Impact of pancreatic head tumor size on the outcome of surgical management

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Background and objectives
Tumor size has been identified as a critical prognostic factor after pancreatic adenocarcinoma resection; however, this is still up for debate. The authors aimed to investigate the relationship between size and the results of pancreatic cancer resection.
Patients and methods
The studied subjects were divided into two groups as follows: group A: included 69 patients with pancreatic head/uncinate process tumor ≤3 cm in size (maximum tumor diameter), subjected to elective pancreaticoduodenectomy, group B: included 87 patients with pancreatic head/uncinate process tumor >3 cm in size (maximum tumor diameter), subjected to elective pancreaticoduodenectomy.
From January 1, 2016 to December 31, 2021, at Menoufia University's National Liver Institute, we looked at the clinical, radiological, histological, and survival characteristics of tiny pancreatic cancer tumors (tumors ≤3 cm) in comparison to tumors above 3 cm in size following pancreaticoduodenectomy. Calculations were made of overall cancer-specific survivals. Key factors were assessed for relevance in survival prediction using a Cox proportional hazards model.
Results
Among the tumors measured, 44.2% were ≤3 cm in size 55.8% tumor were greater than 3 cm in size. Larger tumors were associated with worse symptoms, higher Ca19.9, more progressive TNM stages, longer operative time, more blood transfusion, higher grade, more vascular invasion, more involved surgical margin, and more lymph node invasion. Our study compared data of 1-year survival rates of 79.1% and 50% as seen with ≤3 cm tumor size and with above 3 cm tumor size, respectively, also 2-year survival rates of 40.3% and 19.2% were seen with ≤3 cm tumor size and with above 3 cm tumor size, respectively, the result being statistically significant ($P<0.001$). Pancreatic ductal adenocarcinoma size above 3 cm was associated with a worse prognosis together with histologic grading, vascular invasion, involved surgical margin, longer waiting list time, and progressive T stages.
Conclusions
Our findings suggest that early pancreatic ductal adenocarcinoma detection can have clinical benefits, which has positive implications for future screening strategies. Pancreatic ductal adenocarcinoma size above 3 cm is an independent predictive factor for poor prognosis after surgical resection and is associated with more aggressive tumor biology. Future trials are required to evaluate the survival benefit of neoadjuvant therapy in this subset of patients.

Keywords:
pancreatic cancer, surgical management, tumor size

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Introduction

Since patient survival is more directly correlated with tumor size, the 8th edition of the AJCC revised the T-stage classification system for pancreatic cancer. Tumor size was determined from T1 through T3, and the idea of exopancreatic invasion of the tumor was dropped. T4 staging omits the term 'resectability' and describes the tumor as invasive of the common hepatic artery, superior mesenteric artery, and/or celiac trunk artery. The maximal sizes of T1 tumors were 0.5, 0.5–1, and 1–2 cm, respectively, after that they were further classified into T1a, T1b, and T1c [1].

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There was greater reliability in the assessment of tumor size for prognostication for both clinical and pathologic staging. Indeed, a number of research examining the prognostic markers in pancreatic ductal adenocarcinoma (PDAC) have demonstrated that one of the most crucial variables in determining how cancer patients would fare clinically is the size of the tumor. The published papers have different cut-off points for PDAC size: 2, 2.5, 3, 4, and 5 cm [2].

Numerous studies contend that the 2 cm cut-off point is not very comprehensive and call for additional study to redefine or propose multiple cut-off points, such as 2, 3, or 4 cm, to offer a more thorough framework for designing treatment plans and predicting the prognosis for patients after surgery [3].

In addition to the current single 2 cm cut-off point defining the tumor stage proposed by AJCC, several studies reported that survival time has statistical significance with a 3 cm cut-off. This suggests the 3 cm cut-off may become another new potential tumor size cut-off in the new T stage of pancreatic cancer [4].

Patients and methods

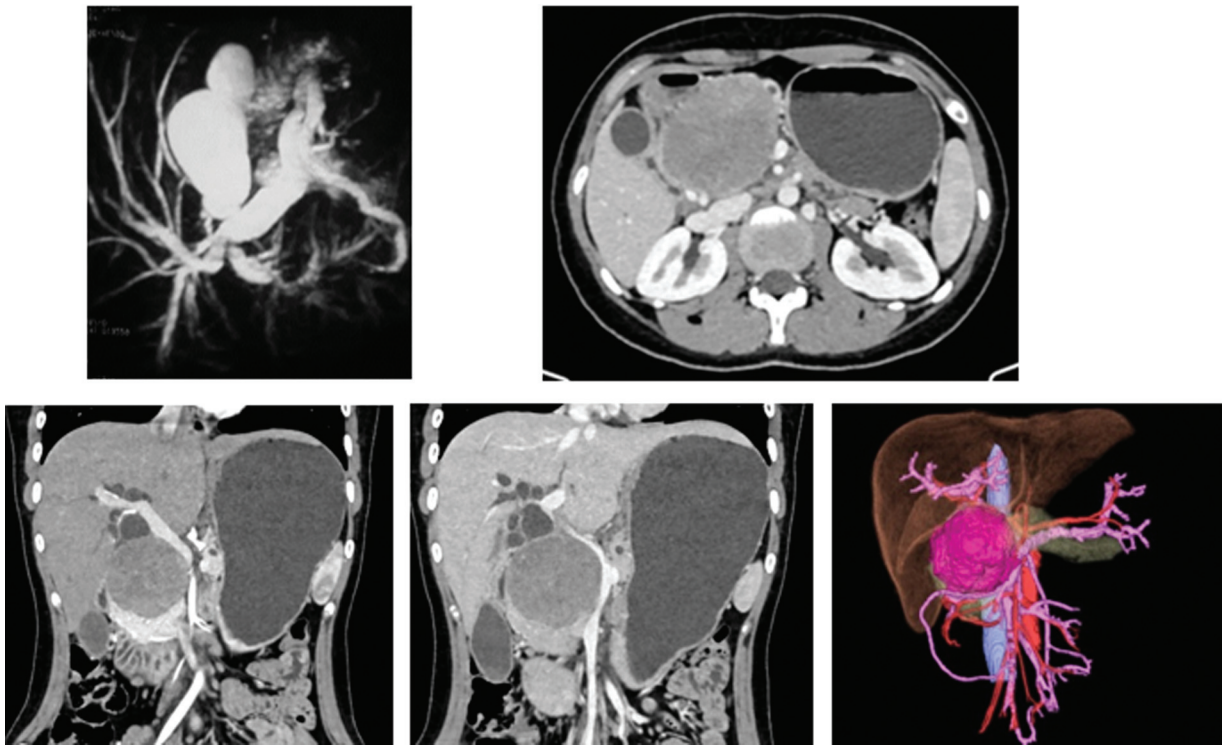
This is a retro-prospective study conducted on medical records of patients with pancreatic head/uncinate process tumors who were subjected to elective pancreaticoduodenectomy (Whipple's procedure) from January 1, 2016 to December 31, 2021 at the National Liver Institute, Menoufia University.

The studied subjects were divided into two groups as follows: group A: included 69 patients with pancreatic head/uncinate process tumor ≤3 cm in size (maximum tumor diameter), subjected to elective pancreaticoduodenectomy, group B: included 87 patients with pancreatic head/uncinate process tumor above 3 cm in size (maximum tumor diameter), subjected to elective pancreaticoduodenectomy.

Files of all patients in the surgery department at the National Liver Institute were revised to collect preoperative, intraoperative, and postoperative data as regards.

Tumor markers (carcinoembryonic antigen (CEA), CA 19.9), comorbidities (diabetes mellitus, hypertension, and cardiovascular illnesses), age, sex,

Figure 1



A male patient 60-year-old with a resectable pancreatic head tumor. A, MRCP shows dilatation of the intrahepatic biliary radicals, common bile duct (CBD) till its distal end, and pancreatic duct (double duct sign) indicating distal biliary obstruction. B, Axial computed tomography (CT) scan in the pancreatic parenchymal phase showing a pancreatic head sizable mass measuring about 4.7 cm at its maximum diameter. C and D, Coronal CT scan at the pancreatic parenchymal/portovenous phases show abutting (<180) superior mesenteric vein (SMV) with no involvement of the superior mesenteric artery, there is no metastasis either hepatic or nodal. D, 3D reconstruction coronal CT image shows relations between pancreatic head tumor and superior mesenteric artery (SMA) and SMV. National Liver Institute (Menoufia University).

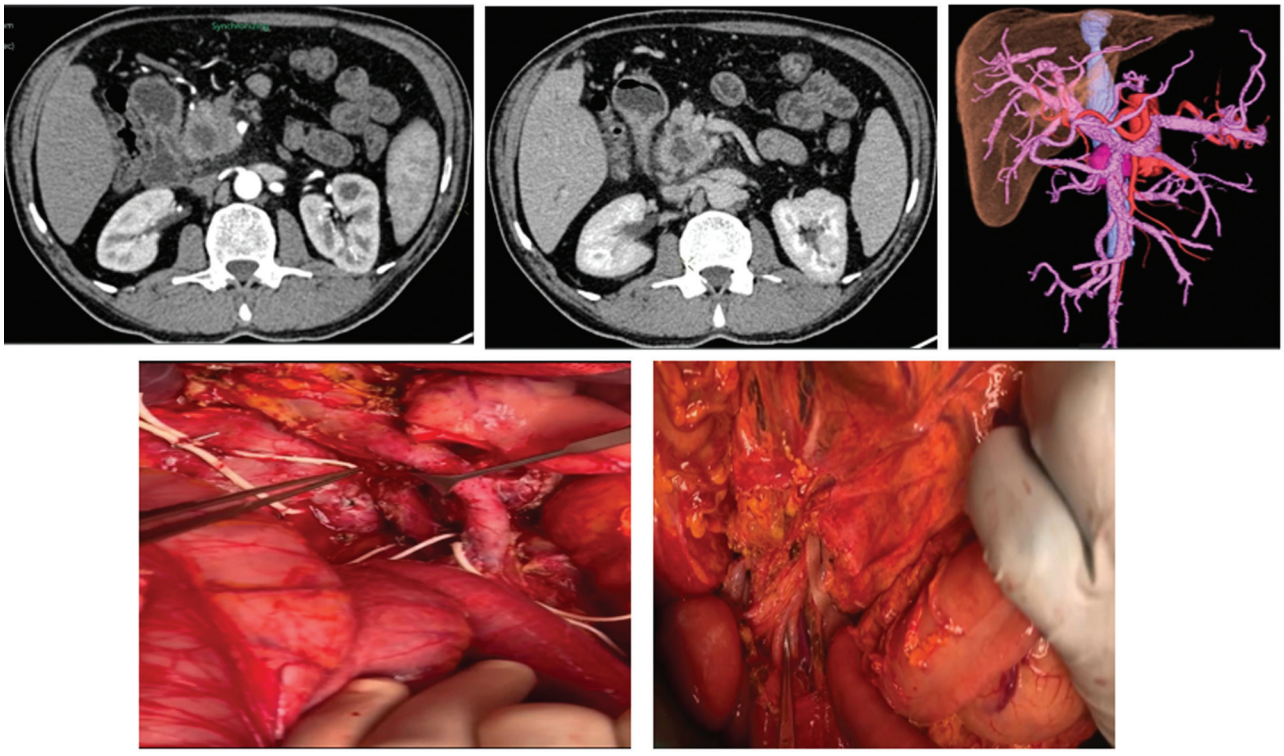
and current smoking within the last year were evaluated. Anorexia, vomiting, pain, weight loss, jaundice, and itching were evaluated as clinical variables.

Preoperative radiological investigations included chest radiography and abdominal ultrasonography done for all patients. Multidetector contrast-enhanced abdominal computed tomography (CT) scan was done for all patients (Seimens, Biograph, 128 slices) using a pancreatic protocol: noncontrast, pancreatographic, delayed arterial, venous, and delayed phases (with slice thicknesses and intervals from 0.5 to 1.00 mm with 2–3 mm thickness at pancreatic region). Coronal and sagittal multiplanner reformatting, 2–3 mm maximum intensity projection (MIP), and 3D projections were done. SYNAPSE 3D simulation software (version 6.6 FUJIFILM, Global Technology, Egypt) was used to acquire thin sub-millimeter below 3 mm axial sections with images obtained in the pancreatic and portal venous phase of contrast enhancement (tumor type and size, vascular invasion, lymph node metastases, liver, or distant metastases) for a more comprehensive image of the tumor and its relationship to the surrounding vessels using an artificial intelligence engine (Figs. 1 and 2).

Dynamic magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) were done for 52 (33.3%) patients using (GE 1.5 T, Optima 450 W) dynamic MRI. An imaging protocol that is commonly used to detect and stage pancreatic cancer in the abdomen includes dynamically enhanced fat-suppressed T1-weighted pictures, axial images with T1 and T2 weighting, and coronal scout T2-weighted images, for MRCP (axial T2, coronal T2, axial fat, and 3D MIP). Endoscopic retrograde cholangiopancreatography (ERCP) was done for 62 (40%) patients as a diagnostic (level and cause of biliary obstruction) and therapeutic (plastic biliary stenting for drainage), endoscopic US, biopsy either CT-guided was done for 10 (6.4%) patients using co-axial tru-cut biopsy needle 16 G or endoscopic US guided for 20 (12.8%) patients.

Operative variables included operative time, vascular reconstruction, blood loss, blood transfusions, and unresectability at surgery. In some cases, superior

Figure 2



A male patient 55-year-old presented with borderline resectable pancreatic head tumor. A and B, Axial contrast-enhanced computed tomography (CT) image pancreatic (a) and portovenous phase (b) shows a pancreatic head tumor measuring about 2.7 cm at its maximum diameter that has 180-degree solid tumor contact with superior mesenteric artery (SMA). C, 3D reconstruction of CT images illustrating relations between pancreatic head tumor and SMA and superior mesenteric vein (SMV). D, Superior mesenteric artery first approach pancreaticoduodenectomy (taping of superior mesenteric artery, superior mesenteric vein, left renal vein, and retracted portal vein). E, Superior mesenteric artery first approach pancreaticoduodenectomy with preserved first jejunal artery, second jejunal artery, and first jejunal vein. National Liver Institute (Menoufia University).

mesenteric artery first approach was done as described by Takaori and Uemoto, by left posterior and trans-mesenteric approach for early assessment of resectability, total mesopancreatic excision, extended lymphadenectomy, and early ligation of inferior pancreaticoduodenal artery to minimize blood loss [5] (Figs. 3 and 4)

Postoperative variables assessing the histopathological features according to the College of American Pathologists protocol; tumor size assessment (3D were measured and for staging at least the maximum dimension of the tumor measured, macroscopic assessment of the tumor size confirmed using microscopic evaluation), type of tumor, histologic grade, perineural invasion, necrosis, lymph node invasion, vascular invasion, surgical margin, CT size *versus* pathological size were assessed (Figs 5–8).

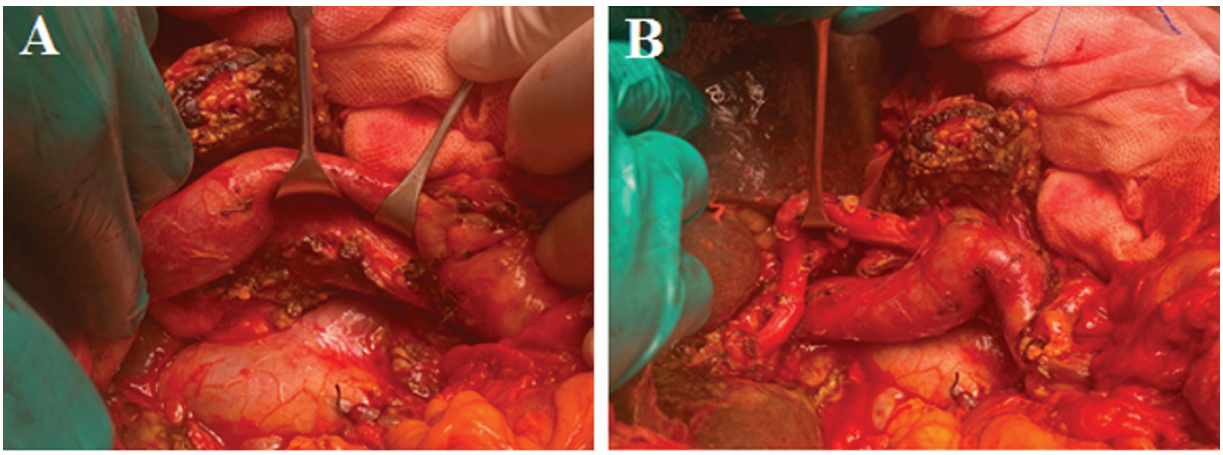
Short-term outcomes: (morbidity/mortality) ICU/hospital stay, pancreatic/bile/gastric leak, postoperative pancreatic fistula, bleeding, wound infection/dehiscence, delayed gastric emptying, and the need for reoperation were assessed.

Long-term outcomes were assessed through surveillance (physical examination/CA19-9/imaging) of pancreatic cancer patients after surgical resection (to detect local/distant recurrence and mortality) overall survival, tumor-free survival, time of recurrence, type of recurrence, and mortality for 2 years postoperative.

Statistical analysis

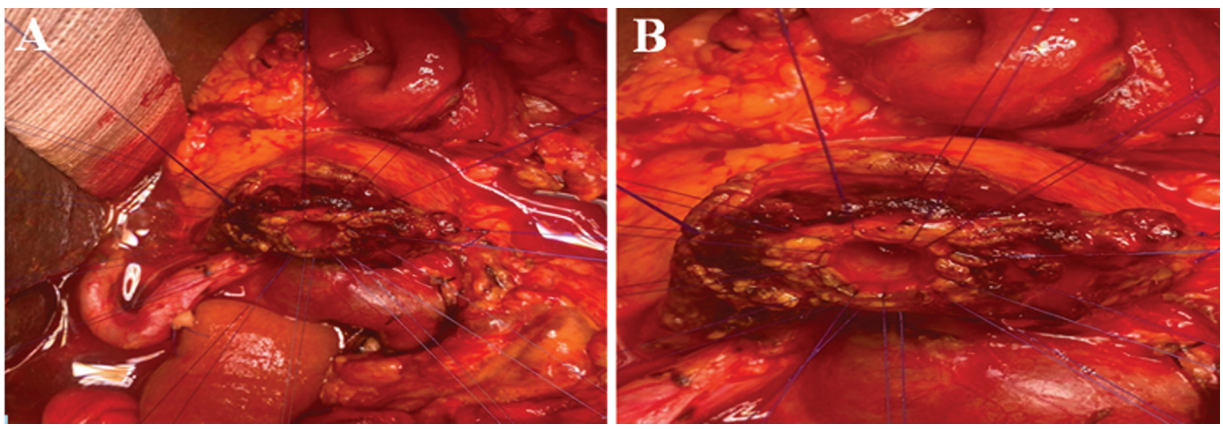
IBM Co. (Armonk, NY, USA) used SPSS version 28 for statistical analysis. The unpaired student *t* test was used to assess the quantitative parametric data, which

Figure 3



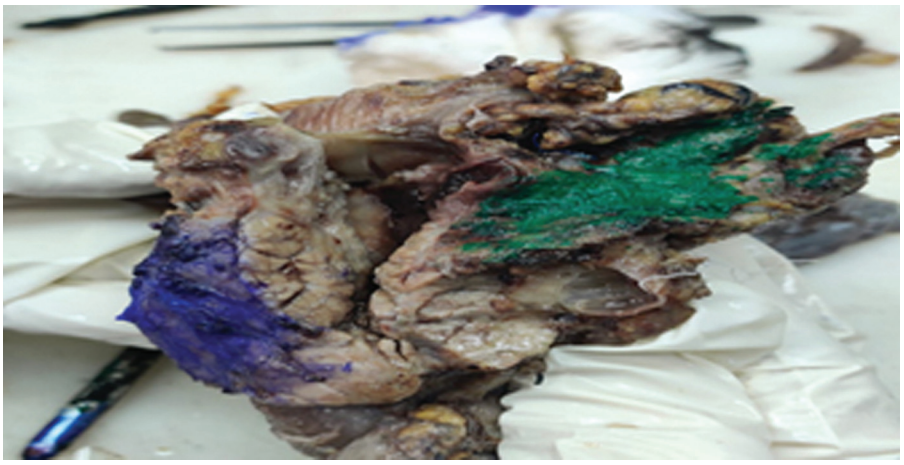
A and B, Operative bed after transection of pancreas showing (transected neck of the pancreas, hepatic artery, superior mesenteric vein, splenic vein, portal vein, left renal vein, and inferior vena cava). National Liver Institute (Menoufia University).

Figure 4



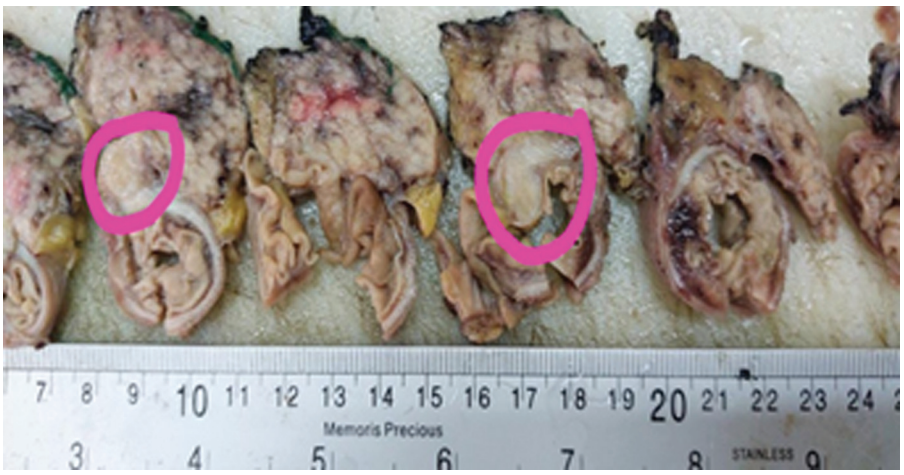
A and B, Dilated pancreatic duct prepared for pancreatico-enteric anastomosis. National Liver Institute (Menoufia University).

Figure 5



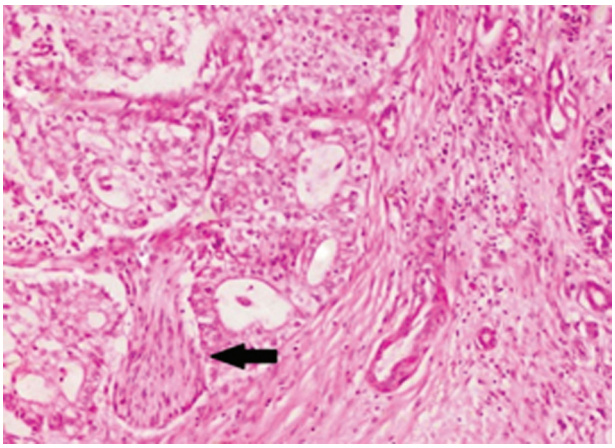
Pancreatoduodenectomy specimen images, pancreatoduodenectomy specimen after fixation [the circumferential soft tissue margins were inked (PTM: violet, PMM: yellow, PPM: green)]. PTM, pancreatic transection margin; PMM, pancreatic medial margin; PPM, pancreatic posterior margin. National Liver Institute (Menoufia University).

Figure 6



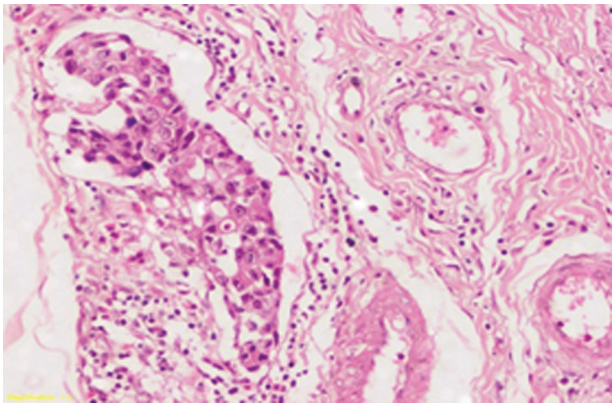
Consecutive parallel sections of 0.5 cm thickness following an axial plane perpendicular to the duodenal axis. Tumor seems to be in contact with. National Liver Institute (Menoufia University).

Figure 7



Moderately differentiated pancreatic adenocarcinoma with perineural invasion highlighted by black arrow (H&E 200×). National Liver Institute (Menoufia University).

Figure 8



A case of poorly differentiated pancreatic adenocarcinoma with lymphovascular invasion (H&E 200×). National Liver Institute (Menoufia University).

were reported as mean and standard deviation (SD). The Mann-Whitney test was used to evaluate quantitative nonparametric data, which were reported as the median and interquartile range. Categorical data were reported as percentages and frequencies, and when applicable, the Fisher exact test or the χ^2 test were used for analysis. A statistically significant result was defined as a two-tailed *P* value less than 0.05.

Results

The age, sex distribution, smoking status, and comorbidities of the two analyzed groups were equivalent, according to one baseline feature of the groups under study (Table 1).

There was a statistically significant association between pancreatic head tumor size and severity of preoperative symptoms as patients with above 3 cm tumor size (group B) elicited higher rates of anorexia, vomiting, pain, loss of weight, jaundice, and itching when compared with those with ≤3 cm tumor size (group A) with *P* values less than 0.001.

Regarding tumor markers, patients with above 3 cm tumor size (group B) had significantly lower CEA levels than those with ≤3 cm tumor size (group A) (*P*=0.002), while both groups were comparable as regards CA 19-9.

Relationship between the size of the pancreatic head tumor and (vascular encasement and lymph node invasion) in CT scan: patients with tumors larger than 3 cm (group B) had a significantly higher incidence rate of LN invasion compared with patients with tumors smaller than 3 cm (group A) (*P*=0.003), while the rates of vascular encasement were similar in both groups.

Association between pancreatic head tumor size and unresectability at surgery, during surgery, we detected 11 unresectable tumors (two of which were ≤3 cm in size and nine were >3 cm), with no statistically significant difference between both groups.

As regards operative data, the duration of surgery on patients with above 3 cm tumor size (group B) was significantly longer than that of patients with ≤3 cm tumor size (group A) (*P*<0.001). Moreover, vascular reconstruction was performed at a significantly higher rate in group B with significantly more blood unit transfusion than in group A (in which no patients underwent vascular reconstruction) (*P*=0.02, <0.001, respectively). The level of blood loss and the percentage of patients who needed blood transfusion were insignificantly different between both groups (Table 2).

There was a statistically significant relation between tumor size and histologic grade as patients with greater than 3 cm tumor size (group B) had more severe grades than those with ≤3 cm tumor size (group A) (*P*<0.001). Also, group B elicited significantly more necrosis, vascular invasion, and involved surgical margin than group A (*P*<0.05). Both CT and pathology confirmed that group B had a larger tumor size with more progressive TNM stages than group A (*P*<0.001) (Table 3).

Regarding short-term complications, patients with >3 cm tumor size (group B) manifested significantly lower incidence rates of pancreatic leak, fistula, and wound infection compared with those with ≤3 cm tumor size (group A) (*P*<0.05) (Table 4).

The size of the pancreatic head tumor did not statistically significantly affect the patient's survival at 1 or 6 months following surgery, according to a Kaplan-Meier study. In contrast, after 12 months

Table 1 Baseline characteristics of the studied groups

	Group A (n=69)	Group B (n=87)	*P*
Age (years)			
Mean±SD	58.51±6.48	58.06±8.51	0.717
Range	41–70	34–82	
Sex			
Male	58 (84.1)	75 (86.2)	0.707
Female	11 (15.9)	12 (13.8)	
Smoking	51 (73.9)	71 (81.6)	0.248
Comorbidities			
DM	13 (18.8)	14 (16.1)	0.652
HTN	12 (17.4)	15 (17.2)	0.98

Data are presented as frequency (%) unless otherwise mentioned. DM, diabetes mellitus; HTN, hypertension.

Table 2 Association between pancreatic head tumor size and operative data

	Group A (n=67)	Group B (n=78)	*P*
Time of surgery (hour)	6 (5–7)	7 (6.5–8)	<0.001*
Vascular reconstruction	0	8 (10.3)	0.02*
Blood loss (ml)	850 (500–1200)	1000 (600–1500)	0.169
Blood transfusion	46 (68.7)	62 (79.5)	0.136
Units of blood transfusion	2 (1–2)	3 (2-–3)	<0.001*

Data are presented as frequency (%) or median (interquartile range) as appropriate. *Statistically significant as *P* value less than 0.05.

Table 3 Association between pancreatic head tumor size and radiological and pathological results

	Group A (n=67)	Group B (n=78)	*P*
Type of tumor			
Adenocarcinoma	56 (83.6)	66 (84.6)	0.865
Variant	11 (16.4)	12 (15.4)	
Histologic grade			
GI low grade	22 (32.8)	4 (5.1)	<**0.001***
GII low grade	40 (59.7)	49 (62.8)	
GIII high grade	5 (7.5)	25 (32.1)	
Perineural invasion	64 (95.5)	74 (94.9)	>0.999
Necrosis	4 (6)	27 (34.6)	<0.001*
LN	58 (86.6)	68 (87.2)	0.913
Vascular invasion	8 (11.9)	23 (29.5)	0.01*
Involved surgical margin	11 (16.4)	30 (38.5)	0.003*
CT size (maximum diameter)	2.8 (2.5–3)	4.45 (4–5.48)	<0.001*
Pathological size	3.5 (3–4.2)	6 (5–7)	<0.001*
Clinical staging			
T1cN0M0	9 (13.4)	0	<0.001*
T1cN1M0	2 (3)	0	
T2N0M0	45 (67.2)	18 (23.1)	
T2N1M0	8 (11.9)	5 (6.4)	
T2N2M0	0	1 (1.3)	
T3N0M0	0	25 (32.1)	
T3N1M0	0	16 (20.5)	
T3N2M0	0	5 (6.4)	
T4N0M0	0	1 (1.3)	
T4N1M0	3 (4.5)	3 (3.8)	
T4N2M0	0	4 (5.1)	
Pathological staging			
T1cN1M0	3 (4.5)	0	<0.001*
T2N0M0	8 (11.9)	1 (1.3)	
T2N1M0	27 (40.3)	0	
T2N2M0	4 (6)	0	
T3N0M0	2 (3)	6 (7.7)	
T3N1M0	21 (31.3)	3 (3.8)	
T3N2M0	0	45 (57.7)	
T4N1M0	2 (3)	0	
T4N2M0	0	23 (29.5)	

Data are presented as frequency (%) or median (interquartile range) as appropriate. *Statistically significant as *P* value less than 0.05.

Table 4 Association between pancreatic head tumor size and short-term complications

	Group A (n=67)	Group B (n=78)	*P*
Pancreatic leak	28 (41.8)	18 (23.1)	0.016*
Bile leak	6 (9)	8 (10.3)	0.791
Fistula	25 (37.3)	14 (17.9)	0.009*
Bleeding	4 (6)	8 (10.3)	0.35
Wound infection	30 (44.8)	22 (28.2)	0.038*
Wound dehiscence	11 (16.4)	8 (10.3)	0.273
DGE	8 (11.9)	8 (10.3)	0.747
Gastric leak	1 (1.5)	3 (3.8)	0.642
Re-operation	5 (7.5)	7 (9)	0.218

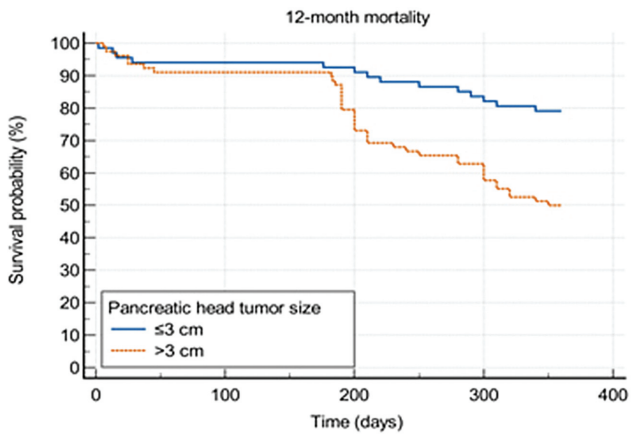
Data are presented as frequency (%). DGE, delayed gastric emptying. *Statistically significant as *P* value less than 0.05

[hazard ratio (HR)=2.69, 95% confidence interval (CI): 1.56–4.64, $P<0.001$], 18 months (HR=2.22, 95% CI: 1.41–3.49, $P<0.001$), and 24 months (HR=2.16, 95% CI: 1.45–3.23, $P<0.001$), patients with tumor sizes greater than 3 cm had a significantly higher mortality rate and a shorter survival time than those with tumor size less than 3 cm (Figs 9–11).

While the nature and timing of recurrence were similar in all groups, the incidence rate of recurrence was considerably greater in patients with tumor sizes >3 cm (group B) than in those with tumor sizes ≤3 cm (group A) (35.9% *vs.* 11.9%, $P<0.001$) (Table 5).

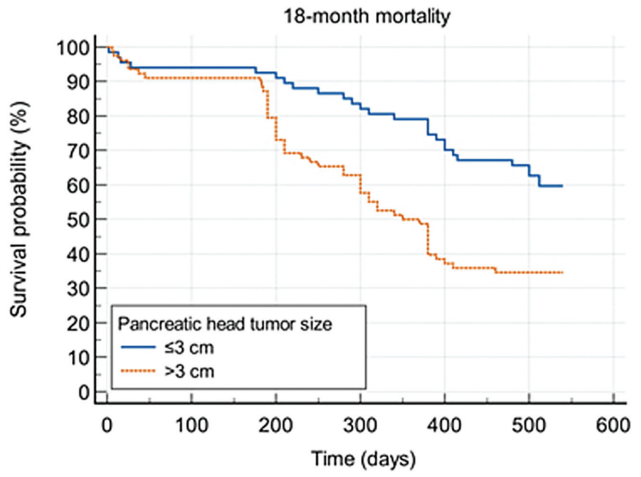
Based on the impact of tumor size analysis of the patients under study, tumor size was found to have a

Figure 9



Kaplan-Meier curve for 12-month survival analysis according to pancreatic head tumor size.

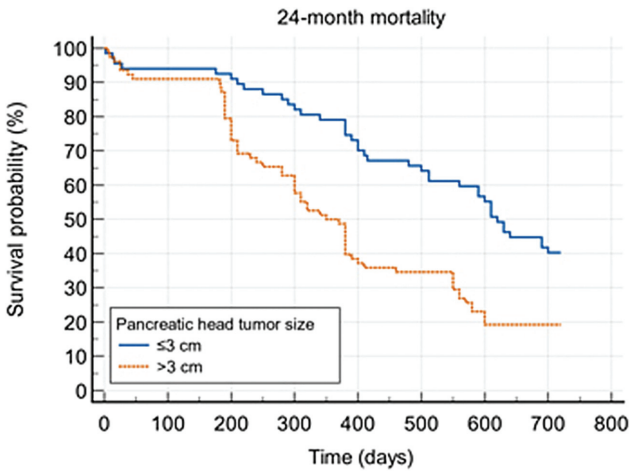
Figure 10



Kaplan-Meier curve for 18-month survival analysis according to pancreatic head tumor size.

statistically significant impact on tumor-free survival. Patients with tumors larger than 3 cm were found to have a significantly higher chance of recurrence and a shorter survival time than those with tumors smaller than 3 cm (HR=4.87, 95% CI: 2.46–9.63, $P<0.001$).

Figure 11



Kaplan-Meier curve for 24-month survival analysis according to pancreatic head tumor size.

According to a survival analysis of patients with resectable pancreatic head tumors (tumors smaller than 3 cm), waiting list duration did not significantly affect patients' survival during the first six months following surgery. However, after 12 (HR=3.56, 95% CI: 1.14–11.15, $P=0.029$), 18 (HR=6.73, 95% CI: 2.77–16.36, $P<0.001$), and 24 months (HR=7.51, 95% CI: 3.37–16.74, $P<0.001$), patients who waited longer than 30 days had a significantly higher mortality rate and a shorter survival time than those who waited less. Waiting list duration had no statistically significant impact on patients' survival at 6, 12, 18, and 24 months following surgery in patients whose tumors were more than 3 cm.

According to the findings of the univariate analysis, the histologic grade was a significant independent predictor of mortality. Patients with GIII high grade, necrosis (HR=2.1, 95% CI: 1.36–3.26, $P=0.001$), vascular invasion (HR=2.21, 95% CI: 1.41–3.47, $P=0.001$), and involved surgical margin (HR=2.12, 95% CI: 1.4–3.2, $P<0.001$) had significantly higher rate of mortality than other patients. Mortality rate was substantially correlated with larger pathological size tumors (HR=1.34, 95% CI: 1.19–1.5, $P<0.001$). In comparison to patients

Table 5 Association between pancreatic head tumor size and its recurrence

	Group A (n=67)	Group B (n=78)	*P*
Recurrence	8 (11.9)	28 (35.9)	<0.001*
Type of recurrence (8 *vs*. 28)			
Local	5 (62.5)	18 (64.3)	0.399
Distant	3 (37.5)	7 (25)	
Both	0	3 (10.7)	
Time of recurrence (months)	9.5 (8.25–11.5)	13 (6–16.75)	0.614

Data are presented as frequency (%) or median (interquartile range) as appropriate. *Statistically significant as *P* value less than 0.05.

Table 6 Univariate and multivariable Cox regression analysis for factors associated with overall survival of patients

	Univariate			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Loss of weight	1.32	0.85–2.03	0.217	1.07	0.66–1.73	0.791
Jaundice	1.18	0.78–1.79	0.423	0.83	0.51–1.37	0.471
CEA (ng/mL)	1	0.99–1.01	0.684	1	0.99–1.01	0.726
LN invasion	1.2	0.8–1.81	0.377	0.64	0.39–1.06	0.085
Time of surgery (h)	1.13	0.99–1.3	0.076	1.05	0.89–1.23	0.55
Histologic grade						
GI low grade	Reference			Reference		
GII low grade	1.04	0.6–1.81	0.884	0.84	0.46–1.53	0.565
GIII high grade	2.16	1.16–4.03	0.015*	0.87	0.34–2.2	0.769
Necrosis	2.1	1.36–3.26	0.001*	0.93	0.47–1.82	0.832
Vascular invasion	2.21	1.41–3.47	0.001*	0.63	0.18–2.25	0.48
Involved surgical margin	2.12	1.4–3.2	<0.001*	0.91	0.47–1.78	0.786
Pathological size	1.34	1.19–1.5	<0.001*	1.23	0.96–1.57	0.101
Waiting list time						
Below 30 days	Ref			Ref		
Above 30 days	2.02	1.34–3.02	0.001*	1.82	1.1–3	0.02*
T staging						
T1	Ref			Ref		
T2	2.27	0.31–16.8	0.421	2.17	0.28–17.03	0.46
T3	3.39	0.47–24.5	0.227	1.82	0.22–14.92	0.577
T4	11.62	1.56–86.84	0.017*	13.7	1.07–174.9	0.044*

HR, hazard ratio; CI, confidence interval. *Statistically significant as *P* value less than 0.05.

who waited less, those who waited more than 30 days had a substantially increased rate of mortality (HR=2.02, 95% CI: 1.34–3.02, *P*=0.001). Patients with T4-stage tumors showed a substantially increased mortality (HR=11.62, 95% CI: 1.56–86.84, *P*=0.017) compared with those with T1-stage tumors (Table 6).

Patients who waited longer than 30 days had a higher mortality rate than those who waited shorter (HR=1.82, 95% CI: 1.1–3, *P*=0.02), and patients with tumors in the T4 stage had significantly higher mortality than those in the T1 stage (HR=13.7, 95% CI: 1.07–174.9, *P*=0.044). These findings were consistent across multiple analyses (Table 6).

Discussion

Using a 3 cm cut-off point, this study evaluates the effect of tumor size on the surgical management results (morbidity/mortality) of pancreatic head/uncinate process tumors.

The study found a statistically significant correlation between the size of the pancreatic head tumor and the severity of symptoms. Specifically, patients in group B with tumors larger than 3 cm had higher rates of anorexia, vomiting, pain, weight loss, jaundice, and itching than patients in group A with tumors smaller than 3 cm (*P* values <0.001).

Numerous investigations on pancreatic cancer have shown that pain is related to prognosis, with more pain being associated with a poorer prognosis [6].

Loss of weight is associated with a reduced response to chemotherapy, a shorter progression-free survival and overall survival (OS), a poorer quality of life, and a decreasing performance status [7].

An analysis of 179 consecutive pancreatoduodenectomies for pancreatic cancer was conducted at the Cleveland Clinic. According to univariate analysis, this study discovered that a high bilirubin level was a significant unfavorable predictor of OS. However, serum bilirubin concentration was not found to be an independent predictor of outcome after multivariate analysis [8].

In our investigation, patients with tumor sizes larger than 3 cm (group B) had significantly greater rates of jaundice, weight loss, and pain; however, these factors did not independently predict prognosis on multivariate or univariate analyses.

A correlation has been seen between a poor prognosis and a greater presurgical CA19-9 level (>100 or >1000 U/ml) in studies by Sugiura *et al.* [9], Brown *et al.* [10], and Dong *et al* [11]. Because of the presumably small number of patients in their

dataset, only Kondo and colleagues showed no connection between presurgical CA19-9 and OS [12].

Since the levels of CA19-9 in both groups were comparable, there was no discernible relationship between tumor size and CA19-9 levels in our investigation. This investigation is the first reliable proof that these possible confounders have no discernible effect on the level of CA 19-9; hence, any rise of CA 19-9, even in the presence of potential confounders, may have biological significance.

When compared with tumor size determined using gross specimens, the tumor size as determined by CT scan in our research was dramatically underestimated. The mean tumor size difference was 7 mm, with group A having a mean CT tumor size of 2.8 cm and a mean pathological size of 3.5 cm. Group B had a mean pathological size of 6 cm and a mean CT tumor size of 4.45 cm, so the difference in the mean tumor size was 1.55 cm resulting in downstaging of the T category and TNM shift.

When compared with pathological specimens, pancreatic parenchymal phase CT scans showed the highest accuracy for PDAC size, with a median measurement difference between imaging and pathology of 2 mm that did not achieve statistical significance (P =0.051). In contrast to pathology specimens, portal venous phase CT showed a statistically significant underestimating of PDAC size (P<0.05), with a median discrepancy ranging from 1 to 6 mm [13].

In other studies, there was a median discrepancy of 7 (n=87) [14], 4 (n=16) [15], and 4.9 mm (n=159) [16] between the tumor diameters on CT and the histological sizes of PDAC.

Previous research has shown that downstaging of the T category may occur when tumor size is underestimated during the imaging of certain PDAC patients. According to Ma *et al.* [17], the mean tumor size of PDACs differed by 4.3 mm on CT evaluation, and the tumor size as determined by CT and MRI was substantially different (P<0.001) from that determined using gross specimens.

Patients with a tumor size of ≤3 cm were identified in our investigation (group A) had pathological staging T1 (4.5%), T2 (58.2%), T3 (34.3%), and T4 (3%), and clinical staging T1 (16.4%), T2 (79.1%), T3 (0%), and T4 (4.5%). Individuals with tumor sizes more than 3 cm (group B) had pathological staging T1 (0%), T2 (1.3%), T3 (69.2%), T4 (29.5%), and clinical staging T1 (0%), T2 (30.8), T3 (59%), and T4 (10.2%). These findings distinguish TNM shift and T category downstaging.

Our findings corroborate those of Legrand and colleagues' earlier study, which showed that T stages significantly impacted the difference in PDAC sizes assessed between pathologic specimens and CT/MRI measures. Tumor size measurements showed a significant rise in discrepancy between T1 and T3 [18].

In the current investigation, 11 unresectable tumors were found during surgery (2 of which were <3 cm and 9 of which had a size <3 cm). Of the tumors that appeared resectable on CT scans, 13.2% were found to be unresectable during surgery, with no statistically significant difference between the two groups (group A 2.9%–group B 10.3%).

A 10–30% of tumors that seem resectable on CT scans turn out not to be resectable when surgery is performed, according to Ma *et al.* [17].

Two limitations of our study related to variation in tumor size estimations between CT and pathologic specimens were that tissues were fixed in formalin (tissue shrinkage) for histological processing, and the mean number of days between the CT scan and surgery was not reported. Still, the histology size is greater than the typical PDAC sizes as established by CT scans.

According to our series' operative data, patients in group B who had tumors larger than 3 cm had surgery for a considerably longer period than patients in group A who had tumors less than 3 cm (P<0.001). Furthermore, group B saw a considerably higher rate of vascular reconstruction and a significantly higher blood unit transfusion rate than group A, where no patients received vascular reconstruction (P=0.02, <0.001, respectively). Between the two groups, there was no discernible difference in the amount of blood loss or the proportion of patients in need of blood transfusions.

Our results are consistent with those of Dusch and colleagues who showed that the PDAC size also affects surgical outcomes. It was discovered that patients with tumors larger than 3 cm had more intraoperative blood loss and required more packed red blood cell transfusions, even though the latter factor may worsen oncologic outcomes due to immunological modulation related to transfusion [19].

Duschand colleagues have shown that one of the main risk factors for complications following pancreaticoduodenectomy is operative blood loss. They clarified that high blood loss causes surgical stress and necessitates blood transfusions, which have been demonstrated to worsen postoperative morbidity, particularly septic complications, and have an immunosuppressive impact [19].

Our study reveals a statistically significant relation between tumor size and histologic grade as patients with tumor size greater than 3 cm (group B) had more severe grades than those with tumor size ≤3 cm (group A) ($P<0.001$). Also, group B elicited significantly more necrosis, and vascular invasion, and involved surgical margin than group A ($P<0.05$).

Our findings are consistent with previous reports that tumor grade in PDAC is a significant independent prognostic indicator of OS following resection. This is probably due to the more aggressive biology of less differentiated tumors, which results in earlier local and distant metastases [20].

The clinicopathological characteristics of tumors larger than 3 cm (group B) and less than 3 cm (group A) were observed in this investigation. In comparison to tumors ≤3 cm, pooled analysis revealed that patients with tumors larger than 3 cm had higher incidences of perineural invasion (94.9% *vs.* 95.5%; $P>0.999$), vascular invasion (29.5% *vs.* 11.9%; P 0.01), positive resection margins (38.5% *vs.* 16.4%; P 0.003), histologic grade GIII high grade (32.1% *vs.* 7.5%; $P<0.001$), and lymph node invasion (87.2% *vs.* 86.6%; P 0.913) but did not reach statistical significance.

Numerous research examined the clinicopathological characteristics of groups with tumors larger than 3 cm and less than 3 cm. Patients with tumors larger than 3 cm exhibited higher occurrences of lymph node metastasis [79.1% *vs.* 64.2%, odds ratio (OR): 2.24, 95% confidence interval], poor tumor differentiation (36.2% *vs.* 28.4%, OR: 1.45, 95% CI: 1.43–3.51; $P<0.001$), positive resection margins (36.9% *vs.* 27.2%, OR: 1.56, 95% CI: 1.22–2.92; $P=0.004$), vascular invasion (39.8% *vs.* 27.7%, OR: 1.78, 95% CI: 1.41–2.24; $P<0.001$), and perineural invasion (80.8% *vs.* 67.1%, OR: 1.89, 95% CI: 1.22–2.92; $P=0.004$) (CI: 1.31–1.87; $P<0.001$), and between patients with tumors ≤3 cm and those with positive intraoperative peritoneal cytology (14.2% *vs.* 2.6%, OR: 5.66, 95% CI: 2.15–14.93; $P<0.001$) [2].

Our results agree with the previously reported higher incidences of histologic grade, vascular invasion, and positive resection margins with tumors above 3 cm as compared with tumors ≤3 cm. On the other hand; incidences of lymph node invasion and perineural invasion are comparable in both groups.

This study noted that patients with tumor size larger than 3 cm (group B) elicited significantly more severe histologic grades, vascular invasion, lymph node invasion, and involved surgical margin as a predictor of overall recurrence following pancreatectomy for PDAC, the incidence rate of recurrence was significantly higher in patients with tumor size larger than 3 cm (group B) than those with ≤3 cm tumor size (group A) (35.9% *vs.* 11.9%, respectively, $P<0.001$), while the type and time of recurrence were comparable between both groups.

In their cohort, Tummers and colleagues discovered a statistically significant difference in OS between the CRM negative and CRM positive groups: 22 months against 12 months for the former. Furthermore, they discovered that the collective recurrence-free survival of their patients was a noteworthy 20 months for distant recurrence and 30 months for local recurrence [21].

Our study reveals a statistically significant effect of tumor size on tumor-free survival as patients with tumor size larger than 3 cm had a significantly higher probability of experiencing recurrence, with shorter survival time than those with ≤3 cm tumor size, while the type and time of recurrence were comparable between both groups.

In addition, the same findings reported by Paniccia *et al.* [22] that long-term survivors with PDAC undergo resection for smaller tumors support the idea that tumor size alone is a good predictor of prognosis; larger cancers are linked to an earlier recurrence; and dimensions have no bearing on the type of recurrence (local *vs.* systemic), as this could be better explained by the tumor genomic assessment.

The literature has found a number of predictors of overall recurrence after pancreatectomy for PDAC, including tumor size and grading, lymph node metastases, R status, lymph node ratio, microvascular and perineural invasion, and adjuvant therapy [23].

Regarding short-term complications, patients with tumor size larger than 3 cm (group B) manifested significantly lower incidence rates of pancreatic leak,

fistula, and wound infection compared to those with ≤3 cm tumor size (group A) ($P<0.05$).

Ferrone and colleagues found similar results in their analysis of the relationship between tumor dimensions and surgical outcomes. While there was no difference in overall morbidity, small cancers are specifically linked to a higher risk of postoperative pancreatic fistula (POPF) following PD, which in turn is linked to a higher rate of abdominal abscesses, in-hospital mortality, and longer lengths of hospital stay. It is well established that a modest mass with a high incidence of POPF often does not cause chronic obstructive pancreatitis that may guard against POPF [24].

Kaplan-Meier analysis showed that there was no statistically significant effect of pancreatic head tumor size on the survival of patients 1 and 6 months after surgery. On the contrary, patients with tumor size larger than 3 cm had a significantly higher probability of mortality, with shorter survival time than those with ≤3 cm tumor size after 12 months (HR=2.69, 95% CI: 1.56–4.64, $P<0.001$), 18 months (HR=2.22, 95% CI: 1.41–3.49, $P<0.001$), and 24 months (HR=2.16, 95% CI: 1.45–3.23, $P<0.001$).

Our study compared data of 1-year survival rates 79.1% and 50% seen with ≤3 cm tumor size (group A) and with tumor size larger than 3 cm (group B), respectively, also 2-year survival rates 40.3% and 19.2% were seen with ≤3 cm tumor size (group A) and with tumor size larger than 3 cm (group B), respectively, the result being statistically significant ($P<0.001$).

In addition, the same outcomes reported by Shrestha and colleagues showed that data on 1-year survival rates were collected from many investigations with a total of 1024 individuals. Tumor sizes less than 3 cm and more than 3 cm had 1-year survival rates of 61.80% and 45.69%, respectively. Similarly, research including 504 patients compared 2-year survival rate data. Tumor sizes of less than 3 cm and larger than 3 cm had 2-year survival rates of 25.6% and 14.36%, respectively. This finding is statistically significant ($P<0.01$) [25].

Our study noted that for patients with a tumor size of ≤3 cm, waiting list time had no statistically significant effect on the survival of patients 1–6 months after surgery. On the other hand, patients who waited for more than 30 days had significantly higher probability of mortality, with shorter survival time than those who waited less, after 12 months (HR=3.56, 95% CI: 1.14–11.15, $P=0.029$), 18 months (HR=6.73, 95% CI: 2.77–16.36, $P<0.001$), and 24 months (HR=7.51, 95% CI: 3.37–16.74, $P<0.001$). In patients with tumor size above 3 cm, waiting list time had no statistically significant effect on the survival of patients 1, 6, 12, 18, and 24 months after surgery.

When comparing preoperative CT data with the dimension determined at pathology, delays in surgical treatment are also linked to increased tumor size, according to the identical results reported by Marchegiani and colleagues. Except for PDAC <30 mm, this delay does not appear to have an impact on either survival or the severity of clinical characteristics. Surgery appears to be losing some of its maximal prognostic advantage for sizable but appear to be resectable PDACs. The prognosis is negatively impacted by PDAC's increased aggression, which occurs when it surpasses a certain threshold and manifests as local invasion and maybe occult distant dissemination [2].

Noteworthy are a few restrictions. First and foremost, it is possible that some patients' scheduled surgical procedures were postponed while they were waiting. Either tumor development or a decline in clinical status might be the cause of this since both would make surgical intervention impossible. Based on registry data, it is not feasible to clearly discriminate between nonoperability and advancement. There could be a bias in the screening process since we lacked clinical information on these patients. Secondly, we lacked knowledge on the causes of the delay (such as preoperative optimization, extra diagnostic testing, administrative concerns, etc.).

According to the findings of the univariate analysis, the histologic grade was a significant independent predictor of mortality. Patients with GIII high grade, necrosis (HR=2.1, 95% CI: 1.36–3.26, $P=0.001$), vascular invasion (HR=2.21, 95% CI: 1.41–3.47, $P=0.001$), and involved surgical margin (HR=2.12, 95% CI: 1.4–3.2, $P<0.001$) had higher mortality rates than those with GI low grade (HR=2.16, 95% CI: 1.16–4.03, $P=0.015$) possessed a noticeably greater mortality rate than the rest. The rate of mortality was strongly correlated with pathological tumor size (HR=1.34, 95% CI: 1.19–1.5, $P<0.001$). In comparison to patients who waited less, those who waited more than 30 days had a substantially increased rate of mortality (HR=2.02,

95%CI: 1.34–3.02, *P*=0.001). Patients with T4 stage tumors showed a substantially increased mortality (HR=11.62, 95% CI: 1.56–86.84, *P*=0.017) compared with those with T1 stage tumors.

Patients who waited longer than 30 days had a higher probability of mortality than those who waited shorter (HR=1.82, 95% CI: 1.1–3, *P*=0.02), and patients with tumors in the T4 stage had a significantly higher probability of mortality than those in the T1 stage (HR=13.7, 95% CI: 1.07–174.9, *P*=0.044). These findings were consistent across multiple analyses.

Conclusion

According to the current study, PDAC size more than 3 cm is linked to more aggressive tumor biology and is an independent predictor of a poor prognosis following surgical excision. Further research on redefining or suggesting multiple cut-off points, such as 2, 3, or 4 cm, is necessary to provide a more comprehensive guideline to plan treatment protocol to predict the survival outcome following surgery. Future trials are required to assess the survival benefit of neoadjuvant therapy in this subset of patients.

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Conflicts of interest

There are no conflicts of interest.

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