

Peer review file

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Reviewer A

Small retrospective study examining usefulness of FDG PET in lymphatic involvement in lung cancers deemed to be asbestos related by Japanese criteria.

It is interesting in that it deals with asbestos related lung cancers.

However, as reference 13 and many other studies have reported, there are no clinical or pathological features distinguishing asbestos related lung cancer from lung cancer due to other causes. So this focus does not really add much.

Some comments:

Comment 1: The industrial histories should be described. How many had silica/coal exposure?

Reply 1:

We have added the occupational history as you suggested, as Table 2, on page 7, line 15, and noted on page 7, line 9, that silica and coal exposure were not included.

Comment 2: The term asbestos body should be used throughout (not particle)
table 1 BI should be defined

Reply 2:

As suggested, we have changed asbestos particles to asbestos bodies, and the definition of the abbreviation BI has been changed to Brinkman index.

Comment 3: It should be made clear whether means plus range or means plus CI are presented (also table 3)

Reply 3:

Thank you for your suggestion. As you pointed out, we examined age, smoking index, and the number of asbestos bodies with mean and standard deviation; however, because of the large variation in smoking index and number of asbestos units, continuous variables are presented as median values plus interquartile range.

Comment 4: table 2 A clear two way summary table showing PET vs pathology diagnosis

positives and negatives should be presented so that the calculated quantities (sensitivity specificity etc) are easily seen

Reply 4:

Thank you for your suggestion. Accordingly, we have shown the 2×2 contingency table and test accuracy for PET scan and pathological diagnosis in Table 3.

Reviewer B

Comment 1: This is a well written paper which is easy to follow. Major comments:

The authors have not made the case as to why or if asbestos related lung cancer is any different to any other lung cancer behavior. If this small group have been picked out because of dust exposure – why only asbestos and no other dusty occupations?

Reply 1:

Thank you for pointing this out. This study focused on occupational dust disease and asbestos-related lung cancer because asbestos is dust that has proven carcinogenic, causing pleural mesothelioma and lung cancer. Silicosis and coal-worker pneumoconiosis are decreasing in Japan, but asbestos-related lung cancer has a long latent period of about 20 years from asbestos exposure to disease onset. It is an occupational dust disease that will continue to increase in the future, although the use, manufacture, and import of asbestos were abolished in 2006.

We have added text from line 9 on page 10 to line 2 on page 11.

Comment 2: I believe what they are basing this paper on is this paper is silico-anthraco- of the mediastinal lymph nodes – not novel and a well recognised cause of bilateral symmetrical FDG-avidity in dust-exposed populations. Where any stains performed for silica?

Reply 2:

Thank you for pointing this out. Staining for silica is not commonly done in Japan, so it was not done in this case either. However, as you pointed out, the false-positive

lymph node in this case, seems to have resulted from anthracosis. We reviewed the literature and found several articles that cite anthracosis as the cause of false-positive PET lymph nodes. The occupational history of the eight patients with false-positive lymph nodes in this case, included four shipbuilders, one bricklayer, one electrician, one casting worker, and one pipeworker, all of whom were in work environments where charcoal dust inhalation was suspected in addition to asbestos. The text has been added on page 12, lines 5–12.

Comment 3: There is no mention of pre-operative staging or investigation of the nodes (EBUS or mediastinoscopy) – which is a routine, gold standard approach to sample nodes. This would have confirmed no malignancy and the presence of silico-anthracosis.

Reply 3:

Thank you for pointing this out. We did not perform mediastinoscopy and EBUS on our patients. We think it is necessary to perform them in the future, as you mentioned.

Comment 4: The authors should justify / explain the use of Glut-1 – it reads as if it was part of the diagnostic process.

Reply 4:

Thank you for pointing this out. Kwon (3) and Chung (17) reported that FDG accumulation in false-positive lymph nodes was caused by lymph node hyperplasia, Glut-1 overexpression, and histiocytes infiltration. The reason for Glut-1 staining in PET false-positive lymph nodes has been moved to page 9, lines 1 to 4, in the Results section.

Comment 5: Why were 4 patients with N2 nodes operated on?

Reply 5:

Thank you for pointing this out. Four patients with p-N2 were surgically managed because two were diagnosed with c-N0 and the rest as c-N1.

Comment 6: Explain abbreviations in table – for instance ‘BI’ in table 1.

Reply 6:

Thanks for the suggestion, annotated Brinkman index is in Table 1, Table 4, and Table

5.

Reviewer C

This is a study on the usefulness of FDG PET/CT in the evaluation of mediastinal lymph node metastasis in 35 asbestos-related lung cancer patients who underwent preoperative FDG PET/CT and surgical resection. Comparing the results of PET/CT with pathological results in patients with asbestos-related lung cancer, a very rare disease, seems to be of some significance.

Major comments:

Comment 1: If the comparison result is only bilateral symmetric accumulation, it can be concluded that the possibility of metastasis is low in bilateral lymph node uptake of PET-CT. However, there is a tendency to actively perform EBUS-TBNA even if there is bilateral lymphadenopathy prior to the actual multidisciplinary clinics.

Reply 2:

Thank you for pointing this out. We did not perform EBUS-TBNA in our patients. We think it is necessary to perform EBUS-TBNA in the future, per your observation.

Comment 2: The finding of chest CT and PET-CT should be compared to determine whether mediastinal lymph nodes have metastasized. In particular, the findings of reactive lymph nodes due to anthracofibrosis may be better understood in chest CT. What were the findings of mediastinal lymphadenopathy on the chest CT in the 35 study patients?

Reply 2:

Thank you for pointing this out.

We have added data on the short axis diameters of PET false-positive and true-positive lymph nodes on chest CT to Tables 4 and 5, and have added text to page 8, lines 14 through 17.

Comment 3: In these days, when EBUS-TBNA is widely used, did the study patients not perform EBUS-TBNA before surgical resection?

Reply 3:

Thank you for pointing this out. EBUS-TBNA was not performed in our patients. We

think it is necessary to perform EBUS-TBNA in the future, as you have mentioned.

Comment 4: The Discussion can be enriched by a discussion on the reasons and mechanisms of the false positive lymph node in FDG PET/CT.

Reply 4:

Thank you for pointing this out. Histological findings of PET false-positive lymph nodes have been reported in the literature to be related to Glut-1 and macrophages, and we hypothesized that Glut-1 or CD68 would be positive in this case, but both were negative. In this case, the false-positive lymph node seems to be a false-positive result due to anthracosis. We reviewed the literature and found several articles that cite anthracosis as the cause of false-positive PET lymph nodes. All false-positive lymph nodes, in this case, showed severe anthracosis.

Comment 5: Is there no difference in the interpretation of PET/CT between ARLC cancer and lung cancer unrelated to asbestos exposure in patients who do not know whether lung cancer is caused by asbestos exposure before surgery?

Reply 5:

Thank you for pointing this out. In Japan, when asbestos exposure is evident in a patient's occupational history, a system of medical examinations is enforced using the Asbestos Health Management Handbook. In this case, the patients had undergone either the above-mentioned asbestos screening or had a prior occupational history of asbestos exposure, and asbestos exposure was proven.

Minor comments:

Comment 1: In the Table 1, express smoking habit as never smoker and ever smoker. What does the abbreviation "BI" mean? Please indicate in pack-years.

Reply 1:

Thank you for your observation. We have changed the smoking habit to never smoker and ever. The smoking index has been expressed in terms of the Brinkman index, and the abbreviations have been explained in Table.

Comment 2: Indicate the location of the primary tumor lesion as the right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe.

Reply 2:

Thank you for your suggestions. We have changed it per your suggestion.

Comment 3: Add the number of mediastinal lymph nodes dissected during surgery for each patient.

Reply 3:

Thank you for pointing this out. However, we have been unable to design a good table that shows the number of dissected lymph nodes in all 35 patients. If you have a good suggestion, we would be happy to comply.

Comment 4: Consider removing “lower”, “peripheral” from the Table 2.

Reply 4:

Thank you for pointing this out.

The reference by Rusch (2) et al. clearly states that "zone" is not a standard nomenclature, and we have removed it from Table 3.