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

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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
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 lesion, 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.  | USA     | Retrospective| EUS-FNA       | 208      | 50    | 66             | M; 16                                |
| 2013 (26)              |         |              | 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.  | USA     | Retrospective| EUS-FNA       | 498      | 45    | 74.5           | m; 21                                |
| 2015 (14)              |         |              | 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 \((n = 2701: 796 \text{ EUS-FNA, } 1905 \text{ non-EUS-FNA})\) \((14,24,26)\). Cancer-free survival was reported in two studies \((n = 667: 298 \text{ EUS-FNA, } 369 \text{ non-FNA})\) \((24,26)\). Four studies reported tumor recurrence \((n = 890, 441 \text{ EUS-FNA, } 449 \text{ non-FNA})\) \((13,24,26,27)\) and peritoneal carcinomatosis \((n = 909: 438 \text{ EUS-FNA, } 471 \text{ non-FNA})\) \((24-27)\). 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 \((\text{WMD, 4.40 months; 95\% CI 0.02 to 8.78; Figure 2})\). With regards the secondary outcomes, cancer-free survival did not differ significantly between the two groups \((\text{WMD, 2.08 months; 95\% CI −2.22 to 6.38})\). Moreover, EUS with FNA was not significantly associated with increased rates of either tumor recurrence \((\text{OR, 0.55; 95\% CI 0.30 to 1.02})\) or peritoneal carcinomatosis \((\text{OR, 0.81; 95\% CI 0.56 to 1.18; Figure 3})\). Post-FNA pancreatitis was rare \((1.9\%)\), with all patients treated conservatively.

### Sensitivity Analyses

Sensitivity analyses yielded similar findings across the different outcomes tested \((\text{Table 4})\). 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...
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 center 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 than 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).

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)               |

Overall survival (all cancers)

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

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) | 3     | 2701       | 5.38 (2.51; 8.25)          | 0.20    | 38%|
| Secondary outcomes      |           |            |                            |         |    |
| Cancer-Free Survival (all cancers) | 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% |

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.
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 difference 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 end-point 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.

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**CONFLICT OF INTEREST**

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