NSCLC: 41%	50 Gy (4 fxs) <sup>a</sup>	2 local failures	PFS: 24% (2 years)
Oshiro et al. <sup>(39)</sup>	21	recurrent or metastatic NSCLC: 95%	25-39 Gy (1-10 fxs)	60% (2 years)	OS: 62.2% (2 years)
Unger et al. <sup>(40)</sup>	20	metastatic NSCLC: 85%; hilar/main bronchial lesions	30-40 Gy (5 fxs)	63% (1 year)	OS: 54% (1 year)
Milano et al. <sup>(41)</sup>	53	NSCLC: 66%; metastatic NSCLC: 37%	20-55 Gy (1-18 fxs)	73% (2 years)	OS: 44% (2 years); T1-2: 72%
Chang et al. <sup>(42)</sup>	27	T1-2 NSCLC: 48%; recurrent NSCLC: 52%	40-50 Gy (5 fxs)	3 failures (40 Gy)	-

NSCLC: non-small cell lung carcinoma; fxs: fractions; DFS: disease-free survival; OS: overall survival; CSS: cancer-specific survival; and PFS: progression-free survival. <sup>a</sup>In 57% of cases.

**Table 3** – Toxicity of stereotactic body radiation therapy for central lesions, in absolute numbers of patients.

Study	Deaths	Grade 3 toxicity <sup>a</sup>	
		Acute	Late
Haasbeek et al. <sup>(36)</sup>	cardiac death: 1; respiratory failure: 1	1	4
Nuyttens et al. <sup>(37)</sup>	-	4	6
Rowe et al. <sup>(38)</sup>	bronchial necrosis: 1	4	
Oshiro et al. <sup>(39)</sup>	hemoptysis: 1	0	2
Unger et al. <sup>(40)</sup>	bronchial fistula: 1	1	0
Milano et al. <sup>(41)</sup>	bronchial/tracheal lesion: 4	0	1
Chang et al. <sup>(42)</sup>	-	1	

<sup>a</sup>Chest wall pain, dyspnea, rib fracture, pneumonitis, or chronic cough.

**Table 4** – Stereotactic body radiation therapy regimens used in the treatment of central lesions in studies showing no grade 3 or 4 toxicity.

Study	Number of lesions/Number of patients	Dose
Xia et al. <sup>(44)</sup>	9/43	50 Gy/10 fxs
Guckenberger et al. <sup>(45)</sup>	22/159	48 Gy/8 fxs 26.0-37.5 Gy/1-3 fxs
Baba et al. <sup>(43)</sup>	29/124	44-52 Gy/4 fxs
Olsen et al. <sup>(46)</sup>	19/130	45-50 Gy/5 fxs 54 Gy/3 fxs
Takeda et al. <sup>(47)</sup>	33/232	50 Gy/5 fxs
Stephans et al. <sup>(48)</sup>	7/94	50 Gy/5 fxs 60 Gy/3 fxs
Janssen et al. <sup>(49)</sup>	29/65	40-48 Gy/8 fxs 37.5 Gy/3 fxs

fxs: fractions.

that the inclusion of benign lesions did not bias the results.<sup>(53)</sup>

In recent years, a rapid increase in the use of SBRT in stage I NSCLC patients in the USA has been accompanied by an increasing number of patients receiving SBRT solely on the basis of a clinical diagnosis; although such patients currently account for less than 10% of cases, a trend toward increased SBRT use without biopsy

has been observed, indicating the possibility of a paradigm change in the near future.<sup>(54)</sup>

One group of authors proposed a model to inform decisions regarding SBRT in patients with solitary pulmonary nodules and comorbidities that increase biopsy risks, recommending the use of SBRT without pathological confirmation when the probability of cancer is higher than 85%.<sup>(55)</sup>

### SBRT in patients with multiple tumors, second primary tumors, or previous treatment

The use of SBRT in patients who have multiple tumors, who have second primary tumors, or who have previously been treated is a concern because it can increase the risk of complications, especially those resulting from multiple overlapping doses or a reduced pulmonary reserve in patients operated on.

To date, all studies investigating patients with multiple tumors, second primary tumors, or previous treatment have been retrospective in nature, and none have clearly separated them. However, patients with multiple primary lung tumors, those with synchronous or metachronous second primary tumors, and those with local recurrence after conventional radiation therapy or surgery can be cured, as shown in previous studies.<sup>(56-58)</sup>

Two studies have investigated such patients.<sup>(59,60)</sup> One of the studies evaluated 101 patients with multiple synchronous or metachronous primary lung tumors initially treated with surgery, SBRT, or conventional radiation therapy and subsequently treated with SBRT for the second tumor. The study showed promising results regarding local control, survival, and toxicity. The incidence of pneumonitis was six times higher in the patients who had previously received conventional radiation therapy than in those who had not. Overall survival was better in the patients who had metachronous tumors than in those who had synchronous tumors.<sup>(59)</sup> The other study showed significant toxicity in 36 patients who received SBRT for the treatment of intrathoracic recurrence after having previously received thoracic radiation therapy for localized or advanced disease (mean dose of 61 Gy); 30% of the patients experienced grade 3 toxicity.<sup>(60)</sup>

One group of authors reported outcomes of SBRT in 15 patients who had second primary

tumors (stage I tumors) and who had undergone pneumonectomy for the primary tumor, half of whom had severe COPD. Only 2 patients developed grade 3 toxicity, and 1-year survival was 90%, showing that SBRT is a safe treatment option.<sup>(61)</sup>

In view of the aforementioned findings, SBRT emerges as a promising therapeutic tool in patients with multiple synchronous or metachronous lung lesions and no evidence of regional or distant spread. However, SBRT should be used with caution in patients who have previously received external beam radiation therapy with conventional fractionation and radical doses.

### SBRT in operable patients

Patients with stage I lung cancer are candidates for curative treatment and can be divided into three major groups: 1) the group of low-risk surgical patients, who are usually treated by lobectomy; 2) the group of high-risk surgical patients, who are treated with sublobar (segmental or wedge) resection or SBRT; and 3) the group of medically inoperable patients, who are treated with external beam radiation therapy or SBRT.

To date, no randomized studies have compared surgical treatment with SBRT in operable (group 1 or group 2) patients; therefore, the only available data are from prospective studies or case series.

With regard to cases of borderline operability undergoing a more conservative surgical procedure (group 2 patients), an analysis of 19 studies reporting outcomes of SBRT or sublobar resection was published in 2013.<sup>(62)</sup> High (90%) local control rates can be achieved with SBRT, being similar to those achieved with lobectomy, which in turn are higher than those achieved with sublobar resection. In comparison with sublobar resection, SBRT results in lower local recurrence rates (20% vs. 4%;  $p = 0.07$ ) and lower toxicity.

With regard to low-risk surgical patients (group 1 patients), the available data are from comparisons across studies and from studies of low-risk surgical patients who refused surgery and underwent SBRT. To date, there have been at least three studies on this topic, a total of 264 patients having been studied (median age, 76 years). Local control rates were 93% and 73% for T1 and T2 tumors, respectively. The 3-year survival rate was similar to that achieved with surgical treatment, and the 5-year survival rates for T1 and T2 tumors were 72% and 62%,

respectively. Regional and distant recurrence was 20%.<sup>(14,63,64)</sup>

In a meta-analysis of studies published between 2000 and 2012, the results obtained with SBRT were compared with those obtained with surgery in operable patients with stage I NSCLC. Forty SBRT studies—30 of which were retrospective—comprising a total of 4,850 patients and 23 surgery studies—all of which were retrospective—comprising a total of 7,051 patients were selected for inclusion. The median age was 74 years among the patients who received SBRT and 66 years among those who received surgical treatment. The median follow-up duration was 28 months for SBRT patients and 37 months for surgery patients. The overall survival rates at 1, 3, and 5 years were lower with SBRT (83.4%, 56.6%, and 41.2%, respectively) than with lobectomy (92.5%, 77.9%, and 66.1%, respectively) and limited lung resections (93.2%, 80.7%, and 71.7%, respectively). After adjustment for proportion of operable patients and age, SBRT and surgery had similar overall and disease-free survival. It is therefore clear that patients are selected to undergo SBRT or surgery, older patients undergoing the former and younger, clinically fit patients undergoing the latter.<sup>(65)</sup>

In view of the excellent results obtained with SBRT for early-stage lung cancer, the idea of substituting this noninvasive technique for surgery, which is the standard treatment, led to randomized studies comparing SBRT with surgery.<sup>(66-68)</sup> Despite the efforts of the investigators, all of the aforementioned studies were terminated early because of poor recruitment. It is unknown whether this was due to a lack of referral of patients to the studies or to patient unwillingness to participate in the randomization process.

The investigators of two of the aforementioned studies<sup>(66,67)</sup> performed a pooled analysis of the collected data.<sup>(69)</sup> Eligible patients were those with clinical T1-2a (< 4 cm), N0M0, operable NSCLC. A total of 58 patients were enrolled and randomly assigned to SBRT ( $n = 31$ ) or surgery ( $n = 27$ ). The median follow-up duration was 40.2 months for the SBRT group and 35.4 months for the surgery group. Only 1 patient in the SBRT group died, compared with 6 in the surgery group. Estimated overall survival at 3 years was 95% in the SBRT group and 79% in the surgery group (hazard ratio = 0.14; 95% CI: 0.017-1.190;  $p = 0.037$ ). Recurrence-free survival

at 3 years was 86% in the SBRT group and 80% in the surgery group (hazard ratio = 0.69; 95% CI: 0.21–2.29;  $p = 0.54$ ). Grade 3 treatment-related adverse events were observed in 3 (10%) of the patients in the SBRT group, no grade 4 events having been observed in that group. In the surgery group, 1 (4%) of the patients died of surgical complications and 12 (44%) had grade 3/4 treatment-related adverse events. The authors concluded that SBRT is at least equivalent to surgery in terms of survival and local control and has reduced toxicity. However, they stated that studies involving larger samples should be conducted in order to corroborate those results.

### SBRT in patients with poor lung function or severe COPD

Most of the lung cancer patients who are candidates for SBRT are not surgical patients; therefore, it is important to evaluate the pulmonary toxicity of SBRT in this group of patients.

Several studies have evaluated lung function changes in patients undergoing SBRT. Although  $FEV_1$  and DLCO are generally reduced and can decrease further over time,<sup>(65,69,70)</sup> this has no impact on patient quality of life or survival.<sup>(70–76)</sup> In one of the aforementioned studies,<sup>(72)</sup> a low body mass index, a high lung volume receiving 20 Gy of SBRT, and a high pre-treatment FVC were predictors of a decline in FVC of more than 10%. In the remaining studies, no clinical or technical risk factors for pulmonary toxicity were identified.

The results of pulmonary function testing in 55 patients included in the RTOG 0236 protocol<sup>(73)</sup> and receiving SBRT for peripheral tumors showed a 5.8% decrease in  $FEV_1$  and a 6.3% decrease in DLCO after 2 years of follow-up. There were no major changes in oxygen saturation or arterial blood gases. Neither pre-treatment pulmonary function test results nor dosimetric parameters were predictive of late pulmonary effects, findings that were consistent with those of the remaining studies. Survival was higher among patients who were not surgical candidates because of poor lung function than among those who had good baseline lung function but were not surgical candidates because of cardiac comorbidities. This finding is consistent with those reported by Stephans et al.,<sup>(74)</sup> who performed a functional assessment of 92 medically inoperable patients undergoing SBRT. Although reduced  $FEV_1$  and

DLCO can be less than significant in patients with severe COPD, they can be significant in patients with normal lung function or mild to moderate COPD.<sup>(72)</sup> In a study evaluating lung function in 30 patients undergoing SBRT, SBRT was found to reduce lung volume and improve DLCO in those without COPD ( $n = 23$ ) when compared with those with COPD ( $n = 7$ ).<sup>(73)</sup>

Patients with severe COPD ( $FEV_1/FVC < 70\%$  and  $FEV_1 \leq 50\%$ ) undergoing SBRT or surgery were evaluated in a review of the literature.<sup>(76)</sup> Despite the negative selection of SBRT patients, the outcomes were comparable between the two treatment modalities: local or locoregional control rates  $\geq 89\%$  and 1- and 3-year survival rates of 79–95% and 43–70%, respectively, for SBRT and of 45–86% and 31–66%, respectively, for surgery. In addition to the fact that SBRT does not require hospitalization, mean 30-day mortality was 0% in the group of patients undergoing SBRT and 10% in that of those undergoing surgery.

There is consensus that poor lung function per se is not a contraindication to SBRT. In fact, SBRT is specifically indicated for such patients. However, individual characteristics such as tumor size, tumor location, comorbidities, and patient performance status should be taken into account when prescribing SBRT.

### Ongoing studies

RTOG-0813<sup>(77)</sup>: a multicenter phase II study evaluating dose escalation in patients with centrally located tumors of less than 5 cm (T1–2N0M0) in order to determine the maximum dose and toxicity profile of SBRT delivered in 5 fractions. Other outcome measures include local control rates, overall survival, and progression-free survival. Although patient recruitment has been completed, no results have yet been published.

RTOG-0915<sup>(78)</sup>: a phase II study of medically inoperable patients with stage I NSCLC. Patients are randomized to receive 34 Gy in 1 fraction or 48 Gy in 4 fractions.

### Final considerations

1. SBRT is an effective treatment option for early-stage (T1/T2N0) NSCLC of  $< 5$  cm.
2. Patients who are not surgical candidates constitute the principal study population. However, SBRT is a treatment option for

patients who are unwilling to undergo surgery.

3. Patients with peripheral tumors and those with central tumors can be treated with SBRT, although with different dose fractionation schedules.
4. Patients with multiple lesions or previous radiation therapy should be evaluated to receive SBRT.
5. Limited lung function and advanced age are not contraindications to SBRT.
6. In special situations, treatment can be initiated without a histopathological diagnosis of neoplasm, on the basis of clinical criteria, when a biopsy cannot be performed.
7. The risk of toxicity should be individually balanced against tumor location and patient prognosis.
8. The early termination of randomized studies comparing SBRT with surgery in operable patients demonstrates the difficulty in conducting phase III studies on this topic. However, evidence from a pooled analysis of two such studies shows that, in operable patients, SBRT is at least equivalent to surgery in terms of local control and survival, and has reduced toxicity.
9. A multidisciplinary evaluation plays a central role in therapeutic decision making, treatment, and follow-up.

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