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Computed tomographic features predictive of local recurrence in patients with early stage lung cancer treated with stereotactic body radiation therapy☆

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ABSTRACT

Introduction: The objective of this study is to identify computed tomography (CT) features of local recurrence (LR) after stereotactic body radiation therapy (SBRT) for lung cancer.
Methods: Two hundred eighteen patients underwent SBRT for lung cancer from January 1st, 2006 to March 1st, 2011. Signs of LR recorded: opacity with new bulging margin, opacification of air bronchograms, enlarging pleural effusion, new or enlarging mass, and increased lung density at the treatment site.
Results: A new bulging margin at the treatment site was the only feature significantly associated with LR (P<.005).
Conclusion: Most CT features classically associated with LR following conventional radiation therapy are unreliable for predicting LR following SBRT.

1. Introduction

Stereotactic body radiation therapy (SBRT) is a therapeutic option for patients with Stage I nonsmall cell lung cancer who are medically inoperable or decline surgery [1,2]. The arrangement of radiation portals used is complex and results in the generation of a step radiation gradient, allowing the delivery of high doses of radiation to the targeted tumor volume while minimizing exposure to normal tissues [3]. The use of SBRT to treat inoperable early stage lung cancer has become widespread and has led to reported local control rates of between 80 and 100% [4].

Computed tomography (CT) is routinely used for imaging follow-up of patients following radiation therapy. Patterns of radiation injury on CT resulting from conventional radiation therapy are well described and tend to progress predictably, conforming to the radiation portal [5]. As conventional radiation-induced lung injury evolves, a linear opacity with sharply demarcated borders, traction bronchiectasis and air bronchograms is typical for radiation fibrosis [3]. Once radiation fibrosis has become established, areas that demonstrate new bulging margins, increasing density, filling in of air bronchograms or the development of new parenchymal nodularity all raise suspicion for recurrent disease [3]. After the first 6 months following treatment, a new or increasing pleural effusion is also suspicious for recurrent disease [3].

In patients treated with SBRT, the complex beam arrangements can lead to the development of parenchymal lung abnormalities that differ substantially from those typically seen following conventional radiotherapy [4]. For example, mass-like fibrosis surrounding the treated tumor is a well-described imaging finding following SBRT, which is not classically associated with conventional radiotherapy [6]. In this setting, detecting local recurrence (LR) becomes challenging [6–8]. The aim of this study is to evaluate the ability of features associated with LR on CT following conventional radiation therapy to predict LR following SBRT.

2. Material and methods

This study was exempt from the requirement for informed consent by our institutional review board.

2.1. Patients

Two hundred eighteen consecutive patients underwent SBRT (total dose 4000–6000 cGy delivered in 3–5 fractions over 1–2 weeks) for local control of Stage 1 nonsmall cell lung cancer from January 1st, 2006 to March 1st, 2011. Patients were included in the analysis if they had baseline imaging and three follow-up CTs available for review in

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our institution. Patients with LR were included in analysis if the CT immediately preceding LR was performed within 6 months of the date of LR. No patient received conventional radiation therapy.

2.2. Imaging technique

CT scans were obtained with a 16-detector row (LightSpeed 16; GE Healthcare, Milwaukee) or 64–detector row (VCT; GE Healthcare Milwaukee) scanner, both of which are routinely used in our institution. Parameters for the 16-detector row scanner were as follows: tube voltage, 120 kVp; tube current, 120–380 mA; detector configuration, 16 detectors×1.25-mm section gap; and pitch, 1.375:1. Parameters of the 64-detector row scanner were as follows: tube voltage, 120 kVp; tube current, 120–380 mA; detector configuration, 64 detectors×0.63-mm section gap; and pitch, 0.984:1. The thoracic images were obtained with or without intravenous contrast material during a breath hold. Axial 5×5-mm images and coronal and sagittal plane CT 2.5×2.5-mm images were reconstructed and transferred to the picture archiving and communication system (PACS) server where all images are stored.

2.3. Imaging evaluation

Images were viewed on the institutional PACS (GE Healthcare, Milwaukee). Lung (width, 1500 HU; level, −500 HU) and soft tissue (width, 400 HU; level, 30 HU) window settings were used for CT evaluation. Images were independently retrospectively reviewed by two radiologists (D.H. and S.H.), who were blinded to the clinical history (other than the history of treatment with SBRT). A third radiologist (C.R.) reviewed clinical data, pathological data, and CT and positron emission tomography (PET)-CT images and reports to identify patients who had recurred.

The pretreatment chest CT was initially evaluated. Subsequently, the next three follow-up CTs were studied in the sequence they were performed. A typical follow-up imaging schedule for asymptomatic patients in our institution sees CT performed at 6, 12, and 24 months after SBRT. If a patient becomes symptomatic, this schedule is altered, and patients are imaged at earlier intervals. To minimize the risk of the results of the third CT being false negative, patients who did not have an additional fourth CT performed more than 6 months after the third follow-up study, had the third scan excluded from the analysis.

The following radiologic signs of LR in the SBRT field were recorded on each CT, if present: opacity with a new bulging margin, opacification of previous air bronchograms, new or enlarging pleural effusion, new/increasing mass and subjective increase in lung density in the irradiated field. A new bulging margin was defined as new or persistent convexity at the site of a previous straight margin within the treated lesion compared to the most recent CT. Opacification of previous air bronchograms was defined as new or increasing opacification of previously air-filled air airways compared to the most recent CT. A new mass was defined as a new or persistent lung lesion, separate to the treated lesion, but occurring within 2 cm of the field of SBRT compared to the most recent CT. Subjective increase in lung density was defined as subjective increased attenuation in the treated lesion compared to the most recent CT.

Local failure was determined if there was evidence of recurrence as described by ACOSOG Z4099 (American College of Surgeons Oncology Group randomized phase II study assessing SBRT in Stage 1 lung cancer), defined in that protocol as “the appearance of residual tumor located within the extent of the primary targeted tumor” [9]. LR was confirmed with histopathology if available, or if not available, by the results of PET/CT. PET and CT reconstructed datasets were fused and viewed on the PACS. PET-CT studies obtained after SBRT were compared to the baseline pretreatment CT and PET-CT study, when available. LR was considered present if there was persistent lesional fluorodeoxyglucose (FDG) avidity on PET-CT [standardized uptake value (SUV)>2.5] within an opacity at the site of treatment, more than 6 months following the completion of SBRT [10–12]. The date of histological confirmation was taken as the date of LR if biopsy was performed. If not, the date of PET/CT demonstrating LR was used as the date of LR.

2.4. Statistical methods

Fisher's Exact Test was used to compare features between the scans of patients with LR and the scans of patients without LR for the two readers separately. A P value of <.005 was assumed to be statistically significant. The interreader agreement on categorical feature was assessed using kappa statistic. Kappa (κ) values were interpreted as follows: 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement [13]. A test with P value <.05 was considered significant. Statistical analyses were performed in software packages SAS 9.2 (SAS Institute, Cary, NC, USA) and R Version 2.13 (The R Foundation for Statistical Computing). All numerical values are expressed as median (range).

3. Results

3.1. Patients, imaging schedule, and LR rate

Of the 218 patients who received SBRT, 125 were excluded because their baseline CT and three follow-up CTs were not available for review in our institution. Of the 93 patients remaining, 10 had LR. LR was confirmed in all 10 patients using FDG-PET with an additional 4 patients undergoing biopsy for pathologic confirmation Table 1. The median time to LR was 17 months (range: 4–37) after SBRT.

Two of the LR patients were excluded because the most recent CT available for review was not performed within 6 months of the date of LR. Eight patients with LR and 83 patients without LR were thus included in the analysis. The CT closest to the date of LR was performed at a median of 1 month (range: 0–6 months) from the date of LR. Of the 83 patients without LR, 41 did not have a fourth follow-up CT more than 6 months after their third follow-up CT. These patients had their third follow-up CT excluded from the analysis, leaving 208 evaluable CT events without LR. Median time to the first follow-up CT was 6 months (range: 3–12), median time to second follow-up CT was 13 months (range: 6–19), and median time to the third follow-up CT was 24 months (range: 16–41).

Median patient age was 81 years (range: 54–99). Tumor pathology was adenocarcinoma in 61 (66%) cases and squamous cell carcinoma in 32 (34%) cases. During the study period, eight patients developed distant metastases (three lung, three thoracic nodal, one adrenal, and one osseous).

3.2. CT features

Table 2 summarizes the CT features of recurrence which were identified on the examination closest to the diagnosis of LR. A new bulging margin at the site of treated tumor was the only feature that was statistically significantly associated with LR (P<.005). Both readers identified this feature in four (50%) patients with LR. A bulging margin was identified in 19 (9%) patients without LR by Reader 1 and in 21 (10%) patients by Reader 2. Density increase and filled-in air bronchograms were both more common in patients with LR, but the presence of neither feature reached statistical significance.

All three features that were more common in patients with LR were also frequently found in patients without LR. In the group without LR, a new bulge was found in up to 10% of patients, filled-in air bronchograms in up to 13% of patients, and density increase in up to 33% of patients.