Transabdominal Ultrasound of Pancreatic Ductal Adenocarcinoma: A Multi-Centered Population-Based Study in Sensitivity, Associated Diagnostic Intervals and Survival

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ABSTRACT

Objectives: To determine the sensitivity of ultrasound (US) in detecting pancreatic ductal adenocarcinoma (PDAC) in our region, to identify factors associated with US test result, and assess the impact on the diagnostic interval and survival.

Methods: Patients diagnosed between 1 Jan 2014- 31 Dec 2015 in (region blinded) were identified by a cancer registry. US performed prior to diagnosis were retrospectively graded as true positive (TP), indeterminate (IN) or false negative (FN). Amongst US results, differences in age, weight and tumor size were assessed (one-way ANOVA). Associations between result and sex, tumor location (proximal/distal), clinical suspicion of malignancy, and visualization of the pancreas, tumor, secondary signs and liver metastases were assessed (Chi-square). Mean follow-up imaging, diagnostic, and survival intervals were assessed (one-way ANOVA).

Results: 113 US of 107 patients (54 women; mean 70±13 years) were graded as follows: 48/113 (42.5%) TPs; 42/113 (37.2%) INs; and 23/113 (20.4%) FNs. Sensitivity was 48/71(67.6%). There was no difference in age, weight or tumor size amongst US result ($p>0.5$). FNs had proportionally more men ($p=0.011$) and lacked clinical suspicion of malignancy ($p=0.0006$); TPs had proportionally more proximal tumors ($p=0.017$). US result was associated with visualization of the pancreas, tumor, secondary signs and liver metastases ($p<0.005$). FNs had longer mean follow-up imaging ($p<0.0001$) and diagnostic ($p=0.0007$) intervals, and worse mean survival ($p=0.034$).

Conclusions: In our region, the sensitivity of US in detecting PDAC is 67.6%. A false negative US is associated with delayed diagnostic work-up and worse mean survival.

KEYWORDS: Pancreatic ductal carcinoma; ultrasound; survival; delayed diagnosis

ABBREVIATIONS: US, ultrasound; PDAC, pancreatic ductal adenocarcinoma; PACS, Picture Archiving and Communication System; CT, computed tomography; US, ultrasound; MRI, magnetic resonance imaging; TP, true positive; IN, indeterminate; FN, false negative

INTRODUCTION

Pancreatic cancer is a devastating and highly fatal disease. The 5-year survival rate is the lowest of all solid cancers, ranging between 5-9% (1). Although the incidence of pancreatic cancer is only eleventh of all cancer sites, pancreatic cancer is the third most common cause of cancer-related deaths (1) and is projected to become the second leading cause by 2030 (1-3).

In our region (blinded), survival of pancreatic cancer is below the national average (ref. blinded). In reviewing imaging examinations of patients with pancreatic ductal adenocarcinoma (PDAC), we have observed several ultrasound (US) examinations where a pancreatic tumor was either not visualized, or secondary findings of pancreatic cancer – which were in retrospect evident - were not detected. This is worrisome because patients with PDAC often present with nonspecific abdominal pain or are suspected to have hepatobiliary disease (4); as such, patients with PDAC are often first imaged with US. For example, patients with PDAC often present with right upper quadrant pain, and according to the American College of Radiology Appropriateness Criteria, US is the first-line test for evaluation of patients with right upper quadrant pain (5); these guidelines have also been endorsed by the American Academy of Family Physicians (6).

Studies from the late nineties reported a high sensitivity (88.6 - 98.0%) and specificity (95.9 – 98.8%) in detecting pancreatic cancer with transabdominal US (7, 8). However, a meta-analysis from 2005 found a summary sensitivity and specificity of only 76% and 75%, respectively (9). A recent meta-analysis in 2017 found much higher pooled sensitivity and specificity of 88% and 94%, respectively, and the authors concluded that US was equivalent to computed tomography, magnetic resonance imaging and endoscopic US (10). However, all 7 transabdominal US studies included in the meta-analysis were contrast-enhanced US examinations. Contrast-enhanced US is not typically used in the first-line, routine setting, nor is it available at all centers including those in our region.

Given our observations in the diagnostic performance of US and the lack of recent evidence, the primary objectives of this study were to assess the sensitivity of transabdominal US in detecting PDAC in our region and to identify clinical and tumoral factors associated with US test result. Because expediency in diagnosis is critical in

managing patients with PDAC, we also sought to evaluate for associations between US test result and the imaging follow-up interval, diagnostic interval, surgical interval, and mean survival.

METHODS

Study Design and Population

This retrospective observational population-based study was performed with approval from our institutional research ethics board, who waived the need for patient consent. The study population was retrieved from the (region blinded) Cancer Registry of patients diagnosed with PDAC between 1 Jan 2014 – 31 Dec 2015. A larger cohort of these patients has been reported previously in a study evaluating imaging-related delays of PDAC and impact on survival (reference blinded). There is no overlap with the current study, which focused on patients that underwent US evaluation of the pancreas during the diagnostic interval. The diagnostic interval corresponded to the time period between two dates: the initial healthcare presentation date, when the patient first sought medical attention for what was felt related to their pancreatic cancer, and the date when pancreatic cancer was diagnosed. The initial healthcare presentation date was obtained from the cancer registry database. The diagnosis date from the registry was not used, as this preferentially listed dates of tissue diagnosis (if available), brushings or other standard means; rather, the date of diagnosis was based on retrospective review of the electronic medical and imaging records, and corresponded to the date when the suspicion of PDAC was confirmed. The diagnosis was most often made with CT or MRI, but may have included biopsy, brushings or surgical resection.US examinations were excluded if a pancreatic abnormality was known at the time of US (from, for example, a previous imaging examination).

US Examination Data Extraction

Study data were stored on a REDCap database hosted at [institution blinded] (11, 12). The following data elements were imported from the cancer registry database: age at diagnosis; sex; weight; location of tumor as either proximal (head and uncinate process) or distal (neck, body, and tail); dates of initial healthcare presentation and if applicable, death. The regional Picture Archiving and Communication System (PACS) was searched for US examinations performed during the diagnostic interval and included evaluation of the pancreas. In our region, 21 centers provide US service, one of which is an academic center.

At all centers, during routine working hours US examinations are performed by a certified sonographer with radiologist supervision. In this study, all but three examinations were performed during routine working hours; the three after-hours US examinations were performed by radiology residents with radiologist supervision. The research database was initially populated by a fourth-year radiology resident (initials blinded). All data including US image review and classification of US examinations was validated by a fellowship-trained board-certified abdominal radiologist (initials blinded) with 5 years of post-fellowship experience.

For each US examination, data were acquired relating to the following three categories: characteristics of the examination; findings on retrospective review of the images and cines available on PACS; and the original interpreting radiologist's report. For the US examination, the date was recorded, and the requisition was reviewed for any clinical suspicion of malignancy: jaundice or scleral icterus; unintentional weightloss; night sweats; a cholestatic pattern of liver serology tests; new-onset diabetes; unexplained pancreatitis; and specific wording regarding suspected malignancy.

For the retrospective US image review, the following data were recorded: visualization of the pancreas (completely visualized (95-100%), mostly visualized (50-95%), parts missed (25-50%) or not well seen (< 25%); visualization of a pancreatic mass (yes, no, no but in retrospect seen); tumor size, where any contemporaneous cross-sectional imaging was used to supplement examinations where the tumor and/or pancreas were not visualized; presence of secondary signs of PDAC, including upstream duct dilation, parenchymal atrophy, pancreatitis, or vascular invasion (present and detected, undetected but present on review of contemporaneous imaging, absent, or not applicable if the pancreas or tumor were not visualized); and the presence of liver metastases (present and detected, present and missed, or absent).

The radiology reports were reviewed for the following: comment on examination quality (yes/no); suspicion of neoplasm raised (yes/no); and any follow-up recommendations (yes/no). Based on review of the images and reports, each US examination was classified according to three categories in accordance with STARD guidelines (13), as follows. True positives (TP) were examinations where a pancreatic mass was identified and the suspicion

of cancer was raised. Indeterminate examinations (IN) were those where the suspicion of cancer was not raised or equivocal, but follow-up imaging was recommended based on the presence of a pancreatic or extra-pancreatic abnormality, such as biliary obstruction or liver lesions. False negatives (FN) were examinations where no sinister abnormality was identified and/or the patient's diagnostic work-up was not advanced, and included equivocal examinations where no follow-up was recommended. Sensitivity was calculated in three ways as outlined by STARD guidelines (14): the conventional approach, [TP/(TP+FN)]; and by incorporating indeterminate examinations in the best [(TP+IN)/(TP+IN+FP)] and worst [TP/(TP+IN+FP)] case scenarios.

For US examinations that corresponded to the initial diagnostic work-up test, the following time intervals were calculated where possible: the number of days between the initial US and the next closest follow-up imaging examination (such as repeat US, CT or MRI); the diagnostic interval (date of first presentation to date of diagnosis); and the surgical interval (date of first presentation to date of surgery with curative intent) in patients who did not undergo neoadjuvant chemotherapy. Survival was calculated as the difference between date of diagnosis to the date of death or end of study (January 10, 2018).

Statistical Analysis

Statistical analysis was performed using Prism version 8.0.3 (GraphPad Software Inc., La Jolla, CA) and R version 3.6.1 (15). Amongst US test results, differences in age, weight and tumor size were assessed (one-way ANOVA). Chi-square was used to assess for association between US result and sex, tumor location (proximal/distal), clinical suspicion of malignancy, radiologist comment on US quality, and visualization of the following structures: pancreatic gland, pancreatic tumor, secondary signs of PDAC, and liver metastases. The following mean time intervals were compared (one-way ANOVA): follow-up imaging interval; diagnostic interval; primary surgical interval; and survival.

RESULTS

From an initial population of 257 patients diagnosed with PDAC 2014-2015 (ref. blinded), we extracted 141 US examinations that were performed in 115 patients during the diagnostic interval. Of these, 28 US examinations in 8 patients were excluded because the presence of a pancreatic abnormality was known at the time of US, resulting in a final

cohort of 113 US examinations in 107 patients (54 women (50.5%); mean age, 70 ± 13 years).

There were 48/113 (42.5%) TP, 42/113 (37.2%) IN, and 23/113 (20.4%) FN; 5 of the 23 FN were indeterminate examinations with no follow-up recommendations. Examples of IN and FN US examinations are provided as Figs. 1 and 2, respectively. Sensitivity results were as follows: conventional approach (TP/(TP+FN)), 48/71 (67.6%); worst-case scenario (which combines INs with FNs), 48/113 (42.5%); best-case scenario (which combines INs with TPs), 90/113 (79.6%).

A summary of patient and tumor characteristics is provided in table 1. Amongst US test results, there was no significant difference in mean age ($p = 0.51$) or weight ($p = 0.96$), however proportionally more women were associated with TPs (31/48, 64.6%) than INs (17/42, 40.5%) and FNs (7/23, 30.4%; $p = 0.011$). There was no difference in tumor size across subgroups ($p = 0.53$). However, more proximal tumors were associated with the TP group (39/48, 81.3%) than the IN (23/42, 54.8%) and FN groups (12/21, 57.1%; $p = 0.02$).

A summary of US examination characteristics according to US test result is provided in table 2. Based on the imaging requisition, malignancy was suspected clinically in 49/113 (43.4%) patients; this was more commonly associated with TP (28/48, 58.3%) and IN (19/42, 45.2%) examinations than FN (2/20, 10.0%) examinations ($p = 0.0006$). There were 35/113 (31.0%) examinations that commented on image quality; the majority of these (24/35) were associated with an indeterminate examination ($p < 0.0001$). However, complete visualization of the pancreas was observed in only 10/113 (8.8%) of cases, and most (9 examinations) were TP.

There was a significant association between US test result and visualization of the pancreatic parenchyma ($p = 0.0004$), pancreatic tumor ($p < 0.0001$), secondary signs ($p < 0.0001$) and liver metastases ($p = 0.0052$). Pancreatic tumors were much more frequently visualized in the TP group (45/48, 93.8%) than the IN (4/42, 9.5%) and FN (0/23, 0%) groups. Of the 64 tumors missed on US, 10 were evident in retrospect (4 IN and 6 FN). Visualization of secondary signs was most common in the TP group (37/44, 84.1%), followed by the IN (11/30, 36.7%) and FN (1/13, 7.7%) groups. Of the 38 examinations

where secondary signs of PDAC were not reported, 32/38 (84.2%) were evident on other imaging examinations. Of the 86 examinations not reporting the presence or suspicion of liver metastases, 8/86 (9.3%) were evident on retrospective review.

A summary of time interval results is provided in table 3. There were 99 patients with first-time US examinations. Of the 95 patients that had imaging follow-up, there was a significantly longer mean follow-up interval in the FN group: 60.0 days vs. 4.0 and 7.4 days in the TP and IN groups, respectively ($p < 0.0001$). Similarly, the mean diagnostic interval was also longer in the FN group: 216.6 days vs. 41.0 and 49.2 days in the TP and IN groups, respectively ($p = 0.0007$). There were 20/99 (20.2%) patients that underwent primary surgery; the mean surgical interval in the FN group (202.8 days) was substantially longer than that of the TP and IN groups (92 and 87 days, respectively), this was not statistically significant ($p = 0.291$). Mean survival was significantly better in the TP and IN groups, with patients surviving on average 196 and 66 days longer than patients in the FN group, respectively ($p = 0.034$). There were no survivors by the censor date.

DISCUSSION

In this study we evaluated the sensitivity of abdominal US in detecting PDAC. We also assessed for associations between clinical and tumoral factors and US test result, as well as impact on various time intervals. There was no association between patient age, weight or tumor size and US test result. However, there were significant associations with patient sex, tumor location, clinical suspicion of malignancy, and comment on examination quality. As expected, there was a significant association between US test result and visualization of all elements evaluated by this study, including the pancreatic gland, the primary tumor, secondary signs of PDAC, and liver metastases. A major takeaway from our study is that a large proportion of US examinations were either IN (37.2%) or FN (20.4%), and that sensitivity was generally low (67.6%, ranging between 42.5-79.6% depending on how INs are accounted for). Patients with a FN US were associated with significantly longer mean imaging follow-up interval, longer mean diagnostic interval, and worse mean survival. The surgical interval was also substantially longer, although this was not statistically significant because of low sample size. Our results are important because a prolonged diagnostic interval can render a patient unresectable and therefore incurable. These results agree with conclusions from clinical studies, which have found that

prolonged diagnostic intervals result in a significantly higher rate of advanced disease (4), lower rate of upfront surgery (16), and worse survival (17).

Although prior CT and MR imaging studies have demonstrated evidence of missed findings of PDAC (18-23), few recent studies have assessed the performance of conventional transabdominal US in the detection of PDAC (24, 25). Wang et al. evaluated 136 solid pancreatic lesions, including 25 patients with pancreatitis and 86 patients with PDAC, and found the diagnostic accuracy of conventional US to be only 55/111 (49.5%) and the indeterminate rate to be 51/111 (45.9%) (25). In addition to a paucity of recent research evaluation, to our knowledge, societal guidelines and expert consensus groups do not address transabdominal US in the evaluation of patients with known or suspected PDAC (26). However, abdominal pain is the most common presenting complaint of patients with PDAC (27); not only is US commonly performed to investigate patients with abdominal pain, it is the recommended first-line test for patients with right upper quadrant pain (5, 6). In our cohort, we observed many patients with PDAC referred for US evaluation, however the majority (63/112, 56.3%) of clinical indications did not suggest malignancy. Similarly, one study found that approximately one-third of patients with PDAC were initially misdiagnosed clinically (4). In our study, the proportion of requisitions not suspecting malignancy was significantly higher in the FN group.

Our study conveys important implications for radiologists reporting US, and referring physicians ordering US for patient work-up. First, the overall sensitivity of US in detecting PDAC was low and has clinical implications; this should be recognized by all physicians and ideally addressed by societal guidelines. Second, although our study found diagnostic limitations of US, with generally poor visualization of the pancreas, PDAC tumors, and associated secondary signs, only 24/42 (57.1%) IN and 5/23 (21.7%) FN examinations commented on the quality of the examination. A description of examination quality, including any limitations in evaluating an organ, might avoid false reassurance with a negative or equivocal study. Third, there were significantly more distal tumors in the IN and FN groups; patients with distal tumors are less likely to present with jaundice, particularly in the earlier stages, and are therefore more difficult to diagnose clinically (27). Another takeaway for radiologists is that we found 10 PDAC tumors which were missed or misinterpreted on US, but were in retrospect evident, as well as 8 examinations where

liver metastases were present but missed on US. We found opportunities for improvement with respect to US interpretation, and in this study, the sensitivity of US reflects limitations not only of the modality, but of the readers as well. To address this, we have retrospectively compiled imaging pearls and pitfalls observed in our cohort (ref blinded).

Our study has limitations, including its retrospective nature and evaluation of a specific region and population, which may limit generalizability. Although our study was multi-centered, diagnostic work-up practices in our region may not reflect those of other centers or healthcare systems. Because we only included patients with PDAC and not patients without the disease, we did not evaluate other measures of diagnostic performance, such as specificity or accuracy. It is important to note that the diagnosis and management of PDAC is a multifaceted problem, and our study only evaluated US-related factors. We did not evaluate non-imaging factors that may impact a patient's diagnostic work-up, and also cause delays to diagnosis and surgery, and worsen survival.

In conclusion, our study found that a high proportion of US examinations of patients with PDAC are indeterminate or falsely negative, and the sensitivity of US for detecting PDAC is low. In our population, patients with false negative first-time US examinations are associated with longer mean imaging follow-up and diagnostic intervals, as well as worse mean survival. We found opportunities for improvement with respect to US interpretation and reporting, including comment on the quality of the examination and specific organ assessment. Our results convey important implications for radiologists reporting US, referring physicians relying on US for diagnostic work-up, and healthcare professionals working to improve the survival of PDAC.

FIGURE CAPTIONS

Figure 1. Example of an indeterminate US examination. A 59 year-old man presented to emergency with severe right upper quadrant pain and tenderness, and US was requested to evaluate for cholecystitis. (a) Transverse grayscale US image of the pancreas shows an ill-defined hypoechoic mass in the pancreatic body (arrow), however, there was no mention of the pancreas in the radiologist's report. (b) Transverse grayscale US image of the right liver shows innumerable rounded hypoechoic masses, which were reported as suspicious for metastatic disease or abscesses. (c) CT performed one day later with positive oral and intravenous contrast shows a hypoenhancing mass in the pancreatic body invading the splenic vein (arrowhead), with upstream duct dilation and atrophy. There are numerous hypoenhancing liver metastases.

Figure 2. Example of a false negative US examination. A 76 year-old woman was admitted to hospital with epigastric pain, nausea and vomiting. There is a history of gallstones and US was requested to assess for cholecystitis or pancreatitis. (a) Transverse grayscale US image of the pancreas shows hypoechoic mass-like thickening of the pancreatic body (arrow). The finding was interpreted as evidence of pancreatitis, and no follow-up was recommended. The patient underwent upper endoscopy, which found an ulcer in the duodenum with possible perforation or fistulization to the biliary tree, which prompted CT evaluation. (b) Axial CT image with positive oral and intravenous contrast shows an ill-defined mass in the pancreatic body deforming the pancreatic contour and invading the peripancreatic vasculature.

TABLES

Table 1. Characteristics of Patients and Tumors According to US Test Result

	Entire Cohort	True Positive	Indeterminate but follow-up advised	False Negative	p-value
Number of examinations	113	48	42	23	-
Patient sex					
M	53	17	25	16	0.011
F	54	31	17	7	
Mean age (yrs)	70.3 ± 13	70.9 ± 12	70.2 ± 13	67.3 ± 14	0.513
Mean weight (kg)	71.7 ± 16	72.1 ± 17	72.2 ± 13	71.0 ± 18	0.956
Mean tumour size (cm)‡	3.3 ± 1.3	3.4 ± 1.4	3.3 ± 1.1	3.1 ± 1.4	0.531
Location of tumour†					
Head/Uncinate	74	39	23	12	0.017
Neck/Body/Tail	37	9	19	9	

† The location was unknown in 2 patients (2 US examinations) due to lack of follow-up imaging and incomplete registry data

‡ Size was unknown or not discernible in 8 patients and 8 US examinations

Table 2. Characteristics of US Examinations According to US Test Result

	Entire Cohort	True Positive	Indeterminate but follow-up advised	False Negative	p-value
Number of US examinations	113	48	42	23	-
Clinical suspicion of malignancy*					
Yes	49	28	19	2	0.0006
No	63	20	23	20	
US quality comment					
Yes	35	6	24	5	<0.0001
No	78	42	18	18	
Pancreas visualization					
Completely visualized	10	9	1	0	0.0004
Mostly visualized	48	26	12	10	
Parts missed	34	11	17	6	
Not visualized	21	2	12	7	
PDAC visualized					
Yes	49	45	4	0	<0.0001
No or missed	64	3	38	23	
PDAC not visualized but in retrospect seen	10/64	0/3	4/38	6/23	-
Secondary signs§					
Present and seen	49	37	11	1	< 0.0001
Present and missed	32	6	15	11	
Absent	6	1	4	1	
Liver metastases‖					
Present and seen	21	7	14	0	0.0052
Absent or missed	86	37	28	21	

Liver metastases not visualized but in retrospect seen	8/86	2/37	2/28	4/21	-
Suspicion of neoplasm raised?					
Y	67	48	19	0	<0.0001
N	46	0	23	23	
Follow-up recommendations					
Y	89	47	42	0	<0.0001
N	24	1	0	23	

PDAC, pancreatic ductal adenocarcinoma

[*] The requisition for one study was unavailable

[§] Based on imaging quality and lack of imaging follow-up, the presence or absence of secondary signs of PDAC were unavailable in 5 patients and 5 US examinations. Only US examinations with sufficient imaging of the tumour and/or pancreas were included in assessment of secondary signs

[|] The presence of absence of liver metastases was unknown in 6 patients and 6 US examinations

Table 3. Time Intervals and Survival According to Ultrasound Test Result

	Entire Cohort	True Positive	Indeterminate but follow-up advised	False Negative	p-value
Number of patients with first-time US studies	99	44	37	18	-
Mean follow-up imaging interval (days)*	15.1 ± 45	4.0 ± 6	7.4 ± 11	60.0 ± 96.9	< 0.0001
Mean diagnostic interval (days)	75.4 ± 174	41.0 ± 53	49.2 ± 77	216.6 ± 363	0.0007
Number of patients with primary surgery	20	11	4	5	-
Mean surgical interval (days)†	130.8 ± 106	111.3 ± 78	115.8 ± 70	202.8 ± 174	0.291
Mean survival (days) ‡	263.5 ± 298	346.7 ± 376	216.3 ± 217	150.3 ± 123	0.034

* Based on 92 studies due to no imaging follow-up in 7 patients

† Based on the number of patients undergoing primary surgery in the row above

‡ There were no survivors in the cohort

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Fig. 1

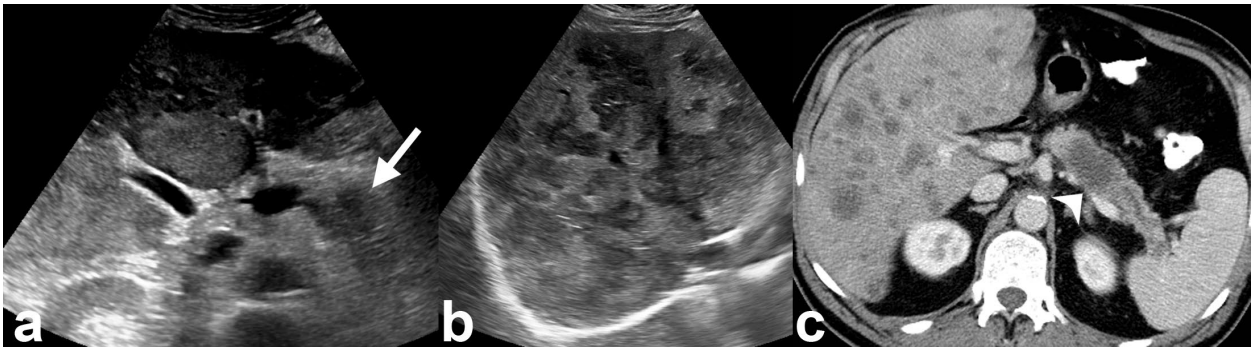

Fig. 2