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Intraoperative frozen section for identifying the invasion status of lung adenocarcinoma: A systematic review and meta-analysis

Feng Li[a,1], Lin Yang[b,1], Yue Zhao[a], Ligong Yuan[a], Shuaibo Wang[a], Yousheng Mao[a,*]

[a] Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

[b] Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

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ABSTRACT

Background: For early-stage lung adenocarcinoma, determining the extent of surgical resection and lymphadenectomy according to the invasion status of the tumour may be more reliable. Intraoperative frozen section (FS) is a potentially effective method to identify the invasion status while its accuracy is still unknown. This meta-analysis aimed to evaluate the accuracy of FS for the invasion status of lung adenocarcinoma.

Methods: We conducted a systematic search of PubMed, Embase, Scopus and Cochrane Library databases (from inception to October 26, 2018) to identify studies investigating the accuracy of FS for the invasion status of lung adenocarcinoma. The accuracy of FS was evaluated by calculating the pooled concordance rates (CCR) between FS and final pathology and the pooled sensitivity, specificity, and other parameters of FS for discriminating pre-/minimally invasive adenocarcinoma from invasive adenocarcinoma (IAC). The negative predictive value (NPV) of FS for diagnosing IAC was also calculated to evaluate the chance of underestimation.

Results: Six eligible studies were included. The pooled CCR for differentiating pre-invasive adenocarcinoma, minimally invasive adenocarcinoma and IAC was 88% (95% CI, 84%–93%). When pre-invasive adenocarcinoma and minimally invasive adenocarcinoma were classified as a group, the pooled CCR, sensitivity, specificity of FS for differentiating pre-/minimally invasive adenocarcinoma from IAC were 95% (95% CI, 94%–97%), 95% (95% CI, 92%–97%), 95% (95% CI, 80%–99%), respectively. The pooled NPV of FS for diagnosing IAC was 95% (95% CI, 92%–97%).

Conclusions: Intraoperative FS is reliable for identifying the invasion status of lung adenocarcinoma, with high diagnostic accuracy for differentiating pre-/minimally invasive adenocarcinoma from IAC.

1. Introduction

The increasing detection of early-stage lung adenocarcinoma has stimulated interest in limited resection, which can preserve lung function, reduce perioperative morbidity and provide a chance of resection for a subsequent primary lung cancer [1,2]. However, to date, the optimal extent of surgical resection and lymphadenectomy for early-stage lung adenocarcinoma remains controversial. Most surgeons select limited resection according to tumour size or imaging characteristics [3–7]. However, there have been no standard criteria for these methods yet. And a recently published study has found that it is not appropriate to decide surgical strategies solely according to the imaging performances [8]. Furthermore, lymph node metastasis can be found even in tumours ≦1 cm or pure ground-glass opacity lesions [3,9,10]. Limited resection has the disadvantage of inadequate lymph node dissection. Thus, the indications for limited resection should not be based on tumour size or imaging characteristics alone.

According to the newly proposed classification by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society, lung adenocarcinoma can be classified into atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma (IAC) [11]. Recent studies have shown that in early-stage lung adenocarcinoma, the invasion status has a significant impact on the extent of surgical resection and lymphadenectomy [8,9,12–15]. For pre-invasive adenocarcinoma (AAH/AIS), limited resection has been considered a standard treatment by the National Comprehensive Cancer Network guideline [16]. For MIA, multiple studies have shown that it

* Corresponding author.
E-mail address: youshengmao@gmail.com (Y. Mao).
[1] These authors contributed equally to the work.

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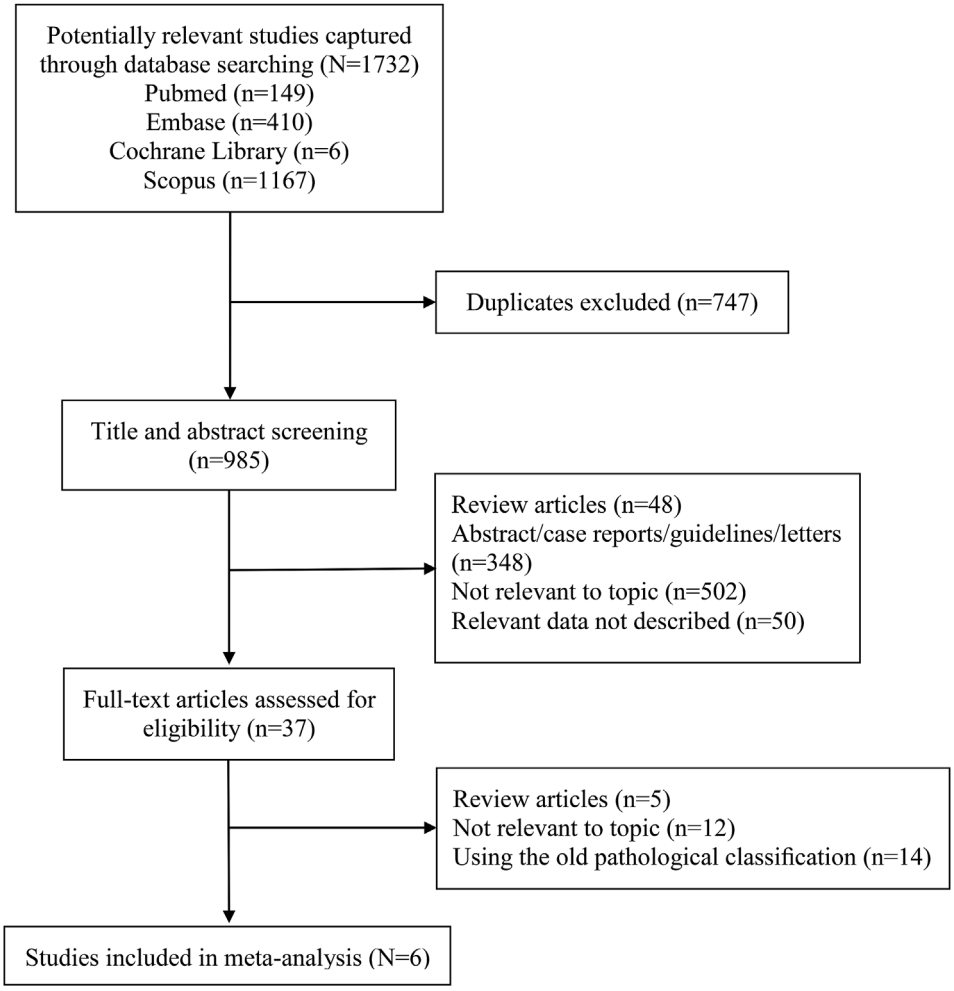

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of inclusion and exclusion of studies.

has an excellent prognosis regardless of the extent of surgical resection [15,17–19]. Moreover, the second European Society for Medical Oncology consensus conference on lung cancer considered limited resection a reasonable treatment for MIA [20]. Besides, AAH, AIS, and MIA are associated with negative mediastinal nodal metastasis [9,12,13]. Therefore, systematic mediastinal lymphadenectomy can be omitted for them. However, for IAC, which is more invasive with a higher rate of lymph node metastasis, more aggressive methods should be used to ensure the oncological validity [9,13,14,21].

Thus, for early-stage lung adenocarcinoma, it would be helpful if the invasion status is available when surgeons are making decisions on the extent of surgical resection and lymphadenectomy. Intraoperative frozen section (FS) may be a feasible option [21]. However, whether FS can accurately identify the invasion status remains unclear. Therefore, we conducted a systematic review and meta-analysis to investigate the accuracy of FS for the invasion status of lung adenocarcinoma.

2. Materials and methods

2.1. Protocol and registration

This systematic review was registered in the PROSPERO database (CRD42018117152) based on a prespecified protocol and it was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22] and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines [23].

2.2. Search strategy

We performed a comprehensive electronic search of PubMed, Embase, Scopus and Cochrane Library databases (from inception to October 26, 2018). MeSH terms, Emtree terms, and free words were all used. The search terms were as follows: “non-small cell lung cancer”, “lung adenocarcinoma”, “adenocarcinoma of lung” and “frozen sections”. We also screened the reference lists of all relevant articles for potentially suitable studies. The detailed search strategy is presented in Appendix A.

2.3. Inclusion and exclusion criteria

The inclusion criteria were: (1) studies investigating the diagnostic accuracy of intraoperative FS for identifying the invasion status or subtypes of lung adenocarcinoma; (2) the reference standard, also known as golden standard, was paraffin-embedded section (final pathology, FP); (3) both FS and FP should be based on the new classification of lung adenocarcinoma. The following studies were excluded: (1) diagnoses were not based on intraoperative FS; (2) FS and FP were based on the old pathological classification; (3) the reference standard was not paraffin-embedded section; (4) studies without information to retrieve true-positive, false-positive, false-negative and true-negative values of FS for the invasion status; (5) reviews, case reports, guidelines, conference abstracts and letters.

Table 1
Main characteristics of the studies included in the systematic review and meta-analysis.

Study	Country	Year	Type of study	Year of diagnosis	No. of patients	Pathological types	Stage	Tumour Size	Sex (M/F)	Surgical strategies	No. of sections	No. of pathologists
Walts et al. [25]	USA	2012	Retrospective	2006–2009	224	AIS, MIA, IAC	NA	0.2–7.0 cm	NA	Wedge resection/more extensive resection	Two or more (mostly)	One (mostly)
Yeh et al. [26]	USA	2015	Retrospective	1995–2009	35	AIS, MIA, IAC	Pathological stage I	≦3 cm	NA	NA	One	Five
Liu et al. [15]	China	2015	Retrospective	2012–2014	803	AAH, AIS, MIA, IAC	Clinical stage I	≦3 cm	258/545	Wedge resection/Segmentectomy/ Wedge plus Lobectomy	Two (mostly)	Two
He et al. [27]	China	2016	Retrospective	2011–2015	136	AIS, MIA, IAC	Clinical stage I	≦3 cm	46/90	Lobectomy/Limited resection	Two	Three
Cheng et al. [12]	China	2018	Retrospective	2012–2015	126	AIS, MIA, IAC	Clinical Stage I	≦3 cm	NA	Lobectomy/Limited resection	One or two (mostly)	Two
Zhu et al. [28],[a]	China	2018	Retrospective	2015–2016	Data set one: 1111; Data set two: 1322;	AAH, AIS, MIA, IAC	NA	NA	NA	Lobectomy/Limited resection	Two or three	Two or three

Abbreviations: AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IAC, invasive adenocarcinoma; NA, not available.
[a] This study had two separate data sets about the concordance rate for differentiating between AAH/AIS/MIA and IAC.

2.4. Study selection

Two authors independently reviewed the titles and abstracts of all retrieved articles to decide which study to retain. Each author was blinded to the other's decisions. Any discrepancies were resolved by discussion and consensus with a third author. The full-text versions of all retained studies were obtained and reviewed in the same way as mentioned above to decide the final eligible studies.

2.5. Quality assessment and data extraction

Two authors assessed the methodological quality of all studies independently, using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [24]. The tool has four domains: patient selection, index test (FS), reference standard (FP), and the flow and timing of tests. The risk of bias of each study was assessed as follows: (1) low, if there was a low risk of bias in all domains; (2) unclear, if we could not assess the risk of bias in one or more domains; and (3) high, if the risk of bias was high for one or more domains. Discrepancies regarding the methodological quality of the studies were solved by discussing with a third author.

For each study, we extracted the following information: study characteristics (first author's name, country, publication year, study design, number of patients), patient characteristics (year of diagnosis, sex, surgical strategies), tumour characteristics (pathological subtypes, stage, tumour size, number of sections examined by FS and number of pathologists for FS diagnosis) and outcomes (true-positive, true-negative, false-positive, and false-negative values).

2.6. Data analysis

The primary outcome of this meta-analysis was the diagnostic accuracy of intraoperative FS for the invasion status of lung adenocarcinoma. To investigate the accuracy, two groups were created: (1) pre-invasive adenocarcinoma (AAH/AIS) vs MIA vs IAC; (2) pre-/minimally invasive adenocarcinoma (AAH/AIS/MIA) vs IAC. The concordance rates (CCR = cases diagnosed correctly/total cases) between FS and FP for the invasion status were calculated, and they were pooled using the random effect model if there was heterogeneity among the studies. Besides, to investigate the impact of tumour size on the accuracy of FS, we separated the patients into two groups by tumour size (≦1 cm vs > 1 cm) if relevant data were available in the studies. The presence of a threshold effect was evaluated using the Spearman's coefficient. If there was no threshold effect, the pooled sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio of FS for discriminating AAH/AIS/MIA from IAC were calculated using a bivariate model. A summary receiver-operating characteristic curve (ROC) was constructed, and the area under the curve (AUC) was computed to assess the overall diagnostic performance of FS. Besides, the pooled negative predictive value [NPV = true negative/(true negative + false negative)] of FS for diagnosing IAC was also calculated.

The Q test and I^2 test were used to assess the significance of heterogeneity among studies. The heterogeneity was considered to be statistically significant if the I^2 value > 50% or the p-value of the Q test < 0.05. If there was significant heterogeneity, multiple univariable meta-regression and subgroup analyses were carried out to explore potential sources. When the meta-regression was carried out, studies were categorized into subgroups according to these variables: “country of studies”, “quality of studies”, “year of diagnosis”, “number of sections examined” and “number of patients included”. Variables were considered to contribute to the heterogeneity if $p < 0.05$. Besides, we used sensitivity analysis to assess the robustness of the results by excluding studies at high risk of bias. Finally, publication bias was assessed using the Deeks funnel plot. Statistical analyses were performed using STATA 15.0 for Windows (Stata Corp, College Station, Texas) and

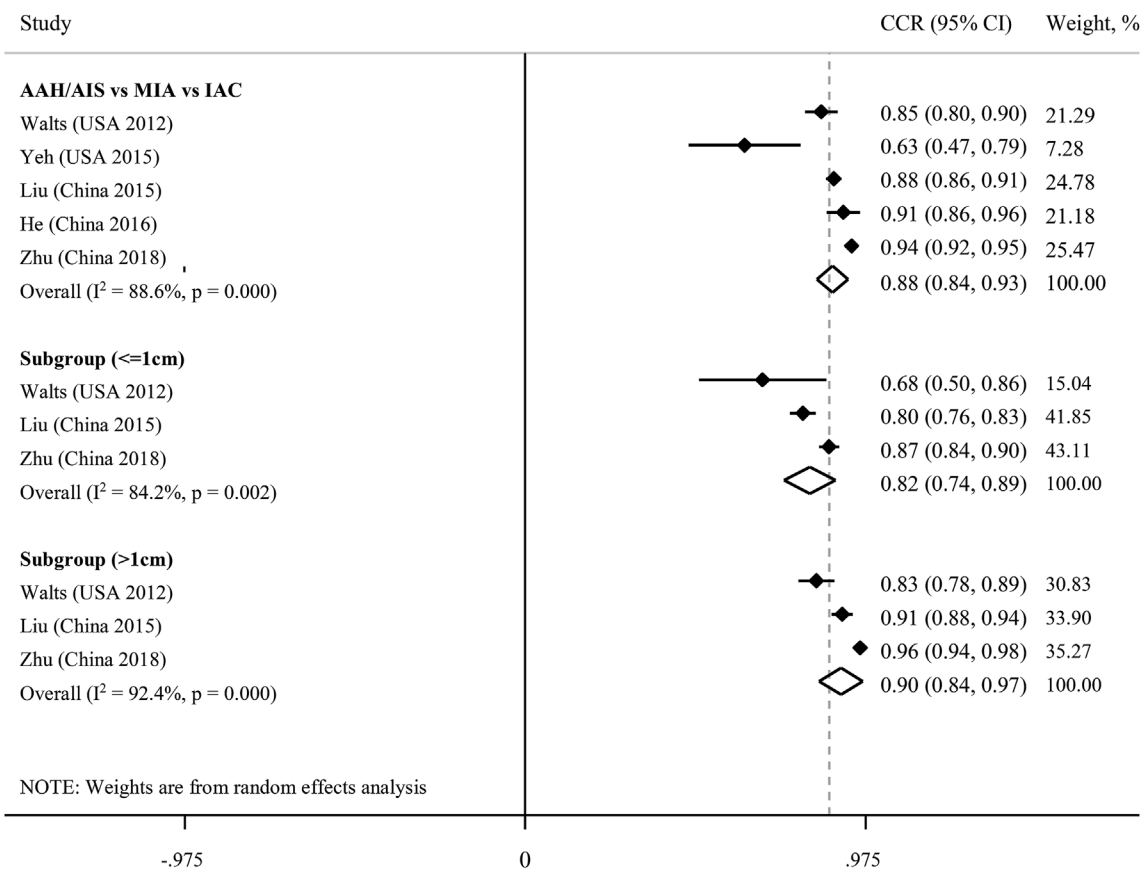

Fig. 2. Concordance rates between frozen section and final pathology for distinguishing AAH/AIS, MIA and IAC. (CCR, concordance rate; CI, confidence interval).

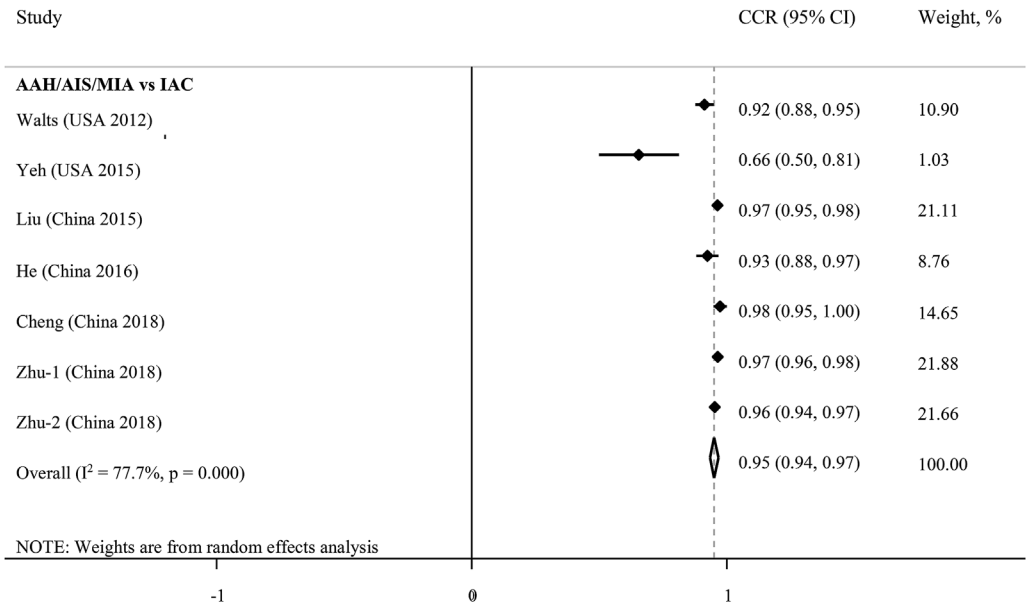

Fig. 3. Concordance rates between frozen section and final pathology for distinguishing AAH/AIS/MIA and IAC. (CCR, concordance rate; CI, confidence interval; Zhu-1,2 stands for two data sets in one study [28]).

Meta-DiSc 1.4 (Ramón y Cajal Hospital, Madrid).

3. Results

3.1. Search results and characteristics of included studies

The search initially generated 1732 relevant articles. Finally, six eligible studies containing a total of 3757 patients met the inclusion criteria and were included (Fig. 1).

The main characteristics of the included studies are displayed in Table 1. All studies were performed in two countries: two in the USA [25,26], four in China [12,15,27,28]. Three studies [15,25,28] included more than 200 patients while the remaining three [12,26,27] included fewer than 200 patients. In most of the studies, tumours were ≤3 cm

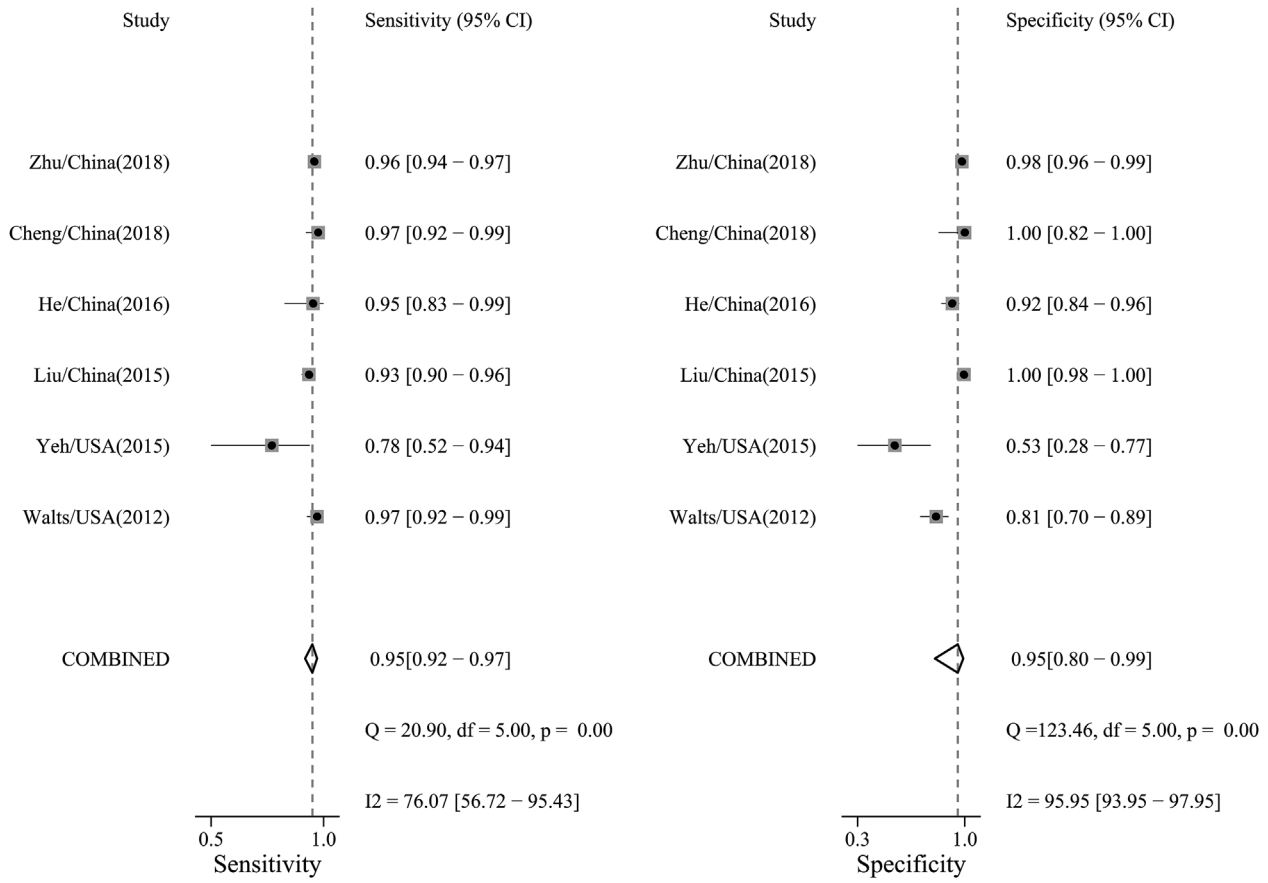

Fig. 4. Forest plots of sensitivity and specificity of intraoperative frozen section for distinguishing between AAH/AIS/MIA and IAC. (CI, confidence interval).

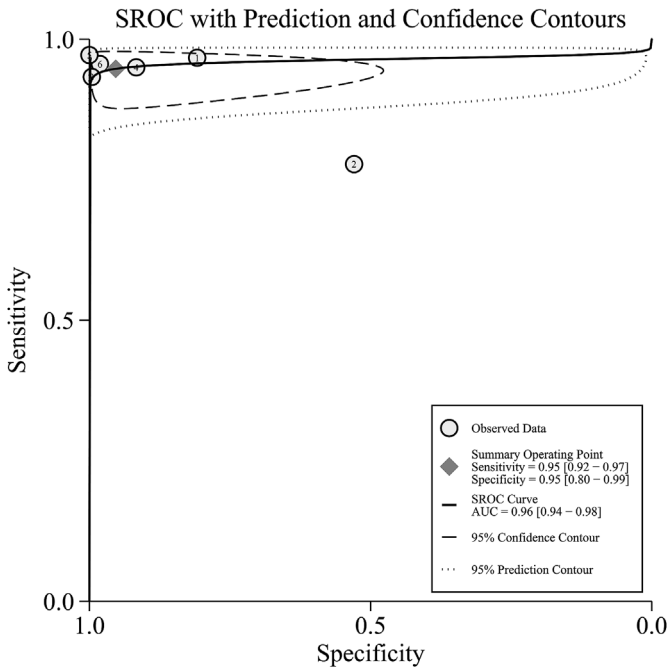

Fig. 5. Summary ROC curve of intraoperative frozen section for distinguishing between AAH/AIS/MIA and IAC.

[12,15,26,27]. As for the number of specimen sections examined during intraoperative FS, four studies [15,25,27,28] examined two or more sections while the other two examined fewer than two sections [12,26]. In almost all studies, frozen sections were reviewed by at least two pathologists [12,15,26–28]. Besides, in two of the included studies [25,26], the new classification was retrospectively applied to the frozen sections which were made before 2011 when the new lung adenocarcinoma classification was first introduced.

3.2. Quality assessment of studies and publication bias

The quality assessment of the included studies is displayed in Supplementary Fig. 1. Two studies [25,26] had a high risk of bias in the domain of patient selection, and they were categorized into the high-risk subgroup. The reference standards in all studies and the index tests in two studies [25,26] were at unclear risk of bias. The Deeks funnel plot identified no publication bias (p = 0.10, Supplementary Fig. 2).

3.3. Accuracy for differentiating AAH/AIS, MIA and IAC

Five of the included studies had relevant data for evaluating the accuracy of FS for distinguishing AAH/AIS, MIA and IAC [15,25–28]. The pooled CCR between FS and FP was 88% (95% CI, 84%–93%; Fig. 2). Three studies [15,25,28] reported CCRs according to tumour size. When the patients in these three studies were separated into two groups by tumour size, the CCR in tumours ≦1 cm was lower than that in tumours > 1 cm (82% vs 90%; Fig. 2).

3.4. Accuracy for differentiating between AAH/AIS/MIA and IAC

When AAH, AIS and MIA were classified as the pre-/minimally invasive group, all studies had relevant information for calculating the accuracy of FS for differentiating AAH/AIS/MIA from IAC, and one of these studies had two separate data sets [28]. The pooled CCR was 95% (95% CI, 94%–97%; Fig. 3). The summary estimates of sensitivity and

Table 2
Pooled results of the meta-analysis of the diagnostic accuracy of FS for the invasion status.

Types	No. of studies	CCR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR-(95% CI)	DOR (95% CI)	NPV (95% CI)	Summary AUC (95% CI)
AAH/AIS *vs* MIA *vs* IAC	5	0.88 (0.84–0.93)	-	-	-	-	-	-	-
AAH/AIS/MIA vs IAC	6 (7 data sets)	0.95 (0.94–0.97)	0.95 (0.92–0.97)	0.95 (0.80–0.99)	20.20 (4.25–95.87)	0.06 (0.03–0.09)	366.30 (64.62–2076.44)	0.95 (0.92–0.97)	0.96 (0.94–0.98)
AAH/AIS/MIA vs IAC (low risk of bias)	4 (5 data sets)	0.96 (0.95–0.97)	0.98 (0.94–0.99)	0.95 (0.93–0.97)	50.54 (15.18–168.24)	0.05 (0.03–0.07)	1083.66 (379.77–3092.19)	0.95 (0.93–0.97)	0.98 (0.96–0.99)

Abbreviations: FS, frozen section; IAC, invasive adenocarcinoma; CCR, concordance rate; LR +, positive likelihood ratios; LR-, negative likelihood ratios; DOR, diagnostic odds ratio; NPV, negative predictive value; AUC, area under the ROC curve.

specificity were 95% (95% CI, 92%–97%) and 95% (95% CI, 80%–99%) (Fig. 4), yielding a summary AUC of 0.96 (95% CI 0.94–0.98; Fig. 5). The pooled LR + and LR– were 20.20 (95% CI, 4.25–95.87) and 0.06 (95% CI, 0.03–0.09), respectively (Table 2). The pooled NPV of FS for diagnosing IAC was 95% (95% CI, 92%–97%; Fig. 6).

3.5. Heterogeneity and meta-regression

The Spearman's coefficient between sensitivity and 1 – specificity was −0.143 (p = 0.787), indicating no threshold effect. However, there was significant heterogeneity regarding the sensitivity (I^2 = 76.07; p = 0.00) and specificity (I^2 = 95.95; p = 0.00) of FS for differentiating AAH/AIS/MIA from IAC (Fig. 4). To figure out the possible source of heterogeneity, we performed meta-regression and subgroup analyses (Fig. 7). According to the characteristics of the included studies, variables were categorized as follows: country (the USA vs China), quality of studies (high risk vs low risk), year of diagnosis (before 2011 vs after 2011), number of sections examined (< 2 vs $\geqq 2$) and number of patients included in the studies (< 200 vs $\geqq 200$).

The result showed that the heterogeneity of sensitivity might be caused by the first three variables (country, quality of studies and year of diagnosis; all $p < 0.001$) while the heterogeneity of specificity might be caused by all five variables (country, quality of studies, year of diagnosis, number of sections and number of patients; all $p < 0.001$). However, in the joint model analysis (not shown), only the first three variables were the major source of heterogeneity. Interestingly, these three variables (studies from the USA; studies at high risk of bias; year of diagnosis < 2011) all corresponded to two studies [25,26]. In these two studies, the new classification was retrospectively applied to the sections which were made before the release of this classification. Before the new classification was proposed, pathologists only focused on the presence of invasion while the main concern of the new classification was the extent and size of invasion [25]. To assess the robustness of the results, we performed a sensitivity analysis by excluding these two studies. As shown in Table 2, the removal of these two studies did not noticeably change the results.

4. Discussion

In early-stage lung adenocarcinoma, the invasion status is a more reliable predictor of biological behaviour than tumour size [29]. Many studies have demonstrated that AAH, AIS, and MIA are associated with negative mediastinal nodal metastasis [9,12,13]. For these subtypes, limited resection is adequate and systematic mediastinal lymphadenectomy may not be required [12,15,19]. However, for IACs, lobectomy with systematic mediastinal lymphadenectomy is more reasonable due to the higher rate of lymph node metastasis and increased risk of recurrence after limited resection [12,13,30,31]. Thus, with the increasing use of limited resection, it is imperative to recognize the invasion status of lung adenocarcinoma before or during surgery to ensure the oncological validity.

Three methods (CT-scan, preoperative biopsy, and intraoperative FS) can be used to identify the invasion status of early-stage lung adenocarcinoma. Even though many studies have investigated the performance of CT-scan, the accuracy is unstable and the reproducibility is unsatisfactory due to different parameters or cut-off values used [32–34]. In terms of preoperative biopsy (transbronchial biopsy or transthoracic fine-needle biopsy), accurate diagnosis is challenging because it is hard to locate and sample the small lesions and the biopsy specimens may not represent the whole tumour [25,35]. Besides, at present, some histological patterns can only be identified on resected specimens rather than biopsy samples [35,36]. Therefore, intraoperative FS seems to be a better option. According to the new classification, the diagnosis of AIS and MIA should be rendered after the entire lesion is submitted for histologic examination [11]. However, surgeons need intraoperative FS diagnosis of the invasive status to

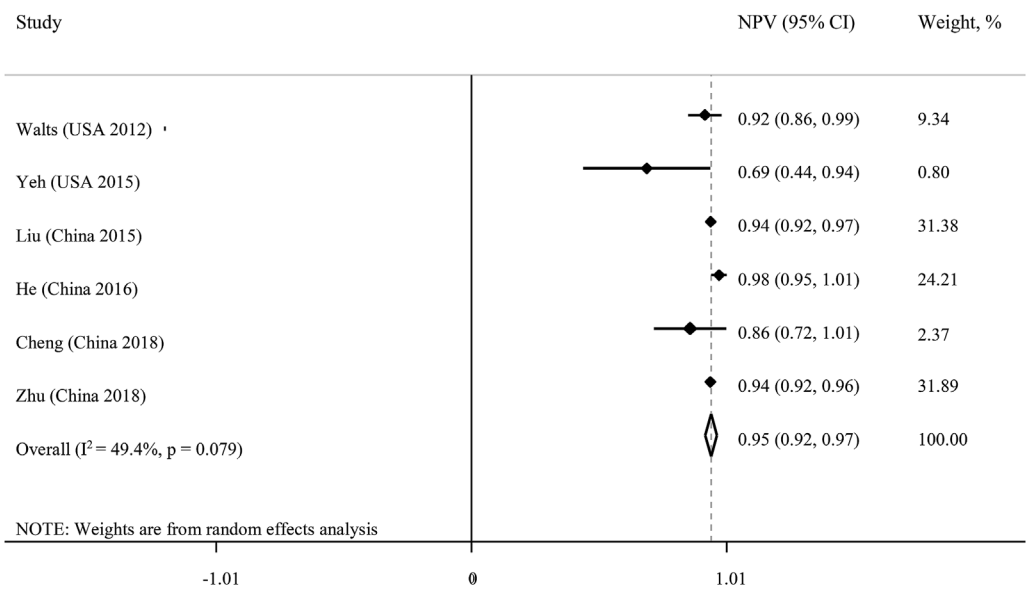

Fig. 6. Negative predictive values of intraoperative frozen section for the diagnosis of IAC. (CI, confidence interval; NPV, negative predictive value).

guide surgical strategies. Thus, it is imperative to figure out whether FS can identify the invasion status accurately.

In this meta-analysis, we found that intraoperative FS had reasonable accuracy for differentiating pre-invasive adenocarcinoma (AAH/AIS), MIA and IAC. The CCR between FS and FP was 88%, and it increased to 95% when AAH, AIS and MIA were merged into a group. AIS and MIA have similar characteristics regarding growth pattern and grade of nuclear atypia [27]. Besides, alveolar spaces are often collapsed in FS [15,26]. All these cause difficulties in distinguishing AIS and MIA [15,26–28]. However, these difficulties may not lead to a difference in patient management. Many studies have demonstrated that AAH, AIS and MIA have excellent prognoses regardless of surgical strategies, with 5-year overall survival approaching 100% [15,17–19,37]. Therefore, there is little clinical significance in differentiating AAH, AIS and MIA in FS. Given the difficulties in distinguishing AIS from MIA, it would be better to treat AAH, AIS and MIA as a whole group when using FS to guide the surgical strategies.

After classifying AAH, AIS and MIA as a group, we found that FS had excellent sensitivity (95%) and specificity (95%) for distinguishing between AAH/AIS/MIA and IAC. Moreover, the overall diagnostic performance assessed by AUC (AUC = 0.96) was also excellent. Likelihood ratios are more meaningful in clinical practice. In this meta-analysis, LR+ of intraoperative FS was more than 10, and LR− was less than 0.1, indicating an excellent performance for distinguishing AAH/AIS/MIA from IAC [38]. Besides, the pooled NPV of FS for diagnosing IAC was 95%. Therefore, the chance of underestimation (AAH/AIS/MIA in FS and IAC in FP) is very low. If patients with a FS diagnosis of AAH/AIS/MIA receive limited resection, only a few of them (5%) would undergo inadequate resection and need a second operation for definitive treatment. Furthermore, most of the underdiagnosed cases were lepidic predominant adenocarcinoma (LPA) [12,15,26,28]. Previous studies have demonstrated that LPA is associated with negative lymph node metastasis and good prognosis, for which, limited resection can achieve outcomes similar to those of lobectomy [9,12,13,37,39].

Although our results demonstrate that intraoperative FS is a promising method to identify the invasion status of lung adenocarcinoma, there is still room for improvement. Tumour size is a significant factor affecting the diagnostic performance of FS [40]. In this meta-analysis, the CCR was significantly better in tumours > 1 cm (90%) than in tumours ≦1 cm (82%). The primary reason was inadequate sampling rather than interpretation error [15,25,26,28]. To improve the accuracy, more sections, at least two, should be taken, but the corresponding costs and benefits need to be evaluated further [15,26]. Elastic stain and inflation can enable pathologists to diagnose more accurately, which may help to reduce the number of sections needed [15,26,41]. Besides, FS results should be considered together with tumour size. For tumours ≧1 cm, if FS diagnoses are AAH/AIS/MIA, surgeons should think over the diagnoses to avoid inadequate resection [28]. Also, specimens should contain adequate adjacent lung parenchyma to avoid missing some histological components [30,42]. Furthermore, good coordination between surgeons and pathologists is essential for intraoperative FS. Thus, pathologists should communicate with surgeons in time when encountering problems in diagnosis and surgeons should not put too much pressure on pathologists during surgery [12,25,27].

There are some limitations in our study. First, even though we had conducted a meticulous search, only six studies were eligible in this meta-analysis and two of them had a high risk of bias [25,26]. Second, the studies included in this meta-analysis all came from expert centres, and in almost all studies, FS diagnoses performed by two or more experienced pathologists. However, in real life, specimens may be analysed by unexperienced pathologists and the methodology of FS in different centres may not be uniform. Furthermore, none of the included studies reported the rate of change in the surgical strategy after FS. Thus, more studies should be conducted, and specific guidelines for intraoperative FS should be set to obtain accurate diagnoses as FS becomes increasingly important. Third, we found substantial heterogeneity in this meta-analysis, even though it is common for meta-analyses of diagnostic studies [43]. To mitigate the heterogeneity, we excluded two studies at high risk of bias. After that, the results were consistent, which validated the robustness of our findings. Finally, we could not investigate the clinical effectiveness of using intraoperative FS to guide surgical strategies because only one study reported clinical outcomes [15]. Thus, prospective studies are warranted to evaluate the feasibility of using FS to aid intraoperative decision-making regarding the extent of surgical resection and lymphadenectomy for early-stage lung adenocarcinoma.

Despite these limitations, this article, to the best of our knowledge, is the first systematic review and meta-analysis to evaluate the accuracy of intraoperative FS for identifying the invasive status of lung adenocarcinoma. Our meta-analysis provides evidence that intraoperative FS is reliable for identifying the invasion status of lung adenocarcinoma. With the expected increase in the detection of small lung nodules, the results presented here may have immediate implications for the individualized treatment of early-stage lung adenocarcinoma and may

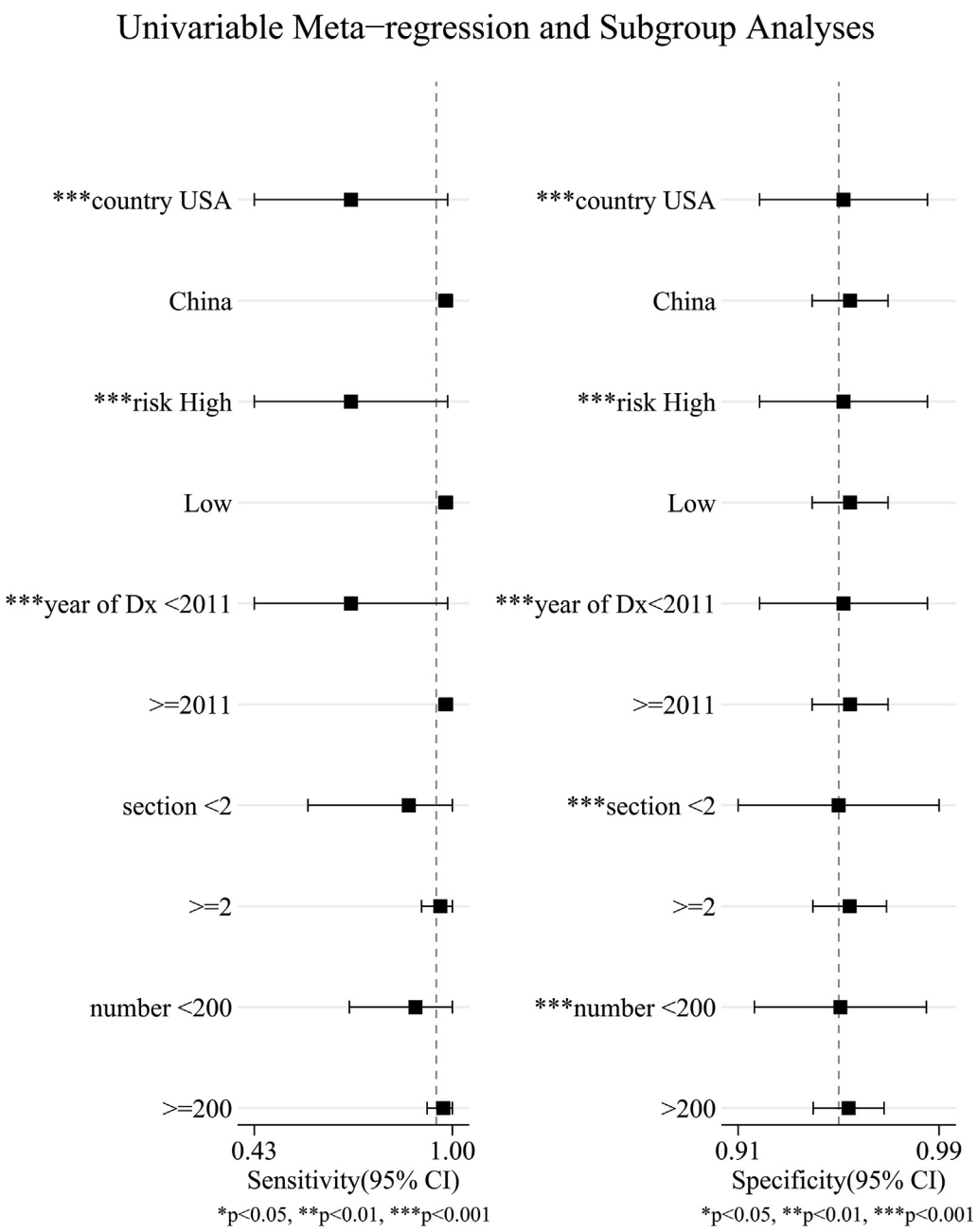

Fig. 7. Multiple univariable meta-regression and subgroup analyses of the diagnostic performance of intraoperative frozen section for distinguishing between AAH/AIS/MIA and IAC. (CI, confidence interval; Dx, diagnosis).

help with the design of future studies.

In conclusion, intraoperative FS based on the new classification is reliable for identifying the invasion status of lung adenocarcinoma, with high diagnostic accuracy for distinguishing AAH/AIS/MIA from IAC.

Ethical approval

Not required.

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Author contribution

Feng Li, Lin Yang and Yousheng Mao contributed to the conception and design of the study.

Feng Li, Lin Yang, Yue Zhao and Ligong Yuan participated in the literature search, study selection, data extraction and quality assessment.

Feng Li and Lin Yang performed the statistical analysis and interpretation of data and wrote the article.

All authors contributed to the revisions of the article.

All authors read and approved the final manuscript.

Trial registry number

Protocol was registered with the International Prospective Register of Systematic Reviews (registration number: CRD42018117152)

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=117152.

Guarantor

Yousheng Mao.

Data statement

Important data are included in Tables 1–2 in the manuscript. More associated data are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.10.047.

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Abbreviations

FS: frozen section
IAC: invasive adenocarcinoma
NPV: negative predictive value
AAH: atypical adenomatous hyperplasia
AIS: adenocarcinoma in situ
MIA: minimally invasive adenocarcinoma
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AMSTAR: Assessing the Methodological Quality of Systematic Reviews
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2
FP: final pathology
CCR: concordance rates
LR+: positive likelihood ratio
LR: negative likelihood ratio
ROC: receiver-operating characteristic curve
AUC: area under the curve
LPA: lepidic predominant adenocarcinoma