Treatment: Radiation Therapy

Sagus Sampath

Abstract

Radiation therapy (RT) is an integral part of treating all stages of lung cancer. Stereotactic ablative radiation therapy (SABR) has emerged as a standard treatment option for stage I–II patients with medically inoperable disease. Stage IIIA–IIIB disease is typically managed with definitive concurrent chemo-radiotherapy (CRT). Intensity modulated radiation therapy (IMRT) has enabled delivery of more potent RT dose while greatly limiting dose to surrounding normal organs, including lung, esophagus, and heart. SABR may have an expanding role in the treatment of stage IV patients, with new clinical trials exploring its combination with systemic immuotherapies.

Keywords

Radiation · Lung cancer · SABR · Stereotactic · Oligometastases · Chemoradiation

Contents

S. Sampath (✉)
Department of Radiation Oncology, City of Hope Medical Center Duarte, Duarte, CA, USA
e-mail: ssampath@coh.org

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1 Stage I–II Disease

1.1 Conventional Radiation Therapy

Prior to the advent of SABR, radiation therapy over 6–7 weeks to small tumors has yielded poor results, with local control rates in the range of 30–60 % [1, 2]. Patients were treated daily over 6–7 weeks. Doses greater than 65 Gy were associated with better local control. Possible explanations for these low local control rates include lack of soft tissue imaging for alignment during treatment, which may have resulted in under-dosing the target, as well as inadequate radiation dosing schedules.

1.2 Stereotactic Ablative Radiation Therapy

1.2.1 Technological Advancements

Advancements in radiation delivery and imaging technology have allowed for the development of stereotactic ablative radiation therapy (SABR) as an acceptable definitive treatment for early stage non-small cell lung cancer (NSCLC). The increased use of positron emission tomography/computed tomography (PET/CT) and bronchoscopy with endobronchial ultrasound for pathological nodal stage has increased the accuracy of tumor staging. This has helped select for a patient subgroup without regional nodal spread who are candidates for aggressive local therapy.

A major challenge in the treatment of lung tumors with SABR is accounting for lung tumor motion. Traditional three-dimensional CT scans capture only a limited phase of the respiratory cycle and do not provide information regarding the entire trajectory of a patient's tumor. Given this uncertainty, clinicians were obligated to add larger 'safety margins' around the gross tumor, in order to ensure that the tumor would not be missed. The introduction of four-dimensional CT (4DCT) scanners into the radiation clinic has revolutionized the treatment planning process, enabling the clinician to incorporate tumor motion data into designing the radiation field. Customized margins based on actual tumor motion data from the 4DCT are now used to generate the radiation field.

The next challenge is limiting the motion of the patient's tumor, especially in the superior–inferior dimension, in order to minimize the size of the radiation field. Tumor motion has been shown to be significantly higher when a patient is free-breathing as compared to using some form of abdominal compression device [3]. Another challenge is verifying the accuracy of patient setup during treatment. Cone-beam CT (CBCT) machines have now been integrated into the linear accelerator device as a single unit, which allows for imaging the patient's tumor prior to each delivered fraction. Once the image is obtained, software can fuse the image to the patient's original treatment planning CT to generate a set of table shifts needs to exactly align to the target. Suzuki et al. [4] have shown table shifts ranging from 3 to 12 mm were necessary to match the target when incorporating this CBCT data, which would have been missed if purely relying on bony anatomy alone. This process is known as image-guided radiation therapy or IGRT. Maintaining the same position during treatment delivery is also crucial, and therefore a tight vacuum cushion around the patient along with abdominal compression can address two sources of setup variability: the patient and the lung tumor.

1.2.2 Clinical Outcomes

Initial phase I/II SABR studies included medically inoperable patients. Patients were typically of poor performance status and had significant comorbidities. Table 1 displays recently published phase I/II trials of SABR. With approximately 3 years median follow-up, primary tumor control across studies is 80–100 % for T1 tumors.

The role of SABR in medically operable patients is an area of ongoing debate and active clinical investigation. Results from randomized trials in Japan (surgery vs. SABR) are maturing and are anticipated to be disclosed in the coming years.

Table 1 Recently published phase I/II trials of SABR

Trial	Years treated, patient number	Tumor stage (n)	Dose/fraction number	Median follow-up (months)	Local control	Overall survival
Timmerman et al. [36]	2000–2003, *N* = 37	T1: 19 T2: 18	24–60 Gy/3	15.2	87 %	1.5 yr: 64 %
Nagata et al. [37]	1998–2004, *N* = 45	T1: 32 T2 (<4 cm): 13	48 Gy/4	22–30	98 %	3 yr: T1: 83 % T2: 72 %
Lindberg et al. [38]	2003–2005, *N* = 57	T1:72 % T2:28 %	45 Gy/3	41.5	4 yr: 79 %	5 yr: 30 %
Koto et al. [39]	1998-2004, *N* = 31	T1: 19/31 T2: 12/31	45 Gy/3 for 20 patients, 60 Gy/8 for 11	32	3 yr: T1: 78 % T2: 40 %	3 yr: 72 %
Fakiris et al. [40]	2002-2004, *N* = 70	T1: 34 T2: 36	T1: 60 Gy/3 T2: 66 Gy/3 fxn	50.2	3 yr: 88 %	3 yr: 43 %

However, in the United States, it has been difficult to encourage patients to participate on a trial that randomizes them between two very different local therapies. Known as the StableMATE trial, it is now reopening with a pre-randomization schema in order to help increase accrual. As these studies reach completion, the role of SABR may be expanded to a more fit patient population.

1.3 Toxicities

Lung SABR is overall associated with very low rates of acute and late toxicity. Possible side effects include chest wall pain, rib fracture, and decline in pulmonary function tests. In the early experience with SABR, Timmerman reported an increased rate of grade 4–5 toxicities in centrally located tumors, defined as less than or equal to 2 cm from the proximal bronchial tree [5]. Lower doses per fraction were recommended as a way to lower risk for toxicities. In a large patient cohort with central tumors, overall grade 3 + toxicity was only 8 % [6]. The incidence Grade 1–2 chest wall pain was found to be associated with both moderate (30 Gy) and high (60 Gy) doses [7]. As reflected in the National Comprehensive Cancer Network (NCCN) guidelines, peripherally located tumors in close proximity to the chest wall are recommended to receive similar fractionation and doses as central tumors.

2 Stage III Disease

2.1 Technological Advancements

4DCT is now commonly used in the treatment planning phase for stage III patients. Motion data is acquired of both the primary lung tumor and mobile lymph node stations (e.g., hilar and subcarinal areas) to ensure that the entire trajectory is captured in the target. The increased certainty of tumor location has facilitated the use of tighter margins, allowing for increased sparing of normal tissues. IGRT is also incorporated in treatment in order to allow for smaller uncertainty margins.

Intensity modulated radiation therapy (IMRT) is commonly employed in the treatment of locally advanced disease, with the main benefit being lower doses to surrounding normal lung, compared to traditional three-dimensional conformal radiation therapy (3D-CRT). Clinical data show significantly lower rates of grade 3 + pneumonitis when using IMRT versus 3D-CRT, despite large tumor size in the patients treated with IMRT [8]. A population-based analysis of 7000 patients using the SEER-Medicare database demonstrated no difference in overall survival between 3D-CRT and IMRT [9]. Limitations of the study included the lack of information on total radiation dose and percentage of patients treated at higher volume academic centers. Besides sparing of regional lung, IMRT can also allow for sparing other critical organs, such as the heart and esophagus. Heart dose and esophageal toxicity were noted to be significant predictors for survival on the recently published RTOG 0617 trial [10]. Improved sparing of these structures is

only feasible with the advanced technologies like IMRT. Despite the lack of robust clinical outcome data supporting its use, the prevalence of IMRT will likely continue to increase in the treatment of NSCLC.

3 Clinical Results

3.1 Radiation Alone

In the past, conventional fractionation over 6–7 weeks with XRT alone was considered the standard treatment regimen in patients unable to tolerate surgery. Radiation Therapy Oncology Group (RTOG) 7301 compared 3 different radiation dose schedules: 40 Gy in 4 weeks, 60 Gy in 6 weeks, and a split-course regimen [11]. Two-year survival rates were 18 % in the 6-week group and 14 % in the 4-week group. At 5 years, all dose groups had uniformly poor overall survival (OS) less than 10 %. This established the standard dose of 60 Gy in 6 weeks, with local control approaching only 50 %.

To improve these outcomes, the RTOG 8311 trial was designed as a dose-escalation study, with the hypothesis that higher doses would result in improved LC and OS [12]. Patients were randomized to three groups using 1.2 Gy/fraction given twice daily: 60 total dose, 64.8, and 69.6 Gy. Two-year OS in the 69.6 Gy arm was 29 %, significantly higher than the 2 lower dose arms. This was demonstrated for the first time that more potent radiotherapy schedules can be given safely and lead to meaningful improvement in outcomes.

In addition to increasing the total radiation dose, another way to increase the potency is to the give the radiation over a shorter period of time. The European Organisation for Research and Treatment of Cancer (EORTC) conducted a phase III randomized trial comparing two different dose schedules: standard RT of 60 Gy in 6 weeks; or CHART, known as continuous hyperfractionated accelerated RT, which was 54 in 1.5 Gy given three times daily for 12 continuous days [13]. The CHART group demonstrated significantly improved local control and overall survival compared to standard RT (17% vs. 12% and 20% vs. 13 %, respectively). The survival benefit did come at a cost: approximately 50 % of the CHART group developed severe dysphagia, versus 19 % in the standard dose arm. The majority of patients on this study had squamous cell carcinoma histology.

Therefore, in poor performance status patients were unable to tolerate chemotherapy; RT alone-regimens usually consist of some form of altered fractionation, with the goal of maximizing potency while also allowing for time for normal tissue repair. Using the latest in radiation treatment technology, colleagues at MD Anderson reported on initial safety data from a proton beam dose-escalation trial starting at 45 up to 60 Gy in 3 weeks [14].

3.2 Sequential Chemotherapy Followed by Radiation

To improve outcomes in the radiation-alone patients with reasonable performance status, multiple cooperative groups embarked on studying the impact of the addition of chemotherapy to radiation in stage III disease. The Cancer and Leukemia Group B (CALGB) trial randomized 155 patients to induction chemotherapy with vinblastine/cisplatin followed by RT 60 Gy/6 weeks, versus RT alone 60 Gy/6 weeks [15]. The combined modality arm demonstrated significantly improved OS at 2 years, 26% versus 13 % ($p = 0.006$). Another phase III trial with similar design, conducted by LeChavalier et al. [16] showed a significant improvement in 3 year OS with combined modality treatment, 12% versus 4 % ($p = 0.02$). Local control at 1 year was very poor at 16 %. Finally, RTOG 8808 included 452 patients and had a three-arm randomization [17]. Arm 1 was sequential chemotherapy (cisplatin and vinblastine for 2 cycles) followed by RT 60 Gy; arm 2 was RT alone 60 Gy/6 weeks; and arm 3 was RT alone 69.6 Gy/6 weeks, given 1.2 Gy twice daily. There was a significantly improved 2-year OS in arm 1 of 32, versus 19 % in arm 2 ($p = 0.003$). Median survival was 13.2 versus 11.4 months, respectively. Patients in arm 3 had an intermediate outcome between arms 1 and 2, with a 2 year OS of 24 % ($p = 0.08$ when compared to arm 1).

Results from several meta-analyses have indicated an absolute OS benefit with the addition of chemotherapy to RT versus RT alone in locally advanced/non-metastatic patients. The non-small cell lung cancer collaborative group included 3033 patients from 22 trials using individual patient data [18]. Chemotherapy was associated with a 10 % reduction in mortality, translating to an absolute benefit of 2 % at 5 years. The most recent meta-analysis of 1764 patients conducted by Auperin et al. [19] demonstrated a 4 % absolute benefit with chemotherapy at 2 years. Only carboplatin or cisplatin-based chemotherapy studies were included. In summation, these large patient analyses clearly indicate the superiority of adding platinum-based therapy with radiation in locally advanced patients.

3.3 Sequential Versus Concurrent Chemotherapy and Radiation Therapy

With survival gains seen in patients receiving combined modality therapy, it was proposed that increasing the intensity of treatment by delivering chemotherapy concurrently with radiation may improve survival. Furuse et al. [20] from the West Japan Lung Cancer Group randomized 320 patients between sequential chemotherapy/radiation (SCR) and concurrent chemotherapy/radiation (CCR). CCR comprised of cisplatin, vindesine, and mitomycin. RT was given in a split-course fashion, with 28 Gy/14 fractions given daily with a 10 day break in between. SCR patients received the identical chemotherapy for 2 cycles, with RT starting after. Median survival was significantly improved in the CCR group, 16.5 versus 13.3 months ($p = 0.04$). Five-year survival in the CCR arm was 16%, versus 9 % in the SCR arm. There were no significant differences in the rates of pulmonary

or esophageal toxicity between the arms, although increased myelosuppression was noted in the CCR group.

In the randomized phase III trial published by Fournel et al. from the French Lung group, patients were randomized between SCR and CCR. SCR was cisplatin/vinorelbine followed by RT to 66 Gy. CCR patients received cisplatin/etoposide with RT 66 Gy. There was improved survival (16.3 vs. 14.5 months) in the CCR group, but this did not reach significance. In contrast to the Japanese trial, there was a marked increase in the rate of esophageal toxicity in the CCR arm (32 vs. 3 %).

Finally, the most recent phase III data come from the Radiation Therapy Oncology Group (RTOG) protocol 9410, which compared 3 arms. SCR to a dose of 63 Gy, CCR one fraction daily to 63 Gy, and CCR two fractions daily to 69.6 Gy. The first two groups received cisplatin/vinblastine, and third received cisplatin/vp16. The primary end point was overall survival. Median survival was the longest in the CCR once-daily arm (17 months), which was significantly higher than the SCR group (14.6 months), but not significantly different from the CCR twice-daily arm (15.6 months). Local failure was reduced in the CCR groups compared to SCR. (39 vs. 30 %). CCR patients had significantly higher incidence of acute grade 3 + esophagitis compared to SCR (only 4 %. $P < 0.001$). The rate in the twice-daily group was significantly higher than the once-daily patients (45% vs. 22 %, $P < 0.001$). However, late esophageal toxicity was similar among the arms. From the knowledge gained from RTOG 0617 regarding the impact of esophageal toxicity and survival (to be discussed), it is plausible that any potential survival advantage to be gained from more intense therapy in the twice-daily CCR group was outweighed by the increased rate of toxicity.

The above studies, in addition to several meta-analyses, have established CCR as the standard of care for locally advanced-stage IIIA/IIIB NSCLC with good performance status and <5 % weight loss. The Cochrane group showed a significant 14 % reduction in mortality risk with CCR versus SCR [21]. Finally, the NSCLC collaborative group (1,205 patients) reported an absolute survival benefit of 4.5 % at 5 years with CCR compared to SCR [22]. Local–regional failure was also significantly improved with CCR (HR 0.77, $p = 0.01$), accompanied by an increase in acute grade 3–4 esophagitis with CCR (RR 4.9, $p < 0.001$).

3.4 Radiation Dose Escalation with Concurrent Chemotherapy

The recently published RTOG 0617 trial was designed to answer two questions: (1) does higher radiation dose translate to improved survival? and (2) does the addition of concurrent cetuximab to chemotherapy improve survival? Approximately 500 analyzable patients were randomized in a 2 by 2 factorial design to 60 versus 74 Gy radiation to the lung primary and involved nodal disease. All patients received concurrent carboplatin/paclitaxel and a second randomization was chemotherapy alone or chemotherapy with cetuximab. Median overall survival in

the 74 Gy arm was 20 months, significantly inferior to the 60 Gy arm (29 months, HR 1.38, $p = 0.004$). Cetuximab-chemotherapy patients had a median OS of 25, versus 24 months in those receiving chemotherapy alone. There was a significantly higher rate of severe esophagitis in the 74 Gy arm (21% vs., 7 %, p <0.001). In fact, on multivariate analysis, only RT dose level and esophagitis grade reached significance for overall survival.

From this publication, significant controversy has arisen among lung radiation oncologists regarding the optimal dose for treatment. Post hoc analyses of radiation planning compliance and margins may help to elucidate why the higher dose arm did so poorly. Identifying the specific causes of death also would be beneficial. Further, dosimetry studies will also be required to better understand esophageal toxicity. Many ongoing clinical trials are using an intermediate dose of 66 Gy as the definitive dose.

3.5 Induction Chemotherapy Prior to Definitive Chemoradiation

With distant disease as the predominant pattern of relapse, the added benefit of induction chemotherapy was explored in the CALGB 39801 trial [23]. A total of 366 patients with unresectable IIIa/IIIb were randomized to induction carboplatin–paclitaxel for 2 cycles followed by concurrent carboplatin–paclitaxel with radiation to 66 Gy, versus the identical chemo-radiotherapy regimen alone. Median OS on the induction arm was 12 months, compared to 14 months on the concurrent chemo-XRT arm ($p = 0.3$). Survival at 2 years was 29 and 31 %, respectively. The only factors predictive for survival were weight loss prior to treatment, age, and performance status. The induction arm had similar rates of grade 3–4 esophageal (32% vs. 36 %) and pulmonary toxicity (14% vs. 19 %) as the concurrent-only arm.

In a randomized three-arm phase II trial by Belani et al., one of the arms included patients receiving induction carboplatin/paclitaxel followed by concurrent CRT to 63 Gy. This was compared to standard concurrent chemo-RT and sequential chemo-RT. With a median follow-up of 40 months, the induction arm demonstrated the poorest survival 12.7 months, although none of the arms were found to be statistically superior to each other. The induction arm was stopped early due to 20 % of patients not being able to receive chemotherapy concurrently with the radiation. Grade 3-4 esophagitis was similar between the induction and concurrent-only groups.

In phase II three-arm randomized trial conducted by Belani et al. [24], 276 unresectable IIIA/IIIB patients received either induction chemotherapy followed by 63 Gy XRT (arm 1), induction chemotherapy followed by concurrent CRT (arm 2), or concurrent CRT followed by consolidation chemotherapy (arm 3). Median OS was highest in arm at 16.3 months, although the study was not powered for individual comparisons between arms. Arms 2 and 3 had higher rates of grade 3/4 esophagitis (19 and 28 %, respectively).

3.6 Role of Consolidation Chemotherapy Following Concurrent Chemoradiation

The Hoosier Oncology Group reported results on 203 patients who were randomized between standard cisplatin/etoposide concurrent with XRT, versus the same concurrent CRT followed by 3 cycles of consolidation docetaxel [25]. The primary end point was overall survival. The study was terminated early due to an interim analysis that showed futility in the consolidation arm. Median OS was 23.2 months in the concurrent CRT alone arm and 21.2 months in the consolidation arm. Approximately 29 % of patients in the consolidation arm required hospitalization, versus 8 % in CRT alone arm, with 5.5 % grade 5 toxicity as a result of docetaxel. The conclusions made were that toxicities were increased with the addition of consolidation chemotherapy without a gain in survival.

SWOG S0023 was a phase III placebo-controlled trial examining the efficacy of adding maintenance targeted therapy following definitive chemoradiation and consolidation chemotherapy. The study closed after accruing 243 patients with stage III disease. Median survival was worse on the gefintib arm (23 vs. 35 months for placebo, $p = 0.013$). As a result, maintenance systemic therapy following chemoradiation was largely discouraged. Recently however, with the advent checkpoint-blockade inhibitors, their role as maintenance therapy is now being examined in clinical trials.

4 Stage IV Patients and Oligometastases

Historically, survival for stage IV NSCLC patients has been poor, with a median value of 6–12 months. However, the idea of 'oligometastases,' first proposed by Hellman and Weichselbaum [26], is now gaining traction in patients with NSCLC, such as thoracic radiation or SABR to further extend their progression-free survival.

4.1 Synchronous Brain Metastases

Hu and colleagues [27] from the MD Anderson Cancer Center reviewed 84 cases presenting with solitary brain metastasis, treated with stereotactic radiosurgery or neurosurgical resection. Eight patients received thoracic radiotherapy alone, 23 patients received chemotherapy alone and 13 received both. Median survival times by local thoracic stage were 25.6, 9.5, and 9.9 months, for stage I, II, and III, respectively. The authors concluded that aggressive local therapy may be justified for local stage I patients, not for locally advanced disease.

A Turkish group reported on 63 NSCLC patients who received brain-directed therapy for solitary brain metastasis, followed by thoracic radiation to 66 Gy with concurrent chemotherapy (2 cycles, cisplatin-based) [28]. With a median follow-up over 2 years, median survival was 28.6 months. Local tumor stage (T1-2 vs. T3-4) and nodal stage (N0-1 vs. N2-3) were a significant predictor for survival on

multivariable analysis. The results illustrate that there exists a select group of favorable patients with brain metastases who exhibit similar survival to stage III patients, warranting the need for aggressive treatment strategies.

Finally, a joint report by Gray et al. [29] reported similarly high median survival rates in 66 patients with 1-4 synchronous brain-only metastases. Only 7 patients had surgery has a component of their brain-directed therapy, while the remaining received a mixture of SRS alone, whole brain RT alone, or a combination of the two. Local tumor–nodal stage breakdown were as follows: 9 stage I, 10 stage II, and 47 stage III. Thoracic radiation to a dose greater than 45 Gy was given in 38 pts (five in conjunction with thoracic surgery), while 28 patients did not receive thoracic RT (17 had chemotherapy alone, 14 had thoracic surgery alone). Those receiving thoracic RT had a median OS of 26.4, versus 10.5 months in the chemotherapy alone group ($P < 0.001$). A reduction in the rate of first failure in brain was found to be significantly associated with those receiving either surgery or SRS in combination with whole brain RT. Similar to previous studies, neurological disease progression was the main factor in determining overall survival. Aggressive brain-directed therapy is considered to be crucial when evaluating the benefit of adding thoracic RT.

Overall, these series indicate better than expected outcomes in stage IV patients receiving thoracic radiotherapy. A major limitation of these studies is that molecular status information has not been uniformly available. The presence of the *epithelial-growth factor receptor (EGFR)* mutation and translocation of the *anaplastic lymphoma kinase-echinoderm microtuble ligand-4 (ALK-EML4)* chromosome translocation are now considered favorable prognostic factors with the advent of more efficacious and selectively targeted agents. Moving forward, having such data may help clinicians better select those stage IV patients who benefit the most from radiation to both local and distant disease.

4.2 SABR in Stage IV Disease

Colleagues at University of Texas Southwestern and University of Colorado published results of a phase II trial utilizing SABR to treat all sites of metastatic disease in patients with stage IV NSCLC receiving concurrent erlotinib [30]. Eligibility was limited to those six or fewer sites of extracranial disease who failed first-line systemic chemotherapy. A total of 24 patients were enrolled. Only 2 patients had previously treated brain metastases. The numbers of SABR sites treated by patient were as follows: 1 ($n = 8$), 2 ($n = 8$), 3 ($n = 5$), 4 ($n = 2$), and 5 ($n = 1$). Common fractionation schemes were 27–33 Gy/3 fractions and 35–40 Gy/5 fractions. The lung parenchyma was the most common site to be treated (35 %), followed by mediastinum/hilum (25 %), and adrenal glands (13 %). The results were promising, with a median PFS of 14.7 months and median OS of 20.4 months, both meaningfully longer than what is observed with historical results with second-line systemic therapy alone. What is remarkable is that only 3/21 patients had a local failure from SABR, and 10 patients had not progressed (both distantly and at the radiation field) at last follow-up. Molecular testing status was not provided, and therefore the

relationship between *EGFR* status and outcome is unknown. These data provide encouragement that aggressive localized therapy with SABR in selected patients with limited metastatic disease burden may translate to more protracted PFS compared to systemic therapy alone.

4.3 Future Directions

With the disappointing results of RTOG 0617, there is a resurging debate on the utility of radiation dose escalation in NSCLC. The protocols to come forward will need to more carefully study the impact of radiation on adjacent normal structures, such as esophagus and heart. Adapting the radiation treatment field midcourse during a patient's radiation treatment is being studied in the open RTOG 1106 trial. This trial incorporates data from a PET/CT acquired during treatment and calls for tailoring the treatment field to match the shrinking areas of PET avidity.

Proton beam therapy is being studied in several institutions and has the potential to deliver more favorable dose distributions to the heart, lungs, and esophagus. A recent outcome analysis with nearly five-year follow-up demonstrates comparable survival and disease-free survival compared to photon-based treatment [31].

The role of immunotherapy in the treatment of NSCLC is now beginning to gain a strong foothold with nivolumab, a programmed death receptor-1 (PD-1) inhibitor, recently receiving FDA approval for patients with squamous cell histology [32]. Recent data now show an overall survival benefit with nivolumab in non-squamous-NSCLC compared to conventional chemotherapy [33]. Therefore, nivolumab has shown to improve OS compared to conventional chemotherapy in the phase III setting for both major types of NSCLC.

There are several pre-clinical reports indicating the immunogenic potentiation from delivering higher doses of radiation in a Lewis lung cancer model, including upregulation of genes involved in antigen presentation, adhesion, and activation of innate immune system. In the report by Fotin–Mleczek et al. [34], 3 fractions of 12 Gy each resulted in increasing immune cell infiltrates, including CD4 and CD8 + T cells, CD8 + dendritic cells, and natural killer T cells. The research group of Johns Hopkins has shown in an autochthonous model that the combination of programmed death receptor ligand-1 (PDL-1) blockade with local radiation showed an abscopal effect in the contralateral non-irradiated lung [35].

These findings are now providing impetus to explore the combination of SABR with immune checkpoint blockade as a way to further provide antigen presentation and synergistically improve the efficacy of systemic therapy. There are clinical trials at New York University (NCT02221739) and MD Anderson (NCT02239900) incorporating SABR-type fractionation with the CTLA-4 inhibitor ipilimumab. Similar trials incorporating PD-1 inhibitors such as nivolumab with SABR are also on the horizon. The sequencing and timing of these targeted therapies with SABR, as well as optimal SABR dose, will require rigorous examination. Immune cytokine assays and panels may also prove useful to better understand the mechanism for a possible synergism with these two therapies.

5 Conclusions

The advent of SABR has radically and permanently altered the treatment landscape in NSCLC, especially in early stage patients who are unable to tolerate surgery. On the forefront is the role of SABR as an 'immune-potentiator' in patients receiving immunotherapies. In stage IIIA–IIIB patients, treatments have shifted from radiation alone 30 years ago to combination chemotherapy–radiation regimens. The new median survival of 29 months in the 60 Gy cohort on RTOG 0617 is now the benchmark for future comparisons, keeping in mind the highly controlled setting (90 % received PET/CT staging) and generally higher performance status patients enrolled on such studies. Despite the RTOG 0617 results, there is still impetus to improve local control outcomes with novel radiation strategies and modalities, including proton therapy. With continued advances in systemic treatments, the focus will eventually redirect to optimizing local control with radiotherapy, both in the early and in the advanced-stage setting.

References

1. Dosoretz DE et al (1992) Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. Int J Radiat Oncol Biol Phys 24(1):3–9
2. Sibley GS et al (1998) Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 40(1):149–154
3. Han K et al (2010) A comparison of two immobilization systems for stereotactic body radiation therapy of lung tumors. Radiother Oncol 95(1):103–108
4. Suzuki O et al (2012) Influence of rotational setup error on tumor shift in bony anatomy matching measured with pulmonary point registration in stereotactic body radiotherapy for early lung cancer. Jpn J Clin Oncol 42(12):1181–1186
5. Timmerman R et al (2006) 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 24(30):4833–4839
6. Modh A et al (2014) Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 90(5):1168–1176
7. Stephans KL et al (2012) Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT). Int J Radiat Oncol Biol Phys 82(2):974–980
8. Yom SS et al (2007) Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 68(1):94–102
9. Chen AB et al (2014) Comparative effectiveness of intensity-modulated versus 3D conformal radiation therapy among medicare patients with stage III lung cancer. J Thorac Oncol 9 (12):1788–1795
10. Bradley JD et al (2015) Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 16(2):187–199
11. Perez CA et al (1980) A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the radiation therapy oncology group. Cancer 45(11):2744–2753

12. Cox JD et al (1990) A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with radiation therapy oncology group stage iii non-small-cell lung carcinoma: report of radiation therapy oncology group 83-11. J Clin Oncol 8(9):1543–1555
13. Saunders M et al (1999) Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART steering committee. Radiother Oncol 52(2):137–148
14. Gomez DR et al (2013) Phase 1 study of dose escalation in hypofractionated proton beam therapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 86(4):665–670
15. Dillman RO et al (1996) Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 88 (17):1210–1215
16. Le Chevalier T et al (1994) Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. Lung Cancer 10(Suppl 1):239–244
17. Sause W et al (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: radiation therapy oncology group, eastern cooperative oncology group, and southwest oncology group. Chest 117(2):358–364
18. BMJ (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small cell lung cancer collaborative group. 311(7010):899–909
19. Auperin A et al (2006) Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol 17(3):473–483
20. Furuse K et al (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17(9):2692–2699
21. Rowell NP O'Rourke NP (2004) Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev (4):CD002140
22. Auperin A et al (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28(13):2181–2190
23. Vokes EE et al (2007) Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: cancer and leukemia group B. J Clin Oncol 25(13):1698–1704
24. Belani CP et al (2005) Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23(25):5883–5891
25. Hanna N et al (2008) Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the hoosier oncology group and U.S. oncology. J Clin Oncol 26(35):5755–5760
26. Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13(1):8–10
27. Hu C et al (2006) Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 106(9):1998–2004
28. Parlak C et al (2014) Definitive chemoradiation therapy following surgical resection or radiosurgery plus whole-brain radiation therapy in non-small cell lung cancer patients with synchronous solitary brain metastasis: a curative approach. Int J Radiat Oncol Biol Phys 88 (4):885–891
29. Gray PJ et al (2014) Aggressive therapy for patients with non-small cell lung carcinoma and synchronous brain-only oligometastatic disease is associated with long-term survival. Lung Cancer 85(2):239–244

30. Iyengar P et al (2014) Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 32(34):3824–3830
31. Nguyen QN et al (2015) Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. Radiother Oncol
32. Brahmer J et al (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 373(2):123–135
33. Paz Ares L (2015) Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). J Clinical Oncol 33: Abstr LBA 109
34. Fotin-Mleczek M et al (2014) mRNA-based vaccines synergize with radiation therapy to eradicate established tumors. Radiat Oncol 9:180
35. Sharabi AB et al (2015) Stereotactic radiation therapy combined with immunotherapy: augmenting the role of radiation in local and systemic treatment. Oncology (Williston Park) 29 (5)
36. Timmerman R et al (2003) Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 124(5):1946–1955
37. Nagata Y et al (2005) 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 63(5):1427–1431
38. Lindberg K et al (2015) Long-term results of a prospective phase II trial of medically inoperable stage I NSCLC treated with SBRT—the Nordic experience. Acta Oncol 1-9
39. Koto M et al (2007) A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. Radiother Oncol 85(3):429–434
40. Fakiris AJ et al (2009) 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 75 (3):677–682