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High-dose, conventionally fractionated thoracic reirradiation for lung tumors

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ABSTRACT

Background: Loco-regional recurrences and second primary lung tumors are not uncommon after high-dose thoracic radiotherapy. The availability of improved radiotherapy techniques increases options for reirradiation. We describe a single-institutional experience with high-dose conventional thoracic reirradiation for both loco-regional recurrences and new primary tumors.
Methods: Retrospective chart review of patients undergoing reirradiation between February 2004 and February 2013.
Results: Of 24 patients identified, 54% had a loco-regional recurrence, and 46% a new primary tumor. The majority (63%) had stage III NSCLC at both initial and second treatment; median interval between treatments was 51 months (5–189), median follow-up after reirradiation was 19.3 months (95% CI: 2.8–35.9). Median overall survival (OS) after reirradiation was 13.5 months, with 1-year survival 51%. Median event-free survival (EFS) was 8.4 months. Median time between reirradiation and local progression ($n = 8$) or distant progression ($n = 8$) was 6.7 and 11.8 months, respectively. Three patients died with possible grade 5 bleeding. Other toxicities were uncommon. Planning target volume (PTV) at reirradiation was the most important prognostic factor; PTV <300 versus ≥300 cc was significantly associated with median OS (17.4 vs 8.2 months, $p = 0.03$) and EFS (14.1 vs 5.5 months, $p = 0.03$). Magnitude of overlap between the initial and subsequent PTVs, and between dose distributions, did not influence survival.
Conclusion: Thoracic reirradiation with high dose conventional radiotherapy appears to deliver a meaningful survival benefit in low volume new primary or recurrent lung cancer. Further studies are needed to confirm these findings, and to establish reliable normal tissue tolerance doses for reirradiation.

1. Introduction

The last few decades have witnessed modest improvements in the survival of patients with non-small cell lung cancer (NSCLC) [1]. However, up to 35% of patients undergoing chemo-radiotherapy (CRT) for locally advanced NSCLC develop a loco-regional relapse [2] and long-term survivors are at risk of developing a second primary lung cancer [3,4]. Although reirradiation dates back several decades [5] reports of high dose conventionally fractionated retreatment remain limited and most address the use of low-dose palliation [5–16]. The use of proton radiotherapy for locally advanced recurrent tumors has been described [17], as has stereotactic ablative radiotherapy (SABR) for second tumors and small volume recurrent disease [18–23]. Although uncertainty persists about the tolerance of mediastinal organs to high dose retreatment [8,10,24], median overall survival (OS) of up to 14–15 months has been reported in selected patients [12,13] compared with a few months for low dose palliative reirradiation [25]. Improved radiotherapy techniques facilitate higher precision and greater sparing of organs at risk [26], with the result that increasing numbers of patients are currently being considered for high dose reirradiation. We retrospectively analyzed our institutional experience to determine (1) whether clinical outcomes including high-grade toxicity and survival were acceptable after high-dose thoracic irradiation, and (2) whether we could identify prognostic factors.

2. Materials and methods

For this retrospective study we identified patients who received their second course of conventionally fractionated thoracic radiotherapy for recurrent lung cancer or a new primary lung cancer between February 2004 and February 2013. Conventional

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fractionation was defined as ≤3 Gray (Gy)/fraction and high dose as ≥39 Gy. Those treated with SABR were excluded. 24 patients met our inclusion criteria. Of these, 12 received the initial treatment at another center.

Prior to re-treatment, patients are reviewed at a multidisciplinary tumor board. If chemotherapy is used then this is usually given sequentially, before reirradiation. Radiotherapy techniques have evolved over time to incorporate developments in technology. During the period 2004–2013 planning 4D-CT has been routinely available. An intensity modulated radiation therapy (IMRT) technique is now standard, either hybrid-IMRT [27] or volumetric modulated arc therapy and treatment is delivered using daily online image-guidance, with adaptive re-planning where needed. Currently, cumulative dose is estimated from original plans with the aid of rigid, and where appropriate deformable, co-registration [28]. To account for differences in dose and fractionation, equivalent doses in 2 Gray/fraction have been derived using the equation for biological effective dose (BED) with a α/β of 10 for tumor effects and the appropriate tissue-specific α/β ratio for late effects. Patients typically remain under follow-up with the treating lung physician and/or our own department. Frequency of follow-up and imaging are therefore heterogeneous.

3. Definitions

Tumors were re-staged using the 7th TNM staging system. A new primary was defined as a second tumor when it was in a new location, if it had a different histology, or if the tumor recurred at the initial location after more than 5 years after the start of the first treatment. A tumor was defined as a recurrence if it relapsed within 5 years of initial treatment. Recurrences were further subdivided based on location: an in-field recurrence was located in the original high-dose radiation treatment volume; an out-of-field recurrence was located outside the high-dose treatment volume (e.g. regional recurrences in previously unsuspicious, and therefore untreated, lymph nodes). The interval between the first and second treatment was the number of months between the start of the first and second radiation treatment. Overall survival after reirradiation was the time between the first day of reirradiation and death from any cause. Event-free survival (EFS) was the time between the first day of reirradiation and the time that any progression (local or distant) was documented, or the date of death from any cause. Follow-up was completed at May 20, 2013. Local and distant progression was scored using clinical and imaging reports and imaging itself when available. Local recurrence was defined as a recurrence in the high-dose treatment volume and a distant recurrence as all recurrences outside this volume. Retrospective toxicity was scored with Common Terminology Criteria for Adverse Events version 4.0, with acute toxicity occurring within 3 months of treatment.

4. Treatment overlap

Two metrics describe the overlap (Fig. 1): Planning target volume (PTV) overlap was the degree of physical overlap of the PTV, which consists of the tumor, pathological lymph nodes and a margin for microscopic disease and uncertainties in the radiotherapy treatment process. The volume of intersection of the first and second PTV was determined and expressed as a percentage of the second PTV. Dosimetric overlap was the overlap between 90% and 50% of the prescribed dose in each treatment plan (90% and 50% isodoses respectively). For example, the volume of intersection of the 90% isodose in the first and second treatment was determined and then expressed as a percentage of the 90% isodose from the second treatment. Analysis of both metrics was carried out after rigid registration on the spine using VelocityAI (v2.8.1, Velocity Medical Solutions, Atlanta, Georgia). If patients did not receive their first treatment at our institution, efforts were made to retrieve the original plan. When available, the digital plan, comprising planning CT and dose distribution was obtained. If this was not available, the first radiation course was reconstructed on the second planning-CT using available information.

5. Statistics

Median OS and EFS in the whole cohort were computed using Kaplan–Meier analysis. Median follow-up was calculated using the reverse Kaplan–Meier method. Median times between first day of reirradiation and known local progression and distant progression were calculated within the subgroup with documented local progression and distant-progression, respectively. Kaplan–Meier analyses were performed to assess whether characteristics of the new tumor and the reirradiation treatment (performance status, new primary or recurrent tumor, stage ≥III versus <III and type of radiotherapy [radiotherapy alone, sequential or concurrent CRT]) were associated with overall survival and event-free survival. Cox regression was used to assess whether age, Charlson comorbidity index and percentage overlap in isodose (50% and 90%) of the two tumors were associated with OS and EFS. Predictors whose distributions were highly non-symmetric (PTV, interval between treatments, percentage overlap in PTV and dose in Gy) were dichotomized using the median as cut-off values and their association with survival was assessed by means of Kaplan–Meier analyses. A p-value of <0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp. Armonk, NY).

6. Results

Baseline patient characteristics are summarized in Table 1, and detailed per patient in Table 2. Thirteen patients (54%) were treated for recurrent disease, and 11 (46%) for a new primary. The median interval between the first and second treatment was 51 months (range: 5–189). Staging prior to reirradiation included a whole-body FDG-PET/CT scan in 92% of patients and a MRI brain in 62%. A diagnostic biopsy was performed in 21/24 patients, one of which was non-diagnostic. The majority (63%) had stage III NSCLC at the time of the initial treatment. Prior to the start of reirradiation, 63% of patients were staged as having 'stage III NSCLC'.

Two patients had stage IV NSCLC at the first treatment, one based on a small contralateral lung lesion and the other on a pathological high cervical lymph node. In both patients, these M1 lesions were considered controlled at the time of retreatment. Two other patients had stage IV disease at reirradiation, one with a solitary brain metastasis (treated with radiosurgery) and the second with axillary lymphadenopathy (included in the reirradiation PTV). At the time of reirradiation, patients underwent sequential CRT (n = 13), concurrent CRT (n = 2) or radiotherapy alone (n = 9), and received a median total radiation dose of 60 Gy (range: 39–66) in a median of 30 fractions (range: 13–33). The median dose of the initial irradiation was 59.8 (range: 24–70) given in a median of 25 fractions (range: 3–35). The median Biologically Equivalent Dose (BED) in 2 Gy/fraction for the two treatments combined was 120 Gy_{10} (range: 84–138). The median PTV overlap volume was 34% (0–97%). Of the 24 patients, only 2 did not exhibit overlap of either the 50% or 90% isodoses. Of the remaining 22 patients, 21 had an overlap that included at least a part of the mediastinum. The median dosimetric overlap volume for 50% and 90% of the prescribed dose was 62% (range: 0–95) and 44% (range: 0–100) respectively.

Median follow-up was 19.3 months (95% CI: 2.8–35.9). At time of analysis 10/24 patients were still alive. Median OS was 13.5