BJR

Received: 3 September 2016 | Revised: 15 November 2016 | Accepted: 21 November 2016

https://doi.org/10.1259/bjr.20160732

Cite this article as:
Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. *Br J Radiol* 2017; **90**: 20160732.

REVIEW ARTICLE

A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer

[1]PATRICK MURRAY, MD, FRCR, [1]KEVIN FRANKS, FRCR and [2]GERARD G HANNA, PhD, FRCR

[1]Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[2]Centre for Cancer Research and Cell Biology, Queen's University of Belfast, Belfast, Northern Ireland, UK

Address correspondence to: Dr Patrick Murray
E-mail: *patrick.murray@nhs.net*

ABSTRACT

Stereotactic ablative body radiotherapy (SABR) describes a radiotherapy (RT) technique where high doses of radiation are precisely delivered to an extracranial target within the body, using either a single fraction of RT or using multiple small numbers of fractions. SABR has now become the standard of care treatment for patients with early-stage non-small-cell lung cancer (NSCLC) for whom surgery is not appropriate. This systematic review considers the evidence supporting the use of SABR in early-stage NSCLC, reported toxicity rates, the use of SABR in centrally located NSCLC, the use of SABR as salvage therapy following surgery or RT, and future potential drug combinations with SABR.

INTRODUCTION

Stereotactic ablative body radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), has been defined by the American Society of Radiation Oncology and the American Society of Radiology as an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions.[1] The UK National Radiotherapy Implementation Group report defines SBRT as the precise irradiation of an image-defined extracranial lesion, using a high total radiation dose delivered in a small number of fractions (hypofractionation).[2]

Even with the increasing number of patient outcome data being published on SABR in early-stage (ES) non-small-cell lung cancer (NSCLC), phase III evidence comparing the treatment against surgery and conventional radiotherapy (RT) is limited. The most compelling evidence for SABR in extracranial sites is available in early lung cancer where systematic reviews have shown 2-year survival rates and local control as high as 70% and 90%, respectively.[3]

Despite this, SABR is now a recognized standard of care in early peripherally located inoperable lung cancer. Use of SABR treatment can produce local control rates which are similar to surgery, with low reported toxicity and patient convenience due to the reduced number of visits required for treatment, when compared with conventionally fractionated RT (3–8 compared with 20–33 treatment visits). There is also an increasing evidence base/clinical experience for the use of SABR in other primary cancer sites such as the prostate, pancreas, liver (metastases and primary hepatocellular carcinoma) and spinal metastases, and for oligometastatic disease.[4–9]

In order to deliver ablative doses of RT to tumours, it is necessary to accurately identify both the target and the surrounding organs at risk (OARs), in addition to accommodating inter- and intrafraction movement of both.[10] The three key components required to achieve this involve patient immobilization, on-treatment image guidance and on-treatment patient motion management.[11] With the use of four-dimensional CT scanning for planning of the tumour motion, and image guidance with cone beam CT during treatment delivery, uncertainties/errors have been reduced significantly, thus increasing the confidence in delivering hypofractionated radiation precisely.[12] In addition, the ability to quantify individual patient's tumour motion can allow patient-specific margins.[13] For tumours with observed significant motion, different methods have been developed to either limit motion (*e.g.* abdominal compression/breath-hold techniques) or to track the tumour with respiratory gating or real-time tumour localization using extra-anatomical or implanted fiducials.[10]

Further advances in planning such as the use of volumetric arc therapy or numerous non-coplanar beams allow increased conformity of dose to the tumour and hence better sparing of OARs. The introduction of flattening filter-free linear accelerators (linacs) with high dose rate delivery means that SABR treatments can be delivered as quickly as standard conventional RT.[14] This is clearly beneficial and more comfortable for patients and means that there are less concerns regarding patient stability during radiation delivery.

In the UK, SABR doses for NSCLC aim to deliver between 54 and 60 Gy in three to eight fractions delivered on an alternate-day basis, depending on the proximity of the OARs.[15] Where the tumour is close to the chest wall, patients are treated with five fractions to reduce the risk of late rib fractures and chest wall toxicity. Tumours close to the vertebral column, brachial plexus and major vessels are usually treated with eight fractions, with the three-fraction regimen mainly used for tumours surrounded by lung parenchyma only with no concerns of radiation toxicity to other OARs. Tumours that lie within 2 cm in the axial plane of the main airways are presently not routinely treated with SABR in the UK outside clinical trials due to increased toxicity seen in the dose escalation studies by Timmerman et al.[16]

Search strategy

PubMed, OVID and Web of Science were searched encompassing the search terms early stage, non-small cell lung cancer and stereotactic RT/SABR/SBRT, resulting in over 2400 articles. The search period was from January 2000 to April 2016. The search parameters were filtered using the terms trials, outcomes, surgery and English. The resulting articles were then selected by assessing the article for relevance, including patient cohorts undergoing SABR, and toxicity of SABR and presenting overall survival (OS) and local control estimates.

Treatment options for early-stage non-small-cell lung cancer

ES-NSCLC is defined according to the TNM seventh edition as T1 (<3 cm) and T2 (<7 cm) lung cancer, with metastatic disease in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary lymph nodes, including direct extension (N1),[17] however, this review focuses on N0 disease. When assessing a patient for optimal treatment of NSCLC, it is important to take into account patient fitness, comorbidities and wishes.[18] In the UK, staging is completed with fluorine-18 fludeoxyglucose positron emission tomography CT (PET-CT) to exclude metastatic disease, in addition endoscopic or surgical assessment of equivocal mediastinal nodes is essential.[19]

The radical treatment options include surgical resection and radical RT, including SABR and conventional fractionated external beam RT (EBRT). Other ablative methods such as radiofrequency ablation are also used.[20,21] Surgical resection is the current treatment of choice for ES-NSCLC.[20] Surgery has the obvious advantage of pathological confirmation and further mediastinal staging; however, the increased morbidity and mortality associated with surgical intervention makes alternative treatments desirable. The use of minimally invasive video-assisted thoracoscopic surgery has the potential to reduce morbidity/mortality in patients at higher risk of surgical morbidity for both lobectomy and sublobar resections.[22]

For those patients who are too frail for surgical intervention, non-surgical management is warranted because the survival of untreated Stage I NSCLC is poor and population-based analysis over time has shown a trend for improved survival with increased active treatment rates.[23,24] In patients who are advised or decide against surgery, the treatment options include non-invasive RT, invasive ablative therapies, systemic therapy or best-supportive/palliative care. There is a paucity of randomized evidence examining these treatments, and most publications are retrospective heterogeneous case series. Despite this, SABR has been adopted widely across the world. In the UK, the delivery of both conventional EBRT and SABR for ES lung cancer has recently been audited by McAleese et al.[25] They found high levels of conformance with quality standards, including respiratory compensation, and onset verification with cone beam image-guided RT in the UK.

Randomized evidence for SABR vs more conventionally fractionated RT regimes is emerging. The Phase II Stereotactic Precision And Conventional Radiotherapy Evaluation (SPACE) study (http://clinicaltrial.gov identifier NCT01920789) has been presented in abstract and randomized 102 patients to SABR (66 Gy in 3 fractions and 45 Gy at the periphery) or conventional RT (70 Gy in 35 fractions). No difference in local control was discovered.[26] They found that conventional treatment was associated with a higher risk of grade 1–2 toxicity (oesophagitis and pneumonitis) and with worse treatment compliance; in addition, the SABR group may have had more unfavourable prognosticating factors (T_2 tumours 47% *vs* 25%; male 45% *vs* 36%). The Trans Tasman Radiation Oncology Group (TROG) CHISEL Phase III trial comparing SABR to conventional RT is currently recruiting patients and is close to completing recruitment.[27]

What is SABR and how is it delivered?

SABR, a synonym for SBRT, has been an "external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions".[28] Stereotaxis was initially defined when treating brain lesions, using an external three-dimensional frame directly fixed to the skull and allowing accurate image-guided surgery using Cartesian coordinates. This allowed development of stereotactic radiosurgery, or Gamma Knife®, using multiple beamlets to ablate metastatic deposits within the brain. Radiosurgery is defined as ablative RT dose in a single fraction, whereas fractionated courses were initially defined as SBRT, and now SABR.

For lung SABR, a rigid frame is not practicable therefore for the initial development of SABR in Karolinska Institute, Sweden, a stereotactic body frame was developed.[29–31] With the advent of sophisticated image-guided RT, the use of stereotactic body frame for target localization has waned, although it is still used for immobilization and abdominal compression to restrict breathing motion. With the small margins used in SABR, target identification and delineation is crucial. To confidently plan lung SABR, planning margins should be individualized to each patient. The most common method to achieve this is a four-dimensional CT

planning scan, where the tumour motion is assessed through multiple phases of breathing. A standard free-breathing three-dimensional CT alone can produce movement artefact, especially with small mobile lung cancers. Underberg et al[32] and Bradley et al[33] have compared helical, average-intensity-projection and maximum-intensity-projection four-dimensional CT for use in lung SABR. The authors found maximum-intensity projection to be superior in defining full motion gross tumour volume (GTV). The motion GTV can be checked against the other breathing phases, and a composite GTV delineated. In SABR, there is no margin given for clinical target volume, therefore the composite GTV/motion GTV is equivalent to the internal target volume. A margin is then applied to allow for setup errors (usually 5 mm) to create the planning target volume (PTV).[34]

Multiple treatment systems have been used to treat patients undergoing SABR. These include the robotic linac (CyberKnife®, Accuray, Sunnyvale, CA), conventional gantry-based linac (Elekta®, Stockholm, Sweden. Varian, Salt Lake City, UT), TomoTherapy® (Accuray) and MRI-cobalt linac (ViewRay™, Oakwood Village, OH).[35,36] The dose delivered is key to the high local control rates seen with SABR in lung cancer. Previous studies have demonstrated that a biologically equivalent dose (BED) for tissue with an alpha/beta ratio of 10 of >100 gives the best chance of local tumour control.[37,38] Koshy et al[39] examined the US National Cancer Database investigating whether even higher doses are more effective. Of 498 patients who underwent SABR for NSCLC between 2003 and 2006, the five most common doses were 60 Gy/3# (34%), 48 Gy/4# (16%), 54 Gy/3# (10%), 45 Gy/3# (10%) and 48 Gy/3# (4%) which represent calculated BEDs of 180, 105.6, 151.2, 112.5 and 124.8 Gy, respectively. They found a statistically significant improvement in OS in patients with T_2 tumours and a calculated BED of >150 Gy.

Lung SABR: reported outcomes and toxicity

There are an increasing number of studies reporting patient outcomes, dosimetry and toxicity following treatment of ES lung cancer with SABR. Table 1 illustrates the cross section of articles in the current literature. These articles report SABR outcomes including the details of 4570 patients in total. The group is heterogeneous and have had a variable number of different dose-fractionation treatments especially in the earlier articles. Gross analysis of the combined reported OS which was reported in 15 articles was 38.44 months, with an average follow-up of 29.4 months (although in three articles, the median survival was not reached at the time of analysis). The OS and local control rates are listed in Table 1. The OS rates in the SABR cohort should be viewed in the context that the vast majority of patients were medically inoperable.

Nagata et al[40] examined the outcomes of patients undergoing SABR for lung cancer in the Japanese Clinical Oncology Group (JCOG) 0403 study. They stratified 104 inoperable patients and 65 operable patients who underwent SABR for T1N0M0 pathologically proven NSCLC. The 3-year OS for inoperable patients was expected at 50% and the actuarial value found was 59.9% [95% confidence interval (CI) 49.6–68.8%]. As expected, the operable patient group was younger and had less comorbidity and a higher 3-year OS of 76.5% (95% CI 64–85.1%). As with other groups, the improvement in OS of patients with ES lung cancer compared with conventional fractionated RT puts forward the case for SABR as the first-line treatment for inoperable ES-NSCLC and as a potential alternative to surgery in this group (Table 2).

The toxicity of SABR appears to be well documented within the articles below (Table 3); 30 articles reported toxicity outcomes. Gross grade 5 toxicity appears to be rare, especially in peripheral tumours, with 11 patient deaths reported in these articles, and possibly attributable to SABR, 1 patient was thought to have underlying interstitial lung disease.[43] The final study patient reported as grade 5 toxicity had no data regarding the cause of death, and the patient died within 30 days of treatment.[46]

Grade 3 and 4 toxicity reports range between 2.7% and 27% of patients. Pneumonitis, dyspnoea, chest pain and pneumonia being the most commonly reported toxicity. These were usually self-limiting, but one patient who died had a grade 4 pneumonitis initially.[43]

Grade 1 and 2 toxicities were very common and reported in up to 100% of cases, especially grades 1–2 fatigue. Many articles have only reported grade 3 and above toxicity due to the self-limiting nature of grades 1–2 toxicities.

Table 1. Summary of the literature reporting stereotactic ablative body radiotherapy outcomes listed below for early-stage lung cancer reporting overall survival (OS) and local control (LC)

Survival reported	No. studies reporting	Average [mean (%), range (%)]
Median survival (months)	15	38.44 (F/u av 29.4) (27.3–57)
1 year OS	15	87 (78–100)
2 year OS	18	82.9 (48–96)
3 year OS	22	59.6 (32–95)
4–5 year OS	8	39.6 (17–83)
1 year LC	10	92.7 (64.7–100)
2 year LC	16	89.9 (77.4–98.5)
3 year LC	19	86.7 (40–97.6)
4–5 year LC	5	89.6 (83–95)

F/u av, follow-up median average.

Table 2. Outcomes following stereotactic ablative body radiotherapy (SABR) in the primary treatment of early-stage non-small-cell lung cancer

Author	Type of study	Technique/ dose	No. Pts	Med follow-up (months)	OS	Local control	Med survival
Haseltine et al 2016[41]	Retrospective analysis of central SABR	IMRT 60 Gy/5# 50 Gy/5# 48 Gy/4# 45 Gy/5#	108	22.7 (range 1.5–71.5)	63.9% at 2 years	77.4% at 2 years	Not reported
Shaverdian et al 2016[42]	Retrospective analysis	IMRT 54 Gy/3# 50 Gy/4#	118	28.9	77% at 3 years	97% at 3 years	Not reported
Navarro-Martin et al 2016[43]	Phase II trial	IMRT/VMAT 54 Gy/3#	42	42 (range 1.44–66)	92% at 1 year 75% at 2 years 66% at 3 years	92% at 3 years	57 months
Chiang et al 2016[44]	Matched cohort comparison	SABR *vs* AH 50–52 Gy/4# 50 Gy/5#	192	32.5 (range 0.3–62.6)	72.4% at 3 years	89.3% at 3 years	Not reached, at 60 months
Chang et al 2015[45]	Meta-analysis of STARs and ROSEL Phase III trials	Arc/IMRT 54 Gy/3# 50 Gy/4# Cent. or 60 Gy/5#	31	40.2 (IQR 23–40.7)	100% at 1 year (95% CI 100–100%) 95% at 3 years (95% CI 85–100%)	96% at 3 years	Not reached at 60 months
Murray et al 2015[46]	Prospective analysis	Arc/IMRT 54 Gy/3# 55 Gy/5# 60 Gy/8#	273	19.63	78% at 1 year 54.9% at 2 years 38.6% at 3 years	95.7% at 3 years	27.3 months (95% CI 22.3–33.2)
Nagata et al 2015[40]	Prospective analysis of inop and op patients	Arc/IMRT 48 Gy/4#	164 100 inop 64 op	47 (range 39–57)	Inop—at 3 years–59.9% (95% CI 49.6–68.8%) Op—at 3 years–76.5% (95% CI 64–85.1%)	Inop—at 3 years–87.3% Op—at 3 years–85.4%	Not reported
Gillespie et al 2015[47]	Review of single centre published data	IMRT 48 GY/4# 50 GY/5#	320	23.75 (range 17–28)	64.25 2 years	95% at 2 years	Not reported
Chang et al 2012[48]	Retrospective analysis	IMRT	130	26 (range 6–78)	93% 1 year 78.2% 2 years 65.3% 3 years	98.5% 2 years	60 55 inop Not reached for borderline
Abelson et al 2012[49]	Retrospective review	Arc/IMRT 60 Gy/3# 54 Gy/3# 50 Gy/4# 40 Gy/4#	54	13.2 (range 3.2–60.5)	87% at 1 year 73% at 2 years	100% 1 year 87% 2 years	Not reached
Taremi et al 2012[50]	Prospective analysis	IMRT 48 Gy/4# 54/3# 60 Gy/3#	108	19.1 (range 1–55.7)	84% at 1 year (95% CI 76–90%) 30% at 4 years (95% CI 15–46%)	92% at 1 year (95% CI 86–97%) 89% at 4 years (95% CI 81–965)	32 months

(Continued)

Table 2. (Continued)

Author	Type of study	Technique/ dose	No. Pts	Med follow-up (months)	OS	Local control	Med survival
Senthi et al 2012[51]	Retrospective analysis	IMRT/VMAT 54–60 Gy/3# 55–60 Gy/5# 60 Gy/8#	676	32.9 months (IQR 14.9–50.9)		4.9% (2 years LRR) (95% CI 2.7–7.1) 10.5% (5 years LRR) (95% CI 6·4–14·6)	40.7 months (95% CI 34.7–46.8)
Palma et al 2012[52]	Prospective analysis	Arc/IMRT 60 Gy/3#–8# PB 54 Gy/3#, 55 Gy/5#, or 60 Gy/8# with AAA algorithm	176	21	79% at 1 year 47% at 3 years 25% at 5 years	89% at 3 years	32 months
Bongers et al 2011[53]	Prospective analysis	IMRT 60 Gy/3# 60 Gy/5# 60 Gy/8#	500	33 (13–86)	53.1% at 3 years	90.4% at 3 years	–
Bral et al 2011[54]	Phase II	IMRT 60 Gy/3# 60 Gy/4#	40	19.1 (range 5–33)	52% at 2 years (SE- 11%)	97% at 1 year (SE 5%) 84% at 2 years (SE 9%)	–
Andratschke et al 2011[55]	Retrospective analysis	Arc/IMRT 30–45 Gy/3# 30–45 Gy/4–5#	92	21 (range 3–87)	38% at 3 years 17% at 5 years	89% at 1 year 83% at 3 years 83% at 5 years	29 months
Haasbeek et al 2011[56]	Prospective analysis of central lesions with SBAR	IMRT	63	35	85.7% at 1 year 69% at 2 years 49.5% at 5 years	94.8% at 1 year 92.6% at 2 years 92.6% at 5 years	–
Haasbeek et al 2010[57]	Prospective analysis (>75 years)'	IMRT 60 Gy/3# 60 Gy/5# 60 Gy/8#	193	12.6 (range 3–52)	85.7% at 1year 45.1% at 3years	89.3% at 3 years	32.5 months
Timmermann et al 2010[58]	Phase II	IMRT 60 Gy/3# (54/3# after heterogeneity correction)	55	38.7 (range 4.8–49.9)	55.8% at 3 years (95% CI 41.6–67.9)	97.6% at 3 years	48.1 months (95% CI 29.6—not reached)
Hamamoto et al 2010[59]	Prospective analysis primary *vs* metastatic lung lesions	IMRT 48 Gy/4#	52	14 (range 3–34)	96% 1 year and 2 years	91% at 1 year 88% at 2 years	–
Grills et al 2010[60]	Retrospective comparison study	IMRT 48 Gy/4# 60 Gy/5#	58	30	72% at 30 months	96% at 30 months	–
Ricardi et al 2010[61]	Phase II	IMRT 45 Gy/3#	62	28 (range 9–60.7)	69.2% at 2 years 57.1% at 3 years	92.7% at 2 years 87.8% at 3 years	–
Bradley et al 2010[33]	Prospective analysis	IMRT Med 54 Gy/3# 45 Gy/5#	91	18	80% at 1 year 72% at 2 years	2 years 86%	38 months

(Continued)

Table 2. (Continued)

Author	Type of study	Technique/ dose	No. Pts	Med follow-up (months)	OS	Local control	Med survival
Crabtree et al 2010[62]	Retrospective analysis	SBRT 54 Gy/3# to 80 or 85% isodose	76	19	32% at 3 years	89% at 3 years	–
Baumann et al 2009[63]	Phase II	IMRT 45 Gy/3#— 67% isodose to PTV ~66 Gy/3#	60	35 (range 4–47)	65% at 2 years	92% at 2 years	40.6 months
Fakiris et al 2009[64]	Phase II	IMRT 60 (T_1)-66 (T_2) Gy/3# to 80% isodose to >95% PTV	70	50.2 (range 1.4–64.8)	42.7% at 3 years (95% CI 31.1–54.3%)	88.1% at 3 years	32.4 months
Lagerwaard et al 2008[65]	Prospective analysis	IMRT 60 Gy/3# T_1 (43%) 60 Gy/5# chest wall/T_2 (45%) 60 Gy/8# Central (12%) to 80% PTV isodose	206	12 (range 3–55)	64% at 2 years	98% at 1 year 93% at 2 years	34 months
Chen et al 2008[36]	Retrospective analysis	Body Gamma-Knife® 48–64 Gy in 3.6–8 Gy# daily. BED 71.8–115.2 GY	65	47 months (range 25–76)	92.3% at 1 year 80% at 2 years 57.3% at 3 years 35.1% at 5 years	–	39 months
Onishi et al 2007[37]	Retrospective analysis	Arc/IMRT 1–14# 4.4–35 Gy/# 30–84 Gy Med BED 111 Gy (range 57.6–180 Gy)	257	38 (range 2–128)	56% at 3 years (95% CI 50.2–63.5%) 47.2% at 5 years (95% CI 38.7–53.5)	86% (3 years)	–
Koto et al 2007[66]	Phase II	Arc/IMRT 45 Gy/3# 60 Gy/8#	31	32 (range 4–87)	71.7% at 3 years	T_1—77.9% at 3 years T_2—40% at 3 years	–
Hoyer et al 2006[67]	Prospective analysis	IMRT 45 Gy/3# to PTV 67% isodose	40	28.8	48% at 2 years	85% at 2 years	-
Nyman et al 2006[68]	Prospective analysis	IMRT 45 Gy/3# to 100% isodose at PTV	45	43 (range 24–74)	80% at 1 year 55% at 3 years 30% at 5 years		39 months
Nagata et al 2005[69]	Phase I/II	Arc/IMRT 48 Gy/4# to isocentre	45	Ia—30 (range 6–71) Ib—22 (range 6–61)	93% at 1 year 72% at 2 years 83% at 3 years 83% at 5 years	100% at 1 year 95% at 5 years	Not reached

(Continued)

Table 2. (Continued)

Author	Type of study	Technique/ dose	No. Pts	Med follow-up (months)	OS	Local control	Med survival
McGarry et al 2005[70]	Phase I study —dose escalation	IMRT 24 Gy/3# to 80% isodose at PTV escalated to 72 Gy/3#	47	15.2	64% at 3 years	64.7% at 1 year	–
Zimmermann et al 2005[71]	Prospective analysis	Arc/IMRT 24–37.5 Gy/ 3–5# 69% 37.5 Gy/ 3# to 60% isodose	30	18 (range 6–38)	80% at 1 year 75% at 2 years	100% at 1 year 83% at 2 years	–

AAA, Analytical Anisotropic Algorithm; AH, accelerated hypofractionation; Arc, Arc therapy; BED, biologically equivalent dose; CI, confidence interval; IMRT, intensity-modulated radiotherapy; inop, inoperable; IQR, interquartile range; LRR, local relapse rate; Med, median; op, operable; OS, overall survival; PB, pencil beam algorithm; Pts, patients; PTV, planning target volume; VMAT, volumetric modulated arc therapy; SE, Standard Error.

SABR *vs* surgery in NSCLC

Chang et al[45] recently published a pooled analysis of two randomized trials in the USA and Netherlands (ROSEL and STARS) comparing SABR with lobectomy. Although small numbers, with 31 patients randomized to SABR and 27 patients to surgery, the results and conclusions drawn raised interest on publication. The authors advocate SABR for ES lung cancer even in the operable group of patients. They report an estimated 3-year OS of 95% (95% CI 85–100) in the SABR group compared with 79% (95% CI 64–97%) in the surgical arm, with a hazard ratio of 0.14 (95% CI 0.017–1.19), statistically significant log rank $p = 0.037$. There was no significant difference in recurrence-free survival. This report is the first of randomized data between the two treatment options, but interpretation of the data is severely limited by failure to complete recruitment in either study and by small patient numbers. Furthermore, the apparent outlier of surgical morbidity and perioperative mortality of 1 patient in a small cohort of 27 may be misleading. The surgical arm also had a significant proportion of three (11%) patients who did not undergo a lobectomy, confounding the results further.

The other studies listed in Table 4 are attempts at matched pair retrospective analyses. The larger studies have shown improved OS in the surgery groups; however, these are usually confounded by older patients with more comorbidities in the SABR arms due to inoperability.[72–76]

van den Berg et al[78] report outcomes of 340 patients treated with surgery ($n = 143$) or SABR ($n = 197$) for ES lung cancer. They found no difference in OS, local recurrence or distant recurrence. However, they did find that locoregional recurrence was significantly more frequent with SABR (adjusted sub-hazard ratio 2.51; 95% CI: 1.10–5.70; $p = 0.028$). Verstegen et al[77] matched two groups of patients with ES lung cancer using propensity scores based on patient demographics such as cTNM stage, age, gender, Charlson comorbidity score, lung function and performance score. They retrospectively matched 64 patients who received SABR to the same number of patients who underwent a video-assisted thoracoscopic surgery lobectomy. They found superior local regional control, but no difference in OS. The difference between the two publications may be the definitions of local and locoregional control, especially regional lymph node recurrence. van den Berg et al defined any mediastinal lymph node recurrence as locoregional failure, whereas Verstegen et al only defined ipsilateral lymph node recurrence as locoregional.

Grills et al[60] have an earlier report of outcomes between lung SABR or wedge resection. In the non-randomized group comparing SABR and wedge resection at 30 months, they found OS was improved in the surgical group (87% *vs* 72%, $p = 0.01$), however, cause-specific survival was equal. SABR was superior for local (5% *vs* 24%, $p = 0.05$), locoregional (5% *vs* 29%, $p = 0.03$) and regional relapse (0% *vs* 18%, $p = 0.07$).

The data supporting the use of SABR in ES lung cancer appear to be strengthening. Nagata et al[40] reported their outcomes of SABR in operable patients, which were improved compared with inoperable patients.

Further robust, appropriately powered trials are required to accurately compare the two treatment groups. In the UK, the SABRTooth Trial has recently opened.[79] This is a feasibility study to randomize "high-risk" operable patients with ES-NSCLC to surgery or SABR, depending on their perioperative risk. If recruitment is successful, it will extend into a Phase II study. In addition, the "Stablemates" trial (chief investigator Robert Timmerman) in the USA is also directly randomizing high-risk patients to SABR or sublobar resection,[80] and the Veterans Affairs lung cancer surgery or stereotactic RT study (chief investigator D Moghankaki) is due to open in the very near future.

SABR for central lesions in lung cancer

Central ES lung cancer tumours are defined by their proximity, usually within 2 cm, to central organs at risk, such as the proximal bronchial tree, oesophagus, great vessels, spinal cord or heart/pericardium. Earlier studies identified the increased risk of

Table 3. Lung stereotactic ablative body radiotherapy toxicity

Study	Scale	Gd 1	Number	Gd 2	Number	Gd 3	Gd 4+
Navarro–Martin et al 2016[43]	CTCAE V3	89% Gd 1 acute 100% chronic Gd 1 Pneumonitis (68%)	34 42 26	16% acute 2 pleuritis 1 dyspnoea 1 cough 1 dermatitis 1 pneumonitis 18% chronic Dyspnoea Pneumonitis Cough Dermatitis Anorexia	6 7	1 Gd 3 pneumonitis (5%) 1 chronic AF and dyspnoea	1 Gd 5 (developed late from Gd 3 toxicity −2.65)—Pt thought to have subclinical ILD
Heseltine et al 2016[41]	Not reported					13 Gd 3+ events (12%) Significantly more Gd 3+ events in those pts with GTV <1 cm from PBT	4 potential Gd 5 events 2 pneumonia 2 pulmonary haemorrhage (both previous exposure to bevacizumab)
Shaverdian et al 2016[42]	CTCAE v3	88% reported no ≥ Gd 2 toxicity		≥Gd 2 toxicity in 12% Pneumonitis (9%) Rib# (3%)	8 3	2 pneumonitis Gd 3	No Gd 3+ toxicity reported
Chang et al 2015[45]	NCI-CTC V3					SABR 3 pts (10%) 2 cough/dyspnoea 3 Chest wall pain 1 fatigue and rib# Surgery 12 pts (44%)4 Gd 3 dyspnoea 2 Gd 3 pneumonia 4 Gd 3 chest pain	No Gd 4 or above in SABR arm Sx arm—1 Gd 5 death from surgical complications 12 Gd 3–4 Surgery 12 pts (44%) 1 Gd 4 dyspnoea
Murray et al 2015[46]	NCI-CTC V4					Acute—1 Gd 3 dyspnoea 4 Gd 3 fatigue Delayed (>6 weeks, <12 weeks) 1 Gd 3 cough 10 Gd 3 dyspnoea 3 Gd 3 fatigue 1 Gd 4 fatigue Late (>12 weeks) 8 Gd 3 dyspnoea 1 Gd 3 pneumonitis	No grade 4 toxicity during tx 1 pt died within 30 days of SABR, but CoD unknown; had been asymptomatic (potential Gd 5) 1 patient died at 12 weeks from COPD
Nagata et al 2015[40]	CTCAE V3					Inop—Gd 3 11 (10.6%) Dyspnoea 10 Hypoxia 8 Pneumonitis 8	No Gd 5 toxicity reported Gd 4 inop—2 pts

(Continued)

Table 3. (Continued)

Study	Scale	Gd 1	Number	Gd 2	Number	Gd 3	Gd 4+
						Chest pain 2 Cough 1 Op—Gd 3 4 (6.2%) Dyspnoea 2 Hypoxia 1 Pneumonitis 1	2 Dyspnoea 1 Hypoxia 1 pneumonitis No Gd 4 toxicity in operable pts.
Gillespie et al 2015[47]	CTCAE V2			Over 3 studies Acute Gd 2 range 8.7–19%		Gd 3 toxicity range 0–2%	No Gd 4 or 5 toxicity reported
Palma et al 2012[52]	CTCAE V3	Common Gd 1/2–55% Fatigue Dyspnoea/ cough Chest wall pain Nausea/ appetite	55 24 18 10			Acute—1 pt developed Gd 3 pneumonitis late (>6 weeks)—2 pts Gd 3 pneumonitis 2 pts rib# 1 pt haemoptysis	No Gd 4 or 5 toxicity reported
Chang et al 2012[48]	CTCAE v3	Oesophagitis 1.5%	2	Chest wall pain (8.5%) Pneumonitis (9.2%)	12 15	1 Chest wall pain Gd 3 (0.8%) 8 Dermatitis Gd 2/3 (6.2%) 3 Pneumonitis Gd 3 (2.3%)	No reported Gd 4 or 5 toxicity
Taremi et al 2012[50]	CTCAE V3	29% denied any acute toxicity 31% denied late toxicity		Late—rib# (14.8%) Mostly asymptomatic	16	Acute Gd 3–4 (3.7%) 1 Fatigue 2 Dyspnoea 1 Chest wall pain Late Gd 3 (>3 months)—6 pts 3 rib# 2 Dyspnoea 1 Pneumonia	No grade 4 or 5 toxicity reported
Bongers et al 2011[53]	CTCAE v4			Chest wall pain Gd 1–2 (5.4%)	27	5 Chest wall pain Gd 3 (1%) 8 rib# (1.6%)	Not reported
Bral et al 2011[54]	NCI-CTC V3/RTOG			Dyspnoea (12%)	2	Gd3—8 pts (20%) Pneumonitis 2 (12%) Cough 2 (12%) Stenosis 1 (10%)	
Andratschke et al 2011[55]	NCI-CTC V3	Radiological pneumonitis (34.8%)	32	Pneumonitis (13%)	12	Pneumonitis 2 (2.2%) Dyspnoea 7 (7.3%)	Gd 4 dyspnoea —4 (4.1%)
Haasbeek et al 2011[56]	CTCAE v3	Gd 0 or 1 acute Gd 0 or 1 late	56 50	Gd 2 acute (10%) Grade 2 late (14%)	6 9	1 Gd 3 acute (2%) 4 Gd 3 late (6%)	No Gd 4 or 5 toxicity reported
Haasbeek et al 2010[57]	RTOG acute toxicity RTOG/	116 patients reported no acute toxicity		32% fatigue		Late—4 pts Gd 3–4 pneumonitis (2.1%) 3 pts rib# (1.6%) Chest wall pain 5	No grade 5 toxicity reported

(Continued)

Table 3. (Continued)

Study	Scale	Gd 1	Number	Gd 2	Number	Gd 3	Gd 4+
	EORTC late toxicity					pts (2.6%) 3 pts non-malignant effusion	
Timmerman et al 2010[58]	NCI-CTC V3					7 pts reported Gd 3 (12.7%) 2 reduced FEV1 2 Hypoxia 2 Pneumonitis 3 PFTS altered 2 pts reported Gd 4 (3.6%) 1 hypocalcaemia 1 Pulmonary	No Gd 5 toxicity reported
Grills et al 2010[60]	NCI-CTC V3	Chest wall pain— 9 (9.8%)		9% pneumonitis 6% rib# 4% chronic dyspnoea	Rib# 3 (3.3%)	2% pneumonitis Dyspnoea Myositis	
Ricardi et al 2010[61]	RTOG acute and late	Fatigue 15% Skin erythema 10% Dyspnoea and cough 10% Chest pain 7%		3 pts had chronic pain (4.8%)		2 patients had Gd 3 radiation pneumonitis (3.2%)	
Bradley et al 2010[33]	CTCAE V3			3 pts Gd 2 pneumonitis 4 pts rib pain or #		1 pt developed brachial plexopathy	
Baumann et al 2009[63]	NCI-CTC V2					16 (28%)	1 Gd 4 dyspnoea No Gd 5
Fakiris et al 2009[64]	NCI-CTC V2					Gd 3 pneumonia 1 Pleural effusion 2 Pts 2 Gd 4 apnoea	Gd 5 (possible) Pneumonia 3 Haemoptysis 1 Resp failure 1
Lagerwaard et al 2008[65]	–	51 % No toxicity Fatigue 31% Chest wall pain 12% Nausea 9% Dyspnoea 6% Cough 6%				Gd 3–6 pts (3%)—pneumonitis 4 rib fractures 3 chronic pain	
Chen et al 2008[36]	NCI-CTC/ RTOG	28% had no reported toxicity 7 pts Gd 1 bone marrow toxicity		3.1% Gd 2 toxicity Bone marrow		No Gd 3 toxicity	
Onishi et al 2007[37]	NCI-CTC v2	Cough/ dyspnoea Gd 1	28 (10.9%)	Gd 2 pneumonitis —14 pts (5.4%)		Gd 3–6 pts pneumonitis requiring O2 3 oesophagitis 3 pts skin reaction (1.2%) 4 pts rib# (1.6%)	

(Continued)

Table 3. (Continued)

Study	Scale	Gd 1	Number	Gd 2	Number	Gd 3	Gd 4+
Koto et al 2007[66]	NCI-CTC v3	24 pts Gd 1 pneumonitis		Gd 2 pneumonitis 3 pts		Gd 3 pneumonitis in 1 pt 1 pt lobar collapse	
Hoyer et al 2006[67]	WHO PS and Tox	8 Gd 1–2 dyspnoea 6 Gd 1–2 nausea 14 Gd 1–2 pain				3 Gd 3 dyspnoea 2 Gd 3 pain 1 Gd 4 dyspnoea	1 death due to pneumonia felt unrelated to treatment
Nyman et al 2006[68]	RTOG acute/late	9 pts skin reaction (20%) oesophagitis in 4 pts (9%) 4 pts had transient chest pain 4 pts had pneumonia/ infections 3 pts had cough	51% did not have any toxicity			2 pts had rib# 3 pts atelectasis	No pneumonitis reported
Nagata et al 2005[69]	NCI-CTC v2	10 pts Gd 1 cough or malaise (22%)		2 pts Gd pneumonitis		No Gd 3 toxicity reported	
McGarry et al 2005[70]	NCI-CTC	4 Gd 2 pts—bronchitis, pericardial effusion, pneumonitis, distant pneumonia				6 Gd 3 pts—2 pneumonitis, tracheal necrosis, hypoxia, dermatitis, pericardial effusion	1 pt Gd 4 pneumonitis 72 Gy/3#
Zimmermann et al 2005[71]	CTC-RTOG RTOG late	Gd 1–2—fatigue 20 % 1 pt pain, fever, pneumonia. 8 pts Gd 1, 5 pts Gd 2 pneumonitis 1 nausea and dermatitis Gd 1				1 Gd 3 pneumonitis (3%)	

AF, atrial fibrillation; CoD, cause of death; COPD, Chronic Obstructive Pulmonary Disease; CTC, common toxicity criteria; FEV1, forced expiratory volume in 1 second; Gd, grade; ILD, interstitial lung disease; inop, inoperable; NCI, national cancer institute; op, operable; PBT, proximal bronchial tree; PFTs, pulmonary function tests; Pt, patient; resp, respiratory; rib#, rib fracture; RTOG, Radiation Therapy Oncology Group; Sx, surgical; tx, treatment; WHO, World Health Organisation.

toxicity in treating central tumours, including 6 of 70 patients deemed to have suffered grade 5 toxicity due to SABR and a further early case report of proximal airway necrosis and haemoptysis.[16,81] The fact that these patients are usually medically inoperable may increase the risk of complications following central SABR.

Subsequently, the "no-fly-zone" planning organ-at-risk volume of 2 cm around the proximal airways has been adopted in SABR treatments for lung cancer. Patients with central tumours were excluded from the Radiation Therapy Oncology Group 0236 trial[58] which demonstrated the safety of 54 Gy/3# in peripheral ES-NSCLC. However, the use of a risk-adaptive SABR technique to control the total BED to OARs has been demonstrated to be relatively safe.[56,82]

Further studies have reported the use of SABR to treat tumours in ultracentral positions, defined as the GTV in direct contact with the proximal airway.[56,83] Chaudhuri et al[83] compared 68 patients with ES lung cancer suitable for SABR (50 Gy in 4 or 5#), 34 patients with peripheral tumours and 34 with central tumours, and found no significant difference in OS, primary tumour failure or local failure between the two groups (median OS 38.1 months, 2-year OS 73.8%). They reviewed six patients

Table 4. Studies comparing outcomes between surgery and stereotactic ablative body radiotherapy (SABR)

Study	Study type	Patients	Follow-up (median)	Notes	Outcome
Eba et al 2016[72]	Propensity score analysis of two separate trials	21 patients SABR 21 patients lobectomy		Older SABR group Median age 79 *vs* 62 years	HR 9 (95% CI 1.14–71.04) favouring lobectomy HR 1.19 (CI 0.38–3.73) in younger group (<75)
Chang et al 2015[45]	Pooled analysis of two randomized controlled trials (STARS and ROSEL)	31 SABR 27 surgery (19 open *vs* 5 VATS)	SABR—40.2 months IQR 23–47.3 Surgery—35.4 months IQR 18.9–40.7	1 patient node positive 1 patient surgery aborted due to progression	Pooled estimated 1- and 3-year OS was 100% (95% CI 100–100) and 95% (95% CI 85–100) in the SABR group, and 88% (95% CI 77–100) and 79% (95% CI 64–97) in the surgical group Log-rank $p = 0{\cdot}037$; HR 0·14 (95% CI 0·017–1·190)
Hamaji et al 2015[73]	Retrospective analysis of VATS lobectomy *vs* SABR	VATS 413 SABR 104	48 months	Propensity score matching	3-, 5- and 10-year OS 80.1%, 68.5% and 61.65 with VATS *vs* 52.7%, 37.3% and 20.7% with SABR
Zheng et al 2014[74]	Meta-analysis	40 SABR studies, 4850 patients with Stage 1 disease 23 Surgical 7071 patients	SABR 28 months Surgery 37 months		Mean 1-, 3- and 5-year OS with SBRT were 83.4%, 56.6% and 41.2% compared with 92.5%, 77.9% and 66.1% with lobectomy and 93.2%, 80.7% and 71.7% with limited lung resections
Shirvani et al 2014[75]	SEER database review >66 years	9093 pts reviewed Lobectomy 7215 (79.4%) SLR 1496 (16.5%) SABR 389 (4.2%)	Unadjusted 90 days mortality and 3 years survival were analysed	Unadjusted 90-day mortality was the highest for lobectomy (4.0%) followed by sublobar resection (3.7%, $p = 0.79$) and SABR (1.3%, $p = 0.008$). At 3 years, unadjusted mortality was the lowest for lobectomy (25.0%), followed by sublobar resection (35.3%, $p < 0.001$) and SABR (45.1%, $p < 0.001$)	Compared with lobectomy, sublobar resection was associated with worse OS (HR 1.32; 95% CI 1.20–1.44; $p < 0.001$) and worse lung-cancer-specific survival (HR 1.50; 95% CI 1.29–1.75; $p < 0.001$)
Zhang et al 2014[76]	Matched pair meta-analysis	864 matched patients from 6 studies 432 SABR 432 surgery	1- and 3-year OS OR 1.31 (0.90–1.91), and 1.82 (1.38–2.40)		3-year OS superior in surgery *vs* SABR. But CSS, DFS, LC and DC was not significant
Verstegen et al 2013[77]	Retrospective matched analysis	64 SABR 64 VATS lobectomy	SABR—30 months VATS—16 months	Unsuspected nodal disease in 12 (18.8%)	Locoregional recurrence 1 and 3 years 96.8% and 93.3% *vs* 86.9% and 82.6%,

(Continued)

Table 4. (Continued)

Study	Study type	Patients	Follow-up (median)	Notes	Outcome
					respectively, $p = 0.04$ No significant difference in OS
Solda et al 2013[3]	Systematic review and historical cohort comparison	3641 pts form 45 reports 2038 stage Ia pts from IASLC database			2-year OS 70% in SABR group (range 35–96%, 95% CI 67–72%) 67% in surgery (95% CI 66–70%)
Grills et al 2010[60]	Prospective comparison SBRT *vs* wedge resection	58 SABR 69 Wedge resection	Potential F/U 2.5 years	N+ve patients excluded. 21% SABR *vs* 71% wedge underwent mediastinal LN sampling	Improved LR in SBRT 4% *vs* 20% for wedge ($p = 0.07$) at 30 months. OS superior with wedge 87% *vs* 72% SBRT; $p = 0.01$. CSS 94% wedge *vs* 93% SBRT; $p = 0.53$. No difference in regional recurrence, locoregional recurrence, distant mets, or freedom from failure
Crabtree et al 2010[62]	Retrospective analysis	462 surgery 76 SBRT	Sx—31 months SBRT—19 months	80% bx proven in SBRT	OS 5 years 55% in Sx group Sx OS 3 years—68% SBRT OS 3 years—32% CSS—82% similar LC (3 years)—94% sx *vs* 89% SBRT DFS (3 years)—77% *vs* 86%

Bx, Biopsy; CI, confidence interval; CSS, cause-specific survival; DC; disease control; DFS, Disease-free survival; HR, hazards ratio; IASLC, International association for the Study of Lung Cancer; IQR, interquartile range; LC, Local control; LR, local relapse; mets, metastases; N+ve, node positive; OR, odds ratio; OS, overall survival; SLR, sublobar resection; Sx, surgical group; VATS, video-assisted thoracoscopic surgery.

with "ultracentral" NSCLC tumours and found that the 2-year OS was 80.0% for patients with ultracentral NSCLC compared with 63.2% for the remaining patients with central NSCLC and 86.6% for patients with peripheral NSCLC ($p = 0.62$). They report that one patient had grade 4 pneumonitis with a central tumour and two patients had grade 3 chest wall pain with peripheral tumours. No grade 5 toxicity was reported, and they found no statistically significant correlation between toxicity and tumour site.

Tekatli et al[84,85] report the outcomes of 80 patients with tumour PTV within 2 cm of the proximal bronchial tree and 47 patients with more ultracentral tumours, defined as the PTV in contact with the trachea or main bronchi. The patients were treated with 60 Gy/8# (BED for tissue with an alpha/beta ratio of 10 = 105 Gy). Of the 80 patients with central tumours, a total of six (7.5%) patients were considered to have possible ($n = 3$) or likely ($n = 3$) treatment-related death. They made a contemporaneous comparison with a cohort of patients with peripheral tumours treated with SABR and found no significant difference in OS between the two groups. Median OS was 38 months (95% CI: 26–50) for central and 44 months (95 CI%: 38–51) for peripheral tumours.

The 47 ultracentral patients were treated with SABR (70 Gy/12#) and reported to have a median OS of 15.9 months and a 3-year OS of 20.1%. Of more concern was the expected increase in toxicity, Grade 3 or higher toxicity was recorded in 38% of patients, with 21% scored as having a "possible" ($n = 2$) or "likely" ($n = 8$) treatment-related death between 5.2 and 18.2 months after treatment. Fatal pulmonary haemorrhage was observed in 15% of patients.[85]

The promising reported outcomes and toxicity profile, as well as the prognostic sequelae of not adequately treating ES central lung cancer would suggest that SABR will be offered to these patients with increasing frequency.[86] However, those patients with tumours involving the trachea or main bronchus will be at a much higher risk of treatment toxicity, including death. Bezjak et al[87] have recently reported the primary study end point

analysis of NRG Oncology/Radiation Therapy Oncology Group 0813 SBRT for central NSCLC dose escalation trial. They report a dose-limiting toxicity rate of 7.2% with the maximum dose of 12 Gy/# over 5 #. However, they report four deaths, one at 10.5 Gy/#, two at 11.5 Gy/# and one at 12 Gy/#. Efficacy data are awaited.

In Europe, the European Organisation for Research and Treatment of Cancer, LungTech study is currently evaluating 60 Gy in eight fractions for central tumours in a prospective Phase 2 study with robust RT quality assurance and robust patient follow-up data.[88] This should hopefully provide high-quality data on the efficacy and safety of this regimen for central tumours.

SABR as salvage following surgery or radiotherapy

Recurrence rates of lung cancer following radical surgical treatment have been reported between 30% and 75%, increasing with the more advance stages; those patients with the pathological Stage I disease reported 27–38% recurrence, and those patients with Stage IIIa disease having the highest risk.[89,90] The majority of these are distant recurrences, and usually occur within 2 years of surgery. Post-surgical local recurrence can be managed with surgical resection, EBRT or more recently SABR has been used.[91] However, this cohort of patients, who are usually of poor performance status, are at a significant increased risk of complications due to intra-thoracic re-operation.

The detection on local recurrence post-SABR is also challenging. Fibrotic change is common and can be progressive for a number of months following treatment, in addition to causing local anatomical changes around the radiation field.[92] Current UK guidelines recommend regular post-SABR CT assessment of the thorax,[15] and high risk CT features and PET-CT are being investigated to improve the diagnosis of post-SABR local recurrence.[93,94]

Trovo et al[95] report 17 patients with "in-field" central recurrence of NSCLC using SABR 30 Gy/5–6#, following previous radical RT (50–60 Gy). They reviewed 17 patients, with a local control rate of 86% at 1 year due to 2 patients having local failures. However, Kaplan Meier OS estimates at 1 and 2 years were 59% and 29%, respectively. They also report one fatal occurrence of pneumonitis and one patient who died of fatal haemoptysis 2 months following SABR; in addition, they report 4 patients who developed grade 3 pneumonitis. The treatment of local recurrence following surgical resection is not straightforward. There are increased risks of mortality and toxicity associated with surgical resection as well as SABR.

Trakul et al[96] report their single institution experience of SABR reirradiation of in-field recurrent lung cancer, previously treated with conventional fractionated RT and SABR; 15 patients with 17 lung tumours compared with a standard group undergoing SABR with no previous RT. Local control at 1 year was 65.5% compared with 92.1% of the control group. 1-year actuarial progression-free survival and OS were 58.2% and 80%, respectively. They had no grade 4+ toxicities in either group; and grade 2+ pneumonitis was not seen in the reirradiated group but reported in 13 patients (11.6%) in the control group. Hearn et al[97] identified 22 of 436 patients with local recurrence following treatment with SABR for ES lung cancer. 10 of these were deemed suitable for re-treatment SABR, and 30% are disease free since treatment (follow-up range 11.7–43.5 months). Two patients developed distant disease, with four other patients with local relapse at a median 9.9 months.

As patients initially treated with SABR usually have significant comorbidity that precludes surgery, re-treatment SABR may be a viable treatment option in local recurrent disease.

Lung cancer SABR and adjuvant treatments

The use of SABR for ES lung cancer raises the question of benefit of additional treatments. SABR induces local ablation of tumour cells and surrounding normal stroma. Lung cancer is known to have high metastatic potential, and micrometastatic nodal disease is beyond the scope of PET-CT to detect.[98,99] This raises the concern of undetected metastatic deposits which may then affect outcome. Interestingly, there are additional hypotheses postulated around the tumour microenvironmental changes associated with SABR. These include the release of tumour-associated antigens, which can prime the host immune system, thereby potentially encouraging the abscopal effect on distant sites of disease.[100]

Conventional treatment such as chemotherapy may be considered, certainly for those tumours with associated increased risk of nodal involvement. There are currently no reported randomized trials comparing SABR for ES lung cancer with or without adjuvant chemotherapy. Chen et al[36] report a small analysis of SABR for early lung cancer with a cohort of 65 patients, of which 17 patients then received adjuvant chemotherapy. Albeit a small sample size, they report a trend in improvement of OS of patients receiving adjuvant chemotherapy with three to four cycles of a cisplatin-containing regimen. Although not statistically significant, the 3- and 5- year survival rates for the patients who received SABR plus adjuvant chemotherapy were 80.5% and 46%, compared with 49.6% and 31.5% receiving SABR alone, respectively.

SUMMARY AND OUTLOOK

The use of stereotactic ablative RT for ES lung cancer is currently routine for medically inoperable patients and is well tolerated with high local control rates. There remains equipoise regarding the effectiveness of SABR compared with surgical resection in higher-risk patients and medically operable patients, which is hopefully being addressed by randomized clinical trials in this setting. For patients with ES-NSCLC suitable for surgery, there may be an argument for using SABR upfront and for reserving surgical resection for those patients who relapse locally. Finally, there is growing interest in the potential abscopal effect of SABR and the addition of immune-modulating systemic therapies in combination with SABR, and this may have the potential to eradicate potential micrometastatic deposits within central draining lymph nodes and beyond.

REFERENCES

1. Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2010; **76**: 326–32. doi: https://doi.org/10.1016/j.ijrobp.2009.09.042
2. board NC. Clinical commissioning policy: stereotactic ablative body radiotherapy for non-small-cell lung cancer (adult); 2013.
3. Soldá F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. *Radiother Oncol* 2013; **109**: 1–7. doi: https://doi.org/10.1016/j.radonc.2013.09.006
4. Hanna GG, Landau D. Stereotactic body radiotherapy for oligometastatic disease. *Clin Oncol (R Coll Radiol)* 2015; **27**: 290–7. doi: https://doi.org/10.1016/j.clon.2015.02.003
5. Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013; **14**: e28–37. doi: https://doi.org/10.1016/S1470-2045(12)70510-7
6. Mellon EA, Strom TJ, Hoffe SE, Frakes JM, Springett GM, Hodul PJ, et al. Favorable perioperative outcomes after resection of borderline resectable pancreatic cancer treated with neoadjuvant stereotactic radiation and chemotherapy compared with upfront pancreatectomy for resectable cancer. *J Gastrointest Oncol* 2016; **7**: 547–55. doi: https://doi.org/10.21037/jgo.2016.03.15
7. Baker BR, Basak R, Mohiuddin JJ, Chen RC. Use of stereotactic body radiotherapy for prostate cancer in the United States from 2004 through 2012. *Cancer* 2016; **122**: 2234–41. doi: https://doi.org/10.1002/cncr.30034
8. Kirichenko A, Gayou O, Parda D, Kudithipudi V, Tom K, Khan A, et al. Stereotactic body radiotherapy (SBRT) with or without surgery for primary and metastatic liver tumors. *HPB (Oxford)* 2016; **18**: 88–97. doi: https://doi.org/10.1016/j.hpb.2015.07.007
9. Chang EL, Shiu AS, Mendel E, Mathews LA, Mahajan A, Allen PK, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine* 2007; **7**: 151–60. doi: https://doi.org/10.3171/SPI-07/08/151
10. Cole AJ, Hanna GG, Jain S, O'Sullivan JM. Motion management for radical radiotherapy in non-small cell lung cancer. *Clin Oncol (R Coll Radiol)* 2014; **26**: 67–80. doi: https://doi.org/10.1016/j.clon.2013.11.001
11. Radiologists RCo. On target: ensuring geometric accuracy in radiotherapy: Radiologists RCo; 2008.
12. Cole AJ, O'Hare JM, McMahon SJ, McGarry CK, Butterworth KT, McAleese J, et al. Investigating the potential impact of four-dimensional computed tomography (4DCT) on toxicity, outcomes and dose escalation for radical lung cancer radiotherapy. *Clin Oncol (R Coll Radiol)* 2014; **26**: 142–50. doi: https://doi.org/10.1016/j.clon.2013.11.024
13. van Herk M. Errors and margins in radiotherapy. *Semin Radiat Oncol* 2004; **14**: 52–64. doi: https://doi.org/10.1053/j.semradonc.2003.10.003
14. Prendergast BM, Fiveash JB, Popple RA, Clark GM, Thomas EM, Minnich DJ, et al. Flattening filter-free linac improves treatment delivery efficiency in stereotactic body radiation therapy. *J Appl Clin Med Phys* 2013; **14**: 4126. doi: https://doi.org/10.1120/jacmp.v14i3.4126
15. Consortium US. Stereotactic ablative body radiotherapy (SABR): a resource v. 5.1. SABR UK Consortium; 2016. Available from: http://www.actionradiotherapy.org/wp-content/uploads/2016/02/UKSABR-ConsortiumGuidelinesv51.pdf
16. Timmerman R, 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. doi: https://doi.org/10.1200/jco.2006.07.5937
17. Sobin LH, Gospodarowicz MK, Wittekind C. *Lung. TNM Online*: Wiley-Blackwell; 2010. p. 138–46.
18. NICE. *NICE guideline CG121: lung cancer: diagnosis and management*; 2011.
19. Vansteenkiste J, De Ruysscher D, Eberhardt WE, Lim E, Senan S, Felip E, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24**(Suppl. 6): vi89–98. doi: https://doi.org/10.1093/annonc/mdt241
20. Medford-Davis L, DeCamp M, Recht A, Flickinger J, Belani CP, Varlotto J. Surgical management of early-stage non-small cell lung carcinoma and the present and future roles of adjuvant therapy: a review for the radiation oncologist. *Int J Radiat Oncol Biol Phys* 2012; **84**: 1048–57. doi: https://doi.org/10.1016/j.ijrobp.2012.03.018
21. Bilal H, Mahmood S, Rajashanker B, Shah R. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? *Interact Cardiovasc Thorac Surg* 2012; **15**: 258–65. doi: https://doi.org/10.1093/icvts/ivs179
22. Nakanishi R, Nakagawa M, Tokufuchi H, Okumura T, Maeda M, Kuboi S, et al. Video-assisted thoracoscopic lobectomy for clinical stage I non-small cell lung cancer: experience with 111 consecutive patients demonstrating comorbidity. *Minerva Chir* 2012; **67**: 67–75.
23. Haasbeek CJ, Palma D, Visser O, Lagerwaard FJ, Slotman B, Senan S. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. *Ann Oncol* 2012; **23**: 2743–7. doi: https://doi.org/10.1093/annonc/mds081
24. Raz DJ, Zell JA, Ou SH, Gandara DR, Anton-Culver H, Jablons DM. Natural history of stage I non-small cell lung cancer: implications for early detection. *Chest* 2007; **132**: 193–9. doi: https://doi.org/10.1378/chest.06-3096
25. McAleese J, Baluch S, Drinkwater K. The quality of curative-intent radiotherapy for non-small cell lung cancer in the UK. *Clin Oncol (R Coll Radiol)* 2015; **27**: 498–504. doi: https://doi.org/10.1016/j.clon.2015.05.006
26. Nyman J. SPACE—a randomized study of SBRT *vs* conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiat Oncol J* 2014; **111**(Suppl. 1): s221.
27. (TROG) T-TROG. Hypofractionated radiotherapy (stereotactic) *versus* conventional radiotherapy for inoperable early stage I non-small cell lung cancer (NSCLC) (CHISEL); 2009 (NCT01014130).
28. Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, et al; American Society for Therapeutic Radiology and Oncology; ; American College of Radiology. American Society for Therapeutic

Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2010; **76**: 326–32. doi: https://doi.org/10.1016/j.ijrobp.2009.09.042

29. Blomgren H, Lax I, Näslund I, Svanstrom R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol* 1995; **34**: 861–70. doi: https://doi.org/10.3109/02841869509127197
30. Lax I, Blomgren H, Näslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994; **33**: 677–83. doi: https://doi.org/10.3109/02841869409121782
31. Wulf J, Hädinger U, Oppitz U, Olshausen B, Flentje M. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. *Radiother Oncol* 2000; **57**: 225–36. doi: https://doi.org/10.1016/S0167-8140(00)00226-7
32. Underberg RW, Lagerwaard FJ, Slotman BJ, Cuijpers JP, Senan S. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. *Int J Radiat Oncol Biol Phys* 2005; **63**: 253–60. doi: https://doi.org/10.1016/j.ijrobp.2005.05.045
33. Bradley JD, El Naqa I, Drzymala RE, Trovo M, Jones G, Denning MD. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. *Int J Radiat Oncol Biol Phys* 2010; **77**: 1146–50. doi: https://doi.org/10.1016/j.ijrobp.2009.06.017
34. Peulen H, Belderbos J, Rossi M, Sonke JJ. Mid-ventilation based PTV margins in Stereotactic Body Radiotherapy (SBRT): a clinical evaluation. *Radiother Oncol* 2014; **110**: 511–6. doi: https://doi.org/10.1016/j.radonc.2014.01.010
35. Martin AG, Thomas SJ, Harden SV, Burnet NG. Evaluating competing and emerging technologies for stereotactic body radiotherapy and other advanced radiotherapy techniques. *Clin Oncol (R Coll Radiol)* 2015; **27**: 251–9. doi: https://doi.org/10.1016/j.clon.2015.01.034
36. Chen Y, Guo W, Lu Y, Zou B. Dose-individualized stereotactic body radiotherapy for T1-3N0 non-small cell lung cancer: long-term results and efficacy of adjuvant chemotherapy. *Radiother Oncol* 2008; **88**: 351–8. doi: https://doi.org/10.1016/j.radonc.2008.07.013
37. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007; **2**(7 Suppl. 3): S94–100. doi: https://doi.org/10.1097/JTO.0b013e318074de34
38. Stephans KL, Djemil T, Reddy CA, Gajdos SM, Kolar M, Mason D, et al. A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. *J Thorac Oncol* 2009; **4**: 976–82. doi: https://doi.org/10.1097/JTO.0b013e3181adf509
39. Koshy M, Malik R, Weichselbaum RR, Sher DJ. Increasing radiation therapy dose is associated with improved survival in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2015; **91**: 344–50. doi: https://doi.org/10.1016/j.ijrobp.2014.10.002
40. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan Clinical Oncology Group Study JCOG0403. *Int J Radiat Oncol Biol Phys* 2015; **93**: 989–96. doi: https://doi.org/10.1016/j.ijrobp.2015.07.2278
41. Haseltine JM, Rimner A, Gelblum DY, Modh A, Rosenzweig KE, Jackson A, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. *Pract Radiat Oncol* 2016; **6**: e27–33. doi: https://doi.org/10.1016/j.prro.2015.09.012
42. Shaverdian N, Veruttipong D, Wang J, Schaue D, Kupelian P, Lee P. Pretreatment immune parameters predict for overall survival and toxicity in early-stage non-small-cell lung cancer patients treated with stereotactic body radiation therapy. *Clin Lung Cancer* 2016; **17**: 39–46. doi: https://doi.org/10.1016/j.cllc.2015.07.007
43. Navarro-Martin A, Aso S, Cacicedo J, Arnaiz M, Navarro V, Rosales S, et al. Phase II trial of SBRT for Stage I NSCLC: survival, local control, and lung function at 36 months. *J Thorac Oncol* 2016; **11**: 1101–11. doi: https://doi.org/10.1016/j.jtho.2016.03.021
44. Chiang A, Thibault I, Warner A, Rodrigues G, Palma D, Soliman H, et al. A comparison between accelerated hypofractionation and stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer (NSCLC): results of a propensity score-matched analysis. *Radiother Oncol* 2016; **118**: 478–84. doi: https://doi.org/10.1016/j.radonc.2015.12.026
45. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy *versus* lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; **16**: 630–7. doi: https://doi.org/10.1016/S1470-2045(15)70168-3
46. Murray L, Ramasamy S, Lilley J, Snee M, Clarke K, Musunuru HB, et al. Stereotactic ablative radiotherapy (SABR) in patients with medically inoperable peripheral early stage lung cancer: outcomes for the first UK SABR cohort. *Clin Oncol (R Coll Radiol)* 2016; **28**: 4–12. doi: https://doi.org/10.1016/j.clon.2015.09.007
47. Gillespie EF, Atwood TF, Sandhu AP. Lung stereotactic body radiotherapy (SBRT): a single institution's outcomes and methodology in the context of a literature review. *Transl Cancer Res* 2015; **4**: 372–80.
48. Chang JY, Liu H, Balter P, Komaki R, Liao Z, Welsh J, et al. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. *Radiat Oncol* 2012; **7**: 152. doi: https://doi.org/10.1186/1748-717x-7-152
49. Abelson JA, Murphy JD, Trakul N, Bazan JG, Maxim PG, Graves EE, et al. Metabolic imaging metrics correlate with survival in early stage lung cancer treated with stereotactic ablative radiotherapy. *Lung Cancer* 2012; **78**: 219–24. doi: https://doi.org/10.1016/j.lungcan.2012.08.016
50. Taremi M, Hope A, Dahele M, Pearson S, Fung S, Purdie T, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. *Int J Radiat Oncol Biol Phys* 2012; **82**: 967–73. doi: https://doi.org/10.1016/j.ijrobp.2010.12.039
51. 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**: 802–9. doi: https://doi.org/10.1016/S1470-2045(12)70242-5
52. Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. Curative treatment of stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. *Int J Radiat Oncol Biol Phys* 2012; **82**: 1149–56. doi: https://doi.org/10.1016/j.ijrobp.2011.03.005
53. Bongers EM, Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Incidence and risk factors for chest wall toxicity after risk-

adapted stereotactic radiotherapy for early-stage lung cancer. *J Thorac Oncol* 2011; **6**: 2052–7. doi: https://doi.org/10.1097/JTO.0b013e3182307e74

54. Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a phase II trial. *Int J Radiat Oncol Biol Phys* 2011; **80**: 1343–9. doi: https://doi.org/10.1016/j.ijrobp.2010.04.056
55. Andratschke N, Zimmermann F, Boehm E, Schill S, Schoenknecht C, Thamm R, et al. Stereotactic radiotherapy of histologically proven inoperable stage I non-small cell lung cancer: patterns of failure. *Radiother Oncol* 2011; **101**: 245–9. doi: https://doi.org/10.1016/j.radonc.2011.06.009
56. 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. doi: https://doi.org/10.1097/jto.0b013e31822e71d8
57. Haasbeek CJ, Lagerwaard FJ, Antonisse ME, Slotman BJ, Senan S. Stage I nonsmall cell lung cancer in patients aged > or =75 years: outcomes after stereotactic radiotherapy. *Cancer* 2010; **116**: 406–14. doi: https://doi.org/10.1002/cncr.24759
58. Timmerman 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. doi: https://doi.org/10.1001/jama.2010.261
59. Hamamoto Y, Kataoka M, Yamashita M, Shinkai T, Kubo Y, Sugawara Y, et al. Local control of metastatic lung tumors treated with SBRT of 48 Gy in four fractions: in comparison with primary lung cancer. *Jpn J Clin Oncol* 2009; **40**: 125–9. doi: https://doi.org/10.1093/jjco/hyp129
60. 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. doi: https://doi.org/10.1200/jco.2009.25.0928
61. 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. doi: https://doi.org/10.1016/j.lungcan.2009.05.007
62. Crabtree TD, Denlinger CE, Meyers BF, El Naqa I, Zoole J, Krupnick AS, et al. Stereotactic body radiation therapy *versus* surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2010; **140**: 377–86. doi: https://doi.org/10.1016/j.jtcvs.2009.12.054
63. 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. doi: https://doi.org/10.1200/jco.2008.21.5681
64. 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. doi: https://doi.org/10.1016/j.ijrobp.2008.11.042
65. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; **70**: 685–92. doi: https://doi.org/10.1016/j.ijrobp.2007.10.053
66. 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. doi: https://doi.org/10.1016/j.radonc.2007.10.017
67. Hoyer M, Roed H, Hansen AT, Ohlhuis L, Petersen J, Nellemann H, et al. Prospective study on stereotactic radiotherapy of limited-stage non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; **66**: S128–35. doi: https://doi.org/10.1016/j.ijrobp.2006.01.012
68. Nyman J, Johansson KA, Hultén U. Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer—mature results for medically inoperable patients. *Lung Cancer* 2006; **51**: 97–103. doi: https://doi.org/10.1016/j.lungcan.2005.08.011
69. Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1427–31. doi: https://doi.org/10.1016/j.ijrobp.2005.05.034
70. McGarry RC, Papiez L, Williams M, Whitford T, Timmerman RD. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1010–5. doi: https://doi.org/10.1016/j.ijrobp.2005.03.073
71. Zimmermann FB, Geinitz H, Schill S, Grosu A, Schratzenstaller U, Molls M, et al. Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. *Lung Cancer* 2005; **48**: 107–14. doi: https://doi.org/10.1016/j.lungcan.2004.10.015
72. Eba J, Nakamura K, Mizusawa J, Suzuki K, Nagata Y, Koike T, et al. Stereotactic body radiotherapy *versus* lobectomy for operable clinical stage IA lung adenocarcinoma: comparison of survival outcomes in two clinical trials with propensity score analysis (JCOG1313-A). *Jpn J Clin Oncol* 2016; **46**: 748–53. doi: https://doi.org/10.1093/jjco/hyw058
73. Hamaji M, Chen F, Matsuo Y, Kawaguchi A, Morita S, Ueki N, et al. Video-assisted thoracoscopic lobectomy *versus* stereotactic radiotherapy for stage I lung cancer. *Ann Thorac Surg* 2015; **99**: 1122–9. doi: https://doi.org/10.1016/j.athoracsur.2014.11.009
74. Zheng X, Schipper M, Kidwell K, Lin J, Reddy R, Ren Y, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2014; **90**: 603–11. doi: https://doi.org/10.1016/j.ijrobp.2014.05.055
75. Shirvani SM, Jiang J, Chang JY, Welsh J, Likhacheva A, Buchholz TA, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. *JAMA Surg* 2014; **149**: 1244–53. doi: https://doi.org/10.1001/jamasurg.2014.556
76. Zhang B, Zhu F, Ma X, Tian Y, Cao D, Luo S, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) *versus* surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. *Radiother Oncol* 2014; **112**: 250–5. doi: https://doi.org/10.1016/j.radonc.2014.08.031
77. Verstegen NE, Oosterhuis JW, Palma DA, Rodrigues G, Lagerwaard FJ, van der Elst A, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. *Ann Oncol* 2013; **24**: 1543–8. doi: https://doi.org/10.1093/annonc/mdt026
78. van den Berg LL, Klinkenberg TJ, Groen HJ, Widder J. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. *J Thorac*

Oncol 2015; **10**: 826–31. doi: https://doi.org/10.1097/jto.0000000000000483

79. Franks K. Comparing stereotactic ablative radiotherapy with surgery in patients with peripheral stage I non small cell lung cancer considered at higher risk of complications from surgical resection; 2015 [ISRCTN13029788]. Available from: http://www.isrctn.com/ISRCTN13029788?q=SABRTooth&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search
80. Timmerman R. JoLT-Ca sublobar resection (SR) *versus* stereotactic ablative radiotherapy (SAbR) for lung cancer (STABLE-MATES); 2016.
81. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. *N Engl J Med* 2012; **366**: 2327–9. doi: https://doi.org/10.1056/NEJMc1203770
82. Senthi S, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. *Radiother Oncol* 2013; **106**: 276–82. doi: https://doi.org/10.1016/j.radonc.2013.01.004
83. Chaudhuri AA, Tang C, Binkley MS, Jin M, Wynne JF, von Eyben R, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. *Lung Cancer* 2015; **89**: 50–6. doi: https://doi.org/10.1016/j.lungcan.2015.04.014
84. Tekatli H, Senan S, Dahele M, Slotman BJ, Verbakel WF. Stereotactic ablative radiotherapy (SABR) for central lung tumors: plan quality and long-term clinical outcomes. *Radiother Oncol* 2015; **117**: 64–70. doi: https://doi.org/10.1016/j.radonc.2015.09.028
85. Tekatli H, Haasbeek N, Dahele M, De Haan P, Verbakel W, Bongers E, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "Ultracentral" non-small cell lung cancer. *J Thorac Oncol* 2016; **11**: 1081–9. doi: https://doi.org/10.1016/j.jtho.2016.03.008
86. Iyengar P, Timmerman RD. Stereotactic ablative radiotherapy for non-small cell lung cancer: rationale and outcomes. *J Natl Compr Canc Netw* 2012; **10**: 1514–20.
87. Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, et al. Primary study endpoint analysis for NRG oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2016; **94**: 5–6. doi: https://doi.org/10.1016/j.ijrobp.2015.10.040
88. Adebahr S, Collette S, Shash E, Lambrecht M, Le Pechoux C, Faivre-Finn C, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. *Br J Radiol* 2015; **88**: 20150036. doi: https://doi.org/10.1259/bjr.20150036
89. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. *Ann Thorac Surg* 2007; **83**: 409–17; discussioin 17–8. doi: https://doi.org/10.1016/j.athoracsur.2006.08.046
90. Hung JJ, Hsu WH, Hsieh CC, Huang BS, Huang MH, Liu JS, et al. Post-recurrence survival in completely resected stage I non-small cell lung cancer with local recurrence. *Thorax* 2009; **64**: 192–6. doi: https://doi.org/10.1136/thx.2007.094912
91. Takeda A, Sanuki N, Eriguchi T, Enomoto T, Yokosuka T, Kaneko T, et al. Salvage stereotactic ablative irradiation for isolated postsurgical local recurrence of lung cancer. *Ann Thorac Surg* 2013; **96**: 1776–82. doi: https://doi.org/10.1016/j.athoracsur.2013.06.014
92. Huang K, Rodrigues G, Yaremko BP, Yu E, Dar R, Palma DA. Stereotactic ablative radiation therapy (SABR) and pulmonary re-irradiation: a systematic review of the literature assessing safety and oncologic outcomes. *Int J Radiat Oncol Biol Phys* 2014; **90**: S633.
93. Huang K, Senthi S, Palma DA, Spoelstra FO, Warner A, Slotman BJ, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. *Radiother Oncol* 2013; **109**: 51–7. doi: https://doi.org/10.1016/j.radonc.2013.06.047
94. Takeda A, Kunieda E, Fujii H, Yokosuka N, Aoki Y, Oooka Y, et al. Evaluation for local failure by 18F-FDG PET/CT in comparison with CT findings after stereotactic body radiotherapy (SBRT) for localized non-small-cell lung cancer. *Lung Cancer* 2013; **79**: 248–53. doi: https://doi.org/10.1016/j.lungcan.2012.11.008
95. Trovo M, Minatel E, Durofil E, Polesel J, Avanzo M, Baresic T, et al. Stereotactic body radiation therapy for re-irradiation of persistent or recurrent non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014; **88**: 1114–9. doi: https://doi.org/10.1016/j.ijrobp.2014.01.012
96. Trakul N, Harris JP, Le QT, Hara WY, Maxim PG, Loo BW Jr, et al. Stereotactic ablative radiotherapy for reirradiation of locally recurrent lung tumors. *J Thorac Oncol* 2012; **7**: 1462–5. doi: https://doi.org/10.1097/jto.0b013e31825f22ce
97. Hearn JW, Videtic GM, Djemil T, Stephans KL. Salvage stereotactic body radiation therapy (SBRT) for local failure after primary lung SBRT. *Int J Radiat Oncol Biol Phys* 2014; **90**: 402–6. doi: https://doi.org/10.1016/j.ijrobp.2014.05.048
98. Fischer B, Lassen U, Mortensen J, Larsen S, Loft A, Bertelsen A, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med* 2009; **361**: 32–9. doi: https://doi.org/10.1056/NEJMoa0900043
99. Moloney F, Ryan D, McCarthy L, McCarthy J, Burke L, Henry MT, et al. Increasing the accuracy of 18F-FDG PET/CT interpretation of "mildly positive" mediastinal nodes in the staging of non-small cell lung cancer. *Eur J Radiol* 2014; **83**: 843–7. doi: https://doi.org/10.1016/j.ejrad.2014.01.016
100. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol* 2016; **13**: 516–24. doi: https://doi.org/10.1038/nrclinonc.2016.30