1. General remarks

The authors conducted a systematic review to evaluate the efficacy of intravenous ICG in identifying the intersegmental plane in patients undergoing segmentectomy via a minimally invasive approach. This systematic review showed that visualization of the intersegmental plane after administration of intravenous ICG is successful in up to 94% of cases, even after administration of a low dose of ICG. It also showed that the use of intravenous ICG is safe with no adverse effects in the immediate perioperative period. A recent randomized trial showed that overall survival after segmentectomy is superior to patients who underwent lobectomy for stage I NSCLC ≤2 cm, and recognition of the intersegmental plane is becoming increasingly important when performing anatomic segmentectomy. Therefore, I believe that the content of this article is appropriate for this journal. However, I have some concerns about this study. Therefore, I recommend that this paper be accepted after minor revisions. Below are some thoughts and comments to improve the paper.

2. Specific Comments

a) Minor

I) Page 5 line 16

Is the number of mVATS studies correct? I think that the number of mVATS studies is 14.

Dear reviewer,

Thank you very much for your thorough review of our article and for your valuable feedback. We appreciate your attention to detail. Regarding your comment there seems to be some confusion about the number of mVATS studies, and we would like to clarify that the data related to the Misaki study is, split into two separate arms. This may give the impression in the table that there are 14 studies with mVATS but actually there are 13.

II) Table 2

Isn't the mean total time in the paper by Pischik et al. 90 seconds instead of NR?

Thank you for your question regarding the paper by Pischik et al. The value of 90 seconds represents the median duration of achieving intensive ICG staining in the article, rather than the total duration until no staining is visible. We would like to make clear that we meant to report the total duration until no staining is observable. The total duration until no staining is visible is not reported in the article.

III) Table 2

Is the mean total time given for the Misaki et al. paper? I could not find it.

Thank you for your query regarding the Misaki et al. paper and the mean total time for intensive ICG staining. In the article, the marking time was reported in minutes. However, I

must clarify that the Misaki et al. paper specifically provided the median time with interquartile range (IQR) for the marking duration.

The conversion from median time with IQR to a mean value was performed using the formula derived from Wan et al as stated in the 'Methods' section. This transformation allowed us to present the data in a manner consistent with the statistical analysis across the studies in our systematic review.

IV) Table 2
The dose of ICG in the article by Matui et al. article is 0.05 tot 0.1 mg/kg; please correct to 0.05 to 0.1 mg/kg or 0.05-0.1 mg/kg.

Thank you. This is corrected.
(Table 2, page 28)

We are pleased to have the opportunity to review this paper.
The author's systematic review of the identification of pulmonary intersegmental planes using intravenous injections of indocyanine green is an interesting study. However, there is a problem that need to be corrected.

Major comments

1. Misaki et al. reported that in 3 of 10 cases (30%), all intersegmental planes were visualized and marked. They stated that fluorescence was either thin, mottled, or washed out early in the other cases, and did not state that identification was unsuccessful. In fact, their identification rate is far from the other papers. Is it appropriate to include their data in the analysis?

Thank you for your comment. It's important to emphasize that our systematic review aims to include studies based on predefined criteria. Excluding studies on a subjective basis is not aligned with the systematic review approach. However, we acknowledge the significance of mentioning and providing context for the difference in the identification rate reported by Misaki et al., and we will ensure to briefly highlight this aspect in the manuscript text.

It is believed that the frequency of segmentectomy is increasing worldwide. Indocyanine green (ICG) is widely used as a general method for demarcating segments, and this review will be valuable. However, some revisions might be necessary.

Major
Page 3, Line 37 – 39

"The primary outcome was the frequency and percentage of patients in whom the intersegmental plane is adequately visualized with the use of intravenous ICG such that a segmentectomy could be performed, including calculation of a weighted mean. Secondary outcomes were ICG dose, time to visualization, time to maximum ICG visualization, time to disappearance of ICG effect and the adverse reactions to ICG. Studies not reporting on the primary outcome were excluded."

As for the primary endpoint, can I understand it as the rate of achievement of segmentectomy in the end?　So, about Table 2, does "ISP visible?" mean equal to the achievement rate of segmentectomy of the target segment?

Thank you for your insightful question regarding the primary endpoint and the clarification needed for Table 2. The primary outcome refers to the frequency and percentage of patients in whom the intersegmental plane (ISP) is adequately visualized with intravenous ICG. Regarding Table 2, the column "number of segments" has been modified to "Number of surgical procedures," providing a more accurate reflection of the data. (Table 2, p28)
In all these procedures, patients underwent segmentectomy, and the utilization of intravenous ICG played a significant role in successfully visualizing the intersegmental plane (ISP). Among the patients who underwent a segmentectomy with the use of ICG, the intersegmental plane was adequately visualized in 94 percent of cases.

About Table 2
Could the number of segments be divided into simple and complex segmentectomy?

We appreciate your suggestion regarding the division of the number of segments into simple and complex segmentectomy. However, we did not make this distinction for the following reasons:

1. Not all studies included in our systematic review provided information to differentiate between simple and complex segmentectomies. The variability in reporting across studies limited our ability to consistently categorize the data in this manner.
2. The primary focus of our research was to assess the effectiveness of ICG in visualizing the intersegmental plane, rather than placing a strong focus on the technical differences in complexity among various types of segmentectomy procedures. Our goal was to primarily assess how well ICG enhances visibility during segmentectomy procedures overall.

About Table 2
By "AE" in these papers, do you mean "AE" caused by ICG drugs?

Correct, by "AE" in these papers, we are referring to adverse reactions specifically associated with the administration of ICG drugs.

Page 7, Line 21 – 24

"When looking at the outcome of inflation and deflation compared to ICG, the retrospective study of Sun et al. (2021) already highlighted that time to ISP visualization was significantly faster after ICG injection than after the use of the inflation-deflation method with visualization time respectively of 23.59 (SD 4.47) seconds vs. 1026.80 (SD 318.34) seconds (p < 0.001). (28) Thus, based on this data, ICG25 provides fast yet only short-term visualization of the ISP."

I believe the inflation-deflation method with visualization time is not only time-consuming.

A report by Suzuki et al. (Interdiscip Cardiovasc Thorac Surg
. 2023 Apr 3;36(4):ivad054. doi: 10.1093/icvts/ivad054.)
In which the inflation-deflation line is almost instantaneously visualized.
The authors should not be misled.

Thank you for bringing up the report by Suzuki et al. (Interdiscip Cardiovasc Thorac Surg. 2023 Apr 3;36(4):ivad054) and your suggestion regarding the inflation-deflation method. We appreciate your attention to detail. However, we would like to clarify that the inflation-deflation method discussed in our article refers to the conventional technique where the anesthesiologist reventilates the operated lung after clamping the relevant bronchus. This classic approach, as described in the studies we reviewed, involves a specific sequence of events. In the study you referenced, where the inflation-deflation line is almost instantaneously visualized, it appears to involve a different technique. Specifically, the bronchus is selectively inflated during the procedure by making a small incision in the target bronchus. While this may indeed be a promising alternative, it represents a distinct method from the traditional inflation-deflation approach described in our article. The study by Sun et al. (2021) focuses on the traditional inflation and deflation method. In our opinion, it's like comparing apples to oranges since those are two different techniques.

<mark>Reviewer D</mark>
While your review provides valuable insights into an important thoracic surgery topic, there are some areas that could be refined to further enhance the quality and impact of the work. Here are some respectful suggestions that could potentially improve the manuscript if you choose to implement them:

Introduction
- Consider expanding the explanation of the underlying mechanism facilitating intersegmental plane identification after ICG administration to assist readers' comprehension.
Thank you for your suggestion to expand the explanation of the underlying mechanism facilitating intersegmental plane identification after ICG administration. We have revisited the relevant section in the introduction and have now provided a more detailed and clarified explanation of the procedure. (P5,L 21-26)

- Consider expanding the description of the clinical significance of properly identifying the intersegmental plane. Highlight how it can improve outcomes in segmentectomies by

enabling better lung function preservation and reducing complications. This will better showcase the motive for evaluating the use of ICG for identifying intersegmental planes.

Thank you for your suggestion to expand the description of the clinical significance of properly identifying the intersegmental plane. We would like to highlight that the importance of precise intersegmental plane identification and its impact on outcomes in segmentectomies are already addressed in the introduction. Specifically, the following paragraph emphasizes the necessity of a careful division of the intersegmental plane for functional lung preservation, complication prevention, and achieving optimal oncological outcomes:
"A careful division of the intersegmental plane is mandatory in terms of functional lung preservation, prevention/avoidance of complications, adequate tumor margins for providing the best oncological outcome in terms of disease-free survival and recurrence." P5L15-20

Methods
- For the data analysis, you may consider examining the relationship between ICG dose and visualization rates through regression analysis to elucidate any potential dose-response trends. This may better guide optimal dose recommendations.

Thank you for your suggestion to examine the relationship between ICG dose and visualization rates through regression analysis in our data analysis. Although we fully agree that regression analysis may yield information regarding the dose-response, it was statistically not feasible to perform such analysis. This is because not all studies used identical units (e.g., mg/kg vs mg) nor was the number of dosages provided always clear. It would be possible to use the mean weight of included patients to convert these units, however, this introduces uncertainties due to which interpretation of its results becomes troublesome. In this case it is best to clearly describe the limitations instead of trying to produce results with even greater limitations.

Results
- Consider including quantitative indicators of heterogeneity (e.g., I2 statistic) to characterize variability across protocols.

Thank you for your suggestion to include quantitative indicators of heterogeneity, such as the I2 statistic, to characterize variability across protocols in our systematic review. As mentioned earlier, adjusting the source data to address this heterogeneity might compromise the integrity of the results.

- Reporting intra-study variability (e.g., standard deviations) in outcomes would provide deeper insights into the consistency of ICG performance for each study setting.

Thank you for your suggestion regarding reporting intra-study variability in outcomes. We have now incorporated standard deviations where possible and made corresponding

adjustments to Table 2 to provide a more comprehensive overview of the consistency of ICG performance within each study setting.
Table 2, P28

Discussion
- Consider elaborating further when contrasting findings of special interest studies (e.g., Misaki et al.) to guide interpretation of discordant results.
We appreciate your suggestion to provide additional elaboration to guide the interpretation of discordant results. In our revised manuscript, we have made efforts to offer a more in-depth discussion, explaining the factors that might contribute to discrepancies in study outcomes. P13, L28-37

- Consider discussing limitations related to subjectivity of intersegmental plane visualization scoring by surgeons as an area needing better standardization.
Thank you for your suggestion to discuss limitations related to the subjectivity of intersegmental plane visualization scoring by surgeons. The following paragraph highlights the subjective nature of the primary endpoint and the need for better standardization: "Perhaps the most important limitation is that the primary endpoint, adequate visualization of the ISP, is not a clearly objectively measurable primary endpoint. The visualization is obviously subjective and is co-determined by the surgeon's interpretation, the NIR camera used, the darkening in the operating theatre, etc." P15 L19-22

- Further comparing ICG to alternative intersegmental plane identification modalities may better position its advantages and disadvantages for adoption.
Thank you for your suggestion to further compare ICG to alternative intersegmental plane identification modalities. We do think that we have thoroughly discussed the advantages and disadvantages of various techniques in the manuscript. As evidence of this, we provided a comprehensive overview of alternative methods, including endobronchial administration of ICG and the inflation-deflation technique.
For the endobronchial approach, we highlighted its advantage of not requiring lung inflation, conserving space during thoracoscopic surgeries. However, we also addressed the drawback of potential retrograde spread of the dye, compromising ISP identification, and emphasized the need for a bronchoscopy-experienced professional.
Regarding the inflation-deflation technique, we discussed its simplicity but noted limitations such as impaired surgical visualization, particularly in minimally invasive procedures, and potential complications related to collateral ventilation. Additionally, we presented data from the retrospective study of Sun et al. (2021) comparing ICG injection to the inflation-deflation method, showing that ICG provides fast yet short-term visualization of the ISP. We also compared outcomes between ICG and the inflation-deflation method in terms of intersegmental line development, operation time, and prolonged air leaks. The literature suggests that ICG is more user-friendly, with faster ISP visualization and minimal side effects, albeit with the requirement of an infrared camera, which may entail additional costs.

In conclusion, we have extensively covered the advantages and disadvantages of various techniques, providing readers with a well-rounded understanding of their respective merits and drawbacks.

- Discussing cost-benefit implications of the technique could help readers weigh financial considerations when considering its adoption.

Thank you for highlighting the importance of discussing cost-benefit implications. Intravenous ICG administration during segmentectomy offers potential advantages, including a shorter operation time and a reduced risk of air leakage. While initial costs may be involved, improved surgical outcomes could lead to long-term cost savings. However, it's crucial to acknowledge that these are speculative benefits, and comprehensive cost-benefit analyses are needed to validate these assumptions.
P15 L9-15

- You may consider providing clearer best-practice recommendations based on review findings, as guidelines for ICG dose, delivery method, and repeating doses to maximize intersegmental plane visualization.
We have provided clearer best-practice recommendations based on the review findings for indocyanine green (ICG) administration to maximize intersegmental plane (ISP) visualization. P15, L 29-38
Overall, inclusion of these suggested supplementary details and analyses would serve to strengthen the clarity, thoroughness, transparency, and impact of this well-executed systematic review assessing an important evolving surgical technology.

<mark>Reviewer E</mark>
This review article was well written.
I think the limitation of ICG usage for ISP identification should be added such as black-pigmented anthracite lung, and poor liver function.

Thank you for your positive feedback on the review article. Regarding the limitations of ICG usage for ISP identification, we appreciate your suggestion. We have indeed addressed the aspect of anthracosis more specifically in the article, referring to the study by *Iizuka et al. (2016)*. However, regarding the impact of poor liver function, we did not find immediate references within our current scope. In a brief search on PubMed, we came across studies indicating the potential of ICG in liver surgery as a predictor of poor liver function, such as the study by *Schwarz et al. (2019)*.
P13 L 22-27

Schwarz C, Plass I, Fitschek F, Punzengruber A, Mittlböck M, Kampf S, Asenbaum U, Starlinger P, Stremitzer S, Bodingbauer M, Kaczirek K. The value of indocyanine green clearance assessment to predict postoperative liver dysfunction in patients undergoing liver resection. Sci Rep. 2019 Jun 10;9(1):8421. doi: 10.1038/s41598-019-44815-x.   PMID: 31182746; PMCID: PMC6557886.

P2L1

The decimal point is incorrectly written as ", " (comma), so it should be ". " (dot). This error is found throughout the manuscript and needs to be corrected.

Thank you for pointing out the inconsistency in the use of decimal points throughout the manuscript. We appreciate your attention to detail, and we acknowledge the importance of maintaining consistency in this matter.
We will promptly correct this error by ensuring that decimal points are consistently represented as ".".

P3L20

"The aim of this systematic … while performing minimally invasive segmentectomies."
This is about the above sentence. The term "minimally invasive" might be used because this review summarizes reports under uVATS, mVATS, and RATS and does not include open thoracotomy, but thoracoscopic or robot-assisted segmentectomy is already a standard procedure, so the term "minimally invasive" is not necessary. Consideration of alternative phrases such as "thoracoscopic segmentectomy", "video or robot-assisted surgery", or "video/robot-assisted thoracoscopic segmentectomy" is recommended.

Thank you for your insightful suggestion regarding the term "minimally invasive" in the sentence you mentioned.   We will make the necessary adjustments to replace "minimally invasive" with more specific and accurate alternatives. P1 L 8 and 14; P6 L2, L9 and L13

P6L43

"." (dot) in "CT(LAA) > 1.0%." is unnecessary.
We will make the necessary adjustments. P13 L21

Table X

The reference number seems to be different from other tables. Please check.
Thank you for bringing the inconsistency in the reference numbers to our attention. We will ensure that the reference numbers in the table align consistently with the rest of the manuscript.

Overall, I think this is a well-written review. As a minor comment, the extremely low ISP visualization rate of 30% at the lowest bolus dose concentration of 0.09 mg/kg, is not adequately discussed. This should have been discussed in the original paper, but unfortunately it was not, and should be discussed in more detail in the Discussion section of this review manuscript to help readers. The patient's weight, circulating blood volume, blood pressure, liver function, bolus speed, detector type, sensitivity, position, etc. may also be relevant.

Thank you for your positive feedback on our review, and we appreciate your minor comment regarding the low intersegmental plane (ISP) visualization rate at the lowest bolus dose concentration. We have taken your suggestion into consideration and have added a more detailed discussion in the manuscript. We agree that various factors, including patient-related parameters such as weight, circulating blood volume, blood pressure, liver function, bolus speed, and detector specifications might influence ISP visualization. However, it's essential to note that many (or all) of these factors were not consistently reported in the reviewed publications, making it challenging to make comprehensive assessments.
We hope this additional information addresses your concern.

"The mean time before the effects of ICG became visible ranged from 10 to 40 seconds, with adequate visibility lasting from 90 to 140 seconds The following bolus injection and 170 seconds after continuous infusion (Page 6 line 50-52)" is simply a repetition of the results and should be deleted or some discussion added.

We appreciate your keen observation, and we agree that this information seems redundant. We will promptly revise the text to eliminate the repetition. P14 L1-3

The tense of "The primary outcome was the frequency and percentage of patients in whom the intersegmental plane is adequately visualized (Page 3 line 38)' is wrong. It should be "was", because all other sentences in Methods were past.

We appreciate your careful review, and we have promptly corrected the tense to "was" to align with the past tense used in the rest of the Methods section.
P6 L19