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Isotoxic Radiotherapy Planning for Non-Small Cell Lung Cancer: Is IMRT The Answer?

Lay summary

This project will investigate two different methods for giving external beam radiotherapy to patients with non-small cell lung cancer (NSCLC). In particular, it will be looking at how to give isotoxic radiotherapy. In isotoxic radiotherapy, the dose of radiotherapy given to the tumour is different for each patient, and is determined by assessing how much dose the patient's healthy tissues can tolerate without bringing about any lasting side effects. This research will investigate which type of radiotherapy treatment delivery (3-dimensional conformal radiotherapy (3DCRT) or Intensity Modulated Radiotherapy (IMRT)) will allow more patients to receive the highest dose that can be delivered (76Gy in 20 fractions or equivalent). The study will also look at why IMRT needs to be used instead of 3DCRT for certain patients.

Principal Aim of the Study

To investigate the targeted use of Intensity Modulated Radiotherapy (IMRT) to treat Non-Small Cell Lung Cancer (NSCLC) patients with isotoxic lung radiotherapy. To quantify the effect that IMRT will have on the ability to escalate prescribed dose whilst keeping dose to normal tissues below tolerance levels.

Primary Research Question: Are patients more likely to achieve a dose escalation to 76 Gy in 2 Gy per fraction (or biological equivalent) if IMRT is used instead of 3-dimensional conformal radiotherapy (3DCRT) during isotoxic radiotherapy planning for NSCLC?

Secondary Research Question: Which patient characteristics can be used to predict the need for IMRT in isotoxic radiotherapy planning for NSCLC?

Outcomes and Impact

The research questions above are novel, and they build upon knowledge established in the literature. They will provide a practical basis from which the international radiation oncology community can implement isotoxic radiotherapy practically and safely. Results from this study will contribute to:

- A general methodology for isotoxic dose escalation with or without IMRT,
- A selection method between IMRT and 3D CRT,
- An IMRT class solution for isotoxic lung radiotherapy.
- A dataset of prescription doses and Organ at Risk (OAR) Dose Volume Histogram (DVH) information that will inform treatment decision by enabling the prediction of the maximum dose escalation level for individual patients.

These outcomes will influence the methodology of any future clinical studies or randomised controlled trials. It provides a basis on which radiotherapy departments can carefully select patients for isotoxic IMRT planning for NSCLC and appropriately target resources. Results from this study will directly feed into a clinical pilot study of isotoxic radiotherapy within the investigator's NHS Trust. This project will be a collaborative process between radiographers, physicists and clinicians to test the predictive nature of data supplied from this study. Local control, survival and toxicity will then be correlated with prescribed dose and OAR DVH data.

This study has the potential to change practice. Results would facilitate the successful implementation of isotoxic radiotherapy treatment. This could result in improved survival for a group of patients that have poor outcomes. Not all patients may need IMRT for isotoxic treatment, but the targeted use of IMRT has the potential to both reduce side effects and improve the therapeutic ratio within the patient cohort. This research will also allow planning radiographers to adequately advise clinicians on the benefits of selecting IMRT for isotoxic radiotherapy.

Review of the literature

Background

Local failure in patients with NSCLC is high and 2 year local control rates have been reported at around 20% (van Baardwijk A et al 2010). For locally advanced disease and inoperable disease, patients who are not able to tolerate concurrent chemoradiotherapy are offered sequential chemoradiotherapy or radiotherapy alone (Lim et al 2011). In this situation, evidence from dose escalation trials suggests that doses higher than the standard 60Gy in 30 daily fractions (or BED equivalent) can lead to greater local control and overall survival (Belberos JSA et al (2006), Kong F et al 2005, 2006), Adkison JB et al (2008)). However, delivering higher prescription doses can be limited by late toxicity caused by higher doses to the OAR such as the lung and spinal cord (Kong F et al 2006).

Radiotherapy prescriptions have traditionally been tailored for the entire NSCLC population in a one-size-fits-all manner (e.g. 60 Gy in 30 daily fractions). However, the achievable maximum dose in a NSCLC radiotherapy treatment varies from patient to patient depending upon the size and position of the tumour in relation to the OARs. As higher prescription doses are more difficult to achieve in some patients, the literature suggests that it may be beneficial to treat patients with isotoxic radiotherapy, which involves prescribing each patient the maximum dose possible limited solely by their individual OAR dose constraints. Recently, van Baardwijk et al (2010, 2008a, 2008b) have published the results of an ongoing study where total tumour dose was maximised to each NSCLC patient and limited only by OAR constraints to the spinal cord, lung, brachial plexus and main bronchi. This study resulted in the treatment of 166 patients treated with individualised prescriptions ranging from 51.9 Gy to 79.2 Gy in twice daily fractions of 1.8 Gy. The series showed similar survival rates to patients treated with concurrent chemoradiotherapy, and minimal toxicity. All patients were treated with a 3DCRT.

The Problem

Cases series demonstrate improved clinical outcomes when IMRT is used instead of 3DCRT for treatment of NSCLC (Liao ZX et al 2010). The use of IMRT in NSCLC has been shown to produce superior target coverage to 3DCRT (Christian JA et al 2007). IMRT has also been shown to spare dose to OAR such as the heart, spinal cord and oesophagus (Liu et al 2004); in the lung, predictors of late toxicity such as mean lung dose and V20 can also be reduced compared to 3DCRT (Christian JA et al 2007, Murshed H et al 2004). These characteristics make IMRT a promising modality for isotoxic radiotherapy, and IMRT has already been used safely in dose escalation studies to keep dose to normal tissues low (Adkison JB et al 2008, Sura S et al 2008). However, the comparative effect that IMRT has compared to 3DRCT on the ability to reach a maximum prescribed dose is uncertain.

Planning case studies have investigated the effect that IMRT has on the ability to increase prescribed dose without exceeding normal tissue constraints. The largest planning study investigating IMRT in isotoxic radiotherapy for NSCLC found that for 35 patients, average prescribed dose was increased between 8.6-14.2 Gy if a patient was planned using IMRT instead of 3DCRT (Leivens Y et al 2011). Furthermore, inverse planning constraints for OARs were optimised on a reference IMRT plan and not on the resultant isotoxic plan, suggesting that IMRT could be of greater benefit still. However, other planning studies suggest that IMRT may not escalate prescribed dose further than 3DCRT in all situations, and there is evidence that IMRT and 3DCRT produce similar isotoxic plans for node negative patients (Schwarz M et al 2006, Grills IS et al 2003).

In order to quantify the size of the effect that IMRT has in increasing prescribed dose, planning case studies have often escalated the prescribed dose over the 76Gy in 2 Gy per fraction (or BED equivalent) limit used by van Baardwijk et al 2010). Van Baardwijk et al set this maximum dose due to the radiation tolerance of great vessels and main bronchi, and it is unclear from the literature if IMRT is superior to 3DCRT at achieving 76 Gy. IMRT is also resource intensive, and clinical implementation must include a robust quality assurance programme, as well additional staff training and time for planning and dose verification (James H et al 2008). In order for IMRT to be implemented successfully in future clinical trials or studies, it is important to discover whether its use is advantageous over 3DCRT when a maximum prescribed dose of 76Gy in 2Gy per fraction or BED equivalent is applied. For further targeting of resources, patient groups that will benefit greatest from IMRT need to be identified, and a general methodology for dose escalation determined.

Methodology

Sample Size, Study Design and data analysis: In this case series, the null hypothesis is that there is no difference in ability to escalate dose to 76 Gy using IMRT rather than 3DCRT. The literature suggests that 40% of patients are more likely to be escalated with IMRT than 3DCRT, with an increase in prescription dose of 15% over 3DCRT (Leivens Y et al 2011, Schwarz M et al 2006, Grills IS et al 2003). A sample size of 20 patients will have over 90% power to detect a difference in success proportions of 0.38 when the proportion of discordant pairs is expected to be 0.40. The method of analysis will be a McNemar's test of equality of paired proportions with a 0.05 two-sided significance level.

An exploratory regression analysis will also be performed to determine whether certain patient characteristics (PTV/ GTV volume, healthy lung volume, distance of PTV from the spinal cord and location of the tumour) are more likely to warrant the use of IMRT.

An analysis of plan quality between the two methods of 3DCT and IMRT will be conducted.

Selection Criteria: Patients with Stage II/III NSCLC not suitable for concurrent chemoradiotherapy or stereotactic radiotherapy will be selected for this retrospective study.

To guarantee that the study population is representative of the clinic, only patients that have had a radiotherapy planning scan, followed by an approved treatment plan and prescription for radical radiotherapy at The Christie NHS Foundation Trust will be entered. Patients will be selected concurrently from the start date of the study.

Ethics and Research Governance: All plans generated for the study will not be used for the patient's treatment; the patient will have their treatment following the normal process and according to the existing departmental protocol. However, ethical approval will be sought from the local ethics committee via research governance framework at The Christie NHS Foundation Trust. As this research will form the basis of an MSc dissertation, approval will also be sought from Sheffield Hallam University Ethics Board if necessary. Subject to the approval of the Ethics Boards, informed consent will be sought. Patient information will remain confidential and only anonymous data will be transferred out of the departmental planning system.

Target volume and OAR definition: The Gross Tumour Volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV) and OAR from the clinical plan used to treat the patient will be used for this study. All delineation will be carried out in accordance with The Christie NHS treatment protocols.

Methods: Each patient will be re-planned using 3 separate treatment methods:

- Method 1 (3DCRT): will be produced using 3-5 6MV photon beams using a standard prescription of 60 Gy in 30 fractions. Wedges and MLCs will be used to produce a clinically acceptable plan. This method represents the most common method of 3DCRT, and will allow comparisons to the literature (Schwarz et al 2005)

- Method 2 (Inverse-planned 3DCRT): will be produced using 7 equi-spaced 6 MV photon beams and the Pinnacle3 (Philips) inverse planning software. The inverse planning software will be used to optimise beam weights and blocking, limiting each beam to one segment. This will represent an ideal achievable 3DCRT plan, with the same beam numbers as the IMRT method (see below). Although recent studies have found that the increasing the number of photon beams on a 3DCRT plan does not necessarily improve target coverage or reduce Mean Lung Dose (Christian et al 2007, Schwarz et al 2005), there is evidence that inverse planning can yield better V20 results and improves conformality (Webster G et al 2010).

- Method 3 (IMRT): will be produced using 7 equispaced 6MV photon beams using the Pinnacle3 (Philips) Inverse planning software.

Plan production
Dose distributions will be calculated using Pinnacle3 Collapsed Cone Convolution and tissue heterogeneities will be taken into account. Although every step will be taken to maximise PTV coverage with the prescription dose, as a result of using Collapsed Cone Convolution coverage may vary between 107% and 80% (Morgan et al 2008).
The following constraints will be placed upon OAR and attempts will be made to minimise dose to them either through beam angle selection (all methods) and manual optimisation of wedges and MLC (method 1) or through the assignment of objectives in the Pinnacle3 Inverse Planning software (methods 2 and 3). Re-optimisation of inverse planning objectives will occur at each dose level for Method 2 and Method 3.
Heart: V40 < 30% V30 <40% Spinal Cord: maximum dose to 1cc< 54Gy Healthy lungs: V20< 35%, Mean lung dose <19 Gy Oesophagus: no dose constraints are clinically determined for the oesophagus (van Baardwijk et al 2010), but plans will be optimised to limit high doses to the oesophagus provided that target coverage is not compromised.

Dose Escalation
The prescription dose of 60 Gy in 30 fractions will be applied initially to each method in order to create a reference plan. For each method the prescription dose will be increased in 4 Gy intervals until either the healthy lung or spinal cord tolerance is exceeded. Although other escalation planning studies have included an oesophageal tolerance (Leivens et al 2011), there is currently no universally accepted tolerance and clinical studies have used IMRT to escalate prescription doses to 76 Gy without a significant increase in oesophageal toxicity (van Baardwijk et al 2010, Sura et al 2008).
Once healthy lung or spinal cord tolerances have been exceed, the prescription dose will then be de-escalated by 2Gy until all OAR constraints are below tolerance. This will produce the Isotoxic Plan.

Data collection
Target Volume data: prescription dose, dose limiting OAR (if applicable), plan quality such as heterogeneity index and conformality index in accordance with ICRU Reports 62 and 83 (ICRU 1999, 2010), GTV size (litres), PTV size (litres) and location of tumour (lobe and distance to OAR) will be recorded for the Reference Plan and the Isotoxic Plan for each 3DCRT method and for IMRT. The highest prescribed dose achieved between the two 3DCRT methods will be used in the statistical analysis for comparison against IMRT.
Organs at risk: DVH data for Heart V40, V30; Oesophagus V30, V35 and mean dose; Spinal Cord maximum dose to 1cc; Healthy Lungs V20, V5 and mean lung dose will be recorded for the Reference Plan and the Isotoxic Plan for all methods.

Dissemination strategy
Interim reports and final results are expected to be of national and international interest. Abstracts will be prepared for the SOR Annual Radiotherapy Weekend, ESTRO, and UKRO conferences. Suitable journals such as Clinical Oncology, The International Journal of Radiation Biology Oncology Physics, Radiotherapy and Oncology, Journal of Radiotherapy in Practice will be targeted for publication of results.

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