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Phase II randomised trial

Multi-criteria optimization achieves superior normal tissue sparing in a planning study of intensity-modulated radiation therapy for RTOG 1308-eligible non-small cell lung cancer patients

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ABSTRACT

Purpose: In this planning study, we studied the benefit of intensity-modulated radiation therapy (IMRT) with multi-criteria optimization (MCO) in locally advanced non-small cell lung carcinoma (NSCLC).
Methods: We selected 10 consecutive patients with gross tumor within 1 cm of the esophagus eligible for RTOG 1308, randomized phase II trial of 70 Gy protons vs photons. Planning was performed per protocol. In addition, a novel approach for esophagus sparing was applied by making the contralateral esophagus (CE) an avoidance structure. MCO and non-MCO plans underwent double-blinded review. Plan differences in dose–volume histogram parameters were analyzed.
Results: Median plan differences were mean lung dose = 0.8 Gy ($p = 0.01$), lung V20 = 1.1% ($p = 0.06$), heart V30 = 1.0% ($p = 0.03$), heart V45 = 0.6% ($p = 0.03$), esophagus V60 = 1.2% ($p = 0.04$), and CE V45 = 3.2% ($p = 0.01$), all favoring MCO over non-MCO. PTV coverage with 95% dose was $\geqslant$98.0% for both plans. There were 5 minor protocol deviations with non-MCO plans and 2 with MCO. Median improvement of active planning time with MCO was 88 min ($p < 0.01$). Physicians preferred 8 MCO and 2 non-MCO plans ($p = 0.04$).
Conclusions: MCO plans yielded significant improvements in organ-at-risk sparing without compromising target coverage, consumed less dosimetrist time, and were preferred by physicians. We suggest incorporating MCO into prospective clinical trials.
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Intensity-modulated radiation therapy (IMRT) has become an increasingly popular radiation treatment technique for multiple disease sites over the past decade, due to its ability to increase dose conformality and provide greater sparing of normal tissues than traditional 3D conformal forward planning, thereby reducing toxicities to organs-at-risk (OARs) [1–3]. However, due to the large number of degrees of freedom in IMRT planning there can be a multitude of possible approaches to meeting the specified goals. The optimization process is based on dose prescriptions for targets and avoidance organs; weight factors are thus assigned to each structure [4]. Often, compromises have to be made in order to meet certain goals, and as a result the ensuing plan may not be clinically acceptable. Several iterative optimizations may need to be run until an acceptable plan is found. In addition, when a plan is accepted for treatment, it is unclear whether a better plan would have been found if the planner had utilized different parameter settings or invested more time.

Multi-criteria optimization (MCO) has been proposed by our group as a utility to help get around the above issues, and to reduce the iteration loop required to find the optimal plan [4]. In MCO planning, objectives can be explored interactively. However, one criterion cannot be improved without worsening another [5]. This allows the planner to experience, in real-time, the sensitivity to changes in certain structures and thereby decide on a clinically optimal compromise, without having to re-run iterations for every adjustment [4–7].

IMRT is increasingly used in the treatment of patients with non-small cell lung carcinoma (NSCLC) though its benefits remain to be determined [1–3,8]. Severe esophagitis (grade 3+) is encountered in 15–20% of lung cancer patients undergoing definitive chemoradiation therapy [9–12]. IMRT has been proposed as a solution to

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spare the esophagus without reducing dose to the primary tumor. However, clinical data still show high rates of severe esophagitis associated with IMRT with optimal dose-volume histogram (DVH) parameters unknown [8,13,14]. Different models of radiation esophagitis predictors are currently being built and validated in the IMRT-era [15]. The ongoing RTOG 1308 trial is a randomized phase II trial of protons versus photons (IMRT or 3D conformal radiation therapy) to 70 Gy (RBE) with concurrent chemotherapy for the treatment of patients with locally advanced, inoperable NSCLC (NCT02394548). No esophagus constraints other than a maximum dose of 74 Gy were specified.

We recently reported a promising approach to esophagus sparing, the Contralateral Esophageal Sparing Technique (CEST), where a steep dose gradient beyond the gross tumor is enforced by contouring the contralateral esophageal wall as an avoidance structure, thereby sparing approximately one half the esophageal cross section from receiving full prescription dose [16]. We showed that by using CEST in 20 consecutive patients with locally advanced, inoperable lung cancers and gross tumor within 1 cm of esophagus, no patients experienced grade $\geqslant 3$ esophagitis despite a high median radiation dose of 70.2 Gy [16]. Further, only 4 patients developed grade 2 esophagitis. Preserving partial organ function in this manner has the potential to dramatically reduce the rates of severe acute esophagitis.

To our knowledge, a benefit of MCO has not been reported in NSCLC patients. In this dosimetric planning study, we thus set out to compare IMRT plans derived with or without MCO in a cohort of NSCLC patients using a contemporary treatment approach as defined by RTOG 1308. As a secondary goal, we sought to understand how MCO planning might improve esophagus sparing using CEST.

Materials and methods

Patients

We selected patients with locally advanced, inoperable NSCLC who were eligible for the RTOG 1308 protocol (www.rtog.org). All patients featured gross tumor within 1 cm of the esophagus. We identified 10 consecutive patients who underwent 4DCT simulation and were treated with IMRT to a median dose of 70 Gy and concurrent chemotherapy between January 2013 and January 2014 (Supplementary Table S1).

Target structures and OARs

We followed RTOG 1308 protocol guidelines to outline target volumes and OARs, with additional structures being contralateral esophagus (CE), left ventricle, and spinal cord (see Supplementary Table S2 and Fig. 1). Per RTOG protocol, the clinical target volume (CTV) was generated by expanding the motion corrected GTV volume by 8 mm. The CTV was edited such that it did not extend into nearby organs such as the esophagus, spine, or heart. The planning target volume (PTV) was generated by expanding the CTV by 5 mm. Prescription dose was 70 Gy in 2 Gy fractions. Per protocol guidelines, 100% of the CTV and 95% of the PTV had to be covered by 70 Gy. Coverage of 99% of the CTV by 70 Gy was an acceptable minor deviation as was a minimum PTV dose to a volume of 0.03 cc of at least 52.5 Gy (75% of prescription dose). Regarding esophagus sparing, in addition to limiting 74 Gy to $\leqslant 1$ cc of partial circumference, a maximum dose to the CE of 60 Gy and V55 $\leqslant$ 0.5 cc and V45 $\leqslant$ 2.5 cc were recommended [16]. Other OAR constraints are listed in Supplementary Table S2.

IMRT planning with and without MCO

Planning was performed with RayStation (RaySearch Laboratories, v4.0.3) by two experienced dosimetrists, each randomly assigned to carry out five MCO and five non-MCO plans for different patients (20 plans total). Dosimetrists were blinded to the patients and were blinded to each other (i.e. a dosimetrist could not see the MCO plan while planning a non-MCO plan for the same patient). For all plans, five IMRT beams were used with angles agreed upon by the planners beforehand for each patient, and these beams were kept the same for both MCO and non-MCO. All intermediate or temporary structures, as well as any leading nomenclature were deleted prior to plan review. This ensured an equal starting point for each planner when beginning a new plan for each anonymized patient as well as a completely blind plan review with the physicians.

As previously reported [4–7], the MCO treatment planning approach gives the treatment planner the ability to explore potential benefits and trade-offs regarding sufficient target coverage versus adequate OAR sparing. The RayStation MCO approach makes the distinction between trade-off objectives and constraints. Constraints restrict the range of potential plans, and they cannot be mutually incompatible. Objectives are input to define the Pareto

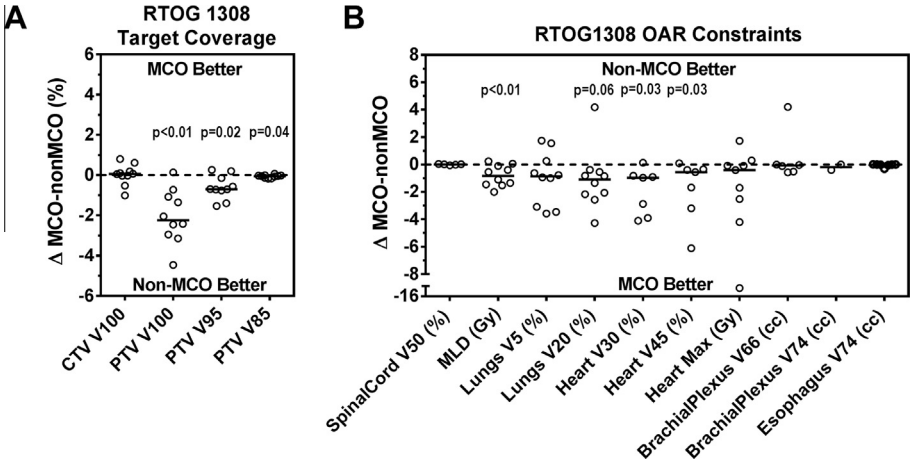

Fig. 1. Pairwise comparisons of multi-criteria optimized (MCO) and non-MCO IMRT plans generated per RTOG 1308 protocol guidelines. (A) Coverage of target structures. For every patient's MCO and non-MCO plan, the percentage of contour volume covered by at least the percentage of prescription dose as indicated on the *X*-axis was recorded. Each data point was derived from subtracting the volume percentage achieved with non-MCO from the one achieved with MCO. Horizontal bars indicate median values. (B) Analogously to panel A, for each organ at risk (OAR) contour the relevant constraint (expressed in percentage (%), dose (Gy), or absolute volume (cc)) that was achieved with the non-MCO plan was subtracted from the corresponding value achieved with the MCO plan. MLD, mean lung dose.