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Short Communication

Feasibility of stereotactic body radiotherapy for locally-advanced non-small cell lung cancer

Katrina Woodford [a,b,*], Vanessa Panettieri [a], Trieumy Tran Le [a], Sashendra Senthi [a,b]

[a] Alfred Health Radiation Oncology, The Alfred, Melbourne, Victoria, Australia
[b] Monash University, Clayton, Victoria, Australia

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ABSTRACT

SBRT was feasible for approximately half of the locally-advanced NSCLC patients we assessed and for these patients has the potential to reduce a 30 fraction course to 12 fractions. Using SBRT in this setting requires compromises in techniques and further compromises may allow SBRT in a greater proportion of patients.

Introduction

The majority of patients diagnosed with potentially curable non-small cell lung cancer (NSCLC) have locally-advanced disease [1]. The standard of care treatment for such patients is high dose radiotherapy with or without chemotherapy [2]. Following such treatment, recurrence and significant toxicity are both frequent [3]. As a result the logistics associated with 6 weeks of daily treatment frequently represents a significant barrier to offering care [4]. Up to 40% of locally-advanced NSCLC patients do not receive curative treatment with the majority of these receiving no treatment whatsoever [5–8]. Not surprisingly, this is more frequent with increasing age [5,6,8] and the presence of comorbidities [7], as these are independent poor prognostic factors and associated with an increased risk of toxicity [9].

For early stage NSCLC, stereotactic body radiotherapy (SBRT) has replaced conventional radiotherapy by offering at least similar control rates with less toxicity and better post-treatment quality of life [10]. SBRT also reduced logistic barriers, allowing a 30 treatment course to be delivered in 8 or less [11]. When such barriers are removed, the proportion of early stage NSCLC patients going untreated reduces and population survival improves [12]. As there may be potential population survival improvements if SBRT can be implemented for locally-advanced disease, we performed a planning study to determine the feasibility of SBRT in this setting.

Material and methods

Population

Twenty three patients with N2 and/or N3 locally-advanced lung cancer who underwent four-dimensional computed tomography (4DCT) simulation were included. Simulation position was supine with arms up, supported by a personalised fixation device. Target volumes were delineated using all 4DCT phases following the ITV principle [13]. The oesophagus, trachea and proximal bronchial tree (to segmental bronchi) were delineated like the ITV, using all 4DCT phases to maximally account for position during respiration. The spinal canal, heart/pericardium, lungs, aorta (ascending and descending) and chest wall were contoured on the average intensity projection using published guidelines [14]. Prior to commencing this study we applied for and were given institutional ethics board approval.

Treatment planning

Plans were generated using RapidArc on the Eclipse Vn 13.6 treatment planning system (Varian, Palo Alto). Dose calculations

* Corresponding author at: Alfred Health Radiation Oncology, The Alfred, 55 Commercial Road, Melbourne, Victoria 3004, Australia. Fax: +61 3 9076 2669.
E-mail address: K.Woodford@alfred.org.au (K. Woodford).

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were performed using Acuros XB algorithm (v.13.6) reporting dose-to-medium (D_m). Treatment plans typically comprised two to three 6 MV partial arcs, sweeping 200–220 degrees across the ipsilateral side of the tumour such that beam paths avoided the contralateral lung.

Dose regimes

The following dose regimes were assessed: 40 Gy in 5 fractions, 46 Gy in 8 fractions and 50.4 Gy in 12 fractions. These maintained a dose that is biologically equivalent to 60 Gy in 30 fractions (BED_{10} = 72 Gy), the standard radical dose for locally advanced NSCLC [15]. OAR constraints were adapted from those recommended by Timmerman [16] and used in SABR COMET [17] as defined in Table 1.

Planning approach

Three planning approaches were assessed: conventional radiotherapy, SBRT and a hybrid approach combining aspects from both. Approaches varied by the margin applied from the ITV to generate the PTV, the prescription isodose and resultant dose homogeneity. These differences are outlined in Table 1.

Plan acceptance

The primary aim was to determine the least number of fractions that achieved an acceptable plan and which planning approach enabled this. Plans were defined as acceptable when PTV coverage was 95% or more and all OAR tolerances were achieved.

Image guidance considerations

Planning risk volumes (PRV) were generated around the oesophagus and trachea/bronchi to observe doses to these organs should there be online mismatching during treatment. These OARs were chosen as toxicity here may have significant quality of life impacts or associated with a risk of death [18]. PRVs using a 2 mm and a 3 mm expansion are reported here but were not used in plan acceptance.

Statistical analysis

Results were reported using descriptive statistics. Unpaired *t*-tests were used to compare clinical characteristics of patients with acceptable and unacceptable plans ($p < 0.05$).

Table 1
Summary of plan details.

OAR maximum dose tolerance per prescription			
	40 Gy in 5#	46 Gy in 8 #	50.4 Gy in 12#
Heart	38 Gy	46 Gy	54 Gy
Trachea/Bronchi	36 Gy	44 Gy	50 Gy
Oesophagus	35 Gy	40 Gy	48 Gy
Spinal Canal	28 Gy	34 Gy	40 Gy
Lung V_{20Gy}	Aim <30% but <35% acceptable		
Lung mean	20 Gy		
Planning Approach			
	Conventional	SBRT	Hybrid
ITV-PTV expansion	1.0 cm	0.5 cm	0.5 cm
Prescribed isodose	100%	80%	100%
PTV dose homogeneity	95–107%	100–140%	95–107%

Results

Patient characteristics

Fourteen patients had N2 involvement whilst nine had N3 involvement. Mean ITV size was 207.7 cc (range 31–706.1 cc).

Plan acceptance

Overall we found in 48% (11/23) of patients we were able to generate an acceptable plan, using a hybrid approach. When a purely conventional or SBRT approach was used, 26% (6/23) and 4% (1/23) of patients respectively had acceptable plans. Among patients in whom an acceptable plan was generated, none were using 5 fractions, one (9%, 1/11) used 8 fractions and 91% (10/11) were using 12 fractions. Of the plans that failed the hybrid approach, 6/12 achieved a PTV coverage between 90 and 95%, whilst 5/12 had a PTV coverage <90%. One plan had acceptable coverage but failed due to unacceptably high lung doses.

Clinical factors predicting plan acceptance

Plans that failed on average had smaller ITVs (133.4 vs 288.7 cc, $p = 0.02$), a greater volume of PTV overlap with the oesophagus (6.0 vs 1.5 cc, $p = 0.004$) and a greater percentage of PTV overlapping with either the trachea/bronchi or oesophagus (8.0% vs 3.0%, $p < 0.001$).

Image guidance considerations

PRV maximum doses for the oesophagus and trachea/bronchi and their corresponding percentage over the OAR dose tolerance are presented in Table 2.

Discussion

The aim of this study was to assess to what extent SBRT could be safely utilized for locally-advanced NSCLC where the logistics of conventional treatment represent a significant barrier to care. We found by using a hybrid planning approach combining aspects of SBRT and conventional radiotherapy approximately half of all locally advanced NSCLC patients can be safely treated using SBRT. For these patients a 30-treatment course can be reduced to 12 treatments. Such a reduction may address perceived or actual logistic barriers such that an increasing proportion of locally advanced NSCLC patients are offered curative treatment.

Despite being a potentially curative disease, significant proportions of patients with stage III NSCLC do not receive standard-of-care treatment. Retrospective Canadian data indicates up to 36% of all stage III patients do not receive curative treatment, with this number rising to 45% in patients aged 66–75 and 79% in patients over 76 [5]. Analysis of nearly 84,000 stage III NSCLC cases in the US National Cancer Database shows 17% of patients received no treatment whatsoever with increasing age being a significant factor [7]. Despite guidelines recommending comorbidities should be a consideration for treatment choice in older patients, data has shown treatment rates decrease with increasing age than with worsening comorbidities [6]. This is in spite of the fact that elderly patients experience similar outcomes from curative treatment compared to younger patients [19,20]. The introduction of SBRT has allowed patients with early stage disease to receive curative treatment in 8 fractions compared to 30. This has had a significant impact on the elderly, with less going untreated, resulting in improvements in population-based survival [12]. NSCLC is a disease of the elderly and they represent the largest growing popula-

Table 2
Summary of mean PRV D_{max} values and the corresponding percentage over the OAR dose limit. D_{max} = maximum dose.

	Oesophagus PRV				Trachea/Bronchi PRV			
	0.2 cm		0.3 cm		0.2 cm		0.3 cm	
Plan Approach	D_{max}	%	D_{max}	%	D_{max}	%	D_{max}	%
Conventional	49.3	3.4	49.9	4.8	50.7	1.9	51.3	3.1
SBRT	50.8	5.8	51.8	7.8	53.1	6.3	54.2	8.4
Hybrid	48.8	2.9	49.5	4.2	50.7	2.0	51.2	2.9

tion of patients in the future. Additionally, with more patients presenting with locally-advanced disease, the need for an alternative, more convenient treatment option cannot be understated.

Hypofractionation-use in patients ineligible for standard chemoradiotherapy has been explored. 45 Gy in 15 fractions has been demonstrated to be an effective alternative to conventional radiotherapy for patients with poor performance status [21]. When compared to 60–63 Gy and >63 Gy in 6 weeks, no difference was seen in local/distant tumour control or overall survival, whilst treatment related toxicity was significantly less in the hypofractionated arm [22]. Overall survival at 2 years was 12% for the hypofractionated arm. Indeed, lower doses such as 45 Gy in 15 fractions may achieve acceptable results in selected patients and are undoubtedly better than no treatment at all. However translation of these results to a broader range of patients, including those with higher performance status, requires further investigation. Phase 1 data has explored the tolerability of escalating dose from 50 to 60 Gy over 15 fractions in patients with Stage II to IV NSCLC whom were ineligible for surgical resection, SBRT or concurrent chemoradiotherapy [23]. They found all dose levels were well tolerated and did not cause worse acute toxicity compared to 45 Gy in 15 fractions. The most common grade 2 or higher toxicities were dyspnoea and esophagitis, with the latter corresponding to patients with oesophagus doses exceeding the recommended maximum constraints for the study. Median overall survival for the entire cohort was 6 months. Due to limited patient numbers and poor overall survival, differences in tumour control between the dose levels was not possible. Although safety has been shown with these doses, the patient cohort included patients with early-stage disease, making it difficult to discern the extent of mediastinal involvement and its influence on toxicity. In our study we've taken a conservative approach, by testing doses biologically equivalent to 60 Gy in 30 fractions and in patients with N2 or N3 locally-advanced disease.

Our study is limited by the method we used to define the critical OARs. The oesophagus and trachea/bronchi were outlined on all phases of the 4DCT, ensuring the resultant contour encompassed the maximum extent of the organ at all stages of the breathing cycle. This generates a larger volume than if it were contoured on the average dataset as is standard, thereby requiring greater dose compromise to the PTV in regions of overlap. Our results may therefore underestimate the potential utility of SBRT in the locally advanced setting. Fig. 1 provides example dosimetry for a 12-fraction plan and the PTV compromises required to fulfil the oesophageal and bronchi dose tolerances.

The PRV doses reveal the potential for OAR overdose if a treatment setup deviation of 0.2 cm or 0.3 cm were to occur. With the hybrid approach, these PRVs received on average 2.5% and 3.6% over their maximum dose limits respectively. Although this highlights the need for precise treatment verification if SBRT were to be attempted in these patients irrespective of the technique used, Table 2 suggests the hybrid approach is more forgiving than either a conventional or purely SBRT approach.

We found SBRT was feasible for approximately half of the locally-advanced NSCLC patients we assessed and for these a 12-fraction scheme would be feasible. If the alternative to SBRT is no treatment at all, compromises to tumour coverage or OAR tolerances may be acceptable, increasing feasibility. To employ SBRT in the locally-advanced setting, accepting limitations of using the BED equivalence [24], the risk of toxicity is greater than using 74 Gy with conventional radiotherapy. For these patients SBRT cannot be safely used unless there is phase 1 data confirming its safety. This data will inform a phase 1 study testing the safety of SBRT for locally-advanced NSCLC.

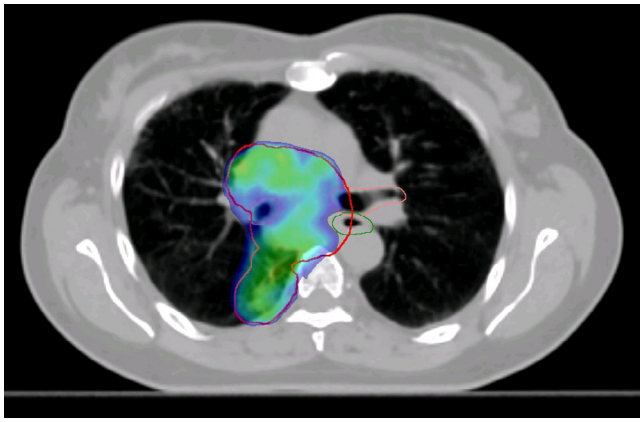

Fig. 1. Dosimetry of a 12-fraction plan requiring PTV (red) compromise over the oesophagus (green) and sparing of the bronchi (pink) from high doses, indicated by the 'cooler' blue regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Conflict of interest statement

None.

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