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Original Article

Predictive Factors for Local Control in Primary and Metastatic Lung Tumours after Four to Five Fraction Stereotactic Ablative Body Radiotherapy: A Single Institution's Comprehensive Experience☆

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Abstract

Aims: We report the outcomes of a large lung stereotactic ablative body radiotherapy (SABR) programme for primary non-small cell lung cancer (NSCLC) and pulmonary metastases. The primary study aim was to identify factors predictive for local control.
Materials and methods: In total, 311 pulmonary tumours in 254 patients were treated between 2008 and 2011 with SABR using 48–60 Gy in four to five fractions. Local, regional and distant failure data were collected prospectively, whereas other end points were collected retrospectively. Potential clinical and dosimetric predictors of local control were evaluated using univariate and multivariate analyses.
Results: Of the 311 tumours, 240 were NSCLC and 71 were other histologies. The 2 year local control rate was 96% in stage I NSCLC, 76% in colorectal cancer (CRC) metastases and 91% in non-lung/non-CRC metastases. Predictors of better local control on multivariate analysis were non-CRC tumours and a larger proportion of the planning target volume (PTV) receiving ≥100% of the prescribed dose (higher PTV V100). Among the 45 CRC metastases, a higher PTV V100 and previous chemotherapy predicted for better local control.
Conclusions: Lung SABR of 48–60 Gy/four to five fractions resulted in high local control rates for all tumours except CRC metastases. Covering more of the PTV with the prescription dose (a higher PTV V100) also resulted in superior local control.

Key words: Colorectal cancer; lung metastases; non-small cell lung cancer; oligometastases; stereotactic body radiotherapy

Introduction

Stereotactic ablative body radiotherapy (SABR), also called stereotactic body radiotherapy, has become an effective option to treat malignant lung tumours. It is indicated for early stage non-small cell lung cancer (NSCLC) in patients who are medically inoperable, at high surgical risk or who refuse surgery. SABR is also increasingly used in patients with pulmonary oligometastases. Its role in metastatic patients is controversial, but seems promising, as eradication of oligometastatic disease may delay progression or postpone the need to start or change systemic therapy [1].

Several studies have reported favourable outcomes after SABR for either primary NSCLC or oligometastases. The safety and efficacy are well documented [2–6]. Whether the same lung SABR dose fractionation scheme should be used in all tumours is unknown. Some advocate the use of a lower SABR dose for central tumours and others support a size- or volume-adapted dosing approach [4,7]. However, few studies have compared clinical outcomes between primary versus metastatic lung tumours of various histologies.

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At our centre, the lung SABR programme started in 2008. The treatment policy stipulated different dose fractionation regimens based on location (central versus peripheral), size and tumour histology (NSCLC versus others). The primary objective of our study was to evaluate local control and to investigate potential clinical and dosimetric predictive factors for local control. Secondary objectives were to evaluate the patterns of recurrences, survival and the toxicity profile with a focus on chest wall toxicities and severe pneumonitis requiring steroids or oxygen supplementation.

Materials and Methods

From our prospective lung SABR database, we identified 311 pulmonary tumours in 254 patients treated with SABR between May 2008 and December 2011. This study was approved by our Research Ethics Board. Tumour histology, initial stage, local failure, regional failure and distant failure data were collected prospectively. All other data were collected retrospectively. Patients were eligible for lung SABR if they had a pathological confirmation or radiological documentation of an early stage lung cancer or pulmonary oligometastases. If pathological confirmation was not possible, then there had to be significant fluorodeoxyglucose activity on positron emission tomography-computed tomography defined by a maximum standardised uptake value (SUV_{max}) $\geq$2.5 or evidence of tumour growth over serial computed tomography scans. All patients with a solitary tumour were deemed not suitable for surgery or declined surgery. Patients with multiple lung tumours were eligible if limited to $\leq$4 lesions with no active or untreated disease elsewhere, and if surgery or chemotherapy were not appropriate as deemed by a thoracic surgeon and medical oncologist. Patients with a past diagnosis of lung cancer were categorised as having a second primary NSCLC if there was histological confirmation of a different NSCLC subtype, or if a new malignant nodule developed more than 2 years after the initial diagnosis of lung cancer with no evidence of distant metastatic disease. Other new fluorodeoxyglucose-avid or enlarging solid lung nodules occurring within the first 2 years after the initial lung cancer diagnosis were classified as lung metastases from NSCLC. Tumours should be $\leq$5 cm in size.

Regarding our lung SABR technique, patients were immobilised using one of two techniques: the Elekta BlueBAG vacuum cushion (Elekta AB, Stockholm, Sweden) with an abdominal compression plate, or the full Elekta BodyFIX system, as described previously [8]. Four-dimensional computed tomography was acquired with phase-binning reconstruction software. The gross tumour volume was delineated by the radiation oncologist on the 0% (peak inspiratory), 50% (peak expiratory) and maximum intensity projection image sets, and their combined volume was used to generate the internal target volume (ITV). There was no expansion for microscopic disease. A 5 mm isotropic margin was added to form the planning target volume (PTV). The radiotherapy plan was calculated on the computed tomography average image set [9] and optimised using seven to 10 beam angles. Step and shoot intensity-modulated radiotherapy was used since 2009 (224/311 tumours). The institutional policy was to deliver 48–52 Gy/four fractions for peripheral NSCLC tumours (48 Gy if $\leq$3 cm, 52 Gy if $>$3 cm), 52 Gy/four fractions for peripheral pulmonary metastases (non-NSCLC) and 50 Gy/five fractions for all central tumours (defined as tumours immediately adjacent to the oesophagus, trachea, main stem bronchi, great vessels and/or heart), regardless of size or histology. Since 1 January 2011, the dose for peripheral colorectal cancer (CRC) metastases has increased to 60 Gy/four fractions because an informal analysis of the prospective database revealed a larger proportion of local failures in that population. Plans were optimised to aim for $\geq$99% of the ITV to receive the prescription dose (ITV V100 $\geq$ 99%), and $\geq$99% of the PTV to receive 95% of the prescription dose (PTV V95 $\geq$ 99%). All dosimetric data were collected from radiotherapy plans corrected for tissue inhomogeneity using the collapsed cone convolution algorithm.

Treatment was delivered using the Elekta Synergy units equipped with the Elekta Synergy Beam Modulator (high resolution 4 mm multileaf collimator), a kilovoltage cone-beam computed tomography image-guidance system and the Hexapod robotic couch permitting 6 degrees of freedom patient positioning.

All patients were treated and followed by one of two radiation oncologists (PC or IP). Follow-up with computed tomography thorax/abdomen/pelvis was carried out every 4 months after SABR for the first 3 years. After that, follow-up was decreased to every 6 months. Local control and lobar local control were assessed based on each pulmonary lesion treated; regional control, distant control and overall survival according to each patient treated. The time to recurrence and overall survival were calculated from the start of SABR to the date of the event or last follow-up. A local recurrence was defined as a relapse within or $\leq$1 cm beyond the PTV, with the requirement that there had to be consecutive enlargement of the lesion over two to three computed tomography scans. Lobar local control was defined as the absence of recurrence within the treated lobe. A tumour was classified as adjacent to the chest wall if the PTV was overlying the chest wall. The initial planning computed tomography, all follow-up computed tomography scans and their respective radiologist's report were reviewed by IT to determine whether a rib fracture occurred within the treated volume. In cases where it was unclear, imaging was reviewed with a radiologist blinded to the treatment provided. The incidence of radiation pneumonitis requiring treatment with steroids or supplemental oxygen was collected retrospectively.

Statistical Analysis

Descriptive statistics were used to list the relevant patient, tumour and treatment factors. Categorical variables were compared using the chi-squared test. Kaplan–Meier methodology was used to compute non-parametric estimates of local control, lobar local control, regional control, distant control, overall survival and time to rib fracture.