RESEARCH ARTICLE

Determining the Optimal Dose Prescription for the Planning Target Volume with Stereotactic Body Radiotherapy for Non-Small Cell Lung Cancer Patients

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Abstract

Objective: The aim of this study was to determine a method of dose prescription that minimizes normal tissue irradiation outside the planning target volume (PTV) during stereotactic body radiotherapy (SBRT) for patients with non-small cell lung cancer. Methods: Previous research and patients with typical T1 lung tumors with peripheral lesions in the lung were selected for analysis. A PTV and several organs at risk (OARs) were constructed for the dose calculated; six treatment plans employing intensity modulated radiotherapy (IMRT) were produced, in which the dose was prescribed to encompass the PTV, with the prescription isodose level (PIL) set at 50, 60, 70, 80, 90 or 95% of the isocenter dose. Additionally, four OARs around the PTV were constructed to evaluate the dose received in adjacent tissues. Results: The use of higher PILs for SBRT resulted in improved sparing of OARs, with the exception of the volume of lung treated with a lower dose. Conclusions: The use of lower PILs is likely to create significant inhomogeneity of the dose delivered to the target, which may be beneficial for the control of tumors with poor conformity indices.

Keywords: Prescription dose level - stereotactic body radiotherapy - lung - intensity modulated radiotherapy

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Introduction

Lung cancer is one of the most common and most lethal types of cancer with poor treatment results (Shi et al., 2015; Li et al., 2015; Ji et al., 2014; Cui et al., 2014). Radiation therapy has an important role in the treatment of lung cancer. (Liu et al., 2013; Malik et al., 2014). Stereotactic body radiation therapy (SBRT) has been an effective treatment for early-stage non-small cell lung cancer (NSCLC) and other small volume tumors (Van Baardwijk et al., 2012; Salguero et al., 2013). Various treatment planning and dose prescription strategies are employed, and the prescribed dose encompassing the planning target volume (PTV) is at an isodose level between 65 and 90%, relative to the isocenter dose. Occasionally an intended gradient between gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) is also present (Wulf et al., 2005; Lagerwaard et al., 2008; Chang et al., 2008; McGarry et al., 2005). No consensus has been reached in this area, predominantly due to lacking information with regard to what is the optimal prescription isodose level (PIL) for minimizing the dose received by tissues outside the PTV. However different concepts of 'optimal' have been employed. Studies conducted in 1999 and 2010 investigated this issue and obtained conflicting results (Cardinale et al., 1999; Widder et al., 2010). Cardinale (1999) proposed that the optimal block margin was in the 0.0 mm range between the PTV and the beam aperture for the sparing of normal tissue; this dose creates significant target-dose inhomogeneity, which may be beneficial for tumor control. Widder (2010) demonstrated that the prescribed dose must be at an isodose <80% of the isocenter dose in SBRT in order to improve normal tissue sparing, when the conformal arc technique was utilized with Monte Carlo (MC) dose calculation. In this study, 'optimal' was defined as minimum mean doses for the three shells constructed around the PTV at 1 cm intervals, and the minimum volumes of the lung receiving 30 or 40% of the prescription isodose. These optimal parameters may be arbitrary in SBRT, and additional parameters must also be analyzed to minimize the irradiation of normal tissue. The aim of the current study was to determine the optimal PIL in SBRT for lung tumors in order to minimize the normal tissue irradiation outside of the PTV.

Materials and Methods

Search strategy and patient characteristics

We searched PUBMED, by using the following search terms: (non-small-cell lung cancer) and (stereotactic radiotherapy). All clinical studies defining the block margin that minimizing normal tissue irradiation outside

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of the planning target volume for stereotactic radiotherapy in patients with non-small-cell lung cancer published in English prior to May 2016 were identified. If samples of two studies overlap, only the newest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports. Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies defining the block margin that minimizing normal tissue irradiation outside of the planning target volume for stereotactic radiotherapy in patients with non-small-cell lung cancer published in English prior to May 2016 (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified non-small-cell lung cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) of less than 2. Studies were excluded if one of the following existed: (a) duplicate data; (b) no sufficient data were reported.

Data collection and analysis

The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors: author, publication data, country of the first or corresponding author, the number of patients. Outcome presented in at least 3 studies were extracted for combined analysis. Clinical data was reported as following: an adult patient (male, 47 years old) with peripheral NSCLC stage T1N0M0 (diameter, 30 mm), who was eligible for an institutionally approved treatment course of SBRT, was selected for analysis. The patient was positioned frameless in a vacuum-mattress with the arms raised above the head. Subsequently, a four-dimensional (4D) planning computed tomography (CT) image was acquired with free breathing, scanning with 3-mm slices. The CT scans were analyzed using the 3D treatment planning system software (Varian Eclipse Medical Systems, Palo Alto, CA, version 8.6). Informed consent was obtained.

Planning of target volumes

The GTV, internal tumor volume (ITV), PTV and four surrounding organs-at-risk (OARs) were contoured and all subsequent planning was conducted on the commercial 3D treatment planning system. GTV represented the primary lesion visualized on the CT images, ITV encompassed all GTVs delineated on 10-phase 4D-CT scans, and PTV was created by isotropically expanding the ITV with a 5 mm margin. OARs included: Spinal cord, ipsilateral lung-PTV, trachea and chest wall.

Treatment plans

Six treatment plans were devised in which the dose was prescribed to encompass the PTV, with the PIL set at 50, 60, 70, 80, 90 and 95% of the isocenter dose. Each of these six treatment plans was created using fixed gantry and intensity-modulated beams, delivering the dose by means of the step and shoot approach (Cao et al., 2007; Fenwick et al., 2006). Plans were individually optimized using seven coplanar fields, whereas the final dose calculation was performed using the AAA method, which includes heterogeneity management instead of the pencil beam. A total dose of 60 Gy in 15 Gy fractions was prescribed to the PTV, and plans were all normalized to provide the mean dose to the PTV in order to avoid any bias or rescaling effect in the comparison (Vrdoljak et al., 2005). For PTV, the planning objectives were to cover ≥95% of the PTV with the 90% isodose, to ensure a minimum dose of >90%; there were no limitations for the maximum dose. As the aim of SBRT is to destroy tissues within the PTV, these tissues were not considered to be at risk for complications in this analysis. Therefore, dose inhomogeneity inside the PTV was considered to be acceptable and was not considered a priority in the design of the plan.

Calculation of dose volume histograms

For each plan, dose volume histograms (DVH) were calculated for the PTV and OARs. Dose-volume parameters were calculated for PTV: The target homogeneity was expressed by maximum dose divided by prescription dose (MDPD); the degree of conformity of the plans was measured with a conformity index (CI), which is defined as the volume of the prescription isodose surface divided by the PTV volume. For OARs, the analysis included the maximal dose to spinal cord, the ipsilateral lung minus PTV, which included V_{30} (the volume of lung treated to a dose of 30 Gy), V_{20}, V5, and the mean lung dose, and the mean dose to chest wall and trachea.

Results

There were 2988 papers relevant to the search words by the end of May 2016. Via steps of screening the title and reading the abstract, 5 studies were identified (Cardinale, et al, 1999; Jinet al., 2007; Widder et al., 2009; KOPP et al., 2010; Brock et al., 2011). All these studies had been carried out in Europe and the US. The following outcomes were presented in at least one study and extracted for combined analysis: treatment plans employing dynamic conformal arc technique were made in which the dose was prescribed to encompass the PTV with the prescription isodose level (PIL) set in a range between 50% and 80% of the isocenter dose, 3 shells of respectively 10 mm thickness around the PTV were constructed to assess the dose in the tissues directly adjacent to the PTV.

As presented Table 1, the MDPD increases with decreasing PIL from 1.07 to 2.37, and the CI increases with decreasing PIL from 1.05 to 1.22, with the exception of the 95% PIL, with CI 1.08. The 90% PIL plans are almost identical for CI and OARs sparing, with the exception of the volume of the lung receiving the lower dose. Overall, the plans tend to improve with higher PILs, with the exception of the volume of the lung receiving a lower dose. As shown in Figure 1, the volume of the lung receiving

Table 1. MDPD, CI and Dosimetric Results for the OARs for Different PIL

	PTV		OARs						
			Spinal cord	Ipsilateral lungs-PTV				Trachea	Chest wall
PIL(%)	MDPD	CI	Max(cGy)	V_{30}(%)	V_{20}(%)	V_5(%)	Mean(cGy)	Mean(cGy)	Mean(cGy)
95	1.07	1.08	596	3.0	17.0	33.6	736	335	220
90	1.14	1.05	619	3.1	16.5	33.2	711	341	231
80	1.28	1.10	675	4.2	16.1	33.1	714	363	258
70	1.53	1.12	767	8.9	15.6	32.5	756	412	294
60	1.67	1.15	843	12	14.5	32.3	801	459	321
50	2.37	1.22	1109	11.5	13.1	31.9	892	586	441

MDPD, maximum dose divided by prescription dose; CI, conformity index; OAR, organ at risk; PTV, planning target volume; PIL, prescription isodose level; V_{30}, volume of lung receiving 30 Gy or more; V_{20}, volume of lung receiving 20 Gy or more; V5, volume of lung receiving 5 Gy or more

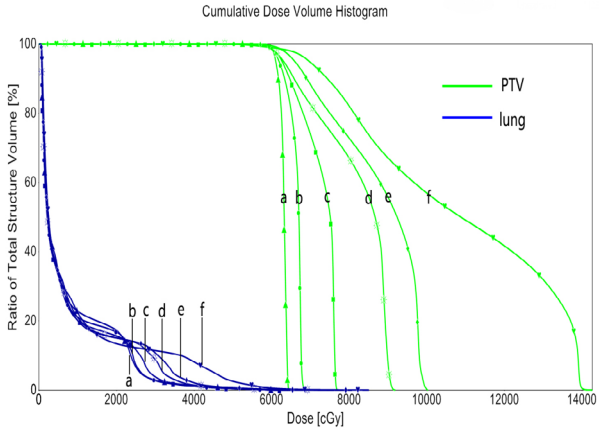

Figure 1. Dose–volume Histograms of the PTV and Ipsilateral Lung-PTV with Different Prescription Isodose Levels: a 95%, b 90%, c 80%, d 70%, e 60% and f 50%, Respectively. PTV, planning tumor volume

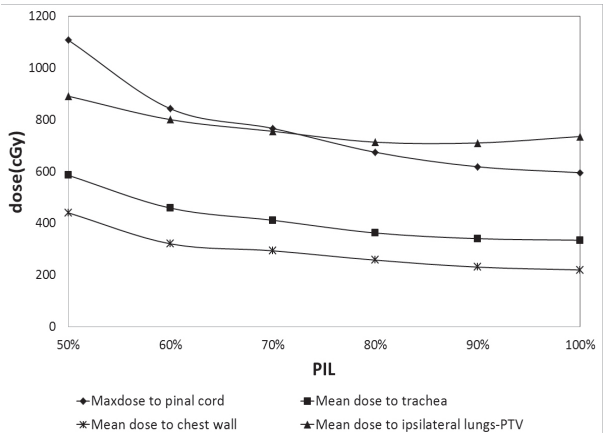

Figure 2. Dose in Organs at Risk Surrounding the PTV for Various Prescription Isodose Levels. PIL, prescription isodose level; PTV, planning target volume

the lower dose of radiation increases with increasing PIL, while the volume of the lung receiving a higher dose is conflicting. Additionally, from Figure 1, it is evident that the PTV coverage is similar among the six PIL plans, and the MDPD increases with decreasing PIL. Figure 2 shows the maximal dose received by the spinal cord, and mean doses for ipsilateral lung-PTV, trachea and chest wall, respectively, and the dose is observed to increase with decreasing PIL. In Figure 3, it is demonstrated that the V_{20} and V5 for the ipsilateral-lung increase with increasing

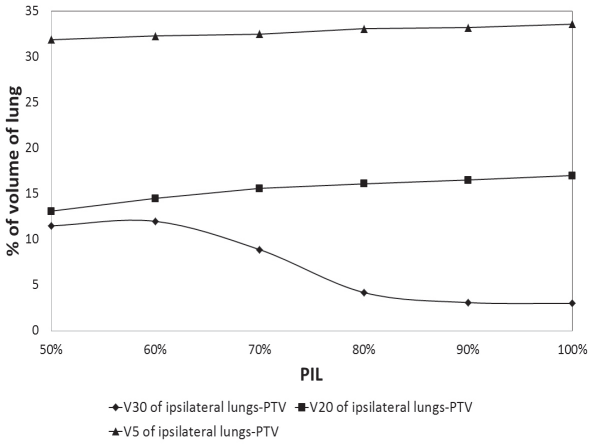

Figure 3. Percentage of Volume of Ipsilateral Lung-PTV for Various Prescription Isodose Levels. PIL, prescription isodose level; PTV, planning target volume

PIL, while for V_{30}, the converse is observed.

Discussion

SBRT provides high local control rates and allows for painless ambulatory treatment, with minimal toxicity for the treatment of pulmonary lesions (Navarria et al., 2013; Parashar et al., 2013; Rosen et al., 2014). Koto (2007) reported a three-year local control rate of 77.9 and 40.0%, for patients with stages T1-2 tumors, respectively, and proposed that a more intensive treatment regimen should be used for stage T2 tumors.

Planning and delivery techniques for SBRT vary (Balagamwala et al., 2012; Zhang et al., 2011; Wala et al., 2012; Ohtakara et al., 2012). As a dose-response association has been demonstrated (Mcgarry et al., 2005;mWulf et al., 2005), the comparison of treatment planning between different studies is challenging. However, similarly to cranial stereotactic RT, inhomogeneous dose distributions are usually used. The degree of inhomogeneity in doses in the PTV differs greatly: The PIL has been used for establishing the PTV, including at 50% (Xia et al., 2006), 60% (Zimmermann et al., 2005), 65% (Blomgren et al., 1995; Wulf et al., 2004; Nyman et al., 2006), 80% (Onishi et al., 2004; Uematsu et al., 2001; Hof et al., 2003), 85% (Beitler et al., 2006), or 90% (Lee et al., 2003) PIL. However, the optimal PIL remains unknown. Guckenberger (2007), compared 65 and 80% PIL for the

PTV (Isocenter at 100%) of 3DCRT plans. The authors found that PTV coverage showed almost no difference between the two PILs; the effect of the non-static, variant dose distribution was significantly decreased in plan-80%, and the doses to the ipsilateral lung were not significantly different between plan-65% and plan-80%. It was hypothesized that treatment planning with the 65% PIL is beneficial compared with the dose prescription of the 80% PIL, as the dose to the tumor was increased by 35% in plan-65% compared with plan-80%, yet there was no difference in the dose to the ipsilateral lung.

In the current study, the dose to the PTV was observed to increase with decreasing PIL, which was similar to the results obtained by Guckenbergerl (2007), however, in the current study, the volume of lung receiving a lower dose increases with increasing PIL while the volume of lung receiving the higher dose decreases. Additionally, for the mean dose to the lung, no significant difference was observed between the six PIL plans. Widder (2010) investigated various PILs ranging between 50 and 80% of the isocenter dose to encompass the PTV; the authors suggested that for optimum normal tissue sparing, the dose should be prescribed at an isodose <80% of the isocenter dose in SBRT when determined using MC dose calculation. However, the current study found that the use of higher PILs for SBRT resulted in improved OARs sparing, only with the exception the volume of lung receiving the lower dose of radiation. Conversely, the dose heterogeneity within the target volume has not been of major concern for SBRT, and is considered to be beneficial by certain investigators, therefore, the plan with lower PIL may offer certain benefits for tumor control using SBRT.

In conclusion, according to this study, in SBRT for lung-lesions and other small volume tumors using IMRT, dose prescription at a higher PIL is predicted to result in a lower dose to the surrounding tissues and lungs compared with employing a marginally lower PIL; this is with the exception of considering the volume of lung treated with a lower dose.

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