Journal of the Canadian Association of Gastroenterology, 2022, 5(3), 121–128
https://doi.org/10.1093/jcag/gwab037
Original Article
Advance Access publication 16 November 2021

Original Article

Preoperative Endoscopic Ultrasound Fine Needle Aspiration Versus Upfront Surgery in Resectable Pancreatic Cancer: A Systematic Review and Meta-analysis of Clinical Outcomes Including Survival and Risk of Tumor Recurrence

Adel Alghamdi, MD[1,2], Vincent Palmieri, MD[1], Nawaf Alotaibi, MD[1,2], Alan Barkun, MD, MSc[1], George Zogopoulos, MD[3], Prosanto Chaudhury, MD[3], Jeffrey Barkun, MD, MSc[3], Corey Miller, MD[4], Amine Benmassaoud, MD[1], Josee Parent, MD[1], Myriam Martel, MSc[1], Yen-I Chen, MD, MSc[1]

[1]Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Quebec, Canada; [2]Present address: Department of Gastroenterology and Hepatology, King Fahad Medical city, Riyadh, Saudi Arabia; [3]Department of Surgery, McGill University Health Centre, Montreal, Quebec, Canada; [4]Division of Gastroenterology and Hepatology, Jewish General Hospital, Montreal, Quebec, Canada

Correspondence: Yen-I Chen, MD, MSc, Division of Gastroenterology and Hepatology, McGill University Health Centre, Glen Site, 1001 Décarie Blvd., Montreal, Quebec, H4A 3J1, Canada, e-mail: yen-i.chen@mcgill.ca

ABSTRACT

Background and Aim: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the standard of care in advanced pancreatic cancer. Its role in resectable disease, however, is controversial. This meta-analysis aims to ascertain the clinical outcomes of patients with resectable pancreatic cancer undergoing preoperative EUS-FNA compared to those going directly to surgery.

Methods: A literature search was performed from 1996 to April 2019 using MEDLINE, EMBASE, and ISI Web of Knowledge for studies comparing preoperative EUS-FNA to EUS without FNA in resectable pancreatic cancer for clinical outcomes. The primary outcome is overall survival (OS). Secondary outcomes include cancer-free survival, tumor recurrence and peritoneal carcinomatosis, and post-FNA-pancreatitis rate.

Results: Six retrospective studies were included. Preoperative EUS-FNA had better OS than the non-FNA group (WMD, 4.40 months [0.02 to 8.78]). Cancer-free survival did not differ significantly between the two groups (WMD, 2.08 months [−2.22 to 6.38]). EUS with FNA was not associated with increased rates of tumor recurrence or peritoneal carcinomatosis.

Conclusion: Preoperative EUS-FNA in resectable pancreatic cancer may be associated with significantly greater OS when compared to the non-FNA group, with no significant difference in the rates of tumor recurrence or peritoneal seeding. Important limitations of our meta-analysis include the lack of prospective controlled data, which are unlikely to emerge given feasible constraints.

Keywords: *Endoscopic ultrasound; Fine needle aspiration; Pancreatic cancer*

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in North America (1,2). Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is the current standard of care for tissue acquisition in pancreatic cancer (3,4). When compared with CT scan, EUS is more sensitive in detecting pancreatic lesions that are < 2 cm while fine needle aspiration with EUS is associated with lower risk of tumor seeding when compared to CT guided biopsy (5–7). EUS-FNA or fine needle biopsy is also associated with high diagnostic yield with

Received: April 25, 2021; Accepted: September 4, 2021.

sensitivity and specificity as high as 90% and 100% respectively with an excellent safety profile (adverse events of 0.5% to 2%) (3,4,8). Tissue acquisition is currently advocated for pancreatic lesions that will require neoadjuvant chemotherapy or palliative chemotherapy (4). The role of EUS-FNA in resectable pancreatic lesions, however, is controversial.

The risk of tumor seeding and pancreatitis are the main concerns regarding preoperative EUS-FNA in resectable pancreatic cancer. Cases of tumor seeding have been reported with EUS sampling (9–11); however, the risk appears to be exceedingly small while the risk of pancreatitis is approximately only 1% (4). In addition, when the tumor is located in the head of the pancreas, any seeding will be part of the surgical resection with pancreaticoduodenectomy. In terms of benefits, preoperative EUS-FNA can confirm the diagnosis and avoid resection of a benign lesions, which has been shown to be as high as 10% to 18% in surgical series (9,10,12). Considering the high-risk nature of pancreatic surgery, resection of benign lesions has the potential to be extremely detrimental to the patient. There have been several studies comparing preoperative EUS-FNA versus upfront surgery without tissue diagnosis in resectable pancreatic cancer suggesting better clinical outcome with the former (13,14); however, most of the data are underpowered to assess survival and tumor seeding especially considering the extremely low rates of tumor seeding with EUS-FNA. The following is a systematic review and meta-analysis of studies assessing the role preoperative EUS-FNA in resectable pancreatic cancer. More specifically we aim to adequately compare the clinical outcomes of patients with resectable pancreatic cancer undergoing preoperative EUS-FNA with those that proceeded directly to surgery.

METHODS

This study was performed in accordance with the PRISMA statement for reporting systematic reviews and meta-analysis (15) and the MOOSE proposal for meta-analysis for observational studies in epidemiology (16).

Search Strategy

A comprehensive literature search was performed from 1996 to April 2019 using OVID MEDLINE, EMBASE, Cochrane Library, and ISI Web of Knowledge databases with MeSH and controlled vocabulary for terms specified for (1) pancreatic neoplasm and (2) Fine Needle Aspiration (Supplementary Appendix 1). Additional relevant studies were identified from cross-referencing and hand-searches of references of the retrieved articles. All human adult studies published in English were considered

Study Selection

We included retrospective and prospective studies that compared the clinical outcomes of preoperative EUS-FNA with upfront surgery without EUS-FNA in patients with resectable pancreatic cancer. We excluded studies without a comparator group and studies looking at unresectable pancreatic cancer. Two reviewers evaluated the eligibility of all identified citations (A.A., V.P.) independently with a third resolving disagreements (Y.C.).

Data Extraction and Validity Assessment

Data were extracted from included studies in a predetermined data sheet by one investigator and verified by a second. Extracted data included study information, comparator intervention, baseline characteristics and outcome events. Study quality was assessed using the Ottawa-Newcastle criteria for observational studies (17).

Choice of Outcome

The primary outcome is overall survival, which was defined as the time from surgery to death. Secondary outcomes include cancer-free survival, recurrence rate, peritoneal recurrence and the rate of post FNA-pancreatitis. Cancer-free survival was calculated from the period between the operation date and the date of recurrence of cancer in any organ. Peritoneal recurrence was defined as the presence of peritoneal nodules or infiltrations detected using imaging studies or malignant ascites confirmed using cytology. Pancreatitis and its severity were defined according to the criteria proposed by Cotton et al. (18).

Addressing Clinical Heterogeneity

The presence of heterogeneity across studies was ascertained using a chi-square test of homogeneity with a 0.10 significance level (19). The Higgins I^2 statistic (19) was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity. Values of <40% are considered not important heterogeneity, 30–60% moderate, 50–90% substantial, 75–100% considerable, respectively while taking into account the magnitude and direction of effects (20). For all comparisons, publication bias was evaluated using funnel plots if at least 10 citations were identified. In order to ensure that zero event trials did not significantly affect the heterogeneity or *P*-values, a sensitivity analyses was performed were a continuity correction was added to each trial with zero events using the reciprocal of the opposite treatment arm size (21).

Statistical Analysis and Sensitivity Analyses

Descriptive results were reported as proportions and 95% confidence intervals (CI), and summary statistics expressed as means and standard deviations (SD) for continuous variables and proportions for categorical variables. Effect size was calculated with weighted mean differences (WMDs) for continuous variables, medians were used if means were not available and SDs were calculated or imputed when possible (22). Odds ratios (ORs) were calculated for categorical variables.

The DerSimonian and Laird method (23) for random effect models was applied to determine corresponding overall effect sizes and their confidence intervals, sensitivity analyses were performed using the Mantel-Haenszel method for fixed effect model when no statistical heterogeneity was noted. WMD were handled as continuous variables using the inverse variance approach. All statistical analyses were done using Revman 5.3 and meta package in R version 2.13.0, (R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS

Included Studies, Quality Assessment, and Publication Bias

The initial search yielded 2814 citations, of which 114 studies were duplicates (Figure 1). After screening based on title and abstract, 18 articles were reviewed in full. Of these, six retrospective studies were included with 1155 patients in the EUS-FNA group versus 2067 patients in the comparator

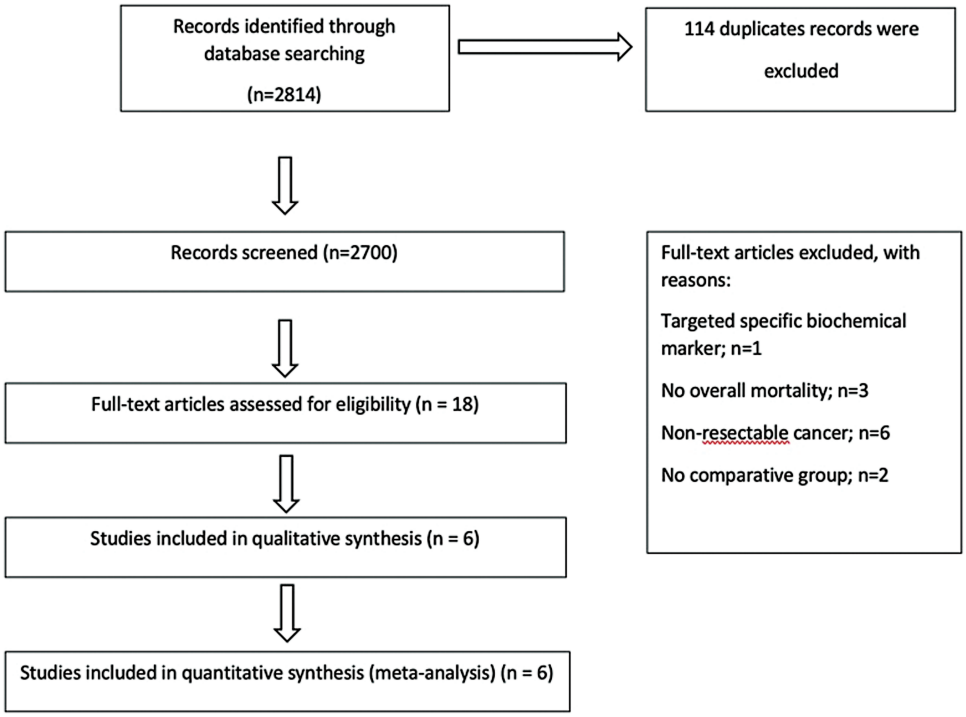

Figure 1. STROBE diagram.

Table 1. Characteristics of the included studies

Years & Authors	Country	Study design	Pre-op groups	Patients	Male%	Mean age, years	Median (or mean)** follow-up, months
Bean et al. 2011 (13)	USA	Retrospective	EUS-FNA	179	37	61	M; 16*
			Non-EUS-FNA	51	43	57	
Ngamruengphong et al. 2013 (26)	USA	Retrospective	EUS-FNA	208	50	66	M; 16
			Non-EUS-FNA	48	50	66	
Kudo et al. 2014 (25)	Japan	Retrospective	EUS-FNA	54	63	63	NR
			Non-EUS-FNA	28	73	70	
Ngamruengphong et al. 2015 (14)	USA	Retrospective	EUS-FNA	498	45	74.5	m; 21
			Non-EUS-FNA	1536	47	74.6	
Tsutsumi et al. 2016 (27)	Japan	Retrospective	EUS-FNA	126	58	66.6	m; ≥12
			Non-EUS-FNA	38	57	63.5	
Kim et al. 2018 (24)	Korea	Retrospective	EUS-FNA	90	59	67.6	M; 16.2
			Non-EUS-FNA	321	60	63.6	

*Patients with adenocarcinoma only,

**M: median, m: mean.

group (13,14,24–27). Of these studies, five were single centered (13,24–27) with one study being multicentered using the US medicare database (14). The final diagnosis of the resected pancreatic specimens was mainly adenocarcinoma and all series included both distal pancreatectomy and pancreaticoduodenectomy except for Bean et al. (13) who included only patients who underwent distal pancreatectomy. Tables 1–3 summarize included studies.

The Newcastle-Ottawa quality scale ranged between 7 and 9 points out of a possible score of 9 (two studies scored 7, two studies scored 8 and two studies scored 9; Supplementary Appendix 2). Significant heterogeneity was noted only in the rate of tumor recurrence ($P = 0.08$, $I^2 = 61\%$). Publication bias was not assessed since less than 10 articles were included.

Primary and Secondary Outcomes

Overall survival in all cancer types was reported in three studies (n = 2701: 796 EUS-FNA, 1905 non-EUS-FNA) (14,24,26). Cancer-free survival was reported in two studies (n = 667; 298 EUS-FNA, 369 non-FNA) (24,26). Four studies reported tumor recurrence (n = 890, 441 EUS-FNA, 449 non-FNA) (13,24,26,27) and peritoneal carcinomatosis (n = 909; 438 EUS-FNA, 471 non-FNA) (24–27). Post-FNA pancreatitis was reported in three studies (n = 731) (13,14,25).

In the primary outcome analysis, patients with preoperative EUS-FNA had better overall survival compared to the non-FNA group (WMD, 4.40 months; 95% CI 0.02 to 8.78; Figure 2). With regards the secondary outcomes, cancer-free survival did not differ significantly between the two groups (WMD, 2.08 months; 95% CI −2.22 to 6.38). Moreover, EUS with FNA was not significantly associated with increased rates of either tumor recurrence (OR, 0.55; 95% CI 0.30 to 1.02) or peritoneal carcinomatosis (OR, 0.81; 95% CI 0.56 to 1.18; Figure 3). Post-FNA pancreatitis was rare (1.9%), with all patients treated conservatively.

Sensitivity Analyses

Sensitivity analyses yielded similar findings across the different outcomes tested (Table 4). Due to heterogeneity, sensitivity analyses were not performed for recurrence rate.

Discussion

EUS FNA has established itself as the current gold standard in tissue diagnosis in solid pancreatic lesions (28). It has proven to be an effective and safe modality with higher diagnostic yield and lower risk for tumor seeding when compared to CT-guided biopsies (1,2,28). The role of tissue diagnosis in the setting of resectable disease, however, is unclear. Most notably the fear of tumor seeding (30,31) and complications such as pancreatitis

Table 2. Cancer treatment and tumor location

Years & Authors	Pre-op groups	Adjuvant Chemotherapy n (%) 20 (35)	Mean tumor size, mm	Tumor location %		Type of surgery, n (%)		
				Head	Body/tail	Distal/partial pancreatectomy	Total pancreatectomy	Pancreatoduodenectomy
Bean et al. 2011 (13)*	EUS-FNA	20 (35)	NR	0	100	100	0	0
	Non-EUS-FNA	1 (17)				100	0	0
Ngamruengphong et al. 2013 (26)	EUS-FNA	89 (42.8)	47	70	29	53 (26)	24 (12)	131 (63)
	Non-EUS-FNA	28 (58)	40	69	29	14 (29)	4 (8.3)	30 (63)
Kudo et al. 2014 (25)	EUS-FNA	40 (74)	30	33	21	22 (41)	1 (2)	32 (59)
	Non-EUS-FNA	14 (50)	29.5	20	8	6 (21)	1 (4)	21 (75)
Ngamruengphong et al. 2015 (14)	EUS-FNA	304 (61)	NR	77	15	138 (28)	63 (13)	284 (57)
	Non-EUS-FNA	777 (51)		72	15	447 (29)	190 (12)	855 (56)
Tsutsumi et al. 2016 (27)	EUS-FNA	68 (54)	24	67	33	37 (29)	4 (3)	85 (68)
	Non-EUS-FNA	21 (25)	27.9	69	31	26 (31)	0 (0)	57 (69)
Kim et al. 2018 (24)	EUS-FNA	56 (62)	30.7	66	30	26 (29)	8 (9)	56 (62)
	Non-EUS-FNA	180 (56)	31.3	69	30	101 (31)	16 (5)	204 (64)

*Patients with adenocarcinoma only.

Table 3. Tumor grading

Years & Authors	Pre-op groups	Histology grade, *n* (%)		
		Well differentiated	Moderately differentiated	Poorly differentiated
Bean et al. 2011 (13)	EUS-FNA	4 (7%)	53 (93%)	
	Non-EUS-FNA	0	6 (100%)	
Ngamruengphong et al. 2013 (26)	EUS-FNA	35 (17)	84 (40)	59 (28)
	Non-EUS-FNA	6 (13)	22 (46)	16 (33)
Kudo et al. 2014 (25)	EUS-FNA	NR		
	Non-EUS-FNA	NR		
Ngamruengphong et al. 2015 (14)	EUS-FNA	55 (11)	211 (42)	133 (27)
	Non-EUS-FNA	193 (13)	657 (43)	508 (33)
Tsutsumi et al. 2016 (27)	EUS-FNA	NR		
	Non-EUS-FNA	NR		
Kim et al. 2018 (24)	EUS-FNA	9 (10)	63 (69)	14 (16)
	Non-EUS-FNA	29 (9)	200 (62)	86 (27)

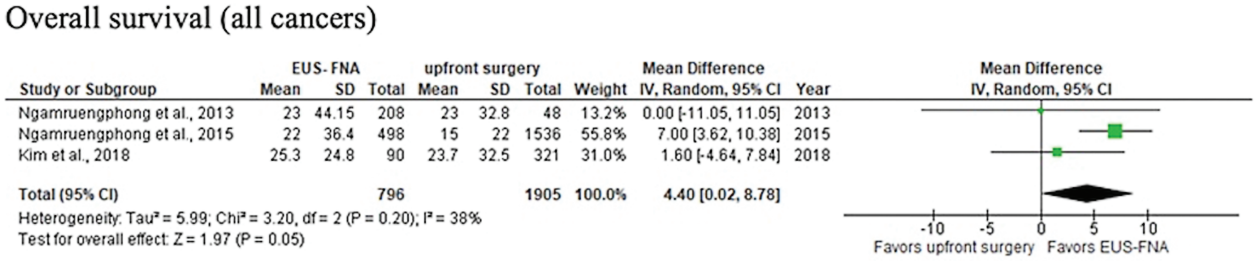

Figure 2. Forrest plot for overall survival of preoperative EUS-FNA vs. upfront surgery.

has led many to advocate against preoperative tissue diagnosis with resectable pancreatic lesions (28,32). This approach, however, runs the risk for resection of benign disease in approximately 10% to 18% of pancreatic surgeries (10). In this systematic review and meta-analysis, we identified six retrospective studies with over 3000 patients comparing preoperative EUS-FNA with upfront surgery without preoperative tissue diagnosis in resectable pancreatic cancer. Our results suggest better overall survival with preoperative EUS-FNA. In addition, there was no significant difference in cancer free survival, risk for tumor seeding, or cancer recurrence.

Given that EUS-FNA is purely a diagnostic modality, its association with greater overall survival may be potentially related to its effect on downstream care including better patient selection for surgery and neoadjuvant chemotherapy keeping in mind the significant risk for residual confounders. Our results are consistent with a previous study suggesting increased overall survival in patients with pancreatic cancer (of any stage) who have undergone EUS assessment when compared to patients without EUS examination (33). Studies assessing EUS vs. CT scan for locoregional staging of pancreatic cancer have suggested similar performance characteristics with some studies showing better T staging with EUS (1,2,29). Therefore, the addition of EUS-FNA to the work-up of pancreatic cancer could potentially complement CT tumor staging leading to more precise patient selection for neoadjuvant chemotherapy, which has been shown to increase overall survival in patients undergoing pancreatic cancer resection (34,35).

Several confounding factors could also have affected survival results including expert center bias and stage migration. Patients who underwent EUS-FNA are more likely to have been treated at a pancreaticobiliary expert center than those who did not undergo this endoscopic exam given that EUS is generally not available outside of academic, tertiary institutions. The included studies did not control for centre expertise in their analysis. Stage migration or the 'Will Rogers Phenomenon' occurs with improvements of diagnostic and staging technology (36). Patient who are classified as resectable may now be classified as locally advanced and falsely improve survival for both categories given that the prognosis of patients who have migrated although worse than the 'good' stage group is generally better that the 'bad' stage group. Each group will then have better survival without improving individual outcomes. Previous studies; nevertheless, have suggested an increased overall survival in pancreatic cancer with the addition of EUS examination beyond merely an increase in stage survival (33).

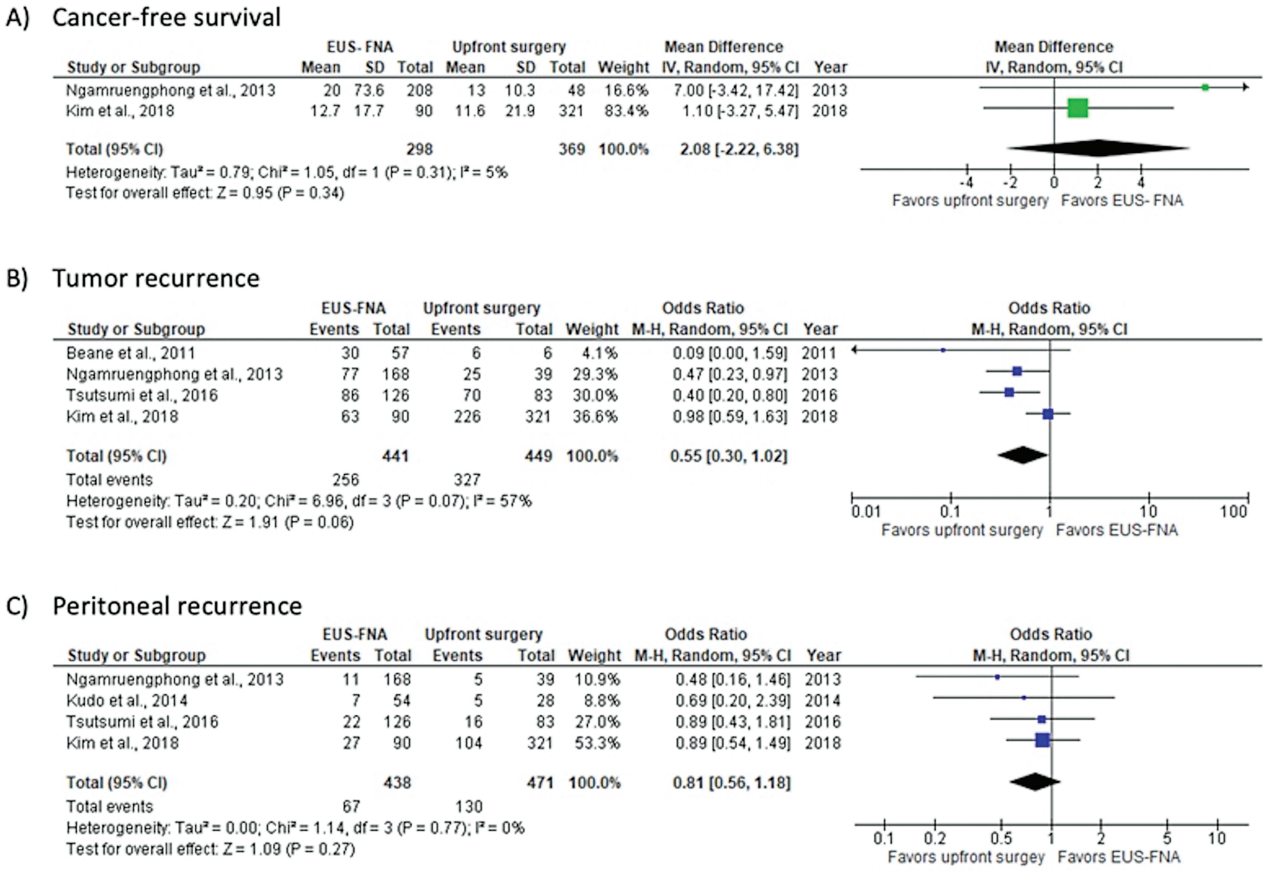

Figure 3. Forest plot of the secondary outcomes; Cancer-free survival (A), tumor recurrence (B), and peritoneal recurrence (C); CI, Confidence interval; SD, Standard deviation.

Table 4. Sensitivity analysis of primary and secondary outcomes

	N studies	*N* patients	WMD (95% CI) or OR (95% CI)	*P*-value	I
Primary outcome					
Overall Survival (all cancers)					
Fixed-effect model	3	2701	*5.38 (2.51; 8.25)*	0.20	38%
Secondary outcomes					
Cancer-Free Survival (all cancers)					
Fixed-effect model	2	667	1.98 (−2.05; 6.01)	0.31	5%
Peritoneal recurrence					
Fixed-effect model	4	909	0.82 (0.57; 1.19)	0.77	0%

Tumor seeding with EUS-FNA of the pancreas has been described in a few case reports (30,31,37). In this meta-analysis, however, tumor and peritoneal recurrence were not significantly different between patients who underwent preoperative EUS-FNA compared to those who did not. Tumor seeding appears to be exceedingly rare. In addition, in the case pancreatic head lesions, any seeding would be part of the surgical resection. Lesions needing transgastric needle sampling, on the other hand, are theoretically at higher risk for seeding due to the fact that the needle track is outside of the resection margins. Although subgroup exploration was not possible in this meta-analysis due to lack of specific reporting on the clinical outcome based on tumor location, univariate and multivariate analyses in four of the included studies did not show a difference in overall survival, cancer-free survival, and/or peritoneal recurrence between lesions sampled from the transduodenal or transgastric route (14,24,26,27). Also, Bean et al. included 179 patients who underwent predistal pancreatectomy EUS-FNA and did not note a significant difference in survival or tumor recurrence when compared to patient who

did not undergo preoperative EUS-FNA (13). Moreover, gastric recurrence was evaluated in two of the six included studies (26,27) and both showed no clinically significant different between EUS-FNA and non-EUS-FNA group. In addition, 20% of patients in our meta-analysis had tumor location in the body or tail of the pancreas. Nevertheless, given the lack of a subgroup analysis, our study could not directly assess the risk of tumor seeding for lesions located in the body and tail of the pancreas, thereby, limiting the strength of our conclusion in regard to this feared complication. Finally, our data showed very low rates of post-EUS-FNA pancreatitis (1.9%) all of which were treated conservatively.

There are several limitations to our study. First, although generally of good quality according to the Newcastle score, the studies included in the meta-analysis are retrospective with its inherent issues including confounding, selection, and reporting biases. Although a prospective trial would have been ideal, it is unlikely to be feasible. There is also a relatively small number of reported studies and we did not include any grey literature, having said that, large number of patients have been included in this meta-analysis. Moreover, the increase in survival associated with preoperative EUS-FNA is largely driven by one study (14) with the others showing no survival difference. In addition, our data on tumor seeding should be interpreted with caution given that no subgroup analysis was possible to differentiate seeding risks between tumors located in the body and tail of the pancreas from lesions in the head of the pancreas. Lastly, follow-up time in the included studies was also relatively short. The major strength of our study is the large sample size of over 2700 patients for the primary endpoint of overall survival without significant heterogeneity of the included studies.

In conclusion, our meta-analysis and systemic review of observational studies suggest better clinical outcomes in patients with resectable pancreatic cancer who underwent preoperative EUS-FNA when compared with non-EUS-FNA, with no observed increase risk for tumor recurrence or peritoneal seeding. Risk of pancreatitis post FNA was rare and all patients were treated conservatively. It is important, however, to keep in mind that our analysis is limited by the lack of controlled trials and suboptimal levels of data granularity for subgroup evaluations. Nevertheless, EUS-FNA before surgical resection in pancreatic cancer appears safe overall, which is reassuring given the likelihood of its increasing role, especially as we approach an era in which neoadjuvant chemotherapy is becoming more common, even in resectable disease.

Funding

None declared.

CONFLICT OF INTEREST

A.B. is a consultant for Pendopharm Inc., Boston Scientific Inc., Olympus Inc., Cook Inc., and ATGen Inc. Y.I.C. is a consultant for Boston Scientific. No disclosures for the remaining authors.

References

1. Bronstein YL, Loyer EM, Kaur H, et al. Detection of small pancreatic tumors with multiphasic helical CT. AJR Am J Roentgenol 2004;182(3):619–23.
2. Micames C, Jowell PS, White R, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc 2003;58(5):690–5.
3. Eloubeidi MA, Chen VK, Eltoum IA, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: Diagnostic accuracy and acute and 30-day complications. Am J Gastroenterol 2003;98(12):2663–8.
4. Eloubeidi MA, Decker GA, Chandrasekhara V, et al. The role of endoscopy in the evaluation and management of patients with solid pancreatic neoplasia. Gastrointest Endosc 2016;83:17–28.
5. Akhtar-Danesh GG, Finley C, Akhtar-Danesh N. Long-term trends in the incidence and relative survival of pancreatic cancer in Canada: A population-based study. Pancreatology 2016;16(2):259–65.
6. Fogel EL, Shahda S, Sandrasegaran K, et al. A multidisciplinary approach to pancreas cancer in 2016: A review. Am J Gastroenterol 2017;112(4):537–54.
7. Saad AM, Turk T, Al-Husseini MJ, et al. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. BMC Cancer 2018;18(1):688.
8. Lai R, Stanley MW, Bardales R, et al. Endoscopic ultrasound-guided pancreatic duct aspiration: Diagnostic yield and safety. Endoscopy 2002;34(9):715–20.
9. Abraham SC, Wilentz RE, Yeo CJ, et al. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: Are they all 'chronic pancreatitis'? Am J Surg Pathol 2003;27(1):110–20.
10. Manzia TM, Toti L, Lenci I, et al. Benign disease and unexpected histological findings after pancreaticoduodenectomy: The role of endoscopic ultrasound fine needle aspiration. Ann R Coll Surg Engl 2010;92(4):295–301.
11. Paquin SC, Gariépy G, Lepanto L, et al. A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. Gastrointest Endosc 2005;61(4):610–1.
12. Sasson AR, Gulizia JM, Galva A, et al. Pancreaticoduodenectomy for suspected malignancy: Have advancements in radiographic imaging improved results? Am J Surg 2006;192(6):888–93.
13. Beane JD, House MG, Coté GA, et al. Outcomes after preoperative endoscopic ultrasonography and biopsy in patients undergoing distal pancreatectomy. Surgery 2011;150(4):844–53.
14. Ngamruengphong S, Swanson KM, Shah ND, et al. Preoperative endoscopic ultrasound-guided fine needle aspiration does not impair survival of patients with resected pancreatic cancer. Gut 2015;64(7):1105–10.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009;339:b2700.
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283(15):2008–12.
17. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [cited October 19 2009].
18. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: Report of an ASGE workshop. Gastrointest Endosc 2010;71(3):446–54.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
20. Deeks JJ, Higgins JPT, Altman DG, on behalf of the Cochrane Statistical Methods Group. Identifying and measuring heterogeneity. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds.) Cochrane Handbook For Systematic Reviews Of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. www.training.cochrane.org/handbook.
21. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004;23(9):1351–75.
22. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med 1998;17(8):841–56.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.

24. Kim SH, Woo YS, Lee KH, et al. Preoperative EUS-guided FNA: Effects on peritoneal recurrence and survival in patients with pancreatic cancer. Gastrointest Endosc 2018;88(6):926–34.
25. Kudo T, Kawakami H, Kuwatani M, et al. Influence of the safety and diagnostic accuracy of preoperative endoscopic ultrasound-guided fine-needle aspiration for resectable pancreatic cancer on clinical performance. World J Gastroenterol 2014;20(13):3620–7.
26. Ngamruengphong S, Xu C, Woodward TA, et al. Risk of gastric or peritoneal recurrence, and long-term outcomes, following pancreatic cancer resection with preoperative endosonographically guided fine needle aspiration. Endoscopy 2013;45(8):619–26.
27. Tsutsumi H, Hara K, Mizuno N, et al. Clinical impact of preoperative endoscopic ultrasound-guided fine-needle aspiration for pancreatic ductal adenocarcinoma. Endosc Ultrasound 2016;5(2):94–100.
28. ASGE Standards of Practice Committee, Eloubeidi MA, Decker GA, et al. The role of endoscopy in the evaluation and management of patients with solid pancreatic neoplasia. Gastrointest Endosc 2016;83:17–28.
29. Dewitt J, Devereaux BM, Lehman GA, et al. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: A systematic review. Clin Gastroenterol Hepatol 2006;4(6):717–25; quiz 664.
30. Chong A, Venugopal K, Segarajasingam D, et al. Tumor seeding after EUS-guided FNA of pancreatic tail neoplasia. Gastrointest Endosc 2011;74(4):933–5.
31. Paquin SC, Gariépy G, Lepanto L, et al. A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. Gastrointest Endosc 2005;61(4):610–1.
32. O'Reilly D, Fou L, Hasler E, et al. Diagnosis and management of pancreatic cancer in adults: A summary of guidelines from the UK National Institute for Health and Care Excellence. Pancreatology 2018;18(8):962–70.
33. Ngamruengphong S, Li F, Zhou Y, et al. EUS and survival in patients with pancreatic cancer: A population-based study. Gastrointest Endosc 2010;72(1):78–83, 83.e1–2.
34. Cloyd JM, Heh V, Pawlik TM, et al. Neoadjuvant therapy for resectable and borderline resectable pancreatic cancer: A meta-analysis of randomized controlled trials. J Clin Med 2020;9.
35. Versteijne E, Vogel JA, Besselink MG, et al.; Dutch Pancreatic Cancer Group. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg 2018;105(8):946–58.
36. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312(25):1604–8.
37. Ahmed K, Sussman JJ, Wang J, et al. A case of EUS-guided FNA-related pancreatic cancer metastasis to the stomach. Gastrointest Endosc 2011;74(1):231–3.