Stereotactic Radiotherapy for Stage I Small Cell Lung Cancer

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Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy, is a burgeoning radiotherapy modality that involves precisely directing radiation to the tumor site, with increased focus on patient immobilization during treatment (including respiratory motion accountability), and, by definition, administers large doses of radiation in five or fewer treatments [1]. SABR is an excellent alternative to surgery in patients with medically inoperable non-small cell lung cancer (NSCLC), demonstrating local control rates of greater than 90%, minimal treatment morbidity, and essentially no risk of treatment-related mortality [2]. In the absence of completed phase III data and mature phase II data [3, 4] on SABR in patients with operable NSCLC, its use in these patients remains controversial. However, the successes of SABR in achieving high local tumor control and low toxicity bring forth the question of whether SABR can be a viable option in patients with stage I small cell lung cancer (SCLC), particularly those who are medically inoperable.

Per the National Comprehensive Cancer Network guidelines [5], treatment for T1–2 N0 (no regional lymph node metastasis) M0 (no distant metastasis) SCLC includes lobectomy with mediastinal lymph node dissection. If nodes are pathologically negative, adjuvant chemotherapy is warranted, whereas adjuvant chemoradiation is endorsed if nodes are involved. For inoperable patients or those who refuse surgery, chemotherapy with or without radiation that is delivered in conventional fractionation is the only option listed. Thus, SABR is not currently part of management options for operable/inoperable disease, owing to the paucity of stage I SCLC data, and essentially no data on the use of radiotherapy in such situations.

Randomized data have failed to demonstrate a survival benefit for surgery in SCLC. Median survival was longer in patients randomized to radiotherapy compared with surgery on the British Medical Research Council trial (10 vs. 6.5 months; $p = .04$), which included generally more advanced patients [6]. In the Lung Cancer Study Group 832, among 146 patients achieving a partial or complete response to chemotherapy, patients randomized to surgery did not have a survival benefit over those randomized to chemoradiation ($p = .78$) [7]. Three percent postoperative mortality was observed. Of note, most patients in that study were node positive and only 13% had T1–2 N0 disease. Most evidence supporting the use of surgery in SCLC has come from modestly sized retrospective studies examining surgery and chemotherapy [8, 9], in which 5-year overall survival (OS) ranged from 40% to 60%.

Despite current recommendations, it is clear that relatively low levels of evidence exist for surgery in management of stage I SCLC. Thus, at many centers, it is not uncommon to forego surgery in favor of chemoradiotherapy. The gap in recommendations and clinical practice sheds light as to whether SABR is an appropriate option for these patients. Because of the absolute dearth of evidence in this realm, it is important to scrutinize data on SABR in NSCLC [10].

SABR is the treatment of choice for medically inoperable NSCLC; new pooled data from discontinued phase III randomized trials now support that OS for SABR in operable patients is not inferior to that of surgery [11]. This is in keeping with high OS rates for medically operable patients reported for prospective phase II studies at interim analysis in the Japan Clinical Oncology Group (JCOG 0403) trial (76.0% at 3 years) [4] and the Radiation Therapy Oncology Group (RTOG 0618) trial (84.4% at 2 years) [3]. Furthermore, patterns-of-failure analyses for SABR in NSCLC have demonstrated that most recurrences occur distantly [12], a finding supported by seminal SABR trials [2]. Hence, surgical sampling to assess for occult nodal disease in patients with radiographically and metabolically negative lymph nodes may be of less consequence than administering systemic therapy in efforts to decrease distant (and regional) failure. This fact is especially applicable to SCLC, which presents with distant metastases more frequently than NSCLC.

Outcomes of SABR have been consistently superior to those for conventional radiotherapy for early-stage NSCLC, including those from a meta-analysis that demonstrated more than double the 5-year OS [13, 14]. Thus, there is no reason to think differently for SCLC if chemoradiation is electively performed in lieu of surgery, as is done at some institutions.

SABR versus surgery in SCLC (and NSCLC) is less clear cut. Given the evolving role of SABR in patients with medically operable NSCLC but the complete dearth of literature supporting SABR for patients with medically operable SCLC, it is likely too presumptive to assume equivalence in outcomes (resection is still performed if operable clinical stage I). However, specifically in medically inoperable patients with stage I SCLC, SABR with chemotherapy may be most optimal. This is a particularly important patient population, given that patients with SCLC generally present with heavier smoking

histories, more advanced age, and higher medical comorbidity scores than their NSCLC counterparts and, thus, may often be found as medically inoperable. The only current recommendation for medically inoperable patients is chemoradiation, with conventionally fractionated radiation recommended simply because of the lack of available data with SABR as the radiation modality. However, as mentioned, the clear success of SABR versus conventionally fractionated radiation for early-stage NSCLC is evidence that SABR should be evaluated for stage I SCLC. It is, therefore, very possible that SABR could produce increased OS in patients with SCLC as compared with conventional radiotherapy, although this needs to be tested prospectively. Thus, continuing to perform conventional radiotherapy in patients with stage I inoperable disease, as occurs in many practices, could ultimately prove to compromise survival.

In all likelihood, however, there are a few patients at many centers who have undergone SABR for stage I SCLC, and the best way to accumulate data at this point is through case reports/series until systematic reviews and meta-analyses can be performed. Although a few studies have examined SABR for SCLC and found equivalent or better outcomes compared with historical conventionally fractionated treatments, there are essentially no patients with stage I disease without stratification of outcomes based on stage [15].

Based on thorough PubMed and EMBASE searches, there have been three published case series, with a total of 22 patients, examining SABR for stage I SCLC. In one report, eight patients with cT1–2 N0 M0 biopsy-proven SCLC, two of whom refused surgery, underwent SABR (48 Gy in four fractions) [16]. Six patients underwent chemotherapy before ($n = 4$) or after ($n = 2$) SABR. At median follow-up of 32 months, local control was 100% and 3-year OS was 72%, with only one patient dying of SCLC; this patient refused chemotherapy and disease recurred nodally. Another series of six patients with inoperable SCLC, from Cleveland Clinic [17], underwent chemotherapy and SABR with local control of 100%, 1-year OS of 63%, and limited toxicity (one and zero patients with grade 2 and grade ≥3 toxicities, respectively). Among three patients who died, only one died with distant failure; there were no nodal failures. This suggests that similar to experiences with early-stage NSCLC, some patients will die of comorbid conditions other than lung cancer. The final case series [18] treated eight inoperable patients with SABR (50 Gy in four fractions) and adjuvant chemotherapy per physician's discretion. Although local control was 100%, 3-year OS was 60%, and only 37% in patients not receiving chemotherapy.

The largest studied cohort is only published in abstract format—a Japanese multi-institutional pool of 64 patients with biopsy-proven stage I SCLC who were inoperable or refused surgery [19]. SABR was performed at doses of 35–60 Gy in three to eight fractions. Thirty-six patients received chemotherapy (three or four cycles). Although 3-year local control was 90%, distant metastases were seen in 26 patients and nodal metastases in 18 patients. The 3-year OS was 62%.

There are several points to be gleaned from these limited data. First, local control with SABR is, in many cases, close to 100%, which means that there may be little extrapolation of this parameter needed between early-stage NSCLC and SCLC. Second, whereas 5-year OS after surgery and chemotherapy ranges from 40% to 60% in aforementioned

retrospective data, 3-year OS with SABR and chemotherapy has ranged from 60% to 72%, despite most patients who were treated with SABR/chemotherapy being medically inoperable because of greater comorbidities. Third, just as chemotherapy has been shown to significantly improve survival in patients with more advanced SCLC [20], chemotherapy should be considered for patients with stage I SCLC, as well, given the limited data on patients not receiving chemotherapy tending to show poorer outcomes.

These incomplete data create an interesting conundrum: albeit low sample sizes, because of the aforementioned comparable survivals, is there a chance that SABR/chemotherapy could also be comparable to surgery/chemotherapy in patients with operable stage I SCLC who tend not to die of comorbidities? Although the field is a long way from testing this hypothesis, population modeling studies (e.g., Markov modeling or Cancer Intervention and Surveillance Modeling Network) can be compelling ways to test these notions and estimate survivals in large groups of patients with stage I SCLC who are undergoing SABR with chemotherapy, in efforts to provide estimates on outcomes, given the strikingly obvious lack of existing data.

There are several questions of interest that can change clinical practice in these patients if more data are elucidated. What is the optimal timing of chemotherapy with SABR? Published studies [16–18] have used neoadjuvant, concurrent, and adjuvant chemotherapy. Furthermore, what is the role of prophylactic cranial irradiation (PCI) in these patients, done routinely in both limited- and extensive-stage SCLC owing to OS benefits? Although no data have demonstrated intracranial failure, some institutions have used PCI [17] and others have not [16]. In a study examining the role of PCI in patients with surgically treated SCLC, the authors only noted two of 32 patients (6.25%) developed brain metastases, provided complete surgical resection was performed [21]. Additionally, receipt of induction or adjuvant chemotherapy did not affect the risk of brain metastasis, a notion worth considering in light of previously published results. Although it is problematic to assume that the numbers for complete surgical resection would be equivalent to those of SABR, the incidence can be used as a benchmark on which to argue for (or against) PCI in these patients.

Although stage I SCLC is rare overall, the recent approval of low-dose computed tomography screening by Medicare will certainly bring forth more cases of stage I SCLC, given that 8% of detected cancers in the National Lung Cancer Screening Trial were SCLC [22–25]. Although the use of SABR for stage I SCLC is in its infancy, there are many reasons to believe that with more time and experience, it could emerge as the standard of care in inoperable patients, similar to early-stage NSCLC, and perhaps even have equipoise with surgery for operable patients. Reporting of modeling studies and as much clinical data as possible are very much needed.

AUTHOR CONTRIBUTIONS

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