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Research article

Pro-con of proton: Dosimetric advantages of intensity-modulation over passive scatter for thoracic malignancies

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ABSTRACT

The use of passively scattered proton therapy (PSPT) or intensity modulated proton therapy (IMPT) opens the potential for dose escalation or critical structure sparing in thoracic malignancies. While the latter offers greater dose conformality, dose distributions are subjected to greater uncertainties, especially due to interplay effects. Exploration in this area is warranted to determine if there is any dosimetric advantages in using IMPT for thoracic malignancies. This review aims to both compare organs-at-risk sparing and plan robustness between PSPT and IMPT and examine the mitigation strategies for the reduction of interplay effects currently available. Early evidence suggests that IMPT is dosimetrically superior to PSPT in thoracic malignancies. Randomised control trials are required before any clinical benefit of IMPT can be confirmed.

Introduction

Photon-based Radiation Therapy (RT) is used as a surgical alternative for early stage NSCLC and is the mainstay of treatment for locally advanced NSCLC [1]. Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide [2]. This number is expected to double to 3 million deaths by 2035 [3].

Dose escalation has been shown to improve local disease control, but is currently limited by toxicities to critical structures [4]. Indeed, the RTOG 0617 trial reported poorer survival with 74 Gy compared to 60 Gy in locally advanced NSCLC [5]. Dose to the lung, heart, and oesophagus across multiple dosimetric parameters were associated with worse overall survival [6].

The use of proton therapy opens the potential for dose escalation owing to its unique Bragg peak, which delivers the majority of the dose at depth with no exit dose. Proton Therapy can be divided into Passively Scattered Proton Therapy (PSPT) and Intensity Modulated Proton Therapy (IMPT). PSPT delivers and shapes the beam using a series of physical scatterers, apertures, energy selection systems, range modulators, and compensators [4]. The use of a compensator only allows the beam to conform to the distal edge but not the proximal edge of the target volume. IMPT uses magnets to deflect the beam laterally and alters the proton energy to direct the beam longitudinally, delivering dose to multiple spots within the target volume [4]. Hence, target conformality can be achieved.

The dosimetric superiority of IMPT over PSPT is expected in sites where motion is not a concern. However, there is debate over its use in the thoracic region [7]. This is because planned dose distributions in IMPT are subjected to more uncertainties than PSPT [7]. This results in poor robustness of IMPT as large deviations exist between the delivered and planned dose. Uncertainties when using IMPT in this region mainly arise from range and setup uncertainties [8], anatomical changes [9], and motion [10]. Additionally, the motion of the tumour interferes with the sequential delivery of spots, leading to over and underdosage of the target; a phenomenon referred to as the interplay effect [10].

Abbreviations: BSPTV, Beam Specific Planning Target Volume; CT, Computed Tomography; DIBH, Deep Inspiration Breath-Hold; EUD, Equivalent Uniform Dose; HI, Homogeneity Index; iCTV, Internal Clinical Target Volume; iGTV/HU, Internal Gross Tumour Volume/Hounsfield Unit; ITV, Internal Target Volume; IMPT, Intensity Modulated Proton Therapy; IMRT, Intensity Modulated Radiation Therapy; MFO, Multi Field Optimisation; MU, Monitor Unit; NSCLC, Non-Small-Cell Lung cancer; OAR, Organ-At-Risk; PSPT, Passively Scattered Proton Therapy; PTV, Planning Target Volume; RT, Radiation Therapy; SFO, Single Field Optimisation; SFUD, Single Field Uniform Dose.

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The Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee released a consensus statement on the use of proton therapy in NSCLC [7]. It is stated that IMPT can spare more normal tissue than PSPT but is less robust to uncertainties. However, increasing robustness may come at the price of normal tissue sparing [11]. This study aims to supplement the PTCOG consensus statement by quantifying critical structure sparing between IMPT and PSPT. Additionally, it establishes the basis of such comparison to determine if sparing can be achieved with equally robust plans.

In comparing the dosimetric advantages of both techniques, the effects of interplay in IMPT cannot be ignored. The PTCOG Thoracic and Lymphoma Subcommittee recently released guidelines on planning with IMPT for thoracic malignancies. For a comprehensive overview of the clinical implications and implementation of these techniques, the reader is referred to the two PTCOG publications [7,12]. While measures to reduce interplay are listed, it is not known if they are enough to fully account for interplay effects in all patients.

Additionally, the guidelines included studies on liver tumours which are relatively homogenous with assumed rigid motion [13,14]. Although these studies form an appropriate early basis to understand interplay effects, the highly heterogeneous and deformable nature of the lung warrants further investigation [15].

This review aims to determine whether there is evidence of a dosimetric advantage in using IMPT over PSPT for thoracic malignancies. This work compares the dosimetric parameters of organs-at-risk (OARs) for IMPT and PSPT and reviews the methods available to mitigate interplay effects in thoracic malignancies.

Search strategy for identification of studies

A systematic approach was used to search and select studies from three electronic databases: EMBASE, PubMed, and ScienceDirect. Filters were applied to only include studies within the past 10 years. The first search aimed to compare the dosimetric parameters of OARs for IMPT and PSPT in thoracic malignancies. The primary search terms were: lung AND IMPT AND PSPT. Advanced search terms using Boolean operators and wildcards were used to include synonyms of IMPT and PSPT. The second search aimed to report on the available measures to reduce interplay effects. The search terms were: lung AND proton AND interplay.

Studies were screened based on their title and abstract for relevance. Full-text assessment was conducted on the remaining studies using specific predefined inclusion and exclusion criteria. Included studies must have been conducted on real patient data and not phantoms. Studies must have investigated dosimetry on thoracic malignancies. This was defined to include the lung and mediastinum, while the chest wall, breast, and liver were excluded. These sites were excluded as they have different dosimetric characteristics despite being in the thoracic region. The inclusion of both the lung and mediastinum allowed for a greater scope of findings and is consistent with the joint consensus on IMPT planning by both the PTCOG Thoracic and Lymphoma Subcommittee. Included studies must have been in English with full-text. Reference list of included studies were searched for additional studies.

There is variability in how IMPT is defined in the literature. Single field uniform dose (SFUD), also known as single field optimisation (SFO), is sometimes referred to as pencil-beam scanning with the term IMPT being solely used for multi-field optimisation (MFO). For this review, IMPT will refer to both SFO and MFO and will be specified when necessary.

Dosimetric advantages of IMPT

It is generally reported that IMPT results in significant reduction of OAR dose across all dose metrics (Table 1). For dose-volume parameters that favoured PSPT, none were shown to be statistically significant. This is likely due to the inherent lack of proximal conformity in PSPT. However, having superior dose-volume constraints does not naturally translate to the sparing of critical structures, especially in the context of proton therapy for thoracic malignancies. The ability for a delivery technique to retain nominal doses in the face of uncertainties must also be considered.

A number of studies used physical smearing as described by Moyers et al. [16–22]. PSPT was equally robust against respiratory motion compared to intensity modulated radiation therapy (IMRT) when such a planning approach is used [23]. One study rendered PSPT robust by using a beam specific planning target volume (BSPTV) approach that incorporates 4D CT [24]. This is an extension of the BSPTV approach proposed by Park et al. which incorporates range, setup, and motion uncertainties within target design [25]. As such, this approach can be applied to both PSPT and SFO-IMPT [25].

Robustness of IMPT has also been considered in some studies [16,17,20,24] (Table 2). Berman et al. reported a decrease in CTV coverage and an increase in OAR dose when setup errors were introduced for IMPT [16]. This was attributed to the use of mostly anterior beams, which in the presence of lateral setup errors, resulted in beam overshoot to the lungs [16]. Another reason could be because robustness of IMPT was not prospectively considered by using robust optimisation for MFO or BSPTV for SFO. A robustness comparison with PSPT was not made. It is likely that PSPT would have fared better as such uncertainties are taken in account via smearing. In the study, IMPT significantly reduced OAR doses in all investigated organs except the oesophagus. These dosimetric findings are consistent with Zeng et al., which found significantly lower doses with IMPT when treating the mediastinum with equally large volumes, albeit for mediastinal lymphoma [20]. Further studies incorporating robust comparisons are warranted to confirm these findings.

In their study, Chang et al. used worst-case scenario optimisation to account for MFO-IMPT robustness [17]. It is also the only study within this review that delivered IMPT clinically to patients [17]. This is not surprising as robust optimisation was previously developed in-house and was only recently implemented in commercial planning systems (e.g. Varian Eclipse™ 13.7). Less than 5% deviation from target dose and normal tissue constraints under the worst-case scenario were achieved for all patients. Even with robustness objectives incorporated, the study reported significantly reduced lung and oesophagus dose with IMPT [17]. A concern with robust optimisation is the trade-off between target robustness and nominal OAR doses [26]. This study showed that even with robust objectives in MFO-IMPT, significant reductions in lung and oesophagus dose are retained. However, one must be cautious when projecting these findings into specific sites as the study sample is highly heterogeneous. Additionally, the study only included patients with motion amplitude of less than 5 mm.

Lin et al. used BSPTV that incorporated 4D CT to account for the robustness of both PSPT and SFO-IMPT in Stage III NSCLC [24]. The study reported statistically significant lower doses for the lung, heart, oesophagus, and spinal cord when SFO-IMPT was used. The improvement for heart V_{45Gy} with SFO-IMPT was non-significant. This is consistent with the findings by Chang et al. which did not find significant differences in heart V_{40Gy} [17]. However, significant improvements of heart V_{30Gy} and mean dose were observed by Lin et al. [24]. It is possible that similar findings could be found by Chang et al. had a wider range of parameters been used, especially since the use of MFO allowed for greater conformity of dose [17]. Additionally, both studies used similar dose prescriptions and the majority of the study participants had Stage III NSCLC [17]. The sparing of the heart is crucial in improving survival for locally advanced NSCLC.

Table 1
PSPT and IMPT dosimetric end-points in identified studies.

Authors/Year	Dose prescription (RBE)	Difference in OAR doses (PSPT-IMPT)							Result presented/test
		Lung			Heart	Oesophagus	Cord		
		Combined	Ipsilateral	Contra-lateral					
Georg et al. (2008) [18]	45 Gy, 3#, 65% isodose	N/A	D_{mean}: 0.2 Gy V_{2Gy}: 3.2% V_{4Gy}: 3.3% V_{6Gy}: 3% V_{12Gy}: 1.2%	N/A	$D_{1\%}$: 0.2 Gy V_{2Gy}: 0.3 cc V_{4Gy}: −0.1 cc	$D_{1\%}$: −0.2 Gy	N/A	DIBH	Mean Statistical significance not tested
		N/A	D_{mean}: 0.4% V_{2Gy}: 3.5% V_{4Gy}: 3.6% V_{6Gy}: 2.9% V_{12Gy}: −1.7%	N/A	$D_{1\%}$: −0.2 Gy V_{2Gy}: 0.2 cc V_{4Gy}: −0.1 cc	$D_{1\%}$: −0.2 Gy	N/A	SB + AC	
Zhang et al. (2010) [21]	74 Gy, NA	V_{5Gy}: 5.3% V_{10Gy}:5.3% V_{20Gy}: 4.0% V_{30Gy}: 3.3% D_{mean}: 2.7 Gy	V_{5Gy}: 6.2% V_{10Gy}:7.3% V_{20Gy}: 6.9% V_{30Gy}: 5.4% D_{mean}: 4.3 Gy	V_{5Gy}: 4.3% V_{10Gy}:3.0% V_{20Gy}: 1.0% V_{30Gy}: 1.0% D_{mean}: 1.0 Gy	$V_{40Gy:}$ 0.8%	V_{40Gy}: 2.6% V_{55Gy}: 2.3%	D_{max}: −1.7 Gy $D_{1\%}$: 1.7 Gy		Median Statistical significance not tested
Register et al. (2011) [19]	50 Gy, 4#, 100% isodose	V_{5Gy}: 1.4%*** V_{10Gy}:2.1%*** V_{20Gy}: 1.2%*** D_{mean}: 0.7 Gy***	N/A	N/A	D_{max}: 1.9Gy^{ns}	D_{max}: 10.2 Gy*	D_{max}: 4.8 Gy**		Mean Paired t-test
Berman et al. (2013) [16]	50.4 Gy, 28#, 95% isodose	V_{5Gy}: 8.7%*** V_{10Gy}:9.7%*** V_{20Gy}: 8.2%*** V_{30Gy}: 5.9%*** D_{mean}: 3.4 Gy***	V_{5Gy}: 8.4%** V_{10Gy}:11.1%*** V_{20Gy}: 11.7%*** V_{30Gy}: 10.2%*** D_{mean}: 4.8 Gy***	V_{5Gy}: 8.6%*** V_{10Gy}:8.7%*** V_{20Gy}: 6.1%** V_{30Gy}: 3.3%*** D_{mean}: 2.5 Gy***	$V_{40Gy:}$ 5.6%*** D_{mean}: 3.7 Gy***	$V_{40Gy:}$ 5.0%$^{n/a}$ D_{mean}: 2.2Gy$^{n/a}$	D_{max}: 20.8 Gy*** $D_{1\%}$: 16.0Gy$^{n/a}$		Mean Paired t-test
Chang et al. (2014) [17]	D_{median} = 66 Gy (45–78)	V_{5Gy}: 1.2%^{ns} V_{20Gy}: 4.4%* D_{mean}: 2.4 Gy*	N/A	N/A	V_{40Gy}: 2.1%^{ns}	V_{60Gy}: 11.1%*	N/A		Mean Paired t-test Values were digitised from graph.
Lin et al. (2015) [24]	66.6 Gy in 18#, 99% isodose	V_{5Gy}: 4.3%** V_{20Gy}: 4.5%*** D_{mean}: 2.3 Gy***	N/A	N/A	$V_{30Gy:}$ 2.3%** $V_{45Gy:}$ 2.0%^{ns} D_{max}: 4.5 Gy*	D_{max}: 3.7 Gy*	D_{max}: 5.3 Gy*		Mean Paired t-test
Zeng et al. (2016) [20]	30.6 Gy in 17#, 97% isodose	V_{5Gy}: 5.0%* V_{10Gy}:5.0%* V_{20Gy}: 6.0%* V_{30Gy}: 4.0%* D_{mean}: 2 Gy*	N/A	N/A	V_{5Gy}: 2.0%^{ns} V_{10Gy}: 2.0%* V_{20Gy}: 4.0%* V_{30Gy}: 8.0%* D_{max}: 2.0 Gy* D_{mean}: 1.3 Gy*	N/A	D_{max}: 10 Gy*		Median Wilcoxon signed rank test

Abbreviations: IMPT = intensity modulated proton therapy; PSPT = passive-scattered proton therapy; RBE = Radiobiological Effectiveness, OAR = organ-at-risk; DIBH = deep inspiration breath-hold; SB + AC = shallow breathing and abdominal compression; N/A = Not available; V_{xGy} = volume of OAR receiving × Gy; D_{mean} = mean dose; D_{max} = max dose; D_{median} = median dose; $D_{x\%}$ = Dose to x% volume of OAR.

* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.
^{ns} $p > 0.05$.
$^{n/a}$ p-value not reported.

Table 2
Comparison of study characteristics and robustness management.

Authors/Year	Participants					IMPT		Robustness Management/Analysis
	n	Indications	Location	Motion Amplitude/Management	Treatment Volume	Type of optimisation	Spot Size (mm)	
Georg et al. (2008) [18]	12	Lung lesions (SBRT)	4/12 UL 2/12 ML 6/12 LL	SB + AC DIBH	PTV_{mean}:40 cm^3 ± 33(9–99) PTV_{mean}:35 cm^3 ± 26(8–78)	N/A	3	N/A
Zhang et al. (2010) [21]	20	Inoperable Stage IIIB NSCLC	N/A	N/A	N/A	MFO	N/A	N/A
Register et al. (2011) [19]	15	Inoperable Stage I NSCLC (SBRT)	15/15 C[a] 6/15 S[b]	FB	GTV_{median}:6.49 cc (1.63–50.92)	N/A	5–15	N/A
Berman et al. (2013) [16]	10	Post-operative completely resected Stage IIIA NSCLC	Mediastinum	N/A	N/A	N/A	N/A	Retrospective robust analysis on 1 IMPT plan with ±3 mm shift in 3 orthogonal direction resulted in decrease of CTV $V_{95\%}$ from 97.5% to 94.5%. Ipsilateral lung V_{20Gy} increased from 21.7% to 27.9% and heart V_{40Gy} increased from 5.5% to 6.3%.
Chang et al. (2014)* [17]	34	Mixed[c]	Mixed[d]	≤5 mm	GTV_{median}: 65 cm^3 (2.3–1692.1) CTV_{median}: 239 cm^3 (23.4–2449)	SFO & MFO with worst-case scenario optimisation	N/A	<5% of deviation from target dose and normal tissue constraints are met under worst-case scenario for all plans
Lin et al. (2015) [24]	10	Stage III NSCLC	Mixed[e]	Mean SI:8.3 mm ± 2.2 AP:3.7 mm ± 1.2 RL:2.4 mm ± 1.0	$iCTV_{mean}$: 243 cm^3 ± 131	SFO with BSPTV (4D)	3–7	Retrospective robust analysis on all plans with uncertainties of 3 mm setup and 3% stopping power ratio showed that iCTV received more than 97% of prescription dose for both IMPT and PSPT
Zeng et al. (2016) [20]	10	Mediastinal Lymphoma	3/10 AMM 6/10 ALM 1/10 APMM	Mean[f] SI: 5.3 (<1–10) AP: 1.6 (<1–4) RL:1.75 (<1–6)	ITV_{median}: 275 cm^3 (104–725)	SFO with BSPTV	Motion <5 mm: 4–8 motion perpendicular to beam: 6–16	N/A

Abbreviations: n = number of study participants; IMPT = intensity modulated proton therapy; SBRT = stereotactic body radiation therapy; UL = upper lobe; ML = middle lobe; LL = lower lobe; SB + AC = shallow breathing & abdominal compression; DIBH = deep inspiration breath hold; PTV = planning target volume; N/A = not available; NSCLC = non-small cell lung cancer; MFO = multi-field optimisation; C = central; S = superior; FB = free breathing; GTV = gross tumour volume; $V_{x\%}$ = volume receiving x% of prescription dose; CTV = clinical target volume; V_{xGy} = volume receiving xGy of dose; SFO = single field optimisation; SI = superior-inferior; AP = anterior-posterior; RL = right-left; iCTV = internal clinical target volume; BSPTV = beam specific planning target volume; AMM = anterior middle mediastinum; ALM = anterior lower mediastinum; APMM = anterior & posterior middle mediastinum; ITV = internal target volume.

[a] Centrally located tumours were defined as tumours within 2 cm of critical structures (tracheal (above carina) bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, bronchus intermedius, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi), oesophagus, heart, major vessels, and/or spinal cord).

[b] Superiorly located tumours were defined as tumours in the lung apices or within 2 cm of the brachial plexus.

[*] Participants received IMPT as part of treatment. i.e non-virtual study.

[c] 44% Adenocarcinoma, 29% Squamous cell carcinoma, 6% NSCLC, 3% Small cell carcinoma, 3% Large cell neuroendocrine carcinoma, 15% other thoracic malignancies; Out of 20 primary lung cancer, 5% Stage I, 5% Stage II, 85% Stage III, 5% Stage IV (isolated brain metastasis).

[d] Mixture of bilateral upper and lower lungs, hilum, main bronchus, mediastinum, hemithorax, and others.

[e] All patients had mediastinal nodal metastases with various primary tumour locations.

[f] Target motion specified as <1 mm was assumed to be 0.5 when calculating mean.

Lin et al. also performed a retrospective robust analysis on all plans incorporating setup and stopping power ratio uncertainties and identified that the internal clinical target volume (iCTV) received more than 97% of prescription dose for both SFO-IMPT and PSPT [24]. The finding of this study is surprising as it is commonly believed that IMPT is more sensitive to uncertainties than PSPT [12]. This study shows that when uncertainties are properly accounted for, SFO-IMPT can produce comparable, if not superior, plans in terms of both target robustness and OAR sparing compared to PSPT [24]. This is the only study that compared these parameters simultaneously. Future studies should incorporate both robustness and OAR doses in their comparison, especially for MFO as it is more sensitive to uncertainties. Additionally, a comparison between MFO and SFO-IMPT is warranted to determine whether MFO-IMPT can be made equally robust with superior dosimetric parameters.

Interplay effects in IMPT

In addition to plan robustness, interplay effects must be addressed for nominal dose agreement in IMPT. Interplay is not an issue in PSPT as all energy layers are delivered simultaneously within 0.1 s [24].

Interplay effects can be reduced when using robust target concepts [27–29] (Table 3). This is despite robust optimisation and BSPTV not explicitly accounting for interplay effects. Liu et al. compared 4D robust optimisation that considers range changes to 3D robust optimisation and found improvement in $D_{95\%}$ and HI [29]. This finding is consistent with the study by Jakobi et al. which compared BSPTV to iGTV/HU and found significant improvement in $V_{95\%}$ and $V_{98\%}$, especially when patients have large motion amplitudes [28]. The key takeaway message of these two studies is that improving plan robustness does not appear to be a confounding factor for addressing interplay effects, but rather also indirectly mitigates them. Engwall et al. explicitly accounted for interplay effects by incorporating respiratory motion and delivery characteristics in the optimisation phase [27]. In this manner, adequate coverage can be achieved in a single fraction.

Liu et al. improved both $D_{95\%}$ and HI by the usage of big spots but the differences were not statistically significant when compared with small spots [30]. Despite the non-significant findings, 3 patients had large improvements in dose parameters with the use of big spots. Grassberger et al. and Dowdell et al. also found reduced interplay effects with big spots but did not test for significance [10,31]. It is interesting to note that the use of small spots has a larger standard deviation and range in the second and third study respectively [10,31]. The greater statistical variability of small spots, coupled with the non-significant findings from Liu et al. [30], has several possible implications. First, big spots are less sensitive to interplay effects. Second, the benefits of applying big spots to a group of patients may not be apparent but may be the crucial factor when looking at individual patients. Conversely, the blanket use of small spots on a group of patients may not negatively impact on the majority of patients, but it may severely worsen interplay in selected patients. Small spots have a sharper lateral penumbra which can reduce dose to surrounding critical structures [31]. In centres with variable spot size, the trade-off between interplay resistant plans and critical structure sparing must be weighed. This also highlights the need for interplay analysis tools to be incorporated into commercial treatment planning systems to facilitate the making of such clinical decisions.

Rescanning can be used to average out interplay effects at the expense of increased delivery time [32–36]. However, two studies did not find any rescanning strategy that can achieve satisfactory coverage for one patient with large motion amplitude within their study [32,33]. Conversely, Kardar et al. achieved satisfactory coverage for all the study participants by using a higher magnitude of isolayered rescanning for two patients that have a small tumour volume and large motion [35]. It should be noted that these three studies investigated interplay within a single fraction. Fractionation can further average out any residual interplay effects [37]. However, there are concerns that dose heterogeneity within a single fraction may compromise tumour control [32]. Hence, a conservative approach is often adopted in minimising interplay within fractions. Li et al. proposed a novel strategy to reduce interplay by optimising the delivery sequence. Instead of delivering spots successively, an alternating sequence was used [38]. The optimised sequence yielded a superior performance to the regular sequence. However, an absolute dose error of 10.6% was still present. This could potentially be improved by combining an alternating sequence with rescanning [38].

Fractionation can average out the interplay effects as patients start at a different breathing cycle between fractions [10,28,37,38]. Despite the effectiveness of fractionation, Jakobi et al. reported large degradation in dose coverage for patients with motion amplitude of more than 5 mm [28]. This is opposed to the findings by Li et al., which identified that interplay effects were not a concern after fractionation [37]. However, the study by Li et al. used isolayered rescanning [37] (Table 4). Additionally, large spots were used as opposed to the study by Jakobi et al. which used small spots [28]. This is consistent with the study by Dowdell et al. which found that the Equivalent Uniform Dose (EUD) for one patient was only 84.7% even after 35 fractions when using small spots [10]. An EUD of 100% was only achieved when big spots were used [10]. Li et al. also reported reduced interplay effects when comparing hypofractionation to regular fractionation [37]. Hypofractionated regimes were found to have fewer interplay effects in both fractional and overall simulations. This was attributed to the longer time needed to deliver a treatment, which led to greater averaging effects [37]. Additionally, since the maximum MU delivered to each spot is limited, more rescanning was used [37].

Kanehira et al. investigated various windows of gating and found that decreasing the gating window improves the $D_{99\%}$, HI, and lung V_{20Gy} [15]. A 2 mm gating window was chosen as it had adequate coverage while having an acceptable treatment time of approximately 3.5 minutes. Grassberger et al. also investigated gating and found that a duty cycle of 30% can achieve adequate EUD for all patients when big spots are used [33]. However, one patient had an unsatisfactory EUD of 93.1% when small spots were used [33]. The spot size used by Kanehira et al. was not reported [15]. Nonetheless, the findings by Grassberger et al. suggest that gating alone cannot fully account for interplay effects, especially in centres with fixed small spots.

Other motion management strategies were not investigated. Jakobi et al. showed that patients with motion amplitude of >5 mm generally had larger interplay effects [28]. Hence, motion mitigation strategies, such as the use of an abdominal compression plate, can be valuable in patients that present with large motion amplitude. However, it should be used in tandem with the aforementioned strategies to fully account for interplay effects, as motion amplitude alone is not a reliable predictor of dose degradation [39].

IMPT has been shown to be robust against inter-fractional shifts for peripheral lung tumours when breath-hold was used [40]. However, there is no study that investigated the ability of breath-hold in reducing interplay effects. Even with breath-hold, intra-fractional tumour motion still exists which can potentially lead to interplay effects [40]. Further investigations in this area are needed to determine the rescanning required to account for this residual motion. An advantage of breath-hold is that it can reduce the target volume and potentially allow for the reliable use of small spots, providing greater critical structure sparing. However, multiple breath-holds are required every fraction which

Table 3
Methods to reduce interplay effects in thoracic malignancies.

Authors /Year	Dose (RBE)	Investigation (x vs. y)	Findings[a] (x vs. y)	Residual interplay	Result presented/test	Remarks
Liu et al. (2016) [29]	66 Gy in 33#	4D robust optimisation vs. 3D robust optimisation	$D_{95\%}$:64.5 Gy vs. 63.8 Gy (p = 0.0068) HI ($D_{5\%}$-$D_{95\%}$): 5.0 Gy vs. 6.7 Gy (p = 0.18)	N/A	Mean Wilcoxon signed rank test	N/A
Jakobi et al. (2018) [28]	66 Gy in 33#	BSPTV vs. iGTV/HU and fractionation	Single fraction (motion < 5 mm): $\Delta V_{95\%}$ = 1% vs. 2% (n.s) Single fraction (motion > 5 mm): $\Delta V_{95\%}$ = −10% vs −13%(p < 0.01); $\Delta V_{98\%}$: –23% vs. −26% (n.s) Fractionated (motion < 5 mm): $\Delta V_{95\%}$: 1% vs. 0% (p = 0.02) Fractionated (motion > 5 mm): $\Delta V_{95\%}$: −2% vs. −4% ($p \leq 0.01$); $\Delta V_{98\%}$: −11% vs. −17% ($p \leq 0.01$)	Large number of patients with motion > 5 mm had dose deteriorations of $\Delta V_{98\%}$: −11% even with fractionation	Mean Paired t-test	N/A
Engwall et al. (2018) [27]	60 Gy in 30#	4D robust optimisation with time structures vs. 4D robust optimisation	CTV $D_{95\%}$: 59.6 Gy vs. 58.5 Gy HI ($D_{5\%}$-$D_{95\%}$): 3.95 Gy vs. 4.99 Gy	Adequate coverage achieved for all patients	Mean	Values were digitised from graph and mean was calculated Data for '4D resc' and 'IPR 2 resc(40)' are used
Grassberger et al. (2013) [31]	87.5 Gy in 35#	Big Spot(11–15 mm) vs. Small spot(2–3 mm)	ΔHI ($D_{5\%}$-$D_{95\%}$): 5.6 ± 4.2% vs. 15.8 ± 11.1%	For largest motion amplitude, $D_{5\%}$-$D_{95\%}$ increased by 10.8% even with fractionation for small spots.	Mean	N/A
Liu et al. (2018) [30]	66 Gy in 33#	Big spot(5–15 mm) vs. Small spot(2–6 mm)	$D_{95\%}$: 62.60 Gy vs. 61.25 Gy (p = 0.23) HI ($D_{5\%}$-$D_{95\%}$): 6.31 Gy vs. 7.34 Gy (p = 0.19)	N/A	Mean Wilcoxon signed-rank test	3 patients had large improvement in dose parameters with big spots despite non-significance among the 10 patients.
Dowdell et al. (2013) [10]	87.5 Gy in 35#	Big Spot (11–15 mm) vs. Small spot(2–3 mm) and fractionation	Single fraction EUD: 100.4% (93.7–103.5) vs. 90.7% (65.3–99.0) Fractionation EUD: 102.2% (100–103.0) vs. 96.6% (84.7–101.7)	Even with fractionation, small spots resulted in 84.7% EUD for one patient	Mean	N/A
Kraus et al. (2011) [36]	60 Gy in 30#	Volumetric rescanning vs. no rescanning	$D_{99\%}$: 59.4 Gy vs 36.2 Gy; 52.1 Gy vs 44.3 Gy $D_{95\%}$: 47 Gy vs 44.1 Gy; 54 Gy vs 48.5 Gy $D_{1\%}$: 66.1 Gy vs. 74.3 Gy; 63.6 Gy vs 67.1 Gy	N/A	N/A	Individual findings were presented as n = 2. Data presented in findings are nominal values from study.
Kardar et al. (2014) [35]	70 Gy in 35#	No rescanning vs. isolayered rescanning	$\Delta V_{100\%}$: −5.6% vs MU = 0.04 −4.26% MU = 0.01 −2.08% MU = 0.005 −0.5%	A higher order of isolayered rescanning kept $\Delta V_{100\%} < -3\%$ for all patients	Mean	Lower MU values signify a higher magnitude of rescanning. Values were digitised from graph and mean was calculated
Inoue et al. (2016) [34]	60 Gy in 25#	Energy layer rescanning vs. no rescanning	HI ($D_{2\%}$-$D_{98\%}$): 2.8 Gy ± 0.7 vs. 3.6 Gy ± 1.1	N/A	Mean	N/A

Table 3 (*continued*)

Authors /Year	Dose (RBE)	Investigation (x vs. y)	Findings[a] (x vs. y)	Residual interplay	Result presented/test	Remarks
Grassberger et al. (2015) [33]	48 Gy in 4#	Breath sampled vs. layered vs. volumetric rescanning with big and small spots	Breath sampled rescanning is significantly better than the same number of continuous scanning for small spots for all 5 patients ($p \leq 0.05$) but not significant for big spots. For 4/5 patients, 2x layered or volumetric rescanning was enough to achieve > 98% of planned EUD dose with big spots, while 2x-6x rescanning is required for small spots.	Rescanning was unable to reach >98% of EUD dose for one patient with either big or small spots.	t-test	N/A
		Gating	Gating resulted in > 98% EUD for all patients and spot size except the patient with largest motion amplitude and small spot size.	Interplay resulted in EUD of 93.1% with gating and small spot size for one patient	N/A	Gating is performed with duty cycle of 30% over the T40-50-60 phases around end-exhale(T50).
Engwall et al. (2018) [32]	60 Gy in 30#	No rescanning vs. various forms of rescanning	HI ($D_{95\%}/D_{5\%}$): 0.923 ± 0.017 vs BS: 0.964 ± 0.006; CBS: 0.962 ± 0.007; Volumetric: 0.958 ± 0.006; Layered: 0.942 ± 0.006	For one patient, interplay effects cannot be adequately addressed regardless of rescanning strategies	Mean	N/A
Li et al. (2015) [38]	60 Gy in 30#	Optimised delivery sequence vs. regular sequence and fractionation	Single fraction ΔD_{max}: 10.6% vs. 13.9% Fractionation ΔD_{max}: 3.17% vs. 4.72%	ΔD_{max} is kept < 3% in the CTV for all patients	Mean	D_{max} in this context refers to absolute maximum dose error
Li et al. (2014) [37]	70 Gy in 35#	Regular Fractionation vs. single fraction	$\Delta V_{100\%}$: 0.2% (−0.3–1.1) vs. −1.7% (−6.2–0.4)	Residual interplay is not a concern after fractionation	Mean	Values were digitised from graph for regular motion.
	50 Gy in 10#	Hypofractionation vs. single fraction	$\Delta V_{100\%}$: 0.1% (−0.6–0.5) vs. −0.4% (−2.1–1.1)			
Kanehira et al. (2017) [15]	70 Gy in 10#	Gating vs. free breathing	$D_{99\%}$: 98.4% (97.7–99.1) vs. 90.4% (86.5–95.7) HI ($D_{5\%}$-$D_{95\%}$): 3.5% (1.5–4.0) vs. 10.8% (5.2–14.5)	All patients had CTV $D_{99\%}$ > 95% and $D_{5\%}$-$D_{95\%}$ < 5%	Median	Values were digitised from graph. Data from 2 mm gating window was used from study.

Abbreviations: RBE = relative biological effectiveness; $D_{x\%}$ = Dose (in Gy or in % of prescription dose) received by x% of structure; HI = homogeneity index; N/A = not available; BSPTV = beam specific planning target volume; iGTV = internal gross target volume; HU = Hounsfield; n.s = not significant; $V_{x\%}$ = Volume receiving x% of prescription dose; CTV = clinical target volume; EUD = equivalent uniform dose; MU = monitor unit; BS = breath-sampled; CBS = continuous breath-sampled; D_{max} = Absolute maximum dose error.

[a] Absolute findings are presented unless denoted with Δ ((Parameter with interplay considered (dynamic) – parameter without interplay (composite)).

Table 4
Comparison of studies that reported on interplay management.

Authors/Year	Participants				IMPT Parameters		
	n	Indications	Median Motion Amplitude (mm)	Treatment Volume (cm^3)	Robust Optimisation	Spot Size (mm)	Rescanning
Liu et al. (2016) [29]	11	Stage II (1), III (9), IV (1) NSCLC	5.0 (2.0–15)	CTV_{median} = 484.9 (103.8–1248.0)	4D and 3D robust optimisation	6–14	N/A
Jakobi et al. (2018) [28]	40*	Patients receiving SBRT to the lung	<5 mm: 1.6 (0.6–4.5) >5 mm: 10.2 (5.7–23.3)	GTV_{median} = 9.0 (0.3–37.0)	N/A	3–8	N/A
Engwall et al. (2018) [27]	3	N/A	6.0 (3.7–12.2)	CTV_{mean} = 44.3 (6.5–73.7)	4D robust optimisation with and without time structures	N/A	Layer
Grassberger et al. (2013) [31]	10	N/A	10.3 (2.9–30.6)	GTV_{median} = 23.1 (2.6–82.3)	N/A	Small spot: 2–3 Big spot: 11–15	N/A
Liu et al. (2018) [30]	10	Stage II (1), III (8), IV (1) NSCLC	5.0 (2.0–15)	ITV_{median} = 553.2 (124.3–1314.0)	3D voxel-wise worst-case robust optimisation	Small spot: 2–6 Big spot: 5–15	Isolayered
Dowdell et al. (2013) [10]	5	N/A	15.1 (2.9–30.6)	CTV_{50} = 83.3 (50.4–167.1)	N/A	Small spot: 2–4 Big spot: 9–16	N/A
Kraus et al. (2011) [36]	2	N/A	10.3 (9.5–11)	CTV = 108.5 (82.2–134.8)	N/A	N/A	Volumetric
Kardar et al. (2014) [35]	7	Stage III NSCLC	4.6 (1.4–16.6)	GTV = 236.8 (20.6–545.1)	3D worst-case robust optimisation	5.4–14.6	Isolayered
Inoue et al. (2016) [34]	10	Stage III NSCLC	3.5 (1.4–6.6)	$iCTV_{median}$ = 152.4 (21.8–428.2)	Minimax robust optimisation	3	Layer
Grassberger et al. (2015) [33]	5	N/A	10.7 (2.9–30.6)	GTV_{median} = 26.0 (21.1–82.3)	N/A	Small spot: 2–4 Big spot: 8–17	Varied
Engwall et al. (2018) [32]	7	N/A	6 (3.7–12.2)	CTV_{mean} = 52.5 (6.5–176.8)	4D robust optimisation	2.5–6.8	Varied
Li et al. (2015) [38]	10	Stage II, III NSCLC	8.5 (5–17)	CTV_{median} = 222.85 (158.9–539.6)	N/A	5.6–14.9	N/A
Li et al. (2014) [37]	11	Stage III NSCLC	4.3 (1.4–16.6)	CTV_{median} = 370.4 (26.2–1119.8)	N/A	5.4–14.6	Isolayered
Kanehira et al. (2017) [15]	7	Stage I NSCLC	SI: 11 (5.8–24.7)	GTV_{median} = 3.5 (2.0–14.4)	N/A	N/A	N/A

Abbreviations: n = number of study participants; NSCLC = non-small cell lung cancer; CTV = clinical target volume; N/A = not available; SBRT = stereotactic body radiation therapy; GTV = gross tumour volume; ITV = internal target volume; CTV_{50} = clinical target volume at phase 50 of 4D scan; iCTV = internal clinical target volume; SI = superior inferior.

* Only 30 participants were used for comparison in study.

increases treatment time [40]. This increase in treatment time can potentially be offset by a reduced need to perform rescanning.

Limitations

The included studies used deformable image registration to simulate the interplay effect which may introduce a new set of error. It was also assumed that breathing motion is constant throughout treatment.

The type of dose calculation algorithm has a considerable impact in proton therapy planning, especially in a heterogenous site such as the lung [41]. Not all the included studies used Monte Carlo for dose calculation. Additionally, routine CT scanners used in these studies may not have the required resolution to adequately resolve the fine lung structure [42]. Hence, range uncertainties in these studies may potentially be underestimated when generic margins (3.5% + 1 mm) are used for dose calculation.

None of the studies concurrently simulate both setup uncertainties and interplay effects. However, it is likely that random variations in setup and breathing can blur out interplay effects [12]. Errors arising from anatomical changes between fractions were also not considered. These errors can be addressed using volumetric imaging with adaptive planning and is beyond the scope of this review. As the included studies are dosimetric studies, randomised control trials are required before any clinical benefit of IMPT can be confirmed.

Conclusion

Early evidence suggests that IMPT is dosimetrically advantageous compared to PSPT in thoracic malignancies. IMPT can produce equally robust plans to PSPT, with superior sparing of critical structures. The effects of interplay in most patients can be accounted for through a combination of techniques such as robust target concepts, fractionation, rescanning, gating, and the use of big spots. However, these measures cannot reliably account for interplay in some patients, especially those with large motion and when small spots are used. In such cases, motion mitigation strategies and the individual analysis of interplay are warranted.

Declaration of Competing Interest

All authors declare no conflict of interest.

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