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Scientific Article

Implications for high-precision dose radiation therapy planning or limited surgical resection after percutaneous computed tomography-guided lung nodule biopsy using a tract sealant

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Abstract

Purpose: Precision radiation therapy such as stereotactic body radiation therapy and limited resection are being used more frequently to treat intrathoracic malignancies. Effective local control requires precise radiation target delineation or complete resection. Lung biopsy tracts (LBT) on computed tomography (CT) scans after the use of tract sealants can mimic malignant tract seeding (MTS) and it is unclear whether these LBTs should be included in the calculated tumor volume or resected. This study evaluates the incidence, appearance, evolution, and malignant seeding of LBTs.

Methods and materials: A total of 406 lung biopsies were performed in oncology patients using a tract sealant over 19 months. Of these patients, 326 had follow-up CT scans and were included in the study group. Four thoracic radiologists retrospectively analyzed the imaging, and a pathologist examined 10 resected LBTs.

Results: A total of 234 of 326 biopsies (72%, including primary lung cancer [n = 98]; metastases [n = 81]; benign [n = 50]; and nondiagnostic [n = 5]) showed an LBT on CT. LBTs were identified on imaging 0 to 3 months after biopsy. LBTs were typically straight or serpiginous with a thickness of 2 to 5 mm. Most LBTs were unchanged (92%) or decreased (6.3%) over time. An increase in

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LBT thickness/nodularity that was suspicious for MTS occurred in 4 of 234 biopsies (1.7%). MTS only occurred after biopsy of metastases from extrathoracic malignancies, and none occurred in patients with lung cancer.

Conclusions: LBTs are common on CT after lung biopsy using a tract sealant. MTS is uncommon and only occurred in patients with extrathoracic malignancies. No MTS was found in patients with primary lung cancer. Accordingly, potential alteration in planned therapy should be considered only in patients with LBTs and extrathoracic malignancies being considered for stereotactic body radiation therapy or wedge resection.

Introduction

Improvements in radiation techniques and delivery, including stereotactic body radiation therapy (SBRT), 3-dimensional conformal radiation therapy (CRT), intensity modulated radiation therapy, and proton therapy, have improved local control (LC) and survival in patients with non-small cell lung cancer (NSCLC).[1-7] In this regard, SBRT allows for the delivery of high therapeutic dose to the tumor, decreased radiation dose to normal tissue, and improved local tumor control rates.[8-10] In fact, SBRT achieves LC rates of 80% to 95%[5,6] and is now being used more frequently with curative intent in patients with early stage NSCLC.[7] In addition, SBRT is being used instead of surgical resection to treat metastases from extrathoracic malignancies.[7,11-15]

SBRT, 3-dimensional CRT, and intensity modulated radiation therapy have steep dose gradients that allow for the delivery of a highly precise therapeutic radiation dose conformed to the shape of the tumor. However, because the target volume is typically small and breathing motion may affect the location of the tumor in the thorax, tumor volume delineation must be accurate.

A potential dilemma in calculating accurate tumor volume is whether to include the visible and persistent tract that often occurs when a patient undergoes a pretherapy transthoracic needle aspiration biopsy with a tract sealant system. In this newer transthoracic biopsy technique, a hydrogel plug is injected while withdrawing the needle at the completion of the biopsy procedure to decrease the incidence of pneumothoraces, the most common complication of transthoracic lung biopsy.[16-18] The resulting biopsy tract can be visible within the lung parenchyma on follow-up chest computed tomography (CT) and/or ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET) CT imaging and can potentially mimic malignant tract seeding. This could result in a larger gross tumor volume (GTV) and planning target volume (PTV) or larger limited resection in those patients undergoing wedge resection.

The purpose of this study was to evaluate the incidence, appearance, temporal relationship to procedure performance, and evolution of visible biopsy tracts and the incidence of malignant seeding of these tracts.

Methods and materials

Patient selection

We retrospectively reviewed our database and obtained the records of 406 consecutive CT-guided transthoracic needle aspiration biopsies of lung nodules performed using the BioSentry Tract Sealant System (Surgical Specialties Corp, Braintree, MA) from June 2013 to December 2014 at a single institution. The eligibility criteria also required chest CT and/or ^{18}FDG PET CT imaging after the procedure and no surgical or radiation therapy prior to follow-up cross-sectional imaging. A total of 326 patients met the inclusion criteria, and 80 patients were excluded because of nodule resection after the procedure and before follow-up imaging (n = 18 of 406; 4%), radiation therapy after the biopsy (n = 4 of 406; 1%), or absence of follow-up CT imaging (n = 58 of 406; 14%). This study was approved by the institutional review board and was performed in compliance with the Health Insurance Portability and Accountability Act.

CT and image analysis

Follow-up imaging with chest CT and/or ^{18}FDG PET/CT was obtained in 326 cases per clinical treatment protocols. CT imaging was performed with multiple scanners from 2 vendors (LightSpeed plus, LightSpeed 16, LightSpeed VCT, 750 HD from GE Healthcare, Little Chalfont, United Kingdom; Somatom Definition Flash from Siemens, Munich, Germany). PET/CT imaging was performed with multiple scanners from 2 vendors (Discovery PET/CT 710, Discovery RX VCT and Discovery STE from GE Healthcare; Biograph mCT Flow from Siemens). Axial, coronal, and sagittal reconstructed images with 2 to 2.5 mm collimation were available for review.

Four fellowship-trained thoracic radiologists with 20 years, 18 years, 8 years, and 6 years of clinical experience retrospectively interpreted the imaging studies to determine the incidence, appearance, temporal relationship to the biopsy, and evolution of biopsy tracts. The following parameters were recorded: patient's primary malignancy;

nodule location; biopsy result; presence or absence of a visible tract along the needle biopsy path; location, length, thickness, continuous versus interrupted course, contour, and margination of the tract; timing of follow-up imaging; and FDG avidity if follow-up PET/CT was available. Biopsy tracts in cases in which the biopsied lesions were benign were considered benign. Tracts that decreased or did not change on follow-up imaging >6 months after biopsy were considered benign. Conversely, tracts that increased in size or nodularity after biopsy were considered malignant.

Pathologic analysis

A dedicated thoracic oncology pathologist with 27 years of experience retrospectively examined the tissue blocks of 10 resected cases with documented LBTs.

Statistical analysis

The statistical analysis of the data included calculation of confidence intervals (CIs) and 2-sided Fisher's exact test.

Results

A total of 326 cases met the inclusion criteria and were analyzed (primary lung cancer [n = 98], metastases [n = 81], benign nodule [n = 50], and nondiagnostic [n = 5]). A visible biopsy tract on CT within the lung parenchyma created by the injection of a self-expanding hydrogel plug occurred in 234 of 326 patients (72%; 95% CI, 0.6656-0.7660). The incidence of a visible tract was independent of biopsy results, occurring in 0.7183 of benign biopsies (95% CI, 0.599-0.819) and in 0.7479 of malignant biopsy results (95% CI, 0.6883-0.8013).

When present, tracts were identified on the first follow-up imaging 0 to 3 months after the biopsy. The tracts were lobulated (n = 129; 55%) or smooth (n = 105; 45%) and straight (n = 95), serpiginous (n = 71), or a combination of straight and serpiginous (n = 166). Analyzed biopsy tracts had a mean thickness of 2.9 mm (range, 1-10 mm). Metastatic tracts reached an average of 12.5 mm in greatest thickness (range, 10-15 mm). Mean tract length was 25.2 mm (range, 3-66 mm). The majority of tracts extended completely from the pleural surface to the lesion (n = 143; 61%), but 91 of 234 tracts (39%) were incomplete.

The tracts were followed for a mean of 15 months (range, 8-25 months). The majority remained stable in appearance (n = 215 of 234; 92%), but the others decreased (n = 15 of 234; 6.3%) or increased in thickness (n = 4 of 234; 1.7%). The increase in tract thickness was documented as early as 57 days (mean: 91 days; range, 57-126 days) and occurred only with extrathoracic malignancies (sarcoma [n = 1], colon cancer [n = 1], renal cell carcinoma [n = 1], melanoma [n = 1]). Additionally, the increase in tract thickness only occurred in patients who had an increase in metastatic disease after biopsy. This increase in tract thickness or nodularity was considered positive for malignant tract seeding. No biopsy tracts in primary lung cancer biopsies increased in thickness.

A total of 147 patients underwent PET/CT imaging after biopsy. The ^{18}FDG uptake in the analyzed biopsy tracts had a mean maximum standardized uptake value (SUV_{max}) of 0.91 (range, 0.6-2.35). None of the tracts with malignant seeding had follow-up PET/CT imaging.

Ten malignancies (5 primary NSCLCs, 5 metastases) with visible biopsy tracts were surgically resected, and none of the resected cases showed malignant tract seeding on histology.

Discussion

A percutaneous biopsy of pulmonary nodules is often clinically necessary to establish a diagnosis and obtain tissue for immunohistochemical analysis to guide targeted therapy. Complications of lung biopsy include pneumothorax, parenchymal hemorrhage, air embolism, and malignant seeding of the biopsy needle track.[18] Pneumothorax is the most common complication, and tract sealant systems have been developed as a method of decreasing the incidence after lung biopsy. The procedure involves injection of a self-expanding hydrogel plug into the pleural space during withdrawal of the biopsy needle to seal the pleural puncture site. The hydrogel plug is made of a biodegradable synthetic polymer and is designed to be resorbed by the body from the pleural space.

In this study, transthoracic needle biopsies were performed using the BioSentry Tract Sealant System because its efficacy in reducing the number of biopsy-related pneumothoraces and chest-tube placements has been validated in other trials.[16,19] Although the injected plug is 2.5 cm in length and is deposited peripherally, this study shows that the injection of the hydrogel plug commonly results in a visible and persistent tract within the lung parenchyma that can mimic tumor cell dissemination along the biopsy needle tract.

Tumor dissemination along a biopsy needle track is a rare complication of transthoracic percutaneous biopsy, occurring in <1% of biopsies in the thorax.[18,20-23] There is no association between needle size, tumor size or location, and the incidence of malignant seeding of a needle track in the lungs.[22] However, histology of the tumor does constitute a risk factor because tumor seeding is more frequent (up to 4% of biopsies) in malignant pleural mesothelioma compared with other thoracic malignancies after transthoracic biopsy.[24] None of the 98 patients with biopsy tracts related to biopsy of primary lung cancers had malignant tract seeding. The absence of malignant tract seeding after percutaneous biopsy of primary lung cancers in our study

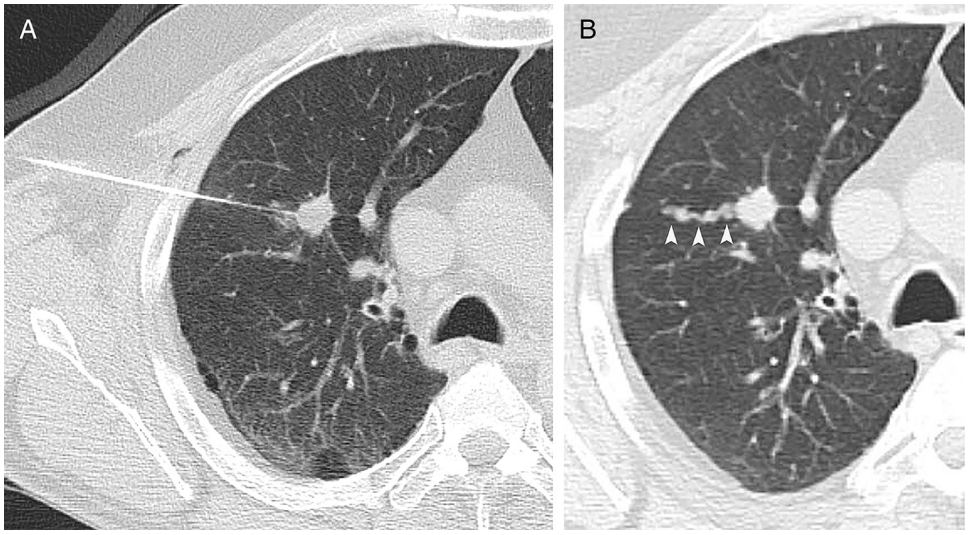

Figure 1 A 70-year-old man with non-small cell lung cancer who had a computed tomography (CT)-guided transthoracic biopsy and injection of a hydrogel plug to prevent pneumothorax. (A) Axial CT image shows the biopsy needle path; (B) Axial CT image 3 months after (A) shows a serpiginous tract within the lung parenchyma along the path of the biopsy needle (arrowheads). The tract remained unchanged on follow-up imaging 12 months later (not shown).

correlates with the lung biopsy seeding rate in the published literature (0.012%).[22]

In terms of malignant tract seeding, this study shows that a visible biopsy tract is rarely due to malignant tract seeding although a visible tract is common (72%) on CT after percutaneous lung biopsy with a biopsy tract sealant (Fig 1). These biopsy tracts typically extended from the pleural surface to the lesion; most (92%) were unchanged over time (mean follow up: 15 months), although 6.3% decreased in thickness and 4 (1.7%) increased in thickness and/or nodularity. The increase in thickness and/or nodularity of the tracts occurred only in the setting of biopsy of metastases from extrathoracic primary malignancies (renal cell carcinoma, colon carcinoma, sarcoma, and melanoma) in patients who had an increase in metastatic disease after biopsy.

In 3 of these patients, the change in the tract was considered to be due to malignant tract seeding because of a continued increase in thickness and/or nodularity on serial CT imaging (Fig 2) and a concomitant overall increase in metastatic disease. The increase in thickness and/or nodularity of the tracts was documented on serial CT imaging (mean: 10.8 months; range, 7-15.5 months) until patient death from progressive metastatic disease. In the fourth patient with melanoma, the tract increased from 1 mm in thickness to a 12-mm nodular tract at 2 months after the biopsy. The tract decreased in thickness and nodularity after commencement of monoclonal antibody therapy with ipilimumab (Yervoy, Bristol-Myers Squibb Company, New York, NY), and this occurred in association with response of the primary malignancy and metastases to therapy.

FDG PET/CT imaging was not performed in any of the 4 patients with malignant seeding of the biopsy tract. However, the 147 patients with visible biopsy tracts who underwent PET/CT imaging had little or mild background FDG activity along the tracts. Accordingly, if PET/CT is performed, the presence of FDG uptake greater than background or increasing SUV values over time in the tract should be considered suspicious for metastatic seeding.

Although rare, tumor seeding in a lung biopsy tract can alter the primary tumor designation (T descriptor) in tumor node metastasis staging. Additionally, there are potential management and therapeutic implications in those patients who are considered candidates for limited surgical resection or radiation therapy that requires precise target delineation, such as SBRT.[20,21] In this regard, although surgical resection is the treatment of choice for early stage NSCLC, up to 29% of patients with early stage NSCLC have moderate to severe comorbidities that may preclude lobar resection.[25] These patients are increasingly being treated with high-precision dose radiation therapy such as SBRT because this achieves LC and overall survival (OS) rates that are comparable with those of lobectomy or wedge resection in nonrandomized studies of medically inoperable or elderly patients with early stage NSCLC after adjusting for age and operability between patients.[7,14,26,27]

This adjustment is necessary because there is a substantial difference between median age and operability between patients treated with SBRT and video-assisted thoracoscopic surgery (VATS) and SBRT trials having significantly older patients and fewer operable patients. In a recent meta-analysis comparing OS and disease-free survival between VATS and SBRT in patients with stage I and II NSCLC (13 VATS studies [3436 patients], 24 SBRT studies [4433 patients]), OS and disease-free survival did

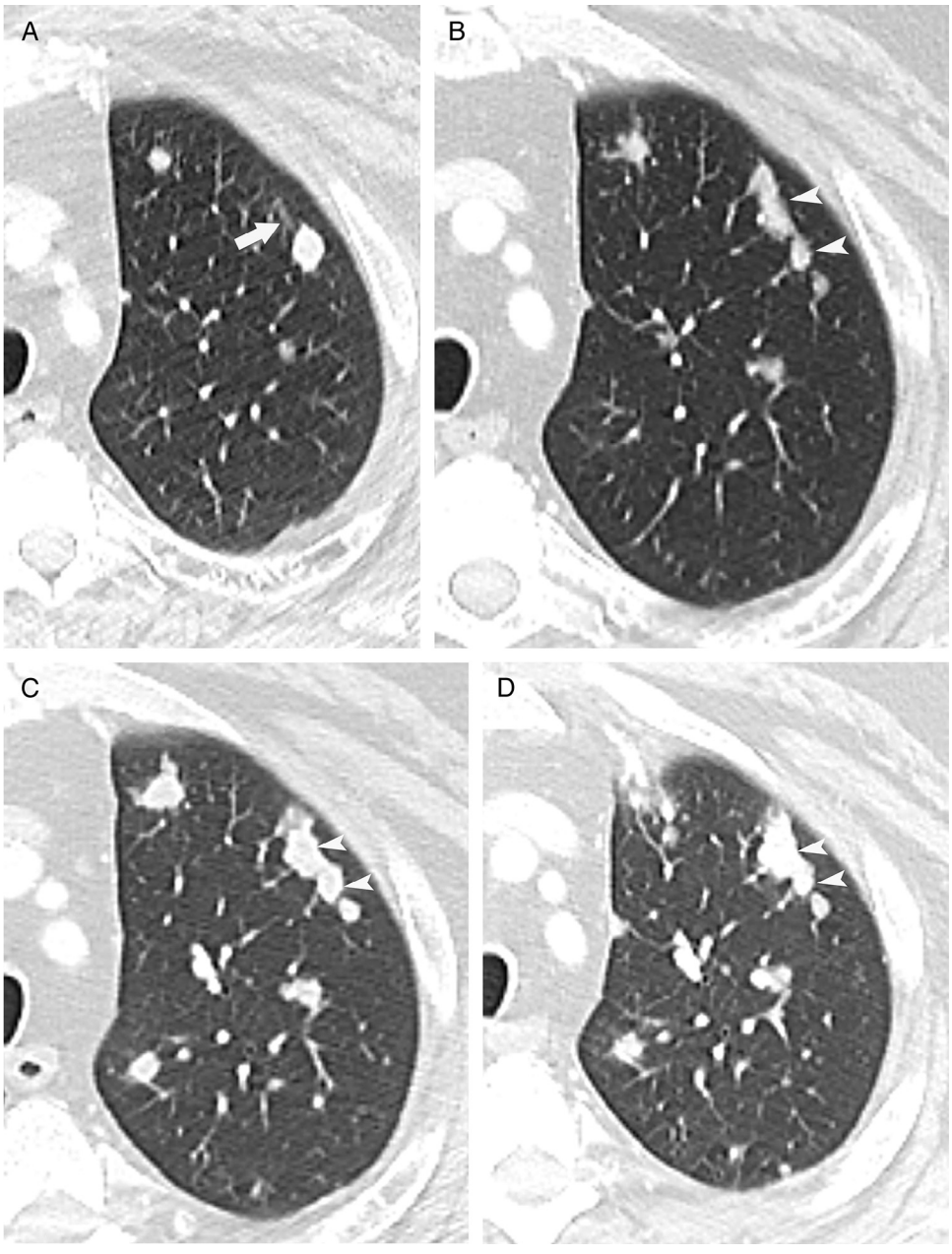

Figure 2 A 65-year-old man with metastatic renal cell carcinoma with an increase in thickness and nodularity of a biopsy tract consistent with malignant seeding. (A) Axial computed tomography (CT) image 6 weeks after biopsy shows a linear tract (arrow) that corresponded to the biopsy needle path. (B) Axial CT image 7 months after (A) shows thickening and nodularity of the tract (arrowheads). (C) Axial CT image 11 months after (A) shows increasing thickening and nodularity of the tract (arrowheads). (D) Axial CT image 14 months after (A) shows further thickening and nodularity of the tract (arrowheads). Note the overall increase in the size and number of lung metastases.

not differ significantly after adjustment for age and operability.[28] However, in a propensity-matched comparative analysis between patients with clinical stage Ia NSCLC undergoing wedge resection (with or without brachytherapy) or SBRT, overall recurrence (local and distant) was significantly higher after SBRT (SBRT: 30%; wedge: 9%; $P = .016$).[29] Additionally, recurrence-free 3-year survival was significantly better after wedge resection (88% vs 72%; $P = .001$), although there was no difference between the 2 groups in disease-free 3-year survival (77% vs 59%; $P = .066$]).

However, a pooled analysis of 2 randomized trials comparing SABR with surgery in operable patients with early stage NSCLC showed that 5-year local recurrence rates and OS were comparable in both groups, but surgery resulted in an increased rate of procedure-related mortality and

morbidity compared with SABR (30- to 90-day postoperative mortality for VATS lobectomy 2%; open thoracotomy lobectomy, 5.4%; SABR 0.7%).[7] These findings suggest that although lobar resection is the current standard of care for patients with medically operable early stage NSCLC, SBRT is comparable with surgery in patients with early stage NSCLC. Similarly, in patients with peripheral lung metastases and limited oligometastatic disease, SBRT achieves high LC.[30,31]

Importantly, SBRT with a high LC rate and low toxicity has become the new standard of care for medically inoperable patients with stage 1 NSCLC and for those who refuse surgical intervention. It is increasingly being used as a curative treatment option in these patients.[12,25,28,32-35]

In patients with stage 1 NSCLC who are candidates for SBRT, precise target delineation is required. Knowledge that a biopsy tract is often created by using a tract sealant and can mimic tumor cell dissemination along the biopsy needle path (although tract seeding is highly unlikely in patients with NSCLC) can be important in determining appropriate target delineation before radiation therapy. In this regard, the findings of our study are potentially clinically important in the appropriate planning of radiation therapy and the determination of GTV and PTV or in patients who are considered for limited surgical resection.

In patients with NSCLC, the presence of a biopsy tract should not alter the planned management. However, because malignant biopsy tract seeding can occur after biopsy of lung metastases from extrathoracic primary malignancies, therapy may need to be altered to maintain the high LC rates of these procedures. Specifically, when there is development of nodularity and/or increasing thickness of the biopsy tract in patients who are candidates for SBRT or wedge resection, an increase in the GTV and PTV to encompass the tract or a larger excision, respectively, may need to be performed.

Conclusions

A visible biopsy tract on CT is common after percutaneous lung biopsy with a tract sealant. However, malignant seeding of the tract is uncommon and in this study occurred only after biopsy of lung metastases from extrathoracic primary malignancies. Awareness of this manifestation of lung biopsies with a tract sealant is important in patients who are candidates for focused radiation therapy such as SBRT or for limited resection because an alteration in therapy should only be considered when there is a continued increase in thickness and/or nodularity of the biopsy tract or if the tract is FDG avid on PET/CT imaging.

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