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Original article

Can dose outside the PTV influence the risk of distant metastases in stage I lung cancer patients treated with stereotactic body radiotherapy (SBRT)?

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ABSTRACT

Background and purpose: In an era where little is known about the "abscopal" (out-of-the-field) effects of lung SBRT, we investigated correlations between the radiation dose proximally outside the PTV and the risk of cancer recurrence after SBRT in patients with primary stage I non-small cell lung cancer (NSCLC).
Materials and methods: This study included 217 stage I NSCLC patients across 2 institutions who received SBRT. Correlations between clinical and dosimetric factors were investigated. The clinical factors considered were distant metastasis (DM), loco-regional control (LRC) and radiation pneumonitis (RP). The dose (converted to EQD2) delivered to regions of varying size directly outside of the PTV was computed. For each feature, area under the curve (AUC) and odds ratios with respect to the outcome parameters DM, LRC and RP were estimated; Kaplan–Meier (KM) analysis was also performed.
Results: Thirty-seven (17%) patients developed DM after a median follow-up of 24 months. It was found that the mean dose delivered to a shell-shaped region of thickness 30 mm outside the PTV had an AUC of 0.82. Two years after treatment completion, the rate of DM in patients where the mean dose delivered to this region was higher than 20.8 Gy_2 was 5% compared to 60% in those who received a dose lower than 20.8 Gy_2. KM analysis resulted in a hazard ratio of 24.2 (95% CI: 10.7, 54.4); $p < 10^{-5}$. No correlations were found between any factor and either LRC or RP.
Conclusions: The results of this study suggest that the dose received by the region close to the PTV has a significant impact on the risk of distant metastases in stage I NSCLC patients treated with SBRT. If these results are independently confirmed, caution should be taken, particularly when a treatment plan results in a steep dose gradient extending outwards from the PTV.
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Lung cancer is both the leading cause of cancer deaths worldwide and one of the most frequent cancers [1]. Despite advances in cancer treatment, metastatic lung cancer is still related to a poor prognosis [2]. Cancer recurrence, including distant metastasis, is possibly due to microscopic disease extensions (MDE) of the primary lung tumor, although there has been little research done specifically on MDEs or their possible distribution to verify this hypothesis [3–8].

Stereotactic body radiation therapy (SBRT) is a technique used to deliver a highly accurate dose in a well-defined target volume [9,10]. The localized nature of this technique is one of the primary advantages: it allows for a maximal dose to the tumor, while minimizing the dose to healthy tissue and thus the risk of treatment complications. However, one clinical difficulty when treating localized lung cancers with SBRT is precisely defining the gross tumor volume (GTV). This inaccuracy may increase the chances that microscopic disease outside of the GTV is not eradicated. Furthermore, as the precise location of MDEs is unknown, the requisite planning target volume/clinical target volume (PTV/CTV) margins are unclear. If the area outside the tumor contains microscopic disease, minimizing the dose to a region that is overly constrained could increase the probability of microscopic cancer cells surviving after SBRT, increasing the risk of cancer recurrence. The conformal nature of SBRT amplifies this problem due to the sharp dose gradient outside of the PTV.

The present investigation was conceived from a previous study [11] that correlated biomarkers and dosimetric parameters in a small cohort of patients. The study found that target volume size

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was inversely correlated with distant metastasis. As this seemed counter-intuitive, we investigated further, eventually leading to an analysis of the dose falloff around the PTV. Thus, the aim of the present study was to determine if there is a correlation between the radiation dose immediately outside the PTV and cancer recurrence in patients with stage I non-small cell lung cancer (NSCLC) treated with SBRT.

Methods

Patient selection

Two hundred and seventeen patients with primary stage I NSCLC treated using SBRT (either 3D-CRT or VMAT) between 2011 and 2015 were included in this study. 44% of patients were treated by the McGill University Health Centre (MUHC), the remainder were treated at the Centre Hospitalier de l'Université de Montréal (CHUM). Diagnosis of NSCLC was confirmed through histology in 139/217 (64%) of patients. The remainder (36%) had no biopsy due to either refusal or risk considerations and the diagnosis of primary NSCLC was assumed based on clinical history and PET-CT images. 195/217 of all patients (90%) received a PET-CT scan, which was used for staging. None of the patients received any form of chemotherapy or alternative cancer treatment. All patients had only one well-defined lung tumor and did not have a prior cancer within the past 5 years.

Follow-up and clinical factors

The clinical factors considered for this study were distant metastasis (DM), loco-regional control (LRC) and radiation pneumonitis (RP) (grade ≥ 3 based on Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [12]). Follow-up was performed 1–3 months after treatment completion and then every 3–6 months. Only patients with at least 12 months of follow-up data were included in the analysis. A patient was considered to have LRC if they had a radiographic response to treatment on CT images and no progression of the tumor was seen in the CT or PET scans done at each follow-up visit. If evidence of progression was observed at any point, the patient was considered to have loco-regional failure (LRF).

Sub-cohort selection

To confirm the significance of the observations, analyses were performed on sub-cohorts of patients with an additional set of selection criteria as shown:

- Sub-cohort A: The group containing 139 patients whose histology was confirmed by biopsy, 28 of whom developed distant metastasis (20%). This group was chosen to determine if the lack of biopsy for some patients influenced the results.
- Sub-cohort B: The group of patients who had a more sharply defined follow-up time, between the first and third quartiles, i.e., month 14 – month 32 (23 metastasis events in 122 patients, 19%). This group was chosen to determine if the wide range of follow-up times influenced the results.
- Sub-cohort C: The group of patients who had a PTV volume between the first and third quartiles, i.e., 16 cc-40 cc (16/109, 15%). This group was chosen to determine if the wide range of PTV volumes influenced the results.
- Sub-cohort D: The group of patients who received one of the majority fractionation schemes, either 48 Gy/3 fractions or 60 Gy/3 fractions (27/159, 17%). This group was chosen to determine if the variation in fractionation schemes influenced the results.
- Sub-cohort E: The group of patients treated at MUHC (19 metastasis events in 96 patients, 20%).
- Sub-cohort F: The group of patients treated at CHUM (18 metastasis events in 121 patients, 15%). This group and sub-cohort E were chosen to determine if the variation in modality (3D-CRT versus VMAT), contouring style and dose prescription (described below) influenced the results.

CT acquisition and tumor segmentation

Target delineation was performed on radiation therapy planning CTs using Eclipse (Varian Medical Systems, Palo Alto, CA, USA). The internal target volume (ITV) was drawn based on the inspiration, expiration and the maximum intensity projection (MIP) images obtained from the 4DCT taken in conjunction with the planning CT. The CTs were acquired per a standard scanning protocol with a resolution of 512×512 pixels and 3 mm slice thickness. The contours were drawn manually and individually verified by an expert radiation oncologist. The PTV was a 3–5 mm extension margin (due to institutional variability) to the ITV. The MUHC patients' prescription isodose surfaces were chosen such that 95% of the PTV was covered by the prescription dose and 99% of the PTV received at least 90% of the prescription dose with a 5 to 11-field 3D conformal technique using Novalis TX 6 MV photon beams (Varian Medical Systems, Palo Alto, CA, USA; Brainlab, AG, Munich, Germany CHUM patients' prescription isodose surfaces were chosen such that 95% of the PTV was covered by the prescription dose while maintaining the requirement that the prescription isodose must be within 65–85% of the maximum dose. SBRT was delivered using RapidArc (Volumetric Arc Therapy) on a 6 MV photon beam (Varian Medical Systems, Palo Alto, CA, USA). Dose calculation was originally performed using the Analytical Anisotropic Algorithm (AAA) for all patients. The dose analysis was verified on recalculated Monte Carlo plans (EGSnrc, Ottawa, Canada, [13]). Image verification was performed prior to and during each treatment using cone-beam CT (CBCT).

Region of interest (ROI) creation

An algorithm to evaluate the dose parameters in a region of varying size outside of each patient's PTV was developed using Python's *pydicom* module [14]. The algorithm consisted of five primary steps, described in detail within the Supplementary material:

- Superimpose PTV point cloud onto dose grid, generate convex hull of PTV.
- Grow the PTV point cloud in 3D space isotropically.
- From the grown point cloud, generate a convex hull.
- Exclusive OR (XOR) logic applied to both convex hulls, resulting in a shell-shaped region radially extending outwards from the PTV.
- Analysis of dose applied to this region.

The algorithm generated two types of regions. $ROI_{cont}(x\ mm)$ represents a shell-shaped region including the entire volume up to x mm outside of the PTV. $ROI_{diff}(x\ mm)$ represents a 1 mm thick shell-shaped region at a distance of x mm away from the PTV boundary. x was varied from 1 mm to 100 mm in 1 mm increments. This maximal range was chosen to be significantly beyond the range which is suggested to contain microscopic spread [6,7,15]. A realistic depiction of the algorithm is shown in the left side of Fig. 1 (green inner volume represents PTV, black represents the boundary of $ROI_{cont}(30\ mm)$). A two-dimensional example of the ROIs created for a hypothetical circular tumor is shown in the right side of Fig. 1.

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