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...
In this regard, SBRT achieves improved local tumor control rates. In fact, SBRT allows for the delivery of high therapeutic dose to the tumor, decreased radiation dose to normal tissue, and improved local tumor control rates. SBRT achieves LC rates of 80% to 95% and is now being used more frequently with curative intent in patients with early stage NSCLC.

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 conformal 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. The resulting biopsy tract can be visible within the lung parenchyma on follow-up chest computed tomography (CT) and/or 18fluorodeoxyglucose (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.

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.

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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).

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. In fact, SBRT achieves LC rates of 80% to 95% and is now being used more frequently with curative intent in patients with early stage NSCLC. In addition, SBRT is being used instead of surgical resection to treat metastases from extrathoracic malignancies.

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 conformal 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.

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 18FDG 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 18FDG 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;
Pneumothorax is the most common complication after lung biopsy. Histology of the tumor does constitute a risk factor because tumor seeding is more frequent (up to 4%) in malignant pleural mesothelioma compared with other thoracic malignancies after transthoracic biopsy. 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 tract. 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. 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 tract is a rare complication of transthoracic percutaneous biopsy, occurring in <1% of biopsies in the thorax. There is no association between needle size, tumor size or location, and the incidence of malignant seeding of a needle tract in the lungs. 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. 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

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 18FDG uptake in the analyzed biopsy tracts had a mean maximum standardized uptake value (SUVmax) 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
correlates with the lung biopsy seeding rate in the published literature (0.012%).

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. 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. 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.

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
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%; \( P = .016 \)). 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...
These findings suggest that Rosenthal SA, Bittner NH, Beyer DC, et al. American Society Bentzen SM, Saunders MI, Dische S. From CHART to CHARTWEL Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell NSCLC. Similarly, in patients with peripheral lung metastases and limited oligometastatic disease, SBRT achieves high LC.

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.

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 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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References

1. Wang S, Liao Z, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys. 2006;66:1399-1407.
2. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys. 2005;63:324-333.
3. Chen M, Hayman JA, Ten Haken RK, Tatro D, Fernando S, Kong FM. Long-term results of high-dose conformal radiotherapy for patients with medically inoperable T1-3N0 non-small-cell lung cancer: Is low incidence of regional failure due to incidental nodal irradiation? Int J Radiat Oncol Biol Phys. 2006;64:120-126.
4. Chen GY, Jiang GL, Qian H, et al. Escalated hyperfractionated accelerated radiation therapy for locally advanced non-small cell lung cancer: A clinical phase II trial. Radiother Oncol. 2004;71:157-162.
5. Manon RR, Jaradat H, Patel R, et al. Potential for radiation therapy technology innovations to permit dose escalation for non-small cell lung cancer. Clin Lung Cancer. 2005;7:107-113.
6. Bentzen SM, Saunders MI, Dische S. From CHART to CHARTWEL in non-small cell lung cancer: Clinical radiobiological modelling of the expected change in outcome. Clin Oncol (R Coll Radiol). 2002;14:372-381.
7. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: A pooled analysis of two randomised trials. Lancet Oncol. 2015;16:630-637.
8. Fang LC, Komaki R, Allen P, Guerrero T, Mohan R, Cox JD. Comparison of outcomes for patients with medically inoperable Stage I non-small-cell lung cancer treated with two-dimensional vs. three-dimensional radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:108-116.
9. Bradley JD, Ieumwananonthachai N, Purdy JA, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiotherapy for non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys. 2002;52:49-57.
10. Rosenzweig KE, Fox JL, Yorke E, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. Cancer. 2005;103:2118-2127.
11. Rosenthal SA, Bittner NH, Beyer DC, et al. American Society for Radiation Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the transperineal permanent brachytherapy of prostate cancer. Int J Radiat Oncol Biol Phys. 2011;79:335-341.
12. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. Med Phys. 2010;37:4078-4101.
13. Armstrong JG, Minsky BD. Radiation therapy for medically inoperable stage I and II non-small cell lung cancer. Cancer Treat Rev. 1989;16:247-255.
14. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): Outcomes of a propensity score-matched analysis. Ann Oncol. 2013;24:1543-1548.
15. Baumann P, Nyman J, Hoyer M, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer—a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. *Radiother Oncol*. 2008;88:359-367.

16. Ahrar J, Ensor J, Mahvash A, et al. Efficacy of a self-expanding tract sealant device in the reduction of pneumothorax and chest tube placements rates after percutaneous lung biopsy: A matched controlled study using propensity score analysis. *Cardiovasc Intervent Radiol*. 2017;40:270-276.

17. Kuban JD, Tan AL, Huang SY, et al. The effect of needle gauge on the risk of pneumothorax and chest tube placement after percutaneous computed tomographic (CT)-guided lung biopsy. *Cardiovasc Intervent Radiol*. 2015;38:1595-1602.

18. Wu CC, Maher MM, Shepard JA. Complications of CT-guided percutaneous needle biopsy of the chest: Prevention and management. *AJR Am J Roentgenol*. 2011;196:W678-W682.

19. Grage RA, Keogh S, Naveed M. Comparison analysis pre and post implementation of a BioSentry tract sealant system after percutaneous transthoracic CT guided needle biopsy. *J Vasc Intervent Radiol*. 2015;26:S149.

20. Tyagi R, Dey P. Needle tract seeding: An avoidable complication. *Diagn Cytopathol*. 2014;42:636-640.

21. Voravud N, Shin DM, Dekmezian RH, Dimery I, Lee JS, Hong WK. Implantation metastasis of carcinoma after percutaneous fine-needle aspiration biopsy. *Chest*. 1992;102:313-315.

22. Ayar D, Golla B, Lee JY, Nath H. Needle-track metastasis after transthoracic needle biopsy. *J Thorac Imaging*. 1998;13:2-6.

23. Tomiyama N, Yashahara Y, Nakajima Y, et al. CT-guided needle biopsy of lung lesions: A survey of severe complication based on 9783 biopsies in Japan. *Eur J Radiol*. 2006;59:60-64.

24. Agarwal PP, Seely JM, Matzinger FR, et al. Pleural mesothelioma: Sensitivity and incidence of needle track seeding after image-guided biopsy versus surgical biopsy. *Radiology*. 2006;241:589-594.

25. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys*. 2012;84:1060-1070.

26. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: Can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys*. 2011;81:1352-1358.

27. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol*. 2010;28:928-935.

28. Ma L, Xiang J. Clinical outcomes of video-assisted thoracic surgery and stereotactic body radiation therapy for early-stage non-small cell lung cancer: A meta-analysis. *Thorac Cancer*. 2016;7:442-451.

29. Port JL, Parashar B, Osakwe N, et al. A propensity-matched analysis of wedge resection and stereotactic body radiotherapy for early stage lung cancer. *Ann Thorac Surg*. 2014;98:1152-1159.

30. Norihisa Y, Nagata Y, Takayama K, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. *Int J Radiat Oncol Biol Phys*. 2008;72:398-403.

31. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol*. 2009;27:1579-1584.

32. Crino L, Weder W, van Meerbeeck J, Felip E. ESMO Guidelines Working Group. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v103-v115.

33. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys*. 2010;76:326-332.

34. Buyyounouski MK, Balter P, Lewis B, et al. Stereotactic body radiotherapy for early-stage non-small-cell lung cancer: Report of the ASTRO Emerging Technology Committee. *Int J Radiat Oncol Biol Phys*. 2010;78:3-10.

35. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: A meta-analysis. *Int J Radiat Oncol Biol Phys*. 2014;90:603-611.