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Systematic review

Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis

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ABSTRACT

Purpose: To assess hypo-fractionated particle beam therapy (PBT)'s efficacy relative to that of photon stereotactic body radiotherapy (SBRT) for early stage (ES) non-small cell lung cancer (NSCLC).
Methods: Eligible studies were identified through extensive searches of the PubMed, Medline, Google-scholar, and Cochrane library databases from 2000 to 2016. Original English publications of ES NSCLC were included. A meta-analysis was performed to compare the survival outcome, toxicity profile, and patterns of failure following each treatment.
Results: 72 SBRT studies and 9 hypo-fractionated PBT studies (mostly single-arm) were included. PBT was associated with improved overall survival (OS; $p = 0.005$) and progression-free survival (PFS; $p = 0.01$) in the univariate meta-analysis. The OS benefit did not reach its statistical significance after inclusion of operability into the final multivariate meta-analysis ($p = 0.11$); while the 3-year local control (LC) still favored PBT ($p = 0.03$).
Conclusion: Although hypo-fractionated PBT may lead to additional clinical benefit when compared with photon SBRT, no statistically significant survival benefit from PBT over SBRT was observed in the treatment of ES NSCLC in this hypothesis-generating meta-analysis after adjusting for potential confounding variables.

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Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC), which represents the majority of lung cancer diagnosed, often presents in late stages. Low-dose (LD) CT screening of patients who are at a high risk to develop lung cancer has been associated with a decrease in lung cancer related mortality and a high specificity in selected studies [2–5]. Its clinical adaptation in the high-risk population has caused an increase in the number of patients diagnosed with stage I NSCLC in recent years [2–8]. Early-stage (ES) NSCLC has traditionally been treated with surgery in operable patients. As an alternative, excellent clinical outcome following high dose irradiation delivered with stereotactic body radiotherapy (SBRT) has been observed in inoperable patients with ES, lymph node negative, NSCLC [9]. This treatment technique is also known as stereotactic ablative radiotherapy (SABR). An ablative dose is delivered to the tumor with SBRT over one to two weeks. This is administered under daily image guidance to ensure accurate tumor localization and maximal sparing of the surrounding normal tissue. SBRT has been quickly adopted into clinical practice worldwide. Its efficacy was found to be potentially comparable to surgery in selected patients [10–12]. As more patients are diagnosed with ES NSCLC through LD-CT screening, high dose irradiation with precision, such as SBRT, may become increasingly considered for this disease. However, SBRT is not without limitations. For example, its application is still limited by tumor location with severe toxicity more frequently encountered in patients with centrally located lesions [13]. This problem may be mitigated by increasing dose fractionation because of photons' physical characteristics. However, tumor proximity to critical thoracic structures still prohibits the utility of SBRT in many patients due to the risk of severe toxicity associated high doses to these structures if a therapeutic dose were to be delivered. Also, photon SBRT poses

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great challenges in the delivery of subsequent high dose re-irradiation for loco-regional recurrence in many patients as a result of the high dose already delivered to critical thoracic organs during the first course of treatment. As an emerging technology, particle beam (proton and heavy ions, such as carbon ions) therapy (PBT) possesses unique physical properties that allow the irradiation of tumors at any depth within the body with a very sharp dose gradient at the distal edge of the tumor target [14]. This may greatly decrease the dose to the healthy tissues surrounding the tumor in the setting of high dose irradiation in comparison with photon SBRT. Heavy ions, such as carbon ions, also have a biological advantage over photons due to the higher probability of tumor DNA damage associated with their high linear energy transfer (LET). In recent years, more facilities have been delivering PBT for the treatment of ES NSCLC. In this comprehensive critical review and hypothesis-generating meta-analysis, we aim to analyze and compare the efficacy of hypo-fractionated PBT, which is delivered with highly-advanced technology, with that of photon SBRT, a relatively more mature technique that has been in clinical use for over a decade, in the treatment of ES NSCLC.

Methods

Search strategy and selection criteria

A systematic search was conducted in PubMed, Medline, Google-scholar, and the Cochrane library for studies published between January 2000, and June 2016. The subject heading "non-small cell lung cancer/ carcinoma" was combined with the following terms: "early stage", "stage I", "T1", "T2", "stereotactic body radiation therapy", "stereotactic body radiotherapy", "stereotactic ablative radiotherapy", "SBRT", "SABR", "hypo-fractionated radiotherapy", "particle beam therapy", "proton therapy", "carbon ion therapy", "carbon ion radiotherapy", and "carbon ion radiation therapy". Relevant articles, abstracts, and review articles were selected and reviewed. The references from these sources were searched for additional studies. Proceedings of the annual meetings of the American Society of Radiation Oncology, American Society of Clinical Oncology, and the European Society of Radiotherapy & Oncology from 2000 onward were manually searched for relevant abstracts, then a search for a fully published manuscript was done. The Physician Data Query (PDQ) clinical trials database was searched for relevant ongoing trials. The last search was conducted on July 1, 2016.

Only studies published in English in peer-reviewed journals were included. Eligible studies include prospective or retrospective studies of SBRT or SABR, and hypo-fractionated PBT, such as proton therapy and carbon ion therapy, as definitive treatment for ES NSCLC (T1, T2, or T3, N0, M0 per the 7th edition of cancer staging by the American Joint Committee on Cancer (AJCC)). Only the latest study with the most comprehensive report of clinical outcome and treatment toxicity was selected when multiple studies on the same patient population from the same institution were found. Multiple reports from the same institution were included if the patient populations were from different time periods, treated differently, or the reports on the same patient population complement each other in data reporting. The search was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [15], and a structured literature search schema was followed (Suppl. Fig. 1).

Data extraction

Studies were extracted independently by two investigators. All relevant characteristics, such as first author, publication year, country, study design, age, sample size, tumor stage, follow up period, clinical outcome (including patterns of failure and survival data), and treatment related toxicity, were collected. For each study, the radiation dose fractionation regimen used was recorded. For survival endpoints, 1, 2, 3, 4, and 5 year data were collected when available. Local control was defined as freedom from any local progression. Survival data were extracted from Kaplan–Meier survival curves when survival rates were not explicitly stated. The biologically effective dose (BED_{10}) for tumor was calculated based on the linear-quadratic equation: $BED_{10} = D\,[1 + d/(\alpha/\beta)]$, where D and d represents the total and fractional radiation dose. α/β for tumor equals to 10 Gy^{-1}.

Statistical analysis

The clinical outcomes of interest include local control, overall survival, progression-free survival at 1, 2, 3, 4 and 5 years and treatment related toxicity. Descriptive statistics and exploratory data analysis were used to summarize the data, including summary tables, box-plots, proportions, mean, median, and range. Summary estimates of event proportion, and relative risk (RR) were estimated from the available data at each time point, using the weighted regression model, and the random-effects model/ mixed-effects model (Supplementary material) [16,17]. Continuous data such as tumor size and median follow-up were evaluated using weighted mean with 95% confidence intervals (CI). Dichotomous data such as adverse effects were summarized using proportion and relative risk with 95% CI. Forest plots were used to evaluate relative risk on local control and 3-year survival between two conditions such as T1 vs. T2 groups, where 95% confidence intervals for RR in each study were represented by horizontal lines and the point estimate by a square. The height of each square is inversely proportional to the standard error of the estimate. The summary RR is represented by a diamond with horizontal limits at the 95% confidence interval and width inversely proportional to its standard error. A multivariate meta-regression model was used to assess treatment effect, including covariates, such as patient/tumor characteristics, and treatment modality, to account for population heterogeneity. Data analysis was performed using the meta-analysis package "meta" [18,19] and statistical software R (version 3.31, R Foundation, Vienna, Austria).

Results

Study selection and characteristics

The study selection process is shown in Suppl. Fig. 1. Among 501 relevant publications on SBRT and 113 relevant publications on PBT, 205 full text articles for SBRT and 19 full text articles for hypo-fractionated PBT (proton and carbon ion therapy) were assessed for eligibility. Of these, 72 studies on photon SBRT and 9 studies on PBT for ES NSCLC were selected [10,12,20–99]. Relevant information on the long term clinical outcome was also extracted from an abstract for 1 phase 2 SBRT trial [20,21]. Two SBRT studies reporting the results of the same phase 2 trial complemented each other, and were counted as 1 study. One phase 3 study comparing SBRT and surgery (only the SBRT data was used) [12], 10 phase 2 [20–31], 1 phase 1 [32], and 56 retrospective [33–51,53–89] photon SBRT studies were included in the survival outcome comparison analysis. Among them, treatment-related toxicities were reported in all the prospective studies [12,20–32], and 40 retrospective studies [34,37,39–40,42,44–47,49,52–61,65,67–73,76–78, 80–82,84–89]. These studies were included in the treatment-related toxicity comparison analysis. For 1 retrospective study without toxicity reporting, a similar retrospective study reporting on patients from the same institution treated in the same fashion and in similar time periods was used in the toxicity analysis

[51,52]. Patterns of failure were analyzed based on the information provided in 57 studies, which included 1 phase 3 (only the SBRT data was used), 10 phase 2, 0 phase 1, and 46 retrospective studies [12,20–31,34–46,48–51,54–57,59–65,68–71,73–75,77–79,82,84–90]. Among them, 1 retrospective study was not included in the survival outcome or toxicity profile analysis [90]. It was included in the patterns of failure analysis because of a lack of information in a study from the same institution that was used for survival outcome analysis. At last, 8 studies providing adequate clinical information were included in the clinical outcome comparison for T1 vs. T2 NSCLC analysis [10,24,30,45,58,59,87,90]. Among them, 1 retrospective study was not included in previous analyses as a study of larger sample size was included instead [10,73]. PBT studies included 4 prospective studies (1 phase 2, and 3 phase I/II), and 5 retrospective studies [91–99]. All were included in the survival outcome and toxicity profile comparison analyses [91–99]. For patterns of failure analysis, 8 studies were included [92–99]. Five studies were included in the clinical outcome comparison for T1 vs. T2 NSCLC analysis [91–93,97,99]. The study characteristics are shown in Table 1. Overall, no significant difference in gender, age, functional performance status, the percentage of patients with a pathological diagnosis, utilization of PET/CT staging, treatment time period, % operable patients (%Op), the percentage of patients receiving at least 100 Gy_{10} at the tumor target periphery, and the tumor location was observed. On the contrary, PBT studies appear to be associated with longer follow up time, larger tumors, and higher T stage. The details of the individual studies, including dose prescription information, are shown in Suppl. Tables 1 & 2, while no patients treated with PBT was selected based on respiratory motion amplitude.

Survival outcome

Based on the mixed-effects model [17], the overall survival (OS) and progression-free survival (PFS) following PBT were significantly higher than that following SBRT for ES NSCLC (Fig. 1A & B). The 1, 3 and 5 year OS for PBT vs. SBRT were 91.7% (95% CI 82% – 100%) vs. 86.9% (95% CI 70% – 100%), 69.5% (95% CI 39% – 100%) vs. 58.8% (95% CI 30% – 88%), and 60% (95% CI 23% – 97%) vs. 41.3% (95% CI 2% – 81%), $p < 0.05$. The survival advantage associated with PBT remained significant when studies including patients with peripheral tumors only were analyzed, $p < 0.05$. In the fitted meta-regression model, PBT remains to be associated with better OS than SBRT ($p = 0.03$ for 2-year OS & 0.01 for 3-year OS). The 1, 3 and 5 year PFS for PBT vs. SBRT were 85.3% (95% CI 76% – 95%) vs. 80.2% (95% CI 66% – 94%), 63.5% (95% CI

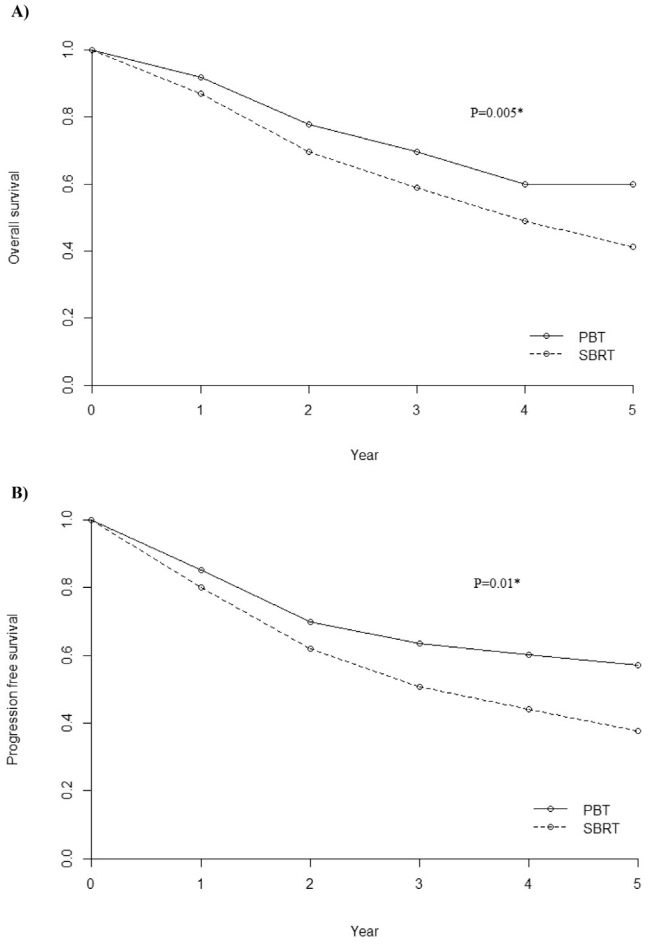

Fig. 1. A) Overall survival (OS), and B) Progression-free survival (PFS) following particle beam therapy (PBT) and photon stereotactic body radiation therapy (SBRT) for node-negative, early stage non-small cell lung cancer. A mixed-effects model [17] with an interaction term of treatment and time was used to assess the differences in OS ($p = 0.005$) and PFS ($p = 0.01$) between the two treatments.

Table 1
Study characteristics.

	PBT	SBRT	*p* value
Studies (total n)	9	72*	–
Patients (total n)	614	7291	–
Gender (% male)			0.23
Median (range)	69% (20%, 87%)	58% (20%, 95%)	
Median age (SE)	75.75 (2.51)	74.09 (0.86)	0.53
ECOG PS 0-1/ KPS 80–100			
Median (range)	89% (60%, 98%)	78% (24%, 100%)	0.23
Pathological diagnosis			
Median (range)	100% (0,100%)	100% (0,100%)	0.97
PET/CT staging (%)	71%	81%	0.44
Treatment Period (year)			
Median (SE)	2006(1.08)	2007(0.36)	0.37
Operability%	38%	16%	0.07
Median follow up (months)			
Mean (SE)	39.99 (3.82)	27.79 (1.29)	0.003
Median tumor size (cm)			
Mean (SE)	2.92 (0.19)	2.41 (0.07)	0.02
Tumor stage (% T1)			
Median (range)	57% (0, 90%)	71% (0, 100%)	0.05
% $BED_{periphery} \geq 100$ Gy_{10}	50%	63.6%	0.62
Tumor location (% P only)	30%	28.6%	0.93

* 2 studies reporting on the same phase II trial and 1 study and 1 abstract reporting on the same phase II trial in a complementary manner were counted as 1 single study each. The *p* value was obtained with the meta-regression model weighted by sample size described in Supplementary materials, using statistical software R with the statistical package "Meta" [18,19].

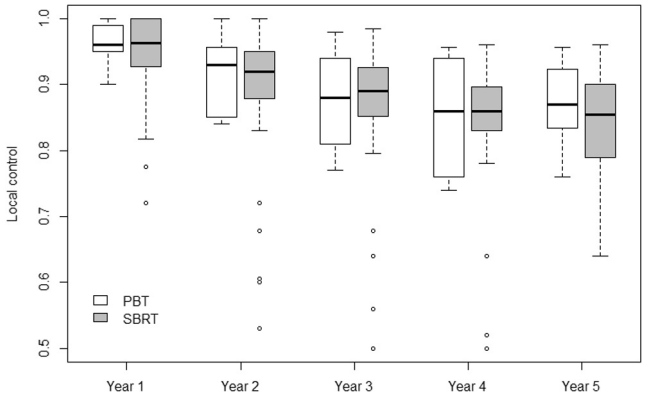

Fig. 2. Local control following particle beam therapy (PBT) and photon stereotactic body radiation therapy (SBRT) for node-negative, early stage non-small cell lung cancer.

Table 2
Treatment-related severe toxicities and rib fractures of any grade following PBT and SBRT (meta-regression model weighted by sample size described in Supplementary materials, using statistical software R with the statistical package "Meta" [18,19]).

Toxicity type	PBT (N = 614) Events percentage (95% CI)	SBRT (N = 4805) Events percentage (95% CI)	*p* value
Grade 3–5 toxicity	4.8% (3.4%, 6.7%)	6.9% (6.1%, 7.9%)	0.05
Grade 5	0% (0%, 0.6%)	0.2% (0.1%, 0.4%)	0.41
Grade 4	1.8% (1.0%, 3.1%)	1.3% (1.0%, 1.6%)	0.34
Radiation Pneumonitis (≥grade 3)	0.9% (0.4%, 1.9%)	3.4 % (2.9%, 4.0%)	<0.001
Chest wall toxicity (≥grade 3)	1.9% (1.1%, 3.3%)	0.9% (0.6%, 1.3%)	0.03
Rib fractures	13% (11%, 16%)	3.2% (2.7%, 3.8%)	<0.001

Table 3
Relative risk of treatment related toxicities based on the meta-regression model weighted by sample size described in Supplementary materials, using statistical software R with the statistical package "Meta" [18,19].

Toxicity type	PBT = 0 SBRT = 1 RR (95% CI)	*P* value
Grade 3–5 toxicity	0.69 (0.22, 3.08)	0.53
Grade 5	–	0.38
Grade 4	2.02 (0.38, 10 +)	0.40
Radiation Pneumonitis (≥grade 3)	0.49 (0.06, 2.03)	0.19
Chest wall toxicity (≥grade 3)	2.02 (0.83, 10+)	0.14
Rib fractures	5.26 (1.91, 10+)	<0.001

RR: relative risk.

37% – 90%) vs. 50.7% (95% CI 31% – 70%), and 57.2% (95% CI 19% – 95%) vs. 37.7% (95% CI 10% – 66%), $p < 0.05$. Overall, no statistically significant difference in local control (LC) was observed between PBT and SBRT (Fig. 2). The 1, 3 and 5 year LC for PBT vs. SBRT were 96.3% (95% CI 90–100%) vs. 95% (95% CI 84–100%), 87.4% (95% CI 73–100%) vs. 86.1% (95% CI 63–100%), and 87.2% (95% CI 73–100%) vs. 80.8% (95% CI 46–100%).

Treatment-related toxicity

The incidence of severe (grade 3–5) toxicity per Common Terminology Criteria for Adverse Events (CTCAE) following either PBT or SBRT was low (Table 2). However, significantly higher incidence of severe toxicity was observed following SBRT in the weighted-regression analysis ($p = 0.05$). No statistically significant difference in the incidence of grade 4–5 toxicity was observed between PBT and SBRT populations. The overall incidence of ≥grade 3 chest wall (CW) toxicity and radiation pneumonitis (RP) was low. The incidence of ≥grade 3 RP following PBT vs. SBRT was 0.9% (95% CI 0.4–1.9%) vs. 3.4% (95% CI 2.9–4.0%), $p < 0.001$. On the contrary, the incidence of ≥grade 3 CW toxicity following PBT vs. SBRT was 1.9% (95% CI 1.1–3.3%) vs. 0.9% (95% CI 0.6–1.3%), $p = 0.03$. The overall incidence of rib fractures for PBT vs. SBRT was 13% (95% CI 11–16%) vs. 3.2% (95% CI 2.7–3.8%), $p < 0.001$. Only the difference in the incidence of rib fractures reached statistical significance in the meta-analysis (Table 3).

Patterns of failure

There was no statistically significant difference in the crude incidence of local failure, regional failure, or distant metastasis with the weighted-regression model. Local failure, regional failure, and distant metastasis for PBT vs. SBRT were 12% (95% CI 6–18%) vs. 10% (95% CI 8–12%), 13% (95% CI 0–56%) vs. 16% (95% CI 0–32%), and 23% (95% CI 15–31%) vs. 20% (95% CI 18–22%). Among studies providing information based on T stage (T1 vs. T2), better 3-year LC and OS were associated with T1 tumors following either PBT or SBRT. As shown in Fig. 3, the relative risks (RRs) for 3-year LC were 3.19 (95% CI 1.93–5.28) and 2.29 (95% CI 1.63–3.20) for PBT and SBRT. The RRs for 3-year OS were 2.43 (95% CI 1.39–4.25) and 1.85 (95% CI 1.41–2.41) for PBT and SBRT. Both favored T1 tumors. The local control and OS among patients with the same T stage were not influenced by treatment type (PBT or SBRT).

Influence of study characteristics on survival endpoints

The influence of various study characteristics on study outcome was assessed with a multivariate analysis using the weighted-regression model. The factors assessed were age, functional performance status, tumor location (peripheral vs. central), T stage, treatment type (PBT vs. SBRT), and the BED at the tumor periphery. Among these factors, OS was significantly influenced by treatment type and functional performance status. Patients with ECOG score of 0–1 or its equivalent, and treatment with PBT were found to be associated with significantly better 2 and 3-year OS ($p = 0.01$ & 0.01, and 0.03 & 0.01). The survival benefit remained significant when treatment time period and PET/CT staging were added into the multivariate analysis ($p < 0.05$). However, this statistical significance was not observed ($p = 0.11$) after further adjusting for %Op ($p = 0.02$ for 2-year OS) in the final multivariate analysis (Suppl. Table 3). While improved LC was initially found to be significantly associated with tumor BED ≥100 Gy_{10} for the entire patient population (88% vs. 76% at 5 years, $p = 0.03$), BED's correlation with LC only trended toward statistical significance without, and with the 3 additional factors in the multivariate analysis ($p = 0.09$ & 0.07 for 2-year LC, respectively). LC was significantly influenced by treatment period, PET/CT staging, tumor T stage, age, and treatment modality; favoring more recent treatment periods (starting > 2005 and/or finishing > 2010), inclusion of PET/CT for staging, T1 lesions, younger age, and PBT in the final multivariate analysis that included the 3 additional factors ($p < 0.05$ for 3 year LC).

Discussion

Through a systematic review of the literature, data extracted from 72 studies on SBRT and 9 studies on hypo-fractionated PBT for ES NSCLC from North America, Europe and Asia were analyzed in a meta-analysis, which represents the most comprehensive review of the subject matter to date. Even with relatively more advanced tumors in size and T stage, patients treated with PBT were found to have significantly better OS and PFS than those treated with photon SBRT in the weighted multivariate analysis ($p < 0.05$). This survival benefit did not reach its statistical significance after adding %Op into the final multivariate analysis ($p = 0.11$). %Op appeared to be the strongest factor affecting patient survival among all study characteristics, implying significant influence of patients' functional performance and comorbidities on survival following high-dose irradiation in patients with ES NSCLC [100]; and the importance of identifying and adjusting for valid prognostic and predictive factors for survival and treatment-related toxicities following high dose irradiation when comparing the efficacy of different treatments [101–103]. These include patient, tumor, dosimetric, imaging characteristics, and biomarkers. Such adjustments are critical for the generation of meaningful data and the reduction of confounding in comparative effectiveness research (CER), which is important to guide treatment decision making especially in the absence of randomized controlled trials (RCTs) [104]. Different conclusions are often reached after such adjustments. This has been previously shown in a meta-analysis, which identified similar survival rates between patients who received SBRT and those who received surgery only after adjusting for age and %Op [102]. This finding has been corroborated in a pooled analysis of 2 RCTs, while unadjusted data still

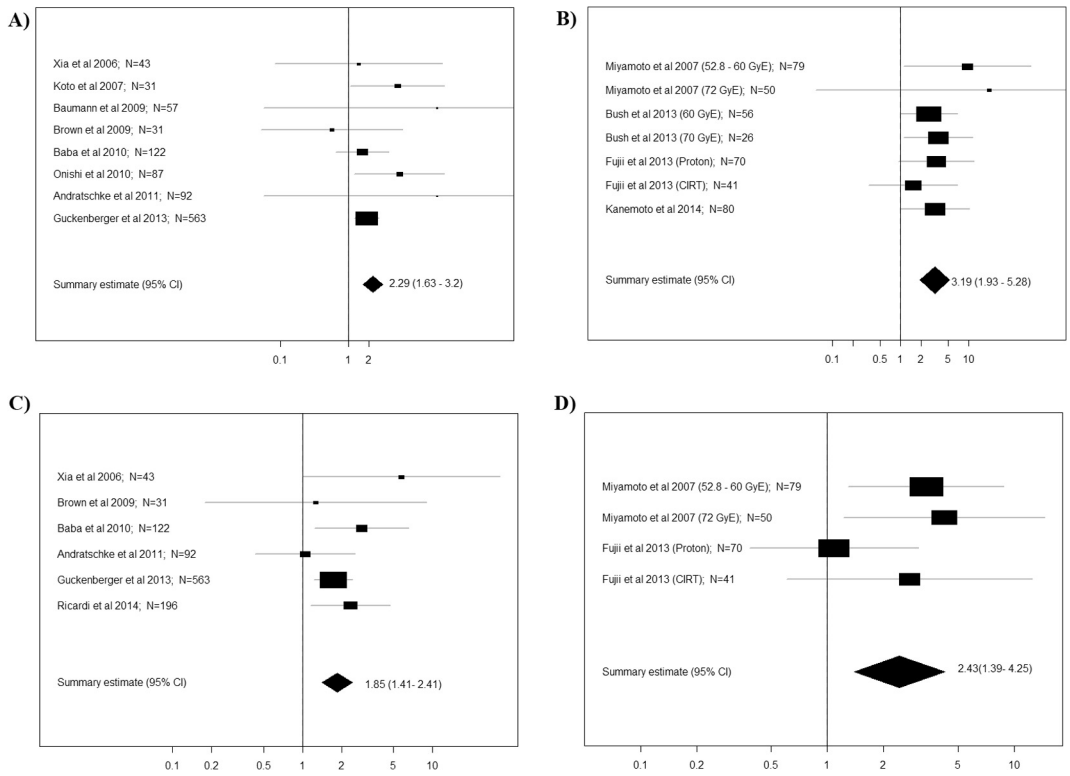

Fig. 3. Forest plots of relative risk (RR) on: A) 3-year local control (SBRT). The summary RR = 2.29 with 95% CI (1.63, 3.20) between T2 and T1 groups, implying that local control is better for T1 tumors (95% CI does not cover 1); B) 3-year local control (PBT): the summary RR = 3.19 with 95% CI (1.93, 5.28) between T2 and T1 groups, implying that the local control is better in T1 group (95%CI does not cover 1); C) 3-year survival (SBRT): the summary RR = 1.85 with 95% CI (1.41, 2.41) between T2 and T1 groups, implying that the 3-year survival is better for T1 tumors (95% CI does not cover 1); D) 3-year survival (PBT): the summary RR = 2.43 with 95% CI (1.39, 4.25) between T2 and T1 groups, implying that the 3-year survival is better for T1 tumors (95% CI does not cover 1). The meta-analyses and forest plots were performed using the statistical package "Meta" in the R software [18,19].

favored surgery [12,101,105]. The current study is limited by considerable selection bias due to that most studies included in the analysis were single- institutional, single-arm, observational studies from various continents of the world with great heterogeneity, including variation in quality. Ideally, controlling for various factors through randomization remains the most effective approach to generate meaningful data when comparing different treatments [106]. Confounding can be minimized by the analysis of individual patient data while controlling for various patient, tumor and treatment characteristics. Such a process may not totally eliminate confounding due to the presence of unknown confounding factors, and is not feasible with the current study. Therefore, our analyses may be biased with significant confounding due to the nature of the studies included, and our results are only exploratory and hypothesis-generating. However, they present useful information to guide the design of future RCTs.

Tumor BED has been previously shown to be correlated with local control and possibly patient survival [46,58,73,107]. Overall, local control following PBT or SBRT was significantly better with tumor BED $\geq$ 100 Gy_{10}. However, this association did not reach statistical significance after adjusting for various patient characteristics. The 3-year LC approached 90% following either PBT or SBRT. No statistically significant difference in LC was observed between PBT and SBRT cohorts without the inclusion of 3 additional factors into the multivariate analysis: treatment period, PET/CT staging, and %Op. However, the 3-year LC favored PBT after these factors were added into the multivariate analysis. This suggests a potential clinical improvement associated with PBT after multiple factors were adjusted for, which can only be discerned in a randomized trial as this can be affected by many unknown confounding factors. The 3-year LC was also significantly affected by treatment period, PET/CT staging, tumor T stage, and age. This suggests the importance of technical advances, rigorous quality assurance programs developed in recent years, and the accumulation of experience for accurate treatment delivery with high precision [104]. While smaller tumors have been known to be associated with better LC, older age should not prevent the utility of hypo-fractionated PBT or photon SBRT for ES NSCLC as they may lead to a survival benefit in elderly patients [108,109].

Low incidence of severe toxicity (grade 3–5) was observed following either PBT or SBRT. Overall, the most commonly reported severe toxicities were pulmonary or chest wall toxicities [12,22–30,34,37,39,42,44,46,49,52–53,56,58–60,65,73,76–77,80–82,84,87,89,92,94–98]. Severe radiation pneumonitis occurred significantly less, while severe chest wall toxicity and any-grade rib fracture were observed more frequently following PBT in the pooled analysis ($p < 0.05$). Only the difference in the incidence of rib fractures remained significant in the meta-analysis. The increased incidence of rib fractures was observed in studies on proton therapy or have the majority of patients treated with proton therapy [95–99]. Decreased dose to the lung parenchyma and other critical thoracic organs, such as the heart, spinal cord, and the esophagus, with PBT for ES NSCLC has been consistently shown in various dosimetric studies [110–117]. Although not statistically significant after controlling for multiple factors, the low incidence of radiation pneumonitis after PBT suggests its potential clinical benefit in OAR sparing. This may have an impact on patients' survival after irradiation as suggested in the correlation between cardiac dose and pulmonary toxicity, as well as cardiac dose and survival, especially for patients with significant co-morbidities and of older age [118–121]. PBT may also help to expand the indications for hypo-fractionated radiotherapy in the treatment of ES NSCLC given its

advantage in OAR sparing, such as treating lesions immediately adjacent to critical thoracic organs that cannot be safely treated with photon SBRT and recurrences or second primary lung cancer (SPLC) after surgery or previous high dose irradiation for maximal normal-tissue protection. No difference in the patterns of failure following PBT and that following SBRT was observed. The pattern of failure remains to be primarily distant following either treatment. Tumor stage, which is dictated by tumor size, has shown to be a significant prognostic factor for LC and OS among the studies which provided information based on T stage (Fig. 3). This corroborates with the newest (8th) edition of the AJCC lung cancer staging criteria, which places more emphasis on tumor size in ES NSCLC based on clinical evidence. It also suggests a need to individualize radiation dosing for ES NSCLC of different T stage, delivering higher doses to >T1 tumors. PBT may be especially advantageous for this, as it may further lower the normal tissue dose from what could be achieved with photon SBRT.

Passively scattered (PS) particle therapy (PT) has been most commonly used clinically worldwide. Despite reducing the dose at the distal end of the tumor target, the entry dose is often unmodulated. This leads to increased dose at the skin and the chest wall, especially for proton therapy. Thus, explaining why increased incidence of chest wall toxicity/rib fractures was observed following PBT in this meta-analysis. To reduce the proximal normal tissue dose, the layer-stacking method, which longitudinally sweeps the Bragg peak through the target and creating a series of short SOBPs for better dose conformity, has been commonly used in PS heavy-ion therapy [122]. Active scanning beams, which deliver pencil-thin particle beams to dose paint slices of the tumor target at various depths in a sequential manor, further enhance dose conformity to the shape of the PTV and decrease dose to the surrounding normal tissue. Scanning beams deliver significantly less dose at tissue depths superficial to the PTV, thus reducing the dose to the chest wall & skin and lowering the risk for chest wall injury and rib fractures [116]. Alternatively, increasing the number of beams may also help to mitigate the dose effect on the chest wall, while the sharper penumbra from carbon ion therapy may further reduce the chest wall dose, thus providing a clinical advantage over proton therapy in hypo-fractionated thoracic PBT.

Unlike PSPT, which delivers a highly homogeneous dose to a target volume at once, intensity modulated PT (IMPT) through beam scanning is very sensitive to internal tumor motion [123–125]. This is mainly due to the necessity for precise and accurate dose deposition at specific voxels iso-energy layer by iso-energy layer longitudinally through a tumor target during IMPT. Commonly used motion management methods are shown in Suppl. Fig. 2. Gating and irradiation of an internal target volume (ITV) have been frequently used with PSPT in the studies analyzed, which did not select patients based on the amplitude of respiratory motion [91–99]. Gating reduces range uncertainties due to motion, and the amount of normal tissue irradiated with the prescription dose. Phase-controlled rescanning (PCR) through various iso-energy layers sequentially has led to improved dose conformity and OAR sparing during the irradiation of lung tumors with scanning CIRT, while fast rescanning can maximally suppress the interplay effect due to scanning motion and intra-fractional organ motion [126,127]. Irregularities in respiratory pattern and inconsistencies between the external marker position and the internal target motion remain challenges with gating [128,129]. These issues may be mitigated through the adaptation of amplitude-based gating and internal positional tracking with or without fiducial markers [125,130,131]. Alternative to gating, 4D planning may improve dose conformity and homogeneity, which warrants further clinical exploration [132].

Photon SBRT, which has been quickly adopted worldwide as a potentially curative treatment option for ES NSCLC, has been associated with excellent LC. However, how LC relates to survival and quality of life (QoL) remains unclear [100]. This is especially true for patients with significant co-morbidities, as they may not gain any survival or QoL benefit from SBRT. Clinical studies on SBRT for ES NSCLC with survival and QoL as primary endpoints, and how this treatment interacts with existing non-malignant co-morbidities are urgently needed to better define how to select patients with ES NSCLC for high dose irradiation and to avoid treating patients who will not benefit from it [100,104]. Secondly, prospective dose defining studies are lacking and the current dosing is largely based on retrospective data. This may not be appropriate for all tumor sizes and patients [100]. Lower than commonly accepted dose may be adequate for certain patients, while over-dosing may lead to worse survival [107,133]. Thus, how to individualize the dosing for ES NSCLC warrants further investigation. Other areas for future research include the validation of models of clinical diagnosis for patients who are unable to undergo a biopsy; identification and treatment of SPLC, and the treatment of ground glass opacities (GGOs) [104]. The roles of hypo-fractionated PBT in comparison to SBRT in addressing the questions raised above are largely unknown. Despite the lack of information on the clinical efficacy of hypo-fractionated PBT in comparison to SBRT in the absence of RCTs, our exploratory and hypothesis-generating study suggests that PBT's theoretical advantages may be of clinical significance in benefiting more patients with ES-NSCLC, even when no statistically significant survival benefit from PBT was observed.

Conclusion

Although hypo-fractionated PBT may lead to additional clinical benefit when compared with photon SBRT, no statistically significant survival benefit from PBT over SBRT was observed in the treatment of ES NSCLC in this hypothesis-generating meta-analysis after adjusting for potential confounding variables.

Conflict of interest

None

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.05.007.

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