Is radiofrequency ablation or stereotactic ablative radiotherapy the best treatment for radically treatable primary lung cancer unfit for surgery?

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Abstract

A best evidence topic was constructed according to a structured protocol. The question addressed was whether radiofrequency (RF) offers better results than stereotactic ablative therapy in patients suffering from primary non-small-cell lung cancer (NSCLC) unfit for surgery. Of the 90 papers found using a report search for RF, 5 represented the best evidence to answer this clinical question. Concerning stereotactic ablative therapy, of the 112 papers found, 10 represented the best evidence to answer this clinical question. A manual search of the reference lists permitted us to include seven more articles. The authors, journal, date, country of publication, study type, group studied, relevant outcomes and results of these papers are given. We conclude that, on the whole, the 23 retrieved studies clearly support the use of stereotactic ablative therapy rather than RF in patients suffering from primary NSCLC unfit for surgery. Indeed, stereotactic ablative therapy offered a 5-year local control rate varying between 83 and 89.5%, whereas the local control rate after RF ranges from 58 to 68%, with a short follow-up of ~18 months. Furthermore, both overall survival and cancer-specific survival were better with stereotactic ablative therapy, with a 3-year overall survival ranging from 38 to 84.7% and the 3-year cancer-specific survival from 64 to 88%, whereas the 3-year OS, only reported in two studies, ranged from 47 to 74% for RF. Moreover, the post-interventional morbidity was superior for RF ranging from 33 to 100% (mainly composed by pneumothorax), whereas radiation pneumonitis and rib fracture, ranging, respectively, from 3 to 38% and 1.6 to 4%, were the primary complications following stereotactic ablative therapy. Hence, the current evidence shows that stereotactic ablative therapy is a safe and effective procedure and should be proposed first to patients suffering from primary NSCLC unfit for surgery. However, the published evidence is quite limited, mainly based on small studies of <100 patients. Moreover, so far there is no blind, prospective control, randomized study comparing these two techniques. Consequently, despite the encouragement of these preliminary results, they must be interpreted with caution.

Keywords: Radiation therapy • Radiofrequency • Stereotactic radiotherapy • Non-small-cell lung cancer

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. The protocol is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients suffering from a primary lung cancer unfit for surgery], is [radiofrequency pulmonary ablation] or [stereotactic ablative therapy] the best for [local control and survival]?

CLINICAL SCENARIO

You are in charge of a patient suffering from a stage IB primary non-small-cell lung cancer (NSCLC). This patient is unfit for surgical treatment because of a predicted FEV1 of 35% and several

cardiac comorbidities. During the multidisciplinary board, the radiotherapist argues for stereotactic ablative therapy (SABR), whereas the interventional radiologist claims that radiofrequency (RF) ablation is better for the patient because it can be performed ambulatory and with only one session. You decide to scrutinize the published literature concerning both techniques on primary NSCLC.

SEARCH STRATEGY

Medline 1998–2012 using the OVID Pubmed, Pascal and Cochrane interfaces, with results limited to English language articles: ('Radiofrequency ablation.mp') AND ('non-small-cell lung cancer.mp') AND ('primary.mp') AND ('stereotactic radiotherapy.mp'). Finally, a manual search was used to follow-up on references from the retrieved studies.

Table 1: Overview of the studies

Author, date, journal country, Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Uematsu <i>et al.</i> (2001), Int J Rad Onc Biol Phys, Japan [2] Prospective cohort study (level 2C)	SABR 50 patients (24 IA and 26 IB) Histology type: SCC: 13 AdenoK: 33 Undifferentiated: 4	LCR Survival rate Toxicity	60% with a median follow-up of 36 months 3-year OS: 66% 3-year CSS: 88% None	No histological data during the follow-up, which was only based on CT without PET-CT
Onimaru <i>et al.</i> (2003), Int J Rad Onc Biol Phys, Japan [3] Prospective cohort study (level 2C)	SABR 26 patients (stage 1, 19; stage 2, 1; stage 3, 1; stage 4, 4) Histology type: SCC: 9 AdenoK: 7 Unspecified: 1	LCR Survival Toxicity	3-year LCR: 55.1% 2-year OS: 41.5% 2-year CSS: 60.2% Radiation oesophagitis: 3.8%	No histological data on recurrence; follow-up only based on chest-CT without PET-CT
Lee <i>et al.</i> (2003), Lung Cancer, South Korea [4] Prospective cohort study (level 2C)	SABR 9 patients Histology type: SCC: 4 AdenoK: 2 Undifferentiated: 2 SCLC: 1	LCR Survival Toxicity	89% with a median follow-up of 18 months OS: 100% with a median follow-up of 18 months None	No histological data on recurrence; short follow-up; small number of patients
Timmerman <i>et al.</i> (2003), Chest, USA [5] Prospective cohort study (level 2C)	SABR 37 patients (19 IA, 18 IB <7 cm) Histology type: SCC: 10 AdenoK: 9 BAC: 3 Undifferentiated: 15	LCR Survival Toxicity	65% with a median follow-up of 15.2 months Complete radiological response: 27% Partial radiological response: 60% OS: 64% and DFS: 50% with a median follow-up of 15.2 months RP: 16%	No histological data on recurrence; short follow-up
Wulf <i>et al.</i> (2004), Int J Rad Onc Biol Phys, Germany [6] Prospective cohort study (level 2C)	SABR 20 patients (2 T1N0, 10 T2N0 and 8 T3N0) Histology type: SCC: 7 AdenoK: 8 Other: 1 Unknown: 4	LCR Survival Toxicity	95% with a median follow-up of 11 months 5-year OS: 18% 1-year DFS: 60% >2 years: 25% RP: 20%	No histological data on recurrence; short follow-up; small number of patients
Nagata <i>et al.</i> (2005), Int J Rad Onc Biol Phys, Japan [7] Prospective cohort study (level 2C)	SABR 45 patients (32 IA and 13 IB) Histology type: SCC: 24 AdenoK: 20 Undifferentiated: 1	LCR Survival Toxicity	2-year LCR: 98% 5-year DFS: 72% 5-year OS: 78% RP: 22%	No histological data on recurrence
Fakiris <i>et al.</i> (2009), Int J Radiat Oncol Biol Phys, USA [8] Prospective cohort study (level 2C)	SABR 70 patients (34 T1N0 and 36 T2N0)	LCR Survival Toxicity	3-year LCR: 88.1% Median survival: 32.4 months 3-year OS: 42.7% 3-year CSS: 81.7% RP: 7.1%	No histological data on recurrence
Baumann <i>et al.</i> (2009), J Clin Oncol, Sweden [9] Prospective cohort study (level 2C)	SABR 57 patients (40 T1N0 and 17 T2N0) Histology type: SCC: 8 AdenoK: 19 Undifferentiated: 1 Unspecified: 29	LCR Survival Toxicity	3-year LCR: 92% 3-year OS: 60% 3-year CSS: 88% Median survival: 40.6 months RP: 18%	No histological data on recurrence

Continued

Table 1: (Continued)

Author, date, journal country, Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Timmermann <i>et al.</i> (2010), JAMA, USA [10]	SABR 55 patients (44 T1N0 and 11 T2N0)	LCR Survival	3-year LCR: 90.6% 3-year DFS: 48.3% 3-year OS: 55.8% Median DFS: 34.4 months Median OS: 48.1 months RP: 3.6%	No histological data on recurrence
Prospective multicenter control study RTOG 0236 trial (level 2C)	Histology type: SCC: 17 AdenoK: 19 Undifferentiated: 3 Unspecified: 16	Toxicity		
Andratschke <i>et al.</i> (2011), Radiother Oncol, Germany [11]	SABR 92 patients (31 IA and 61 IB)	LCR	1 year: 89% 3 years: 83% 5 years: 83%	No histological data during the follow-up
Prospective cohort study (level 2C)	Histology type: SCC: 49 AdenoK: 35 BAC: 2 Unspecified: 6	Survival rate	1-year OS: 79% 3-year OS: 38% 5-year OS: 17% 1-year CSS: 93% 3-year CSS: 64% 5-year CSS: 48%	All recurrence concerned T2N0 tumours
		Toxicity	Rib fracture: 3.3% Radiographic pneumonitis: 34.8% Clinical pneumonitis: 15.2%	
Onishi <i>et al.</i> (2011), Int J Radiat Oncol Biol Phys, Japan [12]	SABR 87 patients (64 IA and 23 IB)	LCR Survival rate	5 years: 86.7% 5 year OS: 69.5% 5 year CSS: 76.1%	No PET at the preoperative evaluation
Retrospective analysis of a multi-institutional database (level 3C)	Histology type: SCC: 25 AdenoK: 54 Unspecified: 8	Toxicity	Rib fracture: 4.6% RIPC: grade 1, 70.1%; grade 2, 4.6%; grade 3, 1.1%	No histological data during the follow-up
Onishi <i>et al.</i> (2004), Cancer, Japan [13]	SABR 245 patients (155 T1N0 and 90 T2N0)	LCR Survival	84.8% 3-year OS: 56% 5-year OS: 47% 5-year CSS: 78% RP: 6.9%	No histological data on recurrence: follow-up only based on CT without PET-CT
Retrospective review of a prospective database (level 3C)	Histology type: SCC: 110 AdenoK: 109 Unspecified: 26	Toxicity		
Onishi <i>et al.</i> (2007), J Thorac Oncol, Japan [14]	SABR 257 patients (164 IA and 93 IB)	LCR	With a median follow-up up of 38 months: - Complete radiological response: 25.7% - Partial radiological response: 61.1%	No PET in the preoperative staging
Multi-institutional retrospective cohort study (level 3C)	Histology type: SCC: 111 AdenoK: 120 Unspecified: 26	Survival rate	3-year OS: 56.8% 5-year OS: 47.2% 3-year CSS: 76.9% 5-year CSS: 73.2% Rib fracture: 1.6% Symptomatic RIPC: 10.9%	No histological data during the follow-up
		Toxicity		
Verstegen <i>et al.</i> (2011), Radiother Oncol Netherlands [15]	SABR 591 patients (315 IA and 276 IB)	LCR	3 years (with proof): 90.4% 3 years (without proof): 91.2% 3-year OS (with proof): 53.7% 3-year OS (without proof): 55.4% Rib fracture: 2% RP: 3%	No histological data during the follow-up
Retrospective analysis of a prospective database (level 3C)	Two groups: with histological proof of NSCLC (<i>n</i> = 209, 36%); without proof (<i>n</i> = 382, 64%) Histology type: SCC: 73 AdenoK: 67 Unspecified: 69	Toxicity		34% of patients had a prior history of cancer (from which 50% were lung cancer): inclusion of metastasis?

Continued

Table 1: (Continued)

Author, date, journal country, Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Lagerwaard <i>et al.</i> (2011), Int J Radiat Oncol Biol Phys, Netherlands [16] Retrospective cohort study (level 3C)	SABR 177 patients (106 IA and 71 IB) Histology type: SCC: 16 AdenoK: 20 BAC: 2 Undifferentiated: 24	LCR Survival rate Toxicity	1 year: 98% 3 years: 93% 1-year OS: 94.7% 3-year OS: 84.7% 5-year OS: 51.3% Rib fracture: 3% Grade 3 RP: 2%	No histological data during the follow-up
Senthi <i>et al.</i> (2012), Lancet Oncol Netherlands, [17] Retrospective review of a multi-institutional database (level 3C)	SABR 676 patients (379 IA and 297 IB) Histology type (<i>n</i> = 235): SCC: 82 AdenoK: 78 BAC: 2 Unspecified: 73	LCR Survival rate	2 years: 95.1% 5 years: 89.5% Median OS: 40.7 months Median local free recurrence: 14.9 months 5-year CSS: 48%	No histological data during the follow-up No data on toxicity
Grutters <i>et al.</i> (2010), Radiother Oncol Netherlands, [18] Meta-analysis (level 1A)	SABR Meta-analysis ~11 studies on SABR: including more than 20 patients, reporting data on 2- or 5-years survival	Survival rate (stage I) Toxicity	Corrected 2-year OS: 70% (63–77%) Corrected 5-year OS: 42% (32–50%) Corrected 2-year CSS: 83% (75–92%) Corrected 5-year CSS: 63% Pneumonitis grade 3–4: 2% (1.15–3.23%) Irreversible dyspnoea: 0.78% (0.29–1.69%) Treatment-related death: 0.69% (0.25–1.5%)	No histological data during the follow-up All recurrence concerned T2N0 tumours
Belfiore <i>et al.</i> (2004), Am J Roentgenol, Italy [19] Prospective cohort study (level 2C)	RF 33 patients divided into three groups according to tumour size: Group 1: <3 cm Group 2: >3 and <5 cm Group 3: >5 cm Histology type: SCC: 11 AdenoK: 21 SCLC: 1	Procedure efficiency Histology Morbimortality	Complete radiological response: 13.8% (6 months) Local radiological progression: 3.5% (6 months) 36.8% of total coagulation necrosis (6 months) Morbidity: 33% (3 pneumothorax, 3 pleuresis, 5 pneumonia) Mortality: 0	Seven patients lost during the follow-up; no immuno-histochemical analysis; Only short-term results (1-year maximum); no data on DFS and OS
Fernando <i>et al.</i> (2005), J Thorac Cardiovasc Surg, USA [20] Retrospective and prospective cohort study (level 2C)	RF 18 patients (9 I, 2 II, 3 III and 4 IV) Histology type: SCC: 10 AdenoK: 5 BAC: 1 Undifferentiated: 1	Procedure efficiency Morbimortality	LCR: 67% with a median follow-up of 14 months Mean survival: 20.9 months. Median DFS: 18 months Morbidity: 61% (7 pneumothorax, 2 pneumonia, 1 pulmonary embolism and 1 persisting air leak) Mortality: 1	Association of multiple stages of NSCLC; weak follow-up; small number of patients; progression only based on a radiologic evaluation (no histological data)
Hiraki <i>et al.</i> (2007), J Thorac Cardiovasc Surg, Japan [21] Prospective cohort study (level 2C)	RF 20 patients, all stage I NSCLC (14 IA and 6 IB) Histology type: SCC: 7 AdenoK: 13	Procedure efficiency Morbimortality	LCR: 65% with a median follow-up of 21.8 months Median DFS: 9 months. 1-year OS: 90% 1-year OS: 90% 2-year OS: 84% 3-year OS: 74% Morbidity: 85% (4 pleuresis and 13 pneumothorax) Mortality: 0	Weak follow-up; small number of patients; progression only based on a radiologic evaluation (no histological data)

Continued

Table 1: (Continued)

Author, date, journal country, Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Lanuti <i>et al.</i> (2009), J Thorac Cardiovasc Surg, USA [22] Prospective cohort study (level 2C)	RF 31 patients (34 tumours), all stage I NSCLC (29 IA and 5 IB) Histology type: SCC: 4 AdenoK: 20 BAC: 10	Procedure efficiency Morbimortality	LCR: 68.5% with a median follow-up of 17.3 months 1-year OS: 85% 2-year OS: 78% 3-year OS: 47% Median DFS: 25.5 months Morbidity: 100% (5 pneumothorax, 3 BPF, 1 recurrent nerve palsy, 8 pleuresis, 6 pneumonia, 2 haemothorax and 6 haemoptysis) Mortality: 0	Weak follow-up; small number of patients; progression only based on a radiologic evaluation (no histological data)
Pennathur <i>et al.</i> (2007), J Thorac Cardiovasc Surg, USA [23] Retrospective cohort study (level 3C)	RF 19 patients, all stage I NSCLC (11 IA and 8 IB) Histology type: SCC: 8 AdenoK: 8 Others: 3	Procedure efficiency Morbimortality	LCR: 58% with a median follow-up of 28 months 1-year OS: 95% 2-year OS: 68% Median DFS: 27 months Morbidity: 68.4% (1 persisting air leak and 13 pneumothorax) Mortality: 0	Retrospective study; weak follow-up; small number of patients; progression only based on a radiologic evaluation (no histological data)

AdenoK: adenocarcinoma; BAC: bronchioloalveolar carcinoma; BPF: bronchopleural fistula; CSS: cancer-specific survival; CT: computed tomography; DFS: disease-free survival; LCR: local control rate; NSCLC: non-small-cell lung cancer; OS: overall survival; PET: positron emission tomography; RF: radiofrequency; SCC: squamous cell carcinoma; SCLC: small-cell lung cancer; SABR: stereotactic ablative therapy. RP: radiation pneumonitis; RIPC: radiation-induced pulmonary complication. To make comparable across studies, staging of NSCLC has been harmonized according to the 2009 TNM-staging system.

SEARCH OUTCOME

Concerning RF, a total of 90 papers were identified, of which five represented the best evidence to answer the question. Concerning SABR, 112 papers were identified, from which 10 articles were selected. Manual searches of the reference lists permitted the inclusion of seven more articles. Articles dealing with cryotherapy, or that did not provide independent results on primary and metastatic tumours, as well as case reports were excluded. The papers are summarized in Table 1 [2–23].

RESULTS

Concerning SABR, 11 studies were based on a population of <100 individuals [2–12]. Among them, two studies provided data on a 5-year local control rate (LCR) [11, 12], ranging from 83 to 86.7%. The 3-year LCR ranged from 55.1 to 92% [3, 8–11], whereas the 2-year LCR, ~98%, was only given by one study [7]. The last studies reporting an LCR varying between 60 and 95%, with an inhomogenous follow-up ranging from 11 to 36 months [2, 4–6]. The 1-year overall survival (OS) was only reported by one study and approached 80% [11]. Onimaru *et al.* [3] were the only one ones to report a 2-year OS, ~42%. The 3-year OS was reported in five studies and varied between 38 and 66% [2, 8–11]. Plus, the 5-year OS ranged from 17 and 78% [6, 7, 11, 12]. Finally, Lee *et al.* [4] reported an OS of 100% with a short median follow-up of 18 months, whereas Timmermann *et al.* reported 64% with a shorter median follow-up of 15.2 months [5]. The 2-year cancer-specific survival (CSS) was only reported by Onimaru *et al.* [3] and was

~60%, while the 3-year CSS ranged from 64 to 88% [2, 8, 9, 11]. In 2011, Andratschke *et al.* [11] and Onishi *et al.* [12], respectively, reported a 5-year CSS of 48 and 76.1%. In these 11 articles, the reported procedure-related mortality was null. Although several articles reported no toxicity [2, 4], radiation pneumonitis (RP) was the main radiation-induced toxicity reported by the others, ranging from 3.6 to 34.8% [3, 5–11]. This must be interpreted with caution, because some authors included only symptomatic RP while others included both clinical and radiological RP. Onishi *et al.* [12] reported a grade 1 radiation-induced pulmonary complication rate of 70.1% but did not specify the complications they included. Finally, the rib fracture was the second-most predominant complication varying between 3.3 and 4.6%, most of them asymptomatic [11, 12]. Five papers were based on more than 100 patients [13–17]. The reported 3-year OS ranging from 53.7 to 84.7% [13–16], whereas the 5-year OS varied between 47 and 51.3% [13, 14, 16]. The 3-year CSS was only reported by Onishi *et al.* [14], ~77%. The 5-year CSS varied between 48 and 78% [13, 14, 17]. Regarding the LCR, the 3-year LCR ranged from 90.4 to 93% [15, 16], whereas the 5-year LCR, only reported in one study, was ~89.5% [17]. Once again in this larger series, the related mortality was null. The rate of the rib fracture varied between 1.6 and 3% [14–16]. Finally, the RP rate ranged from 3 to 6.9% [13, 15]. Lagerwaard *et al.* [16] reported a rate of 2% of grade 3 RP, whereas Onishi *et al.* [14] reported only 1.6% of symptomatic RP.

In their meta-analysis performed on 11 studies concerning SABR, Grutters *et al.* [18] reported a corrected 2-year OS of 70%, whereas the corrected 5-year OS was ~42%. In addition, the corrected 2-year CSS was ~83%, whereas the corrected 5-year CSS was ~63%. They reported a mortality rate of 0.69%, with an acceptable grade 3–4 RP rate of 2%.

Concerning RF, the data were very inhomogenous with the median follow-up varying between 6 and 28 months [19–23]. Consequently, the LCR ranged from 13.8% at 6 months to 58% at 28 months [19–23]. Only three studies provided data on OS [21–23]. The 1-year OS varied between 85 and 95% [21–23], whereas the 2-year OS ranged from 68 to 84% [21–23]. Finally, the 3-year OS was only given by two studies and ranged from 47 to 74% [21, 22]. Concerning the mortality, only one paper reported one case of mortality (5.5%) in a patient who underwent both RF and lobectomy at the same time [20], whereas it was null in the other papers. The morbidity for its part ranged from 33 to 100% [19–23], mainly composed of pneumothorax (varying from 9 to 68%), but with a persisting air leak rate of ~5% [20, 23].

CLINICAL BOTTOM LINE

On the whole, we recorded 23 papers meeting the criteria for comparing RF with SABR. The studies concerning SABR are performed on a larger number of patients and include a longer follow-up. Furthermore, the results of SABR seem more encouraging, reporting a better LCR, overall and CSS. In addition, the morbidity of SABR seems low and is usually controllable by steroid therapy. Hence, the current evidence shows that SABR, if accessible, should first be proposed to patients suffering from a primary NSCLC non-suitable for surgery. Nevertheless, to date, there is no prospective blind randomized study comparing SABR to RF. Plus, the published literature provides a low level of evidence and no histological data on recurrence (only based on imaging). Thus, a greater number of prospective control trials are necessary to confirm these preliminary results.

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eComment. Standardizing our cooking

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We read with interest the article by Renaud *et al.* on radiofrequency ablation or stereotactic ablative radiotherapy as the best treatment for radically treatable primary lung cancer patient who are unfit for surgery [1]. The scenario of the