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Original article

Photons, protons or carbon ions for stage I non-small cell lung cancer – Results of the multicentric ROCOCO *in silico* study

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ABSTRACT

Purpose: To compare dose to organs at risk (OARs) and dose-escalation possibility for 24 stage I non-small cell lung cancer (NSCLC) patients in a ROCOCO (Radiation Oncology Collaborative Comparison) trial.
Methods: For each patient, 3 photon plans [Intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and CyberKnife], a double scattered proton (DSP) and an intensity-modulated carbon-ion (IMIT) therapy plan were created. Dose prescription was 60 Gy (equivalent) in 8 fractions.
Results: The mean dose and dose to 2% of the clinical target volume (CTV) were lower for protons and ions compared with IMRT ($p < 0.01$). Doses to the lungs, heart, and mediastinal structures were lowest with IMIT ($p < 0.01$), doses to the spinal cord were lowest with DSP ($p < 0.01$). VMAT and CyberKnife allowed for reduced doses to most OARs compared with IMRT. Dose escalation was possible for 8 patients. Generally, the mediastinum was the primary dose-limiting organ.
Conclusion: On average, the doses to the OARs were lowest using particles, with more homogenous CTV doses. Given the ability of VMAT and CyberKnife to limit doses to OARs compared with IMRT, the additional benefit of particles may only be clinically relevant in selected patients and thus should be carefully weighed for every individual patient.
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Introduction

The introduction of stereotactic body radiation therapy (SBRT) has led to an increase in radiotherapy use in early stage non-small cell lung cancer (NSCLC) patients and fewer untreated patients, which has driven up population-based survival for lung cancer [1]. SBRT is a form of high-precision radiotherapy, using large (ablative) radiation doses per fraction, generally in one to eight fractions over one to three weeks. A Biologically Effective Dose (BED) of more than 100 Gy has allowed for high local tumor control rates (>90%), comparable to those obtained with surgery, supporting its consideration in operable patients [2–4]. A pooled meta-analysis of the STARS and ROSEL trials has indicated non-inferiority of SBRT compared to surgery with respect to survival and disease progression, albeit in a small patient population with limited follow up. Furthermore, treatment related toxicity was generally low and found to be favorable compared to surgery, even though damage to central structures and the chest wall have been reported [4,5]. The photon-based SBRT techniques have evolved over the years from 3-dimensional (3D) conformal photon radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT).

In recent years, there has been a massive expansion in particle therapy centers (mainly proton therapy) in clinical operation. Charged particles are characterized by the presence of the so-called 'Bragg peak', *i.e.*, dose deposition at an energy-dependent tissue depth, and a sharp dose falloff at the distal edge with no further dose deposition. Some centers use particles for (stereotactic) treatment of lung cancer and report outcomes seemingly comparable to photon radiotherapy despite the known difficulties with the delivery of particle beams to a moving tumor in the lung (e.g., range uncertainties, interplay effect) [6,7]. Several

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dosimetric studies on particles have shown a significant reduction in dose to surrounding organs at risk (OAR) and thus short- and long-term toxicities [8–12].

While there are multiple options for delivery of photon- or particle-based radiation therapy in early stage lung cancer patients, it is currently not known which technique is best in terms of target coverage and low dose to OARs. A randomized controlled trial comparing these techniques would require a very large patient cohort to show significant differences in local control and/or toxicity and likely be fraught with accrual difficulties. Hence, the multicenter international Radiation Oncology Collaborative Comparison (ROCOCO) was initiated in 2007 conducting several comparative *in silico* trials in multiple primary tumor sites, including lung cancer [8,13].

In this study on twenty-five patients with stage I NSCLC, we compared the doses to the OARs and the dose escalation probability for one SBRT fractionation schedule using five contemporary radiotherapy techniques with either photons (IMRT, VMAT and CyberKnife), double scattered protons (DSP) or intensity-modulated carbon ions (IMIT).

Patients and methods

Patients

Twenty-five consecutive patients with stage I NSCLC who underwent SBRT at MAASTRO clinic (Department of Radiotherapy, Maastricht University Medical Center+, The Netherlands) between February 2011 and June 2013 were included in this *in silico* planning study. The maximum tumor diameter was 3 cm and all tumors were at least 2 cm separated from the mediastinal structures and bronchial tree [14]. Most tumors were located peripherally, with 15 tumors (or their planning target volume; PTV) overlapping chest wall and ribs. This retrospective *in silico* planning study was approved by the Institutional Review Board of MAASTRO clinic.

Target and OAR definitions

Delineation of the target volumes and OARs was performed at MAASTRO clinic according to institutional guidelines. The OARs, gross tumor volume (GTV), clinical target volume (CTV) and PTV were delineated in the mid-ventilation phase of a four-dimensional-18F fluorodeoxyglucose positron emission tomography-computed tomography (4D-FDG-PET-CT) scan. For this purely dosimetric comparison between the modalities, a gated treatment was assumed without the use of an internal target volume (ITV) accounting for breathing motion. The following dose limiting OARs were delineated: the mediastinum (consisting of heart, great vessels, trachea, main bronchi and esophagus), lungs, esophagus, spinal cord and brachial plexus. The 'mediastinum' was expanded 5 mm to create a planning risk volume (PRV mediastinal envelope) to account for setup inaccuracy or movement. The ribs were contoured within 5 cm of the PTV (excluding the intercostal space; [15]). The chest wall constituted of a 1.5-cm expansion from the lungs. For comparison of the total lung dose, the GTV was subtracted from the total lung volume.

Treatment planning

For each patient, three photon plans (IMRT, VMAT and Cyberknife), a DSP plan and an IMIT plan were calculated at Catherina Hospital Eindhoven (CHE; the Netherlands), MAASTRO clinic, the Centre Hospitalier Universitaire de Liège (CHU; Belgium), the Hospital of the University of Pennsylvania (UPENN; USA), and the University Hospital of Marburg (UHM; Germany), respectively.

Irrespective of the clinically used dose, the prescribed dose was 60 Gy in 8 fractions, achieving a Biologically Effective Dose (BED) of 105 Gy, roughly equivalent to 87.5 Gy in 2 Gy fractions (EQD_2). Each center used its in house, clinically commissioned treatment planning system (TPS) assuring state-of-the-art dose calculations. Planning objectives were in accordance with several multi-institutional trials (e.g., RTOG 0618 and RTOG 0236), where 95% of the PTV should receive at least 100% of the prescribed dose, and the maximum dose (D_{max}) was not to exceed 140%. The dose was prescribed to the given PTV by all centers except for UPENN, which employed individualized uncertainty margins for DSP. According to the study protocol, the dose to the CTV was eventually evaluated. In order to guarantee uniform CTV dose level enabling comparison of the dose to the surrounding OARs, all plans were rescaled such that 99% of the CTV received 60 Gy (RBE equivalent).

For the OARs, consensus constraints were defined *a priori* among investigators from all centers prior to planning and largely mirrored 8-fraction radiotherapy institutional constraints: spinal cord, $\leq$32 Gy to 0.03 cm^3; esophagus and PRV mediastinal envelope, $\leq$41 Gy to 0.03 cm^3; heart, $\leq$46 Gy to 0.03 cm^3; volume of 'healthy' lungs (total lungs minus GTV) V_{20Gy} <15%; brachial plexus, $\leq$38 Gy to 0.03 cm^3 (delineated only for case where the caudal border of the brachial plexus was within 5 cm of the PTV); and cardiac device (if present) D_{max} = 2 Gy. Planning objectives for the thoracic wall included: ribs: $V_{32.5Gy}$ <1 cm^3 and D_{max} = 35 Gy; chest wall: $V_{32.5Gy}$ <30 cm^3 and D_{max} = 40 Gy. The following priorities were set for the objectives (numbered in order of decreasing importance): 1 = spinal cord, 2 = brachial plexus, 3 = lungs, 4 = PRV mediastinal envelope, 5 = ribs, 6 = chest wall, 7 = esophagus, and 8 = heart.

Photons

The step-and-shoot IMRT plans were calculated using Pinnacle v. 9.6 (Philips Radiation Oncology Systems, Fitchburg, WI). Five to seven (mainly equispaced) 6MV photon beams were employed, avoiding beam entrance through the contralateral lung. The VMAT plans were created using Eclipse v. 11.0 (Varian Medical Systems, Palo Alto, CA). The plans generally consisted of two 180 degree arcs with an energy of 10MV. CyberKnife plans were created using Multiplan v. 5.2.1 (Accuray Inc., Sunnyvale, CA). The non-coplanar beam arrangement was chosen from a large set of predefined nodes (full-path). A maximum of three collimators were used and the collimator diameter was case dependent (usually ranging from 60 to 80% of the largest PTV diameter).

Protons

In the DSP plans, the relative biological effectiveness (RBE) doses were calculated using an RBE of 1.1 for protons using Eclipse v. 11.0 (Varian Medical Systems). The field size was limited to 12 cm. Beam arrangements were chosen based on the path of least variation. PTV margins were determined by range * 3.5% plus 3 mm. Portals were designed to avoid OARs distal to the target. Plans used 2–3 fields as a tradeoff between treatment time and target conformity.

Carbon ions

The IMIT plans were calculated at the UHM using Syngo PT Planning (Siemens Health Care Systems, Erlangen, Germany), typically using 3 or 4 fields with a patient-specific beam arrangement assuming the use of a gantry. The RBE was calculated using the first version of the Local Effect Model (LEM1). The following spot scanning parameters were employed: a nominal spot size of 8 mm, a scanning grid and energy step size of 3 mm. The base data (e.g., energy range) used for planning was representative of facilities such as the ion-beam therapy centers in Heidelberg and Marburg.

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