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Radiation Therapy in Non-Small-Cell Lung Cancer

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The management of non-small-cell lung cancer (NSCLC) varies according to stage. Surgical resection is reserved for operable patients with early-stage NSCLC, while high-dose target radiation—stereotactic body radiation therapy (SBRT)—is reserved for patients whose comorbidities prohibit them from a major surgical procedure. The treatment of locally advanced NSCLC (LA-NSCLC) is stratified according to resectability. Those with resectable disease may require additional treatments such as chemotherapy and radiation, while patients with unresectable disease will require definitive chemoradiation therapy with adjuvant durvalumab. Patients with limited metastatic disease benefit from the combination of SBRT and systemic therapy.

The treatment and prognosis of patients with non-small-cell lung cancer (NSCLC) vary substantially depending on the burden of disease; therefore, it is of utmost importance that patients undergo proper staging procedures. The typical treatment paradigm for patients with early-stage NSCLC (ES-NSCLC) is resection for those willing and able to undergo surgery, while stereotactic body radiation therapy (SBRT) is reserved for inoperable patients. Patients with resectable locally advanced NSCLC (LA-NSCLC) will require adjuvant therapies following resection, potentially including postoperative radiation. Patients with unresectable LA-NSCLC now receive definitive chemoradiation followed by adjuvant durvalumab as standard of care. Unfortunately, despite aggressive treatment, many of these patients, especially those with LA-NSCLC, may develop metastatic disease. Historically, the standard of care focused on chemotherapy, with radiation used mostly for palliative intent; however, there are those with limited metastatic disease burden who may derive long-term benefit from aggressive multimodal therapy including SBRT and immunotherapy. In this article, we discuss the management of patients with NSCLC, the data supporting these recommendations, and the new and upcoming studies seeking to advance the field.

EARLY-STAGE NON-SMALL-CELL LUNG CANCER (ES-NSCLC)

Currently, surgical resection remains the standard of care for patients with operable

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ES-NSCLC. Hence, initial workup of patients with newly diagnosed ES-NSCLC should include an assessment of a patient's eligibility for operative treatment. Preoperative evaluation should include pulmonary function testing with calculation of predicted postoperative (PPO) FEV_1 and diffusing capacity for carbon monoxide (DLCO); cardiac workup may also be necessary depending on patient comorbidities (Brunelli et al. 2013). Patients with both PPO FEV_1 and PPO DLCO >60% are considered low risk and may proceed to surgery without further testing. If patients have either PPO FEV_1 or PPO DLCO <60%, further testing with an exercise test is recommended. Per National Comprehensive Cancer Network (NCCN) guidelines, initial workup should also include positron emission tomography/computed tomography (PET/CT) imaging and bronchoscopy; in peripheral tumors without suspicion for mediastinal lymph node involvement, bronchoscopy may be performed intraoperatively but PET/CT should still be performed prior to surgery.

In patients with ES-NSCLC who undergo complete resection of their tumors with negative margins and without findings of nodal involvement, there is no indication for postoperative radiotherapy (PORT). The PORT Meta-analysis Trialists Group analyzed individual patient data from nine prospective randomized trials with a total of 2128 patients randomized to PORT to 30–60 Gy versus surgery alone (PORT Meta-analysis Trialists Group 1998). The study demonstrated a statistically significant decrease in 2-yr overall survival (OS) in the PORT cohort (48% vs. 55%), with subgroup analysis finding the greatest detriment to be in patients with stage I/II NSCLC and in patients with N0-N1 disease. An update of the meta-analysis, which included data from an Italian trial, did not substantially change the results (Burdett and Stewart 2005). A retrospective analysis of 7465 patients with resected stage II or III NSCLC in the Surveillance, Epidemiology, and End Results (SEER) database also investigated the association between PORT and survival (Lally et al. 2006). On subset analysis based on nodal stage, the authors found a statistically significant decrease in survival in patients with N0 disease who underwent PORT (hazard ratio [HR] = 1.176; $P = 0.0435$). Margin status was unavailable within the database and was not included in the analysis.

For patients who are not surgical candidates due to underlying comorbidities, extent of disease, or patient preference, the preferred treatment is SBRT. Historically, patients with inoperable ES-NSCLC were treated with definitive intent, conventionally fractionated radiotherapy with limited success. In a review examining outcomes after treating ES-NSCLC with conventional radiotherapy alone, Qiao et al. (2003) analyzed 18 studies published between 1988 and 2000. The majority of the included studies were retrospective and local failure rates varied widely, ranging from 6.4% to 70% with the use of various conventional regimens. The median local recurrence rate among the reported studies was 40% with local failure listed as the most common cause for treatment failure. In an effort to improve local failure rates, Timmerman et al. (2003) initially explored the impact of dose escalation and hypofractionation using SBRT in a single institution phase I trial of 37 patients with T1-T2 (tumor size ≤7 cm), N0, M0 disease. Patients with T1 versus T2 disease were dose escalated separately from a starting dose of 24 Gy in three fractions to a maximum dose of 60 Gy in three fractions for T1 tumors and 66 Gy in three fractions for T2 tumors with neither cohort ultimately reaching the maximum tolerated dose (MTD) in tumors <5 cm. In patients with tumors measuring 5–7 cm, 72 Gy in three fractions was considered to be the dose-limiting regimen. In a subsequent phase II trial from the same group, 70 patients with T1-T2 (tumor size ≤7 cm), N0, M0 disease underwent SBRT to a total dose of 60 Gy in three fractions for T1 tumors and 66 Gy in three fractions for T2 tumors with excellent local control (LC) (Timmerman et al. 2006; Fakiris et al. 2009). The trial reported 2-yr and 3-yr LC rates of 95% and 88.1%, respectively. Median survival (MS), 3-yr OS, and 3-yr cancer-specific survival were 32.4 mo, 42.7%, and 81.7%, respectively. Protocol-specified grade 3–5 toxicities were reported in 11 patients with an additional six patients experiencing non-protocol-specified toxicities. Although not statistically significant, patients with

central tumors, defined as tumors within the hilar/perihilar region, tended to have higher rates of grade 3–5 toxicities (10.4% in central tumors vs. 27.3% in peripheral tumors). In a large multiinstitutional Japanese retrospective study of 257 patients with T1-T2 disease treated to a total of 18–75 Gy in 1–22 fractions and median follow-up of 38 mo, Onishi et al. (2004, 2007) reported a similarly low local progression rate of 14.0. The median calculated biological equivalent dose (BED) administered was 108 Gy. Patients receiving higher BED doses were found to have statistically significantly better LC and OS rates; local progression and 5-yr OS were 8.4% and 53.9%, respectively, for patients with BED ≥100 Gy versus 42.9% and 19.7%, respectively, for those with BED <100 Gy.

Following promising results from both retrospective studies and prospective single institution studies, the Radiation Therapy Oncology Group (RTOG) initiated RTOG 0236, a North American phase II multicenter trial investigating the use of SBRT in medically inoperable patients with T1-T2 (tumor size ≤5 cm), N0, M0 disease (Timmerman et al. 2010, 2018a). A total of 55 evaluable patients were treated to a total dose of 60 Gy in three fractions; dose was later corrected to 54 Gy in three fractions when accounting for tissue density heterogeneity. Given the prior concerns of increased toxicities in patients with central tumors, the study excluded patients with planning target volumes extending within 2 cm of the proximal bronchial tree, defined as the area including the distal trachea, carina, and proximal lobar bronchi to their first bifurcation. With median follow-up of 48 mo, 3-yr and 5-yr primary tumor control rates were 97.6% and 92.7%, respectively. LC, defined as no recurrence in the primary tumor or involved lobe, was 90.6% at 3 yr and 80.0% at 5 yr. Disease-free survival (DFS) and OS at 3 yr was 48.3% and 55.8%, respectively; at 5 yr, DFS and OS was 25.5% and 40.0%, respectively. Protocol-specified grade 3–4 treatment-related toxicities occurred in 17 patients (30.9%). No grade 5 toxicities were reported. As RTOG 0236 was limited to peripheral tumors, RTOG 0813 sought to establish MTD and assess toxicity and efficacy for SBRT in centrally located tumors (Bezjak et al. 2019). In this phase I/II dose escalation study, 100 patients with medically inoperable T1-T2 (tumor size ≤5 cm), N0, M0 centrally located tumors were accrued into five dose levels beginning at 50 Gy in five fractions and escalated by 0.5 Gy per fraction to a maximum dose of 60 Gy in five fractions. The majority of patients ($n = 71$) were accrued into the two highest dose levels. The study found the MTD to be 60 Gy in five fractions with a dose-limiting toxicity (DLT) rate of 7.2% at this dose. Although not considered DLT, four patients in the two highest dose levels experienced grade 5 toxicities more than a year after completing treatment. Median follow-up was 37.9 mo with 2-yr LC rates in the 11.5 Gy per fraction group and the 12 Gy per fraction group of 89.4% and 87.9%, respectively. Two-year OS and progression-free survival (PFS) was 67.9% and 52.2%, respectively, in the 11.5 Gy per fraction group and 72.7% and 54.5%, respectively, in the 12 Gy per fraction group. RTOG 0915, a randomized phase II trial of 84 evaluable patients with peripheral T1-T2, N0, M0 tumors, compared the impact of different SBRT schedules on toxicity and tumor control (Videtic et al. 2015, 2019). Patients were randomized to receive either 34 Gy in one fraction (Arm 1, $n = 39$) or 48 Gy in four fractions (Arm 2, $n = 45$). With a median follow-up of 4.0 yr, protocol-specified grade 3–5 toxicity rates were 2.6% in Arm 1 and 11.1% in Arm 2. Primary tumor failure rate at 5 yr was 10.6% in Arm 1 and 6.8% in Arm 2. There was no statistically significant difference in PFS or OS at 5 yr; 5-yr PFS and OS was19.1% and 29.6%, respectively, in Arm 1 and 33.3% and 41.1%, respectively, in Arm 2. However, the study was not powered to detect survival differences.

Recent prospective multicenter studies comparing outcomes from SBRT versus conventional radiotherapy have confirmed SBRT to be the standard of care in inoperable ES-NSCLC. SPACE, a Scandinavian multicenter randomized phase II trial, compared SBRT to 66 Gy in three fractions with conventional radiotherapy to 70 Gy in 35 fractions in 102 patients with inoperable peripheral T1-T2 (tumor size ≤6 cm), N0, M0 tumors (Nyman et al. 2016). Median follow-up was 37 mo with no statistically significant difference in PFS, OS, or LC between the groups. Of note, the study was underpowered to detect

differences in PFS, and there was a trend toward better disease control with SBRT (70% with SBRT vs. 59% with conventional radiotherapy). Despite the SBRT cohort having significantly more T2 disease, patients treated with SBRT exhibited significantly less toxicity and reported improved quality of life. CHISEL, a multicenter phase III trial from Australia and New Zealand, randomized 101 patients with inoperable peripheral T1-T2, N0, M0 tumors in a 2:1 ratio to either SBRT or conventional radiotherapy (Ball et al. 2019). Patients in the SBRT arm received 54 Gy in three fractions or 48 Gy in four fractions (if the tumor was <2 cm from the chest wall) while those in the conventional radiotherapy arm were treated with 66 Gy in 33 fractions or 50 Gy in 20 fractions depending on institutional preference. With a median follow-up of 2.6 yr for the SBRT arm and 2.1 yr for the conventional radiotherapy arm, the authors reported a statistically significant improvement in both LC (HR 0.32) and OS (HR 0.53) with SBRT.

In recent years, a number of studies have also addressed the use of SBRT in operable patients. In a Japanese retrospective multi-institutional study of 87 patients with operable T1-T2, N0, M0 disease treated with SBRT to a total dose of 45–72.5 Gy in 3–10 fractions, Onishi et al. (2011) reported outcomes potentially comparable with surgical resection. With a median follow-up of 55 mo, 5-yr LC for the total cohort was 86.7%; 5-yr LC for T1 and T2 tumors was 92% and 73%, respectively. OS at 5 yr was 69.5% for the total cohort with 5-yr OS of 72% and 62% for patients with T1 and T2 tumors, respectively. In a meta-analysis of 40 SBRT studies ($n = 4850$) and 23 surgery studies ($n = 7071$) examining treatment outcomes for T1-T2, N0, M0 disease, Zheng et al. (2014) also reported similar LC, OS, and DFS for SBRT and surgery after adjusting for the proportion of operable patients and patient age. RTOG 0618 was a North American multicenter single-arm phase II study, which prospectively investigated the use of SBRT in patients with operable ES-NSCLC (Timmerman et al. 2018b). A total of 26 evaluable patients with operable biopsy-proven peripheral T1-T2 (tumor size ≤5 cm), N0, M0 tumors were treated with SBRT to a total dose of 54 Gy in three fractions. With a median follow-up of 48.1 mo, the study reported excellent rates of primary tumor control. Both 4-yr primary tumor control rate and LC rate were 96% with a 4-yr local-regional control (LRC) rate of 88%. MS was 55.2 mo with 4-yr DFS and OS of 57% and 56%, respectively. Protocol-specified grade 3 toxicities were reported in two patients (8%) with an additional two patients experiencing non-protocol-specified toxicities. No grade 4 or 5 toxicities were reported. A pooled analysis of STARS and ROSEL, two randomized phase III trials comparing SBRT and surgery that closed early due to poor accrual, has reported significantly better OS and lower rates of treatment-related toxicities with SBRT (Chang et al. 2015). In these trials, a total of 58 patients with T1-2a, N0, M0 tumors were randomized to either SBRT ($n = 31$) or lobectomy with mediastinal lymph node dissection or sampling ($n = 27$). Patients on the SBRT arm were treated to a total dose of 54 Gy in three fractions or 60 Gy in five fractions for peripheral tumors and to a dose of 50 Gy in four fractions for central tumors. With a median follow-up of 40.2 mo for the SBRT arm and 35.4 mo for the surgery arm, the authors reported a 3-yr OS of 95% for the SBRT arm versus 79% for the surgery arm. The rate of treatment-related grade 3–5 toxicities was 10% in the SBRT arm compared to 48% in the surgery arm; of note, no grade 4–5 toxicities were reported in the SBRT arm. There was no significant difference in local, regional, or distant failure between the two arms. Although promising, these results are met with skepticism given the small sample size and high rate of treatment-related toxicities in the surgical arm (compared to historical controls).

Several ongoing prospective randomized trials are also directly comparing SBRT to surgery. In the United States, the Joint Lung Cancer Trialist's Coalition (JoLT-Ca) STABLEMATES trial, a randomized phase III trial comparing SBRT to sublobar resection in high-risk patients with operable stage I NSCLC, is currently accruing patients. The Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy (VALOR) trial, another randomized trial comparing SBRT to surgery with lobectomy or segmentectomy in patients with stage I NSCLC, is also underway but is currently on temporary recruitment hold. In Chi-

na, the Radical Resection vs. Ablative Stereotactic Radiotherapy in Patients with Operable Stage I NSCLC (POSTLIV) trial is a randomized phase II trial comparing SBRT to radical resection in patients with T1, N0, M0 peripheral tumors and is also currently accruing patients.

LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER (LA-NSCLC)

Resectable

Primary disease extension and nodal involvement determines the resectability of LA-NSCLC. The initial workup typically includes PET/CT followed by endoscopic ultrasound/endobronchial ultrasound as needed to rule out potential false negative findings from PET/CT imaging (Dong et al. 2013). Surgical candidates will likely have T3-4, N0-1 disease; patients with N2 disease are considered surgical candidates in select cases (single nodal station location with disease <3 cm). The PORT meta-analysis, retrospective analysis of the adjuvant Navelbine International Trialist Association (ANITA) randomized trial data, and several large database analyses have sought to establish the role PORT in resectable LA-NSCLC (PORT Meta-analysis Trialists Group 1998; Burdett and Stewart 2005; Lally et al. 2006; Douillard et al. 2008; Robinson et al. 2015). While the PORT meta-analysis demonstrated a detriment to OS in ES-NSCLC, the updated analysis showed that OS in stage III patients with N2 disease was unaffected. These data included an era where patients received much higher doses of radiation to the heart and lungs. In contrast, an OS benefit was shown in the ANITA, SEER, and NCBD analyses for patients with N2 disease who received PORT. ANITA was a phase III trial that randomized patients with stage IB-IIIA NSCLC who underwent surgical resection to receive adjuvant cisplatin and vinorelbine versus observation; PORT was recommended in patients with pathologically confirmed nodal disease. Approximately 33% and 22% of patients in the experimental and observation arms, respectively, received PORT; PORT improved MS for patients with pN2 disease in both the experimental and observation arms (47.4 vs. 23.8 mo and 22.7 vs. 12.7 mo). The Lung Adjuvant Radiotherapy Trial (ART) (NCT00410683) is a current phase III, randomized trial comparing PORT to no PORT in patients with completely resected NSCLC with N2 disease; results were presented at the European Society for Medical Oncology 2020 Annual Meeting (Le Pechoux et al. 2020) and showed no survival advantage to PORT for pN2 patients, so its use is being reconsidered. American Society for Radiation Oncology (ASTRO) guidelines still recommend PORT following chemotherapy in patients incidentally found to have R1 resections or N2 disease. The ANITA data demonstrates that patients with N1 disease who are not receiving adjuvant chemotherapy should be considered candidates for PORT as well. The dose of radiation should be escalated in the presence of residual disease (50–54 Gy for R0 resection, 54–60 Gy for R1 or extracapsular extension, 60+ Gy for gross disease) (Douillard et al. 2008; Rodrigues et al. 2015). Recommended clinical target volumes can be found in the Lung ART protocol (NCT00410683).

Patients with known T1-3, pN2 disease who are otherwise healthy are candidates for trimodality therapy (TMT), which includes neoadjuvant cisplatin/etoposide and radiation followed by resection and adjuvant cisplatin/etoposide. This regimen is based on the Intergroup 0139 trial, which compared definitive chemoradiation therapy to TMT. TMT remains controversial as results showed improved PFS but did not affect OS (mortality was higher in patients who underwent pneumonectomies) (Albain et al. 2009).

Unresectable

The gold standard for patients with unresectable LA-NSCLC is definitive chemoradiation. RTOG 7301 established 60 Gy in 30 fractions as a minimum dose for the management of LA-NSCLC in the 1970s (Perez et al. 1980). CALGB 8433 was one of the first phase III randomized trials that showed the addition of sequential chemotherapy (cisplatin and vinblastine) to radiation improved PFS and OS in patients with stage III NSCLC (Dillman et al. 1996). RTOG 9410 reported improved OS in patients receiving concurrent chemoradiation therapy compared to sequential

chemoradiation therapy (MS 17 mo vs. 14.6 mo, respectively); however, there were higher incidences of acute esophagitis in the concurrent chemoradiation arm (Curran et al. 2011). Improved OS (4.5% absolute survival benefit at 5 yr) at the expense of increased esophageal toxicity (18% vs. 4%) was similarly reported in a large meta-analysis (Aupérin et al. 2010).

There have been several trials that have evaluated the impact of dose escalation (Bradley et al. 2005, 2015; Rosenzweig et al. 2005). RTOG 0617 was a phase III trial with a 2×2 design that randomized patients to 60 Gy in 30 fractions or 74 Gy in 37 fractions with concurrent carboplatin and paclitaxel followed by adjuvant carboplatin and paclitaxel (± cetuximab). Patients in the dose-escalated arm had worse OS, higher incidence of grade 3 toxicities, and worse quality of life as measured by the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) (Bradley et al. 2015; Movsas et al. 2016). These results were surprising as prior studies had shown higher doses were safely tolerated. Concerns were raised that practitioners underdosed targets to meet protocol constraints and this may have led to worse oncologic outcomes. Subanalyses from this trial have provided important data such as the benefit of using intensity-modulated radiation therapy (vs. 3D conformal) to reduce the heart V40, a marker that was associated with increased mortality (Chun et al. 2017).

Consolidative durvalumab has recently been added to the standard of care regimen given the positive results reported from the PACIFIC trial published in 2017. This trial showed consolidative durvalumab (vs. placebo) improved median PFS (18.1 mo vs. 5.6 mo) and OS (2-yr 83.1% vs. 74.6%, respectively; 3-yr 66.3% vs. 55.6%, respectively) in patients with unresectable LA-NSCLC previously treated with concurrent chemoradiation (Antonia et al. 2017, 2018; Gray et al. 2020). A subset analysis showed no benefit in patients whose tumors were programmed death-ligand 1 negative, so its use in that subset of patients is controversial. Similar rates of grade 3 or 4 toxicities were reported between the two groups, and therapy discontinuation occurred in 15.4% of patients in the experimental arm versus 9.8% of patients in the placebo arm. Separately, other institutions have seen as many as 30% of patients not initiating durvalumab because of rapid disease progression or toxicities due to chemoradiation (Sakaguchi et al. 2019; Shaverdian et al. 2020). Pneumonitis in particular can lead to many patients either not starting durvalumab or discontinuing durvalumab therapy.

Groups are exploring the use of SBRT and proton therapy for treating patients with LA-NSCLC. Lee et al. published their tolerability outcomes from their phase II prospective trial evaluating 28 patients treated with hypofractionated chemoradiation therapy (40 Gy in 10 fractions) followed by a dose-escalated SBRT boost (5 Gy × 5, 6 Gy × 5, or 7 Gy × 5); the 70 Gy in 15 fractions regimen was determined to be the MTD, and OS was similar to historical controls (Lee et al. 2019). Phase I and II studies have investigated the use of protons in definitive chemoradiation therapy for patients with LA-NSCLC; both trials were closed early due to poor accrual. There were minimal treatment-related events (Hoppe et al. 2016, 2020).

STAGE IV AND OLIGOMETASTATIC NSCLC

Metastatic NSCLC (mNSCLC) has a poor prognosis with only 5% of patients living past 5 yr. Systemic therapies, including immunotherapies such as pembrolizumab, are the standard of care with radiation therapy historically held in reserve for palliative treatments (Reck et al. 2019). Over the last several decades, SBRT has been used for patients with limited metastatic disease known as oligometastatic disease. For these patients, aggressive local therapies could provide long-term disease control or even cure (Hellman and Weichselbaum 1995; Pastorino et al. 1997). Many clinical trials have used various definitions to clinically outline the patient characteristics that may reflect oligometastatic disease; the reader can review the studies cited, but, in summary, patients typically have fewer than six targetable lesions in fewer than four sites (Gomez et al. 2016; Iyengar et al. 2018; Dingemans et al. 2019).

Early evidence suggesting the benefit of aggressive local therapy for patients with oligome-

tastatic disease stems from surgical literature (Patchell et al. 1990; Patrini et al. 2018). As not all patients are candidates for surgery or are willing to undergo surgery, SBRT is an effective alternative modality that significantly reduces and even eliminates recovery time; this is particularly beneficial for those needing to return to systemic therapy quickly. Gomez et al. (2016, 2019) and Iyengar et al. (2018) were some of the first to publish randomized data evaluating the use of SBRT in oligometastatic NSCLC. Gomez et al. reported on 49 patients with ≤3 metastatic lesions after first-line systemic therapy (four or more cycles of platinum doublet therapy or three or more months of epidermal growth factor receptor or anaplastic lymphoma kinase inhibitors) who received maintenance treatment ± local therapy (SBRT, chemoradiation, or surgery). The study closed early after the local therapy arm was noted to have superior PFS (11.9 mo vs. 3.9 mo). These results were later supported and augmented when longer follow-up showed both a PFS and OS benefit (median OS 41.2 mo vs. 17.0 mo; median PFS 14.2 mo vs. 4.4 mo at a median follow-up of 38.8 mo). Iyengar et al. explored a similar cohort of 29 patients that had nonprogressive oligometastatic disease (primary disease plus ≤5 metastatic sites with ≤3 sites in the liver or lung) who had already received 4–6 cycles of first-line platinum-based chemotherapy randomized to maintenance therapy ± SBRT. This trial was also closed early when interim analysis showed superior PFS in the SBRT arm (9.7 mo vs. 3.5 mo). These data are encouraging; however, extrapolation to a more generalized population is limited since both study cohorts were small (47 and 29 patients, respectively) and patients did not receive immunotherapy.

The results from SABR-COMET, a phase II randomized trial, were recently published. Ninety-nine patients with oligometastatic cancer of various histologies (18 patients with NSCLC) were randomized to receive standard palliative treatment ± SBRT to all sites of metastatic disease; results were notable for improved PFS and OS in patients receiving SBRT along with standard palliative treatment (Palma et al. 2019). We currently await the results of NRG-LU-002 (NCT03137771) and SARON (NCT02417662); both are randomized, multicenter, phase III trials properly powered to detect an OS difference between patients receiving maintenance therapy ± SBRT.

Distinct from oligometastatic disease, some individuals may have more stable widespread metastatic disease with only a few progressive foci. This is referred to as the oligoprogressive state; currently, there is limited data in this patient subset. One single arm phase II trial evaluated 24 patients with less than seven sites of progressive disease following platinum-based systemic therapy who received erlotinib and SBRT. The addition of SBRT allowed patients to continue systemic therapy for an additional 6–9 mo; moreover, median PFS and OS were 14.7 mo and 20.4 mo, respectively, improved compared to historical controls (Iyengar et al. 2014).

Immunotherapies, such as pembrolizumab, are currently incorporated into the standard of care for patients with mNSCLC after the publication of multiple encouraging trials such as KEYNOTE-24. KEYNOTE-24 was a randomized phase III trial that compared the use of platinum-based chemotherapy versus pembrolizumab for patients with metastatic disease with improved survival seen in patients receiving pembrolizumab (30.0 mo vs. 14.2 mo) (Reck et al. 2019). More recently, there have been results published that evaluated the use of immunotherapies in addition to SBRT. One phase II, single-arm study published by Bauml et al. evaluated 45 patients treated with pembrolizumab after undergoing localized therapy (resection, chemoradiation, radiofrequency ablation). Median PFS was 19.1 mo, which was higher than historical controls and OS was 41.6 mo (Bauml et al. 2019). A phase II trial randomized patients with mNSCLC to pembrolizumab or SBRT then pembrolizumab and showed patients in the SBRT arm had improved OS and PFS (15.9 mo vs. 7.6 mo and 6.6 mo vs. 1.9 mo, respectively) (Theelen et al. 2019). There are currently no published phase III randomized data evaluating immunotherapy with SBRT. However, there was a phase III trial comparing patients with ≤5 sites of oligometastatic NSCLC treated with tyrosine kinase inhibitors (TKIs) to those receiving

TKIs + SBRT was recently presented as an abstract at ASCO 2020. Patients in the SBRT arm had improved PFS (20.2 mo vs. 12.5 mo, median follow-up 19.6 mo) (Wang et al. 2020).

CONCLUSION

The management of NSCLC has evolved throughout the years. Initially, patients with ES-NSCLC were managed with surgical resection alone. Decades of evidence now support the use of SBRT in inoperable patients. The LC rates after SBRT for ES-NSCLC are comparable to surgical results; however, data comparing the two are sparse. We eagerly await the results from trials such as STABLEMATES to address this further. The treatment of LA-NSCLC is stratified according to resectability. Patients with resectable disease may require PORT if the patient underwent an R1 resection or had N2 disease. There is even evidence to support the use of PORT in patients with N1 disease who will not be receiving chemotherapy. Patients with LA-NSCLC but still resectable disease may also be managed with TMT; however, this is controversial. There are several phase II trials reporting the utility of SBRT and systemic therapy for treating patients with oligometastatic disease. Currently, we await the results from the phase III trials, NRG-LU-002 (NCT03137771) and SARON (NCT02417662), to see whether there is an OS benefit with the combination of systemic therapy and SBRT in this patient subset.

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