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Treatment of Early Stage Non-Small Cell Lung Cancer: Surgery or Stereotactic Ablative Radiotherapy?

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The management of early-stage Non-small Cell Lung Cancer (NSCLC) has improved recently due to advances in surgical and radiation modalities. Minimally-invasive procedures like Video-assisted thoracoscopic surgery (VATS) lobectomy decreases the morbidity of surgery, while the numerous methods of staging the mediastinum such as endobronchial and endoscopic ultrasound-guided biopsies are helping to achieve the objectives much more effectively. Stereotactic Ablative Radiotherapy (SABR) has become the frontrunner as the standard of care in medically inoperable early stage NSCLC patients, and has also been branded as tolerable and highly effective. Ongoing researches using SABR are continuously validating the optimal dosing and fractionation schemes, while at the same time instituting its role for both inoperable and operable patients.
Keywords: Central lung tumour, peripheral lung tumour, Surgery, SABR, SBRT

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer death worldwide. Approximately 15 to 20% of NSCLC patients present with early or localised disease; this figure is expected to grow with the increased use of low-dose computed tomography (CT) scans for screening (1). The standard treatment for operable stage I NSCLC is lobectomy or pneumonectomy with mediastinal lymphadenectomy. Five-year survival rates of early stage NSCLC patients range between 60 and 80% after surgical resection (2). Despite major developments in minimally-invasive surgical procedures, a substantial proportion of patients are not suitable for surgery due to their comorbidities. Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) has recently emerged as a benchmark of care for medically inoperable patients. SABR is a more concise and well-planned treatment procedure with enhanced local control and survival while minimising treatment cost against conventional radiotherapy.

Cancer-specific outcomes of patients in SABR series are generally comparable to surgical series; however, overall survival results are usually reported to be superior in the surgical cohorts because of major differences in the two groups. Approximately one in every three patient dies as a result of comorbidity-related complications instead of cancer in SBRT series. As a result, in patients with operable stage I NSCLC, surgical operation continues to be the benchmark of care. In this review, we plan to summarise the published evidence for the treatment of early stage NSCLC with surgery and SABR.

THE SURGICAL MANAGEMENT OF EARLY STAGE NSCLC

Surgical resection remains the treatment of choice for patients with stage I or II NSCLC, since it provides the optimal likelihood of cure and long-term survival. Such an operation includes both complete anatomical resection of the tumour and mediastinal lymph node evaluation (3).

PREOPERATIVE EVALUATION

Patients with NSCLC who are surgical candidates are often cigarette smokers, which makes them vulnerable to athero-

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sclerotic cardiovascular and pulmonary diseases. A thorough cardiovascular evaluation and pulmonary function tests (PFT) are extremely important for preoperative evaluation. Forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) are the most common PFT measurements used; their values are inversely correlated with postoperative complications, including death. The American College of Chest Physicians (ACCP) recommends that candidates for resection with either FEV1 or DLCO <80% of normal should undergo an estimation of their postoperative pulmonary reserves. Patients with predicted postoperative FEV1<40% or DLCO<40% are at increased operative risk, and further workup with cardiopulmonary exercise testing should be considered. Further, FEV1 <30% is considered prohibitive for lobectomy, and sublobar resection or radiation treatment should be considered instead (4).

PREOPERATIVE MEDIASTINAL EVALUATION

The status of the mediastinum is very important in determining the optimal treatment for patients with NSCLC. Computed tomography (CT) and 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging helps with analysis of the mediastinum, but the shortcomings of these techniques often oblige an invasive evaluation. False-negative rates of PET-CT in staging the mediastinum vary from 5 to 15%, and false-positive rates vary from 0 to 53% (5). As a result, invasive mediastinal staging is necessary to correctly identify mediastinal involvement. Methods used for this purpose include mediastinoscopy, endobronchial ultrasound and needle aspiration (EBUS-NA), endoscopic ultrasound and needle aspiration (EUS-NA), and video-assisted thoracoscopic surgical (VATS) approaches. The ACCP proposes invasive confirmation of nodal disease in patients with both discrete mediastinal lymph node enlargement, a central tumour, and clinical N1 disease (6); the second two are both predictors of occult N2 disease (5). Needle techniques are most useful in patients with radiographically enlarged mediastinal nodes, while mediastinoscopy remains the gold standard in patients with normal-sized nodes. Eventually, the prevalence of occult N2 disease in patients with clinical stage I NSCLC is low (4.9-6.1%) (7). Consequently, invasive staging of the mediastinum could potentially be abandoned in patients with peripheral clinical stage I NSCLC and PET-negative mediastinal nodes (5-7).

ADVANTAGES OF SURGERY

NSCLC necessitates a complete resection with negative microscopic margins (R0 resection). Furthermore, the location and characteristics of the tumour dictate the magnitude of the operation. Stage I and II NSCLC are susceptible to anatomical resection, which lets both removal of the tumour and its draining lymphatic tissue regardless of some inconsistency in their presentation. Smaller peripheral tumours can be entirely resected with lobectomy (or maybe segmentectomy); however, larger central tumours invading vascular or airway structures may entail bilobectomy or pneumonectomy. If anatomically appropriate and if negative surgical margins can be obtained, lung-sparing anatomic resection (sleeve lobectomy) is selected over pneumonectomy. The scope of resection for early-stage disease remains somewhat controversial. The standard for early-stage NSCLC has been lobectomy with systematic mediastinal lymph node evaluation, even though sublobar "parenchymal sparing" resection is commonly employed in patients with poor cardio-pulmonary reserve. The rates of operative mortality and morbidity for lobectomy are 1-5% (8-10) and 26-37%, respectively (8, 10), and are higher in those with underlying pulmonary disease.

One prospective randomised controlled trial comparing lobectomy with sublobar resection for early-stage lung cancer (T1N0 tumours) was performed between 1982 and 1988 by the Lung Cancer Study Group. This particular experiment recognised lobectomy as the benchmark surgical technique for early stage NSCLC since the recurrence rate was significantly lower, although only a minor increase in overall survival was reported (10). However, over the last decade, predominantly single institution retrospective series have demonstrated equivalent regional recurrence and survival rates for sublobar resections compared with lobectomy for small node-negative tumours (11). Specifically, anatomic segmentectomy may result in better recurrence-free survival compared with wedge resection and have almost similar rates of recurrence and survival following lobectomy (11, 12-13). A prospective, randomised, multi-institutional study (CALGB 140503) is currently being conducted where sublobar resection is compared to lobectomy for stage I, ≤2 cm NSCLC.

MINIMALLY INVASIVE SURGICAL APPROACHES

It has become clear that VATS lobectomy has an advantage over thoracotomy in terms of morbidity, especially in patients with poor pulmonary function (14), and can be performed under sound oncological principles. VATS lobectomy has been demonstrated to have a lower incidence of arrhythmia, blood transfusion, renal failure, need for re-intubation, and shorter length of hospital stay and chest tube duration than open thoracotomy (8, 15). Differences in postoperative mortality between VATS and open lobectomy have been more difficult to show, probably owing to the overall small number of events (8, 15).

INTRAOPERATIVE EVALUATION OF MEDIASTINAL LYMPH NODES

For the management of NSCLC, intraoperative staging is very important and can be done either by dissection or sampling of mediastinal lymph nodes during the operation. Improved pathological staging and theoretical therapeutic benefit are the possible advantages of a systematic mediastinal lymph node dissection. Whether survival is improved by mediastinal lymph node dissection compared to mediastinal lymph node sampling at the time of lobectomy for patients with early-stage NSCLC (T1 or T2, N0 or non-hilar N1) was recently validated in a randomised multi-institutional prospective trial (16). No statistically significant differences were observed for local, regional, or distant recurrence, and overall survival rates between the two groups. Nonetheless, the authors of this research suggested that all patients with operable NSCLC should go through mediastinal lymph node dissection since it delivers the most precise staging information and does not increase surgical morbidity. For patients going through VATS lobectomy this continues to be a vital consideration.

THE STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR EARLY STAGE LUNG CANCER

Even though lobectomy is the standard of care for stage I NSCLC patients, many patients may not have surgery because of medical comorbidities or may refuse the surgery. For such patients, SABR (17) has become an alternative treatment and has the advantage of a shorter and more certain course of high-dose radiation delivery compared to conventional radiation.

SABR TECHNIQUE

Stereotactic radiosurgery for intracranial neoplasms has been in use since the 1950s. Tumour movement with respiration that is outside of the central nervous system (CNS) can be quite significant, and rigid immobilisation is not possible, which makes radiosurgery more complex. The first attempts at radiosurgery outside the CNS were pioneered in the 1990s and have been further refined to the present.

Many of the modern technological advances in imaging and radiotherapy are used in SABR. These include a conventional linear accelerator in fixed field mode (18) or dynamically with intensity modulated fixed field (intensity modulated radiotherapy - IMRT) (19) or arc technique (volumetric arc therapy commercially known as RapidArc or VMAT) (20). It can also be given using Tomotherapy (Wisconsin, USA) (a linear accelerator specifically designed to irradiate using the arc technique) (21) and with a robotic mounted linear accelerator (Cyberknife; Stanford,USA) (22). The reported results utilised most of the technological options. We have a range of platforms that are available which can perform SABR. Nonetheless, the most commonly used are those which can provide highly conformal radiation and some sort of image guidance to identify and compensate for respiratory tumour motion. Outcome comparisons using different techniques appear to be similar. There is, however, a general perception that, as a high precision technique with a need for technical infrastructure and expertise, it is best delivered in departments with the appropriate expertise, regardless of the technology employed.

In systems where 2-D imaging is used for image guidance, metallic fiducial markers are frequently placed in and around the tumour to help with tumour localisation and tracking during the treatment (23). Patients are simulated using a high-quality, 4-dimensional CT (4D-CT), which assesses tumour position at each phase of the respiratory cycle (24). Respiratory cycles can be improved by means of abdominal compression, breath-holding techniques, or respiratory gating, in which treatment is delivered only during the phases of respiration where the tumour location is predictable (25).

Planning treatment volume (PTV) is identified by the tumour itself (termed gross tumour volume, or GTV) on the treatment planning CT, accuracies made to account for respiratory motion (internal target volume, or ITV), and an additional margin (typically 5-7 mm) to calculate for errors in patient position at the time of treatment. The planning algorithm contains a minimum percentage (usually 95%) of this volume to the prescribed dose of radiation. Dose homogeneity is less of a worry in SABR, and radiation doses are frequently 20-30% higher than the prescribed dose in the central portions of the tumour. Dose fall-off from the periphery of the PTV is rapid, often dropping to 50% of the prescribed dose within 1-2 cm. During treatment, tumour location and motion are verified through image guidance techniques (26).

CLINICAL EFFICACY OF SABR

Before the use of SABR, inoperable stage I NSCLC patients were either not treated or treated with conventionally fractionated radiotherapy (CFRT), which is directed as small, daily radiation doses over multiple weeks. Tumour control was suboptimal, even at doses as high as 80 Gy (27). Local control rates were around 30-60% and overall 5-year survival rates were 6-32% (27). SABR was investigated as a method to deliver biologically higher equivalent doses to improve outcomes. A phase I trial from Indiana University was one of the first studies to show that SABR at doses up to 60-66 Gy

in 3 fractions was feasible and secure in early-stage NSCLC (28). These findings led to prospective trials evaluating the use of SABR in the United States (29), Europe (30, 31) and Asia (32-34). Using various dose and fractionation schemes, tumour control rates were uniformly excellent, ranging from 78 to 97%. Despite noteworthy medical comorbidities among the majority of the patients, overall survival rates were remarkable. Radiation Therapy Oncology Group (RTOG) 0236, a multi-institutional cooperative group trial initiated in 2002 and reported in 2010, enrolled 59 patients with peripherally located NSCLC tumours <5 cm which were treated with SABR to a dose of 54 Gy in 3 fractions. There was only one local failure within a treated volume, and the 3-year disease-free survival rate of 48% and overall survival rate of 56% were comparable to those of definitive surgical resection (17). Most patients who recurred had distant metastasis (22% at 3 years). A retrospective and much larger series from the Netherlands notified 2-year rates of local, regional, and distant recurrence of 4.9%, 7.8%, and 14.7%, respectively (35-37).

TABLE 1. Primary outcomes in major stereotactic ablative radiotherapy studies

	Dose/ Fractions	Local Control	Overall Survival
Timmerman et al. RTOG 0236 (17)	54Gy/3	98%	56%
Lagerwaard et al. (30)	60Gy/3-8	97%	64%
Baumann et al. (31)	45Gy/3	92%	60%
Nagata et al. (32)	48Gy/4	94%	72-83%
Hara et al. (33)	30-34Gy/1	78%	41%
Senthi et al. (35)	54-60Gy/3-8	96%	67%
van der Voont et al. (48)	60Gy/3	96%	96%
Widder et al. (56)	60Gy/3-8	95%	72%
Hamamoto et al. (57)	48-60Gy/4-5	87%	96%
Shibamoto et al. (58)	44-52Gy/4	85%	80%

Gy: Gray; RTOG: radiation therapy oncology group

SABR FOR PATIENTS WITH INOPERABLE EARLY STAGE LUNG CANCER

Conventionally fractionated radiotherapy for stage I NSCLC has shown inferior outcomes and these results are linked to insufficient radiation doses. The delivery of 60 Gy (in two phases of 30 Gy in 10 fractions) resulted in a 5-year survival rate of 38% for patients with primary tumours less than 2 cm in size, 22% for tumours 2-3 cm in size, 5% for tumours 3-4 cm in size, and 0% for larger tumours (38). The majority of studies concluded that patients receiving higher radiation doses have better treatment outcomes (39, 40). Based on biological and statistical modelling of tumour responses to various radiation dose levels, it has been shown that doses as high as 80 to 90 Gy ensure a progression-free survival rate of 50% (41). This rate is much higher than those of most CFRT regimens. In SABR, high doses per limited number of fractions are used, although the actual biologically equivalent dose (BED) for the eradication is not yet completely understood (42). When a sufficient dose (BED ≥ 100 Gy) is used, it has been noted in most clinical studies that the success rate of local control is over 90%. This can be verified by the dose-response curve, which stabilises at this level (43). These response levels are 50-60% higher than rates seen in CFRT (40, 42). The outcomes of major prospective and retrospective clinical studies on SABR are summarised in Table 1.

Peripheral versus central tumours

In SABR, which is also known as "radiosurgery," extremely high ablative doses are used to treat the tumour. The dose received by the surrounding tissue is important for toxicity. The sequela of ablation is related to the functional character of the tissue, regardless of whether it is parallel or serial. The lung, kidney and liver are made up of parallel tissues, which can continue to perform their tasks even after partial removal, as long as adequate organ volume is present to maintain its normal tasks. If one section is harmed in serial tissues (e.g. spinal cord or bowel), it will cause the entire organ to fail. The lung primarily consists of parallel tissues, but parts of the lung such as the trachea and proximal bronchial tree are made up of serial tissue. Tumours that are located inside 2cm of the proximal bronchial tree are classified as central, whereas tumours outside are peripheral for SABR classification.

Peripheral tumours

Peripheral lung tumours are surrounded by only parallel tissue, and no maximum point-dose limit has been identified for their treatment. A latest cooperative group study enrolled 55 patients, 80% with stage IA and 20% with stage IB peripheral NSCLC (17). Patients with bronchoalveolar histology were excluded from the study. Patients were given 3x20 Gy (BED of 180 Gy, without heterogeneity correction) radiation doses to their identified tumour, and were re-examined by serial computed tomography (CT). With a median follow-up of 34 months, only one patient had a local tumour failure, establishing a 97.6% local control rate. Out of the 55 evaluable patients, three encountered recurrences in the initially involved lobe with a 90.6% 3-year local control rate. Two patients had nodal failures with an 87.2% 3-year regional control rate, and 11 patients had disseminated recurrences with a 22.1% 3-year distant failure rate. An estimated overall survival of 55.8% was observed after three years. Among the 26 deaths, only 10 were directly due to cancer, whereas the remaining 16 died as a result of comorbidities owing to stroke or myocardial infarc-

tion. This shows the dilemma in identifying the exact survival rate as a way of determining the efficacy of treatment procedures for these medically fragile people. Among the cohort, 7 patients were diagnosed with grade 3 or higher pulmonary complications, such as hypoxia, pneumonitis, and pulmonary function test changes. It is noteworthy to mention that the study scored any changes in pulmonary function as toxicity; on the other hand, almost all of these patients suffered from various lung diseases where chronic obstructive pulmonary disease (COPD) exacerbations were frequently noticed.

Radiation Therapy Oncology Group 0236 has shown a perfect local control rate (97.6%) by applying 3 doses of 20 Gy (18 Gy with heterogeneity correction). As mentioned earlier, the dose response may plateau at 100 Gy BED, which led investigators to question the dose levels used in this study, and whether they were higher than necessary (47). RTOG recently compared 34 Gy in a single fraction versus 48 Gy in 4 fractions in a randomised phase 2 clinical trial. Initial results were recently presented at the ASTRO 2013 meeting and the toxicity rate was 9.8% vs. 13.3%, respectively. One year local control and overall survival rates were 97.1% vs. 97.6% and 85.4% vs. 91.1%, respectively. These studies will ultimately help to set the most effective radiation dose and treatment schedule for patients with inoperable peripheral tumours.

Central tumours

Tumours that are centrally located are too close to both parallel tissues (normal lung) and serial tissues (trachea, bronchial tree, or oesophagus), as well as imperfectly categorised tissues (heart and great vessels), which raised the question of whether 100 Gy BED or a higher dose is applicable without causing damage to the normal tissues. Numerous experiments of SBRT for lung cancer have failed to produce any conclusive evidence of toxicity to the heart and great vessels with focal radiation; nonetheless, there is always a risk of cardiotoxicity with chest radiotherapy. Other clinical experiments have observed that radiotherapy of lung tumours may be affected by other complications of the patients. An early phase 2 study which treated patients with 60 to 66 Gy radiation dose in 3 segments for a period of 1 to 2 weeks caught the attention for the first time on the importance of central versus peripheral tumour locations (17). Forty-six percent of the patients diagnosed with central tumours and 17% with peripheral tumours were found to have grade 3 or higher toxicity over a period of 2 years. Six deaths were reported as treatment-related. They consisted of four bacterial pneumonia, one pericardial effusion and one haemoptysis, which was later found to be related to carinal recurrence.

Several recent studies have revealed that lower fraction radiation doses are very effective and safe for treating central tumours with SBRT. Previous Japanese studies (41, 44), which used lesser fractions without any tissue constraints revealed no differences in toxicity for the treatment of central versus peripheral tumours. A similar study in Europe has shown over 90% local control for a treatment program of 60 Gy in 8 fractions (7.5 Gy/fraction) for 3 years (18). RTOG recently finished the accrual for the 0813 trial, which is a dose escalation study, analysing doses from 50 Gy to 60 Gy (10 Gy to 12 Gy per fraction in 5 fractions). At the conclusion of this trial (60 Gy in 5 fractions), it is evident that the toxicity level was not excessive.

SABR FOR PATIENTS WITH OPERABLE EARLY STAGE LUNG CANCER

Today's standard of care for patients with operable lung cancer is undoubtedly surgical resection. At the same time, further studies are underway to test whether SABR could also be effective for patients with operable tumours. A Japanese study analysed the effects on 87 operable patients who went through SABR for stage I NSCLC and were observed over a 55-month period (19). It showed a 92% local control rate for T1 tumours, which is a success rate that is almost the same as that of lobectomy; however, the local control rate drops to 73% for T2 tumours. Five-year overall survival rates were reported to be 72% for stage IA and 62% for stage IB, again similar to surgical series. Comparable results have also been reported from the Netherlands; outcomes in patients are similar to those reported in the surgical literature (93% local control, 85% 3-year survival rate) (20). This suggests overall consistent results when enrolling patients into randomised trials comparing surgery and SABR. The RTOG 0618 study has been recently presented as a phase II trial in operable patients. With a median follow-up of 25 months, 2-year primary tumour failure rate was 7.7%; 2-year estimates of PFS and OS were 65.4% and 84.4%, respectively. In this trial, it was concluded that SBRT appears to be associated with a high rate of primary tumour control, moderate treatment-related morbidity, and the infrequent need for surgical salvage in operable early stage lung cancer patients with peripheral lesions.

The introduction of SABR faces a major obstacle for operable patients due to inadequate proven data, since SABR is a relatively new technology, which has seen limited application primarily because of the limited number of medically operable patients. Furthermore, it is hard to conclude which patients will be well controlled in the first few months after SABR. An appropriate strategy for an inoperable patient is to wait to verify the response of SBRT where there is no other treatment available; however, for operable patients, certain indications will initiate alternative salvage treatments (21).

On top of that, dissection of lymph nodes during surgery often offers valuable information for tumour staging, but for

TABLE 2. Toxicity outcomes in major stereotactic ablative radiotherapy studies

	TOXICITY(%)								
	General Toxicity	RP	RF	RD	Fatigue	Dyspnea	Esophagitis	Fibrosis	Pain
Timmerman et al. RTOG 0236 (17)	12.7% G1-2	NA	NA	NA	NA	NA	NA	NA	NA
	3.6% G3-4								
	No G5								
Lagerwaard et al. (30)	No G5	2	3	3	25	10	NA	NA	3
Baumann et al. (31)	No G4-5	18	15	44	30	26	4	35	19
Nagata et al. (32)	No more than G3	NA	NA	NA	NA	NA	NA	NA	NA
Hara et al. (33)	Only 2 patients had RP G2-3	NA	NA	NA	NA	NA	NA	NA	NA
Xia T et al. (34)	No Grade 4-5 RP	2.3	NA	NA	NA	NA	NA	NA	NA
Onishi et al. (41)	10.9% total pulmonary complications	5.4	1.6	1.2	NA	NA	0.8	NA	NA
van der Voort et al. (48)	No G3-4 toxicity								
	NA	NA	NA	NA	NA	NA	NA	5.1	
Grills et al. (49)	No G5	9	6	38	27	17	NA	NA	NA
Chang et al. (60)	No G4-5 toxicity	11.5	NA	6.2	NA	NA	1.5	NA	9.3

RP: radiation pneumonia; RF: rib fracture; RD: radiation dermatitis; NA: not applicable; G: grade

patients treated with SABR, such information may be absent. Despite a negative staging PET, the incidence of hilar/mediastinal lymph node involvement found pathologically after surgery is reported to range from 13% to 32%. However, PET-only staged patients treated with SABR show such failure to be only 4-10% with careful evaluation for recurrence by follow-up imaging (45).

At the same time, comparing the efficacy and tolerability of SABR against surgical procedures is complicated as the two patient groups are not alike.

Recently published papers show the matched-pair and propensity score comparison of resection and SABR (46). It is reported to have similar overall survival, local recurrence control and total recurrence control with SABR or surgery after controlling for prognostic and patient selection factors. Using a propensity score to account for selection bias in the multivariate analysis provides the ability to control for the effects of greater numbers of variables and conduct analysis in the larger number of subjects (46).

SABR FOR PATIENTS WITH HIGH-RISK OPERABLE PATIENTS

The comparison between surgery and SBRT for stage I NSCLC are still in their early phase, and do not mention the preference dilemma. Some attempts to create matched populations have confirmed similar conclusions in matched patients (47). Although Markov modelling emphasises improved efficacy for surgery in general, the model favours SABR in patients whose expected surgical mortality rate surpasses 4% (48). Patients with high-risk operable tumours are presently authorised a randomised phase 3 clinical trial which is comparing lobectomy versus sublobar resection for small (<2 cm) peripheral NSCLC for the American College of Surgeons Oncology group (ACOSOG)/RTOG 0870/Cancer and Leukaemia Group B (CALGB) 140503 study. This particular study would clear guidelines to be set on how these higher-risk patients should be managed. In order to establish a high level of evidence to compare surgery and SABR, three randomised trials (ROSEL, STARS and ACOSOG)/RTOG 0870) have been started. Unfortunately, all of those trials were closed early due to poor accrual. There has been a great reluctance for patients and doctors for randomisation between two highly different types of treatments. Until we have more evidence for a head to head comparison between two treatments, SABR represents an effective and safe treatment option for patients with early stage NSCLC who are not able or willing to undergo surgery (20, 49, 50).

TOXICITY OF SABR

One doubt is that the large doses of radiation used in SABR will guide increased normal tissue toxicity. The toxicity of SABR may be related to tumour location, but the overall reported rates of serious toxicity are low, and quality of life studies have shown no significant decrease following SABR (48, 51). Toxicity outcomes from major series are summarised in Table 2. Radiation pneumonitis is a form of radiation-induced lung injury characterised by localised inflammatory symptoms and characteristic radiographic changes. After

SABR, nevertheless, grade 3 and 4 toxicities are less common (<3% pneumonitis and ~16% pulmonary toxicity) (17, 52). Other toxicities notified include chest wall toxicity (skin toxicity, rib fracture, or chronic pain) and, infrequently, brachial plexopathy, oesophagitis, and central airway stenosis or necrosis (53-54).

Centrally located tumours, which are located 2 cm proximal to the bronchial tree or contacting the mediastinal pleura, have a greater risk of toxicity. In the previous trials at Indiana University, the level of toxicity was significantly higher in centrally located tumours, where 6 treatment-related deaths were recorded (17). A systematic analysis of 20 studies and 563 central lung tumours found the grade 3 or 4 toxicity level to be 8.6% and the treatment-related mortality rate to be 2.7%, which shows that the toxicity level is indeed amplified when compared to peripherally located tumours; nonetheless, the overall rates are still significantly low. These findings confirm the centrally located tumours to be safely treated with 4.5 or 8 fraction regimens.

FUTURE ASPECTS OF SABR

The ideal dose and fractionation of SABR for NSCLC has not yet been clearly established. Although most centres use a standard identical dose, some have adopted a risk- or volume-adapted approach depending on the size of the tumour and/or its proximity to critical structures (17, 55). Ongoing trials examining this issue include RTOG 0813 for central tumours, and RTOG 0915 comparing 34 Gy in a single fraction to 48 Gy in 4 fractions, with a planned future comparison of the superior arm to the RTOG 0236 dose of 54 Gy in 3 fractions (30, 40, 55).

The excellent outcomes achieved with SABR in early-stage NSCLC have led to the question of whether it could be more widely applied to the early-stage NSCLC population, particularly in patients who are surgical candidates receiving sublobar or lobar resection. Previous single- institution retrospective analyses have attempted to answer this question, with SABR survival rates at 1 year of 94.7%, at 3 years of 84.7%, (20) and at 5 years for stage IA and IB tumours of 72% and 62%, respectively (19). There is also a sign for improved local control for SABR over wedge resection (local recurrence 4% vs. 20%), with overall survival but not cause-specific survival being significantly better with wedge resection (49). Ongoing trials are attempting to answer the question as to whether SABR is a suitable approach in this population. RTOG 0618 is a prospective phase II trial that treats medically operable patients with early-stage NSCLC with 54 Gy in 3 fractions (59). Three randomised controlled trials have been instituted comparing sublobar resection to SABR in early-stage lung cancer: (1) the ROSEL study, (2) Accuracy incorporated STARS trial and (3) ACOSOG-Z4099 (SABR vs. sublobar resection with or without implanted radioactive sources at the time of surgery). Unfortunately, all three trials were closed early due to slow accrual; the main reason is probably strong preferences at both the patient and physician level for randomisation between two extremely different types of treatment. Until these questions are answered, SABR represents an effective and safe treatment option for patients with early-stage disease who are not able or willing to undergo surgery. Future data will lead to further refinement of the technique and clarification of its role in the treatment of early-stage NSCLC.

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