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Technical Note

A planning study of proton therapy dose escalation for non-small cell lung cancer

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ABSTRACT

In non-small-cell lung cancer (NSCLC), improving local control through radiotherapy dose escalation might improve survival. However, a photon-based RCT showed increased organ at risk dose exposure and worse overall survival in the dose escalation arm. In this study, intensity-modulated proton therapy plans with dose escalation to the primary tumour were created for 20 NSCLC patients. The mediastinal envelope was delineated to spare structures around the heart. It was possible to increase primary tumour dose up to 74.0 Gy without a significant increase in organ at risk doses and predicted toxicity.

1. Introduction

Radiotherapy dose escalation for non-small-cell lung cancer (NSCLC) increases tumour cell kill, theoretically improving tumour control and survival [1–3]. However, recent clinical trials such as RTOG-0617 and the PET-Boost trial unexpectedly showed worse outcomes after photon-based dose escalation [4–6]. Post-hoc analyses on RTOG-0617 data and findings from the PET-boost trial suggest a potential association between worse outcome and radiation dose delivered to mediastinal organs at risk (OARs). This includes the heart, lungs, oesophagus, and circulating immune cells [6–11].

Compared to photon radiotherapy, proton radiotherapy offers distinct advantages in terms of OAR sparing, because more conformal treatment plans can be created. This minimizes dose to OARs [12]. Available literature suggests that dose-escalated intensity-modulated proton therapy (IMPT) still spares more healthy tissue compared to conventional-dose photon radiotherapy [13,14]. Additionally, the post-hoc analysis results described earlier imply that stricter dose limitations to the mediastinal area should be applied [6,8–10]. IMPT may facilitate this.

In this study, we investigated the feasibility of safe IMPT-based dose escalation for stage III NSCLC. The main goal was to achieve dose escalation to the primary tumour without significantly increasing dose to heart, lungs and oesophagus compared to conventional-dose IMPT, and while maintaining lower healthy tissue doses compared to conventional-dose volumetric modulated arc therapy (VMAT). The intention is to apply this planning strategy in a phase 2 randomized controlled trial (RCT) evaluating its safety.

2. Materials and methods

2.1. Participants

Tumor and treatment characteristics are available in supplementary table 1. In total, 20 stage III NSLC patients, treated with 60.0 Gy_{RBE} IMPT at our department between December 2019 and December 2021, were selected. Exclusion criteria were proximity of primary tumour to the brachial plexus, or $>$ 95 % overlap of primary tumour and a 15 mm margin around the mediastinal envelope. According to national protocol, patients were selected for IMPT by comparing VMAT and IMPT plans and by evaluating tumour motion. Criteria were reduction of normal tissue complication probabilities (NTCP) for grade $\geq$ 2 radiation pneumonitis (RP), grade $\geq$ 2 acute oesophageal toxicity (AET), and/or 2-year mortality (2yM) [15]. Additionally, tumour motion should be $<$ 15 mm, or 15–18 mm after favourable evaluation of the 4D-CT by a radiation oncologist and medical physicist. The Code of Ethics of the World Medical Association was adhered to. Written informed consent was obtained for all patients. Data used for this study were collected as

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part of our proPED-lung follow-up protocol (NCT02421718) [16]. The proPED-lung was reviewed by the hospital's institutional review board and declared exempt from ethics committee approval.

2.2. Target and OAR delineation

Delineations and treatment planning were performed using RayStation (RaySearch Laboratories, Stockholm, Sweden). The Gross Tumour Volume of the primary tumour (GTVp) and lymph nodes (GTVn) were delineated on the maximum expiration phase of the 4D-CT. The GTV was expanded for movement using the other breathing phases to create the internal GTV (iGTV). The iGTV was copied to the average CT, expanded with a 5-mm clinical target volume (CTV) margin, and manually adjusted based on anatomical boundaries. For VMAT plans it was further expanded with a 6-mm planning target volume (PTV) margin. OAR were delineated on the averaged planning CT scan.

To prevent potential additional toxicity from dose escalation, a mediastinal envelope OAR was delineated. It was created using a multi-atlas developed using Mirada Research (Mirada Medical, Denver, United States) based on the definition used in the PET-BOOST trial [17]. The structure contains the heart, oesophagus, proximal large blood vessels and proximal bronchi (Fig. 1). The structure was then manually corrected, in particular around the primary tumour. It was expanded with a 5-mm planning risk volume (PRV) margin.

Because of the relation between dose to base of heart and overall survival (OS) [9,18], a base of heart OAR was created. This was done by combining right atrium, superior vena cava and aortic root structures delineated using a deep learning atlas. This volume does not include the proximal coronary arteries, because they were not visible on the non-contrast CTs.

2.3. Dose optimization and constraints

See supplementary tables 2–3 for optimization objectives, nominal dose prescriptions and OAR constraints of 60.0 Gy VMAT (VMAT-60), 60.0 Gy_{RBE} IMPT (IMPT-60), and dose-escalated IMPT plans (IMPT-74). All plans were planned to be delivered in 25 fractions. IMPT plans were generated with a Monte Carlo dose engine for a constant RBE of 1.1 and five times layered rescanning. IMPT-60 and VMAT-60 plans were created prescribing a homogeneous dose of 60.0 Gy to the CTV and PTV, respectively. IMPT-74 plans incorporated three concomitant dose levels. 74.0 Gy_{RBE} was prescribed homogeneously to the iGTVpEsc, defined as the part of the iGTVp $\geq$ 15 mm outside of the mediastinum. 64.0 Gy_{RBE} was prescribed to the iGTVpPRV, defined as the iGTVp $<$ 15 mm from the mediastinum. 60.0 Gy_{RBE} was prescribed to the rest of the CTV. A maximum dose of 70.0 Gy_{RBE} was prescribed to the mediastinal PRV.

2.4. Robust treatment planning and evaluation

Robust planning and evaluation were used for IMPT-60 and IMPT-74 plans [19]. See supplementary tables 4–5 for robust dose prescriptions. A 6-mm isotropic position uncertainty and 3 % density uncertainty were used. Plans were optimized using 90 scenarios, and evaluated using the voxel-wise minimum/maximum of 28 scenarios. IMPT-74 plans were simultaneously optimized on two versions of the planning CT to increase robustness. One version used a 1.050 g/cm^3 density override to the CTV, the other did not. IMPT-60 plans were optimized on a CT with density override, or on two CTs if robust evaluation objectives could not be met by optimizing on one CT. Plan evaluation was performed without density overrides. It was performed using a 3D approach considering setup errors and range uncertainties. For IMPT-74, 4D robustness was evaluated by warping doses from all breathing phases of the 4D-CT back to the maximum expiration phase [20]. Criterium was D98 $\geq$ 98 %. For VMAT-60 plans, PTV-based planning was used rather than robust planning.

2.5. Statistics

Dose to the tumour and OARs, in addition to predicted risks of AET, RP and 2yM were compared to those obtained with the IMPT-60 and VMAT-60 plans using Friedman ANOVA, with Bonferroni correction for multiple comparisons in post-hoc analysis. See supplementary table 6 for the predictors used to calculate complication probabilities [15].

3. Results

3.1. Target coverage

Median (IQR) mean iGTVp dose was 72.0 (71.0–74.0) Gy_{RBE} for the IMPT-74 plans, with 75 % (IQR: 58–87 %) of the iGTVp volume receiving a dose of $\geq$ 70.3 Gy_{RBE}, *i.e.*, 95 % of the prescribed dose level for the iGTVpEsc. All patients met 4D robustness criteria, except one patient for GTVpPRV and two patients for CTV (supplementary table 7).

3.2. OAR doses

A maximum mediastinal dose of 70.0 Gy was achieved in all patients. It was 68.4 (SD: 1.7) Gy for IMPT-74, compared to 63.8 (SD: 0.5) Gy for IMPT-60; P<0.001, and 63.8 (SD: 0.7) Gy for VMAT-60; P<0.001.

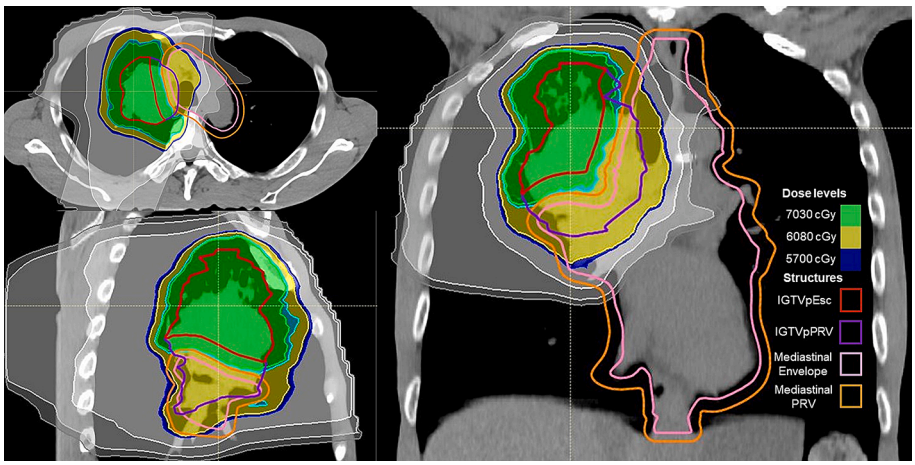

Fig. 1. Mediastinal envelope delineation and dose levels. A: Transversal view. B: Sagittal view. C: Coronal view. Mediastinal envelope: heart, oesophagus, proximal large blood vessels and proximal bronchi. Mediastinal PRV: mediastinal envelope + 5 mm. iGTVpEsc internal gross tumour volume prescribed 74.0 Gy_{RBE}. iGTVpPRV internal gross tumour volume prescribed 64.0 Gy_{RBE}.

Supplementary Fig. 1 shows DVH of a representative patient.

Other OAR doses were significantly lower in IMPT-74 compared to VMAT-60 plans and were comparable to IMPT-60 plans (Fig. 2). Mean heart dose, heart V5 and heart V30 of the IMPT-74 plans were significantly lower compared to those obtained in the VMAT-60 plans and did not significantly differ from those of the IMPT-60 plans (Fig. 2). The same was true for oesophagus average dose, V20 and V50, and lung minus gross tumour volume (lung-GTV), mean dose, V5, V20, and V40 (Fig. 2).

Median (IQR) mean dose to the base of heart for IMPT-74 plans was 5.7 (IQR: 0.5–11.4) Gy, which was comparable to IMPT-60 plans: 6.3 (0.7–12.4) Gy; P=0.25, and lower compared to VMAT-60 plans: 14.7 (IQR: 7.6–20.4) Gy; P<0.001. Median (IQR) maximum dose to the base of heart was 64.4 (IQR: 23.5–67.1) Gy for IMPT-74, which was similar to IMPT-60 (62.2 (IQR: 31.3–62.7) Gy) and VMAT-60 (61.2 (IQR: 31.8–62.5) Gy); overall P=0.45. Doses to atria, ventricles, pulmonary trunk, proximal aorta and superior vena cava for IMPT-74 were similar to those of IMPT-60 and significantly lower than those of VMAT-60. See supplementary table 8.

3.3. NTCP

Predicted NTCP of grade ≥ 2 AET, RP and 2yM were lower in the IMPT-74 plans compared to VMAT-60 plans: 22 % vs 34 %, 11 % vs 17 %, and 44 % vs 52 %, respectively (P<0.001 for all comparisons). Predicted NTCP of RP and 2yM of IMPT-74 plans were comparable to IMPT-60: 11 % vs 11 % (P>0.99), 44 % vs 45 % (P=0.17), respectively. Predicted NTCP of AET was lower in IMPT-74 compared to IMPT-60: 22 % vs 26 %, P=0.03.

4. Discussion

The results of this IMPT-based in-silico planning study for stage III NSCLC patients suggest that dose escalation to the primary tumour using a concomitant heterogeneous boost is feasible. Dose to OARs was not increased for IMPT-74 compared to IMPT-60 and was decreased compared to VMAT-60. With IMPT-74 plans, patients would still qualify for IMPT based on expected reduction of NTCP compared to VMAT [15].

Compared to photon-based radiotherapy techniques, IMPT allows for a lower OAR dose. This is expected to result in lower toxicity and lymphocytopenia rates, as well as improved clinical condition after chemoradiotherapy [9–11,15,18,21]. In this context, the results of the ongoing randomized phase 3 RTOG-1308 trial are eagerly awaited (ClinicalTrials.gov ID: NCT01993810). This trial compares OS, cardiac toxicity and lymphopenia between proton and photon chemoradiotherapy in 330 patients with locally advanced NSCLC. Compared to the dose escalation group of the photon-based RTOG-0617 trial that was associated with worse survival, lung V5 heart V30 and oesophagus V20 were lower in our IMPT-74 plans. They were 29 % versus 58 %, 4 % versus 13 %, and 22 % versus 48 %, for the IMPT-74 versus RTOG-0617 plans, respectively [5].

IMPT is more sensitive to tumour motion compared to VMAT. Based on an earlier IMPT dose escalation study, limiting motion amplitudes, and applying spot rescanning and robust treatment planning, improve target coverage [14]. All have been applied in this study and adequate 4D robustness was achieved in most cases.

Several studies observed a relation between oesophagus, heart and mediastinum dose, and mortality [6–11]. Therefore, a dose constraint of 70.0 Gy_{RBE} in 25 fractions, or 81.2 Gy_{EQD2} was applied to the mediastinal PRV for the current study (supplementary table 3). By contrast, the PET-Boost trial reported median D0.1 % of approximately 90.4 Gy_{EQD2} to the mediastinal envelope [17]. Notably, stricter mediastinal constraints resulted in reduced mortality in the PET-Boost trial [6]. Lung dose has also been related to survival [22,23]. In the present study, all lung parameters were similar for IMPT-74 to IMPT-60 and lower compared to VMAT-60.

A different approach to radiotherapy dose escalation has been used in the ongoing phase III randomized photon-based NARLAL2 trial.

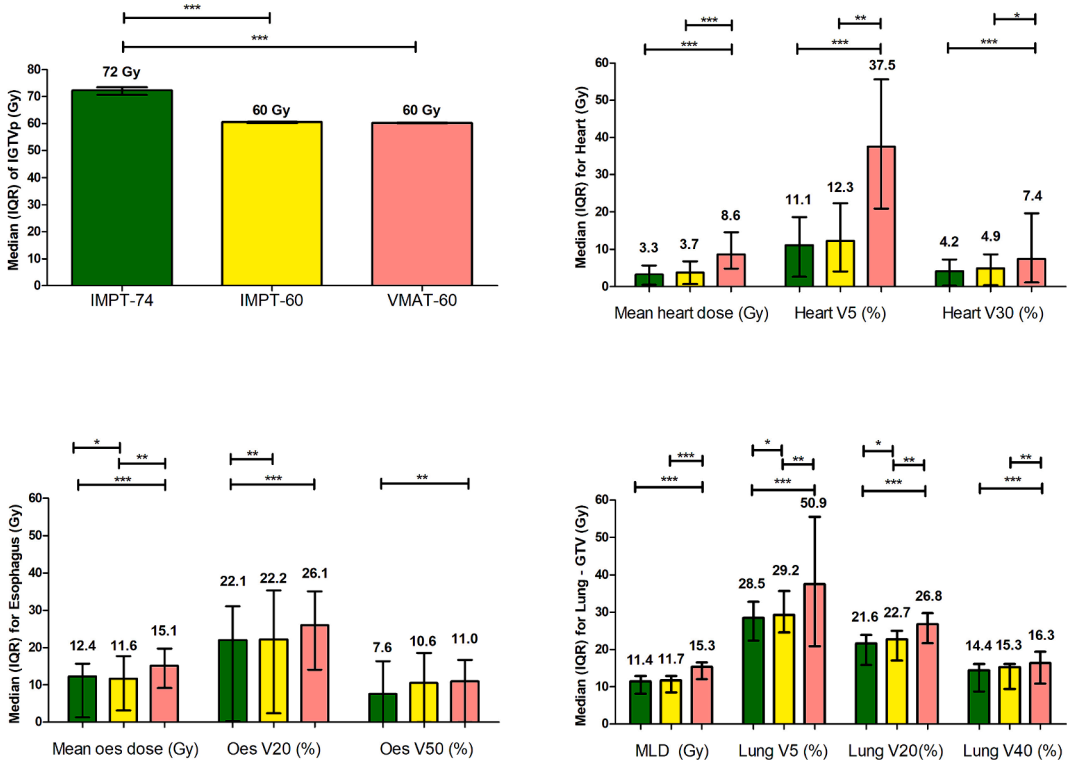

Fig. 2. Dose-volume parameters for IGTVp and organs at risk. Green: dose escalation (up to 74.0 Gy) IMPT; Yellow: 60.0 Gy IMPT; Red: 60.0 Gy VMAT. MLD mean lung dose; Oes oesophagus; V5/V20/V30 volume % receiving ≥ 5.0/20.0/30.0 Gy. *P<0.05; **P<0.01; *** P<0.001. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

There, doses up to 111.7 Gy_{EQD2} and 77.6 Gy_{EQD2}, were prescribed to FDG-PET positive regions of primary tumour and lymph nodes, respectively. The degree of dose escalation was determined by OAR constraints. With this approach, similar mean doses to critical OARs were maintained, while peak doses to OARs were increased [24]. By contrast, in our study, dose escalation was not prescribed to the lymph nodes. Additionally, the dose escalated volumes of the iGTVp were defined based on proximity to critical mediastinal structures rather than FDG-PET uptake.

This study has several limitations. One, we could not stratify for tumour location because of the small patient numbers. Nevertheless, a wide range of tumour locations was included. For over 50 % of treatment plans in our study it was possible to have at least 75 % of the iGTVp receive 95 % of the 74Gy_{RBE} prescribed to the iGTVpEsc. Second, we did not evaluate interplay effect or inter-fraction robustness in this study. Still, in an earlier study we evaluated both on standard-dose IMPT plans in our centre and showed adequate target coverage for tumour motions up to 17 mm [25]. Therefore, we expect no significant issues for dose dose-escalated IMPT plans.

In conclusion, it is feasible to create IMPT-based concomitant dose escalation plans for NSCLC without compromising OAR dose compared to standard-dose IMPT. In fact, doses to OARs were still significantly lower compared to standard-dose VMAT. This planning study provides the framework for a phase 2 clinical trial evaluating IMPT-based dose escalation for NSCLC patients in our centre.

CRediT authorship contribution statement

Arno C. Hessels: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **Sabine Visser:** Investigation, Methodology, Writing – review & editing. **Stefan Both:** Writing – review & editing. **Erik W. Korevaar:** Methodology, Writing – review & editing, Supervision. **Johannes A. Langendijk:** Supervision, Resources, Writing – review & editing. **Robin Wijsman:** Conceptualization, Data curation, Project administration, Resources, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: No specific funding related to this project was obtained. The Department of Radiation Oncology of the University Medical Center Groningen has research contracts with IBA, RaySearch, Siemens, Elekta, Leonia, and Mirada and has received grants from Dutch Cancer Society and EU. Prof. dr. J.A. Langendijk is a member of the Global Scientific Advisory Board of IBA and a member of the RayCare International Advisory Board of RaySearch. He has given presentations for local scientific meetings for IBA. Payments in all cases have been made to UMCG Research BV. Prof. dr. J.A. Langendijk is the chair of the Netherlands Society for Radiation Oncology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100616.

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