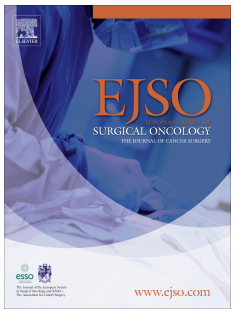
The role of laparoscopy and laparoscopic ultrasound in the preoperative staging of pancreatico-biliary cancers - a meta-analysis

D. Hariharan, V.A. Constantinides, F.E.M. Froeling, P.P. Tekkis, H.M. Kocher

Accepted Manuscript



Title: The role of laparoscopy and laparoscopic ultrasound in the preoperative staging of pancreatico-biliary cancers – a meta-analysis

Authors: D. Hariharan, V.A. Constantinides, F.E.M. Froeling, P.P. Tekkis, H.M. Kocher

PII: S0748-7983(10)00123-X

DOI: 10.1016/j.ejso.2010.05.015

Reference: YEJSO 2977

To appear in: *European Journal of Surgical Oncology*

Received Date: 5 October 2009

Revised Date: 13 October 2009

Accepted Date: 10 May 2010

Please cite this article as: Hariharan D, Constantinides VA, Froeling FEM, Tekkis PP, Kocher HM. The role of laparoscopy and laparoscopic ultrasound in the preoperative staging of pancreatico-biliary cancers – a meta-analysis, European Journal of Surgical Oncology (2010), doi: 10.1016/j.ejso.2010.05.015

The role of laparoscopy and laparoscopic ultrasound in the preoperative staging of pancreatico-biliary cancers – a meta-analysis

D Hariharan[1,2,*], VA Constantinides[3*], FEM Froeling[1], PP Tekkis[3], HM Kocher[1,2].

[1]Queen Mary University of London, Institute of Cancer, Barts and the London School of Medicine and Dentistry, London, [2]Barts and the London HPB Centre, The Royal London Hospital, London, and [3] Department of Biosurgery and Surgical Technology, Imperial College London, London, United Kingdom

* These authors contributed equally to the work. DH and FEMF did searches of literature and extracted data. VC performed analysis under supervision of PPT and HMK supervised the whole project and will act as a gurantor for the study

Corresponding Author –
Mr. H.M. Kocher
Senior Lecturer and Consultant HPB Surgeon, NIHR Clinician Scientist, Centre for Tumour Biology, Institute of Cancer, Barts and the London School of Medicine & Dentistry, Charterhouse Square, London, EC1M 6BQ
Email – h.kocher@qmul.ac.uk
Tel/Fax: +44 (0) 20 7882 3884

Key words - peritoneal metastases, liver metastases, cholangiocarcinoma, meta-analysis, yield.

Running head: Staging laparoscopy for pancreatico-biliary cancer

Word count: manuscript – 2985 words, abstract: 249 words
Figures – 2; Tables – 3; References - 43

Sources of support and conflict of interest: NIHR, UK, funds HMK with a clinician scientist fellowship. NIHR has no role in the study. There are no conflicts of interest with any of the authors.

Abstract

Background: Staging laparoscopy (SL) may prevent non-therapeutic laparotomy in patients with otherwise resectable pancreatico-biliary cancers, but evidence is inconclusive. This meta-analysis aims to ascertain the true benefit of SL.

Methods: All studies undertaking SL as a diagnostic sieve were included and data homogenised. Standard meta-analytical tools with emphasis on sensitivity testing and meta-regression to detect the cause for heterogeneity between studies were used.

Results: 29 studies satisfied the criteria. 3,305 patients underwent SL of which 12 were incomplete. Morbidity (n=15) and mortality (n=1) was low. True yield of SL for pancreatic cancers (PPC) was 25% (95% CI 24-27) with a Diagnostic Odds Ratio (DOR) of 104 (95% CI 48-227). Resection rate improved from 61% to 80%. For biliary cancers (PBC), SL increased the curative resection rate from 27% to 50%, with true yield of 47% (95% CI 42-52) and a DOR 61 (95%CI 19-189). Sub-group analysis for detection of liver and peritoneal lesions demonstrated a sensitivity of 88% (95% CI 83-92) and 92% (95% CI 84-96) for PPC; 83% (95% CI 69-92) and 93% (95% CI 81-99) for PBC, respectively. There was no between-study heterogeneity for peritoneal lesions. However for detection of local invasion, sensitivity was low: 58% (95% CI 51-65) for PPC and only 34% (95% CI 22-47) for PBC. Meta-regression did not reveal any cause for the observed heterogeneity between studies

Conclusion: SL offers significant benefit to patients with resectable pancreatico-biliary cancers in avoiding non-therapeutic laparotomy and should be adopted in routine clinical practice in a judicious algorithm.

INTRODUCTION

Cancers affecting the pancreas and the biliary tract carry poor prognosis[1,2,3]. Surgery, in the form of pancreatico-duodenectomy and/or liver resection, currently remains the only potential curative treatment modality but the majority of patients have advanced or metastatic disease precluding curative resection[4,5]. Accurate pre-operative staging is vital to identify patients who would truly benefit from resection, while excluding patients with locally advanced disease or distant metastases. Despite technological advances in imaging modalities used to assess patients preoperatively, 20-70% of patients undergo 'open and close' (non-therapeutic) laparotomy[4,5,6,7]. Staging laparoscopy (SL), with or without laparoscopic ultrasound (LUS), is a minimally invasive technique enabling direct assessment of the peritoneal cavity, liver, lymph nodes and related vascular structures. Its use has been inconsistent as the available supporting evidence is controversial and inconclusive. Also, as with all 'diagnostic tests', evidence synthesis is difficult in the absence of randomised controlled trials.

The aim of our study was to clarify the role of SL/LUS in patients with potentially resectable malignant pancreatico-biliary neoplasms by performing a meta-analysis on all available literature with particular emphasis on sensitivity analysis such as that for high quality studies (STAndards for the Reporting of Diagnostic accuracy (STARD) scores > 18)[8] and large (>100 patients) studies.

METHODS

The published literature was searched using Pubmed and free text search engines using the terms 'staging laparoscopy', 'laparoscopic ultrasonography', 'utility', 'role', 'pancreatic cancer', 'pancreatic ductal adenocarcinoma', 'biliary cancer', 'gallbladder cancer', 'cholangiocarcinoma', 'hilar cholangiocarcinoma' and 'intrahepatic cholangiocarcinoma'. Journal articles were further cross-referenced by manually searching bibliographies and using the 'related article' tool on PubMed. No language restrictions were made and the date of the last search was 31st June 2009.

Eligibility criteria and data extraction

All studies that examined the effect of SL/LUS on the surgical management of patients with potentially resectable pancreatic/peripancreatic cancers (PPC) and peri-biliary cancers (PBC) (which include gall bladder cancers (GBC) along with hilar and intrahepatic cholangiocarcinomas (HC & IHC)), based on pre-operative imaging were included. Operative surgical evaluation was considered the gold standard for staging, except when laparoscopy detected obvious metastatic lesions (in most cases biopsy-proven) affecting liver and/or peritoneum, lymph node metastases, locally advanced disease (invasion of vascular structures and/or adjacent organs), confirmed benign pathology or proven absence of disease, thus preventing surgical exploration.

Data were extracted on author, date of publication, institution, study design, patient demographics and technical aspects of the studies. All data were extracted independently by two reviewers (DH and FEMF), and discrepancy (3% of all data points) was resolved by HMK. Sensitivity and specificity were required for analysis and so studies providing insufficient information for calculations were excluded. In addition, studies which included

patients with known metastatic disease precluding resection and where laparoscopy was not performed due to failure to attain pneumoperitoneum, older studies from single institutions where authors admitted to including patients numbers from their previous publications in addition to new data in subsequent publications and when an indirect assessment of laparoscopy was performed i.e. when laparotomy detected lesions that theoretically could be detected using SL/LUS, while the procedure was not actually performed, were excluded. Quality of the studies was assessed using the STARD initiative guidelines [8].

Endpoint definitions

The primary endpoint was the sensitivity and specificity of SL/LUS to alter management in patients with potentially resectable PPC and PBC. This was either quoted directly in the studies or was extractable from analysis of the true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) on a per patient basis. Secondary endpoints included the ability of SL/LUS to detect liver metastases, peritoneal deposits, locally advanced disease (invasion into adjacent vessels or organs) and lymph node lesions. To enable statistical comparisons amongst studies, the extracted data from each study was homogenised to the following definitions: True positive (TP) was defined as the total number of unresectable patients diagnosed by laparoscopy and surgery. False positives (FP) were the number of patients diagnosed by laparoscopy to be unresectable, whilst they were resectable on surgery. True negative (TN) comprised of patients who were diagnosed as resectable by laparoscopy and went on to have curative surgical resection, while false negatives (FN) included the total number of patients who were resectable on laparoscopy but on laparotomy were unresectable. The yield of laparoscopy in a series was defined as the ratio of the number of patients benefiting from laparoscopy i.e. those in whom unnecessary laparotomy was avoided to the number of patients submitted to SL/LUS, whilst the true yield

of SL was defined as those patients who benefited when the SL/LUS procedure was complete. For the purpose of this study, patients with positive resection margins (RM) were considered to be unresectable (FN). The individual study sensitivities and specificities were extracted or calculated using two by two contingency tables for each endpoint. Pooled sensitivity (TP/[TP+FN]) and specificity (TN/[TN+FP]) with 95% confidence intervals were calculated using a random effects model to incorporate variation amongst studies. Overall and true yield of laparoscopy was calculated using sample size weighting for the mean and 95% exact binomial confidence intervals were fitted around the estimates. Verification bias occurs when the result of one test influences selection for the other test. Every patient included in the analysis underwent SL/LUS and laparotomy (reference standard), therefore primary verification bias should be zero.

Statistical analysis

Diagnostic odds ratios (DOR) were calculated that showed how much greater the odds of having unresectable disease were in the presence of a positive laparoscopy compared to a negative laparoscopy. Cochran's Q-test based on a χ^2 distribution was calculated that allowed a measure of heterogeneity between the studies. Inconsistency (I^2) index value was calculated that determined the percentage of total variation across all studies that was due to heterogeneity, rather than chance. SROC (Summary Receiver Operator Characteristic) analysis was used to evaluate SL/LUS using area under the curve (AUC) and Q value as the summary estimates. The Moses-Shapiro-Littenberg model based on weighted (sample size) regression analysis was used and results were compared to the hierarchical SROC model to ensure consistency. Sensitivity analysis assessed the effect of sample size (studies with >100 successful laparoscopies), study quality (STARD score≥18) and the use of LUS. Subgroup analysis was performed to assess diagnostic accuracy of SL/LUS for liver metastases,

peritoneal metastases and local/vascular invasion. Meta-regression analysis was performed to explore sources of heterogeneity arising from variables such as year of study publication, sample size, use of LUS and study quality. Analysis was conducted using Meta-Disc for Windows version 1.4 (XI Cochrane Colloquium, Barcelona, 2006) and STATA version 10 (StataCorp LP, Texas, USA) software. The study was undertaken in accordance with previously published guidelines for meta-analyses evaluating diagnostic modalities[9]. All values are presented rounded to nearest integer for simplicity.

RESULTS

Literature review identified 343 articles, of which 302 were eliminated after abstract review. 80% of articles extracted were review articles, whilst the remaining did not assess SL/LUS as staging modality. Of the remaining 41 articles, 12 studies did not satisfy the eligibility criteria; 22 were for potentially resectable PPC and 7 for PBC [10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37] (**Supplemental information, Table ST1, ST2, Figure SF1)**. Computerised tomography (CT) scan remained the investigation of choice to assess resectability across all studies, supported by the use of either ultrasound (US), magnetic resonance cholangio-pancreatography (MRCP), angiography, endoscopic retrograde cholangio-pancreatography (ERCP), endoscopic ultrasound (EUS) and/or colour flow doppler. Altogether 3,439 patients (2,957 PPC, 482 PBC) were initially considered for SL/LUS. However, 77 had evidence of metastatic disease, 24 had no laparoscopy and 33 (29 PPC, 4 PBC) had documented failures to attain pneumoperitoneum and were therefore excluded from our analysis. Therefore, a total of 2,827 patients with PPC and 478 patients with PBC, deemed potentially resectable on preoperative staging, were included for analysis. In 12 patients with PPC, laparoscopic ultrasound examination was not feasible due to previous adhesions, making the staging procedure incomplete. Only 2 studies, clarified RM status and where RM was positive, they were included as false negative [11,32].

SL/LUS in PPC

Of the 2,827 patients that were subjected to SL/LUS, 26% were deemed unresectable (**Supplemental information Figure SF2)**. However, 44 / 722 patients (6%) were given a trial of surgical resection, of these only 14 underwent curative surgery (false positive); suspected local vascular invasion (n=3[11,13]) and metastases from neuroendocrine tumour

of the pancreas did not prevent curative surgery (n=2[12]), no reasons mentioned (n=9[10]). The remaining 30 patients were considered as true positives (**Supplemental information Table ST3)**.

The overall sensitivity and specificity was 64% (95%CI 61-66) and 99% (95%CI 99-100); overall and true yield was 25% and 25.2% respectively. Following SROC analysis the AUC was found to be 96 (DOR 104; 95%CI 48-226) with significant between-study heterogeneity across all test characteristics (**Figure 1a)**. The addition of SL/LUS improved the resection rate for PPC from 61to 80%.

Of the 22 studies included in our analysis, 18 studies had definitely resectable cancers (Groups 1, **Supplemental information Table ST4**) and 6 studies (Group 2, **Supplemental information Table ST5**) included patients with CT evidence of locally advanced disease (based on size or suspicion of vascular involvement). The DOR decreased from 103 (95% CI 46-231) to 23 (95% CI 6-83), when patients with locally advanced disease were subjected to SL.

SL/LUS in PBC

True positive included liver and/or peritoneal metastases (n=109), locally advanced disease (n=34), metastases to diaphragm (n=8) or omentum (n=3), coeliac lymph nodes (n=7), other pathology (n=20), and unavailable data (n=59). Only 127 / 256 (50%) patients explored surgically had curative resection (S**upplemental information, Figure SF3)**. Reasons for unresectable (false negative) disease included locally advanced disease (n=60), nodal metastases (n=23), liver metastases (n=8), peritoneal metastases (n=3), benign pathology (n=1) and unavailable data (n=34). The addition of SL/LUS increased the curative resection rate from 27% to 50% in patients with PBC.

The overall sensitivity and specificity of SL/LUS in detecting inoperable disease was 63% (95% CI 58–68) and 100% (95% CI 97-100) with significant between-study heterogeneity for sensitivity (**Figure 1b)**. The overall and true yields were 46% (95% CI 42-51) and 47% (95% CI 43-52). SROC analysis revealed an AUC of 95% (DOR 61; 95% CI 19-189). Further data extraction from these studies permitted assessment of the role of SL/LUS in GBC and IHC separately (**Supplemental information, Tables ST6 and ST7** respectively).

Sensitivity and subgroup analysis

Sensitivity analysis, considering large and high quality studies, for PPC revealed no significant improvement in diagnostic accuracy compared to the overall analysis (**Table 3**). On consideration of studies employing LUS, sensitivity improved with a parallel improvement in the DOR to 137 (95% CI 50-376) from 104 (95% CI 48-227) for the overall sample. In the case of PBC, there was only one study[36] with sample size >100 and therefore no analysis was performed on large studies. Sensitivity analysis of high quality studies and of studies employing LUS did not result in any improvement of the diagnostic parameters. Subgroup analysis revealed a high sensitivity for liver and peritoneal lesions (no between-study heterogeneity) and low sensitivity for local/vascular tumour invasion **(Figure 2**).

Meta-regression analysis

Meta-regression analysis to explore potential sources of heterogeneity arising from the included studies (high quality, recent studies and large studies) and use of LUS failed to unearth statistically significant contribution towards between-study heterogeneity. Use of LUS was shown to improve diagnostic accuracy by a factor of 1.34 (**Supplemental**

information, Table ST8) with a relative DOR of 4 (95% CI 0.7-22) but this did not reach statistical significance (p=0.1). Meta-regression analysis also did not show any statistically significant contribution towards between-study heterogeneity arising from study design (prospective versus retrospective), country of origin (USA versus other, UK versus other) and use of pre-operative MRI in cases of PBC (data not shown).

Laparoscopy related complications

The mortality and morbidity attributed to the use of laparoscopy in potentially resectable pancreatico-biliary cancers (PPC & PBC) was reported by 9 of the 29 studies included in our analysis[13,14,15,16,17,18,19,20,21]: haemorrhage requiring laparotomy (n=3), port site abscess/infection (n=3), post operative pneumonia (n=2), post procedure pancreatitis (n=2), bile leak (n=2), port site haematoma (n=2), port site recurrence (n=1). There was one reported postoperative death due to myocardial infarction.

Discussion

Our meta-analysis demonstrate the utility of SL and LUS in potentially resectable cancers of pancreatico-biliary origin suggesting that its adoption in routine clinical practice will benefit up to 50% of patients from undergoing unnecessary laparotomy with its attendant morbidity. Despite being an invasive procedure involving general anaesthetic, SL offers these patients tremendous benefit (early commencement of alternative treatment strategies[38], shortened hospital stay, psychological benefit of minimally invasive surgery[39]) with very little risk (failure rate ~ 1%, morbidity, mainly minor < 0.5%, and mortality < 0.05%).

Limitations

A meta-analysis of a diagnostic modality, particularly an operator-dependent partially subjective test dependent on numerous variables, such as SL, has its inherent disadvantages. The main limitation is the heterogeneity of studies included, as indicated by the I^2 statistic (**Tables 1-3**). We have made every effort to account for this heterogeneity, by performing numerous types of sensitivity analysis and meta-regression such as; that for high quality studies (rigorous reporting and analysis criteria), those with more than 100 patients (experienced, high-volume centres), those performed after year 2000 (to account for changes in imaging modalities as well as laparoscopic experience and instrumentation), using country of origin of study (to account for differences in clinical practice and health care economics), use of additional pre-operative investigative modalities (for example MRI, EUS), use of additional SL tests (such as washings, data not shown). Nevertheless the heterogeneity remains amongst the studies for the estimate of sensitivity of SL in detecting inoperable patients. This heterogeneity is therefore real and reflects the nature of clinical practice. The sensitivity of SL, as a diagnostic test, is affected both by pre-test and post-test parameters defining inoperability.

Pre-test parameter variability

Pre-test variability includes the investigative modality used such as CT scan. There are no set criteria for performing CT scan in patients with these cancers and the amount of information gathered can vary vastly upon, the nature of CT scan machine, the amount and type of contrast used, the phases of scanning, the rapidity of sequence acquisition, the ability to perform 3D reconstruction[38]. This is further compounded by the variable use of other modalities such as endoscopic ultrasound, magnetic resonance imaging and positron emission tomography. Thus the sensitivity of these tests, either alone or in combination, may alter the pre-operative call of operability. Increasing sensitivity of these imaging modalities would decrease the sensitivity of SL. Notwithstanding these characteristics, it is in the authors' experience that the small peritoneal and liver metastatic lesions (less than 0.5 cm and surface lesions) are difficult to diagnose in any of the above imaging methods with certainty and therefore SL would be warranted. Indeed, for detection of peritoneal disease there was no between-study heterogeneity.

Post-test variability

Post-test characteristics include the definition of resectable cancers which varies from centre to centre. Thus, a small portion of portal vein encroachment may be considered resectable in most, but not all centres dealing with these cancers[40,41]. However, arterial involvement is considered operable only by a minority of the centres of excellence and, even in those series of patients, the peri-operative outcome is not good[41,42]. These aspects account for the variability in the resectability criteria for locally advanced disease. Certainly for cancers of the pancreatico-biliary system, non-contiguous liver metastasis and celiac lymph nodal involvement are considered inoperable disease (as opposed to, say, for colo-rectal cancers). Thus the variable criteria for the definition of resectable disease may account

for the heterogeneity observed in this meta-analysis. Only a prospective multi-centre study (which will be practically very difficult to conduct) with previously agreed, uniform criteria for the diagnostic modality methodologies such as CT scan and the definition of 'unresectable cancer' could resolve these biases. Nevertheless, the ability of SL to correctly diagnose a large proportion (20-50%) of patients with metastatic disease merits its use in routine clinical practice, if not for assessing locally advanced disease.

An additional conundrum is the argument that, if the tumour is unresectable, then at least for pancreatic head tumours, laparotomy offers the chance to perform definitive palliative surgery such as biliary and gastric bypass. In a recent synthesis of data from various centres, we have demonstrated that endoscopic palliative procedures such as biliary and/or duodenal stenting offer not only less procedure-related-morbidity and mortality but also a shorter length of hospital stay and faster recovery[43]. Thus, non-therapeutic or palliative laparotomy should be avoided in favour of equivalent, endoscopic or percutaneous, palliative procedures.

Benefits

How this staging strategy should be adopted in routine practice and which patients would most benefit? Proceeding to definitive resection straight after a negative SL offers the benefit of a single general anaesthetic but adds in the waiting time for frozen section, which may not be 100% reliable, and also planning of an operative session becomes difficult and unpredictable. Decoupling SL from the definitive procedure offers these advantages and may have the added benefit of discussing the finding with the patient and their carers (bearing a mind that a SL may still have a false negative rate of up to 20%) and assessing the ability of patients to tolerate a general anaesthetic (thus directly examining the true, not hypothetical, fitness for surgery in these usually elderly patients).

Direct cost-benefit analyses have not been carried out, especially, given the heterogeneity of the studies assessed. However, assuming a median yield of 30% with SL (and a false negative rate of 10%) and an overnight in-patient stay for SL (though in most centres it is performed as a day case procedure) and an in-patient stay of 11 days for 'non-therapeutic laparotomy' and 15 days for a 'therapeutic laparotomy'; performing SL for 10 patients with potentially resectable cancers, would save 30 bed-days as well as 14 hours of operating theatre time. This is equivalent to performing two additional therapeutic procedures for every 10 patients for the same cost, by using SL as a diagnostic sieve. This 20% cost-benefit would be additional to the actual benefit for at least 30% of patients, who can start other modalities of treatment, such as chemotherapy, without any delay.

Conclusions

The continuous evolution of imaging modalities will hopefully be able to identify the unresectable disease (particularly liver and peritoneal metastasis) and render SL, an invasive investigation, obsolete in the near future. In the current clinical practice, SL appears beneficial for patients with pancreatic and biliary cancers for detection of peritoneal disease and small, surface liver metastasis, which are currently below the threshold of imaging modalities. SL should be adopted in routine clinical practice and algorithms designed for its judicious use.

Author Disclosure

Drs. Deepak Hariharan, Vasilis A Constantinides, Fieke EM Froeling, Paris P Tekkis, Hemant M Kocher, have no conflicts of interest or financial ties to disclose.

REFERENCES

1. Hariharan D, Saied A, Kocher HM (2008) Analysis of mortality rates for gallbladder cancer across the world. HPB (Oxford) 10: 327-331.
2. Hariharan D, Saied A, Kocher HM (2008) Analysis of mortality rates for pancreatic cancer across the world. HPB (Oxford) 10: 58-62.
3. Gourgiotis S, Kocher HM, Solaini L, Yarollahi A, Tsiambas E, Salemis NS. (2008) Gallbladder cancer. Am J Surg 196: 252-264.
4. Blechacz B, Gores GJ (2008) Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment. Hepatology 48: 308-321.
5. Ghaneh P, Costello E, Neoptolemos JP (2007) Biology and management of pancreatic cancer. Gut 56: 1134-1152.
6. D'Angelica M, Fong Y, Weber S, Gonen M, DeMatteo RP, Conlon K, Blumgart LH, Jarnagin WR. (2003) The role of staging laparoscopy in hepatobiliary malignancy: prospective analysis of 401 cases. Ann Surg Oncol 10: 183-189.
7. Greten FR, Wagner M, Weber CK, Zechner U, Adler G, Schmid RM. (2001) TGF alpha transgenic mice. A model of pancreatic cancer development. Pancreatology 1: 363-368.
8. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Moher D, Rennie D, de Vet HC, Lijmer JG. (2003) The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Clin Chem 49: 7-18.
9. Irwig L, Tosteson AN, Gatsonis C, Lau J, Colditz G, Chalmers TC, Mosteller F. (1994) Guidelines for meta-analyses evaluating diagnostic tests. Ann Intern Med 120: 667-676.
10. Nieveen van Dijkum EJ, Romijn MG, Terwee CB, de Wit LT, van der Meulen JH, Lameris HS, Rauws EA, Obertop H, van Eyck CH, Bossuyt PM, Gouma DJ. (2003) Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma. Ann Surg 237: 66-73.
11. Doran HE, Bosonnet L, Connor S, Jones L, Garvey C, Hughes M, Campbell F, Hartley M, Ghaneh P, Neoptolemos JP, Sutton R. (2004) Laparoscopy and laparoscopic ultrasound in the evaluation of pancreatic and periampullary tumours. Dig Surg 21: 305-313.
12. Vollmer CM, Drebin JA, Middleton WD, Teefey SA, Linehan DC, Soper NJ, Eagon CJ, Strasberg SM. (2002) Utility of staging laparoscopy in subsets of peripancreatic and biliary malignancies. Ann Surg 235: 1-7.
13. John TG, Greig JD, Carter DC, Garden OJ (1995) Carcinoma of the pancreatic head and periampullary region. Tumor staging with laparoscopy and laparoscopic ultrasonography. Ann Surg 221: 156-164.
14. Kwon AH, Inui H, Kamiyama Y (2002) Preoperative laparoscopic examination using surgical manipulation and ultrasonography for pancreatic lesions. Endoscopy 34: 464-468.
15. Jimenez RE, Warshaw AL, Rattner DW, Willett CG, McGrath D, Fernandez-del Castillo C. (2000) Impact of laparoscopic staging in the treatment of pancreatic cancer. Arch Surg 135: 409-414; discussion 414-405.
16. Mosca F, Giulianotti PC, Balestracci T, Di Candio G, Pietrabissa A, Sbrana F, Rossi G. (1997) Long-term survival in pancreatic cancer: pylorus-preserving versus Whipple pancreatoduodenectomy. Surgery 122: 553-566.

17. Bemelman WA, de Wit LT, van Delden OM, Smits NJ, Obertop H, Rauws EJ, Gouma DJ. (1995) Diagnostic laparoscopy combined with laparoscopic ultrasonography in staging of cancer of the pancreatic head region. Br J Surg 82: 820-824.
18. Goere D, Wagholikar GD, Pessaux P, Carrere N, Sibert A, Vilgrain V, Sauvanet A, Belghiti J. (2006) Utility of staging laparoscopy in subsets of biliary cancers : laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. Surg Endosc 20: 721-725.
19. Dingerkus H, Voller H, Schroder K, Dissmann R, Hennig L, Agrawal R, Linderer T, Wiedenmann B. (1994) [Endocardial fibrosis in neuroendocrine tumors of the gastroenteropancreatic system]. Dtsch Med Wochenschr 119: 647-652.
20. Tilleman EH, de Castro SM, Busch OR, Bemelman WA, van Gulik TM, Obertop H, Gouma DJ. (2002) Diagnostic laparoscopy and laparoscopic ultrasound for staging of patients with malignant proximal bile duct obstruction. J Gastrointest Surg 6: 426-430; discussion 430-421.
21. Kriplani AK, Jayant S, Kapur BM (1992) Laparoscopy in primary carcinoma of the gallbladder. Gastrointest Endosc 38: 326-329.
22. White R, Winston C, Gonen M, D'Angelica M, Jarnagin W, Fong Y, Conlon K, Brennan M, Allen P. (2008) Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. J Am Coll Surg 206:445-50.
23. Enestvedt CK, Mayo SC, Diggs BS, Mori M, Austin DA, Shipley DK, Sheppard BC, Billingsley KG. (2008) Diagnostic laparoscopy for patients with potentially resectable pancreatic adenocarcinoma: is it cost-effective in the current era? J Gastrointest Surg 12: 1177-1184.
24. Thomson BN, Parks RW, Redhead DN, Welsh FK, Madhavan KK, Wigmore SJ, Garden OJ. (2006) Refining the role of laparoscopy and laparoscopic ultrasound in the staging of presumed pancreatic head and ampullary tumours. Br J Cancer 94: 213-217.
25. Doucas H, Sutton CD, Zimmerman A, Dennison AR, Berry DP (2007) Assessment of pancreatic malignancy with laparoscopy and intraoperative ultrasound. Surg Endosc 21: 1147-1152.
26. Ahmed SI, Bochkarev V, Oleynikov D, Sasson AR (2006) Patients with pancreatic adenocarcinoma benefit from staging laparoscopy. J Laparoendosc Adv Surg Tech A 16: 458-463.
27. Karachristos A, Scarmeas N, Hoffman JP (2005) CA 19-9 levels predict results of staging laparoscopy in pancreatic cancer. J Gastrointest Surg 9: 1286-1292.
28. Zhao ZW, He JY, Tan G, Wang HJ, Li KJ (2003) Laparoscopy and laparoscopic ultrasonography in judging the resectability of pancreatic head cancer. Hepatobiliary Pancreat Dis Int 2: 609-611.
29. Taylor AM, Roberts SA, Manson JM (2001) Experience with laparoscopic ultrasonography for defining tumour resectability in carcinoma of the pancreatic head and periampullary region. Br J Surg 88: 1077-1083.
30. Menack MJ, Spitz JD, Arregui ME (2001) Staging of pancreatic and ampullary cancers for resectability using laparoscopy with laparoscopic ultrasound. Surg Endosc 15: 1129-1134.
31. Schachter PP, Avni Y, Shimonov M, Gvirtz G, Rosen A, Czerniak A. (2000) The impact of laparoscopy and laparoscopic ultrasonography on the management of pancreatic cancer. Arch Surg 135: 1303-1307.
32. Durup Scheel-Hincke J, Mortensen MB, Qvist N, Hovendal CP (1999) TNM staging and assessment of resectability of pancreatic cancer by laparoscopic ultrasonography. Surg Endosc 13: 967-971.

33. Reddy KR, Levi J, Livingstone A, Jeffers L, Molina E, Kligerman S, Bernstein D, Kodali VP, Schiff ER. (1999) Experience with staging laparoscopy in pancreatic malignancy. Gastrointest Endosc 49: 498-503.
34. Andren-Sandberg A, Lindberg CG, Lundstedt C, Ihse I (1998) Computed tomography and laparoscopy in the assessment of the patient with pancreatic cancer. J Am Coll Surg 186: 35-40.
35. Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF. (1996) The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg 223: 134-140.
36. Weber SM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR (2002) Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. Ann Surg 235: 392-399.
37. Connor S, Barron E, Wigmore SJ, Madhavan KK, Parks RW, Garden OJ. (2005) The utility of laparoscopic assessment in the preoperative staging of suspected hilar cholangiocarcinoma. J Gastrointest Surg 9:476-80.
38. (2005) Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. Gut 54 Suppl 5: v1-16.
39. Korolija D, Sauerland S, Wood-Dauphinee S, Abbou CC, Eypasch E, Caballero MG, Lumsden MA, Millat B, Monson JR, Nilsson G, Pointner R, Schwenk W, Shamiyeh A, Szold A, Targarona E, Ure B, Neugebauer E. (2004) Evaluation of quality of life after laparoscopic surgery: evidence-based guidelines of the European Association for Endoscopic Surgery. Surg Endosc 18: 879-897.
40. Martin RC, 2nd, Scoggins CR, Egnatashvili V, Staley CA, McMasters KM, Kooby DA. (2009) Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. Arch Surg 144: 154-159.
41. Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thieltges S, Gawad KA, Schneider C, Izbicki JR. (2008) En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. Ann Surg 247: 300-309.
42. Stitzenberg KB, Watson JC, Roberts A, Kagan SA, Cohen SJ, Konski AA, Hoffman JP. (2008) Survival after pancreatectomy with major arterial resection and reconstruction. Ann Surg Oncol 15: 1399-1406.
43. Mukherjee S, Kocher HM, Hutchins RR, Bhattacharya S, Abraham AT (2007) Palliative surgical bypass for pancreatic and peri-ampullary cancers. J Gastrointest Cancer 38: 102-107.

Table legends

Table 1. Individual and overall results following homogenisation of data from studies analysing staging laparoscopy/laparoscopic ultrasound in pancreatic/peripancreatic cancers. DOR – diagnostic odds ratio.

Table 2. Individual and overall results following homogenisation of data from studies analysing staging laparoscopy/laparoscopic ultrasound in proximal biliary cancers

Table 3. Sensitivity and subgroup analysis

DOR – diagnostic odds ratio, AUC – area under the curve, *-no between study heterogeneity detected; **-only one study satisfying criterion

Figure Legends

Figure 1: Sensitivity plot for studies reporting on staging laparoscopy/laparoscopic ultrasound in pancreatic/peripancreatic cancers (a) and proximal biliary cancers (b).

Figure 2. Sensitivity plots for detection of liver lesions (a), peritoneal lesions (b) and local/vascular tumour invasion (c).

Table 1.

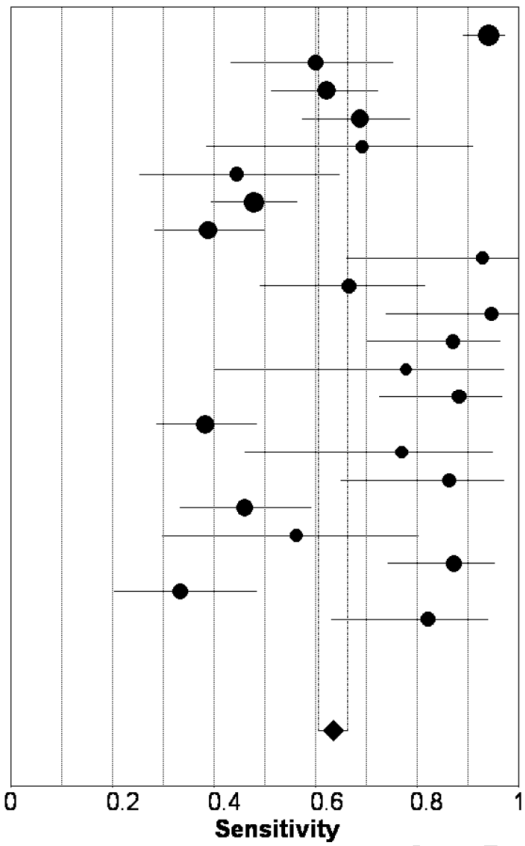
First Author	Laparoscopic examinations	DOR	Overall Yield%
White, R [22]	1045	27308.1	13.8
Enestvedt, CK [23]	86	138.1	27.9
Thompson, BNJ [24]	152	204.7	36.8
Doucas, H[25]	98	80.5	56.1
Ahmed, SI[26]	37	103.4	24.3
Karachristos, A[27]	63	58.9	19
Nieveen Van Dijkum, DJ[10]	286	13.6	24.1
Doran, HE [11]	216	40.9	15.2
Zhao, Z [28]	22	153	59
Vollmer, CM[12]	84	46	28.5
Kwon, AH [14]	52	826.3	34.6
Taylor, AM[29]	51	250.6	52.9
Menack, MJ[30]	27	111	25.9
Schachter, PP[31]	67	454.1	44.7
Jimenez,RE [15]	125	29.2	31.2
Pietrabissa,A[16]	42	177.0	23.8
Durup Scheel_Hincke, J[32]	34	139.3	55.8
Reddy, KR [33]	98	60.7	29.5
Andren-Sandberg, A[34]	24	21.5	37.5
Conlon, KC [35]	108	785.3	37.9
Bemelman, WA [17]	70	22.9	22.8
John, TG [13]	40	50.6	57.5
TOTAL (95% CI)	**2827**	**104(48-227)**	**25 (24-27)**
Heterogeneity χ^2 (p-value), I^2	**-**	**47(p=0.001),56%**	**-**

Table 2

First Author	Laparoscopic examinations	DOR	Overall Yield %
Goere, D [18]	39	42.8	35.8
Agarwal, S [19]	91	135	43.9
Weber, SM [36]	100	64.8	35
Vollmer, CM [12]	11	35	63.6
Connor, S [37]	80 (4 failed laparoscopies)	22.2	45
Tilleman, E [20]	110	105.9	40.9
Kriplani, AK [21]	47	91	95.7
TOTAL (95% CI)	**478**	**61 (19-189)**	**47 (42-51)**
Heterogeneity χ^2 (p-value), I^2	**-**	**1.14 (p=0.98), 0**	**-**

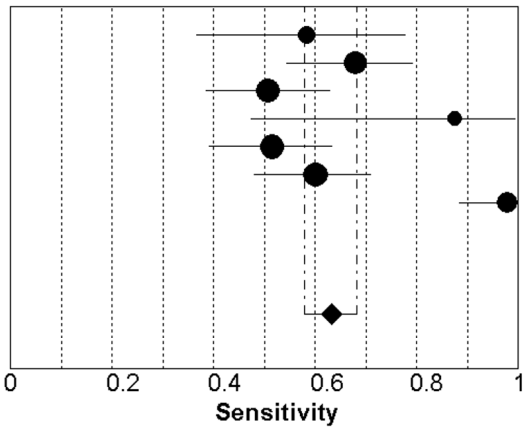
Table 3.

Pancreatic/peripancreatic cancers	**DOR (95% CI)**	**Overall yield % (95% CI)**
Studies with >100 pts[10,11,15,22,24,35]	168 (19-1500)	20(18 – 22)
STARD ≥18 [10,16,31,32]	79 (11-581)	30(26-34)
Liver metastases [11,12,14,16,17,22,24,25,26,28,29,30,33,35]	644 (258-1604)	-
***Peritoneal metastases** [11,12,14,16,1722,24,25,26,29,30,33,35]	854 (308-2372)	-
Local/vascular invasion [11,12,14,22,24,25,28,29,30,35]	176 (67-464)	-
Studies with LUS only [10,11,12,13,14,16,1722,24,25,28,29,30,31,32,35]	137(50-376)	-
Proximal biliary cancers		
****Studies with >100 pts**[20]	-	-
STARD ≥18 [36,37]	38 (5-288)	40 (32-47)
***Liver metastases** [12,19,20,36]	512 (100-2620)	-
***Peritoneal metastases** [19,20,36]	1937 (249-15071)	-
Local invasion [12,19,20]	66 (10-416)	-
Studies with LUS only[12,20,37]	45 (8-257)	-



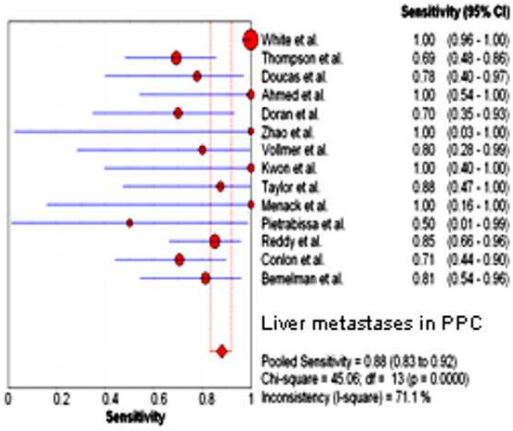
	Sensitivity (95% CI)	
White. R	0.94	(0.89 - 0.97)
Enestvedt. CK	0.60	(0.43 - 0.75)
Thompson. BNJ	0.62	(0.51 - 0.72)
Doucas.H	0.69	(0.57 - 0.79)
Ahmed.SI	0.69	(0.39 - 0.91)
Karachristos. A	0.44	(0.25 - 0.65)
Nieveen Van Dijkum	0.48	(0.40 - 0.56)
Doran. HE	0.39	(0.28 - 0.50)
Zhao.Z	0.93	(0.66 - 1.00)
Vollmer.CM	0.67	(0.49 - 0.81)
Kwon. AH	0.95	(0.74 - 1.00)
Taylor.AM	0.87	(0.70 - 0.96)
Menack.MJ	0.78	(0.40 - 0.97)
Schachter.PP	0.88	(0.73 - 0.97)
Jimenez.RE	0.38	(0.29 - 0.48)
Pietrabissa.A	0.77	(0.46 - 0.95)
Durup Scheel_Hincke	0.86	(0.65 - 0.97)
Reddy.KR	0.46	(0.33 - 0.59)
Andren-Sandberg	0.56	(0.30 - 0.80)
Conlon.KC	0.87	(0.74 - 0.95)
Bemelman.WA	0.33	(0.20 - 0.48)
John.TG	0.82	(0.63 - 0.94)

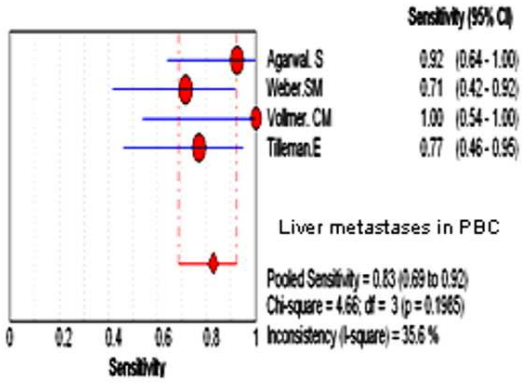
Pooled Sensitivity = 0.63 (0.61 to 0.66)
Chi-square = 237.95; df = 21 (p = 0.0000)
Inconsistency (I-square) = 91.2 %

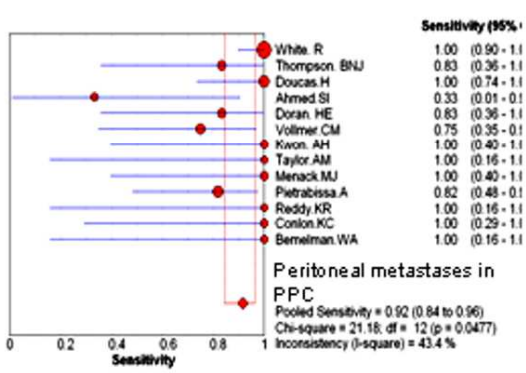


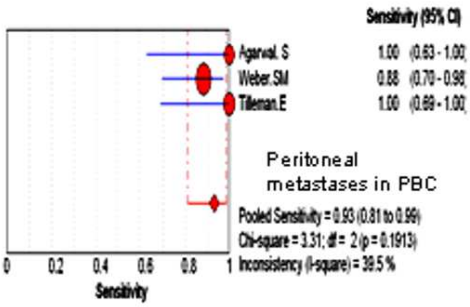
	Sensitivity (95% CI)
Goere.D	0.58 (0.37 - 0.78)
Agarwal. S	0.68 (0.54 - 0.79)
Weber.SM	0.51 (0.38 - 0.63)
Vollmer. CM	0.88 (0.47 - 1.00)
Connor.S	0.51 (0.39 - 0.64)
Tilleman.E	0.60 (0.48 - 0.71)
Kriplani.AK	0.98 (0.88 - 1.00)

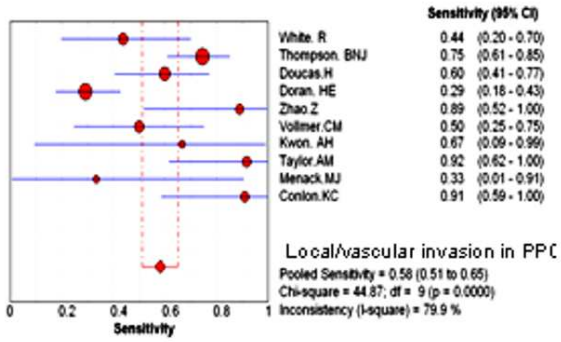
Pooled Sensitivity = 0.63 (0.58 to 0.68)
Chi-square = 45.66; df = 6 (p = 0.0000)
Inconsistency (I-square) = 86.9 %

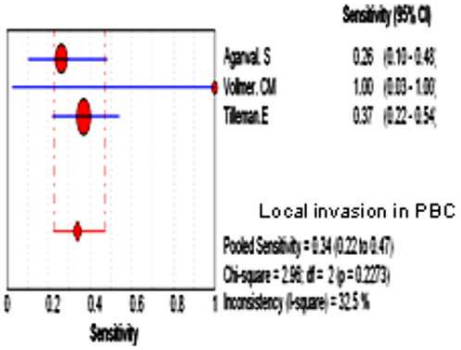

Sensitivity (95% CI)
White et al. 1.00 (0.96 - 1.00)
Thompson et al. 0.69 (0.48 - 0.86)
Doucas et al. 0.78 (0.40 - 0.97)
Ahmed et al. 1.00 (0.54 - 1.00)
Doran et al. 0.70 (0.35 - 0.93)
Zhao et al. 1.00 (0.03 - 1.00)
Vollmer et al. 0.80 (0.28 - 0.99)
Kwon et al. 1.00 (0.40 - 1.00)
Taylor et al. 0.88 (0.47 - 1.00)
Menack et al. 1.00 (0.16 - 1.00)
Pietrabissa et al. 0.50 (0.01 - 0.99)
Reddy et al. 0.85 (0.66 - 0.96)
Conlon et al. 0.71 (0.44 - 0.90)
Bemelman et al. 0.81 (0.54 - 0.96)
Liver metastases in PPC
Pooled Sensitivity = 0.88 (0.83 to 0.92)
Chi-square = 45.06; df = 13 (p = 0.0000)
Inconsistency (I-square) = 71.1 %
0 0.2 0.4 0.6 0.8 1
Sensitivity


Sensitivity (95% CI)
Agarwal. S 0.92 (0.64 - 1.00)
Weber.SM 0.71 (0.42 - 0.92)
Vollmer. CM 1.00 (0.54 - 1.00)
Tilleman.E 0.77 (0.46 - 0.95)
Liver metastases in PBC
Pooled Sensitivity = 0.83 (0.69 to 0.92)
Chi-square = 4.66; df = 3 (p = 0.1985)
Inconsistency (I-square) = 35.6 %
0 0.2 0.4 0.6 0.8 1
Sensitivity


Sensitivity (95%
White. R 1.00 (0.90 - 1.
Thompson. BNJ 0.83 (0.36 - 1.
Doucas.H 1.00 (0.74 - 1.
Ahmed.SI 0.33 (0.01 - 0.
Doran. HE 0.83 (0.36 - 1.
Vollmer.CM 0.75 (0.35 - 0.
Kwon. AH 1.00 (0.40 - 1.
Taylor.AM 1.00 (0.16 - 1.
Menack.MJ 1.00 (0.40 - 1.
Pietrabissa.A 0.82 (0.48 - 0.
Reddy.KR 1.00 (0.16 - 1.
Conlon.KC 1.00 (0.29 - 1.
Bemelman.WA 1.00 (0.16 - 1.
Peritoneal metastases in PPC
Pooled Sensitivity = 0.92 (0.84 to 0.96)
Chi-square = 21.18; df = 12 (p = 0.0477)
Inconsistency (I-square) = 43.4 %
0 0.2 0.4 0.6 0.8 1
Sensitivity


Sensitivity (95% CI)
Agarwal. S 1.00 (0.63 - 1.00)
Weber.SM 0.88 (0.70 - 0.98)
Tilleman.E 1.00 (0.69 - 1.00)
Peritoneal metastases in PBC
Pooled Sensitivity = 0.93 (0.81 to 0.99)
Chi-square = 3.31; df = 2 (p = 0.1913)
Inconsistency (I-square) = 39.5 %
0 0.2 0.4 0.6 0.8 1
Sensitivity


Sensitivity (95% CI)
White. R 0.44 (0.20 - 0.70)
Thompson. BNJ 0.75 (0.61 - 0.85)
Doucas.H 0.60 (0.41 - 0.77)
Doran. HE 0.29 (0.18 - 0.43)
Zhao.Z 0.89 (0.52 - 1.00)
Vollmer.CM 0.50 (0.25 - 0.75)
Kwon. AH 0.67 (0.09 - 0.99)
Taylor.AM 0.92 (0.62 - 1.00)
Menack.MJ 0.33 (0.01 - 0.91)
Conlon.KC 0.91 (0.59 - 1.00)
Local/vascular invasion in PPC
Pooled Sensitivity = 0.58 (0.51 to 0.65)
Chi-square = 44.87; df = 9 (p = 0.0000)
Inconsistency (I-square) = 79.9 %
0 0.2 0.4 0.6 0.8 1
Sensitivity


Sensitivity (95% CI)
Agarwal. S 0.26 (0.10 - 0.48)
Vollmer. CM 1.00 (0.03 - 1.00)
Tilleman.E 0.37 (0.22 - 0.54)
Local invasion in PBC
Pooled Sensitivity = 0.34 (0.22 to 0.47)
Chi-square = 2.99; df = 2 (p = 0.2273)
Inconsistency (I-square) = 32.5 %
0 0.2 0.4 0.6 0.8 1
Sensitivity