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Review

Is stereotactic ablative radiotherapy an alternative to surgery in operable stage I non-small cell lung cancer?

Andrea Riccardo Filippi[a,*], *Pierfrancesco Franco*[b], *Umberto Ricardi*[a]

[a] *University of Torino, Department of Oncology, Radiation Oncology Unit, Torino, Italy*
[b] *Radiation Oncology Department – Tomotherapy Unit, Ospedale Regionale U. Parini, AUSL Valle d'Aosta, Aosta, Italy*

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ABSTRACT

Surgery is the gold therapeutic standard for patients affected with stage I non-small cell lung cancer. Stereotactic ablative radiotherapy is currently considered the preferred treatment option for inoperable patients, representing approximately 25%. Limited data are available directly comparing surgery and SABR in operable patients, none of them prospective. Preliminary results are encouraging, showing that the two treatment modalities are equally effective in terms of tumour control, with expected similar survival projections. Moreover, in elderly patients SABR could represent a valid treatment alternative in comparison to surgery due to the lower morbidity. We here review and discuss the potential role of SABR as an alternative to surgery in operable early stage lung cancer patients.

1. Background

Surgery currently represents the standard treatment option for patients affected with early stage non-small cell lung cancer (NSCLC). Long-term results of surgical resection show survival rates of 60–70% at 5 years, as high as 80% in selected series.[1] Lobectomy or pneumonectomy improves outcomes if compared with sub-lobar resection, but a substantial proportion of patients are ineligible for surgery due to the presence of concomitant medical conditions such as respiratory or cardiovascular comorbidities, associated with a high risk of surgical complications. Moreover, a small group of patients refuse surgery. An observation alone strategy has been shown in the past to obtain worse outcomes if compared to surgery or radiation, and it is now considered inappropriate in the majority of cases.[2] Until recently, patients unfit for surgery typically underwent conventionally fractionated radiotherapy with a total dose of 60–70 Gy delivered over a 6- to 7-week period. The poor outcome achievable with conventional radiotherapy is reflected in the Surveillance, Epidemiology and End Results (SEER) study, showing a global cancer specific 5-year survival rate of 15%.[3] Stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) represents an emerging

* *Corresponding author at*: University of Torino, Department of Oncology – Radiation Oncology Unit, Via Genova 3, 10126 Torino, Italy. Tel.: +39 011 6705352; fax: +39 011 6638680.
E-mail addresses: andreariccardo.filippi@unito.it, andrearic.filippi@gmail.com (A.R. Filippi).
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treatment option and a new standard of care for stage I NSCLC in inoperable patients. Due to the long-term efficacy and the low rate of late toxicity,[4] SABR might be considered a valid alternative to surgery also in operable patients.

2. Aim

The present review provides a focus on the scientific basis and clinical data supporting the potential role of SABR as an alternative to surgery in operable patients, as a step towards a more tailored therapy for early stage NSCLC.

3. SABR vs. conventional radiotherapy in inoperable patients

Results of conventional external beam radiation for early stage NSCLC are disappointing,[5] with local relapse as the predominant pattern of failure leading to different 5-year survival rates according to primary tumour dimensions: 38% for patients with tumours < 2 cm, 22% for tumours between 2 and 3 cm, 5% for tumours between 3 and 4 cm and 0% for larger lesions.[6] In order to improve tumour control and, hence, cancer-specific survival (CSS), dose-escalation gained credit as an option, but when considering the dose–response relationship for lung cancer, doses up to 80–90 Gy would be needed to control approximately 50% of the tumours.[7,8] Dose-escalation achieved by conventionally fractionated radiotherapy is limited by 2 main factors: a prolonged overall treatment time, resulting in a considerable amount of tumour repopulation, and an increased radiation dose delivered to the functional lung tissue, with a possible further functional impairment.

SABR, a radiation technique characterised by the use of very accurate repositioning and advanced image-guidance techniques, allows the administration of few large fractions able to kill the neoplastic cells through radio-ablation at very high biologically equivalent doses (BED > 100 Gy). To date, the largest report on the efficacy of SABR in stage I NSCLC is the one from Vrije University in Amsterdam[9]: 676 patients were treated and 124 (18%) had disease recurrence, with a median follow-up time of 32.9 months. Actuarial 5-year rates of local, regional, and distant recurrence were 10.5%, 12.7% and 19.9%, respectively. Of the 124 recurrences, 82 (66%) were distant and 57 (46%) were isolated distant recurrences. Isolated locoregional recurrences occurred in the remaining 42 patients (34%). The median times to local, regional, and distant recurrence were 14.9, 13.1 and 9.6 months, respectively, and CSS at 5 years exceeds 60%. In this series all patients were staged with CT–PET and had either histological confirmation or "proof of malignancy." Delivered doses were 54–60 Gy in 3 fractions to peripheral tumours, 55–60 Gy in 5 fractions for lesions close to chest wall and 60 Gy in 8 fractions for central tumours. This large series confirms, with an adequate follow up time, the promising results of many mono-institutional Phase II clinical trials.[10–13] In 2010, Radiation Therapy Oncology Group (RTOG) 0236 Trial mature results were published, showing an OS rate at 3 years of 55.8%, with a 97.6% LC rate (median follow-up 34.4 months).[14] These favourable clinical outcomes resulted in a significant practice modification in the last years for inoperable patients, mainly represented by elderly patients with comorbidities. Palma et al. showed, in a population-based time-trend analysis, that the proportion of patients aged >75 years with stage I NSCLC treated with radiotherapy with radical intent increased from 26% in the interval 1999–2001 to 32% in 2002–2004 and 42% in 2005–2007. These changes translated into a significant increase in OS rate for stage I lung cancer elderly patients globally treated in 2005–2007 (surgery and/or radiotherapy, $p < 0.001$), and particularly in the subset of patients treated with radiotherapy ($p < 0.056$ at log-rank test comparing 1999–2001 with 2005–2007).[15] As the results achievable with SABR are significantly superior to those achievable with conventional radiotherapy, SABR is currently considered the preferred treatment option for inoperable patients with stage I NSCLC, and efforts towards the confirmation of these findings by a prospective randomised comparison with conventional radiotherapy have been abandoned.

3.1. *Open issues in SABR for inoperable patients*

3.1.1. *Histological diagnosis*

Histological confirmation of lung nodules in SABR series has been a concern since the introduction of this treatment. The majority of patients referred to Radiation Oncology Departments are elderly and/or with comorbidities: hence, in most of them, there is contraindication to CT-guided Fine Needle Aspiration; in adjunct, peripheral nodules may be difficult to reach by bronchoscopy. As a result, in most series a correct histological diagnosis is available in 50–60% of patients. There are several reports comparing the outcomes between patients with or without histological diagnosis: in the series by Takeda et al.,[16] 56 patients without histological diagnosis and 115 patients with confirmed NSCLC were compared, and local control and survival probability at 3 years after SABR were almost identical for patients with or without histological confirmation. In the Vrije University series,[9] histological confirmation before SABR was obtained in 235 (35%) of 676 patients; the remaining patients had a new or growing lesion with a CT appearance consistent with malignancy and local ^{18}FDG-PET uptake, since the likelihood of a benign diagnosis in such patients is less than 4%.[17,18]

3.2. *Central and large tumours*

An increased risk for severe-fatal toxicity was recorded when treating central tumours at high doses per fraction in pioneering studies. Centrally located lesions are in proximity to critical structures such as trachea, bronchial tree or oesophagus, all tissues characterised by a serial architecture, with high risk of toxicity for large doses per fraction. In the Indiana University series, a 11-fold increase risk of severe toxicity was evident for central tumours treated with 60–66 Gy in 3 fractions. Grade 3 or higher toxicity during 2 years of follow-up was noted for 46% of patients with central tumours, with 6 eventual treatment-related deaths occurred.[19] Afterwards, with risk-adapted treatment schedules (60 Gy in 7.5 Gy fractions), excellent rates of controls were reported also in central tumours.[20] Milano et al.[21] reviewed outcomes and toxicity of SABR in 2009, including published experiences with different total dose/fractionation protocols, and showed that with

adapted fractionation schedules the risk of severe toxicity become comparable to peripheral lesions with similar outcomes in terms of tumour control.

In large tumours, namely those with a diameter > 6 cm, SABR has been poorly investigated and few clinical data are available. As reported by Ong et al., on 18 patients treated with SABR for tumours exceeding 80 cm^3,[22] the risk of symptomatic pneumonitis is higher, and dosimetric parameters such as MLD, contralateral V5, ipsilateral V5 and total lung V5 become essential and should be included as critical dose-volume constraints in planning evaluation. Further clinical data are needed before considering SABR a safe treatment in this patients' population.

3.3. *Late toxicity and quality of life*

SBRT toxicity rate appears very low in all series. Acute toxicities include radiation pneumonitis in a minority of patients (nearly 5%) and skin reactions exclusively when high doses are delivered with a limited number of fields and skin doses exceed 50% of prescription dose. Typical radiological changes after SABR are well documented, and acute findings include diffuse consolidation (in approximately 20–30%), patchy consolidation (10–20%), diffuse ground glass opacities (less than 10%) and patchy ground glass opacities (10–15%). Late radiological changes are very common (approximately 70%), as manifestations of radiation fibrosis, and consist of modified conventional pattern, mass-like pattern or scar-like pattern. These radiological findings apparently do not translate in clinically significant impaired pulmonary function. Ohashi et al. observed no significant changes in Total Lung Capacity, Vital Capacity or FEV1 before or 1 year after SABR for small peripheral lung tumours.[23] Similar results were reported by Stephans et al. in a retrospective study on 92 patients.[24] When the targeted lesions are in close proximity to the chest wall, specific chronic toxicities might include thoracic pain and/or rib fractures; brachial plexopathy is a dose-limiting toxicity in SBRT treatment of apical tumours.

Quality of life has been poorly investigated in patients submitted to SABR. Widder et al. compared 2 prospective cohorts of inoperable patients with T1-2N0M0 primary lung tumours, receiving either 70 Gy in 35 fractions with 3D-CRT or 60 Gy in 3–8 fractions with SABR[25]: Global quality of life (GQoL), physical functioning (PF), and patient-rated dyspnoea were assessed using the respective dimensions of EORTC QLQ-C30 and LC13. GQoL and PF were stable after SABR, while dyspnoea increased after SABR by only 3.2 out of 100 points. Patients self-assessed GQoL has also been studied by Lagerwaard et al.,[26] with questionnaires given at 3, 6, 12, 18 and 24 months after treatment. QOL data were collected prospectively using the EORTC QLQ-C30 in 382 consecutive patients, with 86% judged unfit for surgery, and 14% declining surgery. Data were available for 382 patients at baseline and for 282, 212, 144, 56, and 43 patients at 3, 6, 12, 18, and 24 months post-SABR, respectively. Except for a non-significant decrease in 2–3 points per year in physical functioning, no statistically or clinically significant worsening of any of the QoL functioning or symptom scores at any follow-up time point was observed. Very recently, results of a prospective evaluation of QoL after SABR in 26 patients confirmed these findings.[27]

4. SABR vs. surgery in operable patients

Few clinical reports are available on operable patients refusing surgery and treated with SABR, as surgery is the recognised standard of care. In some retrospective series, few patients refusing surgery were included in separate subgroups. In a Japanese multi-institutional study on 87 operable patients, SABR achieved a LC rate of 92% for T1 and 73% for T2 tumours, with 55 months median follow-up. Five-year OS rates were 72% for stage IA and 62% for stage IB.[28] Similar results were obtained by the group Vrije University group.[29] The local control rate achievable with SABR appears comparable to lobectomy, and the high reported OS rates are mainly due to the lower number of non-cancer related deaths. In a 2010 retrospective study by Grills et al.,[30] 124 patients ineligible for anatomic lobectomy were compared: 55 underwent SABR while 69 underwent wedge resection. Study endpoints were local recurrence (LR), regional recurrence (RR), loco-regional recurrence (LRR), distant metastases (DM), freedom from any failure (FFF), overall survival (OS) and cancer-specific survival (CSS). Respiratory functional tests were similar for both groups. At 30 months, no significant differences were identified in RR, LRR, DM or FFF between the two groups ($p = 0.16$). SABR reduced the risk of LR compared to wedge resection 4% vs. 20% ($p = 0.07$), but OS was higher with wedge. Palma et al.[31] compared surgery and SABR in elderly patients by a matched-pair analysis using population-based data, and found no difference in mortality between the 2 treatments.[31] A total of 120 patients could be matched (60 surgery, 60 SBRT), with a median age of 79 years. Median follow-up was 43 months, and 30-day mortality was 8.3% after surgery and 1.7% after SBRT. OS at 1 and 3 years was 75% and 60% after surgery, and 87% and 42% after SBRT, respectively (log-rank $p = 0.22$). In 2012, Senan et al. presented at the American Society of Clinical Oncology Annual Meeting the results of a study comparing SABR with Video-Assisted Thoracoscopic Surgery (VATS) Lobectomy.[32] The matched cohort consisted of 128 patients with cT1-3N0 NSCLC following SABR ($n = 64$) or VATS-lobectomy ($n = 64$). Median follow-up times were 30 and 16 months, respectively. SABR patients had better LRC rates at 1 and 3 years (96.8% and 93.3% vs. 86.9% and 82.6%, respectively, $p = 0.03$). Three-year PFS, distant recurrence rates and OS did not significantly differ.

Currently there are 2 registered trials recruiting patients and comparing SABR vs. surgery in early stage NSCLC. The first one is from Mayo Clinic, and it is a Phase II randomised trial of sub-lobar resection vs. SABR in high-risk patients (clinicaltrials.gov identifier NCT01622621), with the number of patients alive at 2 years as primary study endpoint and 96 patients to be enrolled. The second one is the Accuray Cyberknife® study, a prospective randomised Phase III trial comparing radiosurgery to surgical resection in stage I NSCLC (STARS study protocol, clinicaltrials.gov identifier NCT00840749), with OS at 3 years as primary endpoint. The Phase III multi-centre randomised trial ROSEL, initiated in 2008 to establish the role of stereotactic radiotherapy in patients with operable stage

IA lung cancer (clinicaltrials.gov identifier NCT00687986) was early terminated due to poor recruitment.

5. Discussion and future perspectives

Twenty-five percent of patients with stage I NSCLC are not eligible for lobectomy due to medical contraindications: in these patients SABR can be now considered the standard choice, even in centrally located tumours and in patients with poor pulmonary function. In the remaining 75% of patients, surgery is the cornerstone of therapy and the best hope for cure. Refinements in surgical techniques and perioperative care reduced treatment-related mortality in the last years, now approximately 1%. Anatomical resection is globally superior to limited surgery, but in small peripheral lesions (<3 cm) sub-lobar resection (rather than wedge resection) can be considered adequate. For central and larger lesions, this approach is not feasible. The few cited retrospective studies investigating a direct comparison between these 2 treatment modalities showed surprising results, as the comparison was in favour of SABR for all endpoints (loco-regional control and survival). As the study by Senan et al. was presented only in abstract form, final results are needed to properly comment its findings. The study by Grills et al. has some flaws that have been extensively discussed by Atorki et al. in the same issue of the Journal of Clinical Oncology in 2010.[33] The two populations differ because the SABR series is prospective, while the surgical one is an historical series. This difference is important as the characteristics of the 2 populations in terms of comorbidities or respiratory function might be non-comparable. Moreover, the surgical arm has a longer follow-up, with a consequent higher probability of late events. Another major criticism could be that wedge resection is not considered the standard surgical procedure, as it is associated with a higher risk of recurrence if compared with lobectomy or with segmentectomy.[34] It has to be noted that in the study by Grills et al.,[30] patients were defined as "marginally operable," a subgroup they refer to as "borderline surgical candidates," with underlying cardiovascular/respiratory problems for which a loss of function – including sublobar anatomic resection or non-anatomic wedge resection would be an issue. In this subgroup, SABR probably offers control rates comparable to surgery, but these results cannot be considered consistent enough to consider SABR an option outside clinical trials. At the same time, as underlined by Robert Timmerman,[35] a prospective Phase III study between anatomic surgery and radiotherapy, two disparate treatment modalities, is difficult to realise in practice, as patients do not easily accept the randomisation, with difficulties in enrolment and early termination. As there is still need of a prospective comparison of two well balanced populations, probably less invasive surgery (for example video-assisted segmentectomy) might be compared vs. SABR in stage I patients, like in the Phase II study by Mayo Clinic. In clinical practice, probably a multidisciplinary approach could be of great value in determining the best treatment strategy in every single patient, taking into account factors like respiratory function, tumours dimension and location, age and comorbidities and offering the proper choice in terms of efficacy and morbidity. In the cited study by Palma et al. dealing with elderly patients[31] (median age 79 years old) SABR, a non-invasive, out-patient treatment had a 30-day mortality rate of <2% in a high-risk population, and this finding can be of particular importance for decision making, as patients are adverse to taking risks that involve the possibility of short-term death. A Markov-model based comparison of surgery vs. SABR for patients aged 65 or older predicted that surgery might confer an overall survival benefit of 2–3% at 5 years over SBRT. However, once operative mortality increases above 4%, the survival advantage of surgery was negated and SBRT preferred.[36]

In conclusion, probably surgery has a potential rival in early stage NSCLC, and in the future SABR might be more used in one patients' subgroup, while surgery will continue to be used in another. At the same time, quality assurance procedures and standardisation of stereotactic treatments in terms of dose prescription and delivery techniques are warranted in order to offer the best available therapy in every Radiation Oncology Department.

Conflict of interest

None declared.

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REFERENCES

1. Smolle-Juettner FM, Maier A, Lindenmann J, Matzi V, Neuböck N. Resection in stage I/II non small cell lung cancer. In: Heide J, Schmittel A, Kaiser D, Hinkelbein W, editors. *Controversies in the treatment of lung cancer*. Basel, Switzerland: Karger; 2010. p. 71–7.
2. McGarry RC, Song G, des Rosiers P, Timmerman R. Observation only management of early stage, medically inoperable lung cancer: poor outcome. *Chest* 2002;**121**:1155–8.
3. Wisnivesky JP, Bonomi M, Henschke C, Iannuzzi M, McGinn T. Radiation therapy for the treatment of unresected stage I–II non-small cell lung cancer. *Chest* 2005;**128**:1461–7.
4. Stephans K. Stereotactic body radiotherapy for Stage I non-small cell lung cancer. *Clev Clin J Med* 2012;**79**(Suppl. 1):S26–31.
5. Cardia J, Calcada C, Pereira H. Treatment of lung cancer in the elderly: influence of comorbidity in toxicity and survival. *Rep Pract Oncol Radiother* 2011;**16**(2):45–8.
6. Noordijk EM, Poest Clement E, Hermans J, Wever AMJ, Leer JWH. Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer. *Radiother Oncol* 1988;**13**:83–9.
7. Mehta M, Manon R. Are more aggressive therapies able to improve treatment of locally advanced non-small cell lung cancer: combined modality treatment? *Semin Oncol* 2005;**32**(2 Suppl. 3):S25–34.
8. Gastelblum P, Roelandts M, van Houtte P. The challenge of local control for non-small cell lung cancer: is it a key issue? *Rep Pract Oncol Radiother* 2004;**9**(4):113–9.
9. Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative

radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012;**13**(8):802–9.
10. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;**27**:3290–6.
11. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, et al. Stereotactic body radiation therapy for early-stage non small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;**75**:677–82.
12. Ricardi U, Filippi AR, Guarneri A, Giglioli FR, Ciammella P, Franco P, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. *Lung Cancer* 2010;**68**:72–7.
13. Koto M, Takai Y, Ogawa Y, Matsushita H, Takeda K, Takahashi C, et al. A phase II study on stereotactic body radiotherapy for stage I non small-cell lung cancer. *Radiother Oncol* 2007;**85**:429–34.
14. Timmermann R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;**303**: 1070–6.
15. Palma DA, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010;**28**(35):5153–9.
16. Takeda A, Kunieda E, Sanuki A, Sanuki N, Aoki Y, Oku Y, et al. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. *Lung Cancer* 2012;**77**:77–82.
17. Herder GJ, Kramer H, Hoekstra OS, Smit EF, Pruim J, van Tinteren H, et al. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. *J Clin Oncol* 2006;**24**:1800–6.
18. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002;**359**:1388–93.
19. Timmerman RD, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;**24**:4833–9.
20. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. *J Thorac Oncol* 2011;**6**:2036–43.
21. Milano MT, Chen Y, Katz AW, Philip A, Schell MC, Okunieff P. Central thoracic lesions treated with hypofractionated stereotactic body radiotherapy. *Radiother Oncol* 2009;**91**: 301–6.
22. Ong CL, Palma D, Verbakel WF, Slotman BJ, Senan S. Treatment of large stage I–II lung tumors using stereotactic body radiotherapy (SBRT): planning considerations and early toxicity. *Radiother Oncol* 2010;**97**(3):431–6.
23. Ohashi T, Takeda A, Shigematsu N, Kunieda E, Ishizaka A, Fukada J, et al. Differences in pulmonary function before vs. 1 year after hypofractionated stereotactic radiotherapy for small peripheral lung tumors. *Int J Radiat Oncol Biol Phys* 2005;**62**(4):1003–8.
24. Stephans KL, Djemil T, Reddy CA, Gajdos SM, Kolar M, Machuzak M, et al. Comprehensive analysis of pulmonary function test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. *J Thorac Oncol* 2009;**4**(7):838–44.
25. Widder J, Postmus D, Ubbels JF, Wiegman EM, Langendijk JA. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. *Int J Radiat Oncol Biol Phys* 2011;**81**(4):291–7.
26. Lagerwaard FJ, Aaronson NK, Gundy C, Haasbeck CJ, Slotma BJ, Senan S. Patient-reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. *J Thor Oncol* 2012;**77**(7):1148–54.
27. Videtic GM, Reddy CA, Sorenson L. A prospective study of quality of life including fatigue and pulmonary function after stereotactic body radiotherapy for medically inoperable early-stage lung cancer. *Support Care Cancer* 2013;**21**(1):211–8.
28. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;**81**:1352–8.
29. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, Slotman BJ, Paul MA, Smit EF. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;**83**(1):348–53.
30. Grills IS, Mangona VS, Welsh R, Chmielewski G, McInerney E, Martin S, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for Stage I non-small-cell lung cancer. *J Clin Oncol* 2010;**28**:928–35.
31. Palma DA, Visser O, Lagerwaard FJ, Belderbos J, Slitrma B, Senan S. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. *Radiother Oncol* 2011;**101**:240–4.
32. Senan S, Verstegen NE, Palma D, Rodrigues G, Lagerwaard FJ, van der Elst A, et al. Stages I–II non-small cell lung cancer treated using either lobectomy by video-assisted thoracoscopic surgery (VATS) or stereotactic ablative radiotherapy (SABR): outcomes of a propensity score-matched analysis. *J Clin Oncol* 2012;**30**(15 Suppl.):7009. ASCO Annual Meeting Proceedings.
33. Altorki NK. Stereotactic body radiation therapy versus wedge resection for medically inoperable Stage I lung cancer: tailored therapy or one size fits all? *J Clin Oncol* 2010;**28**:905–7.
34. Sienel W, Dango S, Kirschbaum A, Cucuruz B, Hörth W, Stremmel C, et al. Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. *Eur J Cardiothorac Surg* 2008;**33**:728–34.
35. Timmerman RD. Surgery versus stereotactic body radiation therapy for early stage lung cancer: who's down for the count? *J Clin Oncol* 2010;**28**:907–8.
36. Louie AV, Rodrigues G, Hannouf M, Zaric GS, Palma DA, Cao GQ, et al. Stereotactic body radiotherapy versus surgery for stage I NSCLC: a Markov model-based decision analysis. *Int J Radiat Oncol Biol Phys* 2011;**81**(4):964–73.