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Non-surgical management of stage I lung cancer

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Abstract

Stage I lung cancer has a high cure rate with surgery, although many patients are not surgical candidates due to comorbid conditions. Historically, non-operative treatment has been disappointing. New and promising ablative therapies offer a curative option.

Introduction and context

The standard of care for stage I non-small cell lung cancer (NSCLC) according to the National Comprehensive Cancer Network Guidelines is lobectomy with lymph node dissection [1]. Radiation is standard treatment for patients who cannot tolerate surgery. Ablative therapy with stereotactic body radiation therapy (SBRT) offers high local control (LC) with limited morbidity. Percutaneous radiofrequency ablation (RFA) is being explored as another option for treating medically inoperable patients. This is a review of ablative non-surgical management of stage I NSCLC.

Recent advances

Stereotactic body radiation therapy

Historically, radiation for early-stage lung cancer has resulted in low rates of LC. Improvements in set-up reproducibility, tumor localization, and compensation for respiratory motion have facilitated the development of SBRT. SBRT uses highly conformal, high-dose, ablative radiation delivered in one to five fractions. Treatment is delivered with multiple fields, limiting the dose to normal tissues while delivering an ablative tumor dose.

Several institutions have reported safe and effective treatment with SBRT since the first results were published in 1995 [2]. LC rates with SBRT are 80-95% (Table 1). Differences in LC rates are partially explained by different total dose, fractionation schedules, and tumor size. An accepted method of normalizing the radiation dose is the biologically equivalent dose (BED) calculation that accounts for total dose, dose per fraction, and elapsed time for treatment delivery. A review of 257 patients treated with stage I NSCLC reported significantly lower local recurrence rates with BED of at least 100 Gy compared with BED of less than 100 Gy (8.4% versus 42.9%) [3]. Nguyen *et al.* [4] published an excellent review of the literature of SBRT outcomes based on BED calculations. Treatment with BED of at least 100 Gy in 14 published series resulted in LC of 74-100% compared with 57-91% with BED of less than 100 Gy in 10 published series [4].

Indiana University (Bloomington, IN, USA) conducted a phase I dose escalation study for medically inoperable lung cancer [5]. The maximal tolerated dose was not reached for T1/2 tumors of less than 5 cm despite reaching 60-66 Gy in three fractions. They subsequently completed a phase II trial with 60 Gy in three fractions for T1 and T2 tumors of less than 5 cm. The actuarial 2-year LC was 95%, and isolated hilar or mediastinal nodal relapse was rare [6]. Grade 5 toxicity (toxicity resulting in death) was reported in patients with centrally located tumors. This led to a definition of a 'central zone' inside of which the radiation dose must be adjusted to prevent unacceptable toxicity [6]. Grade 5 toxicity is effectively avoided with appropriate patient selection and dose modification for central lesions [7-9]. A multicenter phase I/II dose escalation study for centrally located lung tumors is under way. The starting dose is 50 Gy at 10 Gy per fraction.

The phase II data of Timmerman and colleagues [6] were the basis for a multicenter cooperative group phase II

Table 1. Stereotactic body radiation therapy

Study	Radiation	Tumor size	Local control	Overall survival
Nagata *et al.* [12], 2005	12 Gy × 4	<4 cm	94% (3 years)	72% (T1); 71% (T2) (1 year) 83% (T1); 72% (T2) (3 years)
Timmerman *et al.* [6], 2006	20-22 Gy × 3	≤7 cm	95% (2+ years)	55% (2 years)
Hara *et al.* [13], 2006	30-34 Gy × 1	<4 cm	80% (3 years)	75% (1 year) 41% (2 years)
Onishi *et al.* [3], 2007	Variable	7-58 mm (median 28)	BED >100, 84.2%; BED <100, 36.5% (3 years)	BED >100; 5 years 54% (medically inoperable) 75% (operable, refused surgery)
Hof *et al.* [17], 2007	19-30 Gy × 1	≥5 cm	68% (3 years), 100% local control for tumors <12 cm^3	75% (1 year) 65% (2 years)
Lagerwaard *et al.* [8], 2008	7.5-20 Gy × 3-8	T1-2	93% (2 years)	81% (1 year) 64% (2 years)
Baumann *et al.* [18], 2008	15 Gy × 3	T1-2	93% (2 years) T1: 100% (2 years)	52% (3 years)
Timmerman *et al.* [7], 2009	20 Gy × 3	≤5 cm	93.7%	72% (2 years)
Bradley *et al.* [9], 2005	18 Gy × 3 or 9 Gy × 5	1-5 cm (median 2 cm)	86% (2 years); no failures with maximum dose ≥67 Gy	

BED, biologically equivalent dose.

study presented in 2009 that used 60 Gy in three fractions to treat peripherally located tumors [7]. There was no grade 5 toxicity. Grade 3 and grade 4 adverse events were reported in 24% and 4% of patients, respectively. The most common severe adverse events were pulmonary/upper respiratory and musculoskeletal. LC was 93.7% and there were no regional failures [7].

Musculoskeletal complications consist of rib fractures and soft tissue fibrosis. The rate of this complication is low in individual studies but is regularly reported. Improved understanding of chest wall and soft tissue tolerances with hypofractionated treatments minimizes chest wall toxicity [10,11].

Current areas of investigation include evaluation of single-fraction SBRT for inoperable patients. These schedules have been shown to have an efficacy similar to that of 60 Gy in three fractions, may result in less toxicity, and offer a more convenient schedule [12,13]. SBRT in operable patients is being studied in a multicenter cooperative group trial with the primary objective of determining whether SBRT achieves acceptable LC in operable patients. All patients are treated with SBRT and are resected with evidence of progression.

Radiofrequency ablation

Percutaneous image-guided RFA is used to treat solid tumors by inducing controlled coagulation necrosis [14]. This procedure is accepted as a viable option for treatment of hepatic lesions and recently has been proposed as an option to treat inoperable lung tumors, although the US Food and Drug Administration has not cleared any RFA devices for the specific treatment indication of partial or complete ablation of lung tumors. As with other new procedures, patients should be treated in clinical studies. Lesions generally considered eligible for RFA are at least 1 cm from the trachea, main bronchi, aorta, and the pulmonary artery and its major branches. Lesions near the diaphragm, lung apex, and scapula are locations that might be technically difficult to access for RFA.

The efficacy of RFA for NSCLC is difficult to assess as the majority of series include primary and secondary tumors. Additionally, there are few reported prospective studies (Table 2).

The RAPTURE study, a prospective multicenter clinical trial aimed at assessing feasibility, safety, and effectiveness of lung malignancies, has been reported [14]. This study included primary and metastatic lung tumors of 3.5 cm or less. Sustained LC at 1 year was seen in 88% of 85 assessable patients out of a total of 105 patients undergoing therapy. There were no treatment-related deaths. Pneumothorax developed in 27 of the 137 procedures, and pleural effusion requiring drainage developed in 4 patients.

Studies have reported improved control for smaller tumors. Simon and colleagues [15] reported a single-institution retrospective review of 153 consecutive patients with 183 inoperable lesions treated with RFA for metastatic and primary lung tumors. The 1-, 2-, 3-, 4-, and 5-year local tumor progression-free rates, respectively, were 83%, 64%, 57%, 47%, and 47% for tumors of 3 cm or smaller and 45%, 25%, 25%, 25%, and 25% for tumors larger than 3 cm. The overall pneumothorax rate was 28.4%, with a 9.8% chest tube insertion rate. The overall 30-day procedure-specific mortality rate was 2.6%.

Toxicity is generally reported as acceptable, although the reported toxicity varies between series. Zhu and colleagues

Table 2. Radiofrequency ablation

Study	Tumor size	Local control	Comments	Overall survival
Simon *et al.* [15], 2007		83% (1 year) 64% (2 years) 57% (3 years)	Primary lung and metastases; retrospective review	Stage I lung 78% (1 year) 57% (2 years)
Lencioni *et al.* [14], 2008	≤3.5 cm	88% (1 year)	Primary lung and metastases	NSCLC 70% (1 year) 48% (2 years)
Lanuti *et al.* [19], 2009	Mean 2.0 cm	69% 50% (>3 cm)		78% (2 years)
Okuma *et al.* [20], 2009	Mean 2.1 cm (range 0.2 to 9 cm)	68% (mean follow-up 1 year)	Retrospective review 2000-2009; tumor >2 cm independent predictor of local failure	61% (1 year) 57% (3 years)
Pennathur *et al.* [21], 2009	NA	82% (mean follow-up 17 months)	Primary, recurrent, and metastatic lung	Primary lung 49% (2 years)

NA, not applicable; NSCLC, non-small cell lung cancer.

[16] reported a systematic review of 17 studies of RFA treatment for lung tumors. The overall procedure-related morbidity was 15.2-55.6%, and mortality was 0-5.6%. The most common reported toxicity was pneumothorax, with the majority being self-limited. Chest tube was required in 3.3-38.9%. More prospective data are needed to define the role of RFA and proper patient selection in order to minimize procedure toxicity.

Implications for clinical practice

Historically, treatment for medically inoperable early-stage NSCLC was limited to palliation. Currently, SBRT results in excellent LC rates and acceptable toxicity and therefore presents a curative option for patients with medically inoperable NSCLC. SBRT has been systematically studied for primary lung tumors in several studies, including a prospective multi-institution study with strict quality standards. According to early data, RFA for the treatment of lung tumors has been shown to be effective. Additional prospective data are necessary.

Abbreviations

BED, biologically equivalent dose; LC, local control; NSCLC, non-small cell lung cancer; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

Competing interests

The author declares that she has no competing interests.

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