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Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps (Review)

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[Diagnostic Test Accuracy Review]

Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps

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ABSTRACT

Background

Approximately 0.6% to 4% of cholecystectomies are performed because of gallbladder polyps. The decision to perform cholecystectomy is based on presence of gallbladder polyp(s) on transabdominal ultrasound (TAUS) or endoscopic ultrasound (EUS), or both. These polyps are currently considered for surgery if they grow more than 1 cm. However, non-neoplastic polyps (pseudo polyps) do not need surgery, even when they are larger than 1 cm. True polyps are neoplastic, either benign (adenomas) or (pre)malignant (dysplastic polyps/carcinomas). True polyps need surgery, especially if they are premalignant or malignant. There has been no systematic review and meta-analysis on the accuracy of TAUS and EUS in the diagnosis of gallbladder polyps, true gallbladder polyps, and (pre)malignant polyps.

Objectives

To summarise and compare the accuracy of transabdominal ultrasound (TAUS) and endoscopic ultrasound (EUS) for the detection of gallbladder polyps, for differentiating between true and pseudo gallbladder polyps, and for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder in adults.

Search methods

We searched the Cochrane Library, MEDLINE, Embase, Science Citation Index Expanded, and trial registrations (last date of search 09 July 2018). We had no restrictions regarding language, publication status, or prospective or retrospective nature of the studies.

Selection criteria

Studies reporting on the diagnostic accuracy data (true positive, false positive, false negative and true negative) of the index test (TAUS or EUS or both) for detection of gallbladder polyps, differentiation between true and pseudo polyps, or differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps. We only accepted histopathology after cholecystectomy as the reference standard, except for studies on diagnosis of gallbladder polyp. For the latter studies, we also accepted repeated imaging up to six months by TAUS or EUS as the reference standard.

Data collection and analysis

Two authors independently screened abstracts, selected studies for inclusion, and collected data from each study. The quality of the studies was evaluated using the QUADAS-2 tool. The bivariate random-effects model was used to obtain summary estimates of sensitivity and specificity, to compare diagnostic performance of the index tests, and to assess heterogeneity.

Main results

A total of 16 studies were included. All studies reported on TAUS and EUS as separate tests and not as a combination of tests. All studies were at high or unclear risk of bias, ten studies had high applicability concerns in participant selection (because of inappropriate participant exclusions) or reference standards (because of lack of follow-up for non-operated polyps), and three studies had unclear applicability concerns in participant selection (because of high prevalence of gallbladder polyps) or index tests (because of lack of details on ultrasound equipment and performance). A meta-analysis directly comparing results of TAUS and EUS in the same population could not be performed because only limited studies executed both tests in the same participants. Therefore, the results below were obtained only from indirect test comparisons. There was significant heterogeneity amongst all comparisons (target conditions) on TAUS and amongst studies on EUS for differentiating true and pseudo polyps.

Detection of gallbladder polyps: Six studies (16,260 participants) used TAUS. We found no studies on EUS. The summary sensitivity and specificity of TAUS for the detection of gallbladder polyps was 0.84 (95% CI 0.59 to 0.95) and 0.96 (95% CI 0.92 to 0.98), respectively. In a cohort of 1000 people, with a 6.4% prevalence of gallbladder polyps, this would result in 37 overdiagnosed and seven missed gallbladder polyps.

Differentiation between true polyp and pseudo gallbladder polyp: Six studies (1078 participants) used TAUS; the summary sensitivity was 0.68 (95% CI 0.44 to 0.85) and the summary specificity was 0.79 (95% CI 0.57 to 0.91). Three studies (209 participants) used EUS; the summary sensitivity was 0.85 (95% CI 0.46 to 0.97) and the summary specificity was 0.90 (95% CI 0.78 to 0.96). In a cohort of 1000 participants with gallbladder polyps, with 10% having true polyps, this would result in 189 overdiagnosed and 32 missed true polyps by TAUS, and 90 overdiagnosed and 15 missed true polyps by EUS. There was no evidence of a difference between the diagnostic accuracy of TAUS and EUS (relative sensitivity 1.06, P = 0.70, relative specificity 1.15, P = 0.12).

Differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder: Four studies (1,009 participants) used TAUS; the summary sensitivity was 0.79 (95% CI 0.62 to 0.90) and the summary specificity was 0.89 (95% CI 0.68 to 0.97). Three studies (351 participants) used EUS; the summary sensitivity was 0.86 (95% CI 0.76 to 0.92) and the summary specificity was 0.92 (95% CI 0.85 to 0.95). In a cohort of 1000 participants with gallbladder polyps, with 5% having a dysplastic polyp/carcinoma, this would result in 105 overdiagnosed and 11 missed dysplastic polyps/carcinomas by TAUS and 76 overdiagnosed and seven missed dysplastic polyps/carcinomas by EUS. There was no evidence of a difference between the diagnostic accuracy of TAUS and EUS (log likelihood test P = 0.74).

Authors' conclusions

Although TAUS seems quite good at discriminating between gallbladder polyps and no polyps, it is less accurate in detecting whether the polyp is a true or pseudo polyp and dysplastic polyp/carcinoma or adenoma/pseudo polyp. In practice, this would lead to both unnecessary surgeries for pseudo polyps and missed cases of true polyps, dysplastic polyps, and carcinomas. There was insufficient evidence that EUS is better compared to TAUS in differentiating between true and pseudo polyps and between dysplastic polyps/carcinomas and adenomas/pseudo polyps. The conclusions are based on heterogeneous studies with unclear criteria for diagnosis of the target conditions and studies at high or unclear risk of bias. Therefore, results should be interpreted with caution. Further studies of high methodological quality, with clearly stated criteria for diagnosis of gallbladder polyps, true polyps, and dysplastic polyps/carcinomas are needed to accurately determine diagnostic accuracy of EUS and TAUS.

PLAIN LANGUAGE SUMMARY

Transabdominal ultrasound and endoscopic ultrasound for detection of gallbladder polyps and differentiating between polyp types

Background

The gallbladder is an organ situated close to the liver. It stores bile, produced by the liver, before it is released to the small bowel for digestion. Abnormal growths inside the gallbladder, called 'gallbladder polyps', can develop. Most polyps (90%) are harmless; these

are called pseudo polyps. The remaining are true polyps and can be cancerous, have cancer-like parts (precancerous dysplastic polyps), or be benign, but they can potentially turn into cancer. Dysplastic polyps and cancerous polyps should be treated. Most people also treat benign polyps because of their potential to become cancerous. Treatment is done by removal of the gallbladder with the polyp within (cholecystectomy). To decide which patients should undergo surgery, it is important to (1) be certain that a gallbladder polyp is present, (2) know whether it is a true or pseudo polyp, and (3) whether a polyp is (pre)cancerous. Transabdominal ultrasound (TAUS), which uses ultrasound waves to differentiate between tissues, and endoscopic ultrasound (EUS), ultrasound attached to an endoscope introduced into the small intestine through the mouth and stomach, are the two tests currently used to detect gallbladder polyps and identify the type of gallbladder polyps.

We performed a thorough search for studies that reported the accuracy (ability) of TAUS and EUS for the detection of gallbladder polyps and for differentiating between true and pseudo polyps, and between (pre)cancerous and benign polyps.

Study characteristics

A total of 16 studies were included. All studies reported on TAUS and EUS as separate tests and did not use a combination of TAUS and EUS. Six studies (16,260 participants) used TAUS for diagnosis of gallbladder polyps. No studies on the diagnosis of gallbladder polyps by EUS were found. Six studies (1,078 participants) used TAUS and three studies (209 participants) used EUS for differentiating between true and pseudo polyps. Four studies (1,009 participants) used TAUS and three studies (351 participants) used EUS for differentiating between (pre)cancerous and benign polyps.

Key results

In a general population of 1000 people (in which 6.4% have a gallbladder polyp), TAUS will overdiagnose 37 people without a polyp as having a polyp, and in 7 people with a polyp, the polyp will be missed. In a population of 1000 people with a gallbladder polyp, of which 10% have a true polyp, 189 people with a pseudo polyp will be indicated as having a true polyp by TAUS, and 90 people by EUS. These people may be treated, which is not necessary. In 32 people, the true polyp will be misclassified as a pseudo polyp by TAUS and in 15 people by EUS. These people would not be treated, while they may need treatment. In a population of 1000 people with a gallbladder polyp, of which 5% have a (pre)cancerous polyp, 105 people with a benign polyp will be indicated as having a (pre)cancerous polyp by TAUS, and 75 people by EUS. These people may be overtreated for a (precursor of) cancer, which is not there. In 11 people, the (pre)cancerous polyp will be misclassified as a benign polyp by TAUS, and in 7 people by EUS. These participants may not receive proper treatment for their (precursor of) cancer. TAUS will correctly diagnose 956 out of 1000 people regarding the presence or absence of gallbladder polyps. For differentiating between polyp types, fewer people will be correctly diagnosed by TAUS, leading to unnecessary treatment for pseudo polyps and neglect of (pre)cancerous polyps. There was insufficient evidence that EUS is better than TAUS in differentiating between true and pseudo polyps and between (pre)cancerous and benign polyps.

Quality of evidence

All studies were either at high or unclear risk of bias and 13 studies had either high or unclear applicability concerns. This may undermine the validity of the studies.

Future research

Further studies of high methodological quality and with clearly reported criteria for diagnosis of gallbladder polyps, true polyps, and (pre)cancerous polyps are necessary.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Summary of Findings Table. What is the diagnostic accuracy of TAUS and EUS for the detection of gallbladder polyps, for differentiating between true and pseudo gallbladder polyps, and for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder in adults?

Patients / population	Adults with (suspected) gallbladder polyp(s)
Prior testing	None, for patients undergoing TAUS None or TAUS, for patients undergoing EUS
Settings	Primary, secondary, or tertiary hospitals
Index test	TAUS or EUS alone, or combined
Importance	Improved detection and differential diagnosis of gallbladder polyps would prevent unnecessary cholecystectomies
Target condition	Detection of gallbladder polyps: gallbladder polyp Differentiating between true and pseudo gallbladder polyps: true gallbladder polyp Differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps: dysplastic polyps/carcinomas
Reference standard	Histopathological analysis of the gallbladder after cholecystectomy For detection of gallbladder polyps also follow-up by repeated imaging up to six months
Studies	Cross-sectional studies irrespective of language or publication status, either prospective or retrospective Case-control studies and studies from which TP, TN, FP, FN could not be extracted were excluded

Test/target condition	No. of participants (studies)	Summary accuracy (95% CI)	Median Prevalence (IQR) *Expected Prevalence*	Post-test probability (95% CI)*	Consequences in a cohort of 1000*		Quality and comments
					Estimated overdiagnosed cases	Estimated missed cases	
TAUS/gallbladder polyps	16,260 (6)	sensitivity: 0.84 (0.59 to 0.95) specificity: 0.96 (0.92 to 0.98)	6.4% (2.4% to 18.8%)	positive: 0.59 (0.44 to 0.72) negative: 0.01 (0.004 to 0.03)	37 (19 to 75)	7 (3 to 26)	Median prevalence of gallbladder polyps as to be expected.

							Studies with high (3) and unclear (3) risk of bias. Studies with high (5) and unclear (1) applicability concerns
TAUS/true gallbladder polyps	1,078 (6)	sensitivity: 0.68 (0.44 to 0.85) specificity: 0.79 (0.57 to 0.91)	19.2% (16.5% to 23.5%) *10%*	*positive:0.27 (0.15 to 0.42)* *negative:0.04 (0.03 to 0.08)*	*189 (81 to 387)*	*32 (15 to 56)*	High median prevalence of true polyps within the studies. Studies with high (2) and unclear (4) risk of bias. Studies with low (1), high (3) and unclear (1) applicability concerns
EUS/true gallbladder polyps	209 (3)	sensitivity: 0.85 (0.46 to 0.97) specificity: 0.90 (0.78 to 0.96)		*positive: 0.48 (0.25 to 0.72)* *negative: 0.02 (0.00 to 0.09)*	*90 (36 to 198)*	*15 (3 to 54)*	High median prevalence of true polyps within the studies. Studies with high (2) and unclear (1) risk of bias. Studies with high applicability concerns.
TAUS/dysplastic polyps/carcinomas	1,009 (4)	sensitivity: 0.79 (0.62 to 0.90) specificity: 0.89 (0.68 to 0.97)	13.0% (11.0% to 20.1%) *5%*	*positive:0.28 (0.09 to 0.60)* *negative: 0.01 (0.01 to 0.03)*	*105 (29 to 304)*	*11 (10 to 190)*	High median prevalence of dysplastic polyps/carcinomas within the studies. Studies with high (2) and unclear (2) risk of bias. Studies with low (2) and high (2) applicability concerns.

EUS/dysplastic polyps/carcinomas	351 (3)	sensitivity: 0.86 (0.76 to 0.92) specificity: 0.92 (0.85 to 0.95)	*positive:0.35 (0.23 to 0.48)* *negative: 0.01 (0.00 to 0.01)*	*76 (48 to 143)*	*7 (4 to 12)*	High median prevalence of dysplastic polyps/carcinomas. Studies with high (2) and unclear (1) risk of bias. Studies with high (2) and unclear (1) applicability concerns
Direct comparison	No convergence of results in meta-analysis. Two individual studies suggested increased accuracy for EUS compared to TAUS, similar accuracy in other studies					
Indirect comparison	No statistical difference in diagnostic accuracy between TAUS and EUS					

** Post-test probabilities and consequences in a cohort of 1000 for TAUS/true gallbladder polyp, EUS/true gallbladder polyps, TAUS/dysplastic polyps/carcinomas and EUS/dysplastic polyps/carcinomas were based on expected prevalence instead of observed prevalences within the studies.*

EUS:endoscopicultrasound;FN:falsenegative;FP:falsepositive;IQR:interquartilerange;TAUS:transabdominalultrasound;TN:truenegative;TP:truepositive

BACKGROUND

Gallbladder polyps are growths that protrude from the lining of the inside of the gallbladder. Gallbladder polyps are rarely symptomatic, presenting as biliary colic (severe pain episodes in the right upper abdomen or epigastric region lasting at least 15 to 30 minutes), and therefore most are found incidentally when abdominal tests are undertaken for another reason. The precise prevalence of gallbladder polyps is unknown. Based on pathology reports of resected gallbladders, prevalence is 0.4% to 13.8% (Mainprize 2000). Ultrasound studies in healthy people show similar prevalence of 0.3% to 12% (Cha 2011). However, it appears that the prevalence is lower in Western populations (Jorgensen 1990; Kratzer 2008) than in Asian populations (Chen 1997; Okamoto 1999; Lin 2008).

Histopathologically (macroscopic examination of gallbladder tissue), these polyps can be divided into true polyps and pseudo polyps. Pseudo polyps consist of non-neoplastic (non-cancerous) lesions such as cholesterol polyps, inflammatory polyps, and adenomyomatosis (invagination of hypertrophic (enlarged) mucosa of the gallbladder wall) and do not need treatment. True polyps (approximately 10% of all polyps) are neoplastic lesions (abnormal or extensive growth of gallbladder tissue: adenomas (benign lesions that have not (yet) gained the properties of cancer), dysplastic polyps (containing abnormal cells that can become cancer (pre-malignant)), and adenocarcinomas (malignant) (Christensen 1970; Mainprize 2000; Sarkut 2013). About 95% of gallbladder polyps are benign. Cholecystectomy (gallbladder removal) is required for dysplastic and malignant polyps. Adenomas are also suggested to have malignant potential (Kozuka 1982); hence, cholecystectomy is recommended for adenomas as well. Several studies have indicated that polyps with a diameter greater than 1 cm have an increased probability of being adenomas. Most of gallbladder cancers also exceed this diameter (Koga 1988; Moriguchi 1996; Mainprize 2000; Terzi 2000; Lee 2004). Therefore, currently cholecystectomy is advised for gallbladder polyps with a diameter greater than 1 cm, or in case of other malignant features (e.g. rapid growth) (EASL 2016; Wiles 2017). A cholecystectomy can also be performed for people with biliary symptoms due to gallbladder polyps and people with other risk factors for gallbladder cancer, (such as primary sclerosing cholangitis (genetic disease characterized by chronic inflammation and scarring of the bile ducts) or older age), regardless of the size of the polyp (Mainprize 2000; Terzi 2000; Buckles 2002; Ito 2009; EASL 2016).

Target condition being diagnosed

- Gallbladder polyps
- True gallbladder polyps (in people with gallbladder polyps)
- Dysplastic gallbladder polyps or gallbladder carcinoma (in people with gallbladder polyps).

Index test(s)

Transabdominal ultrasound

Transabdominal ultrasound (TAUS) is the current diagnostic modality of first choice to detect gallbladder polyps. It is a portable, safe, noninvasive, and real-time modality with relatively low costs. A transducer transforms electrical energy into sound waves (2 mHz to 8 mHz) and transmits the sound waves into the body. Simultaneously, the transducer detects the sound waves reflected by the underlying tissue. The intensity of these reflected (echo) waves is based on several properties of the tissue, such as density and depth of the tissue and properties of adjacent tissues. The echo waves are converted into electrical energy and displayed as a cross-sectional tomography (two-dimensional) image (Hangiandreou 2003). Structures that appear brighter than their surroundings on the image are described as hyperechoic, and structures that appear darker than their surroundings on the image are described as hypoechoic (Hangiandreou 2003). Gallbladder polyps are seen as hyperechoic structures (compared to the surrounding bile) with a sessile (flat) or pedunculated (protruding) shape and without acoustic shadow (in contrast to gallstones). Polyps are fixed on the gallbladder wall, projecting into the gallbladder lumen (inside of the gallbladder), and should therefore lack displacement secondary to change in the person's position (Lee 2004; Kratzer 2008; Ito 2009). Based on the echogenic (ultrasound) characteristics of the polyps, a differential diagnosis of gallbladder polyps can be made. Cholesterol polyps are pedunculated lesions with a granular surface and an internal tiny, spotty echo pattern. Adenomyomatosis is a sessile mass with an irregular surface containing microcysts or comet tail artefacts (Rokitansky-Aschoff sinuses). Adenomas are pedunculated or sessile masses without echogenic spots, microcysts, or comet tail artefacts. The internal echo is almost homogeneous. Carcinoma often has a nodular surface and a rounded shape. The internal echo is heterogeneous (Choi 2000; Sugiyama 2000; Azuma 2001; Sadamoto 2002; Akatsu 2006; Cheon 2009; Kim 2012).

Endoscopic ultrasound

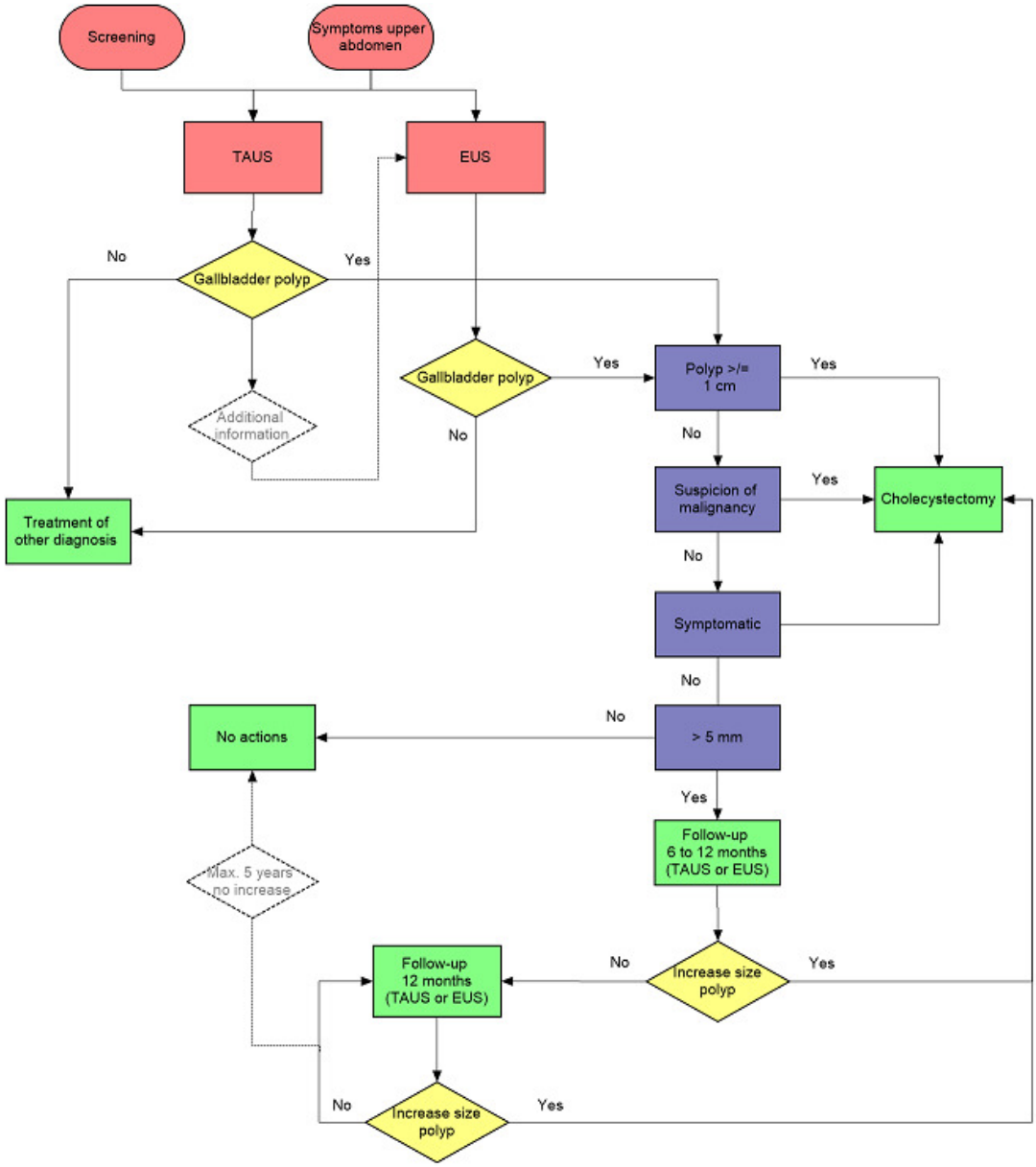
Endoscopic ultrasound (EUS) consists of an endoscope equipped with an ultrasound probe. It is introduced through the mouth and stomach into the small intestine to scan the gallbladder. EUS can provide close contact with the gallbladder and generally uses high ultrasound frequencies (5 mHz to 20 mHz) to create high resolution images (Azuma 2001; Akatsu 2006). The underlying principle of ultrasound and echogenic properties of gallbladder polyp are the same as for TAUS. Additionally, EUS can visualise the layered structure of the gallbladder (three layers corresponding with mucosa (inner layer), muscularis propria (middle layer of muscular tissue), and sub-serosa (outer layer of connective tissue under the peritoneum) and the morphology (appearance/shape) and surface features of the gallbladder polyps (Azuma 2001; Akatsu

2006). The echogenic characteristics of the different type of polyps are the same as for TAUS.

Clinical pathway

Imaging of the gallbladder by TAUS is performed in people with symptoms of the upper abdomen, suspicion of gallbladder disease, or as part of regular abdominal check-ups. Imaging is hardly ever done with the specific intention to find gallbladder polyps as these polyps are mostly asymptomatic or display similar symptoms to gallstones. Therefore, gallbladder polyps are often found incidentally (Mainprize 2000). EUS can also be performed initially in people with upper abdominal symptoms, or can be used as the second stage imaging modality to gain additional information on gallbladder polyps. The latter is done in some centres but is not routinely performed currently. Based on size and features of the polyp seen on TAUS (usually) or EUS (if performed), decision for treatment or follow-up is made. In current guidelines, polyps are considered for elimination once they grow more than 1 cm (Koga 1988; Mainprize 2000; Ito 2009; EASL 2016; Wiles 2017). Polyps less than 5 mm do not need follow-up (Andren-Sandberg 2012; EASL 2016; Wiles 2017). For polyps between 5 mm and 1 cm, surgery can be performed in the case when the polyp bears malignant features (e.g. fast growth, sessile polyps or gallbladder wall disruption), when the person has other risk factors for malignancy (such as primary sclerosing cholangitis or older age) or when the person has biliary symptoms. Otherwise, polyps should be re-evaluated after six to twelve months with additional TAUS (usually) or EUS (in some centres) depending upon the test used to determine the final size of the polyp (EASL 2016; Wiles 2017). Repeated imaging will also be performed if uncertainty exists about the presence of gallbladder polyps. If no changes are present at follow-up, imaging will be repeated after 12 months for a maximum of five years. If again no changes are found, no further follow-up is needed. If the gallbladder polyp has increased in size at follow-up (at least 2 cm increase or above the 1 cm threshold) or has developed malignant features, cholecystectomy will be performed (Mainprize 2000; Andren-Sandberg 2012; Wiles 2017).
Figure 1 shows the clinical pathway.

Figure 1. Clinical pathway for the diagnosis of gallbladder polyps.&br;&br;&supStart;TAUS: transabdominal ultrasound&supEnd;&br;&supStart;EUS: endoscopic ultrasound&supEnd;&br;&supStart;Suspicion of malignancy: e.g. fast growth, sessile polyps, or gallbladder wall disruption&supEnd;



Prior test(s)

TAUS is usually performed without any prior tests as gallbladder polyps are incidental findings. EUS is usually used as a second stage imaging modality after TAUS.

Role of index test(s)

The index tests are used to check for gallbladder diseases, including gallbladder polyps, and differentiate between type of gallbladder polyps after the initial diagnosis. EUS can be considered as an add-on to TAUS for identifying gallbladder polyps. It can be considered as an add-on or replacement test to TAUS for distinguishing the nature of the gallbladder polyp.

Alternative test(s)

Other suggested imaging modalities for diagnosis of gallbladder polyps are computed tomography, magnetic resonance imaging (MRI), and positron emission tomography (PET). None of these modalities have been incorporated in routine clinical practice. Computed tomography does not clearly depict the shape and internal features of gallbladder polyps and is, therefore, not suitable for differentiating between true and pseudo polyps. It may be useful in diagnosing (advanced stages of) gallbladder carcinoma, as gallbladder wall invasion can be visualised (Furukawa 1998; Azuma 2001; Sun 2004). There are no studies on the detection of gallbladder polyps and differentiation between true and pseudo polyps by MRI and PET. A few small cohort studies have suggested a role for diffusion weight imaging MRI and PET as second stage imaging modalities in differentiating gallbladder carcinomas from benign lesions (Lee 2012; Ogawa 2012).

Rationale

Detection of gallbladder polyps

Every year, 800,000 cholecystectomies are performed in the US alone (Everhart 2009), of which 0.6% to 4% are because of gallbladder polyps (Jones-Monahan 2000; Yeh 2001; Chattopadhyay 2005). The decision to perform cholecystectomy is based on gallbladder imaging by TAUS or EUS, or both. A proper and certain diagnosis of the presence of gallbladder polyps is of utmost importance to prevent unnecessary surgeries and avoidable risks of cholecystectomy, but also to prevent the risk of malignant degeneration in undiagnosed polyps.

Differentiation between true polyp and pseudo gallbladder polyp

Cholecystectomy is not needed for pseudo polyps of the gallbladder, as they have no malignant potential. However, the distinction between true and pseudo polyps is often a diagnostic dilemma in clinical practice, and current criteria for cholecystectomy are based on size and growth of polyps. Partly, these are consistent with properties of true polyps. However, postoperatively, many polyps with a diameter larger than 1 cm prove to be pseudo polyps and some polyps less than 1 cm have been shown to be true polyps (Terzi 2000; Sun 2004; Zielinski 2009). Echogenic characteristics that have been described to differentiate between types of polyps can be applied during TAUS and EUS.

Differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder

In current clinical practice, polyps greater than 1cm are operated on; these polyps are thought to have malignant potential. This theory is based on the evidence of an observational study that showed some adenomas having malignant components (Kozuka 1982), and the adenoma-carcinoma sequence of colorectal polyps (Day 1978). The question remains whether this adenoma-carcinoma sequence is in fact applicable to gallbladder adenomas. The gene mutations (K-ras, p53, and p16), microsatellite (repetitive non-coding DNA sequences) instability, and loss of heterozygosity (genetic event whereby one allele of a gene is lost) responsible for malignant transformation of adenomas into colorectal polyps were also found in gallbladder carcinomas and some dysplastic polyps but not in adenomas (Kim 2001). This indicates a pre-malignancy of dysplastic polyps, but not of adenomas. Therefore, it is important to differentiate between adenomas and dysplastic polyps of gallbladder carcinomas to decide on treatment for true polyps. Adenomas may need cholecystectomy, but not as urgently as dysplastic or malignant polyps. Informed decisions can be made. For example, older people with an expected life expectancy of about 10 years may choose not to undergo surgery for adenomas without any dysplastic changes. Although there are no alternatives to surgery for treatment of gallbladder polyps, alternative treatments can be developed if adenomas and dysplastic or malignant polyps can be differentiated with a great deal of certainty. Differentiating between adenomas and dysplastic polyps or carcinomas could be possible, based on the echogenic characteristics that have previously been described.

There has been no systematic review and meta-analysis assessing the diagnostic accuracy of TAUS or EUS in diagnosing gallbladder polyps, in differentiating between true and pseudo polyps and in differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps. Such a systematic review and meta-analysis is

necessary (1) to provide the evidence for a reliable diagnostic work-up for the diagnosis of gallbladder polyps and (2) to address the value of these imaging modalities in classifying polyps as true or pseudo polyps and as dysplastic polyps/carcinomas or adenomas/pseudo polyps, and, thereby, in the decision for treatment.

OBJECTIVES

To summarise and compare the accuracy of transabdominal ultrasound (TAUS) and endoscopic ultrasound (EUS), for the detection of gallbladder polyps, for differentiating between true and pseudo gallbladder polyps, or for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder in adults.

Secondary objectives

To explore the following sources of heterogeneity:

- Methodological quality as assessed by QUADAS-2 (low compared to high/unclear);
- Prospective compared to retrospective studies;
- TAUS characteristics: type of the probe (linear compared to curved), frequency of the probe (low: 2 to 5 MHz compared to high: 5 to 8 MHz), and type of scanning (conventional grey, pulsed, colour, Doppler);
- EUS characteristics; type of endoscope (radial compared to linear), frequency of the probe (less than 15 MHz compared to more than 15 MHz);
- Experience of performer of TAUS and EUS (five years or more compared to less than five years of experience);
- Symptomatic compared to asymptomatic people;
- Presence compared to absence of gallstones.

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional studies, retrospective, and prospective cohort studies and randomised controlled trials, that evaluated the accuracy of the index tests (TAUS and EUS) in the appropriate participant population (see Participants), irrespective of language or publication status, or whether the data were collected prospectively or retrospectively. We excluded case-control studies because these studies are prone to bias (Whiting 2011). We included only studies that reported on, or those from which we could extract data on, true positives, true negatives, false positives, and false negatives (diagnostic test accuracy information). In case of multiple publications, we included the study report with the highest number of participants.

Participants

Detection of gallbladder polyps

Symptomatic (people with biliary colic/upper abdominal pain) or asymptomatic adults (more than 18 years of age).

True polyps compared to pseudo polyps

Adults (more than 18 years of age) in whom histopathology after cholecystectomy confirmed presence of true or pseudo polyp.

Dysplastic polyps/carcinomas compared to adenomas/pseudo polyps

Adults (more than 18 years of age) in whom histopathology after cholecystectomy confirmed presence of dysplastic polyps/carcinomas or adenomas/pseudo polyps.

Index tests

The index tests were transabdominal ultrasound (TAUS) of the upper abdomen and gallbladder, or endoscopic ultrasound (EUS), both without intravenous contrast enhancement. Index tests can be performed because of suspicion of gallbladder disease, another disease in the upper abdomen, and as a part of routine abdominal check-ups (TAUS). We included a study if other diagnostic modalities were compared and we could extract the results of TAUS and EUS separately.

Target conditions

Detection of gallbladder polyps

Gallbladder polyp(s)

Differentiation between true polyp and pseudo gallbladder polyp

True gallbladder polyp(s) compared to pseudo gallbladder polyp(s)

Differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder

Dysplastic polyp(s) or carcinoma(s) compared to adenoma(s) or pseudo polyp(s)

Reference standards

We used histopathological analysis of the resected gallbladder after cholecystectomy as the reference standard for all three target conditions. It enables direct analysis of the entire gallbladder, its content, and the presence and pathological entity of the gallbladder polyp, and can be considered the best reference standard. However, cholecystectomy may not be performed in people without gallbladder polyps or with small polyps (< 5 mm). Therefore, for detection of gallbladder polyps, we also accepted an alternative reference standard of follow-up by repeated imaging up to six months (demonstrating that there is no gallbladder polyp or if there was a small gallbladder polyp, the polyp persisted) for people in whom cholecystectomy was not performed due to above mentioned reasons. For differentiating between true and pseudo polyps and dysplastic polyps/carcinomas and adenomas/pseudo polyps, histological confirmation is needed, which can only be done after cholecystectomy.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Library, MEDLINE, Embase, and Science Citation Index Expanded (Royle 2003). Appendix 1 shows the search strategies with time spans of the searches.

Searching other resources

We searched the references of any included studies to identify additional studies. We also searched online trial registries such as ClinicalTrial.gov (clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), World Health Organization (WHO) International Clinical Trial Registry Platform (www.who.int/ictrp), the Food and Drug Administration (FDA) (www.fda.gov) for ongoing or unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (SW and ML) independently screened the search results to identify relevant studies. We obtained the full texts for references considered relevant by at least one of the review authors. Three review authors (SW, ML, and MDM) independently screened the full-text papers against the inclusion criteria. We resolved any differences in study selection by discussion or by consultation of a fourth review author (KG).

Data extraction and management

Two review authors (SW and MDM) independently extracted the following data from each included study using a data extraction form. A third reviewer (ML) checked all extracted data for errors. Any differences were resolved by discussion with KG.

- First author
- Year of publication
- Study design (prospective or retrospective cohort studies; cross-sectional studies, or randomised clinical trials)
- Inclusion and exclusion criteria for individual studies
- Total number of participants
- Number of women
- Mean age of the participants
- Properties of TAUS (type of probe, probe frequency, and type of scanning)
- Properties of EUS (type of probe, probe frequency)
- Performer of TAUS and EUS
- Criteria for differentiating the type and pathological entity of gallbladder polyps (True polyp compared to pseudo polyp and dysplastic polyp/carcinoma compared to adenoma/pseudo polyp)
- Number of true positives, false positives, false negatives, and true negatives

If the same study reported multiple index tests, we extracted the number of true positives, false positives, false negatives, and true negatives for each index test. If the same study reported the results of the tests at different criteria for the target condition, we extracted the number of true positives, false positives, false negatives, and true negatives for each criterion. The unit of analysis was the participants since the treatment depended upon the polyp with the worst possible histological diagnosis. For example, if there were multiple pseudo polyps and one true polyp, then we treated the participant as having a true polyp; if there were multiple pseudo polyps or adenomas and one malignant polyp, we treated the participant as having a malignant polyp.

In the presence of participants with uninterpretable index results for whom reference standard results were available, we considered the index test results as positive since participants would undergo further investigations, follow-up, or treatment, as if the index test was positive. In the absence of the reference standard results for people with uninterpretable index results, we excluded such participants but recorded the number of uninterpretable index test results for the purpose of determining the quality of evidence (see Appendix 2).

Assessment of methodological quality

Two review authors (SW and MDM) independently assessed study quality using the QUADAS-2 assessment tool (Whiting 2011). We resolved any differences by discussion with KG. Appendix 2 shows the criteria that we used to classify the different studies. We considered studies that were classified as 'low risk of bias' and 'low concern' in all the domains as studies with high methodological quality. We presented the results in 'risk of bias' summaries and graphs in addition to a narrative summary.

Statistical analysis and data synthesis

We plotted individual study estimates of sensitivity and specificity on forest plots to explore between study variation in the performance of TAUS and EUS. To estimate the summary sensitivity and specificity of TAUS and EUS, we performed the meta-analysis by fitting the bivariate random-effects model (Reitsma 2005) with correlation between sensitivity and specificity taken into account, assuming binomial likelihood. The meta-analysis was performed assuming no threshold effect. All studies were expected to express the result of the index test as detection of gallbladder polyps, as differentiating between true and pseudo gallbladder polyps, and as differentiating between dysplastic polyps/carcinomas and pseudo polyps/adenomas. For studies on detection of gallbladder polyps, an implicit threshold of the presence of a polyp was assumed. For studies on differentiation between polyp types, a size-based threshold (most likely 1 cm) was expected. However, only one study reported a size-based threshold. Radiological-based criteria turned out to be the more common indicator for presence of the target conditions. For the studies lacking prespecified criteria, we assumed a similar implicit threshold, because all radiological-based criteria are somewhat similar, since diagnosis is an interpretation of the neoplastic or malignant characteristics. Summary sensitivity and specificity were reported per index test per target condition.

We compared the diagnostic accuracy of the index tests by including a single covariate term for test type in the bivariate model to estimate differences in the sensitivity and specificity of the tests. We allowed the variances of the random-effects model and their covariance to also depend on the test type, thus allowing the variances to differ between tests.

We used likelihood ratio tests to compare the model with and without covariate (test type). Covariates were assumed to affect both sensitivity and specificity. A P value less than 0.05 for the likelihood ratio test indicated differences in model fit with and without the test covariate. To identify differences in diagnostic accuracy between TAUS and EUS, we reported relative summary sensitivity and specificity, their confidence interval, and the P value. For studies that evaluated TAUS and EUS in the same study population (i.e. studies that performed both index tests in all the participants), we performed a direct head-to-head comparison by limiting the test comparison to such studies.

We performed the meta-analysis using SAS. We calculated the post-test probabilities using the median, upper quartile, and lower quartile of the prevalence per target condition (pre-test probabilities) and the expected prevalence based on the literature (10% for true polyps and 5% for dysplastic/malignant polyps). Post-test probability associated with a positive test is the probability of having the target condition (gallbladder polyp or true gallbladder polyp or dysplastic polyp/carcinoma) on the basis of a positive test result and is the same as the term 'positive predictive value' used in a single diagnostic accuracy study. Post-test probability associated with a negative test is the probability of having the target condition (gallbladder polyp or true gallbladder polyp or dysplastic polyp/carcinoma) on the basis of a negative test result and is 1 - 'negative predictive value'. Negative predictive value is the term used in a single diagnostic accuracy study to indicate the chance that the participant has no target condition when the test is negative. We reported the summary sensitivity, specificity, positive and negative likelihood ratios, and post-test probabilities.

Investigations of heterogeneity

We used all sources of heterogeneity listed under Secondary objectives as categorical covariates. We included one covariate at a time in the regression model. We used the likelihood ratio test to determine whether the covariate was statistically significant, using a P value of less than 0.05.

Sensitivity analyses

We planned to perform sensitivity analysis for:

- High-quality studies (as assessed per QUADAS-2 tool). All domains of QUADAS-2 tool have to be classified 'low risk of bias' for a study to be considered as a high quality study.
- Only inclusion of interpretable results (exclusion of participants with uninterpretable test results).

We planned to perform additional sensitivity analyses when the data available from the studies were ambiguous; for example, the numbers in the text were different from the numbers in the figures, in which case, we would assess the impact of different data used by a sensitivity analysis.

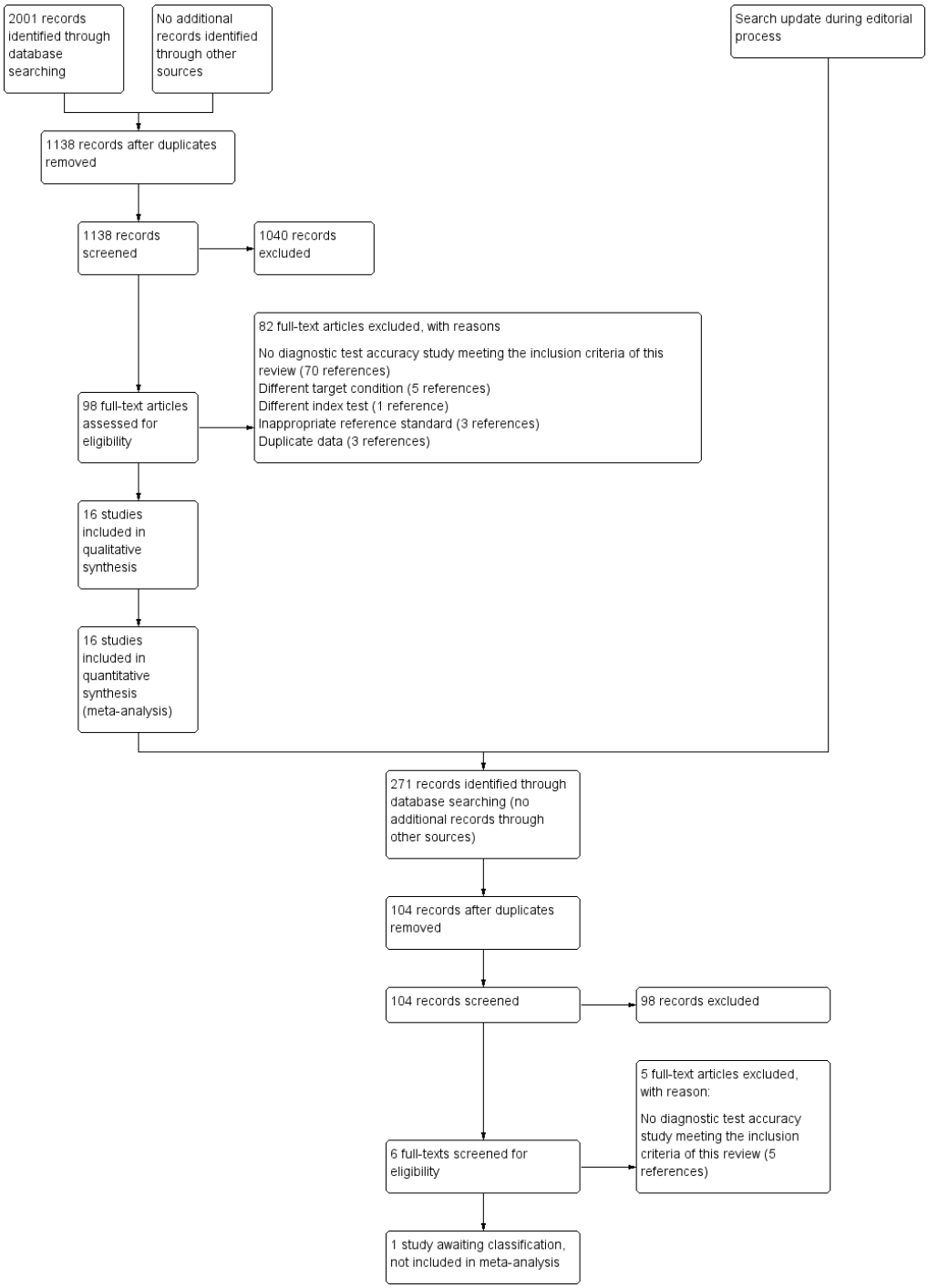
RESULTS

Results of the search

We identified a total of 2001 references through electronic searches of the Cochrane Library, MEDLINE, Embase, and Science Citation Index Expanded. No additional studies were identified from the online trial registries. After we removed duplicate references, there were 1138 articles remaining. We excluded 1040 clearly irrelevant references through reading abstracts. We retrieved the

full-text publication of 98 references for further detailed assessment. We excluded 82 references for the reasons described in the Characteristics of excluded studies section. Sixteen diagnostic accuracy studies fulfilled the inclusion criteria and were included in this review. We have presented a study flow diagram in Figure 2.

Figure 2. Study flow diagram.



Included studies

The characteristics of the included studies are summarised in the Characteristics of included studies. None of the studies reported on diagnostic accuracy of the combination of TAUS and EUS. All results are therefore displayed per index test per target condition. Most studies on differentiating polyp types displayed results either for true versus pseudo polyps or dysplastic polyps/carcinomas versus adenomas/pseudo polyps. One article (Zhang 2010) displayed results of separate polyp subtypes and could therefore be included for both target conditions. In this study 22.8% of true polyps were dysplastic or cancerous.

All studies used TAUS and/or EUS for diagnosis of gallbladder polyps or polyp type at initial presentation. None of the studies used sequential testing.

Detection of gallbladder polyp

We included a total of six studies involving 16,260 participants. Median prevalence of gallbladder polyps in the selected studies was 6.4% (IQR 2.4%to 18.8%). One study was prospective (Inoue 2007) and five studies were retrospective (Akyurek 2005; Spaziani 2012; Ahmed 2013; French 2013; Davies 2016). All studies had only TAUS as the index test. Three studies reported criteria for presence of a gallbladder polyp: an immobile gallbladder lesion without acoustic shadowing (Akyurek 2005; Inoue 2007; Ahmed 2013). In three studies, the criteria for presence of a gallbladder polyp were unclear (Spaziani 2012; French 2013; Davies 2016). Five studies had histopathology as the reference standard (Akyurek 2005; Spaziani 2012; Ahmed 2013; French 2013; Davies 2016). One study had both histopathology (76% of participants) and follow-up by TAUS (24% of participants) as the reference standard (Inoue 2007). The interval between the index test and reference standard was not reported in five of the studies. In Akyurek 2005, the median interval between TAUS and histopathology was seven months.

Differiation between true polyp and pseudo polyp

We included a total of six studies involving 1,078 participants. Median prevalence of true polyps in the selected studies was 19.2% (IQR 16.5% to 23.5%)%). One study was prospective (Xu 2003) and five studies were retrospective (Sugiyama 1999; Cheon 2009; Zielinski 2009; Zhang 2010; Lee 2016). Three studies had only TAUS as the index test (Xu 2003; Zielinski 2009; Zhang 2010). Three studies reported on TAUS and EUS as separate index tests (Sugiyama 1999; Cheon 2009; Lee 2016). EUS was performed after TAUS in all participants in these three studies. However, the diagnostic accuracy results were reported for TAUS and EUS as separate tests and not as combination of TAUS and add-on EUS. The interval between the index test and reference standard was reported and appropriate in two studies (Sugiyama 1999; Zhang 2010). One study reported size-based criteria for differentiating between true and pseudo polyps. Results were reported separately for two criteria for true polyps; size greater than 5mm and greater than 10mm (Zhang 2010). The results of the greater than 10 mm threshold were included in this review, as it was the advised threshold by the authors of Zhang 2010. Three studies used descriptive criteria of echogenic patterns for differentiating between true and pseudo polyps. These descriptive criteria were similar among the studies; cholesterol polyps had a tiny spotty echo pattern, adenomyomatosis was sessile polyps with microcysts or comet tail artefacts, and neoplastic polyps were pedunculated or sessile lesions without echogenic spots, multiple microcysts, or comet tail artefacts and/or the internal echo was hypoechoic to isoechoic (Sugiyama 1999; Xu 2003; Cheon 2009). For two studies, the criteria for differentiating between true and pseudo polyps were unclear (Zielinski 2009; Lee 2016).

Differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder

We included a total of five studies involving 1,127 participants. Median prevalence of dysplastic polyps/carcinoma in the selected studies was 13.0% (IQR 11.0% to 20.1%). One study was prospective (Jang 2009) and four studies were retrospective (Azuma 2001; Chattopadhyay 2005; Zhang 2010; Yoon 2011). Two studies had only TAUS as the index test (Chattopadhyay 2005; Zhang 2010). One study had only EUS as the index test (Yoon 2011). Two studies reported on both TAUS and EUS as separate index tests (Azuma 2001; Jang 2009). In these two studies, EUS was performed after TAUS in all participants. However, the diagnostic accuracy results were reported for TAUS and EUS as separate tests and not as combination of TAUS and add-on EUS. The interval between the index test and reference standard was reported and appropriate in one study (Zhang 2010). Only one study reported size-based criteria for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps. Results were reported separately for two criteria for dysplastic polyps/carcinomas; size greater than 5 mm and greater than 10 mm (Zhang 2010). The results of the greater than 10 mm threshold were included in this review, as it was the advised threshold by the authors of Zhang 2010. Two studies used descriptive criteria of echogenic patterns for the differentiation between dysplastic polyps/carcinoma and adenomas/pseudo polyps (Azuma 2001; Jang 2009). In two studies, the criteria for positive diagnosis of dysplastic polyps/carcinoma were unclear (Chattopadhyay 2005; Yoon 2011).

Shortly before the review publication, we identified one further study on TAUS for differentiation between dysplastic polyps/car-

cinomas and adenomas/pseudo polyps of the gallbladder (Zhang 2018). We added the study under 'Characteristics of studies awaiting classification'.

Excluded studies

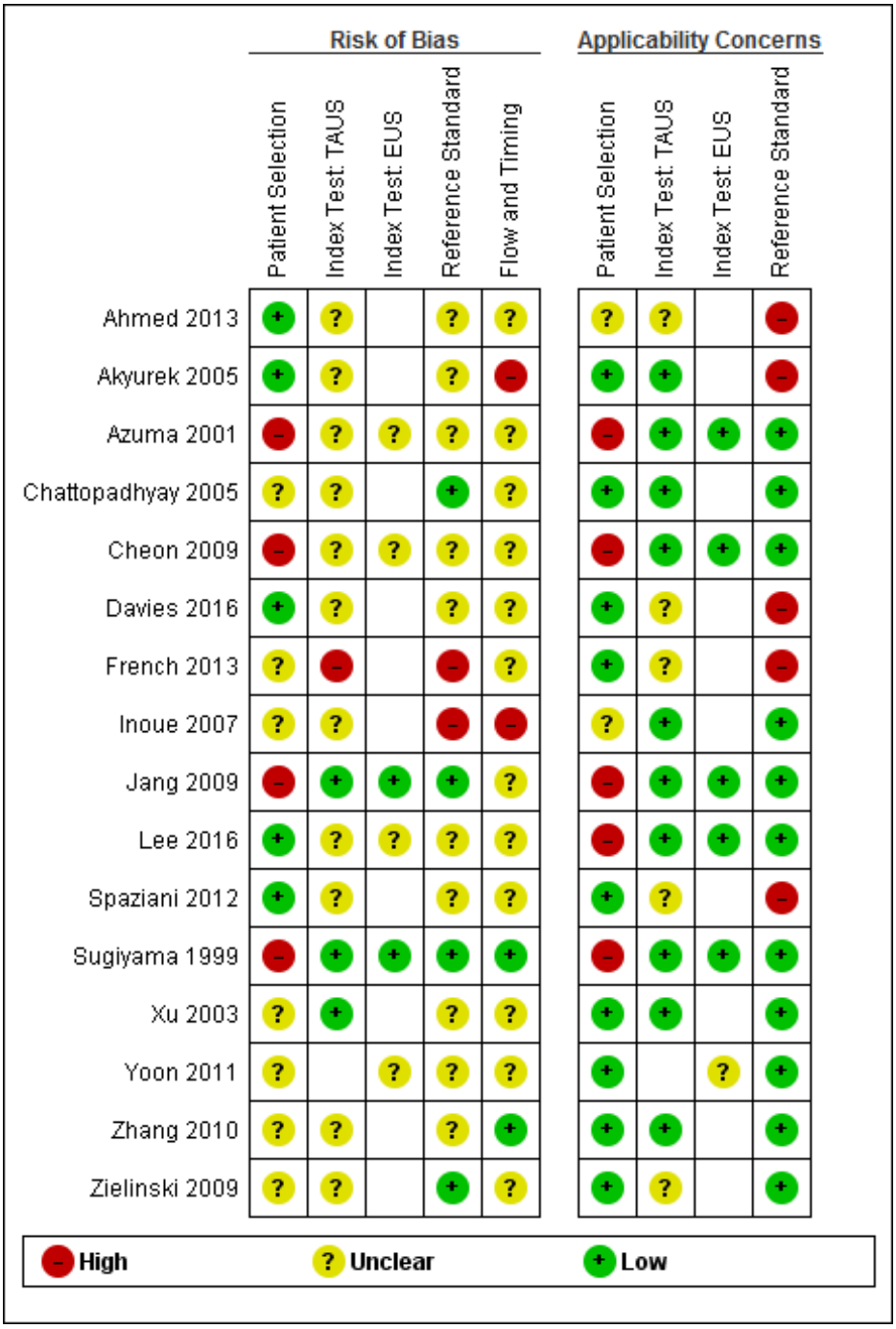
We excluded a total of 82 references for the following reasons:

- Seventy studies were not diagnostic test accuracy studies meeting the inclusion criteria for this review (Ruhe 1979; McIntosh 1980; Lorenz 1982; Price 1982; Nishimura 1984; Lim 1985; Wanatabe 1985; Murohisa 1986; Gjode 1988; Wan 1989; Alekse 1990; Farinon 1991; Demidov 1992; Yang 1992; Onodera 1993; Kubota 1994; Polverosi 1994; Isozaki 1995; Sugahara 1995; Moriguchi 1996; Kim 1999; Zhang 1999; Choi 2000; Jones-Monahan 2000; Kaechele 2000; Mainprize 2000; Terzi 2000; Chung 2001; Csendes 2001; Damore 2001; Huang 2001; Drews 2003; Pejic 2003; Dacka 2004; Guillen 2004; Roa 2004; Sun 2004; Wills 2004; Leonetti 2005; Rosenberg 2005; Akatsu 2006; Escalona (1) 2006; Escalona (2) 2006; Ansari 2007; Cerci 2008; Choi 2008; Cho 2009; Ito 2009; Kamili Polat 2010; Konstantinidis 2010; Shah 2010; Cha 2011; Tomic 2011; Cairns 2012; Konstantinidis 2012; Pedersen 2012; Arikanoglu 2013; Donald 2013; Ersoz 2013; Ichinoche 2013; Jin 2013; Matlok 2013; Sarkut 2013; Yi 2013; Maciejewski 2014; Yuan 2015; Kim 2016; Bavikatte 2016; Aliyazicioglu 2017)
- Five studies had different target conditions (Soiva 1987; Chijiiwa 1991; Covarrubias 1992; Imazu 2014; Kim 2015). Four studies were only on participants with gallbladder cancer (Soiva 1987; Chijiiwa 1991; Covarrubias 1992; Kim 2015), and one study was on participants with thickening of the gallbladder wall (Imazu 2014).
- In three studies on differentiation between true and pseudo polyps and dysplastic polyps/carcinomas and adenomas/pseudo polyps, histopathology was not used as the reference standard or results on participants with histopathology could not be extracted separately (Heyder 1984; Heyder 1990; Choi 2013).
- One study was on the accuracy of an EUS scoring system (Sadamoto 2002).
- Three studies contained duplicated data with another included study (Damore 1999; Sugiyama 2000; Cha 2009).

Methodological quality of included studies

We summarised the risk of bias and applicability concerns of the included studies in Figure 3. Seven studies were at high risk of bias (Sugiyama 1999; Azuma 2001; Akyurek 2005; Inoue 2007; Cheon 2009; Jang 2009; French 2013). All other studies were at unclear risk of bias. Ten studies had high applicability concerns (Sugiyama 1999; Azuma 2001; Akyurek 2005; Cheon 2009; Jang 2009; Spaziani 2012; Ahmed 2013; French 2013; Davies 2016; Lee 2016), three studies had unclear applicability concerns (Inoue 2007; Zielinski 2009; Yoon 2011;) and three studies had low applicability concerns (Xu 2003; Chattopadhyay 2005; Zhang 2010).

Figure 3. Risk of bias and Applicability concerns&supStart;Empty cells for index test: TAUS or index test: EUS occur if a study did not report on the corresponding index test&supEnd;



Participant selection domain

A total of five studies were at low risk of bias in the participant selection domain (Akyurek 2005; Spaziani 2012; Ahmed 2013; Davies 2016; Lee 2016). Four studies were at high risk of selection bias in the participant selection domain because of inappropriate exclusions (Sugiyama 1999; Azuma 2001; Cheon 2009; Jang 2009). Sugiyama 1999; Azuma 2001, and Cheon 2009 only included participants with polyps less than 20 mm. Sugiyama 1999 also excluded eight participants in whom the gallbladder was largely filled with gallstones; thereby, inhibiting polyp evaluation by TAUS. Jang 2009 did not include a consecutive or random sample of participants and excluded participants with polyps less than 1 cm, and clearly invasive or metastasised polyps. All other studies were at unclear risk of bias in the participant selection domain. In these studies, it was unclear whether a consecutive or random sample of participants were enrolled, or whether inappropriate exclusions were avoided, or both (Xu 2003; Chattopadhyay 2005; Inoue 2007; Zielinski 2009; Zhang 2010; Yoon 2011; French 2013).

Five studies had high applicability concerns in the participant selection domain (Sugiyama 1999; Azuma 2001; Cheon 2009; Jang 2009; Lee 2016). Four studies made inappropriate exclusions, eliminating participants for which the review question was relevant (Sugiyama 1999; Azuma 2001; Cheon 2009; Jang 2009); all four studies excluded participants based on polyp size. In addition, Jang 2009 excluded participants with polyps that had invasion or dissemination, and Sugiyama 1999 because of coincident gallstones. One study showed an extremely high percentage of true polyps (60%) (Lee 2016). Although this study included all consecutive participants undergoing US and EUS for gallbladder polyps and no inappropriate exclusions were made, applicability concerns in this study were estimated to be high; potentially, selection of participants at risk for true polyps occurred prior to EUS in this study centre; thereby, eliminating participants for which the review question was relevant. Two studies had unclear applicability concerns because they had a high prevalence of gallbladder polyps (Inoue 2007; Ahmed 2013). It was unclear whether the results of these studies could be extrapolated to a general population with lower prevalence of gallbladder polyps.

Index test domain

Three studies were at low risk of bias in the index test domain (Sugiyama 1999; Xu 2003; Jang 2009). A total of 12 studies had an unclear risk of bias in the index test domain, as it was either unclear whether the results of the index test were interpreted without knowledge of the reference standard (Azuma 2001; Akyurek 2005; Inoue 2007; Cheon 2009; Zhang 2010; Ahmed 2013), or because the criteria for diagnosis of the target condition by TAUS or EUS were unclear (Chattopadhyay 2005; Zielinski 2009; Yoon 2011; Spaziani 2012; Davies 2016; Lee 2016). Even though the reference standard (histopathology) was always done after TAUS or EUS, radiological images might be reviewed at time of analyses and decisions might have changed based on the results of histopathology, introducing bias. If blinding was not explicitly stated in the study, we classified the signalling question related to blinding as unclear. One study was at a high risk of bias in the index test domain, because the results of TAUS were reviewed with the results of the reference test (French 2013).

Five studies had unclear applicability concerns, because neither the type nor the frequency of ultrasound equipment used for diagnosis (Spaziani 2012; Ahmed 2013; French 2013; Davies 2016) or differentiation (Zielinski 2009; Yoon 2011) of the gallbladder polyps were stated. The background (ultrasound technician or radiologist) and experience of the sonographer/endoscopist was stated in only two studies. Although this may be a reason for heterogeneity amongst studies, we did not consider this a concern for applicability as, in clinical practice, the index test will be performed by both technicians/radiologist and endoscopists with different levels of experience.

Reference standard domain

Four studies were at low risk of bias in the reference standard domain (Sugiyama 1999; Chattopadhyay 2005; Jang 2009; Zielinski 2009). A total of ten studies were at an unclear risk of bias in the reference standard domain as it was unclear whether the reference standard was interpreted without knowledge of the index test (Azuma 2001; Xu 2003; Akyurek 2005; Cheon 2009; Zhang 2010; Yoon 2011; Spaziani 2012; Ahmed 2013; Davies 2016; Lee 2016). Two studies were at a high risk of bias in the reference standard domain. In one study, the results of histopathology were reviewed with the results of the index test (French 2013). In the other study, not all participants had histopathological analysis as the reference standard (Inoue 2007).

For studies on detection of gallbladder polyps, only one study had low applicability concerns; Inoue 2007 performed follow-up by repeated imaging as the reference standard for participants not undergoing cholecystectomy due to size of the polyp. All other studies only included histopathology as the reference standard, and they did not take into account participants who did not undergo cholecystectomy because of the size of the polyp (Akyurek 2005; Spaziani 2012; Ahmed 2013; French 2013; Davies 2016). This might mean that the target condition, as defined by the reference standard, did not match the review question in these studies. Therefore, these studies had high applicability concerns for the reference standard domain. For differentiating between true and pseudo polyps, and dysplastic polyps/carcinomas and adenomas/pseudo polyps, we could debate whether histopathological anal-

ysis was the best reference standard, as this would only be done after cholecystectomy. Cholecystectomy is usually only performed for polyps greater than 1 cm, and, therefore, the results may be less applicable for smaller polyps. Unfortunately, there is no other appropriate reference standard for polyp type. This limit in applicability should be taken into consideration when interpreting the results of this review.

Flow and timing domain

A total of two studies were at low risk of bias in the flow and timing domain (Sugiyama 1999; Zhang 2010). A total of 12 studies were at an unclear risk of bias in the flow and timing domain due to lack of information on the interval between the index test and reference standard (Azuma 2001; Xu 2003; Chattopadhyay 2005; Cheon 2009; Jang 2009; Zielinski 2009; Yoon 2011; Spaziani 2012; Ahmed 2013; French 2013; Davies 2016; Lee 2016). Two studies were at high risk of bias in the flow and timing domain (Akyurek 2005; Inoue 2007). In Inoue 2007, the reference standard was different between participants; the index test was compared to histopathology in 76% of participants and to follow-up by TAUS in 24% of participants. In Akyurek 2005, the median interval between the index test and reference test was seven months. In seven months, the polyp could have evolved and gained different histopathological characteristics, not representing the characteristics of the polyp at the time of the index test.

Findings

Summary of findings present the review results.

Sensitivity and Specificity

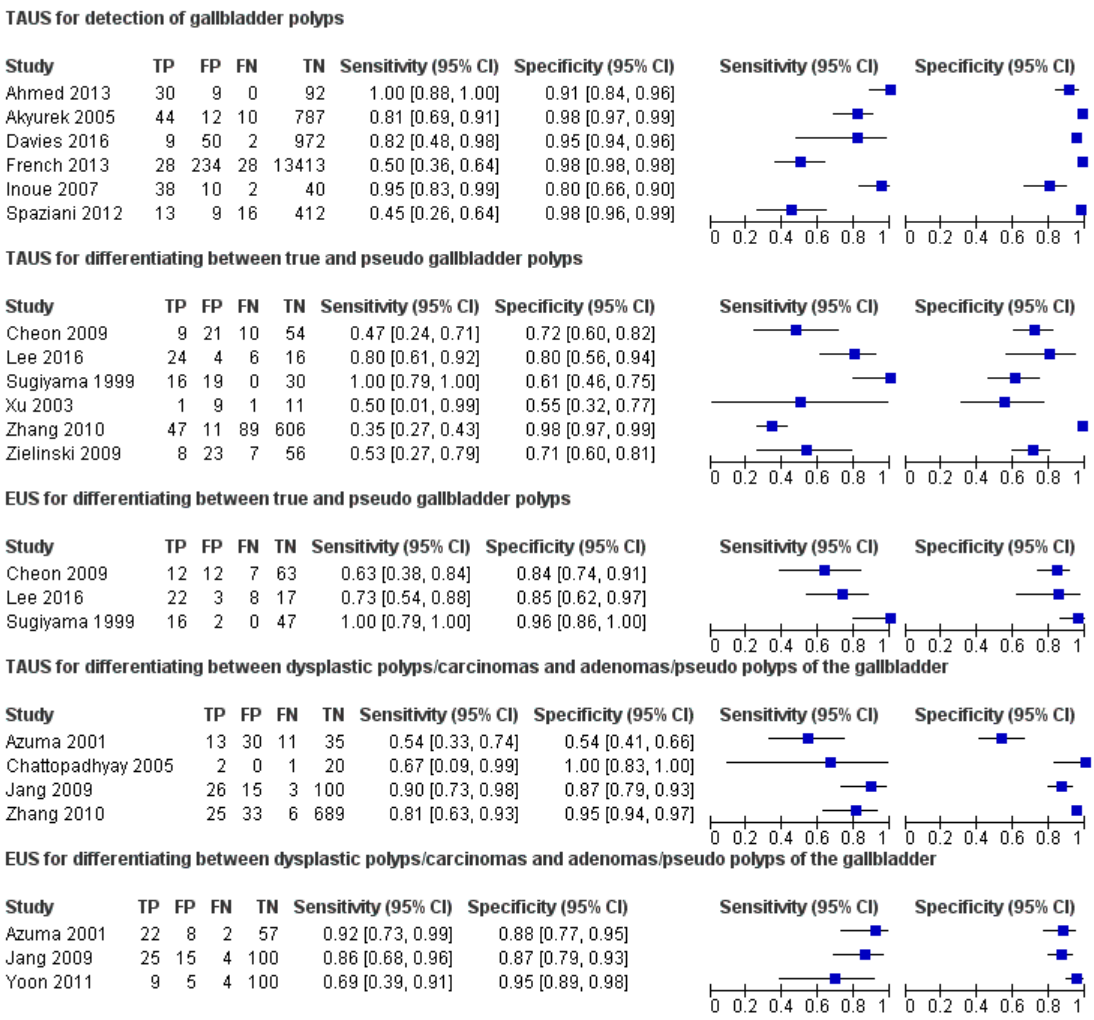
For Zhang 2010, only the results of the criterion of less than 10mm for diagnosis of true or dysplastic polyp/carcinoma were included in the forest plot and the meta-analysis, as it was the criterion used for primary analysis by the authors.

Detection of gallbladder polyps (presence compared to absence of gallbladder polyps)

Transabdominal ultrasound:

(6 studies, 16,260 participants, Akyurek 2005; Inoue 2007; Spaziani 2012; Ahmed 2013; French 2013; Davies 2016)
The sensitivities of the studies ranged between 0.45 and 1.00 (95% CI range 0.26 to 1.00), and the specificities ranged between 0.80 and 0.98 (95% CI range 0.66 to 0.99) (Figure 4). The summary sensitivity was 0.84 (95% CI 0.59 to 0.95) and the summary specificity was 0.96 (95% CI 0.92 to 0.98). The summary positive and negative likelihood ratios were 20.8 (95% CI 11.4 to 37.9) and 0.17 (95% CI 0.06 to 0.49). At the median pre-test probability of gallbladder polyps of 6.4%, the post-test probabilities associated with positive and negative tests were 0.59 (95% CI 0.44 to 0.72) and 0.01 (95% CI 0.004 to 0.03), respectively. At the lower quartile pre-test probability of gallbladder polyps of 2.4%, the post-test probabilities associated with positive and negative tests were 0.38 (95% CI 0.22 to 0.48) and 0.004 (95% CI 0.001 to 0.01), respectively, and at the upper quartile pre-test probability of gallbladder polyps of 18.8%, the post-test probabilities associated with positive and negative tests were 0.83 (95% CI 0.73 to 0.90) and 0.04 (95% CI 0.01 to 0.10), respectively (Summary of findings).

Figure 4. Forest plot of sensitivity and specificity of individual studies



Endoscopic ultrasound:

None of the studies reported the diagnostic accuracy of EUS in the diagnosis of gallbladder polyps.

Differentiation between true polyps and pseudo gallbladder polyps (true polyps compared to pseudo gallbladder polyps)

Transabdominal ultrasound:

(6 studies, 1,078 participants, Sugiyama 1999; Xu 2003; Cheon 2009; Zielinski 2009; Zhang 2010; Lee 2016)

The sensitivities of the studies ranged between 0.35 and 1.00 (95% CI range 0.01 to 1.00), and the specificities ranged between 0.55 and 0.98 (95% CI range 0.32 to 0.99) (Figure 4). The summary sensitivity was 0.68 (95% CI 0.44 to 0.85) and the summary specificity was 0.79 (95% CI 0.57 to 0.91). The summary positive and negative likelihood ratios were 3.25 (95% CI 1.60 to 6.59) and 0.40 (95% CI 0.23 to 0.74). At the median pre-test probability of true polyps of 19.2%, the post-test probabilities associated with positive and negative tests were 0.44 (95% CI 0.28 to 0.61) and 0.09 (95% CI 0.05 to 0.15), respectively. At the lower quartile pre-test probability of true polyps of 16.5%, the post-test probabilities associated with positive and negative tests were 0.39 (95% CI 0.24

to 0.56) and 0.07 (95% CI 0.04 to 0.13), respectively, and at the upper quartile pre-test probability of true polyps of 23.5%, the post-test probabilities associated with positive and negative tests were 0.50 (95% CI 0.32 to 0.67) and 0.11 (95% CI 0.07 to 0.19), respectively. At the expected prevalence of true polyps of 10%, the post-test probabilities associated with positive and negative tests were 0.27 (95% CI 0.15 to 0.42) and 0.04 (95% CI 0.03 to 0.08), respectively (Summary of findings).

Endoscopic ultrasound:

(3 studies, 209 participants, Sugiyama 1999; Cheon 2009; Lee 2016)
The sensitivities of the studies ranged between 0.63 and 1.00 (95% CI range 0.38 to 1.00), and the specificities ranged between 0.84 and 0.96 (95% CI range 0.62 to 1.00) (Figure 4). The summary sensitivity was 0.85 (95% CI 0.46 to 0.97) and the summary specificity was 0.90 (95% CI 0.78 to 0.96). The summary positive and negative likelihood ratios were 8.26 (95% CI 3.01 to 22.68) and 0.17 (95% CI 0.04 to 0.87). At the median pre-test probability of true polyps of 19.2%, the post-test probabilities associated with positive and negative tests were 0.62 (95% CI 0.37 to 0.82) and 0.03 (95% CI 0.01 to 0.15), respectively. At the lower quartile pre-test probability of true polyps of 16.5%, the post-test probabilities associated with positive and negative tests were 0.39 (95% CI 0.24 to 0.56) and 0.07 (95% CI 0.04 to 0.13), respectively, and at the upper quartile pre-test probability of true polyps of 23.5%, the post-test probabilities associated with positive and negative tests were 0.72 (95% CI 0.48 to 0.87) and 0.05 (95% CI 0.01 to 0.21), respectively. At the expected prevalence of true polyps of 10%, the post-test probabilities associated with positive and negative tests were 0.48 (95% CI 0.25 to 0.72) and 0.02 (95% CI 0.00 to 0.09), respectively (Summary of findings).

Differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder (dysplastic polyp(s) or carcinoma(s) compared to adenoma(s)/pseudo polyp(s))

Transabdominal ultrasound:

(4 studies, 1,009 participants. Azuma 2001; Chattopadhyay 2005; Jang 2009; Zhang 2010)
The sensitivities of the studies ranged between 0.54 and 0.90 (95% CI range 0.09 to 0.99), and the specificities ranged between 0.54 and 1.00 (95% CI range 0.41 to 1.00) (Figure 4). The summary sensitivity was 0.79 (95% CI 0.62 to 0.90) and the summary specificity was 0.89 (95% CI 0.68 to 0.97). The summary positive and negative likelihood ratios were 7.47 (95%CI 1.89 to 29.46) and 0.24 (95% CI 0.11 to 0.51). At the median pre-test probability of dysplastic polyps/carcinomas of 13.0%, the post-test probabilities associated with positive and negative tests were 0.53 (95% CI 0.22 to 0.82) and 0.03 (95% CI 0.02 to 0.07), respectively. At the lower quartile pre-test probability of dysplastic polyps/carcinomas polyps of 11.0%, the post-test probabilities associated with positive and negative tests were 0.48 (95% CI 0.19 to 0.79) and 0.03 (95% CI 0.01 to 0.06), respectively, and at the upper quartile pre-test probability of true polyps of 20.1%, the post-test probabilities associated with positive and negative tests were 0.65 (95% CI 0.32 to 0.88) and 0.06 (95% CI 0.03 to 0.11), respectively. At the expected prevalence of dysplastic/malignant polyps of 5%, the post-test probabilities associated with positive and negative tests were 0.28 (95% CI 0.09 to 0.60) and 0.01 (95% CI 0.01 to 0.03), respectively (Summary of findings).

In addition, one study, identified shortly before the review publication, used TAUS for differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder (See Zhang 2018 in Studies awaiting classification; Characteristics of studies awaiting classification). TAUS had sensitivity of 0.82 and specificity of 0.91; these values are the median values of the included studies on TAUS. As inclusion of the study data would have necessitated significant revisions to the numerical values without resulting in revisions in the interpretation or conclusion, we decided to not incorporate this study in the present meta-analysis. The results will be incorporated in a future update of the review.

Endoscopic ultrasound:

(3 studies, 351 participants, Azuma 2001; Jang 2009; Yoon 2011)
The sensitivities of the studies ranged between 0.69 and 0.92 (95% CI range 0.39 to 0.99), and the specificities ranged between 0.87 and 0.95 (95% CI range 0.77 to 0.98) (Figure 4). The summary sensitivity was 0.86 (95% CI 0.76 to 0.92) and the summary specificity was 0.92 (95% CI 0.85 to 0.95). The summary positive and negative likelihood ratios were 10.15 (95% CI 5.77 to 17.84) and 0.15 (95% CI 0.08 to 0.27) . At the median pre-test probability of dysplastic polyps/carcinomas of 13.0%, the post-test probabilities associated with positive and negative tests were 0.60 (95% CI 0.46 to 0.73) and 0.02 (95% CI 0.01 to 0.04), respectively. At the lower quartile pre-test probability of dysplastic polyps/carcinomas polyps of 11.0%, the post-test probabilities associated with positive and negative tests were 0.56 (95% CI 0.42 to 0.69) and 0.02 (95% CI 0.01 to 0.03), respectively, and at the upper quartile pre-test probability of true polyps of 20.1%, the post-test probabilities associated with positive and negative tests were 0.72 (95% CI 0.59 to 0.82) and 0.04 (95% CI 0.02 to 0.06), respectively. At the expected prevalence of dysplastic/malignant polyps of 5%, the post-test probabilities associated with positive and negative tests were 0.35 (95% CI 0.23 to 0.48) and 0.01 (95% CI 0.00 to 0.01), respectively (Summary of findings).

Comparison between tests

Comparison between TAUS and EUS was not possible for detection of gallbladder polyps, as none of the included studies reported on EUS. The comparison between tests for true polyp compared to pseudo polyps, and dysplastic polyps/carcinomas compared to adenomas/pseudo polyps were carried out using the bivariate model.

Direct comparison

Three studies reported results on TAUS and EUS in the same population for differentiating between true and pseudo polyps (Sugiyama 1999; Cheon 2009; Lee 2016). There was no convergence in the meta-analysis because of the few studies included in this analysis (paucity of data), the results were variable, and no inference could be made. Looking at the diagnostic accuracy of the individual studies, specificity of EUS in differentiating true and pseudo polyps was increased compared to TAUS in one study (Sugiyama 1999); 0.96 (95 %CI 0.86 to 1.00) for EUS vs 0.61 (95%CI 0.46 to 0.75) for TAUS. The specificities of EUS and TAUS in the other two studies, and sensitivities of TAUS and EUS in all studies were similar, with overlapping confidence intervals (Figure 4 and Figure 5). However, it should be noted that the same participants received both tests. The study authors did not report the statistical significance of the comparison or did not provide sufficient information to perform a statistical comparison of TAUS and EUS using McNemar's test. The results of EUS were interpreted without knowledge of TAUS results in Sugiyama 1999 and with knowledge of TAUS results in Cheon 2009. This was unclear for Lee 2016.

Two studies reported results on TAUS and EUS in the same population for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps (Azuma 2001; Jang 2009). There was no convergence in the meta-analysis because of paucity of data; the results were variable and no inference could be made. In the individual studies, diagnostic accuracy of EUS was suggested as better compared to TAUS in one study (Azuma 2001) and the same in the other study (Jang 2009) (Figure 4 and Figure 6). However, the comparison between TAUS and EUS in these studies was not statistically tested, nor did the study authors provide sufficient information to perform a statistical comparison between the tests using McNemar's test. For both studies, it was unclear whether the results of EUS were interpreted with or without knowledge of TAUS results.

Figure 5. Summary point estimates of TAUS (including 95% CI) and EUS for differentiating between true and pseudo polyps of the gallbladder.&supStart;The 95% CI ellipse of EUS could not be displayed due to few available studies.&supEnd;

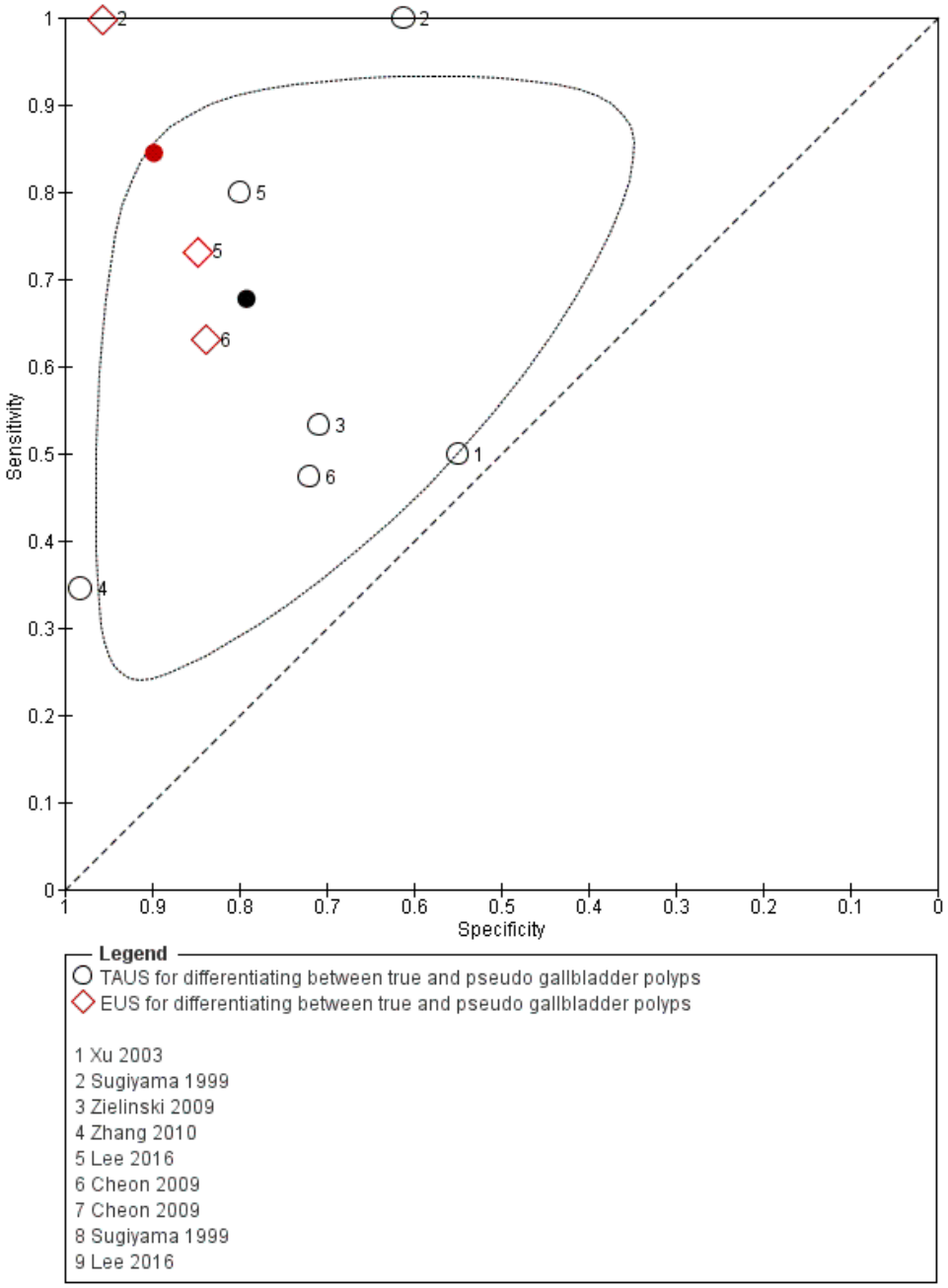
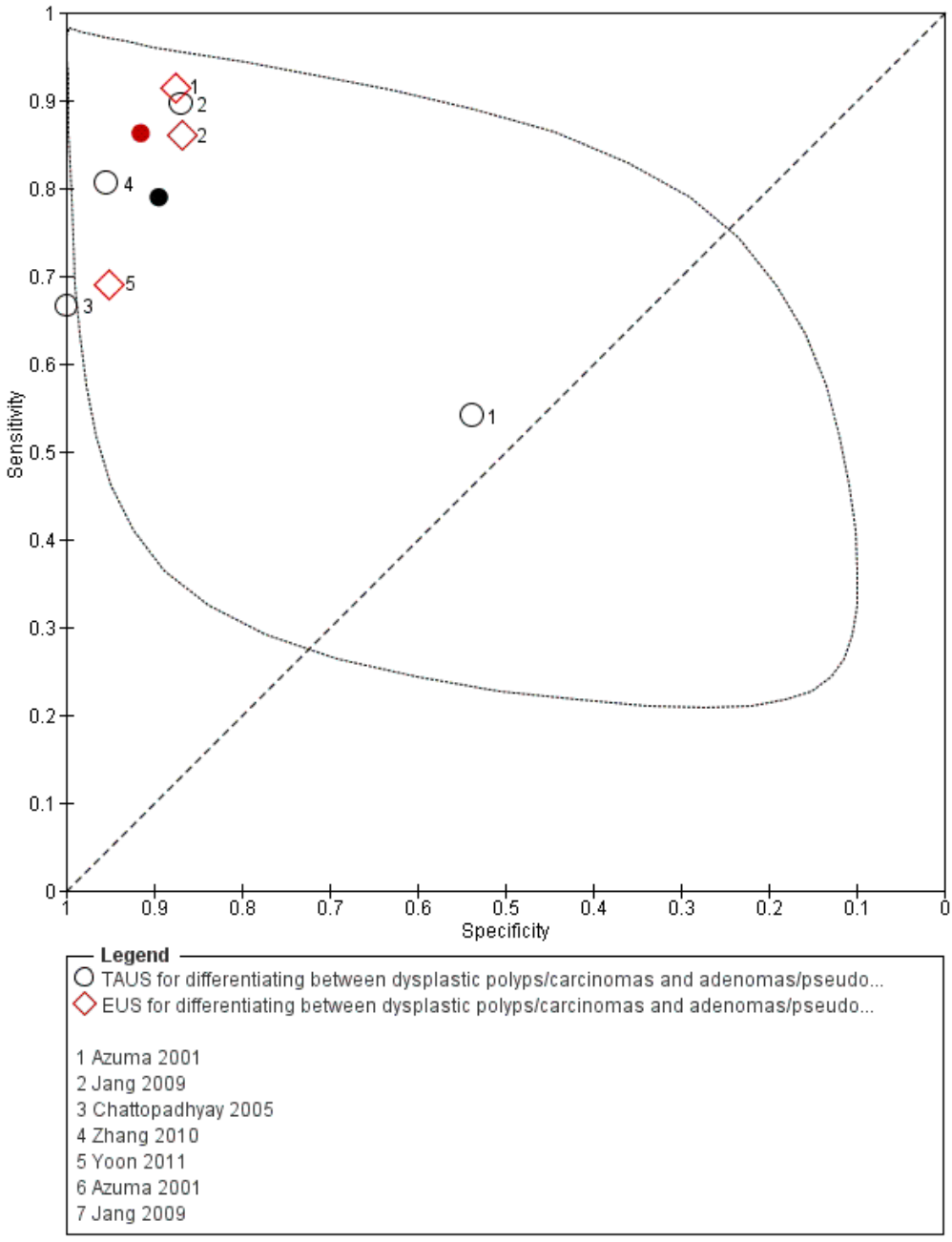


Figure 6. Summary point estimates of TAUS (including 95% CI) and EUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder.&supStart;The 95% CI ellipse of EUS could not be displayed due to few available studies&supEnd;



Indirect comparison

Due to the lack of convergence in the meta-analysis of studies comparing TAUS and EUS in the same population, meta-analysis comparing all studies on TAUS with all studies on EUS was performed per target condition.

True polyp compared to pseudo polyp

The summary sensitivity of TAUS was 0.68 (95% CI 0.44 to 0.85) compared to 0.85 (95%CI 0.46 to 0.97) for EUS. The summary specificity of TAUS was 0.79 (95% CI 0.57 to 0.91) compared to 0.90 (95% CI 0.78 to 0.96). The 95% confidence intervals of the sensitivities of both TAUS and EUS are broad and show extensive overlap. The 95% confidence interval of TAUS is also broad and includes almost the entire 95% confidence interval of EUS (Figure 5). The meta-analysis showed a relative sensitivity of 1.06 (95% CI 0.78 to 1.45) with P value of 0.70 and a relative specificity of 1.15 (95% CI 0.96 to 1.37) with P value of 0.12. Altogether, there is no evidence for a significant difference in the diagnostic accuracy between TAUS and EUS for differentiating between true and pseudo polyps.

Dysplastic polyps or carcinomas compared to adenomas/pseudo polyps

There is also no evidence for a significant difference in diagnostic accuracy between TAUS and EUS for differentiating between dysplastic polyp(s)/carcinoma(s) and adenoma(s)/pseudo polyp(s). The summary sensitivity of TAUS was 0.79 (95% CI 0.62 to 0.90) compared to 0.86 (95% CI 0.76 to 0.92) for EUS, and the summary specificities were 0.89 (95% CI 0.68 to 0.97) and 0.92 (95% CI 0.85 to 0.95) for respectively TAUS and EUS. The 95% confidence intervals of the sensitivities and specificities of TAUS and EUS show extensive overlap (Figure 6). The meta-analysis showed a relative sensitivity of 1.11 (95% CI 0.89 to 1.38) with P value of 0.38 and a relative specificity of 1.02 (95% CI 0.88 to 1.18) with P value of 0.80.

Exploration of heterogeneity

Presence compared to absence of gallbladder polyps

As illustrated in Figure 4, there was significant heterogeneity in the sensitivities of TAUS for detection of gallbladder polyps. Estimated variances of logit sensitivity and specificity were 2.18 and 0.86, respectively. We explored the following sources of heterogeneity using the bivariate model: prospective compared to retrospective studies, symptomatic compared to asymptomatic participants, and presence compared to absence of gallstones. For all sources, there was no convergence in the meta-analysis because of paucity of data. Other sources of heterogeneity were not explored due to lack of reporting on ultrasound equipment and sonographer experience, or similar characteristics amongst the studies.

True polyps compared to pseudo polyps

There was significant heterogeneity in the sensitivities and specificities of TAUS for differentiating true and pseudo polyps (Figure 4). Estimated variances of logit sensitivity and specificity were 1.08 and 1.53, respectively. We explored the following sources of heterogeneity using the bivariate model: asymptomatic compared to symptomatic participants, low compared to high probe frequency, presence compared to absence of gallstones. There was no convergence of results because of paucity of data for symptoms and gallstones, and no significant difference regarding probe frequency (P = 0.68). Other sources of heterogeneity were not explored due to lack of reporting on sonographer experience and diagnostic criteria for polyp differentiation, or similar characteristics amongst the studies. There was significant heterogeneity in the sensitivities of EUS for differentiating true and pseudo polyps. Estimated variances of logit sensitivity and specificity were 1.62 and 0.35, respectively. Due to the limited number of studies, meta-regressions exploring heterogeneity were not useful.

Dysplastic polyps or carcinomas compared to adenomas/pseudo polyps

There was significant heterogeneity in specificities of TAUS for differentiating dysplastic polyps/carcinomas and adenomas/pseudo polyps. Estimated variances of logit sensitivity and specificity were 0.38 and 1.63, respectively. Due to the limited number of studies, meta-regressions exploring heterogeneity were not useful.
No significant heterogeneity was present for EUS for differentiating dysplastic polyps/carcinomas and adenomas/pseudo polyps. Estimated variances of logit sensitivity and specificity were 0.07 and 0.23, respectively.

Sensitivity analysis

We could not perform the planned sensitivity analysis because none of the studies were at low risk of bias, and none of the studies had uninterpretable results.

DISCUSSION

Summary of main results

The summary of the main results is shown in the Summary of findings. The results should be interpreted with caution because all included studies were at high or unclear risk of bias in at least one of the evaluated domains.

TAUS will correctly diagnose 84% of patients with and 96% of patients without a gallbladder polyp. The cause of false diagnoses by TAUS is often the misinterpretation of gallstones or foldings of the gallbladder as polyps, or vice versa; the misinterpretation of polyps as gallstones. Some of these patients are still likely to receive the proper treatment: if the falsely identified 'polyp' (37 out of 1000 people) meets the current criteria for cholecystectomy (size greater than 10 mm), these patients would undergo surgery for a polyp they do not truly have. Thus, unnecessary surgeries would be performed. However, if patients turn out to have (symptomatic) gallstones (also an indication for cholecystectomy), surgery would not have been needless. False negatively diagnosed patients (7 out of 1000 people) would have a potential, though small, risk of developing a malignancy, if the missed polyp was a malignant polyp, dysplastic polyp, or adenoma. However, if these polyps were again mistaken for (symptomatic) gallstones (which is not uncommon), patients would still undergo the cholecystectomy they should have.

Diagnostic accuracy of TAUS decreased when differentiating between polyp types. The meta-analysis showed that 68% of true polyps and 79% of pseudo polyps will correctly be classified by TAUS. These patients with a true polyp, which is potentially pre-malignant, are generally advocated to undergo cholecystectomy. Overall, 32% of patients with a true polyp misclassified as a pseudo polyp (32 patients out of a hypothetical cohort of 1000 patients with gallbladder polyps undergoing TAUS) would not have a cholecystectomy. These patients would potentially risk a malignancy, although the rate and time in which adenomas progress to adenocarcinomas is unclear. On the other hand, 21% of patients with a harmless pseudo polyp misclassified as a true polyp (189 patients out of a hypothetical cohort of 1000 patients with gallbladder polyps undergoing TAUS) would undergo cholecystectomy. Many unnecessary cholecystectomies would be performed.

Diagnostic accuracy of TAUS for differentiating between dysplastic polyps/carcinomas ((pre)malignant) and adenomas/pseudo polyps (benign) was slightly higher compared to differentiating between true and pseudo polyps. Patients with a (pre)malignant polyp should undergo oncological diagnostic work-up (to identify extension and dissemination of the tumour) and oncological resection, if suitable for surgery. Results of the meta-analysis of TAUS suggested that only 79% of patients with a malignant or pre-malignant polyp would be indicated as such. These patients would undergo proper additional oncological work-up and/or resection. In 21% of patients (11 patients out of a hypothetical cohort of 1000 patients with gallbladder polyps undergoing TAUS), the (pre)malignant nature of the polyp might not be revealed until during surgery or at histopathological analysis postoperatively, resulting in non radical resection. By skipping the proper oncological diagnostic work-up, distant metastases (which would require palliative chemotherapy instead of surgery) could also be undetected, resulting in non-curative and unnecessary cholecystectomy (overtreatment). Overtreatment would also occur in the 11% of patients with a benign treatment classified as a (pre)malignant polyp (105 patients out of a hypothetical cohort of 1000 patients with gallbladder polyps undergoing TAUS). However, the false positive classification would have less severe consequences than a false negative diagnosis.

Some individual studies suggested (but it was not statistically tested) higher diagnostic accuracy of EUS compared to TAUS for differentiating polyp types (Sugiyama 1999; Azuma 2001). Overall (indirect) meta-analysis including all studies showed no significant differences. Details on the accuracy of EUS are shown in Summary of findings.

Median prevalence of gallbladder polyps in the included studies was within the expected range, based on previous histology and ultrasound studies (Mainprize 2000; Cha 2011). Median prevalence of true polyps and dysplastic polyps or carcinomas in the included studies was both higher than the expected 5% to 10% in the general population (Kozuka 1982). There are several possibilities for this high prevalence. First, bias in participant selection may have occurred. Most included studies were retrospective cohort studies, and five studies had high risk of bias or applicability concerns regarding participant selection (Sugiyama 1999; Azuma 2001; Cheon 2009; Jang 2009; Lee 2016). Other studies were at unclear risk of bias, as information on participant in- and exclusion was lacking (Xu 2003; Chattopadhyay 2005; Zielinski 2009; Zhang 2010;Yoon 2011). Second, all included studies for these two review questions were of Asian origin, where the prevalence of gallbladder polyps and carcinomas is higher than in the western population (Jorgensen 1990; Chen 1997; Okamoto 1999; Kratzer 2008; Lin 2008). Lastly, the reference standard could have introduced selection bias. Histopathological analysis of the polyp can only be performed after cholecystectomy. According to current clinical practice, cholecystectomy is performed for polyps greater than 1 cm, which are true polyps, dysplastic polyps, and carcinomas more often. Therefore, larger proportions of these types of polyps are to be expected in the included studies. Unfortunately, no other reference standard with a similar high accuracy for differentiation between polyp types is available.

Strengths and weaknesses of the review

We conducted a thorough literature search and included full-text publications and abstracts without any language restrictions. We also did not use any diagnostic test accuracy filters. The use of diagnostic test accuracy filters may lead to the loss of some studies (Doust 2005). Two authors independently identified and extracted data from the studies, potentially decreasing errors related to single data extraction (Buscemi 2006). Thereafter, the data were checked by a third review author to further minimise errors. We used a strict reference standard (histopathology) which is likely to diagnose the

type of gallbladder polyp condition with the highest degree of accuracy. As cholecystectomy may not be performed in patients without gallbladder polyps, we also accepted repeated imaging (six months), demonstrating repeated presence or absence of the polyp as the reference standard, for diagnosis of gallbladder polyps. This was only the case in one study. These were the major strengths of the review.

There were some major limitations in the review process. First, there were sparse data available for all review questions, potentially introducing random errors. The presence of sparse data was reflected in the wide confidence intervals of the sensitivity, specificity, and post-test probabilities, making the presented results less accurate. A direct comparison of TAUS and EUS in the same population could not be performed because only limited studies executed both tests in the same participants. Due to limited information within these studies, a paired proportion comparison, using McNemar's test, was also not possible. Therefore, the meta-analytic evidence relied on an indirect test comparison which is prone to confounding and may give different results compared to a more reliable direct comparison (Takwoingi 2013).

Secondly, significant heterogeneity was seen, mainly amongst studies on TAUS. Therefore, the meta-analysis may represent the expected results less accurately. We were only able to explore some sources of heterogeneity and could not establish any significant sources. Factors like ultrasound equipment, sonographer experience, and criteria for differentiation between polyp types could have influenced the accuracy of TAUS and may explain heterogeneity amongst studies. Unfortunately, this information was not fully available in the included studies.

Thirdly, the criteria for diagnosis of the target conditions (gallbladder polyp, true polyp, or dysplastic polyp/carcinoma) by TAUS or EUS were unclear in 33% to 50% of studies per target condition. Studies in which criteria for positive diagnosis were prespecified used descriptive criteria of echogenic patterns for positive diagnosis. Positive or negative diagnosis will thereby depend on subjective judgement of the polyp. Only one study provided an objective size-based threshold (Zhang 2010). Therefore, the meta-analysis was performed using the bivariate model, assuming no threshold effect. The lack of reported polyp size could have influenced the results of this review because smaller polyps may be harder to diagnose or differentiate than larger polyps. However, as the reference standard of this review was histological evaluation after surgery, it is likely that most polyps were greater than 1 cm. This, in turn, is relevant for the applicability of the review results in the general population.

Lastly, all included studies were at a high or unclear risk of bias, potentially introducing systematic errors. Consequently, the validity of the results may be questionable. The major concerns in the QUADAS-2 tool were: (1) Lack of random or consecutive inclusion of participants, inappropriate participant exclusions, or uncertainty about in- and exclusion criteria, potentially introducing bias in patent selection; (2) Interpretation of the index test with knowledge of the reference standard and vice versa, or uncertainty about blinding. Results of included (endoscopic) ultrasound scans may be reviewed at the time of publication, with knowledge of histopathology results, resulting in overestimation of diagnostic accuracy; (3) Extended or uncertain intervals between index test and reference test. If the latency time between TAUS or EUS and histopathology is too extended (greater than 3 months), the polyp could have evolved and gained different histopathological characteristics, not representing the characteristics of the polyp at the time of the index test. These were the major limitations of this review.

Shortly before the review publication, we identified one further study with TAUS used for differentiation between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder (Zhang 2018; Studies awaiting classification; Characteristics of studies awaiting classification). The sensitivity and specificity in this study was very similar to that of our meta-analysis. Although the confidence intervals may alter slightly if these data were added, our conclusions remained unchanged as this may cause only a minor alteration of the confidence intervals. We will incorporate the data from this study in a future update of the review.

Applicability of findings to the review question

The participants of the included studies on detection of gallbladder polyps were both symptomatic patients with upper abdominal pain as well as asymptomatic patients undergoing TAUS for other reasons (e.g. in trauma evaluation or routine check-up). This inclusion is in line with standard clinical practice and applicable to the standard population. For differentiation between polyp types, adults with known gallbladder polyps underwent TAUS or EUS. However, some studies excluded participants with very small or large polyps, or gallbladders that were particularly easy or difficult to diagnose. As these patients would be part of standard clinical practice, these exclusions diminished the applicability of the findings to differentiation between true and pseudo gallbladder polyps, and differentiation between dysplastic polyps/carcinomas and pseudo polyps/adenomas in the gallbladder of the standard population. Additionally, the median prevalence of polyps, true polyps and (pre)cancerous polyps in this review were higher than in the general population, due to the reference standard used and Asian origin of most studies. Applicability of results in a general population with lower prevalence may be reduced.

Histopathology is the most reliable reference standard for identification of gallbladder polyps and differentiation between polyp types. However, histopathology can only be used as reference in a surgical series and is not applicable to patients with small polyps not having surgery. Unfortunately, there is no reference standard close to the accuracy of histopathology in diagnosing polyp type.

Therefore, the findings of the review are not applicable to patients not having surgery.

Due to the extended amount of unreported criteria for diagnosis of the target conditions in the included studies, the reported diagnostic accuracies of this review are irrespective of criteria for diagnosis. As we cannot conclude which criteria for diagnosis of gallbladder polyps - true polyps or (pre)malignant polyps should be used - the applicability of the findings in current practice is questionable.

AUTHORS' CONCLUSIONS

Implications for practice

TAUS seems quite good at discriminating between gallbladder polyps and no polyps (Summary of findings). Therefore, TAUS should remain the modality of first choice for detection of gallbladder polyps. Due to the low prevalence of gallbladder polyps, the diagnostic accuracy will, however, lead to a significant amount of unnecessary surgeries. TAUS is less accurate in detecting whether the polyp is a true or pseudo polyp and a dysplastic polyp/carcinoma or adenoma/pseudo polyp. Some individual studies suggested higher diagnostic accuracy of EUS compared to TAUS in differentiating polyp types, but these conclusions were not based on statistical comparison of TAUS and EUS. Furthermore, this conclusion was not confirmed in the present meta-analysis. Therefore, there is no distinct preference in using TAUS or EUS for polyp differentiation (Summary of findings). Due to the lack of studies on the diagnostic accuracy of the combination of TAUS and EUS, we cannot state whether a combination of these tests would improve preoperative differentiation between polyp types in clinical practice. The decision to perform EUS or TAUS, or both, for additional analysis on polyp type may be according patients' or clinicians' preference. We cannot state which criteria for differentiation between polyp types should be used, because criteria for differentiating between true and pseudo polyps and dysplastic polyps/carcinomas and adenomas/pseudo polyps were not included in the meta-analysis. Therefore, the current criteria for cholecystectomy (size greater than 1 cm) should be maintained. Although it might lead to unnecessary surgeries for pseudo polyps larger than 1 cm, no appropriate alternative is available at this point.

Implications for research

Further studies of high methodological quality are necessary, mainly for differentiating between true and pseudo polyps, and between dysplastic polyps/carcinomas and adenomas/pseudo polyps. Additional studies should be conducted in a prospective manner and reported clearly, and the studies should be at low risk of bias, with low applicability concerns. TAUS and EUS should be assessed in the same population, or participants should be randomised to receive either TAUS or EUS in order to obtain more reliable comparisons between the tests. The value of EUS as an add-on to TAUS, to gain additional or more detailed information on gallbladder polyps, should be assessed as well. In clinical practice, EUS is often used for this purpose, although no literature reports on the value of this add-on. In all further research, clearly prespecified criteria for diagnosis of gallbladder polyps, true polyps and dysplastic polyps/carcinomas would ensure that the true diagnostic accuracy can be determined.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmed 2013

Study characteristics			
Patient sampling	Type of study: retrospective study		
Patient characteristics and setting	Sample size: 131 Female: unclear Age: unclear Presentation: patients who possessed lesions within the gallbladder on ultrasonography suggestive of gallbladder polyps and who underwent laparoscopic cholecystectomy Setting: UK Prevalence of gallbladder polyps: 30/131 cholecystectomies		
Index tests	Index test: TAUS Further details: nil Technical specifications: not stated Performed by: radiologist and ultrasonographers Criteria for positive diagnosis: presence of an immobile gallbladder lesion with no acoustic shadow and the absence of any intra or extrahepatic biliary dilatation		
Target condition and reference standard(s)	Target condition: presence of gallbladder polyp Reference standard: histopathology Further details: nil Performed by: Consultant and Specialist Registrar pathologists Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Akyurek 2005

Study characteristics			
Patient sampling	Type of study: retrospective		
Patient characteristics and setting	Sample size: 853 Female: unclear Age: unclear Presentation: patients who underwent laparoscopic cholecystectomy (LC) with a US report showing PLGs between 2000 and 2004 Setting: not stated Prevalence of gallbladder polyps: 54/853 cholecystectomies		
Index tests	Index test: TAUS Further details: nil Technical specifications: 3.5 MHz linear-array transducer attached to an EUB-420 scanner (Hitachi, Tokyo, Japan) Performed by: radiologists with special training in abdominal US Criteria for positive diagnosis: a lesion projecting into the lumen of the gallbladder which did not cast an acoustic shadow and did not move with the position of the patient		
Target condition and reference standard(s)	Target condition: presence of gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

Akyurek 2005 (*Continued*)

DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	No		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		High	

Azuma 2001

Study characteristics	
Patient sampling	Type of study: retrospective study
Patient characteristics and setting	Sample size: 89 Female: unclear Age: unclear

Azuma 2001 (*Continued*)

	Presentation: patients who underwent surgery for gallbladder polyps less than 20 mm in maximal diameter (between 1989 and 1998) Setting: Department of Gastroenterological Surgery, Tokyo Women's Medical University Prevalence of malignant polyps: 24/89 polyps
Index tests	Index test1: TAUS Further details: nil Technical specifications: convex-type sonoprobe with a 3.5 or 3.75 MHz transducer Performed by: not stated Criteria for positive diagnosis: Carcinoma is a pedunculated or sessile mass. The internal echo is hypoechoic to isoechoic and almost homogeneous, if not slightly heterogeneous. Carcinoma has a rounded shape with a nodular surface Index test 2: EUS Further details: nil Technical specifications: endoscopic ultrasound probe with a 7.5 or 12 MHz radial scan transducer Performed by: not stated Criteria for positive diagnosis: Carcinoma is a pedunculated or sessile mass. The internal echo is hypoechoic to isoechoic and almost homogeneous, if not slightly heterogeneous. Carcinoma has a rounded shape with a nodular surface
Target condition and reference standard(s)	Target condition: dysplastic gallbladder polyp or carcinoma Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology
Flow and timing	Index test 1:TAUS Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0 Index test 2: EUS Number of indeterminates for whom the results of the reference standard was available: 1 Number of patients who were excluded from the analysis: 1 (1.2%)
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	No		
		High	**High**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Azuma 2001 (*Continued*)

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Chattopadhyay 2005

Study characteristics			
Patient sampling	Type of study: retrospective study		
Patient characteristics and setting	Sample size: 23 Female: 16 Age: 57 years Presentation: presence of a solitary lesion within the gallbladder on preoperative US Setting: district general hospital, UK Prevalence of malignant polyps: 3/23 polyps		
Index tests	Index test: TAUS Further details: nil Technical specifications: 3.5/5.0 MHz transducer Performed by: consultant radiologist Criteria for positive diagnosis: not stated		
Target condition and reference standard(s)	Target condition: dysplastic gallbladder polyp or carcinoma Reference standard: histopathology Further details: nil Performed by: consultant pathologist Criteria for positive diagnosis: formal histology report		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Cheon 2009

Study characteristics			
Patient sampling	Type of study: retrospective study		
Patient characteristics and setting	Sample size: 94 Female: unclear Age: unclear Presentation: patients who underwent EUS for small (maximum diameter ≤ 20 mm) polypoid lesions of the GB detected by transabdominal US and underwent laparoscopic cholecystectomy for GB polyps (between 1996 and 2006) Setting: not stated Prevalence of true polyps: 19/94 polyps		
Index tests	Index test1: TAUS Further details: Technical specifications: real-time scanner with a 3.5-MHz curved array transducer (SSD-2000; Aloka, Tokyo, Japan Performed by: not stated Criteria for positive diagnosis: Neoplastic polyps (adenomas) are pedunculated or sessile masses without echogenic spots, multiple microcysts, or comet tail artefacts; the internal echo is hypoechoic to isoechoic and almost homogeneous Index test 2: EUS Further details: nil Technical specifications: echoendoscope with a 7.5 MHz or 12 MHz radial sector scan transducer (GF-UM2, UM3, UM20; Olympus Co., Tokyo, Japan) Performed by: one of the authors Criteria for positive diagnosis: Neoplastic polyps (adenomas) are pedunculated or sessile masses without echogenic spots, multiple microcysts, or comet tail artefacts; the internal echo is hypoechoic to isoechoic and almost homogeneous		
Target condition and reference standard(s)	Target condition: true gallbladder polyp Reference standard: histopathology Further details: nil Performed by: consultant pathologist Criteria for positive diagnosis: formal histology report		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Cheon 2009 (*Continued*)

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**High**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			

Cheon 2009 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Davies 2016

Study characteristics			
Patient sampling	Type of study: retrospective study		
Patient characteristics and setting	Sample size: 1,033 Female: unclear Age: unclear Presentation: All cholecystectomies completed at WUTH during a 1.5 year period (June 2013 to December 2014). Patients were excluded if histological or radiological data were not complete. Setting: Wirral University Teaching Hospital NHS Trust, Merseyside, UK Prevalence of gallbladder polyps: 11/1033 cholecystectomies		
Index tests	Index test: TAUS Further details: nil Technical specifications: not stated Performed by: not stated Criteria for positive diagnosis: not stated		
Target condition and reference standard(s)	Target condition: presence of gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Davies 2016 (*Continued*)

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		

Davies 2016 (*Continued*)

		Unclear	

French 2013

Study characteristics			
Patient sampling	Type of study retrospective study		
Patient characteristics and setting	Sample size: 13,703 Female: unclear Age: unclear Presentation: only patients with a TAUS report and a corresponding pathology report (between 2000 and 2010) Setting: Wirral University Teaching Hospital NHS Trust, Merseyside, UK Prevalence of gallbladder polyps: 56/13703 cholecystectomies		
Index tests	Index test: TAUS Further details: nil Technical specifications: not stated Performed by: not stated Criteria for positive diagnosis: not stated		
Target condition and reference standard(s)	Target condition: presence of gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

French 2013 (*Continued*)

Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	No		
If a threshold was used, was it pre-specified?	Unclear		
		High	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
		Unclear	

Inoue 2007

Study characteristics			
Patient sampling	Type of study: prospective study		
Patient characteristics and setting	Sample size: 90 Female: 45 (50%) Age: 67 years Presentation: patients with suspected gallbladder diseases based on previous US or CT testing (between 2000 and 2005) Setting: Kinki University Hospital, Japan Prevalence of gallbladder polyps: 40/90 cholecystectomies		
Index tests	Index test: TAUS Further details: nil Technical specifications: LOGIQ 9 and LOGIQ 700 EXPERT unit (GE Medical System, Milwaukee, WI, USA) with a 2 to 4 MHz electrical curved array wide band transducer Performed by: radiologist Criteria for positive diagnosis: if a change in posture did not alter the shape and location of the lesion		
Target condition and reference standard(s)	Target condition: presence of gallbladder polyp Reference standard 1: histopathology (68 patients) Further details: nil Performed by: not stated Criteria for positive diagnosis: histology Reference standard 2: follow-up by B-mode TAUS (22 patients) Further details: nil Performed by: not stated Criteria for positive diagnosis: lesions did not change in appearance over at least 1 year of follow-up		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Unclear**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		High	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Jang 2009

Study characteristics	
Patient sampling	Type of study: prospective
Patient characteristics and setting	Sample size: 144 Female: 72 (50%) Age: 58 years Presentation: Patients with a GB polypoid lesion diagnosis, referred from a primary or secondary health care hospital with an imaging diagnosis achieved by conventional transabdominal US (between Jan 2007 and Aug 2007). Excluded: polyps < 1 cm, lesions highly suspected of GB cancer (definite local invasion of adjacent organ or metastasis), history of upper GI surgery, refusal of participation, history of allergy to drug Setting: tertiary health care hospital Prevalence of malignant polyps: 29/144 polyps
Index tests	Index test 1: TAUS Further details: nil Technical specifications: High resolution ultrasound by LOGIQ 9 (GE, Milwaukee, WI). A broad bandwidth MHz linear array probe named 7L (GE, Milwaukee, WI, United States) with footprint of 53 to 11 mm and a bandwidth of 2.5 to 7.0 MHz Performed by: 2 GI specialist radiologists with over 10 years of US experience Criteria for positive diagnosis: A positive indication of irregular mucosal thickening or irregular wall thickening, including mucosal change combined with loss of normal mural layers. Sonographic findings were classified using a modification of the system proposed by Fujita et al If a change in posture did not alter the shape and location of the lesion Index test 2: EUS Further details: nil Technical specifications: LOGIQ 9 and LOGIQ 700 EXPERT unit (GE Medical System, Milwaukee,WI, USA) with a 2 to 4 MHz electrical curved array wide band transducer Performed by: 2 endoscopists with more than 10 years of EUS experience Criteria for positive diagnosis: A positive indication of irregular mucosal thickening or irregular wall thickening, including mucosal change combined with loss of normal mural layers. Sonographic findings were classified using a modification of the system proposed by Fujita et al If a change in posture did not alter the shape and location of the lesion
Target condition and reference standard(s)	Target condition: dysplastic polyp or carcinoma Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0
Comparative	
Notes	
Methodological quality	

Jang 2009 (*Continued*)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**High**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Jang 2009 (*Continued*)

		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Lee 2016

Study characteristics	
Patient sampling	Type of study: retrospective study
Patient characteristics and setting	Sample size: 50 Female: 26 (52%) Age: 61 years Presentation: Patients who had undergone HRUS and EUS before cholecystectomy. Excluded patients with chronic cholecystitis with/without stone, acute cholecystitis, and metastasis Setting: Korea Prevalence true polyps: 30/50 polyps
Index tests	Index test 1: TAUS Further details: nil Technical specifications: LOGIQ 9 (GE Healthcare, Milwaukee, WI, USA) with a linear high MHz transducer (7 L, bandwidth 2.5 to 7.0 MHz GE Healthcare, Milwaukee, WI, USA) Performed by: three clinically experienced radiologists Criteria for positive diagnosis: not stated Index test 2: EUS Further details: nil Technical specifications: radial echoendoscope (GF-UE 240, Olympus Co., Tokyo, Japan; SSD-alpha 10 Ultrasound System, Aloka Co., Ltd., Tokyo, Japan) with a 7.5 to 12 MHz rotating transducer (GF-UM2, -UM3, -UM20, Olympus Co., Tokyo, Japan) Performed by: clinically experienced gastroenterologist with more than 10 years of EUS experience Criteria for positive diagnosis: not stated
Target condition and reference standard(s)	Target condition: true gallbladder polyp Reference standard: histopathology Further details: nil

Lee 2016 (*Continued*)

	Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		

Lee 2016 (*Continued*)

		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Spaziani 2012

Study characteristics	
Patient sampling	Type of study: retrospective study
Patient characteristics and setting	Sample size: 450 Female: 261 (58%) Age: 54 years Presentation: patients who underwent cholecystectomy in the Department of Surgery (between Jan 2008 and Feb 2011) Setting: hospital 'A. Fiorini', Terracina, Italy Prevalence gallbladder polyps: 29/450 cholecystectomies
Index tests	Index test: TAUS Further details: nil Technical specifications: not stated Performed by: not stated Criteria for positive diagnosis: not stated

Spaziani 2012 (*Continued*)

Target condition and reference standard(s)	Target condition: presence of gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Spaziani 2012 (*Continued*)

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Sugiyama 1999

Study characteristics	
Patient sampling	Type of study: retrospective study
Patient characteristics and setting	Sample size: 65 Female: 35 (54%) Age: not stated Presentation: Patients who underwent cholecystectomy for small ('20 mm in maximum diameter') polypoid lesions of the gallbladder detected by transabdominal US (between Apr 1987 and May, 1998). Eight patients with gallbladders filled with gallstones, and therefore difficult to be evaluated on US, were excluded Setting: Kyorin University Hospital and two affiliated hospitals, Japan Prevalence of true polyps: 16/65 polyps
Index tests	Index test: TAUS Further details: nil Technical specifications: real-time scanner with a 3.5 MHz linear- or curved-array transducer (SAL-77A or SSA-270A, Toshiba, Tokyo, Japan; or SSD- 650 or SSD-2000, Aloka, Tokyo, Japan) Performed by: radiologist Criteria for positive diagnosis: if no echogenic spots, microcysts or comet tail artefacts were present, lesions were adenomas or adenocarcinomas, sessile lesions suggested malignancy Index test: EUS Further details: nil Technical specifications: echoendoscope with a 7.5 MHz rotating transducer (GF-UM2/EU-M2, GF-UM3/EU-M3, or GFUM200/ EU-M30, Olympus, Tokyo, Japan)

Sugiyama 1999 (*Continued*)

	Performed by: endoscopist Criteria for positive diagnosis: if no echogenic spots, microcysts or comet tail artefacts were present, lesions were adenomas or adenocarcinomas, sessile lesions suggested malignancy		
Target condition and reference standard(s)	Target condition: true gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**High**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test EUS			

Sugiyama 1999 (*Continued*)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Xu 2003

Study characteristics	
Patient sampling	Type of study: prospective study
Patient characteristics and setting	Sample size: 22 Female: not stated Age: not stated Presentation: not clear Setting: University hospital, China Prevalence of true polyps: 2/22 polyps

Index tests	Index test: TAUS Further details: nil Technical specifications: commercially available Voluson 730 3D sonographic scanner (Kretztechnik, Zipf, Austria) and a transabdominal convex volume transducer (RAB4-8P) with a frequency range of 4.0 to 8.0 MHz Performed by: 1 investigator. Images independently reviewed by 2 experienced investigators instead of the investigator who performed the examination. Criteria for positive diagnosis: a pedunculated or sessile mass with a round shape, a nodular surface, and an internal hypoechoic-to-isoechoic pattern and no characteristics of non-neoplastic polyps
Target condition and reference standard(s)	Target condition: true gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Xu 2003 (*Continued*)

If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Yoon 2011

Study characteristics	
Patient sampling	Type of study: retrospective study
Patient characteristics and setting	Sample size: 118 Female: not stated Age: not stated Presentation: patients with polypoid GB lesion or suspicious GB cancer and evaluated with preoperative EUS Setting: Korea Prevalence malignant polyps: 13/118 polyps
Index tests	Index test: EUS Further details: nil

	Technical specifications: not stated Performed by: not stated Criteria for positive diagnosis: not stated		
Target condition and reference standard(s)	Target condition: dysplastic polyp or carcinoma Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test EUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			

Yoon 2011 (*Continued*)

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Zhang 2010

Study characteristics	
Patient sampling	Type of study: retrospective study
Patient characteristics and setting	Sample size: 753 Female: 347 (46%) Age: 48 years Presentation: patients who were diagnosed with polyps by abdominal colour Doppler ultrasonography and pathological examination Setting: China Prevalence of true polyps: 136/753 polyps Prevalence of malignant polyps: 31/753 polyps
Index tests	Index test: TAUS Further details: nil Technical specifications: PHILIPS extraordinary type, TOSHIBA SSA-660A colour Doppler ultrasound diagnostic apparatus Performed by: not stated Criteria for positive diagnosis: > 10 mm (data also reported for > 5 mm)

Zhang 2010 (*Continued*)

Target condition and reference standard(s)	Target condition 1: true gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology Target condition 2: dysplastic polyp or carcinoma Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			

Zhang 2010 (*Continued*)

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Zielinski 2009

Study characteristics	
Patient sampling	Type of study: retrospective study
Patient characteristics and setting	Sample size: 94 Female: 57 (61%) Age: not stated Presentation: Patients who had a preoperative ultrasound examination of the gallbladder and subsequently underwent cholecystectomy (between Aug 1996 and Jul 2007). Excluded: known adenocarcinoma Setting: China Prevalence malignant polyps: 15/94 polyps
Index tests	Index test: TAUS Further details: nil Technical specifications: Acuson Sequioa ultrasound systems (Siemens Medical Solutions, Mountain View, CA, USA) Performed by: staff radiologist Criteria for positive diagnosis: not stated

Zielinski 2009 (*Continued*)

Target condition and reference standard(s)	Target condition: true gallbladder polyp Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: not described		
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 0		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test TAUS			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

CT:computertomography;EUS:endoscopicultrasonography;GB:gallbladder;GI:gastro−intestinal;HRUS:highresolutionultrasound;LC:laparoscopiccholecystectomy;MHz:megaher

WUTH: Wirral University Teaching Hospital

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akatsu 2006	Not a diagnostic test accuracy study
Alekse 1990	Not a diagnostic test accuracy study
Aliyazicioglu 2017	Missing diagnostic test accuracy information
Ansari 2007	Missing diagnostic test accuracy information
Arikanoglu 2013	Missing diagnostic test accuracy information
Bavikatte 2016	Missing diagnostic test accuracy information
Cairns 2012	Missing diagnostic test accuracy information
Cerci 2008	Not a diagnostic test accuracy study

(*Continued*)

Cha 2009	Meeting Abstract of Cha 2011 - duplicate data
Cha 2011	Missing diagnostic test accuracy information
Chijiiwa 1991	Wrong target condition
Cho 2009	Not a diagnostic test accuracy study
Choi 2000	Not a diagnostic test accuracy study
Choi 2008	Not a diagnostic test accuracy study
Choi 2013	Inappropriate reference standard
Chung 2001	Not a diagnostic test accuracy study
Corwin 2011	Missing diagnostic test accuracy information
Covarrubias 1992	Wrong target condition
Csendes 2001	Missing diagnostic test accuracy information
Dacka 2004	Missing diagnostic test accuracy information
Damore 1999	Abstract of Damore 2001 - duplicate data
Damore 2001	Missing diagnostic test accuracy information
Demidov 1992	Missing diagnostic test accuracy information
Donald 2013	Not a diagnostic test accuracy study
Drews 2003	Missing diagnostic test accuracy information
Ersoz 2013	Missing diagnostic test accuracy information
Escalona (1) 2006	Missing diagnostic test accuracy information
Escalona (2) 2006	Duplicate
Farinon 1991	Missing diagnostic test accuracy information
Gjode 1988	Not a diagnostic test accuracy study
Guillen 2004	Not a diagnostic test accuracy study

(*Continued*)

Heyder 1984	Inappropriate reference standard
Heyder 1990	Inappropriate reference standard
Huang 2001	Not a diagnostic test accuracy study
Ichinoche 2013	Missing diagnostic test accuracy information
Imazu 2014	Wrong target condition
Isozaki 1995	Not a diagnostic test accuracy study
Ito 2009	Missing diagnostic test accuracy information
Jin 2013	Not a diagnostic test accuracy study
Jones-Monahan 2000	Not a diagnostic test accuracy study
Kaechele 2000	Missing diagnostic test accuracy information
Kamili Polat 2010	Missing diagnostic test accuracy information
Kim 1999	Not a diagnostic test accuracy study
Kim 2015	Wrong target condition
Kim 2016	Not a diagnostic test accuracy study
Konstantinidis 2010	Missing diagnostic test accuracy information
Konstantinidis 2012	Missing diagnostic test accuracy information
Kubota 1994	Not a diagnostic test accuracy study
Leonetti 2005	Missing diagnostic test accuracy information
Lim 1985	Missing diagnostic test accuracy information
Lorenz 1982	Not a diagnostic test accuracy study
Maciejewski 2014	Missing diagnostic test accuracy information
Mainprize 2000	Missing diagnostic test accuracy information
Matlok 2013	Missing diagnostic test accuracy information

(*Continued*)

McIntosh 1980	Not a diagnostic test accuracy study
Moriguchi 1996	Not a diagnostic test accuracy study
Murohisa 1986	Missing diagnostic test accuracy information
Nishimura 1984	Not a diagnostic test accuracy study
Onodera 1993	Missing diagnostic test accuracy information
Pedersen 2012	Missing diagnostic test accuracy information
Pejic 2003	Missing diagnostic test accuracy information
Polverosi 1994	Not a diagnostic test accuracy study
Price 1982	Not a diagnostic test accuracy study
Roa 2004	Missing diagnostic test accuracy information
Rosenberg 2005	Not a diagnostic test accuracy study
Ruhe 1979	Not a diagnostic test accuracy study
Sadamoto 2002	Wrong index test
Sarkut 2013	Missing diagnostic test accuracy information
Shah 2010	Missing diagnostic test accuracy information
Soiva 1987	Wrong target condition
Sugahara 1995	Missing diagnostic test accuracy information
Sugiyama 2000	Duplicate data from another included study
Sun 2004	Not a diagnostic test accuracy study
Terzi 2000	Missing diagnostic test accuracy information
Tomic 2011	Not a diagnostic test accuracy study
Wan 1989	Missing diagnostic test accuracy information
Wanatabe 1985	Missing diagnostic test accuracy information

(*Continued*)

Wills 2004	Not a diagnostic test accuracy study
Yang 1992	Missing diagnostic test accuracy information
Yi 2013	Missing diagnostic test accuracy information
Yuan 2015	Missing diagnostic test accuracy information
Zhang 1999	Missing diagnostic test accuracy information

Characteristics of studies awaiting classification *[ordered by study ID]*

Zhang 2018

Study characteristics	
Patient sampling	Type of study: prospective study
Patient characteristics and setting	Sample size: 94 Female: unclear Age: unclear Presentation: patients with gallbladder lesion on both conventional ultrasound and CEUS who underwent cholecystectomy and had a pathological diagnosis Setting: Shanghai General Hospital, China Prevalence of malignant polyps: 17/94 polyps
Index tests	Index test: TAUS Further details: nil Technical specifications: Acuson Sequoia 512 diagnostic ultrasound system Performed by: ultrasound physician with thirteen years' experience Criteria for positive diagnosis: according to conventional ultrasound features
Target condition and reference standard(s)	Target condition: dysplastic gallbladder polyp or carcinoma Reference standard: histopathology Further details: nil Performed by: not stated Criteria for positive diagnosis: histology
Flow and timing	Number of indeterminates for whom the results of the reference standard was available: 0 Number of patients who were excluded from the analysis: 11 (11 patients had gallbladder sludge and no polyp, these were excluded from analysis, leaving 94 polyps)
Comparative	No comparison with EUS

Zhang 2018 (*Continued*)

Notes	This study was identified by a search update during the editorial process of the review. Adding this study to the meta-analysis would not change the conclusions of the review for the following reason: 1.Sensitivity and specificity of TAUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps in this study were 0.82 and 0.91, respectively. The values of the sensitivity and specificity were exactly the median values of all included studies for this target condition The pooled sensitivity and specificity of differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps were 0.79 and 0.89, respectively 2. There was no comparison between US and EUS in this study and it could therefore not improve direct comparison of the studies 3. This study had the same limitations as the other included studies: no distinct criteria for benign or malignant diagnosis on TAUS In conclusion, adding this study might increase the pooled sensitivity or specificity for the target condition dysplastic polyps/carcinomas by 1% to 2%, but this would not result in revisions in the interpretation or conclusion

CEUS:contrastenhancedultrasound;EUS:endoscopicultrasound;TAUS:transabdominalultrasound

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

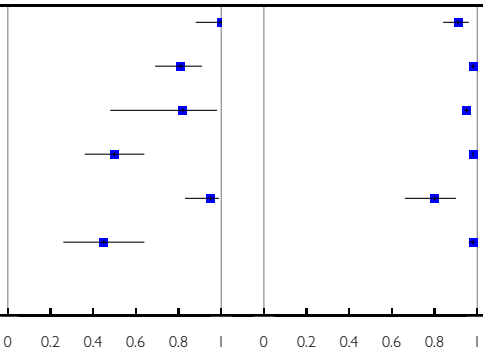
Test	No. of studies	No. of participants
1 TAUS for detection of gallbladder polyps	6	16260
2 TAUS for differentiating between true and pseudo gallbladder polyps	6	1078
3 EUS for differentiating between true and pseudo gallbladder polyps	3	209
4 TAUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder	4	1009
5 EUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder	3	351

Test 1. TAUS for detection of gallbladder polyps.

Review: Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps

Test: 1 TAUS for detection of gallbladder polyps

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ahmed 2013	30	9	0	92	1.00 [0.88, 1.00]	0.91 [0.84, 0.96]
Akyurek 2005	44	12	10	787	0.81 [0.69, 0.91]	0.98 [0.97, 0.99]
Davies 2016	9	50	2	972	0.82 [0.48, 0.98]	0.95 [0.94, 0.96]
French 2013	28	234	28	13413	0.50 [0.36, 0.64]	0.98 [0.98, 0.98]
Inoue 2007	38	10	2	40	0.95 [0.83, 0.99]	0.80 [0.66, 0.90]
Spaziani 2012	13	9	16	412	0.45 [0.26, 0.64]	0.98 [0.96, 0.99]

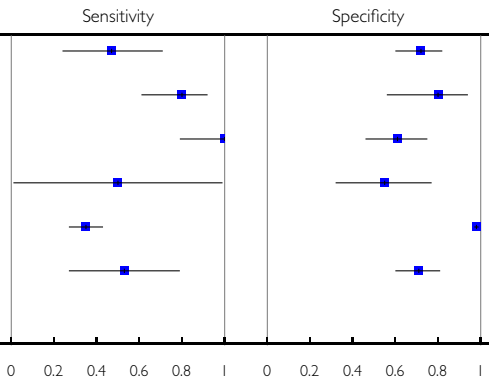


Test 2. TAUS for differentiating between true and pseudo gallbladder polyps.

Review: Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps

Test: 2 TAUS for differentiating between true and pseudo gallbladder polyps

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cheon 2009	9	21	10	54	0.47 [0.24, 0.71]	0.72 [0.60, 0.82]
Lee 2016	24	4	6	16	0.80 [0.61, 0.92]	0.80 [0.56, 0.94]
Sugiyama 1999	16	19	0	30	1.00 [0.79, 1.00]	0.61 [0.46, 0.75]
Xu 2003	1	9	1	11	0.50 [0.01, 0.99]	0.55 [0.32, 0.77]
Zhang 2010	47	11	89	606	0.35 [0.27, 0.43]	0.98 [0.97, 0.99]
Zielinski 2009	8	23	7	56	0.53 [0.27, 0.79]	0.71 [0.60, 0.81]

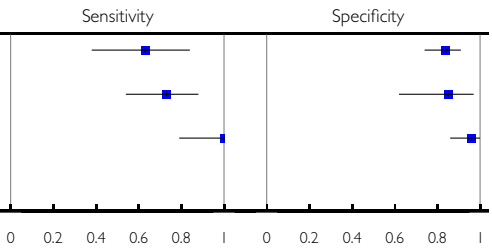


Test 3. EUS for differentiating between true and pseudo gallbladder polyps.

Review: Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps

Test: 3 EUS for differentiating between true and pseudo gallbladder polyps

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cheon 2009	12	12	7	63	0.63 [0.38, 0.84]	0.84 [0.74, 0.91]
Lee 2016	22	3	8	17	0.73 [0.54, 0.88]	0.85 [0.62, 0.97]
Sugiyama 1999	16	2	0	47	1.00 [0.79, 1.00]	0.96 [0.86, 1.00]

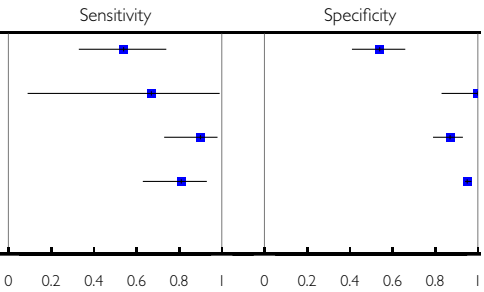


Test 4. TAUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder.

Review: Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps

Test: 4 TAUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder

Study	TP	FP	FN	TN	Sensitivity	Specificity
Azuma 2001	13	30	11	35	0.54 [0.33, 0.74]	0.54 [0.41, 0.66]
Chattopadhyay 2005	2	0	1	20	0.67 [0.09, 0.99]	1.00 [0.83, 1.00]
Jang 2009	26	15	3	100	0.90 [0.73, 0.98]	0.87 [0.79, 0.93]
Zhang 2010	25	33	6	689	0.81 [0.63, 0.93]	0.95 [0.94, 0.97]

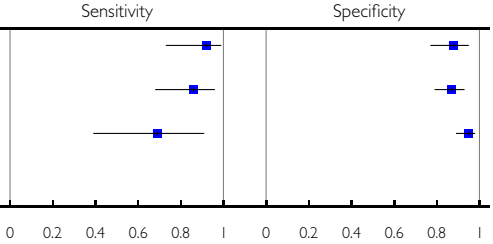


Test 5. EUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder.

Review: Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps

Test: 5 EUS for differentiating between dysplastic polyps/carcinomas and adenomas/pseudo polyps of the gallbladder

Study	TP	FP	FN	TN	Sensitivity	Specificity
Azuma 2001	22	8	2	57	0.92 [0.73, 0.99]	0.88 [0.77, 0.95]
Jang 2009	25	15	4	100	0.86 [0.68, 0.96]	0.87 [0.79, 0.93]
Yoon 2011	9	5	4	100	0.69 [0.39, 0.91]	0.95 [0.89, 0.98]



APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Library	2017, Issue 6	#1 MeSH descriptor: [Polyps] explode all trees #2 MeSH descriptor: [Adenomatous Polyps] explode all trees #3 polyp* or polypoid* or polypectom* or polypos* #4 #1 or #2 or #3 #5 MeSH descriptor: [Gallbladder] explode all trees #6 MeSH descriptor: [Gallbladder Neoplasms] explode all trees #7 MeSH descriptor: [Gallbladder Diseases] explode all trees #8 (gallbladder* or biliary or billiary or gall-bladder*) #9 #5 or #6 or #7 or #8 #10 MeSH descriptor: [Ultrasonography] explode all trees #11 (ultrasound* or ultra-sound* or ultrasonogra*or ultra-sonogra* or ultrasonic or ultra-sonic or echo* or sonogra* or EUS or doppler*) #12 #10 or #11 #13 #4 and #9 and 12
MEDLINE (PubMed)	1946 to 9 July 2018	#1 Gallbladder[Mesh] OR Gallbladder Neoplasms[Mesh] OR Gallbladder Diseases[Mesh] #2 Gallbladder* [tw] #3 Biliary [tw] #4 Billiary [tw] #5 Gall-bladder* [tw] #6 1 OR 2 OR 3 OR 4 OR 5 #7 Polyps [Mesh] OR Adenomatous Polyps [Mesh] #8 Polyps [tw] or Polyp[tw] #9 Polypos* [tw] #10 polypoid*[tw] #11 Polypectom* [tw] #12 7 OR 8 OR 9 OR 10 OR 11 #13 Ultrasonography [Mesh] OR ultrasonography [subheadings] #14 Ultrasound*[tw] OR Ultra-sound*[tw'] #15 Ultrasonogra*[tw] OR Ultra-sonogra*[tw] #16 Ultrasonic[tw] OR Ultra-sonic[tw] #17 Echo*[tw] OR Doppler*[tw] OR Sonogra*[tw] #18 EUS[tw] #19 13 OR 14 OR 15 OR 16 OR 17 OR 18 #20 6 AND 12 AND 19
Embase Ovid	1974 to 9 July 2018	#1 gallbladder*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] #2 exp gallbladder/ #3 exp gallbladder disease/ #4 gall bladder.mp. #5 gall-bladder*.mp.

(*Continued*)

		#6 (biliary or billiary).mp. #7 1 or 2 or 3 or 4 or 5 or 6 #8 exp polyp/ or benign tumor/ #9 (polyp or polyps or polypoid* or polypectom* or polypos*).mp #10 8 or 9 #11 7 and 10 #12 exp echography/ #13 exp endoscopic echography/ #14 (ultrasound* or ultra-sound* or ultrasonogra* or ultra-sonogra* or ultrasonic or ultra-sonic or echo* or sonogra* or EUS or doppler*).mp #15 12 or 13 or 14 #16 11 and 15
Science Citation Index Expanded (Web of Science)	1900 to 9 July 2018	#1 TS=(polyps OR polypoid* OR polypos*OR polyp OR polypectom*) AND (gallbladder OR biliary OR billiary OR gallbladder) AND (ultrasound OR ultrasonogra* OR ultra-sonogra* OR ultra-sound OR ultrasonic OR ultra-sonic OR echo* OR sonogra* OR EUS OR doppler*)

Appendix 2. QUADAS-2

Domain 1: participant selection	Participant sampling	Adults with (suspected) gallbladder polyp(s)
	Was a consecutive or random sample of participants enrolled?	Yes: if a consecutive sample or a random sample of adults with (suspected) gallbladder polyp(s) was included in the study No: if a consecutive sample or a random sample of adults with (suspected) gallbladder polyp(s) was not included in the study Unclear: if this information was not available.
	Did the study avoid inappropriate exclusions?	Yes: if all adults with (suspected) gallbladder polyp(s) were included No: if the study excluded people based on high probability of false negative results (e.g. difficult-to-diagnose people for any reason, for example, presence of coexisting gallstones or people with a high body mass index). Additionally, for differentiating between true and pseudo polyps, and dysplastic polyps/carcinomas and pseudo polyps/

(*Continued*)

		adenomas, patient should not be excluded based on polyp size or other polyp characteristics Unclear: if this information was not available.
	Could the selection of participants have introduced bias?	Low risk of bias: if 'yes' classification for both the above 2 questions High risk of bias: if 'no' classification for either of the above 2 questions Unclear risk of bias: if 'unclear' classification for either of the above 2 questions but without a 'no' classification for either of the above 2 questions
	Participant characteristics and setting	Yes: if all adults with (suspected) gallbladder polyp(s) were included No: if a proportion adults with (suspected) gallbladder polyp(s) were excluded on the basis of the high probability of false negative results (e.g. difficult-to-diagnose people for any reason, for example, presence of coexisting gallstones or people with a high body mass index). Additionally, for differentiating between true and pseudo polyps, and dysplastic polyps/carcinomas and pseudo polyps/adenomas, patient should not be excluded based on polyp size or other polyp characteristics Unclear: if it is not clear whether the people were included on the basis of the probability of positive results
	Were there concerns that the included participants and setting do not match the review question?	Low concern: if the participant characteristics and setting were classified as 'yes' High concern: if the participant characteristics and setting were classified as 'no' Unclear concern: if the participant characteristics and setting were classified as 'unclear'
Domain 2: index test	Index test(s)	Transabdominal ultrasound and endoscopic ultrasound (alone or in combination)
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes: if the index test was conducted and interpreted without the knowledge of the results of the reference standard. Blinding should be explicitly reported to avoid as-

(*Continued*)

		sumptions about bias related to this signalling question No: if the index test was interpreted with the knowledge of the results of the reference standard Unclear: if it was not clear whether the index test was interpreted without the knowledge of the results of the reference standard
	If a threshold was used, was it prespecified?	Yes: if criteria for differential diagnosis of gallbladder polyps or differentiation between true and pseudo polyps were prespecified No: if criteria for differential diagnosis of gallbladder polyps or differentiation between true and pseudo polyps were not prespecified Unclear: if it was not clear whether criteria were prespecified
	Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias: if 'yes' classification for both of the above 2 questions High risk of bias: if 'no' classification for either of the above 2 questions Unclear risk of bias: if 'unclear' classification for either of the above 2 questions but without a 'no' classification for either of the above 2 questions
	Were there concerns that the index test, its conduct, or interpretation differed from the review question?	Low concern: if the performance, conduct, and interpretation of the index tests are similar to the review question High concern: if the performance, conduct, and interpretation of the index tests are aberrant from the review question Unclear concern: if performance, conduct, or interpretation of index test were unclear
Domain 3: target condition and reference standard	Target condition and reference standard(s)	Target conditions: • polyp: present versus absent • polyp: true polyp versus pseudo polyp • polyp: dysplasia or gallbladder cancer versus adenomas or pseudo polyps Reference standard: histopathological analysis of the gallbladder after cholecystectomy or (only for determining presence/absence of gallbladder polyps) repeated imaging

(*Continued*)

	Was the reference standard likely to correctly classify the target condition?	Yes: if diagnosis of (type of) gallbladder polyp was confirmed by histopathological analysis of the gallbladder after cholecystectomy. No: if the reference standard was repeated imaging. Unclear: If the reference standard was not described adequately. We will exclude such studies
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes: if the reference standard was interpreted without the knowledge of the results of the index test. Blinding should be explicitly reported to avoid assumptions about bias related to this signalling question No: if the reference standard was interpreted with the knowledge of the results of the index test Unclear: it was not clear if the reference standard was interpreted without the knowledge of the results of the index test
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias: if 'yes' classification for both of the above 2 questions High risk of bias: if 'no' classification for either of the above 2 questions Unclear risk of bias: if 'unclear' classification for either of the above 2 questions but without a 'no' classification for either of the above 2 questions
	Were there concerns that the target condition as defined by the reference standard did not match the question?	Low concern: if the reference test includes all participants with the target condition relevant to the review High concern: if the reference test does not include all participants with the target condition relevant to the review (For presence of gallbladder polyps, this means that there was low concern if patients with small polyps not undergoing cholecystectomy underwent follow-up by repeated imaging. For differentiating polyp types, this means there was low concern if all patients were included in the histopathological analysis)
Domain 4: flow and timing	Flow and timing	Time interval between index test and reference standard (histopathological analysis) was set at 3 months. This is the estimated

(*Continued*)

		maximum time on the waiting list for elective cholecystectomy Time interval between index test and the alternative reference standard of imaging (in absence of histopathological analysis for determining presence/absence of gallbladder polyps) was set at 6 months
	Was there an appropriate interval between the index test and reference standard?	Yes: if the time interval between index test and reference standard was < 3 months if reference standard was histopathological analysis after cholecystectomy and up to 6 months if the reference standard was a repeated imaging No: if the time interval between index test and reference standard was > 3 months if reference standard was histopathological analysis after cholecystectomy and < 6 months if the reference standard was a repeated imaging Unclear: if the time interval between index test and reference standard was not clear
	Did all participants receive a reference standard?	Yes: if all participants received a reference standard. No: If some of the participants did not receive a reference standard. We will exclude such studies Unclear: If it was not clear whether all participants received a reference standard. We will exclude such studies. Therefore, we anticipated that all studies included in the review would be classified as 'yes' for this item
	Did all participants receive the same reference standard?	Yes: if all the participants received the same reference standard No: if different participants received different reference standards Unclear: if this information was not clear.
	Were all participants included in the analysis?	Yes: if all the participants were included in the analysis irrespective of whether the results were uninterpretable No: if some participants were excluded from the analysis because of uninterpretable results Unclear: if this information was not clear.

(*Continued*)

	Could the participant flow have introduced bias?	Low risk of bias: if 'yes' classification for all the above 4 questions High risk of bias: if 'no' classification for any of the above 4 questions Unclear risk of bias: if 'unclear' classification for any of the above 4 questions but without a 'no' classification for any of the above 4 questions

CONTRIBUTIONS OF AUTHORS

SW and ML identified studies and SW and MDM extracted the data from the studies. KG clarified questions and differences in data extraction. SW entered all study characteristics and performed the analysis together with KG. SW wrote the review, and KG, JD, and CL provided critical comments for the review.

DECLARATIONS OF INTEREST

Sarah Z Wennmacker has no conflict of interest.

Mark P Lamberts has no conflict of interest.

Marcello Di Martino has no conflict of interest.

Joost PH Drenth has no conflict of interest.

Kurinchi Selvan Gurusamy has no conflict of interest.

Cornelis JHM Van Laarhoven has no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Radboud University Medical Center, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The clinical pathway was updated according to the most recent guidelines and better clarified.

Objective differences between protocol and review:

We planned to compare TAUS and EUS either alone or in combination. However, all included studies reported distinct results for TAUS and/or EUS, i.e. none of the studies reported the diagnostic test accuracy of the combination of TAUS and EUS. Therefore, the objective was adapted to only diagnostic accuracy of TAUS and EUS separately.

Statistical differences between protocol and review:

- Because of the lack of studies on the combination of TAUS and EUS, results of the meta-analysis were only reported per index test per target condition.
- We only performed analysis using the bivariate model including all studies, assuming no threshold effect, since there were no specific thresholds mentioned in the studies and we expected the studies to use similar criteria for diagnosis.