MINI REVIEW

Which patients benefit most from stereotactic body radiotherapy or surgery in medically operable non-small cell lung cancer? An in-depth look at patient characteristics on both sides of the debate

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Abstract
The role of stereotactic body radiotherapy (SBRT) in early stage medically operable non-small cell lung cancer is currently under debate. SBRT’s advantage is its ability to provide high radiotherapy doses to a tumor in a short timeframe, without the risk of postoperative complications and mortality. Currently, in part due to limited prospective data comparing both treatments, international guidelines continue to recommend surgical resection as the gold standard for medically operable patients. However, not all patients possess uniform characteristics, and there is some evidence that certain subgroups of patients would benefit more from one form of treatment - SBRT or surgery - than the other. The aim of this review is to provide a brief summary of the evidence comparing SBRT to surgery, followed by a deeper discussion of the subgroups of patients who would benefit most from surgery: those with large tumors, centrally located tumors, increased risk of occult nodal metastases, increased risk of toxicity from radiotherapy and radioresistant histological tumor subtypes. Meanwhile, patients who could benefit most from SBRT might include elderly patients, those with reduced lung function or cardiac comorbidities, those with synchronous lung nodules, and those with specific tumor mutational status. We hope that this review will aid in the clinical decision-making process regarding patient selection for either treatment.

Introduction
Few innovations have had the same impact as stereotactic body radiotherapy in early stage medically inoperable non-small cell lung cancer, with local control rates currently in the region of 85–90%. At the same time, early studies which included medically operable cohorts have reported promising results, hinting at clinical equipoise between lobectomy and SBRT in early stage disease. Questions have therefore arisen regarding the suitability of SBRT for medically operable patients. With a lack of phase 3 data, owing to poorly accrued trials, this dilemma continues to plague us in current clinical practice. This is exemplified in a study by Hopmans et al. where researchers provided 126 clinicians (including pulmonologists, thoracic surgeons and radiation oncologists) with 16 hypothetical cases of patients with stage I NSCLC. They were asked for their treatment recommendation – surgery or stereotactic body radiotherapy (SBRT), and limited consistency was observed. While recently published ASTRO guidelines have offered guidance and recommended surgery in medically operable patients, SBRT as a noninvasive therapy offers an attractive option for patients who are opposed to a surgical option. This is further accentuated by recent technological advancements in motion management and linear accelerator technology, enabling greater and cheaper access to SBRT capabilities.

Background: SBRT
The advantage of SBRT is its ability to provide high radiotherapy doses to the tumor in a short timeframe, without risk of postoperative complications and mortality. The
highly focal nature of SBRT helps to minimize radiation-induced damage to surrounding normal lungs and organs at risk. Treatment is generally delivered in hypofractionated regimens of 3–5 fractions of 10–15 Gy per fraction, on alternate days.

The landmark trial indicating the success of SBRT in medically inoperable NSCLC patients was by Timmerman et al. at the Veterans Affairs Medical Center,7 where tumors responded to treatment in 87% of patients, with 27% showing a complete response. This showed that high radiation doses were tolerated. A subsequent phase 2 study, RTOG 0236,1 accrued 55 evaluable patients with T1 and T2 tumors. The three-year local control rate was 87.2% and the DFS and OS at three years were 43.8% and 55.8%, respectively, with acceptable toxicity levels. All in all, these studies enabled SBRT to gain popularity. A Japanese multi-institutional cohort study determined that local control and survival rates were more favorable with a BED of greater or equal to 100 Gy compared to BED <100 Gy,8 with BED in the range of 106–142 Gy seemingly optimal in terms of tumor control and avoiding adverse effects.9

With the success of SBRT in medically inoperable patients, interest has turned to SBRT as a treatment option for medically operable patients. The phase 2 RTOG 0618 study, consisting of 26 evaluable medically operable patients with T1-T2N0M0 non-small cell lung tumors, found that four-year primary tumor control and local control rate were both 96%. The authors concluded that SBRT is associated with good tumor control and low morbidity in the medically operable population.10 A list of major prospective SBRT trials and survival data are shown in Table 1.

SBRT technology has come a long way in the past few years, though there is room for continued advancements in ensuring reproducibility in terms of tumor location at breath hold, determining tumor volume and location, and shifts and rotations in the matching process.18

**Background: Surgery**

Mirroring the developments in SBRT technology, the advent of minimally invasive surgery has meant that perioperative outcomes have improved, with the ACSOG Z0030/ alliance trial19 showing a five year local recurrence free survival rate of 95% for T1 tumors and 91% for T2 tumors, while five year survival was 72% for T1 tumors and 55% for T2 tumors. At present, the gold standard for surgery for early stage NSCLC is lobectomy, shown since the 1995 prospective mult institutional trial20 was published comparing limited resection with lobectomy for T1N0 NSCLC where patients who underwent limited resection had an observed tripling of the local recurrence rate compared to lobectomy. The Cancer and Leukaemia Group B 39802 trial was subsequently started to evaluate the technical feasibility of VATS lobectomy and showed decreased postoperative complications compared to historical controls, establishing VATS lobectomy as the preferred option for early stage NSCLC tumors. The definition of “operability”, following recent ACCP guidelines, suggests that when postoperative FEV1 and DLCO are >60% of predicted, no further testing is required prior to resection. For either value between 30–60% predicted, further evaluation with exercise testing (e.g., stair climb/shuttle walk) should be performed.21

**Comparison of SBRT and surgery**

For patients who present to clinic with early stage NSCLC, with few medical comorbidities and minimal symptoms, current international guidelines generally recommend surgery rather than SBRT, unless enrolled in a clinical trial. Such guidelines include those issued by the American Society for Radiation Oncology (ASTRO),6 the European Society for Medical Oncology (ESMO),22 the American Society of Clinical Oncology (ASCO),23 and the American College of Chest Physicians,24 among others. While surgery has excellent overall and disease-free survival outcomes and offers advantages such as nodal evaluation, SBRT allows patients to avoid operative and anaesthetic risks altogether. Indeed, for patients who are not eligible for lobectomies due to high operative risk, ASTRO guidelines state that discussions about SBRT as a potential alternative to surgery are encouraged.6,25 Some of the major advantages and disadvantages of the two strategies, surgery and radiotherapy, are listed in Table 2.

Two prospective trials were instituted to evaluate surgery versus SBRT in operable patients, the STARS trial (randomized study to compare CyberKnife to surgical resection in stage I non-small cell lung cancer) and the ROSEL trial (trial of either surgery or stereotactic radiotherapy for early stage IA lung cancer). Both closed due to poor accrual. The combined data were interpreted by Chang et al.31: 58 patients were enrolled in total, 31 randomly assigned to SBRT and 27 to surgery. Overall survival (OS) at three years was 95% in the SBRT group compared with 79% in the surgery group, HR 0.14 (0.017–1.190,  P = 0.037). Recurrence free survival at three years was 86% in the SBRT group and 80% in the surgery group, HR 0.69 (0.21–2.29, P = 0.54). Ninety day mortality rates of surgery and SBRT were 4% and 0% respectively, while grade 3–4 toxicity was 44% with surgery and only 10% with SBRT. This led the authors to declare that SBRT could be an option for treating operable stage IA NSCLC. Certainly in higher risk patients with more comorbidities, these considerations should be paramount in the decision-making process.

Several retrospective analyses using propensity score matching have been performed to compare surgery to...
| Study                      | Patient characteristics     | Study size | SBRT dose   | Primary endpoint | Local control | DFS            | OS              |
|--------------------------|-----------------------------|------------|-------------|------------------|---------------|----------------|-----------------|
| Fakiris et al. (2009)²⁶  | T1/N0/M0 NSCLC up to 7 cm, medically inoperable | 70 patients | 60-66 Gy/3# | Local tumor control | 88.1% at 3 years | 81.7% at 3 years | 42.7% at 3 years |
| Baumann et al. (2009)²⁷ | T1/N0/M0 NSCLC, medically inoperable | 57 patients | 45 Gy/3#    | Progression-free survival | 92% at 3 years | 93% at 1 year, 88% at 2 years, 88% at 3 years | 86% at 1 year, 65% at 2 years, 60% at 3 years |
| Timmerman et al. (2010)²⁸ | T1/N0/M0 NSCLC up to 5 cm, medically inoperable | 55 patients | 60 Gy/3#    | Primary tumor control | 90.6% at 3 years (within lobe) | 97.6% (primary tumor control) | 48.3% at 3 years |
| Ricardi et al. (2010)²⁹  | Stage I NSCLC, medically inoperable | 62 patients | 45 Gy/3#    | Local tumor control | 92.7% at 2 years and 87.8% at 3 years | 79.4% at 2 years and 72.5% at 3 years | 69.2% at 2 years and 57.1% at 3 years |
| Nagata et al. (2015)³⁰   | T1N0M0 NSCLC                  | 100 inoperable 64 operable patients | 48 Gy/4#    | 3 year overall survival | Inoperable patients: 52.8% at 3 years Operable patients: 68.6% at 3 years | Inoperable patients: 49.8% at 3 years Operable patients: 54.5% at 3 years | Inoperable patients: 59.9% at 3 years, 42.8% at 5 years Operable patients: 76.5% at 3 years, 54.0% at 5 years |
| Videtic et al. (2015)³¹  | T1/N0/M0 NSCLC, medically inoperable | 84 patients | 34 Gy/1# (39 patients) 48 Gy/4# (45 patients) | Rates of prespecified grade 3 or higher toxicities at 1 year | 34 Gy/1# 97.0% at 1 year 48 Gy/4# 92.7% at 1 year | 34 Gy/1# 56.4% at 2 years 48 Gy/4# 71.1% at 2 years | 34 Gy/1# 61% at 2 years 48 Gy/4# 77.7% at 2 years |
| Sun et al., (2017)³²     | T1/N0/M0 NSCLC up to 5 cm    | 65 patients | 50 Gy/4# (one patient received 45 Gy/4# and one received 50 Gy/3#) | Progression-free survival | Local control: 98.5% at 1 year, 95.4% at 3 years, 91.9% at 5 years, 91.9% at 7 years Locoregional control: 92.8% at 1 year, 87.7% at 3 years, 82.6% at 5 years, 80.0% at 7 years | 49.5% at 5 years and 38.2% at 7 years | 55.7% at 5 years and 47.5% at 7 years |
| Timmerman et al. (2018)³³ | T1/N0/M0 NSCLC up to 5 cm medically operable | 26 patients | 54 Gy/3#    | Primary tumor control | 96% at 4 years | 57% at 4 years | 56% at 4 years |
SBRT. The advantage of these is that a large number of patients are available for analyses. Overall, these have tended to favor lobectomy in terms of OS, while sublobar resections and SBRT have equivalent results. For instance, Rosen et al. 32 published an analysis of the national cancer database, comparing stage I NSCLC patients free of comorbidities undergoing lobectomy (13,562 patients) compared to SBRT (1,781). Propensity score matching was performed and yielded a 59% five-year survival rate for patients who underwent lobectomy, in contrast to a 29% five-year survival rate for those who received SBRT (P < 0.001). Meanwhile, Shirvani et al. performed an analysis of early stage NSCLC patients from the SEER database between 2003–2009. After propensity score matching, SBRT was associated with better overall survival compared to lobectomy in the first six months after diagnosis (HR 0.45; 95%CI 0.27–0.75), but this picture reversed after six months (HR 1.66; 95%CI 1.39–1.99).12 In a recent meta-analysis by Wang et al. the authors identified two trials and seven cohort studies, using propensity score matching to compare patients in each cohort study. They concluded that the benefits of surgery were significant in terms of three-year OS, cancer-specific survival and recurrence-free survival, as well as five-year OS.13 In contrast, other studies such as Verstegen et al.33 and Crabtree et al.34 showed nonsignificant differences in OS after propensity score matching.

To help explore this question further, several prospective trials are now in the pipeline (Table 3). Perhaps the most sensible approach would be to discuss potential pitfalls in both modalities and identify patients who may benefit most from surgery or SBRT.

**Factors favoring surgery**

### Large tumors

One group of patients who are likely to derive greater benefit from surgery are those with large tumors. It has been shown that for SBRT patients, local control and OS rates decrease as tumor size increases. For instance, in a retrospective analysis, Dunlap et al.39 reported that the median recurrence-free survival for T1 tumors was 30.6 months after SBRT treatment while that for T2 tumors was 20.5 months, and median OS was 20 months and 16.7 months for T1 and T2 tumors respectively. Similar results were obtained by Shamp et al.40 Meanwhile, analysis by Allibhai of 185 patients who received SBRT showed that tumor size was associated with regional failure (P = 0.011) and distal failure (P = 0.021), as well as...

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**Table 2** SBRT versus surgery for early stage NSCLC: major advantages and disadvantages of each modality

| SBRT | Surgery |
|------|---------|
| **Advantages** | **Advantages** |
| Non-invasive: avoids surgical complications, anesthetic risks | Allows full histopathologic analysis of lesion (e.g. T stage, margins) |
| Lower post-treatment mortality at 30 and 90 days11 | Facilitates pathologic lymph node staging |
| Able to target synchronous lung nodules where resection procedures would be extensive | Retrospective literature suggests an overall survival advantage over SBRT14,13 |
| **Disadvantages** | **Disadvantages** |
| Not usually utilized for tumors within 2 cm of the proximal bronchial tree due to high risk of toxicity | Not suitable for patients with poor lung function and numerous medical comorbidities |
| No pathological staging of lymph nodes | Post-surgical mortality (estimates 2–4% at 30 days, 3–5% at 90 days)11,14,15 |
| Side effects include: radiation pneumonitis, skin toxicity, odynophagia, rib fracture, pain, injury to nerves16 | Surgical risks include infection, air leak, hemorrhage, pain, deep vein thrombosis, fistula, injury to nerves16 |
| Response evaluation may be complicated by post-radiotherapy inflammation around the tumor17 | |

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**Table 3** Current randomised trials - SBRT versus surgery in medically operable NSCLC patients

| Trial | Country | Estimated No. of participants | Phase | Estimated study completion date | Comparison |
|-------|---------|-------------------------------|-------|--------------------------------|------------|
| 1     | USA     | 272                           | III   | December 2024                 | This will compare sublobar resection to SBRT in high risk peripheral tumors |
| 2     | China   | 76                            | II    | January 2026                  | This will compare radical resection to SBRT in peripheral tumors |
| 3     | USA     | 670                           | N/A   | September 2027                | This will compare lobectomy or segmentectomy to SBRT in central and peripheral tumors |

The recent SABRTOOTH Trial (UK)38 failed to meet recruitment targets and a large RCT was deemed not to be feasible.
poorer overall survival ($P = 0.001$) and disease-free survival ($P = 0.001$).

Gross tumor volume and planning target volume, which increased with increasing size of tumor, were also significantly associated with grade 2 or worse radiation pneumonitis. Compounding this potential toxicity of SBRT, it also appears that higher SBRT doses may be required to achieve adequate local control in T2 tumors. For instance, in the analysis of Davis et al., local control was associated with higher $BED_{10}$ ($>105$ Gy) for T2 tumors, but not in T1 tumors at a median follow-up of 17 months. All in all, this makes SBRT a less attractive option for larger tumors.

It should be noted that for patients who underwent surgery, the overall survival rate for those with T2 tumors is also less than that for T1 tumors. In an analysis by Nonaka et al., five-year OS for those with T2N0 tumors was 65% while that for T1N0 tumors was 85%. However, unlike toxicity of radiotherapy, which increases with increasing tumor size and PTV, morbidity of lobectomy in stage I tumors is less dependent on tumor size than other tumor factors such as age and other comorbidities, or lower FEV1.

**Centrally-located tumors**

Tumors located too closely (within 2 cm) to central structures such as trachea, bronchial tree or oesophagus result in higher doses to these OARs when delivering SBRT. In an analysis done by Timmerman’s group, where 60–66 Gy total was delivered to the tumor, 83% of the patients with peripheral lung tumors had two years freedom from severe (grade 3–5) toxicity while only 54% of the patients with central lung tumors were spared. Currently, studies have shown reduced toxicity when lower doses per fraction are used, with JROSG 10–1 showing the maximum tolerance dose to be 60 Gy in eight fractions, and RTOG 0813 reporting the maximum tolerance dose to be 60 Gy in 5 fractions, with a 7.2% probability of experiencing a dose-limiting-toxicity. However, it is not disputed that peripherally located tumors that are more distant from OARs have the potential to receive higher radiation doses with less risk of side effects.

**Risk of occult nodal metastases**

The above two factors: larger tumor size and centrally located tumors, have both been shown to correspond to a higher incidence of occult nodal metastases. Overall, 15–20% of patients with early stage NSCLC have occult nodal metastases on surgical pathologic review, but not all stage I tumors are created equal in this respect. Indeed, Seok et al. calculated rates of lymph node metastases by tumor size in 413 patients with tumors of 3 cm or less who underwent lymph node dissection. A total of 75 patients were postoperatively found to have positive nodes, with the largest group as expected being found in those with tumors of 26–30 mm (25/53 patients). In contrast, only 10/178 patients with tumor size 2 cm or less had nodal metastases detected postoperatively. In a retrospective analysis of 894 patients, Koike et al. also showed that preoperative tumor size of greater or equal to 2.0 cm was an independent predictor of mediastinal nodal metastasis, and such patients could be candidates for mediastinal node assessment by invasive modalities.

In a further effort to refine risk of nodal metastases by location of tumor, Bao et al. found that non-upper lobe NSCLC was a predictor of N1 or N2 node involvement. Meanwhile Ketchedian et al. analysed peripheral and central tumors, defined as those visualised within the inner third of the lung field, and determined that centrally located tumors had as high as a 50% risk of lymph node metastases. Indeed, for T1 tumors, central location was an even stronger prediction of lymph node metastases than tumor size.

Park et al. concluded that SUVmax and metabolic total volume were significant risk factors for occult lymph node metastases in patients with small NSCLC tumors. Upon doing a ROC analysis, the optimal cut-off values were 3.250 (sensitivity 83.3%, specificity 60%), and 3.055 (sensitivity 75.0%, specificity 67.8%) for SUVmax and metabolic total volume respectively. This is useful information as patients above the cutoff should be strongly recommended to go for pathologic nodal evaluation. To ensure increased accuracy of nodal staging, the upcoming VALOR trial includes mandatory pathologic assessment of any suspicious nodes >10 mm with SUV > 2.5 on PET CT, and the STABLEMATES trial has similar requirements.

The significance of occult nodal metastases cannot be underestimated. Patients who undergo SBRT without pathological nodal staging are taking the risk that occult nodal metastases may go undetected, thereby depriving the patient of potentially life extending chemotherapy. Indeed, in Rosen’s analysis, only 6% of the SBRT patients had a pathologic assessment of lymph nodes. Meanwhile, Paravati et al. noted that PET-CT staged NSCLC frequently underestimates true pathological stage, and in Crabtree’s analysis, final pathology upstaged 35% (161/462) of surgery patients.

A significant incidence of occult nodal metastases could explain the observation in several comparative studies that survival curves favor radiation over surgery early on (due to the issue of perioperative and postoperative mortality), but then cross between 12–36 months. The early survival advantage of SBRT may thus be “offset” by distal recurrence – indeed in RTOG 0236, Timmerman et al. there was a relatively high risk of disseminated failure of 22.1% despite good local regional control rates at three years.
Hence, the increased risk of lymph node metastasis that comes with larger and more central tumors, as well as presence of marginally PET avid nodes, would be factors pushing patients toward surgery rather than SBRT.

**Increased risk of toxicity from radiotherapy**

A subset of patients who may benefit from surgery are those at higher risk of increased toxicity from radiotherapy. For instance, Gold et al. studied a group of patients with systemic sclerosis who were treated with RT. Grade 1 or 2 late toxicity reactions were noted in 12/20 patients while grade 3 or higher toxicity occurred in 4/20 patients. Hence, in patients with scleroderma, risks and benefits of RT should be carefully discussed. Meanwhile, for patients with psoriasis or vitiligo, the Koebner phenomenon can occur where the skin changes occurring in those conditions can be seen at areas receiving radiotherapy. Finally, in patients who have received prior radiotherapy, late adverse effects have been reported in several studies especially after single fraction doses of >10 Gy. Hence on balance, this group of patients may derive more benefit and less risk from surgery rather than SBRT.

**Radioresistant histological tumor subtypes**

Woody et al. analysed the response of different histological subtypes of NSCLC treated with SBRT. On multivariate analysis, squamous histological subtype (HR 2.4, \(P = 0.008\)) was the strongest predictor of local failure, with a three year cumulative rate of local failure of 18.9\% versus 8.7\% for adenocarcinoma and 4.1\% for not-otherwise-specified. Meanwhile, Mak et al. genotyped lung SBRT patients for KRAS mutations and found that in patients with KRAS mutant tumors, there was significantly lower tumor control (67\% vs. 96\%) at one year. Finally, an analysis was done that found that low miR-29c levels correlated with shorter relapse-free survival of non-small cell lung carcinoma patients treated with radiotherapy, due to increased cell survival and reduced apoptotic response. In contrast, the specific histological subtype of tumor tended to matter less in surgical cases. For instance, in a study of post surgical patients with NSCLC, while patients with SCC tended to present with larger tumors, five-year survival rates were comparable to those with adenocarcinomas.

**Equivocal – favoring neither surgery nor SBRT**

**Pre-existing interstitial lung disease (ILD)**

It should be noted that for NSCLC patients in general, whether they undergo surgery or SBRT, those with interstitial lung disease have poorer prognosis. Indeed, postoperatively, the incidence of pneumonia (acute or exacerbation of disease) was higher in the interstitial lung disease group, while the five year OS was half that of the non-ILD group. It appears that ILD is also a poor predictor of survival and radiation toxicity for SBRT patients as well. Ueki et al. recorded significantly worse incidences of radiation pneumonitis (grade 2 or 3) in ILD versus non-ILD patients, and the three year overall survival tended to be worse in ILD patients (53.8\% versus 70.8\%). Hence for this group of patients, the decision to choose between SBRT or surgery is not an easy one and careful discussion of such cases at a multidisciplinary board of specialists may be advisable.

**Factors favoring SBRT**

**Elderly patients**

Traditionally, surgeons are more hesitant to offer radical operations to elderly patients. Indeed as patients’ ages increase, rates of comorbidities such as diabetes and hypertension are elevated as well, resulting in poorer surgical outcomes. Retrospective analyses have shown that patients are more likely to be offered sublobar resections than lobectomy which also has worse outcomes for tumor control. Meanwhile, SBRT has been known to be superior to no treatment in the “elderly” population, defined as age 70 or over. In an analysis of 3147 patients from the national cancer database, multivariate analysis revealed improved overall survival with SBRT compared with observation. In a retrospective analysis of 58 “very elderly” SBRT patients aged 80 or older (median 84.9), cancer specific survival rates were 73\% at two years. As expected, KPS of more or equal to 75 was associated with improved outcomes.

Most interestingly, in an Amsterdam Cancer Registry Study of 875 elderly patients (age 75 and above), comparing surgery to RT to no treatment across different time periods as SBRT became more widely available, an improvement in OS was confined to RT patients whereas no significant survival improvements were seen in the other groups. This confirms the utility of SBRT in this population. In contrast, for patients who underwent surgery, in a study of 338 patients older than age 70, it was shown that a significant predictor of morbidity by multivariate analysis is age (odds ratio of 1.09 a year), as well as thoracotomy as a surgical approach. Operative mortality in this group of patients was 3.8\% and morbidity was 47\%, on the higher end compared to the general population (generally in the range of 1–4\% at 30 days and 2–6\% at 90 days following lobectomies for NSCLC).

The 2014 recommendations of the EORTC Elderly task force state that surgical treatment should not be denied.
to elderly patients just on the basis of chronological age, but limited resections and omission of systematic mediastinal lymphadenectomy can be considered on the basis of retrospective data. In an analysis of quality of life after lobectomy for patients less than versus greater/equal to 70 years, physical functioning remained below baseline in the older group of patients at 6 and 12 months.73 No equivalent stratification of QOL in elderly/young patients has been carried out in SBRT patients, but it should be noted that overall QOL seems good after SBRT in general. Among the 22 patients in the ROSEL trial, SBRT was associated with better global health status and lower indirect costs of productivity loss. This fits in with other systematic reviews82,24 reporting few clinically significant changes in HRQOL scores after SBRT, whereas analysis of surgical patients showed increased dyspnea and fatigue persisting up to two years after surgery.73 Hence, on balance, SBRT may be a better option than surgery for the medically operable older patient.

Patients with reduced lung function/cardiac comorbidities

For patients with reduced lung function tests scores or increased risk of cardiac complications, SBRT may present lower risks than surgery. “Thorascore76 is a well validated tool that includes nine variables and predicts the risk of perioperative mortality. Thoracic revised cardiac risk index (RCRI) is a validated tool providing four parameters (pneumonectomy, previous ischemic heart disease, previous stroke or transient ischemic attack, creatinine >2 mg/dL) that are used to categorise patients into risk categories.77 Meanwhile, research has shown that in patients with preoperative FEV1 less than 35% predicted, 36% of surgical patients (lobectomies/wedge resections/pneumonectomies) had one or more complications within 30 days postoperatively, for example prolonged air leaks requiring a chest tube, pneumonias, and additional oxygen dependence.78 This underscores the not-insignificant risk of carrying out surgical resections in this group of patients.

In contrast, a number of studies, for example RTOG 0236,79 have shown that baseline PFT did not predict pulmonary toxicity following SBRT, nor did they predict overall survival. For these borderline operative patients, especially those with peripherally located tumors where large doses of radiation can be delivered with relatively low toxicity to OARs,80 SBRT may be a good choice.

Patients with synchronous lung nodules

Meanwhile, for patients who present with synchronous lung nodules in the ipsilateral or contralateral lobe where a curative surgical procedure would be extensive, SBRT has shown relatively good results. For instance, Owen et al.81 analysed 63 subjects with 128 metasynchronous and synchronous lung nodules treated with SBRT at the Mayo clinic between 2006 and 2012. A total of 18 had prior high dose EBRT to mediastinum or chest. With a median follow-up of 12.6 months, median SBRT specific OS and PFS were 35.7 months and 10.7 months respectively. About half the patients experienced acute toxicity but this was mostly grade 1 or 2. This report demonstrated the feasibility of SBRT to synchronous lung nodules. Furthermore, several studies have shown feasibility of lower dose SBRT for recurrent lung cancer,61,82,83 with local control rates of up to 96% at one year and freedom from distant progression rate at 74% at one year and 65% at two years.82

Patients with specific mutational status of tumors

Patients with certain tumor mutations have better outcomes after SBRT. For example, in an analysis by Blumenfeld et al., there was a trend towards improved PFS for EGFR mutation positive patients after SBRT, 25.4 months versus 16.7 months, and KRAS negative patients (17.8 months vs. 9.5 months). There appeared to be no difference in toxicity between patients with or without these mutations.84 Such studies could potentially identify a population of patients with better outcomes from SBRT.

Meanwhile, it should be noted that there are potentially immunogenic effects from SBRT. Studies have identified histologic features such as micropapillary predominant or solid with mucin-predominant subtypes or certain gene expression profiles as higher risk.85,86 For those borderline operable patients who opt for SBRT, these patients may be good candidates for treatment intensification with immunotherapy post SBRT. In comparison, the TRACERx cohort found that intertumor heterogeneity was associated with a higher occurrence of chromosome instability and thereby an increased risk of recurrence or death following surgery.87 Hence, more genomic sequencing of tumors can identify patients at higher risk after surgery or those who would benefit from treatment intensification after SBRT.

Conclusion

While waiting for the results of upcoming trials, upfront recommendation of SBRT as an option for operable patients has not yet entered international guidelines. However, this option should be discussed with borderline operable patients in view of the benefits of avoiding higher surgical mortality and morbidity. In certain cases, especially elderly patients with noncentrally located tumors and worse lung function tests scores, the use of SBRT may be more strongly recommended. However, nodal staging is
paramount: patients should be counselled that there is a possibility of PET scans missing occult positive nodes and pathological staging may well be the gold standard, providing critical information for guidance of adjuvant therapy. As more medically operable patients pursue SBRT as an option, we should keep in mind the additional possibility of surgically salvageable locoregional SBRT failures.

**Disclosure**

The authors declare that they have no potential conflicts of interest, financial interests, relationships and affiliations relevant to the subject of their manuscript.

**References**

1. Timmerman R, Paulus R, Galvin J *et al.* Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; 303 (11): 1070–6.

2. Nagata Y, Hiraoka M, Shibata T *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 (5): 989–96.

3. Onishi H, Shirato H, Nagata Y *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 (5): 1352–8.

4. Roesch J, Andratschke N, Guckenberger M. SBRT in operable early stage lung cancer patients. *Transl Lung Cancer Res* 2014; 3 (4): 212–24.

5. Hopmans W, Zwaan L, Senan S. Differences between pulmonologists, thoracic surgeons and radiation oncologists in deciding on the treatment of stage I non-small cell lung cancer: A binary choice experiment. *Radiother Oncol* 2015; 115 (3): 361–6.

6. Videtic GMM, Donington J, Giuliani M *et al.* Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017; 7 (5): 295–301.

7. Timmerman R, Papiez L, McGarry R *et al.* Extracranial stereotactic radioablation: Results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003; 124 (5): 1946–55.

8. Onishi H, Shirato H, Nagata Y *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.

9. Zhang J, Yang F, Li B *et al.* Which is the optimal biologically effective dose of stereotactic body radiotherapy for stage I non-small-cell lung cancer? A meta-analysis. *Int J Radiat Oncol Biol Phys* 2011; 81 (4): e305–16.

10. Timmerman RD, Paulus R, Pass HI *et al.* Stereotactic body radiation therapy for operable early-stage lung cancer: Findings from the NRG oncology RTOG 0618 trial. *JAMA Oncol* 2018; 4 (9): 1263–6.

11. Stokes WA, Bronsert MR, Meguid RA *et al.* Post-treatment mortality after surgery and stereotactic body radiotherapy for early-stage non-small-cell lung cancer. *J Clin Oncol* 2018; 36 (7): 642–51.

12. Shirvani SM, Jiang J, Chang JY *et al.* Lobectomy, sublobar resection, and stereotactic radiation for early-stage non-small cell lung cancers in the elderly. *JAMA Surg* 2014; 149 (12): 1244–53.

13. Wang S, Wang X, Zhou Q *et al.* Stereotactic ablative radiotherapy versus lobectomy for stage I non-small cell lung cancer: A systematic review. *Thorac Cancer* 2018; 9 (3): 337–47.

14. Peszi CM, Mallin K, Mendez AS, Greer Gay E, Putnam JB Jr. Ninety-day mortality after resection for lung cancer is nearly double 30-day mortality. *J Thorac Cardiovasc Surg* 2014; 148 (5): 2269–77.

15. Powell HA, Tata LJ, Baldwin DR, Stanley RA, Khakwani A, Hubbard RB. Early mortality after surgical resection for lung cancer: An analysis of the English National Lung cancer audit. *Thorax* 2013; 68 (9): 826–34.

16. Ong BH. Surgery versus stereotactic body radiotherapy in medically operable non-small cell lung cancer. *J Xiangya Med* 2018; 3: 26.

17. Van Schil P. Surgery compared to stereotactic body radiation therapy for early-stage non-small cell lung cancer: Better, equivalent or worse? *J Thorac Dis* 2017; 9 (11): 4230–2.

18. Aznar MC, Warren S, Hoogeman M, Josipovic M. The impact of technology on the changing practice of lung SBRT. *Phys Med* 2018; 47: 129–38.

19. Su S, Scott WJ, Allen MS *et al.* Patterns of survival and recurrence after surgical treatment of early stage NSCLC in ACOSOG Z0030 (ALLIANCE) trial. *J Thorac Cardiovasc Surg* 2014; 147 (2): 747–53.

20. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung cancer study group. *Ann Thorac Surg* 1995; 60 (3): 615–22 discussion 622–3.

21. Brunelli A, Kim AW, Berger KI, Addirizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143 (5 Suppl): e166S–905.

22. Postmus P, Kerr K, Oudkerk M *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28 (suppl_4): iv1–iv21.

23. Schneider BJ, Daly ME, Kennedy EB *et al.* Stereotactic body radiotherapy for early-stage non-small-cell lung cancer: American Society of Clinical Oncology endorsement of the
24 Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143 (5 Suppl): e278S–313S.

25 Tian S, Higgins KA, Curran WJ, Cassidy RJ. Stereotactic body radiation therapy vs. surgery in early-stage non-small cell lung cancer: Lessons learned, current recommendations, future directions. *J Thorac Dis* 2018; 10 (3): 1201–4.

26 Fakiris AJ, McGarry RC, Yiannoutsos CT 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 (3): 677–82.

27 Baumann P, Nyman J, Hoyer M 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 (20): 3290–6.

28 Ricardi U, Filippi AR, Guarneri A et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: Results of a prospective trial. *Lung Cancer* 2010; 68 (1): 72–7.

29 Videtic GM, Hu C, Singh AK et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG oncology RTOG 0915 (NCCCTG N0927). *Int J Radiat Oncol Biol Phys* 2015; 93 (4): 757–64.

30 Sun B, Brooks ED, Komaki RU et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. *Cancer* 2017; 123 (16): 3031–9.

31 Chang JY, Senan S, Paul MA 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 (6): 630–7.

32 Rosen JE, Salazar MC, Wang Z et al. Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer. *J Thorac Cardiovasc Surg* 2016; 152 (1): 44–54.e9.

33 Versteegen NE, Oosterhuis JW, Palma DA 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 (6): 1543–8.

34 Crabtree TD, Denlinger CE, Meyers BF et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2010; 140 (2): 377–86.

35 National Library of Medicine (US). Identifier: NCT02468024. JoLT-Ca Sublobar Resection (SR) Versus Stereotactic Ablative Radiotherapy (SABR) for Lung Cancer (STABLE-MATES). Cited [05 May 2019.] Available from URL: https://clinicaltrials.gov/ct2/show/NCT02468024

36 National Library of Medicine (US). Identifier: NCT01753414. Radical Resection Vs. Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC (POSTILV). Cited [05 May 2019.] Available from URL: https://clinicaltrials.gov/ct2/show/NCT01753414

37 National Library of Medicine (US). Identifier: NCT02984761. Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy (VALOR). Cited [05 May 2019.] Available from URL: https://clinicaltrials.gov/ct2/show/NCT02984761

38 National Library of Medicine (US). Identifier: NCT02629458. A Study to Determine the Feasibility and Acceptability of Conducting a Phase III Randomised Controlled Trial Comparing Stereotactic Ablative Radiotherapy With Surgery in patients With Peripheral Stage I nOn-small Cell Lung Cancer considered Higher Risk of Complications From Surgical Resection (SABRTOOTHv1). Cited [05 May 2019.] Available from URL: https://clinicaltrials.gov/ct2/show/NCT02629458

39 Dunlap NE, Larner JM, Read PW et al. Size matters: A comparison of T1 and T2 peripheral non-small-cell lung cancers treated with stereotactic body radiation therapy (SBRT). *J Thorac Cardiovasc Surg* 2010; 140 (3): 583–9.

40 Champ S, Chang TC, Biswas T et al. Results of stereotactic body radiation therapy (SBRT) for T2 lung cancer: Outcomes of longer term follow-up. *J Clin Oncol* 2017; 35 (15_Suppl): 8542–2.

41 Allibhai Z, Taremni M, Bezjak A et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013; 87 (5): 1064–70.

42 Davis JN, Medbery C, Sharma S et al. Stereotactic body radiotherapy for early-stage non-small cell lung cancer: Clinical outcomes from a National Patient Registry. *J Radiat Oncol* 2015; 4 (1): 55–63.

43 Nonaka M, Kadokura M, Yamamoto S et al. Tumor dimension and prognosis in surgically treated lung cancer: For intentional limited resection. *Am J Clin Oncol* 2003; 26 (5): 499–503.

44 Myrødal G, Gustafsson G, Lambe M, Hörte LG, Ståhle E. Outcome after lung cancer surgery. Factors predicting early mortality and major morbidity. *Eur J Thorac Cardiovasc Surg* 2001; 20 (4): 694–9.

45 Timmerman R, McGarry R, Yiannoutsos C 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 (30): 4833–9.

46 Kimura T, Nagata Y, Harada H et al. Phase I study of stereotactic body radiation therapy for centrally located stage IA non-small cell lung cancer (JROS910). *Int J Clin Oncol* 2017; 22 (5): 849–56.

47 Bezjak A, Paulus R, Gaspar LE et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non--small-cell lung cancer: NRG oncology/RTOG 0813 trial. *J Clin Oncol* 2019; 37 (15):
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1316–25. https://doi.org/10.1200/JCO.18.00622. Published online April 03, 2019.

48 White A, Swanson SJ. Surgery versus stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer: Less is not more. J Thorac Dis 2016; 8 (Suppl 4): S399–405.

49 Seok Y, Yang HC, Kim TJ et al. Frequency of lymph node metastasis according to the size of Tumors in resected pulmonary adenocarcinoma with a size of 30 mm or smaller. J Thorac Oncol 2014; 9 (6): 818–24.

50 Koike T, Koike T, Yamato Y, Yoshiya K, Toyabe S. Predictive risk factors for mediastinal lymph node metastasis in clinical stage I A non-small-cell lung cancer patients. J Thorac Oncol 2012; 7 (8): 1246–51.

51 Bao F, Yuan P, Yuan X, Lv X, Wang Z, Hu J. Predictive risk factors for lymph node metastasis in patients with small size non-small cell lung cancer. J Thorac Dis 2014; 6 (12): 1697–703.

52 Ketchedjian A, Daly BD, Fernando HC et al. Location as an important predictor of lymph node involvement for pulmonary adenocarcinoma. J Thorac Cardiovasc Surg 2006; 132 (3): 544–8.

53 Park SY, Yoon JK, Park KJ, Lee SJ. Prediction of occult lymph node metastasis using volume-based PET parameters in small-sized peripheral non-small cell lung cancer. Cancer Imaging 2015; 15: 21.

54 Paravati AJ, Johnstone DW, Seltzer MA, Johnstone CA. Negative predictive value (NPV) of FDG PET-CT for nodal disease in clinically node-negative early stage lung cancer (AJCC 7th ed T1-2aN0) and identification of risk factors for occult nodal (pN1-N2) metastasis: Implications for SBRT. Trans Cancer Res 2014; 3 (4): 313–9.

55 Allbain KS, Swann RS, Rutsch VW et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. Lancet 2009; 374 (9687): 379–86.

56 van Meerbeeck JP, Kramer GW, Van Schil PE et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007; 99 (6): 442–50.

57 Timmerman RD, Hu C, Michalski J et al. Long-term results of RTOG 0236: A phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014; 90 (15): S30.

58 Gold DG, Miller RC, Petersen IA, Osborn TG. Radiotherapy for malignancy in patients with scleroderma: The Mayo Clinic experience. Int J Radiat Oncol Biol Phys 2007; 67 (2): 559–67.

59 Levine EL, Ribeiro GG. Vitiligo and radiotherapy: The Koebner phenomenon demonstrated in patients with vitiligo undergoing radiotherapy for carcinoma of the breast. Clin Oncol (R Coll Radiol) 1994; 6 (2): 133–4.

60 Stevens KR, Britsch A, Moss WT. High-dose reirradiation of head and neck cancer with curative intent. Int J Radiat Oncol Biol Phys 1994; 29 (4): 687–98.

61 Patel NR, Lanciano R, Sura K. Stereotactic body radiotherapy for re-irradiation of lung cancer recurrence with lower biological effective doses. J Radiat Oncol 2015; 4 (1): 65–70.

62 Woody NM, Stephens KL, Andrews M et al. A histologic basis for the efficacy of SBRT to the lung. J Thorac Oncol 2017; 12 (3): 510–9.

63 Mak RH, Hermann G, Lewis JH et al. Outcomes by tumor histology and KRAS mutation status after lung stereotactic body radiation therapy for early-stage non–small–cell lung cancer. Clin Lung Cancer 2015; 16 (1): 24–32.

64 Arechaga-Ocampo E, Lopez-Camarillo C, Villegas-Sepulveda N et al. Tumor suppressor miR-29c regulates radioresistance in lung cancer cells. Tumour Biol 2017; 39 (3): 1–14.

65 Miyazaki K, Satoh H, Kurishima K et al. Impact of interstitial lung disease on survival for patients with non–small–cell lung cancer. Anticancer Res 2009; 29 (7): 2671–4.

66 Ueki N, Matsuo Y, Togashi Y et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung cancer. J Thorac Oncol 2015; 10 (1): 116–25.

67 Tsutani Y, Tsubokawa N, Ito M et al. Postoperative complications and prognosis after lobar resection versus sublobar resection in elderly patients with clinical stage I non-small-cell lung cancer. Eur J Cardiothorac Surg 2018; 53 (2): 366–71.

68 Nanda RH, Liu Y, Gillespie TW et al. Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: A National Cancer Data Base analysis. Cancer 2015; 121 (23): 4222–30.

69 Palma D, 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.

70 Bryant AS, Rudemiller K, Cerfolio RJ. The 30-versus 90-day operative mortality after pulmonary resection. Ann Thorac Surg 2010; 89 (6): 1717–22 discussion 1722–3.

71 Pallis AG, Gridelli C, Wedding U et al. Management of elderly patients with NSCLC; updated expert’s opinion paper: EORTC elderly task force, lung cancer group and International Society for Geriatric Oncology. Ann Oncol 2014; 25 (7): 1270–83.

72 Burfeind WR Jr, Tong BC, O’Branski E et al. Quality of life outcomes are equivalent after lobectomy in the elderly. J Thorac Cardiovasc Surg 2008; 136 (3): 597–604.

73 Chen H, Louie AV, Boldt RG, Rodrigues GB, Palma DA, Senan S. Quality of life after stereotactic ablative radiotherapy for early-stage lung cancer: A systematic review. Clin Lung Cancer 2016; 17 (5): e141–9.
75 Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: A systematic review. Lung Cancer 2013; 81 (1): 11–26.

76 Falcoz PE, Conti M, Brouchet L et al. The thoracic surgery scoring system (Thoracoscore): Risk model for in-hospital death in 15,183 patients requiring thoracic surgery. J Thorac Cardiovasc Surg 2007; 133 (2): 325–32.

77 Brunelli A, Varela G, Salati M et al. Recalibration of the revised cardiac risk index in lung resection candidates. Ann Thorac Surg 2010; 90 (1): 199–203.

78 Linden PA, Bueno R, Colson YL et al. Lung resection in patients with preoperative FEV1 < 35% predicted. Chest 2005; 127 (6): 1984–90.

79 Stanic S, Paulus R, Timmerman RD et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy (SBRT) for early stage peripheral non-small cell lung cancer: An analysis of RTOG 0236. Int J Radiat Oncol Biol Phys 2014; 88 (5): 1092–9.

80 Kelley KD, Benninghoff DL, Stein JS et al. Medically inoperable peripheral lung cancer treated with stereotactic body radiation therapy. Radiat Oncol 2015; 10: 120.

81 Owen D, Olivier KR, Mayo CS et al. Outcomes of stereotactic body radiotherapy (SBRT) treatment of multiple synchronous and recurrent lung nodules. Radiat Oncol 2015; 10: 43.

82 Janssen S, Käsmann L, Rudat V, Rades D. Stereotactic body radiation therapy (SBRT) for recurrent non-small cell lung cancer (NSCLC). Anticancer Res 2016; 36 (2): 825–8.

83 Trovo M, Minatel E, Durofil E 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 (5): 1114–9.

84 Blumenfeld PA, Kreinbrink PJ, Marwaha G. Stereotactic body radiation therapy outcomes for early stage and Oligometastatic non–small cell lung cancer based on molecular profile. Int J Radiat Oncol Biol Phys 2017; 98 (1): 230–9.

85 Postow MA, Callahan MK, Barker CA et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012; 366 (10): 925–31.

86 Leeman JE, Rimner A, Montecalvo J et al. Histologic subtype in Core lung biopsies of early-stage lung adenocarcinoma is a prognostic factor for treatment response and failure patterns after stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2017; 97 (1): 138–45.

87 Jamal-Hanjani M, Wilson GA, McGranahan N et al. Tracking the evolution of non-small-cell lung cancer. N Engl J Med 2017; 376 (22): 2109–21.