Peer Review File

Reviewer A:

Comments:

In this review, the Authors provided, with great details, an overview about the current diagnostic processes and therapeutic procedures for patients with early-stage lung cancer in the era of lung cancer screening. Particular attention has also been given to the lung cancer treatment during the COVID-19 pandemic. The article is well-written, clear and detailed, and it is also provided of a complete and updated bibliography. Particular attention has been paid on the current most controversial issues on this topic, such as the diagnostic management of patients with incidental small pulmonary nodules detected after LDCT screening, and the comparison between lobar and sublobar resection for the surgical treatment of early-stage lung cancer, providing also some interesting point of view. Except for a few minor linguistic imperfections, I have no significant comments to do.

Response to reviewer A:

Thank you for your positive review. Every effort has been made to review the work and correct any imperfections, including linguistic imperfections.

Reviewer B:

Comments:

This is an interesting review of the currently available diagnostic and therapeutic pathways for early stage NSCLC. As a review, the objectivity of the contents should be preserved. I would not structure the review as a series of questions representing each controversial issue but rather presenting the dilemma in an objective way without commenting from a personal perspective. Again, this is a review paper, not an expert opinion nor an editorial. Also, some clinical cases, if available, could help the

Readership in identifying the mainstays of the clinical approach to early stage NSCLC. I would also like to see the authors expanding the section on the choice of sublobar resections with regard to the possible adenocarcinoma subtypes (ie, micropapillary vs lepidic) and their prognostic impact. Lastly, the importance of newly discovered predictors of local recurrence (ie, STAS) should be mentioned. Moreover, the English language should be amended to improve readability.

Response to reviewer B:

Thank you for the review. We do agree with the reviewer that authors should maintain objectivity in accordance with the current medical knowledge. The paper has been reviewed, paragraphs containing particularly biased opinions were corrected. We agree that adding clinical cases would be a great illustration of the topics covered in this review. Nevertheless, due to the limitations of the number of words or figures and tables, adding case reports to each of the topics discussed would be beyond the scope of this report. Therefore, we have finally added the paragraphs suggested by the reviewer regarding adenocarcinoma subtypes, predictors of local recurrence and the influence of resection type.

Lung adenocarcinoma describes a heterogeneous group of neoplasms. Apart from the stage according to the TNM classification, the histopathological diagnosis is one of the most important prognostic factors. In a 2015 publication describing classifications of adenocarcinoma (70) clinically significant subtypes of adenocarcinoma were described such as adenocarcinoma in-situ (AIS), a pre-invasive neoplasm with a purely lepidic growth type. Minimally invasive adenocarcinoma (MIA), a lepidic tumor with an invasive component up to 5 mm in diameter, has also been defined (71). A publication by Yoshizawa et al. analyzed the impact of stage I adenocarcinoma subtype on disease-free survival (DFS) rates. Among the analyzed subtypes of adenocarcinoma, AIS and MIA have the best prognoses, as high as 100% 5-year DFS. Non-mucinous lepidic predominant, acinar predominant, and papillary predominant subtypes of adenocarcinoma have a slightly worse prognosis, with 5-year

DFS of 90%, 84% and 83%, respectively. The worst prognoses are observed among patients with invasive mucinous adenocarcinoma, solid predominant and micropapillary predominant adenocarcinomas, with 5-year DFS of 75%, 70% and 67%, respectively (72). Numerous studies have shown that a micropapillary subtype is a particularly poor prognostic factor (73–75). A study by Lee Geewon et al. found that the presence of > 1% of the micropapillary component influences the appearance of metastases and worsens the prognosis (74). According to Nitadori et al., the presence of more than 5% of micropapillary component is associated with increased risk of tumor recurrence after sublobar resection, but not after lobectomy. Micropapillary subtype is also associated with a higher risk of local recurrence or metastasis to the lymph nodes (75). Nevertheless, the adequate assessment of subtypes of adenocarcinoma is rarely available preoperatively. A sufficient tissue sample is rarely required in clinical stage I NSCLC in a patient who is a prompt surgical candidate. It is difficult to unequivocally assess the subtype of adenocarcinoma based on the radiological analysis of CT images. However, due to the progress in the field of radiomic evaluation, this tool may become helpful in the preoperative prediction of adenocarcinoma subtypes (76–79).

STAS. Another factor that may influence the choice between the sublobar resection and lobectomy is the occurrence of tumor spread through air spaces (STAS). STAS is defined as neoplastic cells — including micropapillary structures, solid nests, or single neoplastic cells — spreading within air spaces in the lung parenchyma beyond the edge of the main tumor (80). Kadota et al. observed the presence of STAS in 38% of operated patients who were diagnosed with adenocarcinoma with a tumor diameter of up to 2 cm. It was shown that the risk of recurrence was significantly higher in STAS-positive patients after sublobar resection compared to STAS-negative patients, 40.6% vs.10.9%. The presence of STAS significantly influences the risk of both local and distant recurrence. In contrast, there was no increased risk of recurrence in STAS-positive patients who underwent lobectomy. The presence of STAS may justify a lobectomy, but not a sublobar resection (80). Similar results were observed by Eguchi et al., who analyzed T1N0M0 patients diagnosed with adenocarcinoma who underwent

sublobar resection or lobectomy. That study confirmed the value of intraoperative examinations for detecting the presence of STAS. It has been shown that lobectomy is associated with better long-term results compared to sublobar resection in T1N0M0 STAS-positive lung adenocarcinoma patients (81). It is even more difficult to predict whether the tumor is STAS-positive comparing to preoperative assessment of adenocarcinoma subtype. Even histopathological sampling does not provide information about eventual STAS status. Radiological image of the solid tumor may be suggestive (82). However, similarly to adenocarcinoma subtypes, we do not have enough data to independently recommend changing of the surgical strategy basing on the premises concerning histopathological subtype or STAS status on the basis of radiomic assessment of solid tumors.

Qualification for sublobar resection of solid adenocarcinoma up to 2 cm should be cautious. Even small tumors may contain aggressive components such as a micropapillary component or the presence of STAS, while both features are unavailable preoperatively. Further work is needed to assess the influence of the adenocarcinoma subtype and the type of the surgery performed on the risk of local recurrence or long - term survival.

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