Challenges in the treatment of early non-small cell lung cancer: what is the standard, what are the challenges and what is the future for radiotherapy?

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Abstract: In the last 15 years, the use of Stereotactic Ablative Radiation Therapy (SABRT) in the management of small peripheral lung tumours has developed considerably, so that it currently represents a standard of care for inoperable stage I non-small cell lung cancer (NSCLC), offering a survival advantage over traditional radiotherapy, local control rates at 3 years around 90%, with a low risk of toxicity. Indications have extended to larger tumours up to 5 cm and centrally located tumours. In this review we will explore the role of SABRT in early stage NSCLC, the state of the art, the challenges and the future for this technique. There are ongoing studies to optimize such approaches within a multicentric setting. Trials comparing surgery to SABRT in operable or marginally operable have failed because of poor accrual. Several questions remain that need to be addressed in prospective studies.

Keywords: Non-small cell lung cancer (NSCLC); radiotherapy; stereotactic radiotherapy; early lung cancer

Submitted Jul 09, 2014. Accepted for publication Jul 23, 2014.
doi: 10.3978/j.issn.2218-6751.2014.08.03
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2014.08.03

Introduction

Lung cancer is one of the most common neoplasms, and is a major cause of mortality and morbidity throughout the world; in 2012 there were 410,000 cases and 353,000 deaths in Europe (1). Surgery is the mainstay of treatment for patients with early disease non-small cell lung cancer (NSCLC). For treated patients, the 5-year overall survival (OS) is 50-43% in patients with clinical stage IA-IB, and 73-58% in surgically staged IA-IB patients, respectively (2). Because of medical co-morbidities related to smoke, about 25% of patients with early stage NSCLC do not receive standard surgery, and in case of no treatment, patients with stage IA-IB have a median survival of 17 months (3) according to an observational study.

But there is now an alternative treatment that can give good results. Conventional radiotherapy (RT) was for years the alternative option of early-stage medically inoperable patients, but the results were quite poor (4). Among patients treated with curative intent, the reported 5-year survival rate was 0-42%; 29-37% in T1 and 4-24% in T2N0M0 tumours. It should be outlined that the population eligible for surgery is very different from the population treated with radiotherapy, as the latter had also many co-morbidities. The cause-specific survival (CSS) was 54-93% at 2 years, and 13-19% at 5 years. It was suggested that OS and local control (LC) were affected by tumour size (cut-off 4 cm) and total dose, with better outcome if RT dose was 60-69 Gy (4). Hypofractionated RT has been described as an interesting treatment option for these patients; a dose of 48-52 Gy in 4 Gy fractions could provide LC rates of 70.1% at 5 years (5). Such results are however poor compared to the results observed with stereotactic radiotherapy that was originally developed to treat small intracranial lesions in the 50 s, and then started to be proposed to patients with inoperable early stage lung cancer.

Stereotactic ablative body radiotherapy (SABRT) is defined as an "external beam radiation therapy method used to very precisely deliver a high dose of radiation to

Table 1 Clinical outcome of SABRT in some selected studies

Author and year publication	N patients	Median follow up (months)	Total dose (Gy)/dose per day	Reference point	LC (%)	OS (%)
Timmerman 2010 (10)	55	34.4	60/20	98% isodose	(3 y) 97.0	(3 y) 55.8
Baumann 2009 (11)	57	35.0	45/15	67%	(3 y) 92.0	(3 y) 60.0
Baumann 2006 (12)	141	33.0	Variable from 45/15 to 30/10	N/A	97.0	52.0
Lagerwaard 2008 (13)	206	12.0	T1 60/20; T1-2 thoracic wall 60/12; 60/7.5 central tumours	80%	(2 y) 93.0	(1 y) 81.0 (2 y) 64.0
Haasbeek 2010 (14)	193	12.6	T1 60/20; T1-2 thoracic wall 60/12; 60/7.5 central tumours	80%	(3 y) LF 10.7	(1 y) 85.7 (3 y) 45.1

LC, local control; LF, local failure; OS, overall survival.

Table 2 Published dose and fractionation schedules according to tumour location

Number of fractions × dose per fraction	BED (Gy)	Tumour localization
3×20 Gy	180.0	Peripheral, surrounded by lung parenchyma
3×18 Gy	151.2	
5×11 Gy	115.5	Peripheral, <1 cm from chest wall
4×12 Gy	105.6	
8×7.5 Gy	105.0	Central (close to mediastinum)
10×5 Gy	75.0	

an extracranial target within the body, using either a single dose or a small number of fractions" (6). The use of SABRT in lung cancer has been developed in the nineties (7,8) and is nowadays more widely used. It has become over the years, the treatment of choice in inoperable patients and in operable patients who refuse surgery (9).

In this review we sought to explain the role of SABRT in early stage NSCLC, the state of the art, the challenges and the future for this technique.

Present role of SABRT in early stage NSCLC

Results in T1-T2N0M0

SABRT has become the standard alternative treatment in inoperable patients, due to co-morbidities or age, because of the good results observed (9). In the main published series of SABRT for stage IA-IB NSCLC (*Table 1*), there is a 3-year LC rate of 90%. Reported early toxicity is quite low, with no treatment-related death in peripheral stage I tumours. The reported acute toxicity (10-14) consists of fatigue (in 31-33% of the patients), local chest pain (in 3-12%) and dyspnea (5-7%). The most frequent late grade III-IV toxicities were pneumonitis (2-3%), thoracic pain (3%) and rib fracture (1-2%).

Optimal dose

Different SABRT schedules, with different fraction sizes, total doses and modalities of dose prescription have been used making direct comparisons difficult. Some of the published regimens are described in *Table 2* (10,13,14). The "Biological Equivalent Dose" or BED may allow easier comparisons of the effects of various treatment protocols (15). A retrospective study has tried to evaluate the optimal SABRT dose by studying the relation between BED and outcome (LC and survival rates) (16). There seems to be a SABRT dose effect, patients treated with higher dose SABRT have lower local recurrence rates: 8.1% if BED ≥100 *vs.* 26.4% if BED <100 (P<0.01). Within this study, differences in OS were only observed in operable patients treated with SABRT and BED ≥100. Differences in OS are difficult to evaluate, as patients with inoperable NSCLC will eventually die because of severe comorbidities.

Thus, European Society of Medical Oncology (ESMO) lung cancer guidelines (9) recommend using a SABRT regimen with a BED of ≥100 Gy, delivered to the encompassed isodose (9).

Challenges

What is the optimal dose fractionation?

There is no standard fractionation for SABRT in early stage NSCLC. The most common schedules are listed in *Table 2*. In a recent overview of SABRT studies (17), as opposed to the multi-institutional Japanese study previously mentioned (16), no relationship was found between LC and total dose suggesting that lower but more uniform doses could be sufficient to get adequate control rates. Another overview divided the studies according to BED in quartiles as "low, medium, medium-high and high" within doses of 51-83, 83-108, 108-145 and 145-196 BED Gy (18). It concluded that there was a tendency of better 2-3-year OS in T1 lesions in the medium BED group, and a better 3-year-OS in the medium-high BED group for T2 tumours. CSS at 3 years was lower in the "low-dose" group.

SABRT for patients with severe pulmonary comorbidities and impact on lung function

In patients with early stage NSCLC with severe chronic ventilatory impairment that undergo surgery (19,20), the postoperative complication rate is quite high (57-70%), with mortality rates of 8-14%. As reported by Lau *et al.* (20), video-assisted thoracic surgery (VATS) may be particularly interesting for such patients, as it increases 2.8-fold the adjusted OS benefit over the open-standard surgery approach suggesting a decrease of morbidity with VATS compared to classical open surgery. SABRT is an interesting treatment option in patients with severe chronic obstructive pulmonary disease (COPD) (21), achieving LC similar to surgery, with less toxicity (postoperative deaths of 7-25% in the surgery group *vs*. 0% in SABRT).

The effect of SABRT in terms of its impact on pulmonary function tests (PFT) has been studied in patients included in a radiation therapy oncology group trial (RTOG 0236) by Stanic (22). No significant change in PFT was observed, nor any correlation between PFT decrease and lung toxicity (pneumonitis), or any relationship between decrease of PFT and survival. In a mono-institutional study (23), a low pretreatment forced expiratory volume in 1 second (FEV1) or diffusing capacity of carbon monoxide (DLCO) did not affect the survival of these patients so it was suggested not to refuse SABRT treatment based on a low FEV1 or DLCO.

Regarding to quality of Life in patients treated either with tridimensional radiotherapy (3D-RT) or SABRT (24), only physical function was negatively affected in the 3D-RT group. The authors insisted on the need of new quality of life studies in this group of patients.

SABRT for elderly patients

Concerning SABRT for the elderly (≥75 years), a large published series of 193 patients (14) comparing them to a younger population, found a similar OS and toxicity profile. Another interesting retrospective observational study based on the SEER database in elderly patients with early-stage NSCLC (25) shows that offering a radical treatment to this population may be beneficial. Comparing patients ≥75 years to younger patients (55-74 years), they concluded that the major cause of death in this older population was actually lung cancer. The authors suggest that the use of SABRT in medically inoperable elderly patients should be more frequently considered. Only 1.1% of them received SABRT compared to 14.8% in the younger group. The study of Palma *et al.* (26) has shown the impact the introduction of SABRT has had, on the outcome of elderly patients in the Netherlands.

Extension of SABRT indications

Larger tumours

In surgically treated patients, tumour size is a well-known prognostic factor. It is not that clear, in SABRT studies, whether outcome varies according to tumour size. In the RTOG 0326 study which included 44 evaluable patients with T1 and 11 patients with T2 tumours treated with 3 fractions of 18 Gy (10), there was no significant difference in terms of median disease-free survival (DFS) between patients with T1 (36.1 months) and T2 tumours (33.7 months).

In the Scandinavian prospective study of Baumann *et al.* treating 57 patients were treated with 3 fractions of 15 Gy (11), the risk of systemic failure was more frequent in higher stage tumours (T1b-T2 *vs*. T1a) and in patients with larger tumour volume. In another retrospective study by Baumann *et al.* (12), the authors studied the factors that could affect the efficacy of SABRT in a series of 138 patients. The authors described a relationship between local failure rate, stage and gross tumour volume (GTV): in T1 tumours, there were less local failures (3%) than in T2 tumours (13%). GTV volume (<26 cm^3) was also related to a decreased local failure rate. No differences in survival or metastatic rates were found between T1 and T2 tumours in this study. The crude distant metastases failure rate was 25%.

In a multi-institutional Japanese study published by

Onishi *et al*. (16) , there was a higher local recurrence rate in stage IB tumours compared to IA in patients treated with a BED <100 Gy (41.4% *vs*. 16.6%). Such difference was not observed in patients who were treated with a BED >100 Gy.

In the systematic review by Chi *et al*. (27) LC was poorer in tumours larger than 5 cm, especially if a BED of <100-120 Gy was administered. For this reason they suggest using higher doses for larger tumours (BED above 120 Gy). It should be underscored that few studies have included patients with tumours over 5 cm. In studies that included patients with tumours over 5 cm, the reported risk of distant metastases approached 30%.

Interestingly, in the recently published Princess Margaret Hospital experience of 185 T1-T2N0 patients treated with SABRT (28), tumour size was not related to local failure whereas regional and distant failure rate as well as OS, DFS and CSS were related to T size. The prescribed dose schedule was risk-adapted based on tumour size and location. They concluded that SABRT was a good therapeutic option and could be proposed in larger tumours up to 5.7 cm in diameter or 100 cc. However they state that larger tumours seem to be associated with more non-local failures so that more extensive staging and adjuvant treatment should be considered.

Based on these retrospective studies, it seems that if a BED over 100 Gy is used, in tumours of 5 cm or less, there may be no difference in terms of LC. However tumour size seems to impact more on the risk of regional or distant failure.

Central early lung cancer

The main limitation to SABRT in centrally located tumours is due to its potential severe toxicity. This has been described by Timmerman (29) in a prospective phase II study that included 70 patients treated with SABRT (60-66 Gy in 3 fractions) whatever the tumour location. Although an excellent LC was observed (95% actuarial at 2 years), the authors reported increased grade III-V toxicity. They described an 11-fold probability of grade III-IV toxicity in central locations as compared with peripheral tumours: at 2 years, 83% of patients with peripheral tumours were free from severe toxicity as opposed to 54% of patients with central tumours. Tumour size of >10 mL was also associated with a higher risk of toxicity. The authors concluded that SABRT in tumours located within 2 cm of the proximal bronchial tree was at high risk of toxicity, so that this regimen (60 Gy in 3 fractions) should not be used in centrally located tumours. Since then, other authors have shown that such severe toxicities were rare if more fractionated regimens were used in central tumours defined as tumours localized within 2 cm of the proximal bronchial tree (13,29).

In a review concerning central tumours treated with SABRT, Senthi *et al.* (30) concluded that a good LC (>85%) could be achieved if BED_{10} ≥100 Gy, as seen in peripheral tumours. Treatment-related mortality was 2.7%, so higher than that observed in peripheral tumours. So, such results could be achieved with fractionation schedules of 50 Gy in 10 Gy-fractions, 54 Gy in 9 Gy fractions, 56 Gy in 8 Gy fractions or 60 Gy in 7.5 Gy fractions. A grade III-IV toxicity was present in <9% of patients. Local, regional or distant control was not affected by tumour location (central *vs.* peripheral) if a BED_{10} ≥100 Gy was administered.

It should be outlined that bronchial stenosis is a very rare complication in patients treated with 3-D conformal radiotherapy at doses of 60-66 Gy. However, there is an increased risk when higher doses are used as shown in a study by Miller *et al*. (31). These authors found a 4% risk stenosis among patients treated with 74 Gy, and a higher risk (25%) among patients who had received 86 Gy. A grade V toxicity occurred in 3% of the patients, of whom one developed a broncho-pleural fistula.

Toxicities observed and implications for risk-adapted SABRT

The concept of risk-adapted fractionated stereotactic radiotherapy was developed, to insure good results and avoid severe toxicities, depending upon location and tumour size (13,28). A study comparing 2 fractionation regimes (32) (60 Gy delivered in 3 fractions *vs*. 50 Gy delivered in 5 fractions) showed an increased grade I-II chronic chest wall toxicity in the 60 Gy regime (18%) compared to the 50 Gy regime (4%) suggesting this second fractionation was preferable for larger lesions close to the chest wall. In the present time dose and fractionation is adapted according to tumour location (central *vs.* peripheral), proximity to the chest wall (more or less than 1 cm) and tumour size.

Several articles have been published recently focusing on clinical factors potentially related with chest wall toxicity secondary to SABRT (33-36). Chest wall pain can be quite frequent (around 20-25%) when tumours are close to chest wall, especially in large tumours. The incidence of rib fractures may vary between 1.6% and 23% in these articles. Rib fractures cause chest wall pain, but in about in 1/3 patients, they are asymptomatic. Even if several

parameters have been proposed, there are no clear and consensual predictive volumetric data for chest wall grade III-IV toxicity because of the low incidence of such events. Most authors propose to lower the dose per fraction in case of larger tumours close to chest wall or in smaller tumours adherent to chest wall.

There are presently multicentre studies evaluating SABRT in central tumours, with more fractionated regimens compared to the prospective RTOG 0236 study (29,37,38). The Lung Tech European Organisation for Research and Treatment of Cancer (EORTC) trial (37) (NCT01795521) is a phase II trial evaluating both the efficacy and toxicity of a risk-adapted SABRT regimen (60 Gy in 8 fractions) within a multicentric setting in medically inoperable patients. The RTOG 0813 trial (38) is a phase I/II multicentric trial, which is also specifically addressing the issue of the optimal dose for central tumours. According to the results and possible toxicity observed, dose will be either increased or decreased by 0.5 Gy per fraction, starting at a dose of 50 Gy in 10 Gy-fractions. In any case, results of prospective studies are needed in order to establish the optimal dose-fractionation schedule. Long-term follow-up is very important.

It is recommended to delineate carefully the target volume and organs at risk, to decide the optimal treatment plan on a 4-D CT (39,40), after staging evaluation including a recent PET-CT and thoracic CT-scan.

Difficulties in assessing local control

Assessing LC may be quite challenging, as radiologic changes after SABRT are difficult to distinguish from local recurrence. Patients should be followed up, as there are radiological changes in all patients. Several types of changes have been described that evolve throughout time as well described by the Amsterdam Free University team (23,41,42) and Guckenberger (43). According to Dahele *et al*. (42), median time of onset for radiologic changes was 17 weeks. The percentage of patients who developed radiological changes was 54% at 6 months, 73% at 12 months and 87% at 24 months (44). The most common late CT changes were: modified pattern of fibrosis (71%), scar-like fibrosis (11%) and "mass-like" fibrosis that can be tricky. The highest severity of radiological changes has been described at 1-2 years, tending to decrease afterwards. A rapidly growing mass after SABRT could be indicative of a real local recurrence. Mattonen *et al.* (45) propose a quantitative analysis of CT-scan changes of tumour lesions based on 3D-volume, T size according to RECIST criteria changes of Hounsfield Units, ground glass opacity textural analysis, to differentiate benign Radiation-induced lung injury (RILI) from recurrence, as early as possible.

Patterns of failure after SABRT

As said previously, the local recurrence rate is about 10% at 3 years in most studies. Patients with an adequate pretreatment study (PET-CT) have a regional failure of 10%, and distant failure rate seems higher, depending upon stage. Concerning regional failure, Hoopes (44) studied a cohort of 58 patients, who all had a 18-FDG PET-CT before SABRT for an early-stage NSCLC. Median follow up was 42.5 months. The authors describe a risk of nodal failure of 25%. Isolated nodal failure was found in 6 patients (10%). However interpretation of PET-CT can sometimes be difficult: a metabolic activity in the treated volume could be found in 7% patients with a SUV of 2.5-5.9, and with no local recurrence proven.

Patterns of failure were well described in a large retrospective cohort study of 676 patients with early-stage NSCLC by Senthi *et al*. (46). All patients had a pre-treatment FDG-PET-CT. With a median follow-up of 32.9 months, 4% patients presented a local recurrence at a median time of onset of 15 months. The regional recurrence rate was 6% with a median time of onset of 13 months, whereas the distant failure rate was 12%, and the median time of onset of 9.6 months. Isolated loco-regional recurrence (and hence potentially resectable patients) represented 34% of all recurrences, of whom only 31% were medically operable. Most common site of distant recurrence was contralateral lung. Among the 42 patients with initial loco-regional recurrence, 17% developed distant metastases at a median time of 9 months. Second primary cancer appeared in 6% of patients at a median time of 18 months, most frequent located in contralateral lung.

Results in operable patients according to size

The patterns of recurrence are quite similar in operable patients treated with stereotactic radiotherapy. Onishi (47) published a series of 87 T1-2N0M0 NSCLC medically operable patients, with a median follow-up of 55 months. The risk of local, nodal and distant recurrence was 9.2%, 15%, and 22%, respectively. LC at 5 years was significantly better in patients with stage IA (92%) than stage IB (73%). However, there was no difference according to stage regarding regional or distant control or OS.

Any role for adjuvant chemotherapy in fit patients treated with SABRT?

As distant failure seems more frequent (20-25% of patients) than local or mediastinal failure, there may be some rationale then to envisage adjuvant chemotherapy in fit patients. The possible role of "adjuvant chemotherapy" has been questioned by a small study by Chen *et al.* (48). They published a series of 65 T1-3N0M0 NSCLC patients treated with SABRT at a BED of 115-72 Gy with or without chemotherapy according to medical co-morbidities. Chemotherapy was a platinum-based regime. The study concluded that adjuvant chemotherapy improved 5-year OS by 14%. No conclusion can be drawn from such a study, as only fit patients could have adjuvant chemotherapy, but it shows it should be further evaluated, if indications of SABRT extend to operable patients.

Series comparing surgery-SABRT

As surgery is the gold-standard treatment for early stage NSCLC, and as the accumulated evidence in favour of SABRT in inoperable patients increases, there has been several studies (overviews and a few matched-pair analyses) trying to compare surgery and SABRT. Onishi was the first one to address this issue, in a series of 87 operable early stage NSCLC patients (47). With a median follow-up of 55 months, LC at 5 years was 87%, regional control (lymph node metastasis) was 85.3% and distant metastasis control was 75%. Five-year OS and CSS was 70% and 76% respectively. Even when they compared these results to surgical series that are, much larger and with longer follow-up times, they concluded that the results of SABRT could be potentially equivalent to surgery.

Grills *et al.* (49) published a comparative retrospective cohort of stage I NSCLC patients treated with either wedge resection (n=58) or SABRT (n=69, of whom 95% were inoperable). Outcomes were similar in both groups. OS was better in the surgery group, but CSS was similar; probably, because SABRT group was composed mainly of inoperable patients, and that patients will eventually succumb of non-cancer related causes.

In a systematic review, Soldà *et al.* (50), compared the 2-year OS of stage I patients who were treated either with surgery (2,038 patients) or SABRT (3,201 patients). Results were similar: 70% for SABRT (95% CI: 67-72%) and 68% for surgery (95% CI: 66-70%). The LC rate at 2 years for patients treated with SABRT was 91% (95% CI: 90-93%). Patients who had SABRT were treated with different available technologies, and the authors could not find any difference in terms of outcome or OS.

A propensity-score matched analysis was published by Verstegen *et al.* (51), matching T1-3N0M0 NSCLC treated with surgery (VATS or lobectomy 64 patients) or SABRT (64 patients). Median follow up was 16 and 30 months respectively. Unsuspected nodal disease was found in 19% of VATS patients. Locorregional control (LRC) was better in SABRT group (1-3-year LCR 97-94%) than in VATS group (1-3-year LCR 87-83%), with a hazard ratio of 3.68, 95% CI: 1.09-12.50, P=0.04. Distant recurrence rate, OS and Freedom from Progression was similar in both groups. Median time to recurrence was 11 months in the SABRT group and 8.2 months in the surgery group.

Two retrospective series of the same team comparing SABRT and surgery by Crabtree and Robinson are also interesting. They underline that nodal dissection may show unforeseen nodal involvement in up to 37% of patients operated for clinical stage I NSCLC (52,53). In a series of patients treated either by surgery (458 patients) or SABRT (151 patients), they showed a regional (N1-N2) upstaging of 15% of the patients from the surgery group. Three-year OS of patients with occult nodal disease was obviously worse (66%) compared to those without occult nodal disease (80%). The median follow up was 2.83 years in the surgical series and 1.95 years in the SABRT group. After a matched comparison according to age, tumour size, tumour location, FEV1 and comorbidities (56 matched patients in each cohort) it was concluded that 3-year OS was better in surgical group (68%) *vs.* SABRT (52%). Disease-free survival was 65% *vs.* 47%, respectively, and 3-year local recurrence-free survival was 91% and 92%, respectively, but not statistically significant.

Such studies provide interesting information, but drawing conclusions from retrospective studies is hazardous. There are few data on long-term outcome after SABRT, and SABRT is a much "younger" treatment than surgery. Randomized trials would be needed to really compare these two treatments. There have been 3 unfortunate attempts to run randomized trials comparing SABRT to surgery that have closed due to poor accrual (54-56). Guidelines have been published about SABRT implementation to propose clinical trials (57).

Conformal Conventional Radiotherapy for early stage NSCLC

Not all inoperable patients with early lung cancer can be

	T1a	T1b	T2a	T2b	T3
N0	IA		IB	IIA	IIB
N1	IIA			IIB	

Green color: SABRT accepted as treatment in inoperable patients.
Orange color: SABRT remains to be evaluated

Figure 1 Possible role of SABRT in early stage NSCLC.

treated with SABRT, and patients especially those with N1 involvement or patients with larger tumours (over 5-7 cm) may be still treated with conventional conformal radiotherapy. In a systematic review of Rowell *et al.* the results of conventional RT for patients with early stage NSCLC were quite mediocre (4). In T1 and T2 tumours, the 5-year survival rate was 29-37%, and 4-24% respectively. Local recurrence rate ranged between 6% and 70% showing the difficulty of LC assessment. As expected, tumour size, nodal involvement, age over 70 years, presence of comorbidities and weight loss, were all factors that impacted negatively on outcome. An improved survival was observed in patients less than 70 years old, higher delivered doses or squamous carcinoma histology.

Altered fractionation has been evaluated, and showed very promising results in the continuous hyperfractioned accelerated radiotherapy (CHART) landmark randomised study (58,59) comparing CHART (54 Gy in 36 fractions and 12 consecutive days with 3 fractions per day) to conventional RT (60 Gy in 30 daily fractions, 5 days per week); 36% of patients had stage I and II NSCLC. The outcome was significantly improved among patients who had accelerated RT, with a 22% of reduction of the relative risk of death. The 2-year OS was 30% in hyperfractionated group against 21% in the control group. However, even if the results are quite interesting, this schedule has not become standard treatment, mostly because of organizational issues. More recently, an individual data-based meta-analysis has validated this approach (60).

SABRT is nowadays accepted as the treatment for medically inoperable cT1-2N0M0 NSCLC patients (9). In patients with cT1-2N1M0, or T3N0M0, conventional RT is still considered the standard in inoperable patients, but the interesting results observed with altered fractionation should be highlighted. SABRT remains to be evaluated in larger tumours; the role of SABRT in centrally located tumours is under study (*Figure 1:* green color: SABRT accepted as treatment; orange color: SABRT remains to be evaluated).

Future of RT in early NSCLC

More prospective studies with defined endpoints and follow-up evaluation are needed in peripheral tumours as well as centrally located tumours. We do not yet know, whether SABRT may have a role in operable patients. As the number of fit patients undergoing SABRT may increase in the future, it will probably lead to better knowledge of long-term outcome. Follow-up of long-term survivors will become of outmost importance, since most patients treated with SABRT up to now, had severe co-morbidities, and would eventually die of non-cancer related causes. More extensive exploration of the mediastinum will probably be needed. Adjuvant treatments will then have to be evaluated.

In the future, individualized treatment in terms of dose and fractionation, may vary according to molecular, radiomics and radiosensitivity profile.

Lung cancer screening represents another challenge. At present, most NSCLC are diagnosed at an advanced stage. The recently reported results of screening trials in a high-risk population are quite provocative for thoracic oncologists. The National Lung Screening Trial (NLST) comparing chest X-ray to low dose CT (61,62), has shown a relative reduction of death from lung cancer of 20% in the low dose CT group. Screening of lung cancer promotes an earlier diagnosis of the disease, allowing the onset of more radical treatments. SABRT may have an important role as an alternative to surgery. In a review about treatment options in early stage lung cancer (surgery or SABRT) (63), authors conclude that operable patients should be operated (lobectomy) with the advantage of having complete pathological results. For unfit patients, SABRT should be offered as the alternative treatment with the main advantage of its low toxicity. For intermediate-fit patients they propose to encourage clinical trials to establish indications of these two treatment modalities, so that we can better individualize the optimal treatment for every single patient.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Cascales A, Martinetti F, Belemsagha D, Le Pechoux C. Challenges in the treatment of early non-small cell lung cancer: what is the standard, what are the challenges and what is the future for radiotherapy? Transl Lung Cancer Res 2014;3(4):195-204. doi: 10.3978/j.issn.2218-6751.2014.08.03

