TCR TRANSLATIONAL CANCER RESEARCH
ADVANCES CLINICAL MEDICINE TOWARD THE GOAL OF IMPROVING PATIENTS' QUALITY OF LIFE
IMPACT FACTOR 0.986

Peer Review File

Article information: http://dx.doi.org/10.21037/tcr-21-78

Reviewer A

Comment 1: The authors say they are using the 8th edition stage classification system, but they seem to intentionally avoid throughout addressing the fact that this is based on the solid tumor size (clinical) and invasive size (pathologic).
Reply 1: We thank the reviewer for the very insightful comment. According to the 8th edition stage classification system, the clinical T stage was dependent on the solid component size excluding the GGO component rather than the total size. However, in the present study, all cases were pure ground glass nodules without solid components, based on the 8th TNM classification, pure GGNs less than 3.0cm were classified as cTis, and pure GGNs exceeding 3.0cm were cT1a, this is new demarcation. We have checked the manuscript and emphasized on this point.
Changes in the text: we have modified our text as advised (see Page 3, line 16-20; Page 4, line 20-22)

Comment 2: There is no definition of the p-stage of the resected lesions
Reply 2: Thanks for your comment and suggestions. According to the 8th edition stage classification system for subsolid nodules, tumors showing pure lepidic growth without invasion are classified as pTis when total size measuring 3 cm or less and pT1a when total size measuring more than 3 cm. tumors meet pathologic criteria for MIA are classified as pTimi when total size measuring 3 cm or less and pT1a when total size measuring more than 3 cm. We have added this content in the revised manuscript.

Changes in the text: we have modified our text as advised (see Page 7, line 6-11)

Comment 3: We are told about pleural, vascular and lymphatic invasion but not about any lymph node involvement.
Reply 3: Thanks for your comment and suggestions. We reviewed pathological datas and found that there were no cases with lymph node metastasis. We have added this content in the revised manuscript.
Changes in the text: we have modified our text as advised (see Page 2, line8-9; Page 5, line 5-6; Page 7, line 6; Page 10, line 18; Page 13, line 17,20; Table2; Table3)

Comment 4: The study is based on "pure" GGNs, but lacks actual definition of what is included. Since this is the key thrust of the paper, I think that details are essential. I think that thin slice scans (~1mm) are necessary to be able to say it is pure GGO. I think there should be definition of whether there are areas of consolidation on lung

windows. The paper implies these are pure GGNs, but then adds that some of them had small solid components on mediastinal windows. So I am very unsure what this cohort of lesions represents.

Reply 4: Thanks for your comment and suggestions. We are sorry for this mistake and we have revised the definition deliberately.

Changes in the text: we have modified our text as advised (see Page 3, line7-9; Page 5, line 9,13-15)

Comment 5: Although the focus is description of resected "pure" GGNs and pathologic invasion, we should be told what sort of resection was done (including node sampling).

Reply 5: Thanks for your comment and suggestions, we have reviewed the clinical datas and added relative details in revised manuscript.

Changes in the text: we have modified our text as advised (see Page 7, line 12-16)

Comment 6: The authors gloss over the fact that selection was almost certainly at play. Very small lesions were likely selected for resection due to increased density, speculation or other characteristics. I don't think we can say that small GGN tend to be denser – we can only say small GGNs selected for resection are denser.

Reply 6: We thank the reviewer for the very insightful comment. After our discussion, it is indeed inappropriate to make this conclusion and we have explained in the discussion.

Changes in the text: we have modified our text as advised (see Page 2, line12-15; Page 11, line 9-10; Page 12, line 8-11)

Comment 7: There is no discussion of a potential bias by excluding MIA – since any invasion ≤5mm is not invasive adeno, it is likely that resected small pure GGNs were excluded simply because of not meeting this threshold.

Reply 7: Thanks for your comment and suggestions. A tumor with predominantly lepidic growth and invasive component≤0.5cm as well as lack of vascular, pleural, or air space invasion was classified as MIA. The invasive size was measured in the largest dimension. If multiple invasive foci existed simultaneously, or the invasive area is difficult to measure, another way to estimate the invasive size is to add up the percentage area of the invasive components and multiply by the total tumor diameter (i.e., a 4.0 cm tumor with a 10% invasive component would have an estimated invasive size of 0.4 cm). If the result is no larger than 0.5 cm, a diagnosis of MIA could be considered [1]. In the current study, the invasive component of all the lesions is more than 0.5cm and diagnosed as IA. Therefore, there was no potential bias.

Changes in the text: we have modified our text as advised (see Page 6, line 21)

1. Travis W, Asamura H, Bankier A, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM

Classification of Lung Cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 2016;11:1204-23.

Comment 8: If survival is going to be part of this paper at all, then we need some actual facts. Reporting what the follow-up was supposed to be, and that a follow-up period of at least 5 years was included does not tell us anything about the actual median follow-up, how many patients are lost to follow- up etc.
Reply 8: Thank you for the very insightful comment, we quite agree with this viewpoint, we have reviewed the clinical data and added relative details in revised manuscript.
Changes in the text: we have modified our text as advised (see Page 8, line 1; Page 9, line 12-14; Page 10, line 15,19,20)

Comment 9: Finally, I think that it is very questionable whether pure GGNs should be resected at all. This may have been less clear in 2013-5, but I think this deserves at least mention in the discussion.
Reply 9: Thanks for your comment and suggestions. We agree with you on this matter, it is not clear and still need to be confirmed by the results of more prospective studies. We have added this comment in the discussion.
Changes in the text: we have modified our text as advised (see Page 14, line 15-17)

Reviewer B

This retrospective study used data from a single institutional series and the authors attempted to investigate the radiological and pathological characteristics as well as prognosis of invasive adenocarcinoma (IA) manifesting as pure GGN. This topic is quite interesting with clinical relevance, because we not uncommonly encounter IA with radiologically pure GGN feature in a daily clinical practice. However, until these days, there have been few reports with such a sizable population as this report. As expected, they found that (1) size was correlated with invasiveness, (2) smaller nodules tended to have higher CT attenuation, (3) larger nodules tended to have shapes known to have invasiveness such as irregular and spiculated margins, pleural indentation, and air bronchogram, and (4) there were not cases with lymphatic, pleural or vessel invasion at all. These pathological findings, in turn, led to excellent prognosis with 100% 5-year disease-free survival regardless of the size and pathologic subtype. Among their findings, this should also be emphasized that there were no cases with micropapillary and solid subtypes, which might be related to the excellent prognosis of this cohort. Based on their findings, it can be inferred that even if we unexpectedly realize that the lesion initially manifesting as pure GGN has invasive pathologic components, we do not have to worry about the presence of more aggressive nature such as micropapillary or solid histologic type and lymphovascular invasion and a resultant risk of poor prognosis regardless of the size. All these points that I have commented regarding their findings are already adequately mentioned in

the manuscript.

Reply: Thank you for the insightful comment. We have emphasized that there were no cases with micropapillary and solid subtypes, which might be related to the excellent prognosis of this cohort (Page 13, line 12-14).