Original Article

A study of imprint cytology in computerized tomography-guided coaxial core biopsies of the lung and mediastinal lesions

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ABSTRACT

Background: Image-guided core biopsy (CB) is a reliable technique for the diagnosis of various deep-seated lesions. It allows precise localization and documentation of the biopsy needle and target lesions. CB imprint cytology (IC) is a rapid, reliable, and accurate technique which enhances the known benefits of CB. **Aims:** The aim of this study was to study the diagnostic accuracy of IC when performing computerized tomography (CT)-guided coaxial CB of lung and mediastinal lesions and to assess whether it could optimize the biopsy procedure. **Methodology:** A total of 30 CT-guided core biopsies with imprint smears were studied. All biopsies were performed using 18 gauge coaxial needle and spring loaded gun. On-site assessment for the adequacy of the sample was done by the pathologist after staining with toluidine blue. The imprint smears were compared with the histopathology (HP) of CB specimens and the accuracy, sensitivity, specificity, and positive and negative predictive values were evaluated. **Results:** The overall accuracy of IC when compared to the HP was 96.7%, with a sensitivity of 100%, specificity of 85.7%, positive predictive value of 95.8%, and negative predictive value of 100%. The value of $P < 0.001$. **Conclusion:** With an on-site approach, IC helps to assess the adequacy of the sample and reduce the number of passes and the possibility of redo procedures. Since the sensitivity of IC is high, it provides a valuable lead time to the clinician, for planning the management protocols, before a final histopathological diagnosis is available.

Key words: Computerized tomography-guided, core biopsy, imprint cytology, mass lesions

INTRODUCTION

Image-guided core biopsy (CB) is a reliable technique for the diagnosis of various deep-seated lesions. Image-guided transthoracic CB, using fluoroscopic, computerized tomography (CT), or ultrasonographic guidance, is a well-established and safe method for diagnosing malignant and benign thoracic lesions.[1]

Despite the high diagnostic accuracy of transthoracic CB, specimens inadequate for histological analysis have been encountered in up to 15% of grossly adequate specimens.[2] Intraoperative cytology of touch preparations has been used as an alternative to frozen section since it was first reported in 1927.[3,4] With the exception of intraoperative diagnosis, imprint cytology (IC) has been used to obtain a rapid diagnosis for intra-abdominal lesions and CB of the breast, as well as bronchoscopic forcep biopsies.[5-7]

However, data regarding IC and transthoracic needle biopsy (TNB) are very limited.[8] Paulose *et al*.[9] showed that IC could assist rapid diagnosis of lung cancer metastasis in mediastinal lymph nodes following CT-guided TNB. Liao *et al*.[10] demonstrated improved diagnostic accuracy by using IC following ultrasound-guided TNB of peripheral lung lesions.

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Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.182052

Cite this article as: Satish S, Shivalingaiah SC, Shivashimpi DK, Manjunath GV. A study of imprint cytology in computerized tomography-guided coaxial core biopsies of the lung and mediastinal lesions. Clin Cancer Investig J 2016;5:230-5.

CBIC is a rapid, reliable, and accurate technique which enhances the known benefits of CB. It allows core biopsies to be used successfully in the "one-stop" clinic setting and obviates the need to use fine needle aspiration cytology (FNAC).[11] When CBIC is used, there is a reduction in diagnostic waiting time (over CB on its own) and an increase in diagnostic performance (over FNAC).[11] As an adjunct to the histopathology (HP) of CB specimens, IC helps to guarantee that the specimens obtained adequately represent the lesion.[10] This translates to an improvement in the management of patients with cancer through the earlier availability of the diagnosis and fewer outpatient appointments.[11]

In this study, the diagnostic accuracy of IC for CT-guided transthoracic coaxial CB was evaluated, and the correlation between cytological and histological results was assessed, to verify the role and reliability of IC during the conduct of core biopsies.

METHODOLOGY

All patients with an image confirmed the diagnosis of mass lesion were included in the study. Patients with vascular lesions or lesions of <1 cm in diameter were excluded. The present study was approved by the Institutional Ethics Committee of the JSS Medical College and Hospital, Mysore.

Detailed information including the necessity of the procedure, methodology, possible complications, and how these complications would be treated were explained to each patient. An informed consent was taken from all the patients. Prior to the biopsy procedure, platelet counts, prothrombin time, and international normalized ratio of all the patients were tested.

A CT scan was done to localize the lesion to be biopsied. Lesion size was measured along the maximum long axis diameter. All biopsy procedures were performed under aseptic precautions, under local anesthesia (2% lignocaine) using 18 gauge coaxial needle and spring loaded gun (Angiotech). This system consists of inserting a thin inner needle through a larger outer needle placed at the edge or within the lesion. Coaxial needle was correctly positioned into the lesion. Check scan was done to localize the traverse of the needle in the lesion [Figure 1a and b]. Three to four cores were taken using the spring loaded gun depending on the size of the mass, its vascularity, and adequacy as assessed on IC. Most biopsy procedures were performed with a single pleural puncture. At the end of the biopsy procedure, check CT scans were obtained to detect pneumothorax or hemorrhage.

The patients were observed in the ward for any increasing air leak if pneumothorax was detected. In the event of respiratory distress, oxygen supplementation would be given and with worsening air leak, intercostal drain (ICD) would be inserted. In patients having pulmonary hemorrhage, conservative treatment with cough suppressants was given as hemorrhages would resolve by itself. In severe cases, hemostatic therapy would be instituted. However, no patient required ICD or hemostatic therapy.

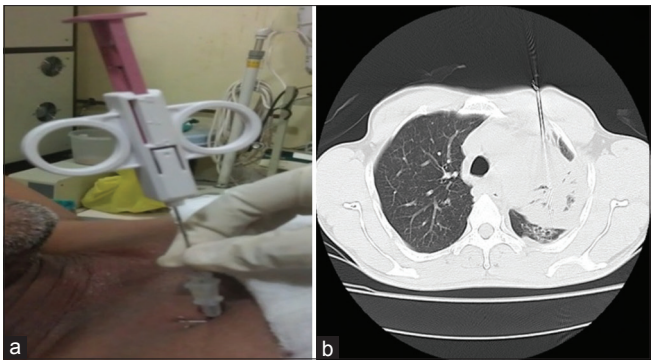

Figure 1: (a and b) Computerised tomography guided core biopsy of lung mass

Four to six imprint smears were made by lightly touching biopsy specimens against slides, which were air-dried, alcohol fixed, and evaluated using May Grunwald giemsa, Papanicolaou, hematoxylin, and eosin stains. The tissue specimens were then placed in 10% formalin for histopathological examination. On-site assessment for the adequacy of the sample was done by the pathologist after staining with toluidine blue. All imprint smears were reviewed by the pathologist, before the final histopathological diagnosis. Cytological diagnoses were classified into one of four categories: Inadequate specimen; negative for malignancy; suspicious for malignancy; or positive for malignancy.

Inadequate specimens were defined as <100 cells (alveolar macrophages and/or pulmonary epithelial cells) in a smear without neoplastic cells. Negative for malignancy was when there were no malignant cells, and the specimen was adequate. IC in the absence of unequivocal malignant cells but with some atypical features was classified as suspicious for malignancy. A benign diagnosis was suggestive of a negative result.

A true-positive result for malignancy was when HP was that of malignancy. A true negative result was when HP was negative for malignancy. A suspicion of malignancy on IC was considered as true positive, if the final diagnosis was malignant and as false positive if the final diagnosis was benign. A false-negative result for IC was considered when IC of the biopsy specimen showed no malignancy, but the final diagnosis was malignant.

The results of cytological analysis of imprint smears and histopathological analysis of biopsy specimens were

compared, and the accuracy, sensitivity, specificity, and positive and negative predictive values were evaluated. A statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 Systat 12.0, and R environment version 2.11.1 (IBM, USA) was used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs and tables. $P < 0.05$ was considered statistically significant.

RESULTS

In this study, of thirty cases, 23 cases (76.6%) were lung lesions and seven (23.4%) were mediastinal masses.

Most of these patients were in the fifth and sixth decade with a male to female ratio of 1.73:1.

Lung

Of the 23 lesions, 16 (69.6%) were neoplastic and seven (30.4%) were nonneoplastic. All the neoplastic cases were malignant. Out of the sixteen malignant lesions, the most common category was nonsmall cell carcinoma with twelve cases, accounting for 75% [Table 1]. A specific diagnosis was possible on IC in two cases of round cell tumors, nine cases of nonsmall cell carcinoma (as squamous cell carcinomas [Figure 2a and b] and adenocarcinomas) and two cases of small cell carcinomas.

In the remaining three cases, a diagnosis of malignancy was made on IC. On HP of CB, the tumor cells were poorly differentiated, and immunohistochemistry (IHC) was recommended for further categorization.

Nonneoplastic lesions

On IC, specific diagnosis was possible in only two cases of lung abscess. In the rest of the five cases, a specific diagnosis was not possible as the IC smears contained fibro-collagenous tissue, macrophages, and mixed inflammatory cells. HP was necessary to arrive at a final diagnosis [Table 2].

However, one case each of chronic granulomatous lesion and nonspecific inflammatory lesion diagnosed on CB later turned out to be Wegener's granulomatosis [Figure 3a and b] after serological tests. These were strongly positive for perinuclear antineutrophil cytoplasmic antibody.

One false positive case was diagnosed. On IC, the diagnosis of malignancy was offered, which turned out to be tuberculosis on HP. The presence of inflammatory atypia on IC was over diagnosed as malignancy [Figure 4a and b].

Mediastinum

Of the seven neoplastic lesions studied, two were benign and five malignant tumors. IC correlated with HP in all the cases [Table 3].

Correlation of imprint cytology with histopathology

Out of the 30 cases, IC correlated with HP in 29 cases (96.7%) [Tables 4 and 5].

DISCUSSION

The role of percutaneous TNB in the evaluation of pulmonary lesions was first reported in 1883 by Leyden[12] However, interventional radiologists are sometimes not sufficiently confident that the tissue cores obtained are adequate by gross inspection. The reported inadequate specimen for

Table 1: Distribution of neoplastic lung lesions

Neoplastic	Number of cases	Percentage
Round cell tumor	02	12.5
Squamous cell carcinoma	06	37.5
Adenocarcinoma	03	18.7
Small cell carcinoma	02	12.5
Poorly differentiated carcinoma (nonsmall cell type)	03	18.7
Total	16	100

Table 2: Distribution of nonneoplastic lung lesions

Nonneoplastic	Number of cases	Percentage
Granulomatous lesion	02	28.6
Abscess	02	28.6
Organizing pneumonia	01	14.3
Vasculitis	01	14.3
Chronic nonspecific inflammatory lesion	01	14.3
Total	07	100

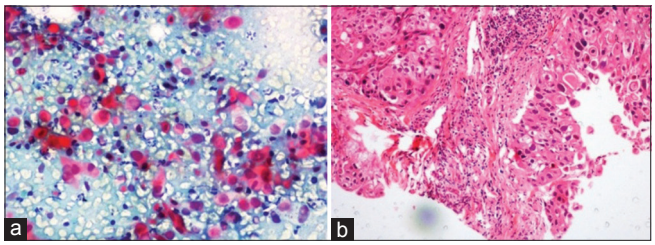

Figure 2: (a and b) Smears showing pleomorphic squamous cells with orangeophilic cytoplasm (Pap, ×200). Squamous cell carcinoma (H and E, ×200)

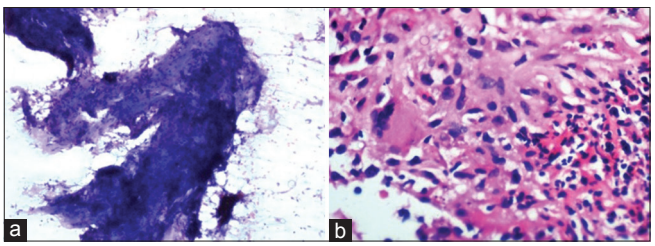

Figure 3: (a and b) Smear with collagenous stromal fragment and mixed inflammatory cells (MGG, ×100). Section showing epithelioid cell granuloma, giant cell and mixed inflammatory cells (H and E, ×200)

image-guided transthoracic CB has ranged 0–15%.[13] Since the introduction of IC for surgical pathology by Dudgeon and Patrick in 1927,[3] this technique has been widely accepted as an adjunct to frozen section HP for intra-operative diagnosis.[10] In addition to its comparable accuracy to frozen section HP, IC has been found to be more advantageous, because it is less costly and less time consuming.[14] The onsite cytology evaluation also can reduce unnecessary passes, optimize the biopsy procedure improve the diagnostic rate and provide a preliminary cytologic diagnosis.[15]

This immediate interpretation not only provides an assessment of whether the CB sample contains representative material but also reduces the number of passes a radiologist may have to perform on a particular patient. Correspondingly, it may also increase the number of passes performed if evidence of malignancy is not apparent on the slides examined and the sample is believed to be nonrepresentative of the lesion, thereby improving the overall diagnostic yield of the procedure. A more specific diagnosis regarding the histologic type of the tumor also can be provided during the immediate assessment of the lung biopsy specimens, which may play a role in the immediate patient care management.[15]

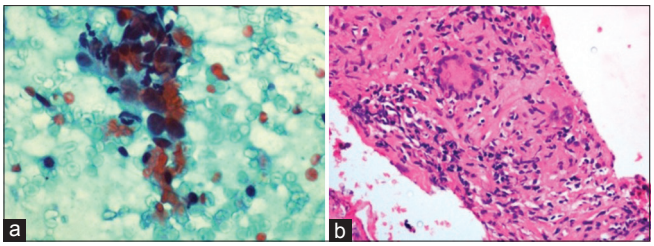

Figure 4: (a and b) Smear showing atypical cells admixed with mixed inflammatory cells and a few red blood cells (Pap, ×200). Section showing epithelioid cell granuloma and Langhan's giant cell (H and E, ×200)

Table 3: Distribution of mediastinal lesions

Neoplastic cases	Number of cases	Percentage
Thymoma	02	28.5
Lymphoma	03	42.9
Germinoma	02	28.5
Total	07	100

Table 4: Correlation of findings of imprint cytology with histopathology -an observation

	True positive	False positive	False negative	True negative	Total
Lung and mediastinum	23	01	00	06	30

IC is also considered an excellent method for giving a correct and rapid diagnosis without compromising the tissue specimen for HP.[16,17]

CB with onsite cytology adequacy assessment using touch preparation has a low unsatisfactory rate.[16,18-20] In a study by Liang *et al.*,[15] the final adequacy rate was 99.5%. In this study, no unsatisfactory result was recorded, and the adequacy rate was 100% also, taking imprints from the CB did not alter the tissue morphology of final HP sections.

The sensitivity, specificity, and accuracy in this study were 96.4%, 100%, and 95.9% respectively, which was in agreement with other studies.[,8,9,10,21,22] [Table 6].

Hayashi *et al.*[23] also demonstrated that IC can yield the correct diagnosis from small lesions with CT-guided biopsy. Motomura *et al.*[24] reported that IC can detect micrometastasis more precisely than final paraffin sections evaluated by hematoxylin and eosin staining in breast cancer. Therefore, touch IC could be superior to conventional HP in the identification of a small proportion of cancer cells against a background of nonmalignancy.[24,25] However, in the present study, no such case was encountered. Studies with large number of cases and core biopsies of smaller mass lesions may be required to establish this fact.

In a study by Liang *et al.*,[15] specific diagnoses was made in 37% of the cases in the benign nonneoplastic category, which included granulomatous inflammation, organizing pneumonia, fungal, and mycobacterial infections, amyloidoma, and lung elastosis. In the present study, specific diagnoses could be offered in only two (28.6%) of the seven patients, which were diagnosed as lung abscesses. However, vasculitis, granulomatous lesions, organizing pneumonia, and chronic inflammatory lesions required HP of CB for a specific diagnosis and were diagnosed as benign/inflammatory on IC.

A single (3.3%) false positive case was diagnosed, and the reactive atypia in the epithelial cells was overdiagnosed as malignancy. IC gave a 1% false-positive rate due to suspicious cytology in various studies, which is comparable to the present study.[8,26,27]

CB has an advantage for obtaining more tissue to perform IHC and/or molecular studies.[17,28] A specific lung cancer classification is often mandatory using the limited tissue material, because of the availability of variable targeted treatments. In addition, some treatment may improve

Table 5: Correlation of findings of imprint cytology with histopathology - an evaluation

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	*P*
Lung and mediastinum	100	85.7	95.8	100	96.7	<0.001

Table 6: Comparison of the tests of significance of the present study with other studies

	Sensitivity (%)	Specificity (%)	Accuracy (%)	*P*
Liao *et al.*[10]	94.0	97.0	94.0	<0.05
Chang *et al.*[8]	96.5	96.0	96.4	<0.05
Paulose *et al.*[9]	89	100	-	<0.05
Tamiolakis *et al.*[21]	99.13	100	-	
Tsou *et al.*[22]	-	-	97.1	
Present study	96.4	100	95.9	<0.001

outcome in a patient subpopulation, but contraindicated in patients with other type of tumor. For example, bevacizumab, a monoclonal antibody against vascular endothelial growth factor can only be used in patients with nonsquamous cell lung carcinoma, due to fatal hemorrhagic events in patients with squamous cell lung carcinoma.[29] With the demands of personalized medicine and improved understanding of the molecular pathways of different lung cancers, multiple analyses are needed, such as epidermal growth factor receptor and Kirsten rat sarcoma viral oncogene homolog mutation analysis and anaplastic lymphoma kinase translocation.[18,30] In 2011, a multidisciplinary expert panel proposed a major revision of lung cancer classification, which also emphasizes that the tissue sample should be preserved for not only morphological diagnosis but also molecular testing.[31] Touch preparation from CB with onsite rapid cytology evaluation can provide adequate assessment and triage specimens for appropriate studies.[15] In the present study, the cores of poorly differentiated carcinomas and round cell tumors were referred for IHC for further categorization and lung tumors for molecular analyses.

CONCLUSION

Nonoperative pathology diagnoses should constitute an essential part of the comprehensive workup of mass lesions. Multiple visits strain the resources of the patient. As an adjunct to HP of CB specimens, IC also helps to ensure that the specimens obtained adequately represent the lesion. It is thus beneficial to the patient as it reduces both the time that the patient has to wait for the results and the number of out-patient appointments required. A reduction in waiting time for the diagnosis of malignancy means that the treating physician can plan and prime the patient earlier. This is as important as the prompt diagnosis of a benign disease so that the patient can be discharged.

In this study, it was possible to classify benign and malignant lesions. Subtyping of neoplastic lesions could also be done on IC. Its use decreased the number of passes required to obtain the cores. The scope and limitations of IC should be fully realized especially in the interpretation of specific diagnosis of benign lesions and poorly differentiated carcinomas.

IC on CB offers an opportunity to get the best of both worlds, i.e., cytology and histology without significant extra cost.

Acknowledgment

We would like to thank Dr. Nagaraj Murthy, Professor of Radiology, JSS Medical College, Mysore for his help in the conduct of core biopsies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Liao WY, Chen MZ, Chang YL, Wu HD, Yu CJ, Kuo PH, *et al.* US-guided transthoracic cutting biopsy for peripheral thoracic lesions less than 3 cm in diameter. Radiology 2000;217:685-91.
2. Sakai T, Hayashi N, Kimoto T, Maeda M, Ishii Y, Murashima S, *et al.* CT-guided biopsy of the chest: Usefulness of fine-needle core biopsy combined with frozen-section pathologic diagnosis. Radiology 1994;190:243-6.
3. Dudgeon LS, Patrick CV. A new method for the rapid microscopical diagnosis of tumours: With an account of 200 cases so examined. Br J Surg 1927;15:250-61.
4. Scucchi LF, Di Stefano D, Cosentino L, Vecchione A. Value of cytology as an adjunctive intraoperative diagnostic method. An audit of 2,250 consecutive cases. Acta Cytol 1997;41:1489-96.
5. Hahn PF, Eisenberg PJ, Pitman MB, Gazelle GS, Mueller PR. Cytopathologic touch preparations (imprints) from core needle biopsies: Accuracy compared with that of fine-needle aspirates. AJR Am J Roentgenol 1995;165:1277-9.
6. Albert US, Duda V, Hadji P, Goerke K, Hild F, Bock K, *et al.* Imprint cytology of core needle biopsy specimens of breast lesions. A rapid approach to detecting malignancies, with comparison of cytologic and histopathologic analyses of 173 cases. Acta Cytol 2000;44:57-62.
7. Popp W, Rauscher H, Ritschka L, Redtenbacher S, Zwick H, Dutz W. Diagnostic sensitivity of different techniques in the diagnosis of lung tumors with the flexible fiberoptic bronchoscope. Comparison of brush biopsy, imprint cytology of forceps biopsy, and histology of forceps biopsy. Cancer 1991;67:72-5.
8. Chang YC, Yu CJ, Lee WJ, Kuo SH, Hsiao CH, Jan IS, *et al.* Imprint cytology improves accuracy of computed tomography-guided percutaneous transthoracic needle biopsy. Eur Respir J 2008;31:54-61.
9. Paulose RR, Shee CD, Abdelhadi IA, Khan MK. Accuracy of touch imprint cytology in diagnosing lung cancer. Cytopathology 2004;15:109-12.
10. Liao WY, Jerng JS, Chen KY, Chang YL, Yang PC, Kuo SH. Value of imprint cytology for ultrasound-guided transthoracic core biopsy. Eur Respir J 2004;24:905-9.
11. Kulkarni D, Irvine T, Reyes RJ. The use of core biopsy imprint cytology in the 'one-stop' breast clinic. Eur J Surg Oncol 2009;35:1037-40.
12. Leyden H. About infectious pneumonia. Dtsch Med Wochenschrift 1883;9:52-4.

13. Chandan VS, Zimmerman K, Baker P, Scalzetti E, Khurana KK. Usefulness of core roll preparations in immediate assessment of neoplastic lung lesions: Comparison to conventional CT scan-guided lung fine-needle aspiration cytology. Chest 2004;126:739-43.
14. Owings RM. Rapid cytologic examination of surgical specimens: A valuable technique in the surgical pathology laboratory. Hum Pathol 1984;15:605-14.
15. Liang L, Liu J, Buryanek J, Zhang S. CT-guided core needle biopsy of peripheral lung lesions with onsite adequate evaluation: Review of 215 cases. J Cytol Histol 2014;S4:18.
16. Tachibana K, Nakazato Y, Tsuchida S, Kazama T, Minato K, Yoshida T, *et al.* Immediate cytology improves accuracy and decreases complication rate in real-time computed tomography-guided needle lung biopsy. Diagn Cytopathol 2013;41:1063-8.
17. Beslic S, Zukic F, Milisic S. Percutaneous transthoracic CT guided biopsies of lung lesions; fine needle aspiration biopsy versus core biopsy. Radiol Oncol 2012;46:19-22.
18. Solomon SB, Zakowski MF, Pao W, Thornton RH, Ladanyi M, Kris MG, *et al.* Core needle lung biopsy specimens: Adequacy for EGFR and KRAS mutational analysis. AJR Am J Roentgenol 2010;194:266-9.
19. Uskül BT, Türker H, Gökçe M, Kant A, Arslan S, Turan FE. CT-guided transthoracic fine needle aspiration of pulmonary lesions: Accuracy and complications in 134 cases. Tuberk Toraks 2009;57:177-85.
20. Rizzo S, Preda L, Raimondi S, Meroni S, Belmonte M, Monfardini L, *et al.* Risk factors for complications of CT-guided lung biopsies. Radiol Med 2011;116:548-63.
21. Tamiolakis D, Mikroulis D, Lambropoulou M, Bitzikas G, Didilis V, Kotini A, *et al.* Imprint cytology for rapid evaluation of lung and mediastinal lesions. Minerva Med 2003;94:97-102.
22. Tsou MH, Tsai SF, Chan KY, Horng CF, Lee MY, Chuang AY, *et al.* CT-guided needle biopsy: Value of on-site cytopathologic evaluation of core specimen touch preparations. J Vasc Interv Radiol 2009;20:71-6.
23. Hayashi N, Sakai T, Kitagawa M, Kimoto T, Inagaki R, Ishii Y, *et al.* CT-guided biopsy of pulmonary nodules less than 3 cm: Usefulness of the spring-operated core biopsy needle and frozen-section pathologic diagnosis. AJR Am J Roentgenol 1998;170:329-31.
24. Motomura K, Inaji H, Komoike Y, Kasugai T, Nagumo S, Noguchi S, *et al.* Intraoperative sentinel lymph node examination by imprint cytology and frozen sectioning during breast surgery. Br J Surg 2000;87:597-601.
25. Okubo K, Kato T, Hara A, Yoshimi N, Takeda K, Iwao F. Imprint cytology for detecting metastasis of lung cancer in mediastinal lymph nodes. Ann Thorac Surg 2004;78:1190-3.
26. Manhire A, Charig M, Clelland C, Gleeson F, Miller R, Moss H, *et al.* Guidelines for radiologically guided lung biopsy. Thorax 2003;58:920-36.
27. Denley H, Singh N, Clelland CA. Transthoracic fine needle aspiration cytology of lung for suspected malignancy: An audit of cytological findings with histopathological correlation. Cytopathology 1997;8:223-9.
28. Lima CD, Nunes RA, Saito EH, Higa C, Cardona ZJ, Santos DB. Results and complications of CT-guided transthoracic fine-needle aspiration biopsy of pulmonary lesions. J Bras Pneumol 2011;37:209-16.
29. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-91.
30. Zhuang YP, Wang HY, Shi MQ, Zhang J, Feng Y. Use of CT-guided fine needle aspiration biopsy in epidermal growth factor receptor mutation analysis in patients with advanced lung cancer. Acta Radiol 2011;52:1083-7.
31. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, *et al.* International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.