Proton Therapy for NSCLC

Non-small cell lung cancer (NSCLC) is the most common malignancy which requires radiotherapy (RT) as an important part of its multimodality treatment. With the advent of the novel irradiation technique, the clinical outcome of NSCLC patients who receive RT has been dramatically improved. The emergence of proton therapy, which allows for a sharper dose of build-up and drop-off compared to photon therapy, has potentially improved clinical outcomes of NSCLC. Dosimetry studies have indicated that proton therapy can significantly reduce the doses for normal organs, especially the lung, heart, and esophagus while maintaining similar robust target volume coverage in both early and advanced NSCLC compared with photon therapy.

1. Introduction

Lung cancer is the most commonly diagnosed malignancy and cause of cancer-related death, and patients affected by non-small cell lung cancer (NSCLC) comprise > 80% of the patients with lung cancer [1]. Radiotherapy (RT) is an important part of the multimodality treatment for NSCLC. With the advent of novel irradiation techniques, such as 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated RT (IMRT), and volumetric-modulated arc therapy (VMAT), the clinical outcome has dramatically improved with modern RT compared to conventional RT [2][3].

Nevertheless, the results of RTOG 0617 show that high prescription RT doses may be compromised in some situations, leading to serious toxicities, such as radiation-induced heart disease and, eventually, reduced survival rates due to the limited tolerance of the surrounding normal tissues (e.g., the lung, heart, and esophagus) [4]. Proton therapy is one of the types of RT that uses charged particles, allowing for a sharp dose build-up and drop-off compared to conventional photon therapy, which may further improve dose conformity, reducing damage to the surrounding normal tissue [3][5][6][7]. Thus, proton therapy is theoretically advantageous compared to conventional photon therapy [8].

During the past decades, proton therapy has been increasingly used worldwide, expanding the clinical trial portfolio rapidly [9]. Currently, emerging published studies have outlined the efficacy of proton therapy for NSCLC with a focus on dosimetry, efficacy, safety, and cost-effectiveness, however, a comprehensive review is lacking. This review summarized the published studies involving these aspects of proton therapy for NSCLC. The published studies were searched on PubMed using the keywords "proton therapy" and "lung cancer". Eligible, studies were published between 1 April 1972 and 30 June 2021. Studies within these parameters that focused on dosimetry, efficacy, and safety, and cost-effectiveness were classified and included.

2. Dosimetry

Proton therapy has a completely different dose distribution compared with conventional photon beams. Unlike X-ray irradiation, the energy during proton therapy is deposited with depth and produces a maximum peak close to the end of the range [8]. The maximum peak is well known as the "Bragg peak", which may be used for dose increment for cancer therapy while reducing the radiation dose to the normal tissue [10][11]. Indeed, published dosimetry studies have indicated that proton therapy significantly reduces the dose to normal structures, especially in relation to the lung, heart, and esophagus, when maintaining similar robust target volume coverage to the clinical target volume (CTV) in both early and advanced NSCLC compared with photon therapy. Currently, passive scattered proton therapy (PSPT) and active pencil beam scanning (PBS) are the two forms of proton therapy in use [12]. The former form uses one or two levels of scatterer to widen the proton beam enough in order to cover the target, while the latter form uses magnets to deflect the proton beams directly, rather than a scatterer. The majority of comparative studies about dosimetry included patients with advanced NSCLC. Studies on the impacts of proton therapy on early-stage cancers were limited, as listed in **Table 1**. Those that do exist were mainly conducted in a retrospective manner, and include only two prospective studies [13][14][15][16][17][18][19][20][21][22][23][24][25][26][27].

Table 1. (**A**). Published dosimetric comparative study involving proton therapy (PSPT) for NSCLC; (**B**) Published dosimetric comparative study involving proton therapy (IMPT) for NSCLC (continued).

(A)

Authors	Design	Year	Cases	NSCLC Stage	Treatment	Dose(Gy)	Fractions	CTV Dosimetric Outcomes (Gy)	OAR Dosimetric Outcomes (Gy)
Wang et al. [13]	-	2009	24	I	PSPT/3D-CRT	66	10	95% isodose line covered 86.4% CTV for proton, and 43.2% for 3D-CRT	Proton delivers lower mean doses to the ipsilateral lung, total lung, heart, esophagus, and spinal cord
Wink et al. [15]	Retrospective	2018	24	I	IMRT/VMAT/CyberKnife/PSPT	60	8	Scattered proton has a lower Dmean of CTV (65.1/65.7/68.1/63.6) and D2% (70.6/70.3/72.9/67.4)	Doses to the spinal cord were lowest with PSPT
Roelofs et al. [17]	Prospective	2012	25	IA-IIIB	3D-CRT/IMRT/PSPT	70	35	-	Higher integral dose for 3D-CRT (59%) and IMRT (43%); Reduced mean lung dose for PSPT (18.9/16.4/13.5, respectively)
Ohno et al. [19]	-	2015	35	3IIB/15IIIA/17 IIIB	Proton/CRT	74	37	45.7% of the X-ray/17.1% of the proton plans were inadequate	Mean lung dose and V5 to V50 were significantly lower in proton
Giaddui et al. [23]	Phase III trial	2016	26	II-IIIB	PSPT/IMRT	70	35	Dose parameters for the target volume were very close for the IMRT and PSPT plans	Lower dose for PSPT plans: lung V5 (34.4 vs. 47.2); maximum spinal cord dose (31.7 vs. 43.5 Gy); heart V5 (19 vs. 47); heart V30 (11 vs. 9); heart V45 (7.8 vs. 12.1); heart V50% (7.1 vs. 9.8) and mean heart dose (7.7 vs. 14.9)
Wu et al. [22]	Retrospective	2016	33	III	PSPT/3D-CRT	60–66	33	-	All the dose parameters of proton therapy, except for the esophageal the dose was lower than 3D-CRT
Shusharina et al. [24]	Retrospective	2018	83	II–IV	IMRT/PSPT	74	37	-	Higher Lung V5 for IMRT, whereas higher V60 for protons; The mean lung dose was similar

(B)

Authors	Design	Year	Cases	NSCLC Stage	Treatment	Dose(Gy)	Fractions	CTV Dosimetric Outcomes (Gy)	OAR Dosimetric Outcomes (Gy)
Register et al. [14]	-	2011	15	I	PSPT/IMPT/SBRT	-	-	Only 6 photons, 12 PSPT, and 14 IMPT were satisfied	PSPT and IMPT reduced mean total lung dose from 5.4 to 3.5 and 2.8, and total lung volume receiving 5 Gy, 10 Gy, and 20 Gy
Zhang et al. [16]	-	2010	20	IIIB	IMRT/PSPT/IMPT	74		IMPT prevented lower-dose target coverage in complicated cases	IMPT spared more lung, heart, spinal cord, and esophagus

Authors	Design	Year	Cases	NSCLC Stage	Treatment	Dose(Gy)	Fractions	CTV Dosimetric Outcomes (Gy)	OAR Dosimetric Outcomes (Gy)
Berman et al. [18]	Retrospective	2013	10	IIIA	PSPT/IMPT/IMRT	50.4	28	-	IMPT decreases the dose to all OARs. PSPT reduces the low-dose lung bath, increases the volume of lung receiving high dose
Kesarwala et al. [20]	-	2015	20	14IIIA/6IIIB	Proton IFRT/ENI vs. photon IFRT/ENI	66.6–72	36–40	Proton IFRT/ENI both improved D95-PTV coverage by 4% compared to photon IFRT	Decreased lung V20/mean lung dose by 18%/36%, mean esophagus dose by 16% with proton IFRT and by 11%/26%, 12% with proton ENI. Heart V25 decreased 63% with both
Inoue et al. [21]	-	2016	10	III	IMPT/VMAT	60	25	IMPT showed better target homogeneity than VMAT	IMRT average and mean lung and heart dose [15]
Li et al. [25]	-	2018	14	III	SPArc/IMPT	66	33	Similar robust target volume coverage	SPArc reduced the structures as well as the interplay effect
Liu et al. [26]	Retrospective	2018	24	III	VMAT/IMPT	60	-	Comparable CTV dose homogeneity	IMPT with lower cord Dmax, heart Dmean and lung V5 and better robustness in heart Dmean, but worse in CTV dose coverage, cord Dmax, lung Dmean and V5 Gy
Ferris et al. [27]	Retrospective	2019	26	III	IMPT/VMAT	60	30		IMPT improves cardiac dosimetry metrics maintaining/improving the IMRT OAR constraints

2.1. PSPT

Among the limited studies using proton therapy for early-stage NSCLC, PSPT has favorable CTV coverage and distributes lower mean doses to the normal tissues, compared with photon therapy. As reported by Winkel in a retrospective study including 25 patients, CTV doses were more homogenous, and the dose directed to the spinal cord was lowest with PSPT, compared with IMRT, VMAT, and CyberKnife. Wang et al. [13] reported that in 24 patients with stage I NSCLC, the 95% isodose line of PSPT covered more CTV than that of 3D-CRT (86.4% versus 43.2%), and the mean dose to lung, heart, esophagus, and spinal cord was also lower, as well as V_{5Gy} and V_{20Gy} to the lungs. The two studies mentioned above were focused on early-stage patients undergoing a hypo-fractionated radiation therapy regimen (60–66 Gy in 8–10 fractions).

For locally advanced NSCLC, PSPT also reduces the dose to the critical normal tissues and prevent lower dose to target coverage. One of the only two prospective studies indicated that PSPT could keep the dose to the target at 70 Gy for patients with stage IA–IIIB NSCLC, while sparing the lung, compared with 3D-CRT/IMRT (mean lung dose, 13.5 Gy versus 18.9 Gy/16.4 Gy) [17]. The second prospective study was a phase III trial, reported by Giaddui T et al. at comparing the dose parameters for 26 lung IMRT, with 26 proton PSPT plans. As a result, the dose parameters for the IMRT and PSPT plans were very close. However, the PSPT plans led to lower dose values for normal structures (including lung V_{5Gy}, 34.4% versus 47.2%; maximum spinal cord dose, 31.7 Gy versus 43.5 Gy; heart V_{5Gy}, 19% versus 47%; and heart V_{30Gy}, 11% versus 19%) [23]. The dosimetry comparative studies of PSPT for advanced-stage patients were mostly using conventional regimens (66–74 Gy in 33–37 fractions).

However, two respective comparative studies revealed similar or worse dose distribution to the lung or esophagus for PSPT. Wu et al. [22] reported that in 33 patients with stage III NSCLC, all of the dose parameters of proton therapy were lower than 3D-CRT, except for the esophageal dose, which was slightly higher than that of the photon plan (V_{50Gy}, 20.2 versus 16.6%), but the difference was not significant. Another study by Shusharina et al. [24] with 83 patients (II-IV stage NSCLC), reported that, although higher lung V_{5Gy} was observed for IMRT, whereas higher V_{60Gy} for was observed for PSPT, the mean lung dose was similar. However, these two studies were both retrospectives and may have been prone to selection bias.

2.2. PBS

PBS may have advantages compared with PSPT in terms of offering greater dose conformality [28]. The entry dose of PSPT is often unmodulated, even after using the layer-stacking method [5]. Meanwhile, the movement of the target during PSPT causes dose distribution disturbances due to interplay and blurring effects, which leads to dose misses and unwanted doses to healthy organs. PBS generates more conformal high-dose volumes than PSPT, with significant sparing of nearby organs, and intensity-modulated proton therapy (IMPT) can be comprehended [29]. Gjyshi et al. [30] compared two independent cohorts with locally advanced NSCLC (86 received PSPT and 53 received IMPT) with data extracted from a prospective registry study, and found that lower mean radiation doses to the lungs (16.0 Gy versus 13.0 Gy, $p < 0.001$), heart (10.7 Gy versus 6.6 Gy, $p = 0.004$), and esophagus (27.4 Gy versus 21.8 Gy, $p = 0.005$) resulted in lower rates of pulmonary (28% versus 3%, $p = 0.006$) and cardiac (14% versus 0%, $p = 0.05$) toxicities for IMPT.

IMPT is also sensitive to uncertainties or target motion. Four-dimensional (4D)-computed tomography (CT) ventilation imaging-guided proton therapy, based on breathing patterns, may be helpful for reducing uncertainties and dosing to the normal tissues [31][32][33]. IMPT via a deep-inspiration breath-hold, deformable image registration with daily adaptive proton therapy, and liver-ultrasound-based motion modeling may also provide additional benefits [34][35][36][37]. FLASH proton therapy which optimizes tissue-receiving dose rate distribution and dose distribution may also provide substantial improvements, compared to IMPT, for normal tissue sparing [38].

As displayed in **Table 1**, published dosimetry comparative studies with proton and photon therapy for IMPT were all retrospective studies with <30 cases. The only study for early-stage NSCLC (15 patients with centrally/superiorly located stage I NSCLC) was reported by Register et al., which revealed that IMPT and PSPT significantly reduced doses to the surrounding normal tissues while maintaining a high radiation dose focused on the tumor, compared with SBRT (total lung volume receiving 5 Gy, 10 Gy, and 20 Gy, respectively) [14]. The rest of the dosimetry studies included patients with stage III NSCLC, and consistent results were observed for IMPT with comparable, if not better, CTV dose homogeneity/coverage while sparing the lung, heart, spinal cord, and esophagus to a greater extent. In addition, IMPT allowed for further dose escalation, compared with photon therapy [16]. Zhang X et al. reported that IMPT might allow further dose escalation (a mean maximum tolerated dose to 83.5 Gy or 84.4 Gy) and prevent lower-dose target coverage for the treatment of stage IIIB NSCLC, while sparing more lung, heart, spinal cord, and esophagus, compared with IMRT, and with similar normal tissue sparing compared with PSPT [16]. Therefore, PBS, which is gradually replacing PSPT in the clinical practice of proton therapy, may potentially overcome the limitations of PSPT and reduce treatment-related toxicity.

Notably, some studies reported special characters for proton, compared with photon therapy. Palma G et al. [39] reported that in 178 patients with advanced NSCLC who were treated with PSPT/IMRT (66/74 Gy, conventional fractionation) with concurrent chemotherapy, significant dose differences of the heart and the lower lungs was found in the 40 patients who developed clinically symptomatic pneumonitis, compared with those without pneumonitis, which may substantiate potential factors in the development of pneumonitis. Harris et al. [40] retrospectively reported that in 160 (78 photons, 82 protons) patients with locally advanced NSCLC who were treated with chemoradiotherapy, among them, 40 (20 photons, 20 protons) patients exhibited grade ≥2 pneumonitis. After multivariate analysis, V_{40Gy} turns out to be statistically significant for proton and a potential pneumonitis predictor is $V_{40Gy} \leq 23\%$, and not V_{20Gy} or Dmean which are traditionally used in photon therapy. However, the dose-response of proton therapy for normal tissue complications has been validated as similar to that of photon therapy, based on a pneumonitis model [41]. Xiang et al. [42] identified 450,373 pediatric and adult patients with cancers (33.5% with 3D-CRT, 65.2% with IMRT, and 1.3% received proton therapy) from the National Cancer Database, and during a median follow-up of 5.1 years, the rate of diagnosed secondary cancer was 1.55% per year, suggesting that proton therapy was associated with lower risk of secondary cancer compared with IMRT (adjusted odds ratio 0.31, $p < 0.0001$). Further study with a long follow-up duration is needed.

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