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Review

Staging accuracy of ampullary tumors by endoscopic ultrasound: Meta-analysis and systematic review

Guru Trikudanathan,[1] Basile Njei,[3] Rajeev Attam,[1] Mustafa Arain[1] and Aasma Shaukat[1,2]

[1]*Division of Gastroenterology, University of Minnesota,* [2]*Division of Gastroenterology, Hepatology and Nutrition, VA Medical Center, Minneapolis and* [3]*Department of Medicine, University of Connecticut, Farmington, USA*

Background and Aim: Accurate preoperative staging of ampullary neoplasms is of paramount importance in predicting prognosis and determining the most appropriate therapeutic approach. The aim of the present review was to evaluate the accuracy of endoscopic ultrasound (EUS) in predicting depth of ampullary tumor invasion (T-stage) and regional lymph node status (N-stage) by carrying out a meta-analysis of all relevant studies.

Methods: We systematically searched PubMed, Medline and Scopus databases for all studies published between January 1980 and December 2012. Only EUS studies involving ≥10 patients with ampullary neoplasms, confirmed by surgical histopathology, with data available for construction of a 2×2 table were included.

Results: Meta-analysis of 14 studies involving 422 patients using the Mantel–Haenszel method was performed. Pooled sensitivity and specificity of EUS to diagnose T1-stage tumor were 77% (95% CI: 69–83) and 78% (95% CI: 72–84), respectively. Pooled sensitivity for T4 tumors was 84% (95% CI: 73–92) and specificity was 74% (95% CI: 63–83). Combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio for diagnosing nodal status were 0.70 (95% CI: 0.62–0.77), 0.74 (95% CI: 0.67–0.0.80), 2.49 (95% CI: 1.91–3.24), 0.46 (95% CI: 0.36–0.59) and 6.53 (95% CI: 3.81–11.19), respectively.

Conclusion: Based on our pooled estimates, EUS had a moderate strength of agreement with histopathology in preoperative staging of ampullary neoplasms in predicting tumor invasion and lymph node involvement. Additional refinement in EUS technologies and diagnostic criteria may be required to enhance staging accuracy.

Key words: accuracy, ampullary tumor, endoscopic ultrasound, preoperative staging

INTRODUCTION

AMPULLARY TUMORS ARE distinct entities arising from the ampullary complex, distal to the bifurcation of the common bile duct and pancreatic duct, accounting for 0.2% of digestive cancers.[1] Established factors predicting prognosis include tumor size, depth of infiltration, degree of histological differentiation, perineural and vascular invasion and, most importantly, lymph node involvement.[2–6] These tumors are typically small when they cause obstruction, enabling early detection. Thus, ampullary cancers have better prognosis when compared to other periampullary malignancies, including cancers of the pancreas or common bile duct, with an estimated 5-year survival of approximately 45%.[7–9] The favorable prognosis of ampullary cancers has been attributed to the early diagnosis, higher resectability rate, and differences in tumor biology.[10]

Standard treatment modalities for ampullary tumors include Whipple procedure or pancreaticoduodenectomy, transduodenal excision and endoscopic papillectomy.[5] Ampullary tumors confined to the ampulla, without submucosal or ductal infiltration are amenable for endoscopic resection.[11–15] This is because neither vascular invasion, lymphatic permeation, nor lymph node metastasis is observed in patients when the disease is restricted to the duodenal mucosa.[15,16] Thus, accurate preoperative staging of ampullary tumors is critical in determining resectability, type of resection and predicting prognosis.[15]

Numerous diagnostic modalities are available to delineate the extent of tumor invasion (T), nodal involvement (N) and to determine resectability. These include computed tomography (CT), magnetic resonance imaging (MRI), angiography, endoscopic ultrasound (EUS) and transpapillary intraductal ultrasound (IDUS). Among these, EUS has been suggested as the modality of choice in the locoregional staging of ampullary lesions, because the high-frequency ultrasound transducer probe can be placed in close proximity

Corresponding: Aasma Shaukat, Division of Gastroenterology, Hepatology and Nutrition, VA Medical Center, One-Veterans Drive, 111-D, Minneapolis, MN 55417, USA. Email: shaukat@umn.edu

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to the periampullary region. This facilitates real-time high-resolution imaging by avoiding interference from soft tissues and bowel gas, and enabling visualization of the unique layers of the duodenal wall.[15,17,18]

Several studies have compared the preoperative endosonographic assessment of T- and N-staging with histopathological staging of the resected specimen. The majority of these studies were limited by small numbers given the relative infrequency of ampullary tumors. Their results were varied and currently there is no consensus on the role of EUS in locoregional staging of ampullary tumors.[19] As a result of this inconsistency and the importance of accurate staging for treatment and prognosis, we carried out a structured meta-analysis of the available evidence on the diagnostic accuracy of EUS in T- and N-staging of ampullary tumors.

METHODS

Literature search

A COMPREHENSIVE SEARCH of the English language literature was carried out to identify articles that examined the diagnostic accuracy of EUS in the evaluation of ampullary tumor depth of invasion and regional lymph node status (according to the American Joint Cancer Committee TNM staging of the tumor) by using histopathology as the reference standard. Our search was restricted to human subjects.

A systematic search of the PubMed, Medline and Scopus databases for all studies published between January 1980 and December 2012 was performed by using the following search terms: 'endoscopic ultrasound', 'EUS', 'endosonography', 'ampullary tumor', 'ampullary cancer', 'ampullary adenomas', 'ampullary adenocarcinoma' and 'ampullary neoplasm'. We searched for additional references by cross-checking bibliographies of retrieved full-text papers. Two reviewers (GT and BN) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any differences were resolved by mutual agreement.

Study selection criteria

Only EUS studies involving 10 or more patients with ampullary neoplasms, confirmed by histopathology, were included. Ampullary tumors were staged based on the tumor (T) and nodal (N) classification – the TNM classification. For tumor staging, a T1 lesion was confined to Vater's ampulla, a T2 lesion had extension to and invasion of the duodenal muscularis propria layer, a T3 lesion showed invasion ≤2 cm into the pancreas, and a T4 lesion had either invasion of >2 cm into the pancreas or infiltration into surrounding structures.[20]

For lymph node (N) staging, patients were staged as N0 if there were no malignant regional lymph nodes (lymph nodes located around the pancreatic head and neck or the portal vein) and N1 if there were malignant regional lymph nodes on surgical histopathology. The presence of metastasis (M) renders these tumors surgically unresectable and hence not assessed by the present study. Only studies with data available for the construction of a 2×2 contingency table with true-positive, false-negative, false-positive and true-negative values were included. The following exclusion criteria were used: Studies that did not evaluate ampullary neoplasms, those with insufficient data, studies that overlapped the selected studies (studies from the same study group, institution and period of inclusion), case reports, reviews, editorials, correspondence letters that did not report their own data, and studies involving fewer than 10 patients.

Quality of studies

Currently, there is no consensus or criteria to evaluate the quality of studies without a control arm.[21] The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) questionnaire was used to evaluate the quality of selected studies.[22] A total of 14 items were appraised in this study and items were rated as 'yes', 'no' or 'unclear'.

Statistical analysis

Meta-analysis for the accuracy of EUS in diagnosing ampullary tumors was done by calculating pooled estimates of sensitivity, specificity, likelihood ratios (LR), and diagnostic odds ratio (DOR). Pooling was carried out using the Mantel–Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model). Forrest plots were constructed to show the point estimates in each study in relation to the summary pooled estimate. Width of the point estimates in the Forrest plots corresponded to the assigned weight of the study. Heterogeneity was assessed by using χ^2 statistics, I^2 measure of inconsistency, and Cochran's Q test.

A summary receiver-operating characteristic (SROC) was constructed as a way to summarize the true-positive and false-positive rates from different studies. Proximity of the area under the curve (AUROC) to 1, is a well-validated overall representation of the diagnostic accuracy of a test.

The robustness of the meta-analysis to publication bias was assessed by funnel plots and bias indicators, including the Begg–Mazumdar test, and the Harbord–Egger test.[23,24] Combined weighted sensitivity, specificity, positive LR, negative LR, SROC curve, and meta-regression were determined by use of Meta-Disc version 1.4 (Unit of Clinical Biostatistics, Ramony Cajal Hospital, Madrid, Spain).

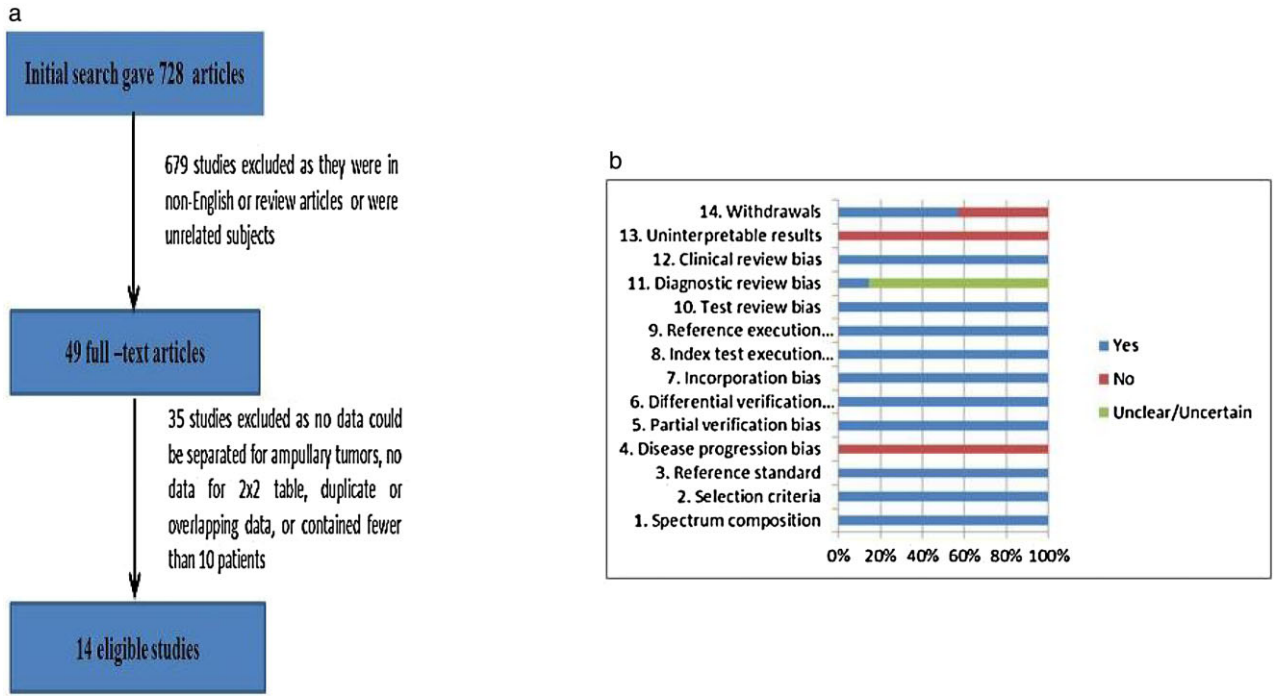

Figure 1 (a) Flow chart depicting the systematic literature search and (b) quality of the eligible studies as assessed according to the 14 items included in the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria.

RESULTS

Eligible studies

AN INITIAL LITERATURE search generated 728 articles (Fig. 1). Titles of papers were reviewed in accordance with the predefined exclusion criteria, yielding 49 potentially relevant articles that were reviewed in depth. Among these, 14 studies ($n = 422$) that met the inclusion criteria were included in the present analysis. All of the 14 studies were published as full-text articles in peer-reviewed journals.[15–17,25–35] Not all studies provided data for all sections; we used the available data for ampullary tumor only. All of the studies were conducted using a radial echoendoscope except the study conducted by Manta *et al*. which used a linear echoendoscope.[25] Figure 1a shows the search results. Calculated pooled estimates were calculated by the fixed effects model.

Quality assessment

Quality of the eligible studies as assessed by the QUADAS criteria is shown in Figure 1b. For most QUADAS items (10/14), all studies were classified as high quality (i.e. those for which a yes response applied). In two of the items (time between EUS [index] test and histopathology [reference standard], uncertain results were reported), the proportion of high-quality studies was <50%.

Pooled sensitivity and specificity of EUS to diagnose T1-stage tumor were 77% (95% CI: 69–83) and 78% (95% CI: 72–84), respectively (Fig. 2). Figure 3 depicts the sensitivity and specificity of EUS to diagnose stage-T1 tumors in a Forrest plot. For stage T2, pooled sensitivity and specificity of EUS were 73% (95% CI: 65–80) and 76% (95% CI: 70–82), respectively. Figure 4 shows the sensitivity and specificity of EUS to stage T2 tumors in a Forrest plot. T3 tumors had a pooled sensitivity of 79% (95% CI: 71–85) and a specificity of 76% (95% CI: 71–83). The sensitivity and specificity of EUS to stage T3 tumors is shown as a Forrest plot in Figure 5. Pooled sensitivity for T4 tumors was 84% (95% CI: 73–92) and specificity was 74% (95% CI: 63–83). The Forrest plot in Figure 6 shows the sensitivity and specificity of EUS to assess T4 tumors. Pooled likelihood ratios and diagnostic odds ratios for various T-stages are shown in Table 1. All the pooled estimates computed by the fixed effects model and the random effects model were similar. There was very little heterogeneity across the studies as shown by the bias indicators.

Lymph node status (N-stage)

Meta-analysis of the eligible studies reporting data on N-stage (positive *vs* negative) to assess the ability of EUS to diagnose regional lymph node status of patients with

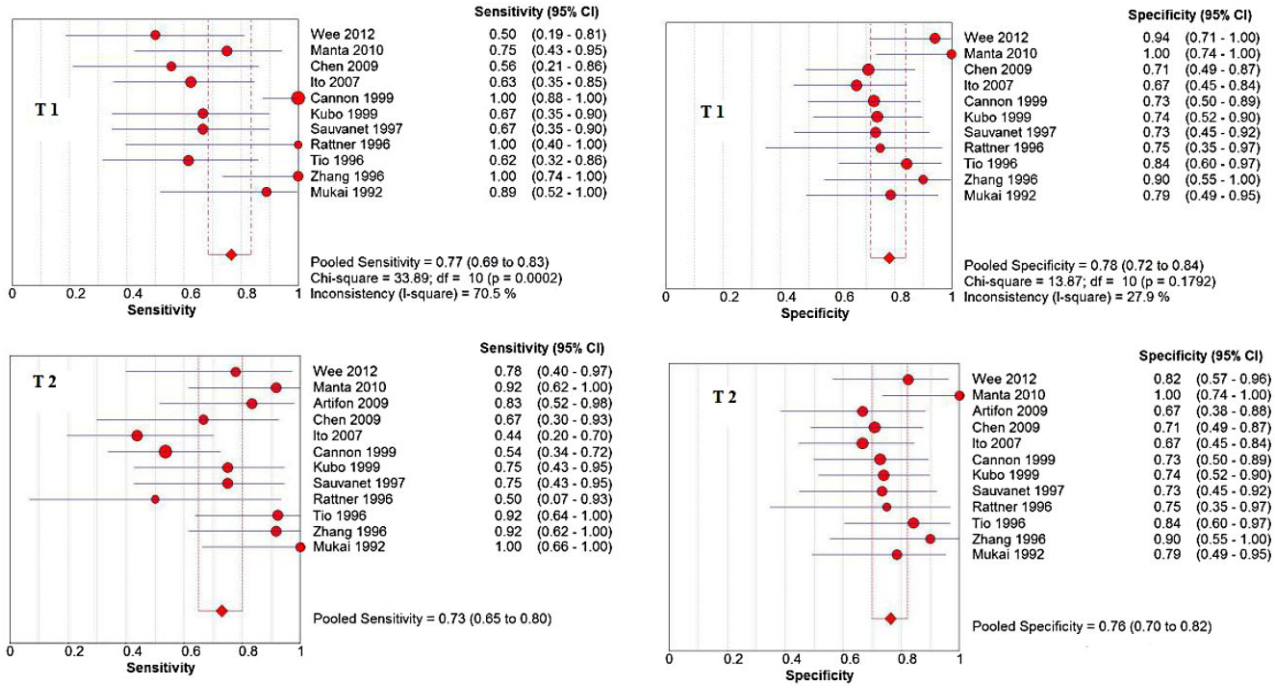

Figure 2 Sensitivity and specificity of endoscopic ultrasonography to diagnose T1 and T2 ampullary tumors.

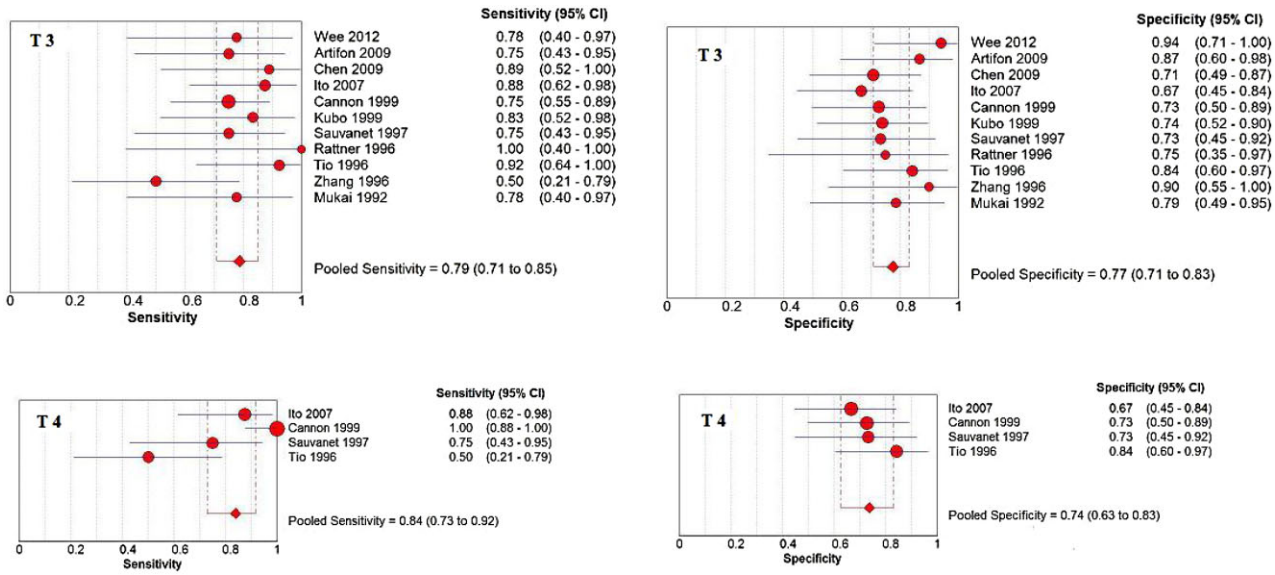

Figure 3 Sensitivity and specificity of endoscopic ultrasonography to diagnose T3 and T4 ampullary tumors.

ampullary neoplasms was then done. To this aim, 12 studies evaluating 332 patients were available. The EUS definition of N-stage disease varied across studies, with some studies relying exclusively on lymph node size (>10 mm) and others on characteristic malignant lymph node morphology (e.g. uniformly hypoechoic, rounded contour, sharply demarcated borders, close proximity to ampullary tumor). Studies also used lymph node size >5 mm and >8 mm as criteria for a malignant lymph node.[17,26] It is to be noted that none of the studies reported endoscopic ultrasound-guided

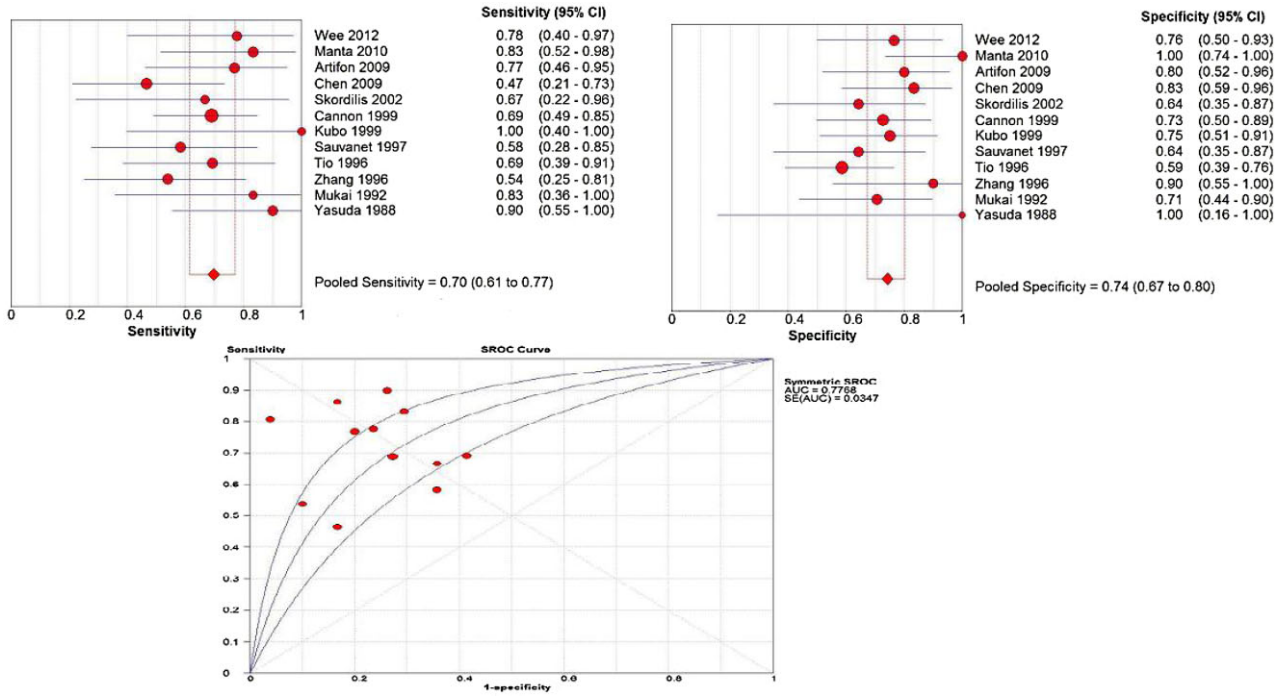

Figure 4 Pooled sensitivity, specificity, and summary receiver-operating characteristic (SROC) of endoscopic ultrasonography to diagnose N-stage. AUC, area under curve.

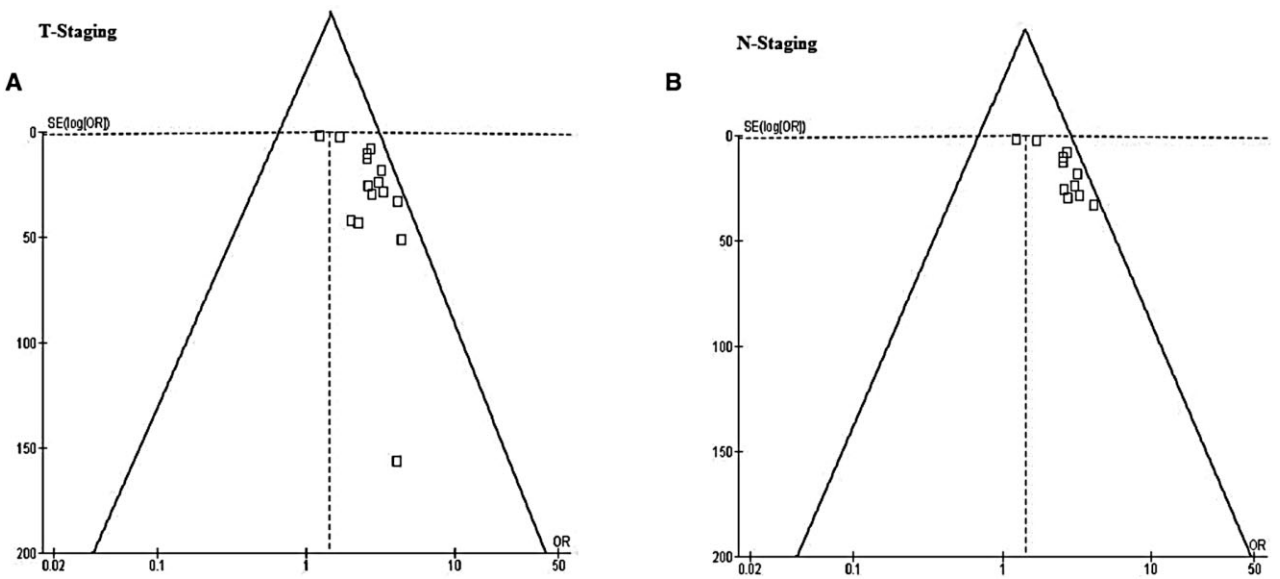

Figure 5 Funnel plots for T and N staging.

fine-needle aspiration (EUS-FNA) sampling of regional lymph nodes.

Sensitivities and specificities of individual studies as well as their pooled values are displayed in Figure 4.

Combined sensitivity, specificity, positive LR, negative LR and DOR were 0.70 (95% CI: 0.62–0.77), 0.74 (95% CI: 0.67–0.0.80), 2.49 (95% CI: 1.91–3.24), 0.46 (95% CI: 0.36–0.59) and 6.53 (95% CI: 3.81–11.19), respectively.

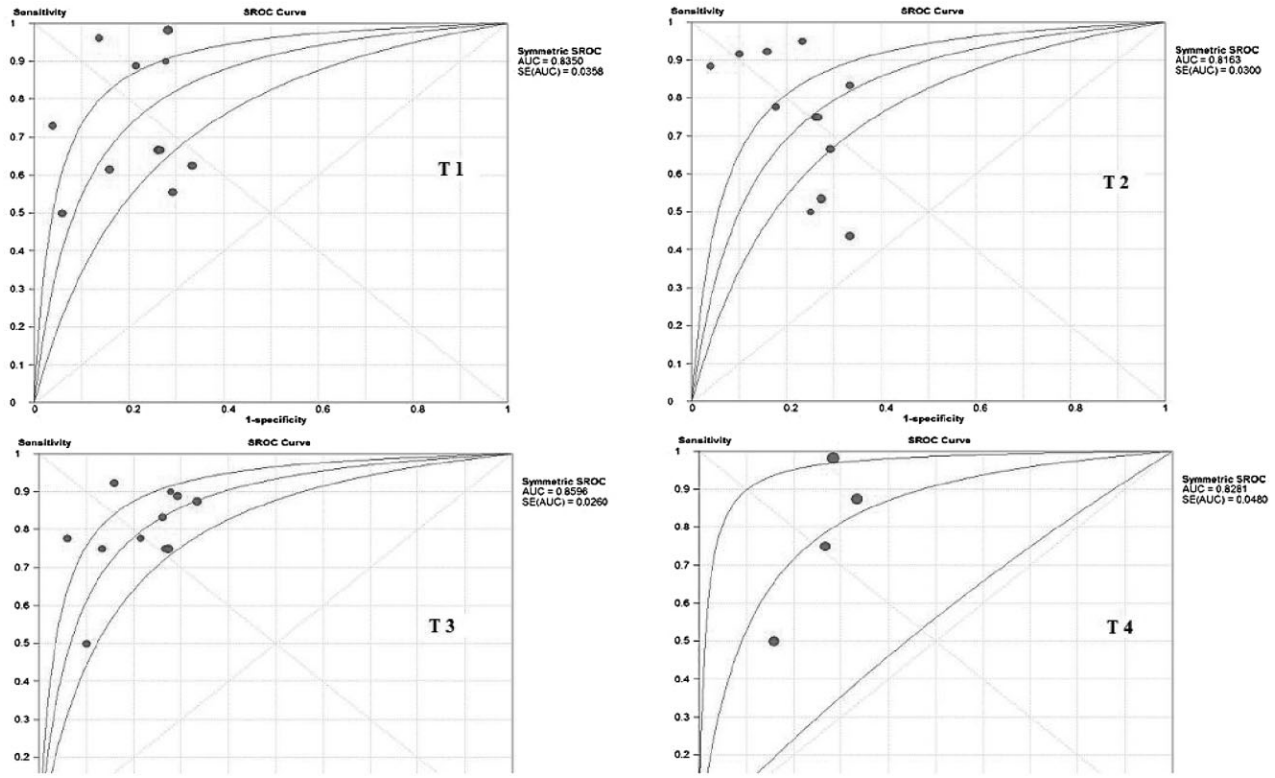

Figure 6 Summary receiver-operating characteristic (SROC) for T-stages of ampullary tumor. AUC, area under curve.

Table 1 Pooled likelihood ratios, diagnostic odds ratios and publication bias for various T-stages

	T1	T2	T3	T4
No. studies	11	12	11	4
Patients	327	351	327	148
Sensitivity (95% CI)	0.77 (0.69–0.83)	0.73 (0.65–0.80)	0.79 (0.71–0.85)	0.84 (0.73–0.92)
Specificity (95% CI)	0.78 (0.72–0.84)	0.76 (0.70–0.82)	0.76 (0.71–0.83)	0.74 (0.63–0.83)
PLR (95% CI)	2.93 (2.20–3.91)	2.78 (2.06–3.75)	3.28 (2.51–4.29)	2.97 (2.04–4.32)
NLR (95% CI)	0.41 (0.28–0.59)	0.36 (0.22–0.57)	0.33 (0.24–0.44)	0.2 (0.08–0.81)
DOR (95% CI)	10.12 (4.81–21.32)	9.32 (4.3–20.18)	14.27 (7.94–25.66)	12.06 (3.96–36.77)
AUC (SE)	0.84 (0.04)	0.82 (0.03)	0.86 (0.03)	0.83 (0.05)
Bias indicators				
Heterogeneity I^2 (%; *P*-value)	31.3; $P = 0.149$	47.5; $P = 0.03$	0.0; $P = 0.94$	27.1; $P = 0.25$
Begg–Mazumdar bias (Kendall's tau, *P*-value)	0.014; $P = 0.968$	–0.646; $P = 0.023$	0.432; $P = 0.184$	0.80; $P = 0.20$
Harbord–Egger bias (95% CI, *P*-value)	0.36 (95% CI, –0.10 to 0.64; $P = 0.23$)	2.815 (95% CI, 2.438 to 3.19; $P = 0.018$)	0.10 (95% CI, –0.22 to 0.42; $P = 0.92$)	0.55 (95% CI, 0.32 to 1.76; $P = 0.22$)

All included studies were retrospective, except three[16,26,28] which were prospective in nature.
All EUS examinations were conducted by a single endosonographer except in four,[15–17,35] where two or more endosonographers carried out EUS.
EUS staging in the presence of transpapillary staging was carried out in three of the included studies.[15,17,27]
EUS definition of T-stage disease was uniform across the studies.
EUS definition of N-stage disease included size >10 mm and morphology (uniformly hypoechoic, rounded contour and sharply demarcated borders) in most of the studies.
Size definition was >5 mm[17] and >8 mm.[26]
No size definition was available in three references.[29,33,34]
AUC, area under curve; DOR, diagnostic odds ratio; EUS, endoscopic ultrasonography; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

There was no heterogeneity across the studies ($I^2 = 0$, $P = 0.63$).

Publication bias

In this meta-analysis, bias calculations using the Harbord–Egger[24] and Begg–Mazumdar[23] bias indicators did not show any statistically significant bias. Furthermore, analysis using the funnel plot showed no significant publication bias among the EUS studies included in the analysis (Fig. 5).

DISCUSSION

ACCURATE PREOPERATIVE STAGING of ampullary tumors is imperative for predicting prognosis and determining the most appropriate therapeutic approach. In recent years, EUS has been added to the diagnostic armamentarium available for ampullary neoplasms. The accuracy of EUS, particularly in preoperative T-staging of ampullary tumors, remains controversial.[17,27,32] It has been suggested that over-staging could occur in the presence of peritumoral inflammation and under-staging can occur in the presence of minimal malignant infiltration of the pancreas.[27,29] To the best of our knowledge, this is the first meta-analysis that quantitatively summarizes all the available evidence of EUS in the locoregional staging of ampullary neoplasms.

The pooled sensitivity of EUS for tumor invasion (T-stage) ranges from 73% to 84%, with relatively higher values observed for T3–T4 lesions compared to T1–T2 lesions (Table 1). For all T-stages, the pooled specificity ranges from 74 to 78%. The modest sensitivity and specificity (77% and 78%, respectively) in predicting T1 lesions suggest that EUS is suboptimal in selecting patients suitable for endoscopic papillectomy. The pooled sensitivity and specificity for detecting nodal invasion was 70 and 74%, respectively. Diagnostic odds ratio is defined as the odds of having a positive test in patients with a true anatomical stage of the disease when compared to patients who do not have the disease. In the present study, for example, if EUS demonstrates that a patient has T3 disease, the patient has 14-fold odds of having the correct anatomical stage of the disease.

The positive likelihood ratio is a measure of how well the test identifies the disease, and the negative likelihood ratio assesses how well the same test performs in excluding the disease. For T-staging, EUS has a lower negative likelihood ratio for T4 disease when compared to T1 disease, suggesting that EUS performs slightly better in excluding T4 disease when compared to T1 disease.

Heterogeneity among the different studies was determined not only with a test of heterogeneity, but also by drawing SROC curves and finding the AUC, as different studies may use slightly different criteria for staging. An AUC of 1 for any diagnostic test indicates that the test is extremely accurate. SROC curves for EUS in ampullary tumors were close to 1, showing that EUS is a reliable test for ampullary tumors.

The biggest challenge in T-staging appears to be in differentiating desmoplastic peritumoral pancreatitis from foci of invasive carcinoma. This associated pancreatitis has been postulated to have the greatest impact on the assessment of the depth of pancreatic invasion (stage T2–T4).[17,32,34] In the study conducted by Cannon *et al*.,[17] EUS understaging of true T3 or overstaging of true T2 carcinomas accounted for most of the errors in EUS T-stage assessment (16%) of the cases. Evaluation of tumor invasion of the sphincter of Oddi has been noted to be challenging, which demands further refinement of the hardware for stable visualization of the sphincter of Oddi.[16] Very recently, contrast-enhanced EUS has emerged as a promising modality to improve characterization of the vasculature inside the organ of interest and for enhanced delineation of hypoechoic masses. A recent meta-analysis demonstrated its improved efficacy to characterize pancreatic masses, particularly its utility in distinguishing pancreatic adenocarcinoma from pseudotumoral pancreatitis.[36] Another approach involves the use of pulsed Doppler, which shows arterial-type signals only in pancreatic adenocarcinoma, but both arterial and venous signals in chronic pseudotumoral pancreatitis.[37] Contrast-enhanced EUS would definitely improve the diagnosis of pancreatic infiltration of ampullary neoplasms and needs further study.[27]

The present meta-analysis showed that EUS has a moderate sensitivity and specificity in differentiating malignant lymph nodes from benign lymph nodes. Recently, EUS-guided FNA biopsy was shown to be effective in obtaining adequate samples for accurate diagnosis in suspected ampullary malignancies.[38] More accurate criteria for malignancy or universal EUS-guided FNA sampling are ways to enhance the accuracy of EUS in diagnosing malignant nodes.[17] Technological innovations such as the use of elastography for image enhancement and target-guided FNA should be considered to optimize locoregional staging for ampullary tumors.[39]

Ampullary tumors sometimes present with obstructive jaundice, necessitating the use of biliary stenting to relieve this obstruction. There has been concern among endosonographers that transpapillary stenting of the common bile duct and pancreatic duct may compromise EUS interpretation of subtle anatomical differences, by introducing air and material artifacts.[17,27] Cannon *et al*. argued that acoustic reverberation and shadowing in the region of the papilla caused by biliary stenting often compromised visualization of the mass. This stent artifact further distorted the tissue planes

between the ampulla, duodenal wall and nearby pancreatic parenchyma, with the theoretical possibility of understaging the tumor.[17,27] In the study conducted by Cannon *et al*.,[17] 25 of the 50 patients had a transpapillary endobiliary stent present at EUS. The authors reported that although not statistically significant, there was a trend suggesting that EUS T-staging with the stent in place was less accurate than staging with no stent in place (72% *vs* 84%, $P > 0.05$).[17] Interestingly, in another study,[27] among the 16 ampullary tumors with transpapillary stents, overstaging ($n = 5$) occurred more often than understaging ($n = 1$), whereas both over- and understaging were similar in N-staging ($n = 3$). The authors reasoned that although the numbers were not statistically significant, an indwelling stent often confers common bile duct wall inflammation and fibrous thickening with false suggestions of pancreatic infiltration.[27] However, the latest Indian study concluded that transpapillary stenting did not significantly affect the outcome of T- or N-staging.[15] Further studies should specifically look at the effect of stenting on accurate staging.

CT scanning has been traditionally used in conjunction with EUS for staging of ampullary cancers. Studies comparing the test performance characteristics of EUS with CT showed that EUS was clearly superior to CT with a higher level of agreement with surgical pathology.[17,26,40,41] CT scanning has been shown to be particularly less sensitive than EUS in recognizing perivascular tumor invasion.[17,40] However, because of the limited extent of examination, EUS is unable to search for distant metastasis.[15] Thus, complementary imaging modalities such as CT scanning should be used primarily for exclusion of metastasis, rather than for assessment of the ampullary region.[15,26]

Intraductal ultrasound (IDUS) has a higher resolution rate because of the use of a higher frequency ultrasound probe (20–30 MHz) and is available in Japanese and German centers. There have been at least three studies comparing the efficacy of EUS and intraductal US for ampullary neoplasms.[16,42,43] IDUS allows for scanning without compression of tissue and, therefore, excellent differentiation between the sphincter of Oddi and the duodenal wall is achieved.[43] All three studies showed that IDUS was significantly superior to EUS in terms of tumor visualization and staging (staging accuracy ranged between 78 and 93%).[21,39,40] IDUS was particularly useful in selecting patients suitable for the application of endoscopic ampullectomy.[16] However, the number of patients undergoing IDUS was limited, and larger series with longer follow up are essential for establishing its clinical significance in ampullary neoplasms.[16]

Our meta-analysis is not without limitations. Most of the studies did not specifically differentiate benign ampullary adenomas from ampullary cancers. Hence, our study findings correspond to all ampullary neoplasms. Second, it is well known that intraobserver variability is present in EUS interpretation, which was not adequately addressed in the individual studies. Moreover, operator experience and volume are key factors when it comes to carrying out EUS. In the majority of the studies, endoscopist experience was not reported and, hence, we could not assess whether EUS results varied with different levels of experience.

CONCLUSION

THE PRESENT META-ANALYSIS shows that EUS has moderate sensitivity for T- and N-staging of ampullary tumors and is inadequate for choosing patients for endoscopic papillectomy. There was a trend towards decreased accuracy with EUS in the presence of transpapillary stenting that needs to be further established. Additional refinements in EUS technologies may enhance its diagnostic accuracy in locoregional staging of ampullary neoplasms. Complementary imaging techniques such as CT should be used in conjunction with EUS for the exclusion of metastasis. Larger multicentric studies in IDUS are awaited to further explore its diagnostic significance in ampullary tumors.

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CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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