Peer Review File

Article Information: https://dx.doi.org/10.21037/jtd-23-1605

Reviewer A

In their retrospective study, the authors have analysed 2077 patients with pathologically confirmed breast cancer between January 2008 and December 2022 in order to assess the incidence of primary lung cancer in this population.

The authors observed incidental findings of GGNs and lung cancer in 5% and 0.9%of patients with breast cancer, respectively.

I have read with particular interest this paper and I want to congratulate with the authors for the well conducted analysis.

Comment 1: Abstract: please insert the time frame also in the abstract, in the method paragraph

Reply 1: Thank you for your comment. I appreciate the adjustment you made to the method paragraph to "We evaluated the prevalence of GGNs and their size changes on follow-up chest CT with volume doubling time and identified independent risk factors associated with the growth of GGN using multivariable logistic regression analyses." Because of retrospective study, we could not define follow-up period on method paragraph. Therefore, we mentioned the median follow-up duration on results section.

Changes in the text: The revised sentence is "We evaluated the prevalence of GGNs and their size changes on follow-up chest CT with volume doubling time and identified independent risk factors associated with the growth of GGN using multivariable logistic regression analyses" **on** abstract **page 2, line 18-20.**

Comment 2: Introduction: line 90: the sentence is incorrect. Breast cancer is not the most common cancer worldwide. Please revise. https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html

Reply 2: Thank you for your valuable comment. We again review our references. According to our reference (https://onlinelibrary.wiley.com/doi/10.1002/ijc.33588revised manuscript and added above referecnes: cancer statistics for the year 2020), It was not the most common cancer but it was the most common, new diagnosed cancer. The most commonly diagnosed cancers worldwide were female breast cancer (reference abstract, table 1) and according to Table 2, breast cancer was the fourth cause of death in 2020.

Changes in the text: The text has been changed from "the most commonly malignant tumor" to "the most diagnosed malignant tumor in 2020" and from the "fifth" to the "fourth." Please refer to **page 5, line 76-78**.

• Methods: well-articulated and accurate

• Results: accurate and detailed presentation

• Discussion: clear and comprehensive

Comment 3: Tables and figure: interesting and not redundant. Table 3: it is not clear for me what rpT4 means, please specify

Reply 3: Thank you for your comment. By rpT4, we meant T stage of recurrent pathology. We therefore changed it to initial TNM stage of cT3a, N1, M0 in Table 3. C indicated clinical stage.

Changes in the text: We changed it to the initial stage of "T3a, N1, M0" **in page 25 Table 3.**

Comment 4: I have only two comments: Since the patient population is relatively young, I recommend to add the smoking history and the familiarity for lung cancer in the cohort.

Reply 4: Thank you for your comment. We reviewed smoking history of all 69 patients and presented their smoking information in Table 1. Out of the 69 patients, only one patient was an active smoker of 12.5 pack-years (0.5 pack x 25 years) and was diagnosed with lung cancer, ADC, while other patients were non-smokers. According to previous studies, ground glass nodule, pre-cancerous/pre-invasive nodules may be associated with lung cancer in non-smoking women (ref; 1) J Thorac Oncol. 2006 Jun;1(5):413-6. 2) Eur J Radiol Open. 2016;3:223–229. 3)Clin Lung Cancer. 2016 Sep;17(5):e45-e56. doi: 10.1016/j.cllc.2016.03.004. Epub 2016 Mar 30., 3:). In our study, most of the patients who were diagnosed with lung cancer had no smoking history. We have also added the family history of patients with lung cancer in Table 1.

Changes in the text: We have added results about the smoking history in the result section, **page 10, line 197-198**. We have also added the same in the discussion section, **page 13, line 269-273**

We have added information regarding the smoking history and family history of patients with lung cancer **in Table1.**

Reviewer B

In this retrospective study, the authors present prevalence numbers on ground glass nodules / opacities in breast cancer patients. They found a prevalence of 5% in their breast cancer population. Although there are some publications on this topic already, it is important to verify this in different populations. However, regarding this study, I have some concerns.

Major:

Comment 5:

1. An important issue is the indication of the chest CT, as this might have caused selection bias. The authors state: For breast cancer patients, contrast-enhanced chest computed tomography (CT) is recommended to monitor for lung metastasis during treatment (15).

As far as I know, at least in my (Western) country, a contras-enhanced chest CT is not recommended to all breast cancer patients. Indeed, 1409 of the 2077 screened patients had a CT scan. Therefore, I would like to know what the indication was for all patients at baseline, but also for follow-up (i.e. follow-up of GGO or regular follow-up).

Reply 5: Thank you for your valuable comment. In our country, CT is not expensive due to the national health insurance service. When referring to clinicians, a preoperative chest CT is usually performed for TNM staging. Subsequently, chest CT scans are performed at every six-month interval within the first 12 months post-operation. Thereafter, annual follow-up chest CTs are performed. If there are lesions suspected of metastasis or infection, chest CT may be taken at shorter intervals. If GGNs were incidentally smaller in size (example, pure GGN <6mm), only regular follow-up will be performed for the breast cancer. Chest CT indication did not differ according to stage of breast cancer including DCIS.

Changes in the text: We have added the general indications for chest CT performed in our hospital **in materials and methods, page 6, line 109-112**.

Comment 6:

2. A major concern is the fact that there is no information on smoking, whereas this is a risk factor for both breast cancer and lung cancer. If available, the authors should include this in their analysis. Also, elaborate on this in the discussion section.

Reply 6: Thank you for your comment. We have added the smoking history for all 69 patients in Table 1. Of all the 69 patients, only one patient was an active smoker of 12.5 pack-years (0.5 pack x 25 years) and was diagnosed with lung cancer, ADC from a growing GGN group. Because there was only one patient, we did not perform additional analysis but mentioned the smoking history in the discussion section.

Changes in the text: We have added results about the smoking history in the result section, **page 10, line 197-198**. We have also added the same in the discussion section, **page 13, line 269-273**. We have added information regarding the smoking history **in Table1.**

Comment 7:

3. There is a large focus on comparing clinical traits between patients with growing GGN and non-growing GGN (Table 1). I would suggest to compare to patients without GGN as well.

Reply 7: Thank you for your comment. We examined other patients (n=1310) and compared them to patients with persistent GGNs or were incidentally diagnosed of lung cancer (supplemental Table 1). Breast cancer has been categorized into four types according to the hormone receptor (the most common used, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and triple negative breast cancer. Therefore, we changed Table 1 and supplemental Table 1 accordingly. When we compared two groups, there were no significant change except age.

Changes in the text: We inserted supplemental Table 1 in page 27 and added results in result section in **page 10, line 202-204**

Comment 8:

4. A limitation stated by the authors:

lack of a comparison with lung cancer patients without breast cancer

Please compare to data from other publications. Is the incidence of 5% higher than in the general (female Asian) population? Further, I would speak of prevalence and not incidence, since the GGO did not develop during follow-up.

Reply 8: Thank you for your important comment. We reviewed previous publications, and we concluded that there is no definite evidence that the incidence of 5% was higher than the general population. It is impossible to compare incidence of GGO to previous studies (ref. Clin Lung Cancer. 2016 Sep;17(5):e45-e56. doi: 10.1016/j.cllc.2016.03.004. Epub 2016 Mar 30), which stated incidental detection of GGNs probably including transient GGNs. Therefore, we have added non-inclusive result in the discussion section. Additionally, we have changed "incidence" to "prevalence" in the manuscript.

Changes in the text: We have provided more explanation in the **discussion section, page 12, line 253-255** and changed incidence to prevalence **at all instances in the manuscript (indicted as comment 8).**

Comment 9:

5. Another limitation is that not all GGO were pathologically evaluated, which is, from a clinical point of view, logical. It does raise the question of the diagnostic significance of GGO's in these patients. Will patients die from their GGO. Does it affect their long term survival? Although this study is not designed to answer these questions, it is an important discussion point.

Reply 9: Thank you for your comment. I agree with your opinion. We did not perform survival analysis but evaluated the prevalence and percentage of growth of GGNs in patients with breast cancer, because GGNs are frequently detected during the interpretation of chest CT scans in patients with breast cancer. We did not obtain pathology results for all. A previous study (Ann Thorac Surg. 2013 Oct;96(4):1190-1195. doi: 10.1016/j.athoracsur.2013.05.062. Epub 2013 Aug 20.) stated that pure GGNs with stable sizes during follow-up showed all AIS, MIA to ADC in 23 cases. Therefore, it may be fair to diagnose patients in the no-change group of GGNs with cancer. Tumor of GGNs is known to show excellent prognosis after surgical resection. Although there are no definite guidelines for surgical resection indication for pure GGN, operation can be performed when nodules grow or solid component area is newly formed. In our study, 39.1% of patients showed interval growth. Therefore, given the increasing incidence of breast cancer in young patients, if incidental GGNs with risk factors are identified, it is advisable to conduct sufficient follow-up until the growth of any nodules is confirmed. Achieving a complete determination of recovery from breast cancer typically requires a prolonged period of approximately 5-10 years. Therefore, if the size of GGNs is small and pure, regular follow-up for breast cancer alone should be sufficient. LUNG RADS 2022 ver. recommend that pure GGNs < 3.0cm in size is recommended for 12 months follow-up.

Changes in the text: We have included the explanation in **the discussion section, page 14, line 302-311.**

Minor:

Comment 10:

1. I would suggest to use the term ground glass opacity (GGO) throughout the paper, as this is more commonly used.

Reply 10: Thank you for your comment. In our case, the term ground glass opacity (GGO) is also right, but previous publications on this topic (1: Front Oncol. 2022 Oct 13:12:985734. doi: 10.3389/fonc.2022.985734. eCollection 2022. 2: Acta Radiol. 2020 Feb;61(2):175-183. doi: 10.1177/0284185119856259. Epub 2019 Jun 19) also used the term GGN and previous study (AJR Am J Roentgenol. 2011 Mar;196(3):533-43. doi: 10.2214/AJR.10.5813, Ground-glass nodules on chest CT as imaging biomarkers in the management of lung adenocarcinoma) defined the term ground glass nodules (GGN) and defined GGNs as GGO in nodular shape. We analyzed only persistent GGO, all of which are nodular in shape. Therefore, I thought that GGN may be more appropriate for our study, but we will change it to GGO , if you additionally recommend .

Changes in the text:

Comment 11:

2. Abstract: Methods: please describe the exact analyses that were used.

Reply 11: Thank you for your comment. We have added the name of analyses that were used.

Changes in the text: We have added "using multivariable logistic regression analyses" in **abstract section page 2, line 20.**

Comment 12:

3. Key findings

Incidental ground glass nodules (GGNs) were found in 5.0% of patients with breast cancer.

- please add: "who underwent chest CT."

Reply 12: Thank you for your comment. We have added those paragraph in key findings

Changes in the text: Incidental ground glass nodules (GGNs) were found in 5.0% of patients with breast cancer who underwent chest CT **in page 4, line 60-61.**

Comment 13:

4. Results: Among 1384 patients who underwent chest CT for breast cancer, 69 (5.0%) had at least one persistent GGN.

How many patients had a non-persistent GGN?

Reply 13: Thank you for your comment. Out of 1384 patients, persistent GGNs were noted in 69 patients, and No GGNs (n=1315) included 20 patients with transient GGNs.

Changes in the text: We have included these numbers on **materials and methods in page 9, line 190-191.**

Comment 14:

5. Some patients had a history of malignancy. Please note the type of malignancy. In addition, how sure are the authors that the GGN with growth were not metastases?

Reply 14: Thank you for your important comment. After a thorough review, we included nine patients with a previous history of malignancy. This decision was based on the very low likelihood of metastasis in these patients and number of our study population was small. Specifically, we included patients who achieved complete treatment for their prior malignancy before breast cancer diagnosis or exhibited solitary persistent ground-glass nodules (GGNs) without interval growth for more than two years. Patients with GGNs growth (n=27) did not have any history of prior malignancy. Out of the nine patients, five had a history of thyroid cancer. Notably, these individuals did not exhibit solid lung nodules indicative of lung metastasis on chest CT. Two patients had a history of cervical cancer, which had been completely treated for approximately five years before they were diagnosed with breast cancer. Additionally, two patients with a history of bladder cancer demonstrated GGNs that displayed no interval change over a two-year period on chest CT. According to a previous study (Radiographics. 2001 Mar-Apr;21(2):403-17. Doi: 10.1148/radiographics.21.2.g01mr17403), lung metastasis from adenocarcinoma can show ground-glass opacities (in these cases diffuse extent of ground glass opacity not nodular shape, like in our cases), but the nine patients did not have prior adenocarcinoma malignancy.

Changes in the text: We added the types of **prior malignancy in Table 1, page 22**

Comment 15:

6. The authors state that the GGO are not related to the RT field. Table 1 shows that 48 patients had RT field related GGO, but also 48 patients had GGO detection before RT. From this I conclude that these 48 patients are not the same subjects, am I correct? It would be informative to have some more information on these patients. For example, how did the radiologists/radiotherapists conclude that the GGO was RT field related or not?

Reply15: Thank you for your comment. Out of the 69 patients, 48 patients had radiation therapy for breast cancer treatment. Therefore, the 48 patients who underwent radiation therapy were examined for the presence of an incidentally found GGO before RT based on the previous chest CT taken before RT or RT planning CT. When we reviewed, 38 out of the 48 patients who underwent radiation therapy had GGNs before radiation therapy. In table 2, expression of "RT-field related" maybe confusing. We wanted to show the location of GGN "ipsilateral or contralateral" with RT location (ex. RLL GGN, left RT history to the case contralateral). Not intended for RT area adjacent GGO.

Changes in the text: We changed "RT-field related" to "Location of GGO related to RT" in **Table 2 (page 24).**

Comment 16:

7. Discussion:

First sentence: In the study, we evaluated the incidence of GGN and the risk factors for its growth.

Would add: in patients with breast cancer.

Reply 16: Thank you for your comment. We have added those paragraphs as advised.

Changes in the text: “In this study, we evaluated the incidence of GGN and the risk factors for its growth in patients with breast cancer” in **page 11, line 240**