ORIGINAL ARTICLE

# Diagnostic accuracy of endoscopic ultrasonography-guided tissue acquisition prior to resection of pancreatic carcinoma: a nationwide analysis

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## Abstract

**Introduction:** Endoscopic ultrasonography guided tissue acquisition (EUS + TA) is used to provide a tissue diagnosis in patients with suspected pancreatic cancer. Key performance indicators (KPI) for these procedures are rate of adequate sample (RAS) and sensitivity for malignancy (SFM). Aim: assess practice variation regarding KPI of EUS + TA prior to resection of pancreatic carcinoma in the Netherlands.

**Patients and methods:** Results of all EUS + TA prior to resection of pancreatic carcinoma from 2014–2018, were extracted from the national Dutch Pathology Registry (PALGA). Pathology reports were classified as: insufficient for analysis (b1), benign (b2), atypia (b3), neoplastic other (b4), suspected malignant (b5), and malignant (b6). RAS was defined as the proportion of EUS procedures yielding specimen sufficient for analysis. SFM was calculated using a strict definition (malignant only, SFM-b6), and a broader definition (SFM-b5+6).

**Results:** 691 out of 1638 resected patients (42%) underwent preoperative EUS + TA. RAS was 95% (range 89–100%), SFM-b6 was 44% (20–77%), and SFM-b5+6 was 65% (53–90%). All centers met the performance target RAS>85%. Only 9 out of 17 met the performance target SFM-b5+6 > 85%.

**Conclusion:** This nationwide study detected significant practice variation regarding KPI of EUS + TA procedures prior to surgical resection of pancreatic carcinoma. Therefore, quality improvement of EUS + TA is indicated.

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## Introduction

Pancreatic ductal adenocarcinoma (pancreatic carcinoma) is the most common malignancy of the pancreas and periampullary region.[1,2] Approximately 2500 patients are newly diagnosed with pancreatic cancer in the Netherlands annually, of whom 78% die within the first year following diagnosis.[3] Recently neoadjuvant treatment was proven to have a significant impact on survival in pancreatic cancer patients.[4,5] However, neoadjuvant treatment demands a tissue diagnosis prior to the start of therapy.[6,7]

EUS-guided tissue acquisition (EUS + TA) plays a central role in establishing a tissue diagnosis in suspected solid pancreatic malignancies.[8] EUS + TA is a complex multistep procedure, involving endosonographers, pathologists and their teams. Multiple equipment and operator variables may influence outcome of these procedures.[9]

In 2015, the American Society of Gastrointestinal Endoscopy (ASGE) defined key performance indicators (KPI) of EUS + TA of solid pancreatic lesions.[8] These include rate of adequate sample (RAS), diagnostic yield of malignancy (DYM) and sensitivity for malignancy (SFM). The performance targets for these KPIs are RAS>85%, DYM>70%, and SFM>85%. These are based on a meta-analysis by Hewitt et al. in which EUS-guided fine needle aspiration (FNA) of solid pancreatic lesions of 4984 patients from 34 studies were analyzed.[10] Although recent controlled trials from tertiary care facilities have indicated a benefit of a subtype of Fine Needle Biopsy (FNB) needles over FNA techniques, this has not led to changes in the performance targets as defined.[11–13]

In Hewitt's meta-analysis SFM ranged from 50 to 100% across studies. In a prospective study of EUS + TA of solid pancreatic lesions conducted in 4 community hospitals in the Netherlands, RAS ranged from 83 to 100% and SFM ranged from 62 to 92%.[14] It is unknown whether these observations can be extrapolated to the nationwide practice of EUS + TA procedures in these patients.

The Dutch Pathology Registry (PALGA) is a nationwide network and automated registry of histo- and cytopathology in the Netherlands.[15] It contains all consecutive reports of cyto- and histopathology evaluations performed in the Netherlands since 1991. Pancreatic surgery in the Netherlands is performed in 17 designated pancreatic surgery centers, collaborating in the Dutch Pancreatic Cancer Group (DPCG). EUS + TA procedures are performed in at least 34 hospitals, designated pancreatic surgery centers included.

Feedback on KPI measurements allows clinicians to calibrate their perception of the quality delivered to their actual performance, and is a necessary first step for quality improvement. Practice variation regarding KPI may indicate that improvement is required.[16,17]

The aim of the present study is to assess practice variation regarding performance (KPI) of EUS + TA in resected pancreatic carcinoma in the Netherlands.

## Patients and methods

This is a retrospective observational study evaluating KPI of first EUS + TA procedures in all consecutive patients who underwent a surgical resection for pancreatic carcinoma from 2014 to 2018 in the Netherlands. The study protocol was approved by the local medical ethics committee (METC Leiden, Den Haag, and Delft. G20.066). This manuscript was prepared using the "strengthening the reporting of observational studies" (STROBE) and "the reporting of studies conducted using observational routinely-collected health data" (RECORD) checklists. All authors had access to the study data and have reviewed and approved the final manuscript.

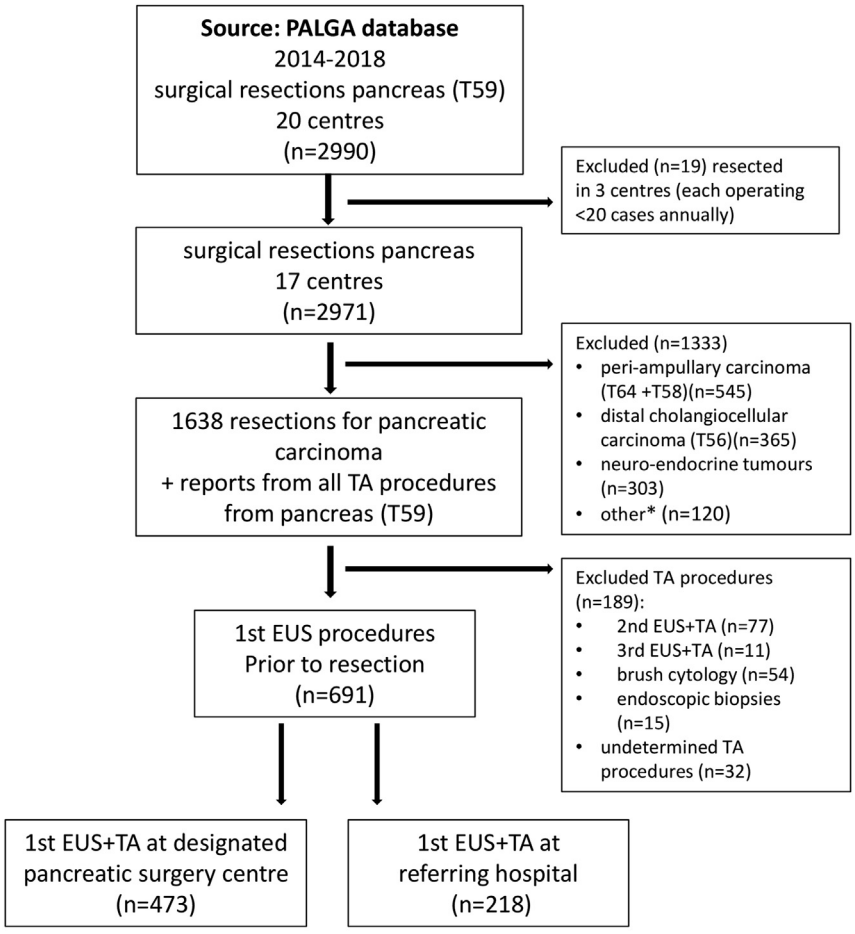
### Selection of study population

Data on all surgical resections of pancreatic tissue (code T59), including results of all cytology and histology acquired prior to surgery, were extracted from the Dutch Pathology Registry (PALGA) in March 2020. Patients with pancreatic resections performed in hospitals with less than 20 pancreatic resections annually, were all without any preoperative tissue analysis and were excluded from analysis (n = 19) (Fig. 1).

Cases were categorized according to the pathology report of the resected specimen. Patients with distal cholangiocarcinoma, periampullary carcinoma, other malignancies, as well as benign diagnoses were excluded aiming to eliminate selection-bias due to case-mix differences across centers.

Reports of cyto- and histopathological specimen acquired by EUS + TA prior to resection were selected. Reports of other tissue acquisition procedures were excluded. Based on dates of the performed EUS + TA procedures, these were classified as 1st




* Other diagnoses: chronic pancreatitis, benign cystic lesions and metastasis.

**Figure 1** Selection of study population

EUS + TA, 2nd EUS + TA and 3rd EUS + TA procedures. First EUS + TA procedures were included for outcome parameter analysis.

Cyto-and histopathology reports of EUS + TA procedures were evaluated and categorized into one of six categories: insufficient for analysis (b1), benign (b2), atypia (b3), neoplastic other (b4), suspicious for malignancy (b5), and malignant (b6) based on the proposed standard for evaluating pancreatic cytology by the Papanicolaou Society of Cytopathology (Supplementary Fig. 1).[18] In case of mixed terminology in cyto-, and histopathology reports, cases were categorized using the description closest to malignancy. For example, if a report mentioned "atypical cells suspected for adenocarcinoma", the case would be classified as "suspicious for malignancy (b5)" instead of "atypia (b3)".

## Outcome parameters

Primary outcome parameters were: 1. RAS, defined as proportion of procedures yielding specimen sufficient for cyto-and/or histopathological analysis, and 2. SFM defined as proportion of patients with a malignant diagnosis at EUS + TA. Since the dataset did not contain any false positives or true negatives, SFM is equal to both the proportion of malignant diagnoses established at EUS + TA, and the proportion of correct diagnoses. Therefore SFM in this study is equal to both diagnostic yield of malignancy and diagnostic accuracy.

Secondary outcome parameters were: 1. rate of atypia (ROA) defined as the proportion of EUS + TA procedures yielding atypia (b3) at pathological evaluation, and 2. Proportion of patients who underwent EUS + TA prior to surgical resection of pancreatic carcinoma.

RAS, SFM, and ROA were calculated overall and per designated pancreatic surgery center. SFM was calculated using a strict definition, based on definite malignant only (b6), as well as a broader definition including suspicious for malignancy (b5+6).

EUS + TA procedures were classified as either performed at a referring hospital or as performed at a designated pancreatic surgery center. Data on specific referring hospitals were not available for analysis.

### Statistical analysis

Baseline characteristics of the patient population, use and outcome of EUS + TA (RAS, SFM, and ROA) are presented as median and range for continuous variables, and as counts with percentages for categorical variables. Point estimates are presented with 95% confidence intervals (CIs). To investigate differences in performance and associations with patient and hospital characteristics, while taking into account that observations from the same center may not be independent, a number of logistic mixed models with a center-specific (random) intercept were fitted.

The between-center variation of performance of first EUS + TA procedures, and proportion of EUS + TA performed, were analyzed using likelihood ratio tests to test if the estimated variance of the random intercept (from models without covariates) was larger than zero. This was repeated in the two subsets containing patients who had their EUS + TA procedure performed at a designated center and those who had their EUS + TA procedure performed in a referring hospital. Additionally, a comparison of performance between these subsets was made, by including an indicator variable identifying the two groups (as only covariate) in the model.

The performance of EUS + TA procedures performed at designated pancreatic surgery centers was visualized by plotting the center-specific measures and corresponding 95% CIs (Wilson score intervals). A funnel plot was created to visualize the centers' performance with regards to SFM-b5+6 in comparison to the ASGE-defined performance target: SFM > 85%.

To gain insight into differences between designated pancreatic surgery centers meeting the performance target SFM>85% ("best practices") and centers who did not ("other practices"), logistic mixed models were fitted for the other performance measures (proportion of EUS + TA performed, RAS, SFM-b6, ROA) with an indicator for "other practices" as covariate.

## Results

A total of 1638 consecutive patients underwent a surgical resection for pancreatic carcinoma. Median age was 67 (19–87) years and 741 (45%) patients were female. Median number of resections per center for pancreatic carcinoma during the study episode was 94, ranging from 56 to 168. A total of 779 EUS + TA procedures were performed prior to resection in 691 patients, of whom 77 (11%) underwent a second, and 11 (1.5%) underwent a third EUS procedure (Fig. 1, Table 1).

**Table 1** Baseline characteristics, EUS + TA procedures prior to surgical resection for pancreatic carcinoma 2014–2018

| | | |
|---|---|---|
| Resections nationwide | n | 1638 |
| Resections per centre | Median [range] | 94 [56–168] |
| Age, years | Median [range] | 67 [19–87] |
| Female | n (%) | 741 (45) |
| 1st EUS + TA procedure | n (%) | 691 (42) |
| 2nd EUS + TA procedures | n (%) | 77 (11) |
| 3rd EUS + TA procedures | n (%) | 11 (1.5) |
| Total EUS + TA procedures | n | 779 |

EUS + TA: endoscopic ultrasonography guided tissue acquisition.

The proportion of patients who underwent EUS + TA prior to surgery was 42%, varying from 17% to 66% across the designated pancreatic surgery centers. Overall, RAS was 95% (89–100%), SFM-b6 was 44% (20–77%), SFM-b5+6 was 65% (53–90%), and ROA (b3) was 11% (3–27%). Practice variation for both SFM-b6, and SFM-b5+6 was statistically significant ($p < 0.01$) (Table 2).

### EUS + TA at referring hospitals versus designated pancreatic surgery centers

Out of all patients, 1393 (85%) underwent their diagnostic workup at one of the 17 designated pancreatic surgery centers, and 244 patients (15%) were referred from other hospitals.

A first EUS + TA procedure was performed in 473 (34%) of the patients diagnosed at a designated pancreatic surgery center, and prior to transfer in a referring hospital in 218 (89%) of patients (OR 15.7, 95%CI [10, 24], $p < 0.001$).

RAS was 100% (80–100%) in referring hospitals, and 97% (89–100%) in designated centers. ROA was 9% (0–27%) in

**Table 2** Performance indicators of all first EUS + TA procedures (n = 691)

| Variable | Median % [range %] | | Variance | p-value |
|---|---|---|---|---|
| RAS | 95 | 89–100 | 0.05 | 0.40 |
| SFM-b6 | 44 | 20–77 | 0.16 | <0.01 |
| SFM-b5+6 | 65 | 53–90 | 0.15 | <0.01 |
| ROA | 11 | 3–27 | 0.08 | 0.18 |

RAS: Rate of adequate sample.
SFM-b6: sensitivity for malignancy definite malignancies only (strict definition).
SFM-b5+6: sensitivity for malignancy including suspected malignancy (broad definition).
ROA: Rate of atypia.

**Table 3** Comparison of performance indicators of EUS + TA in designated pancreatic surgery centers versus referring hospitals

| Variable | 1st EUS + TA in designated center (n = 1394) | | 1st EUS + TA in referring hospital (n = 244)[a] | | OR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| | median % | [range %] | median % | [range %] | | | |
| RAS | 97 | 89–100 | 100 | 80–100 | 0.9 | [0.43, 1.79] | 0.71 |
| SFM-b6 | 50 | 23–92 | 47 | 0–71 | 0.8 | [0.59, 1.09] | 0.16 |
| SFM-b5+6 | 75 | 46–100 | 65 | 30–91 | 0.7 | [0.50, 0.97] | 0.03 |
| ROA | 11 | 0–27 | 9 | 0–27 | 0.9 | [0.57, 1.54] | 0.81 |

RAS: Rate of adequate sample.
SFM-b6: sensitivity for malignancy definite malignancies only (strict definition).
SFM-b5+6: sensitivity for malignancy including suspected malignancy (broad definition).
ROA: Rate of atypia.
[a] Presented data reflect all patients referred to a designated pancreatic surgery center following an EUS + TA procedure at one of the referring centers in the region of a specific designated pancreatic surgery center.

referring hospitals and 11% (0–27%) in designated centers. RAS and ROA are similar in referring hospitals and designated centers, whereas SFM-b5+6 was lower in referring hospitals (OR 0.7, 95%CI [0.50, 0.97], p = 0.03) (Table 3).

## Practice variation amongst designated pancreatic surgery centers

RAS of EUS + TA performed in the 17 designated centers was 97%, ranging from 89 to 100% (Fig. 2a). SFM-b6 was 50% ranging from 23 to 92% (Fig. 2b). SFM-b5+6 was 75% ranging from 46 to 100% (Fig. 2c), and ROA was 11% ranging from 0 to 27% (Fig. 2d).

The performance target RAS>85% was met in all centers, whereas the performance target SFM>85% was only met in 9 out of 17 centers (53%), when the broad definition for SFM (SFM-b5+6) was used (Fig. 3). These 9 centers were therefore qualified as best-practices. Being a best-practice center, appears not to be related to number of EUS + TA procedures performed per center (Fig. 3).

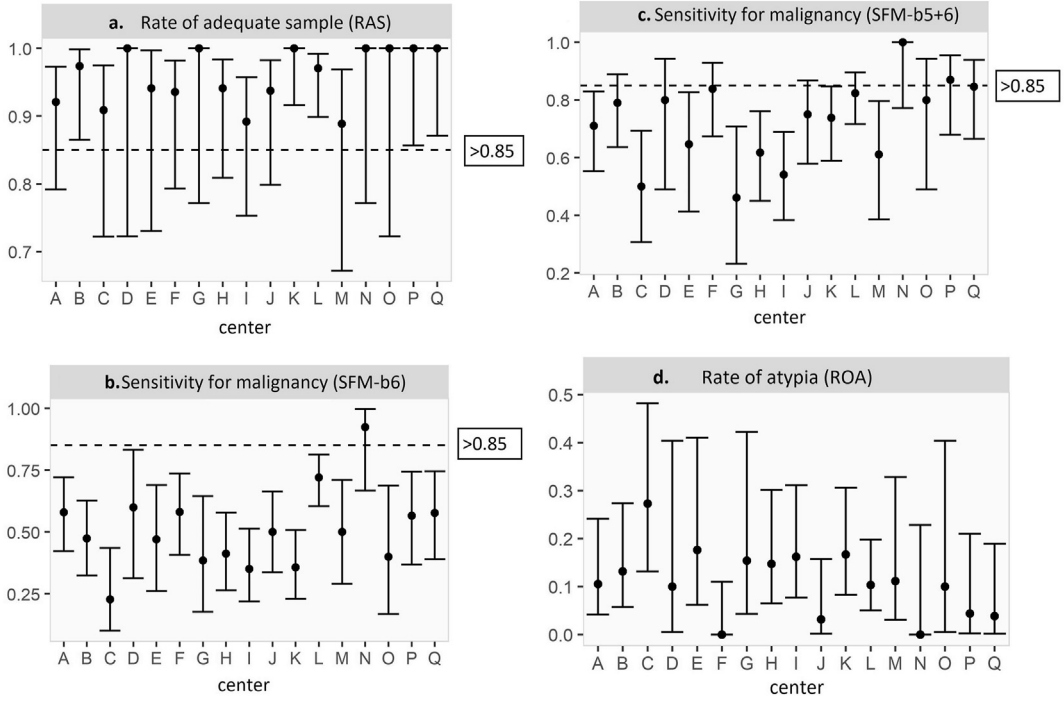



**Figure 2** Performance indicators of EUS + TA per center
X-axis: Centers A-Q.
Y-axis: value and 95% confidence intervals of rate of adequate sample (RAS) per designated pancreatic surgery center. — — — —: ASGE-defined performance target: RAS>85% (in a) or SFM>85% (in b and c).

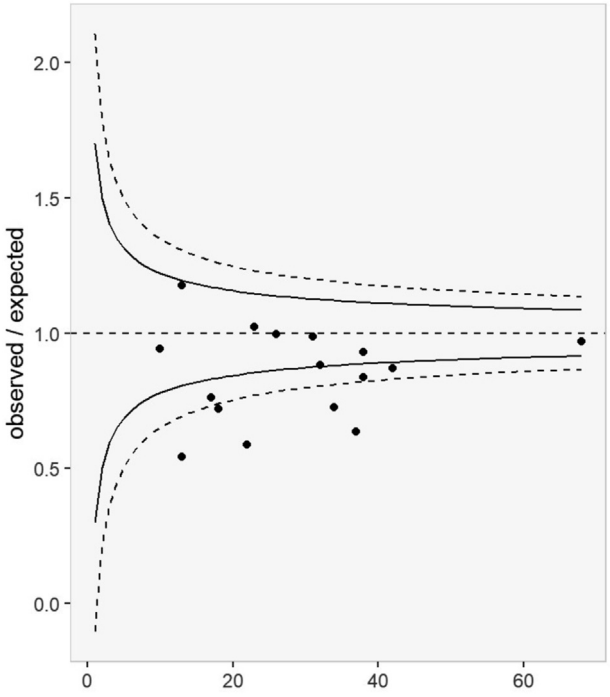



**Figure 3** Funnel plot of SFM-b5+6 and number of EUS + TA procedures per center

Black dots: best practices, meeting performance target SFM-b5+6 > 85%.

Centers D and O are projected as one black dot with both 10 EUS + TA procedures and SFM-b5+6 80%.

Grey-dots: other centers, not meeting performance target.

### Characteristics of best-practice designated pancreatic surgery centers

In the nine best-practices, RAS was 100% (94–100%), SFM-b6 was 58% (40–92%), and ROA was 4% (0–13%). In the other centers RAS was 93% (89–100%), SFM-b6 was 40% (23–58%), and ROA was 16% (11–27%). Comparing the nine best practices to the remaining eight centers, SFM-b6 was higher (OR 2.10, 95% CI [1.36, 3.23], $p < 0.01$), and ROA was lower (OR 0.38, 95%CI [0.21, 0.70], $p < 0.01$) (Table 4). Both the volume of pancreatic resections, the volume of EUS-guided TA procedures, and the proportion of EUS-guided TA procedures performed per center were unrelated to RAS, SFM-b6, SFM-b5+6, or ROA, with ORs ranging from 0.99 to 1.00 and $p > 0.1$ (Supplementary Table 1).

## Discussion

Practice variation is a common phenomenon when analyzing results of pancreatic cancer care delivered in different hospitals across nations.[3,19,20] Regarding performance of EUS + TA this was reported in several publications.[10,14,21]

This retrospective observational study of nationwide performance of EUS + TA prior to resection of pancreatic carcinoma in the Netherlands 2014–2018, shows significant practice variation regarding key performance indicators across the designated pancreatic surgery centers. It also indicates that, while the predefined performance target of RAS >85% was met in all centers, the predefined performance target of SFM > 85% was met in only 9 out of 17 designated centers. Secondary outcome parameters ROA and proportion of patients undergoing EUS + TA prior to resection of pancreatic carcinoma also varied considerably.

Performance indicators of EUS + TA are directly related to patient burden. Each non-diagnostic procedure implies that the patient will be exposed to an additional procedure, potentially also delaying the start of treatment. To our knowledge, this is the first nationwide analysis of the use and quality of EUS + TA of pancreatic carcinoma or of any other specific target lesion.

Aiming for the most reliable comparison of quality delivered across centers using available routinely collected data from the PALGA dataset, resected PDAC patients were studied. As a consequence of this selection, KPI presented should be interpreted with some caution, since both KPI and performance targets are based on studies investigating the yield of EUS + TA in patients with solid pancreatic lesions overall.[8,10] Resected PDAC patients presumably represent a subgroup with smaller lesions, of which the SFM of EUS + TA is known to be lower.[22–24] Moreover, the selected population does not allow for assessment of false-negative and false-positive EUS + TA procedures, limiting the generalizability of KPI reported.

**Table 4** Comparison of performance indicators for first EUS between best practices* with the other designated pancreatic surgery centers

| Variable | Best practices[a] (B,D,F,J,L,N,O,P,Q) | | Other centers (A,C,E,G,H,I,K,M) | | Comparison | | |
|---|---|---|---|---|---|---|---|
| | Median % | [range %] | Median % | [range %] | OR | 95% CI | p-value |
| RAS | 100 | 94–100 | 93 | 89–100 | 0.87 | [0.43, 1.79] | 0.71 |
| SFM-b6 | 58 | 40–92 | 40 | 23–58 | 2.10 | [1.37, 3.23] | <0.01 |
| ROA | 4 | 0–13 | 16 | 11–27 | 0.38 | [0.21, 0.70] | <0.01 |

RAS: Rate of adequate sample.
SFM-b6: sensitivity for malignancy definite malignancies only (strict definition).
ROA: Rate of atypia.
[a] Best practices: pancreatic surgery centres with SFMb5+6 meeting the ASGE-defined quality benchmark SFM > 85% as demonstrated in Fig. 2c (black dots).

In a meta-analysis published by Hebert-Magee and colleagues, studies with histology of resected tumors as a reference standard had a lower SFM in comparison to studies with combined reference standards (i.e. histology and/or follow-up) for a malignant diagnosis, 72.7% versus 89.1% respectively.[21] However, these studies were performed up to 20 years ago, had a relatively small sample size, and did not report on pancreatic carcinoma only.[25–27] Another contrast to the studies on which the performance targets were originally based, is the fact that endosonographers and pathologists in the current study were not aware of the fact that their results were being measured.

The significant practice variation which we observed in the current study, indicates that concerted action is required to improve the outcomes in both endoscopy suites and pathology laboratories. First, endosonographers should aim to increase the amounts of tissue procured without increasing the proportion of procedure related complications. This will likely lead to an increase of adequate sample rates (RAS) and definite malignant diagnoses (SFM-b6), as well as reduced atypia rates (ROA). Second, additional efforts from our pathologists are required to reduce the high atypia rate found in the current study. A meta-analysis of atypical cytology cases of EUS-FNA of solid pancreatic lesions found a mean rate of atypia of 5.3%, ranging from 1 to 14%.[28] Striving for consensus on diagnostic categories of pancreatic tissue samples and providing pathology laboratories with feedback on performance, will probably reduce ROA, and increase SFM. In thyroid cytology similar measures have proven to reduce the proportion of atypia diagnosis by 70%.[29]

Main strength of this study is that it comprises a national dataset of patients that underwent resection for pancreatic carcinoma in the years 2014–2018, and therefore likely includes all operators and hospitals involved in EUS + TA procedures in these patients.

Limitations of this study are its retrospective nature and the fact that data were extracted from a national histo-and cytopathology database containing routinely collected health data. Therefore, misclassification bias and missing data cannot be completely ruled out. Another limitation is the lack of clinical data, including detailed indications for EUS + TA, trial participation, presence of biliary stenosis, whether brush-cytology or intraductal biopsies were obtained, and whether diagnostic procedures have led to any complications. Ideally, this study would have included such patient characteristics as well as practitioner, equipment and procedural variables allowing the search for potential explanations for the practice variation observed. Clinical variables can easily be incorporated into national or regional audits on EUS + TA of solid pancreatic lesions, similar to our regional quality in endosonography initiative.[14,30]

Performing EUS + TA comes with the responsibility to measure KPIs. Feedback on performance is key in order to improve quality.[9,16,17,31,32] Without feedback it is impossible to know whether and which action is required to improve outcome, or whether a certain procedural adaptation indeed improved quality. If KPI are not up to the desired level, scrutinize your protocols regarding patient selection, guideline adherence, and number and experience of practitioners involved. Next, plan and adapt protocols, and keep monitoring. The implementation of this simple concept (plan-do-check-act), including the use of CUSUM curves of KPI per center, amongst collaborating Dutch community hospitals in the Rotterdam region, proved improvement of RAS from 80% to 95%, and of SFM from 63% to 84%.[14]

In conclusion, in this nationwide study in patients who underwent a resection of pancreatic carcinoma, we found significant practice variation regarding performance of EUS + TA indicating ample room for improvement. Considering the increasing body of evidence supporting the use of neo-adjuvant treatment in patients with resectable and borderline resectable pancreatic cancer, in which a tissue diagnosis is considered mandatory, quality improvement of EUS + TA should be prioritized.[5,33]

We hope the current study will serve as a first step towards the establishment of a multidisciplinary audit aiming for continuous improvement of quality of care in these patients. We would encourage all practitioners involved in EUS + TA procedures, not to wait for such an audit to "come their way", but to proactively start to measure, compare and improve their individual performance instead.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Not applicable.

## Conflict of interest

None to declare.


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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.07.900.

 