Stereotactic body radiotherapy for Ultra-Central lung Tumors: A systematic review and Meta-Analysis and International Stereotactic Radiosurgery Society practice guidelines

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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) is an effective and safe modality for early-stage lung cancer and lung metastases. However, tumors in an ultra-central location pose unique safety considerations. We performed a systematic review and meta-analysis to summarize the current safety and efficacy data and provide practice recommendations on behalf of the International Stereotactic Radiosurgery Society (ISRS).

Methods: We performed a systematic review using PubMed and EMBASE databases of patients with ultra-central lung tumors treated with SBRT. Studies reporting local control (LC) and/or toxicity were included. Studies with <5 treated lesions, non-English language, re-irradiation, nodal tumors, or mixed outcomes in which ultra-central tumors could not be discerned were excluded. Random-effects meta-analysis was performed for studies reporting relevant endpoints. Meta-regression was conducted to determine the effect of various covariates on the primary outcomes.

Results: 602 unique studies were identified of which 27 (one prospective observational, the remainder retrospective) were included, representing 1183 treated targets. All studies defined ultra-central as the planning target volume (PTV) overlapping the proximal bronchial tree (PBT). The most common dose fractionations were 50 Gy/5, 60 Gy/8, and 60 Gy/12 fractions. The pooled 1- and 2-year LC estimates were 92 % and 89 %, respectively. Meta-regression identified biological effective dose (BED10) as a significant predictor of 1-year LC. A total of 109 grade 3–4 toxicity events, with a pooled incidence of 6 %, were reported, most commonly pneumonitis. There were 73 treatment related deaths, with a pooled incidence of 4 %, with the most common being hemoptysis. Anticoagulation, interstitial lung disease, endobronchial tumor, and concomitant targeted therapies were observed risk factors for fatal toxicity events.

Abbreviations: SBRT, stereotactic body radiotherapy; BED, biologically effective dose; NSCLC, non-small cell lung cancer; ISRS, International Stereotactic Radiosurgery Society; GTV, gross tumor volume; PTV, planning target volume; EQD2, equivalent dose in 2Gy fractions; OAR, organ at risk; CTCAE, Common Terminology Criteria for Adverse Events; PBT, proximal bronchial tree; MDT, metastasis directed therapy; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; mNOS, modified Newcastle-Ottawa Scale.

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1. Introduction

Stereotactic body radiotherapy (SBRT) involves highly conformal radiotherapy delivered with high doses per fraction over a small number of fractions. It is the standard treatment option for peripherally located medically inoperable early-stage non-small cell lung cancer (NSCLC) patients and may be an option for operable stage I small cell lung cancer patients [1–3]. Its role has also been well established for metastasis-directed therapy (MDT) in the setting of oligometastatic disease [4–6], a treatment paradigm that is rapidly gaining traction across multiple disease sites within oncology.

Generally, lung SBRT is safe and effective, normally without grade 4 or 5 toxicities, for targets in the periphery of the lung parenchyma [7]. In contrast, targets in proximity to the central airway and mediastinal structures may pose increased risks due to the dose tolerances of the nearby organs-at-risk (OARs). The remarkably high toxicity rates observed in the early phase II trial from Indiana University using 60–66 Gy in 3 fractions set the precedence for the RTOG-defined “no-fly-zone”, encompassing the 2 cm radius of the trachea and proximal bronchial tree as well as mediastinal structures [8]. With careful risk-adapted fractionation and total dose reduction however, subsequent studies have shown that SBRT can be safely delivered to central lesions with alternative dose/fractionation schedules [9]. However, a subset of central tumors that abut the central airway, esophagus, or other mediastinal structures are termed, “ultra-central”, and associated with a substantial risk of high-grade toxicity from SBRT [10–12]. A 2019 systematic review of this population determined a 5 % risk of grade 5 toxicity from SBRT, predominantly from endobronchial hemorrhage [11]. More recently, the phase II HILUS trial reported significant risks of grade ≥3 (34 %) and grade 5 (15 %) toxicity following ultra-central SBRT for early-stage NSCLC [12]. While a relatively low dose of 56 Gy in 8 fractions was prescribed, concerns related to dose inhomogeneity within the target volume have been raised, further highlighting the balance of optimizing tumor control and decreasing OAR toxicity when considering SBRT for this patient population [13].

Given these trial results, and the publication of additional institutional series, the objective of this study was to perform an updated systematic review and meta-analysis to inform clinical decision making and guideline recommendations on behalf of the International Stereotactic Radiosurgery Society (ISRS). We hypothesize that with a more nuanced attention to radiotherapy prescription technical details and dosimetric constraints, SBRT for ultra-central lung tumors can be delivered safely and effectively.

2. Methods

2.1. Evidence acquisition

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines were used to guide the conduct of this review [14,15]. A comprehensive search was conducted in PubMed/MEDLINE and EMBASE databases for all articles published from January 1, 1990, to February 2, 2022. Search terms included “SBRT” or “stereotactic body radiotherapy” or “SABR” or “stereotactic ablative radiotherapy” and “ultra-central” or “ultracentral” and “lung” or “pulmonary”. Database searches were supplemented by manual searching of manuscript references. Inclusion criteria consisted of patient cohorts (1) with ultra-central lung tumors, (2) treated with SBRT (defined as ≥5 Gy per fraction using photons), and (3) at least one endpoint of interest was reported in terms of local control (LC) and/or toxicity. The definition of ultra-central varied based on the specific study, but generally included tumors in which the gross tumor volume (GTV) or planning target volume (PTV) abuts or overlaps the PBT or other mediastinal structures. Studies with <5 eligible lesions, re-irradiation, non-English language, hilar/mediastinal nodal tumors, or containing a mixed patient cohort with the inability to discern ultra-central outcomes from others, were excluded. In the event of multiple publications of the same clinical cohort, the most recent study was included while others were excluded.

2.2. Data extraction

Search results were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) for determination of eligibility. All studies were screened by two authors (MY and AVL), with conflicts settled by consensus. Data collection was performed on standardized extraction forms, in which baseline clinical, radiotherapy-specific, and outcomes data were extracted. Risk of bias for individual studies was assessed using a modified Newcastle Ottawa Scale (mNOS) [16]. When outcome measures and their variances were not stated within included studies, Kaplan Meier curves were digitized using Web Plot Digitizer, version 4.6, to extract pertinent 1- and 2-year values [17]. In the setting of heterogeneous dose fractionation schedules, doses were converted to biologically effective dose (BED) using the following formula: \( BED_{\alpha/\beta} = nd(1 + \frac{d}{\alpha/\beta}) \) where \( n \) is the total number of fractions, \( d \) is the dose per fraction, and \( \alpha/\beta \) is the alpha/beta ratio of the tumor (\( \alpha/\beta = 10 \)) or organ at risk (OAR) for late toxicity (\( \alpha/\beta = 3 \)). OAR doses are also expressed as Equivalent Dose in 2 Gy fractions (EQD2) using the formula: \( EQD2_{\alpha/\beta} = nd(1 + \frac{d}{\alpha/\beta}) \). In order to standardize reported maximum doses (Dmax) to OAR, and taking into account heterogeneity between various methods of dose calculation, we selected a volumetric threshold of ≤0.5 cc as representative of Dmax for studies where it was not explicitly reported (e.g. D0.1 cc and D0.5 cc would be extracted as Dmax).

2.3. Outcomes definitions

The primary outcomes of interest were the 1- and 2-year rates of LC and incidences of grade 3–5 toxicity. Toxicity events were based upon grading defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4 or 5 [18,19]. Toxicities were stratified into bronchial and non-bronchial toxicities, with the former including hemoptysis, bronchial stenosis, and bronchial fistulisation.

2.4. Statistical analysis

Endpoints reported in the included studies were weighted by inverse variance and combined using a random effects model, with the pooled effect estimates depicted as forest plots with corresponding 95 % confidence intervals (95 % CI). The presence of publication bias was assessed visually with the use of funnel plots and quantified by Egger’s test [20]. A p-value threshold of 0.05 was used for statistical significance, suggesting the presence of publication bias. The Freeman-Tukey double arcsine transformation was used. Inter-study heterogeneity was quantified by the Cochran Q test and the I² statistic. A Cochran Q < 0.1 represented significant heterogeneity. I² values exceeding 25 %, 50 %, and 75 % representing low, moderate, and high heterogeneity, respectively [21]. We also determined the value of τ, which represents the standard deviation of the pooled endpoint due to study heterogeneity.
An inverse transformation (sin(τ/2)) [2] was performed to express τ as a percentage.

Meta-regression was performed to compare summary effect sizes of LC and bronchial toxicity endpoints in relation to respective predictor variables, that is PTV volume and BED for LC, and PBT Dmax for bronchial toxicity. Meta-regression comprised a univariable linear regression weighted by individual study inverse variance. All data analysis was performed in Stata (Stata Corp) using the metaprop, metabias, and metatunnel packages and R (R Foundation) using the metafor package.

3. Results

3.1. Study descriptions

A total of 27 studies published between 2010 and 2022, consisting of 1183 unique patients, met the criteria for study inclusion (Figure A1, Table 1). One study was presented as an abstract while the others were full publications [22]. All studies were retrospective with the exception of the HILUS trial, which was a prospective phase 2 observational study [12]. Risk of bias assessment using the mNOS scale determined that most studies (81 %) were of high quality and received 7/8 stars. One study received full scores [12] and another received 5/8 stars, representing the lowest score [22] (Table A1). Median follow up ranged from 7.6 to 44.5 months for studies reporting this value. Studies were heterogeneous for the proportion of primary NSCLC versus metastatic disease, with 9 studies (33 %) consisting entirely of the former. The definition of ultra-centralised lesion varied (Table A2). PTV overlap with the PBT was included in the definition across all studies (100 %) while GTV overlap was included in only 16 studies (59 %). PTV overlap with other mediastinal structures including great vessels and esophagus were included in 14 studies (52 %), while only 4 studies (15 %) allowed for direct GTV overlap with these structures.

3.2. Radiotherapy technique and Dose/Fractionation

All studies, except for Sidiqi et al, reported using at least one form of motion management (96 %), most commonly with 4DCT (89 %) [22]. Dose and fractions ranged from 30 to 70 Gy in 3–10 fractions (Figure A2). The most common dose fractionation schemes were 50 Gy/5 fractions (18 %), 60 Gy/8 fractions (17 %), and 60 Gy/12 fractions (10 %) (BED10 range 52.5–180). Most studies treated patients with consecutive daily fractions on weekdays (33 %), while four studies treated patients with a single fraction every other day (15 %), and the remainder with other fractionation schemes (Table 1). Reporting of OAR dosimetry was variable and summarized in Table A3.

3.3. Local control

The 1-year LC rate was reported by 21 studies (78 %) and ranged from 54 to 100 %. Meta-analysis of these studies reported a pooled estimate of 92 % (95 % CI: 86–96; Fig. 1A), although considerable heterogeneity existed between studies (I² = 93.2 %, p < 0.01). Meta-regression determined a significant association between increasing target BED and 1-year LC probability (HR 2.14; p = 0.03; Figure A3A). There was also a trend towards lower 1-year LC probability with increasing PTV volume (HR 0.84; p = 0.08; Figure A3B).

The 2-year LC rates were reported by 19 studies (70 %) and ranged from 57 to 100 %. Meta-analysis reported a pooled estimate of 89 % (95 % CI: 82–94 %; Fig. 1B). Inter-study heterogeneity was high (I² = 94.3 %, p < 0.01). Publication bias was detected in all LC pooled estimates (Figure A6A and B). No significant association was determined between tumor BED (p = 0.66) or PTV volume (p = 0.85) and 2-year LC probability on meta-regression (Figure A3C and D).

When looking specifically at the subset of patients with primary NSCLC only, the 1-year and 2-year LC were 95 %. Inter-study heterogeneity was high for included studies (I² = 96.3 % and 94.2 %).

3.4. Toxicities

All studies reported grade ≥3 toxicity rates. Overall, there were 109 grade 3–4 toxicity events, and 73 grade 5 toxicity events (Figure A4). The most common grade 3–4 toxicity was radiation pneumonitis (25 events), whereas the most common grade 5 toxicity was hemoptysis (42 events). Meta-analysis reports a 6 % (95 % CI, 3–10) risk of any grade 3–4 toxicity (range 0–35 %), albeit with high inter-study heterogeneity (I² = 71 %, p < 0.01). The pooled estimate of any grade 5 toxicity was 4 % (95 % CI: 2–6; range 0–22 %), with considerable inter-study heterogeneity (I² = 68 %, p < 0.01) (Fig. 2A and B). Figure 3 reports the distribution of grade 3–4 and grade 5 toxicity events and PBT doses in relation to airflow anatomy from studies in which this information were discernable. A total of 37 toxicity events were reported from 9 studies [12,23–30]. Data were derived either from text specification of PBT substructure involvement or the graphical presentation of radiotherapy dose distributions. Concomitant toxicity-related risk factors such as anti-coagulation/anti-platelet or targeted agent use were also captured.

Specific to hemoptysis, the pooled estimate of the incidence of grade 3–4 events was 0 % (95 % CI: 0–0 %), ranging from 0 to 6 %, and with low inter-study heterogeneity (I² = 0 %, p = 0.98). Grade 5 hemoptysis incidence was 1 % (95 % CI: 0–3 %) with a range of 0–15 %, and overall considerable inter-study heterogeneity (I² = 65 %, p < 0.01) (Fig. 2C and D). The pooled estimates of the incidences of other specific grade ≥3 toxicities were 0 % for PBT fistula (range 0–5 %), stenosis (range 0–22 %), and esophageitis (range 0–5 %). No significant association was determined between PBT Dmax and the risk of fistula, stenosis, or hemoptysis endpoints on meta-regression (Figure A5). Grade 3–4 pooled pneumonitis incidence was 1 % (95 % CI: 0–2 %) and ranged from 0 to 11 % with low inter-study heterogeneity (I² = 5 %, p = 0.39). The pooled estimate for grade 5 pneumonitis was 0 % (95 % CI 0–0 %) with a range of 0–4 %, with overall low heterogeneity (I² = 0 %, p = 0.99) (Fig. 2E and F). The risk of publication bias was noted amongst all toxicity, hemoptysis, and pneumonitis endpoints (Figure A6C–H).

3.5. Fatal toxicities

Table 2 describes the 18 studies that report a > 0 % incidence of grade 5 toxicity, and of these the incidence was > 10 % in 7 studies [12,27,28,31–33]. The largest of these, and the only prospective study, was the phase II HILUS-trial [12]. Of 65 patients receiving 56 Gy/8 fractions, 8 patients experienced hemoptysis, 1 pneumonitis, and 1 tracheal-esophageal fistula (TEF), all grade 5. One patient had both fatal pneumonia and hemoptysis. Distance between the target and main stem bronchus, as well as D0.2 cc, D0.5 cc, and D1cc to the lumen of the main bronchus plus trachea were significant predictors for fatal hemoptysis. For patients that experienced grade 5 hemoptysis, the dose ranges in 8 fractions were Dmax of 59.2–140.4 Gy, D0.2 cc of 36.8–132.2 Gy, and D1cc of 27.2–109.9 Gy. These correspond to EQD23 values of 123.1–291.8 Gy, 76.6–274.3 Gy, and 56.6–228.0 Gy, respectively. Logistic regression modelling suggested that the risk is ~10 % at EQD23 doses of 60 Gy, and ~20 % at 100 Gy for trachea or mainstem bronchi D0.2 cc doses, and 80 Gy and 140 Gy for Dmax doses, respectively. Six patients received concomitant anti-platelet agents during their treatment, and one received a tyrosine kinase inhibitor (TKI) afterwards. The patient who suffered TEF inadvertently received an esophageal Dmax of 80 Gy (EQD23 166.4 Gy) due to PTV overextension.

Lodeweges et al. treated a cohort of 72 patients with ultra-central early-stage NSCLC with 60 Gy/12 fractions [27]. Grade 5 toxicity occurred in 12 patients, of which 10 were fatal hemoptysis. All 10 patients had PTVs that overlapped the main bronchus with bronchial Dmean was determined to be a significant risk factor in the risk of Grade 5 hemoptysis (49.3 Gy vs 26.4 Gy in 12 fractions, p = 0.001). Of note, 6 patients were on anti-coagulant or anti-platelet therapy, and one patient
<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>Country</th>
<th>Study Design</th>
<th>Number of Lesions Treated</th>
<th>Ratio of Primary NSCLC vs. Mixed Histology Tumors</th>
<th>Median PTV size (cc)</th>
<th>Dose Fractionation Range (Gy/ fractions)</th>
<th>Median BED (Gy)</th>
<th>Prescription Method</th>
<th>Treatment Pattern</th>
<th>Median Follow-up (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al., 2018 [28]</td>
<td>Korea</td>
<td>Retrospective cohort study</td>
<td>30</td>
<td>nr</td>
<td>50-50/6-4</td>
<td>75</td>
<td>95 % IDL prescription</td>
<td>daily</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Song et al., 2009 [33]</td>
<td>Korea</td>
<td>Retrospective cohort study</td>
<td>9</td>
<td>1</td>
<td>44</td>
<td>105.6</td>
<td>D85 &gt; 95 %</td>
<td>daily</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>Tekatli et al., 2016 [28]</td>
<td>Netherlands</td>
<td>Retrospective cohort study</td>
<td>47</td>
<td>1</td>
<td>104.5</td>
<td>90</td>
<td>D100 &gt; 95 %</td>
<td>4 fractions per week</td>
<td>29.3</td>
<td></td>
</tr>
<tr>
<td>Unger et al., 2010 [29]</td>
<td>United States</td>
<td>Retrospective cohort study</td>
<td>20</td>
<td>0.5</td>
<td>73</td>
<td>nr</td>
<td>D100 &gt; 95 %</td>
<td>other</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Wang et al., 2020 [30]</td>
<td>United States</td>
<td>Retrospective cohort study</td>
<td>88</td>
<td>0.6</td>
<td>103</td>
<td>nr</td>
<td>PTV underdose ok</td>
<td>EoD</td>
<td>19.5</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
received bevacizumab 2 months post SBRT. In another series of 18 patients, 4 grade 5 toxicity events occurred, of which two were related to hemoptysis and the others pneumonia leading to sepsis [23]. Of the patients with grade 5 hemoptysis, both patients had bevacizumab exposure before and after SBRT, but was held during treatment. The Dmax to the PBT was 47.2 Gy and 51.4 Gy, both in 5 fractions, for these two patients. Mihai et al. reported a 14 % grade 5 toxicity risk in a cohort of 57 patients, with 5 events of hemoptysis, 2 pneumonias, and 1 pneumonitis/exacerbation of chronic obstructive pulmonary disease (COPD) [34]. Two fatal hemoptysis events were likely related to local recurrence. The authors determined that a PBT D4cc was a significant predictor of developing grade 5 hemoptysis, with a median BED3 of 147.4 Gy versus 47.2 Gy (EQD23 of 88.4 Gy vs 29.2 Gy) for patients with and without this toxicity, respectively. Song et al. reported a 11 % incidence of grade 5 stenosis from 9 ultra central early-stage NSCLC tumours [33]. This patient was treated with 48 Gy/4 fractions and had a tumor involving the main bronchus. In a series of 47 patients treated with 60 Gy/12 fractions, there were 10 fatal toxicity events, of which 7 were hemoptysis, and one each of bronchial stenosis, pneumonitis, and multifactorial respiratory failure [28]. In each case of fatal toxicity, the PTV overlapped with the PBT. The PBT Dmax, D1cc, and D4cc ranged from 70 to 90 Gy, 60–80 Gy, and 30–70 Gy, all in 12 fractions, respectively for all grade 5 hemoptysis patients. Lastly, Wang et al. reported a 11 % incidence of grade 5 toxicity in 88 patients, of which there were 6 events of hemoptysis and 4 of radiation pneumonitis [30]. For the former six patients, the BED3 to the PBT Dmax ranged from 160 to 257 Gy (EQD23 96–154.2 Gy), while the bilateral lung V20 for the latter four patients ranged from 8.8 to 11.38 %.

4. Discussion

Carefully delivered SBRT, with attention to adjacent OAR dosing and location of “hot spots,” is safe and effective in the treatment of ultra-central lung cancers and lung metastases. Local control was high, with pooled estimates of 1-year local of 92 % for both lung cancers and metastatic disease, a 2-year local control of 89 %, and a significant positive correlation with BED10. When looking at NSCLC histology alone, the 1- and 2-year pooled rates of local control were 95 %. Severe toxicity was generally low, with a risk of grade 3–4 toxicity of 6 %, and predominantly related to pneumonitis. Pooled grade 5 toxicity risk was 4 %, with most events (58 %) due to hemoptysis. These results support the observations from a previous systematic review that consisted of only 250 patients [11]. The median 1-year and 2-year local control rates were slightly higher at 96 % and 92 %, respectively. Toxicity rates were higher compared to the current study, with a median treatment-related mortality risk of 5 % and grade ≥3 toxicity risk of 10 %. Similarly, Rim et al. included 291 patients in their meta-analysis and determined an excellent 2-year local control rate of
Fig. 2. Pooled estimates of all (A) grade 3–4 and (B) grade 5 toxicity, (C) grade 3–4 hemoptysis and (D) grade 5 hemoptysis, and (E) grade 3–4 pneumonitis and (F) grade 5 pneumonitis.
increasing uptake in its utilization [44]. Recently, the results of the non-surgical phase-II HILUS trial of 56 Gy/8 fractions in the treatment of ultra-central lung tumors has again called into question the safety of SBRT in this setting, with a reported grade 5 toxicity rate of 15 % [12]. However, several details of the trial warrant mention. Firstly, the prescription isodose line as 67 %, suggesting that the Dmax in the center of the GTV reached on average as high as 150 % (84 Gy). Secondly, the PTV margin was generous, and could be as large as 15 mm beyond the GTV [13]. A combination of these factors, in addition to the minimum coverage requirement of 80 % in any overlapping region of PTV and ipsilateral PBT resulted in very high doses to this critical OAR, with a median Dmax of 97 Gy and D0.5 cc of 53 Gy in 8 fractions.

The results of our meta-analyses suggest an overall low risk of grade ≥ 3 toxicity, of which the pooled fatal toxicity rate was 4 %. No significant association was determined between PBT Dmax and toxicity risk from meta-regression, however, this is likely due to the small number of studies included that provided pertinent dosimetric details. Mihai et. al determined PBT D4cc as a significant predictor of fatal hemoptysis risk, with a median BED3 of 147.4 Gy vs. 47.2 Gy (EQD2 88.4 Gy vs. 28.3 Gy) for patients with and without this toxicity endpoint [34]. Wang et al. observed a Dmax BED3 of 160–257 Gy (EQD2 106.7–171.3 Gy) for all patients who developed fatal hemoptysis [30]. In all cases of fatal hemoptysis in the HILUS trial, the EQD2 Dmax to the main bronchus was 100 Gy (BED3 = 167 Gy) [12]. Tekatli et. al. determined a range of 70–90 Gy in 12 fractions (BED3 205–315 Gy or EQD2 123–189 Gy) for all patients experiencing fatal hemoptysis [28]. Taken together, these results suggest an important role of PBT dose and the risk of developing fatal toxicities, with a threshold that may be lower than the 180 Gy BED3 (EQD2 = 108 Gy) reported in a previous meta-analysis [11]. Nevertheless, a dosimetric study determined a threshold of D0.03 cc < 50 Gy in 5 fractions (BED3 = 217 Gy, EQD2 = 130.2 Gy) as being the optimal dosimetric endpoint for predicting grade 2 + non-pneumonitis toxicity, suggesting a potentially higher threshold [45]. The in-progress SUNSET trial allows for a Dmax of 64 Gy in 8 fractions to the PBT (BED3 = 235 Gy, EQD2 = 141 Gy) [46]. Taken together, these results suggest that increasing dose to the PBT is associated with airway toxicity risk. Care should be taken during the planning process to avoid significant “hot spots” in this critical OAR, likely < 133–150 Gy BED3 (EQD2 80–90 Gy) as a conservative constraint. Appropriate prescription dose schedules should be selected to safely achieve these aims, and tolerance further decreased if other concomitant risk factors exist as described below.

We did note several other potential risk factors for fatal toxicity. Endobronchial tumor was noted in 8 cases of fatal toxicity, largely from hemoptysis or fistula development [12,28,29,33]. Anticoagulant and/or antiplatelet use was noted in 17 cases of grade 5 toxicity hemoptysis [12,27,28]. These are well established risk factors previously observed, with intuitive biological reasoning and observed even in the setting of conventional radiotherapy [47,48]. Use of targeted therapies have been associated with increased toxicity risk in the setting of SBRT. In particular, vascular endothelial growth factor (VEGF) inhibitor therapy has been established as a risk factor for significant SBRT-related toxicities, with a proposed mechanism of decreasing vascular density and inhibiting the repair of mucosal damage [49]. Significant rates of severe bowel toxicity have been reported with VEGF administration within 13 months of SBRT to abdominopelvic targets, a common site of treatment [50]. Specific to ultra-central lung tumors, a retrospective analysis of 88 patients revealed that receipt of a VEGF inhibitor within 30 days of SBRT was associated with a significantly higher risk of fatal hemoptysis (HR 16.9, p < 0.001) than those who did not receive an agent [51]. Use of VEGF inhibitor was also observed with fatal hemoptysis events in several other series included within the current analysis [23,27,28]. The concomitant use of other targeted agents and immunotherapy is less well characterized, however recent reports suggest certain classes are more toxic than others when combined with radiotherapy, such as BRAF and MEK inhibitors or CTLA-4 antibodies.
## Table 2
Studies reporting fatal toxicities.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Total Number of Lesions</th>
<th>Any Grade 5 Event (%)</th>
<th>Grade 5 Hemoptysis (%)</th>
<th>Grade 5 Bronchial-Esophageal Fistula (%)</th>
<th>Grade 5 Bronchial Stenosis (%)</th>
<th>Grade 5 Pneumonitis/ Pneumonia (%)</th>
<th>Other Grade 5 Toxicity (%)</th>
<th>Anti-platelet/ coagulation and/or Targeted Agents/ Immunotherapy</th>
<th>Dosimetry</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breen et al.</td>
<td>110</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>–</td>
<td>–</td>
<td>1 (1)</td>
<td>–</td>
<td>Atelectas2 (1)</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Chang et al.</td>
<td>46</td>
<td>3 (7)</td>
<td>–</td>
<td>–</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>–</td>
<td>Nivolumab associated with RP</td>
<td>RP = V20 = 10 % Stenosis = PBT Dmax 53 Gy Dmax heart 39.2 Gy and 19 Gy.</td>
<td></td>
</tr>
<tr>
<td>Cong et al.</td>
<td>51</td>
<td>2 (4*)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Cardiac 2 (4*)</td>
<td>NS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Haseltine et al.</td>
<td>18</td>
<td>4 (22)</td>
<td>2 (11)</td>
<td>–</td>
<td>–</td>
<td>2 (11)</td>
<td>–</td>
<td>VEGF inhibitor for both hemoptysis, held before and after SBRT</td>
<td>45/5 (3 patients) and 50/5</td>
<td></td>
</tr>
<tr>
<td>Kozets ceder et al.</td>
<td>20</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>BED 132 to target</td>
<td>–</td>
</tr>
<tr>
<td>Lenglet et al.</td>
<td>77</td>
<td>4 (5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3 (3)</td>
<td>Cardiac 1 (1)</td>
<td>NS</td>
<td>All received 50 Gy/5 fractions as per model. D2cc PBT doses &gt; 60 Gy EQD2, (10 %) as per model.</td>
<td>1 potential ILD, however unclear if central or UC. 3 patients had 0 mm to GTV (endobronchial), others were 3, 4, 5, 7, and 13 mm</td>
</tr>
<tr>
<td>Lindberg et al.</td>
<td>65</td>
<td>11 (17)</td>
<td>8 (12)</td>
<td>1 (2)</td>
<td>–</td>
<td>1 (2)</td>
<td>–</td>
<td>6 had anti platelet during SBRT</td>
<td>No VEGF inhibitor, one patient had Everolimus post SBRT</td>
<td>60 Gy/8 for all hemoptysis. Median D4cc PBT (p = 0.005) 147.4 Gy vs 47.2 Gy.</td>
</tr>
<tr>
<td>Lodeweges et al.</td>
<td>72</td>
<td>10 (14)</td>
<td>10 (14)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6/10 received platelet or AC</td>
<td>1/10 had Avastin 2 months post SBRT</td>
<td>PTV overlaps main stem bronchus (all)</td>
</tr>
<tr>
<td>Loi et al.</td>
<td>109</td>
<td>1 (1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mihai et al.</td>
<td>57</td>
<td>8 (14)</td>
<td>5 (9)</td>
<td>–</td>
<td>–</td>
<td>3 (5)</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Nguyen et al.</td>
<td>14</td>
<td>1 (7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1 (7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Regnery et al.</td>
<td>51</td>
<td>1 (2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Urosepsis 1 (2)</td>
<td>NS</td>
<td>–</td>
<td>Maybe SBRT related, non-pulmonary.</td>
</tr>
<tr>
<td>Sidiqui et al.</td>
<td>30</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Song et al.</td>
<td>9</td>
<td>1 (11)</td>
<td>–</td>
<td>–</td>
<td>1 (11)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>48 Gy/4 to PBT</td>
<td>Main stem bronchial GTV (endobronchial)</td>
</tr>
<tr>
<td>Tekatli et al.</td>
<td>47</td>
<td>10 (21)</td>
<td>7(15)</td>
<td>–</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>–</td>
<td>4/7 had AP</td>
<td>60 Gy/12 for all hemoptysis. For grade 5 hemoptysis, main bronchus Dmax = 70–90 Gy, D1cc 60–80, and D4cc 30–70</td>
<td>3 had endobronchial tumor, 3 had interstitial changes. 3 with lung hemorrhage had ILD</td>
</tr>
</tbody>
</table>

(continued on next page)
The management of concomitant systemic therapies and SBRT can be guided by the recent EORTC-ESTRO consensus recommendations, which were developed through a Delphi consensus process following a systematic review of the topic, and provide specific guidance based on the class of systemic therapy [53]. In our analysis, one case of grade 5 pneumonitis and grade 5 hemoptysis occurred in a patient who received nivolumab and another who received everolimus post SBRT, respectively [12,24]. Lastly, we observed 5 cases of grade 5 toxicity in patients with interstitial lung disease (ILD), of which 2 were pneumonitis and 3 were hemoptysis [24,28,30]. In the two cases of pneumonitis, the bilateral lung V20s were about 10% [24,30], suggesting that extra precaution should be taken to minimize lung dose or avoid SBRT in patients with ILD. Previous reports have suggested a treatment related mortality rate of 15.6% in ILD patients, with the risk being as high as 33% in the subset of patients having idiopathic pulmonary fibrosis (IPF) [54]. The phase II ASPIRE-ILD trial aims to better characterize the safety and efficacy of SBRT in ILD patients, in which a strict constraint of V20 < 10% must be adhered to amongst other conformity criteria [44].

Limitations of the current analysis warrant mention. Firstly, there are various potential sources of bias that may influence our effect estimates and results. Although most studies included in this systematic review and meta-analysis scored highly on the mNOS, only 1 of the 27 included studies were prospective, and none were randomized. Retrospective studies are inherently prone to selection bias and variability in endpoint definition. Endpoints are known prior to study initiation, thereby allowing for misattribution of toxicities to treatment or non-treatment related factors, or under-reporting of events such as recurrence. Follow up was also limited, with most studies (60%) having a median follow up < 2 years. Long term toxicities may be under-represented, particularly in patients with good long-term prognoses. Furthermore, significant publication bias was detected in our quantitative analyses. However, our review process was extensive with careful review of many studies in the initial phases of screening. We further mitigated this by restricting our inclusion criteria to studies reporting on 5 or more observations, so that highly selected case reports or series, typically reporting extreme outcomes, were excluded. Significant heterogeneity was observed in our pooled endpoint estimates. This is reflective of the heterogeneous nature of the source evidence in terms of disease histology, dose fractionations, differential radiation prescription techniques, and other clinical factors influencing the risk of toxicity and oncologic outcomes. Not all studies reported each endpoint of interest which may introduce another source of bias. We attempted to mitigate this by maximizing endpoint acquisition from each study, including through the recapitulation of digitally reconstructed Kaplan Meier curves. Lastly, there is evidence suggesting that not all structures of the PBT may have the same sensitivity to radiotherapy. In the HILUS study, the incidence of grade 5 hemoptysis was only 4% in tumors >1 cm from the main bronchi/trachea versus 18% in tumors that were ≤1 cm [12]. Due to the paucity of reporting PBT substructure dosimetry in other included studies, we were unable to further define constraints beyond those reported in HILUS. Based on Fig. 3 however, we show that doses ≥90EQD2 to any part of the PBT poses significant toxicity risk, supporting a constraint lower than this threshold. There appears to be a larger proportion of toxicity events within proximity to larger airway structures such as the trachea and main bronchi.

We anticipate an increasing clinical demand for ultra-central lung SBRT as the evidence supporting its use in early lung cancers and oligometastatic disease amounts. As such, we provide recommendations for the use of SBRT in ultra-central lung tumors in Table 3. Generally, the goal of therapy is to maximize target dose and coverage, but without compromising safety and abiding by strict dose constraints for OARs. Patient selection is also critical, in that underlying diseases and other concomitant drug therapies may influence treatment risk. The results of the ongoing SUNSET (NCT03306680) and LUNGTECH trials (NCT01795521) will provide further prospective evidence to guide the use of SBRT in this patient population [46,55]. The introduction of novel radiotherapy technologies such as the MR-linac may allow for safer use of SBRT in this patient population [46,55]. The introduction of novel radiotherapy technologies such as the MR-linac may allow for safer use of SBRT in this patient population [46,55].
Table 3

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy Delivery and Dosing</td>
<td>Doses of 60 Gy/R or 60 Gy/15 may be appropriate for UC tumors. Care must be taken to avoid hotspots within the PBT or other critical structures such as the esophagus, as well as limiting the global Dmax far &lt; 150 % of the prescription dose, even within the PTV. This can often be accomplished by prescribing to a higher isodose line (i.e., 80–85 %). Consider using motion dampening methods for respiratory motion control to decrease ITV expansion. Prioritize sparing critical OARs by undergoing the PTV and avoiding hotspots in those structures. Dose limits should be in general no higher than the prescription dose. Consider limiting the PBT Dmax &lt; 133–150 Gy BED2 (EQD2 &lt; 80–90 Gy), or even lower if other high-risk factors (below) exist, or if the tumor approximates the trachea and main bronchi. In the presence of endobronchial involvement of disease, non-ablative doses should be considered, as detailed below.</td>
</tr>
<tr>
<td>Anti-platelet/anticoagulation use</td>
<td>Discontinue when risk of pause is low (i.e., in the prophylactic versus active therapeutic setting). If unable to be held, consider de-scalating the PBT Dmax or using non-SBRT dose schedules similar to endobronchial disease (see below).</td>
</tr>
<tr>
<td>Targeted Therapy and Immunotherapy Use</td>
<td>In general, concomitant SBRT with targeted or immunotherapies should be avoided, with at least 2–3 days between SBRT and systemic therapy for targeted therapies, and if VEGF inhibitors 3–4 weeks. Immunotherapy is variable, but we recommend at least 2 days between treatments. Any interruptions of systemic therapy must be balanced with the risk of systemic disease progression. Please refer to the EORTC-ESTRO guideline for further details [53].</td>
</tr>
<tr>
<td>Endobronchial tumors</td>
<td>Given the significant risk of hemoptysis, these patients should be treated with extreme caution. All efforts must be taken to mitigate other risk factors for inducing hemoptysis. Non-SBRT regimes using lower dose per fraction (i.e., 60 Gy/15 fractions) should be considered and a more conservative constraint to the PBT such as a Dmax &lt; 100 Gy BED2 or EQD2 &lt; 60 Gy (10 % grade 5 bleeding risk as per modelling from HLILUS trial [12] from all patients, including those without endobronchial disease) should be adopted.</td>
</tr>
<tr>
<td>Intestinal Lung Disease</td>
<td>Given the high risk of pneumonitis, limiting normal lung volume is critical. A V20 &lt; 10 % is a strict cutoff. All efforts should be made to treat on trial.</td>
</tr>
</tbody>
</table>

and medication factors that may increase the risk of fatal toxicities.

Declaration of Competing Interest

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Society of Stereotactic Radiosurgery assume no liability for the information, conclusions, and recommendations contained in this report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.107281.

References


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