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Outcomes Following Surgery for Locally Advanced Pancreatic Cancer - Single Center Experience. A Retrospective Study

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Rezumat

Rezultatele postoperatorii imediate în tratamentul cancerului pancreatic avansat - experiența unui singur centru. Studiu retrospectiv

Introducere: Cancerul pancreatic reprezintă una din cele mai frecvente tumori cu o incidență în creştere. Marea majoritate a cazurilor la debut sunt diagnosticate in stadii avansate, iar tratamentul chirurgical rămâne cea mai important opțiune terapeutică. Scopul acestui studiu a fost evaluarea morbidității postoperatorii care are un impact asupra inițierii tratamentului adjuvant.
Metode: Am efectuat un studiu retrospectiv pe o bază de date colectată prospective ce a inclus toți pacienții diagnosticați cu cancer de pancreas la care s-a practicat tratament chirurgical cu viză de radicalitate între 2012 şi 2021. Am împărțit lotul de pacienți în tumori avansate si localizate si am urmarit rezultatele imediate postoperatorii.
Rezultate: Au fost incluşi în analiză 58 de pacienți la care s-a practicat 28 (48.3%) de duodenopancreatectomii cefalice şi 30 (51.7%) de pancreatectomii distale. Tumorile localizate (T1 şi T2) au fost la 32 de pacienți (55.2%), iar cele avansate (T3 şi T4) la 26 de cazuri (44.8%). Cu toate că nu a fost nici o diferență semnificativă statistic pentru complicațiile postoperatorii, am observant o tendință pentru pacienții cu tumori avansate de a dezvolta o complicație majoră (15.6% vs 34.6%, p=0.09). La analiza multivariată a factorilor pre-operatori asociați cu apariția unei complicații majore, numai valorile CA19-9 au fost associate cu un risc crescut (odds ratio 0.666, 95% CI 0.5- 1.01; p=0.04)
Concluzie: Acest studiu a arătat ca nu este nici o diferență semnificativă în cee ace priveşte complicațiile postoperatori între pacienții cu tumori avansate sau localizate. CA 19-9 poate fi un marker predictive al dezvoltării unei complicații postoperatori.

Cuvinte cheie: cancer pancreas, pancreatectomie, morbiditate, fistula pancreatică

Abstract

Background: Pancreatic cancer represents one of the most frequent cancers with an increased incidence. Most cases on initial diagnosis are considered to be locally advanced and surgery remains the most important therapeutic option. The aim of this study was to evaluate postoperative morbidity that can impair the association of adjuvant therapy.

Methods: We performed a retrospective study on a prospective database that includes all the patients diagnosed with pancreatic cancer in which surgery was performed between 2012 and 2021. We divided the patients in advanced tumours and localized tumours and we compared the outcomes after surgery.

Results: On 58 patients with pancreatic tumours surgery was performed: 28(48.3%) pancreatico-duodenectomies and 30 (51.7%) distal pancreatectomies. Localized tumours (T1 and T2) were encountered in 32 patients (55.2%) and more advanced tumours (T3 and T4) were present in 26 cases (44.8%). Although there was no significant difference either for major complications, we observed a tendency for patients with advanced tumours to develop a major complication (15.6% vs 34.6%, p=0.09). The occurrence of major complication, such as pancreatic fistula and postoperative hemorrhage, there was no significant difference (6.25% vs 7.69% and 6.25% vs. 23.1%). On multi-variate analysis of preoperative factors associated with the occurrence of a severe complication only the CA19-9 levels were associated with an increased risk (odds ratio 0.666, 95% CI 0.5-1.01; p= 0.04)

Conclusions: This study showed no significant differences in terms of postoperative complications between the two subgroups. CA 19-9 is an accurate biomarker for the prediction of postoperative complications.

Key words: pancreatic cancer, pancreatic resection, morbidity, pancreatic fistula

Introduction

Pancreatic cancer is expected to be one of the cancers with the highest incidence over the next decades with one of the leading causes of cancer-related deaths (1). Surgical resection remains the best therapeutic option for the "resectable" pancreatic cancer, but the overall survival in this case is around 10% (2). The factors involved in this poor outcome are: late on set diagnosis, a lack of standardization of management of preoperative jaundice, inconsistent use of either neo or adjuvant chemotherapy, the poor condition of the patient and nevertheless the higher rates of postoperative morbidity and mortality. The combination of surgery and chemotherapy gives the patient the best chance for cure. One of the limiting factors for achieving this goal is the occurrence of postoperative complications, among those the most important is the pancreatic fistula (3). There is no consensus regarding the best approach in order to reduce the incidence of this complication, current strategies include an early detection and management in order to reduce the severity of this complication (4). In order to improve outcomes after pancreatic resections several solutions were developed: standardization of practices based upon best evidence and routine audits (5).

The definition of resectability in pancreatic cancer varies in between resectable, borderline-resectable and unresectable(6), based on the invasion of important vessels: celiac trunk, superior mesenteric artery and the portal vein or superior mesenteric vein. Borderline resectable pancreatic cancer is defined as a

pancreatic cancer with involvement of the portal vein and/or superior mesenteric vein that allows resection and reconstruction. The International Association of Pancreatology developed a more comprehensive definition of resectability (6) which includes anatomical factors, mentioned above, biological factors (serum carbohydrate antigen (CA) 19-9 level more than 500U/mL or positive regional lymph nodes on biopsy or positron emission tomography and conditional factors such as ECOG classification).

The aim of our study was to evaluate the outcomes after surgery for patients diagnosed with pancreatic cancer in which resection was performed, based on actual staging of the tumour and to evaluate the impact of tumoral stage on early outcomes after surgery.

Methods

We performed a retrospective study based on a prospective collected database that included all the patients diagnosed with pancreatic tumours in which radical surgery was performed between 2013 and April 2021 in the 1st Surgical Unit of the Regional Institute of Oncology Iasi. In all patients an informed consent was obtained and this study was approved by the ethics board committee. Initial evaluation of the tumour was made using thoraco-abdominal tomography, in selected cases in which diagnosis was unclear, a MRI of the pancreas region was performed. In a small number of patients, positive histological diagnosis was performed using endoscopic transgastric or transduodenal eco-guided biopsy. All pancreatic resections were performed by the surgical groups of our institution within the time period. All cases were individual evaluated by a multidisciplinary team and therapeutic decision was made based on tumour stage and associated comorbidities. For patients with cardiac or pulmonary medical history, a thorough cardiopulmonary evaluation prior to surgery in order to optimize medical conditions, including hypertension and diabetes.

Surgery consisted in all patients in pancreatectomy with lymph node dissection. For patients in which pancreatoduodenectomy was performed the lymphadenectomy area included lymph nodes in the suprapyloric, infrapyloric areas, common hepatic artery, hepatoduodenal ligament, anterior and posterior areas of the pancreatic head. In most of cases a pylorus preserving procedure was performed, reconstruction was made by performing a pancreaticogastrostomy duct-to-mucosa, followed by a duodeno-enteroanastomosis and a hepaticojejunoanastomosis. In all patients a jejunostomy feeding tube was used. In patients who underwent a distal pancreatectomy, lymphadenectomy consisted in resection of lymphnodes around the splenic hilum, splenic artery, inferior border of the pancreas, celiac artery. All pateints received a prophylactic administration of octeotride analogue (Sandostatin) after surgery.

We divided the patients in two subgroups based on staging of the tumours, localized tumours were considered tumours that were T1 and T2 on histopathological examination and advanced tumours were considered to be T3 and T4 tumours. Our primary analyses focused on comparing morbidity and 30 day mortality of those subgroups of patients. For baseline characteristics we used age, gender, comorbidities, preoperative laboratory tests results. For surgical details we compared the type of resection and the pathology of the resected specimen. For outcomes data we evaluated the postoperative severe morbidity in terms of pancreatic fistula and secondary hemorrhage.

Statistical Analysis

Statistical analysis continuous variables were summarized using the sample median with range and numbers with percentage. Comparison was done using *t*-test for continuous variables and chi-square test for categorical variables. A univariate analysis was performed to estimate the factors associated with the development of a significant postoperative complication. *p* values less than 0.05 were considered significant. All

statistical analyses were performed using SPSS for Mac version 17 (SPSS, Inc., Chicago, IL).

Results

Based on the results of our study we included in the analysis 58 patients diagnosed with pancreatic tumours in which surgery was performed. Patients demographics and characteristics are shown in *Table 1.* There was no difference in terms of cardiovascular, pulmonary or renal associated diseases. Localized tumours, as considered in our analysis to be tumours T1 and T2 were encountered in 32 patients (55.2%) and more advanced tumours (T3 and T4) were present in 26 cases (44.8%). There was a tendency of more advanced tumours to be located in the body and tail of the pancreas, 61.5% versus 43.75%. Also, there were no differences in terms of hemoglobin and albumin levels, but as expected patients with more advanced tumors presented elevated levels of CEA and CA 19-9. We did not investigate the correlation in patients with tumours located in the head of the pancreas with jaundice and the levels of CA 19-9. Pathology of the resected specimens are shown in *Table 1.* Although there was no statistically significant difference, there was a tendency for the pancreatic adenocarcinoma tumours to be more advanced (84.6% vs 75 %), without difference for the neuroendocrine tumours (11.6% vs 9.4%). Extended resections involving other organs were made in 8 patients, resected organs included: colon in 5 cases, part of the posterior wall of the stomach in 2 cases, left kidney in 2 cases, left adrenal gland in 1 case, small bowel loop in 2 cases. Splenectomy was not considered to be included in the extended resection, because splenectomy was a part of a radical resection of the body and tail pancreatic tumours. All of the extended resections were made for tumours located in the body and tail of the pancreas.

Minor complications (Dindo-Clavien grade 1-3) after surgery were encountered in 23 cases (39.5%) of all patients and there was no statistically significant difference between patients with localized or advanced tumours (37.5 vs 42.3%, p=0.71). Although there was no significant difference either for major complications, we observed a tendency for patients with advanced tumours to develop a major complication (15.6% vs 34.6%, p=0.09). In

Table 1. Patients' characteristics

Characteristics	Total n (%) or mean ± SD	Localised tumours (N=32)	Advanced tumours (N=26)	p
Male/female	30/28	13/9	17/9	0.74
Age	64.5 (± 10.11)	65(±9.34)	64(±10.12)	0.82
Tumor location				
Head	28 (48.3%)	18 (56.25%)	10 (38.5%)	-
Body/tail	30 (51.7%)	14 (43.75%)	16 (61.5%)	0.18
Cardiovascular history	27 (46.5%)	15 (46.9%)	12 (46.1%)	0.95
Diabetes	19 (32.8%)	11 (34.4%)	8 (30.8%)	0.77
Renal disease	4 (6.9%)	2 (6.2%)	2 (7.7%)	0.83
Pathology				
Pancreatic ductal adenocarcinoma	46 (79.3%)	24 (75%)	22 (84.6%)	0.34
Pancreatic cysts (IPMN,MCN,SCN)	6 (10.3%)	5(15.6%)	1(3.8%)	
Neuroendocrine tumour	6 (10.3%)	3(9.4%)	3(11.6%)	
Preop Hb	12.96 (±1.37)	12.9 (±1.08)	10.8 (±1.68)	0.97
Preop alb	4.45 (±0.46)	4.53 (±0.4)	4.01 (±0.6)	0.18
CEA	11.9 (±5.9)	2.5 (±1.8)	23.5 (±10.6)	0.19
CA 19-9	274 (± 36)	242 (±40.5)	312 (±200.1)	0.48
Preoperatory amylase	58.3 (± 35.9)	55,1 (±27.8)	60.1 (±22.5)	0.66
Operative procedure				
Pancreaticoduodenectomy	28 (48.3%)	18 (56.2%)	10 (38.5%)	
Distal pancreatectomy	30 (51.7%)	14 (43.8%)	16 (61.5%)	
Extended resection	8 (13.8%)	-	8 (30.8%)	

Table 2. Postoperative outcomes

Surgical outcomes	Total	Localised tumours	Advanced tumours	p
Minor complications	23 (39.5%)	12 (37.5%)	11 (42.3%)	0.71
Major complications	13 (22.4%)	5 (15.6%)	9 (34.6%)	0.09
30 day mortality	2 (3.4%)	1 (3.1%)	1 (3.8%)	0.88
1st day amilase levels	127.4 (±22.4)	115.5 (±11.6)	145.6 (±15.3)	0.48
2nd day amilase levels	131.3 (±30.3)	121.6 (±16.7)	146.8 (±17.2)	0.68
3rd day amilase levels	93.61 (±25.7)	82.9 (±27)	103.17 (±42)	0.70
Pancreatic fistula	10 (17.2%)	2 (6.25%)	6 (23.1%)	0.06
Postpancreatectomy hemorrhage	4 (6.9%)	2 (6.25%)	2 (7.69%)	0.89
Total lymph nodes	20 (±10.7)	19(±)	21(±)	0.34
Positive lymphnodes	2.7 (± 1.7)	2(±0.5)	4 (±2)	0.05
Lymphovascular invasion	47 (81%)	23 (71.9%)	24(92.3%)	0.05

most of the patients which developed a major complication a multiorgan resection was performed, only 2 patients without an extended resection, but with an advanced tumours a severe complication (Dindo-Clavien grade 4-5). Although the patients with more advanced tumours had slightly more elevated blood serum levels of amylase and lipase in the first 72 hours after surgery, those were not correlated with the stage of the tumour.

When we investigate the occurrence of major complication, such as pancreatic fistula and postoperative hemorrhage, there was no significant difference (6.25% vs 7.69% and 6.25% vs. 23.1%). The only difference on pathological examination of the resected specimen was on the number of positive lymph nodes and on the lymphovascular invasion.

On multivariate analysis of preoperative factors associated with the occurrence of a severe complication only the CA19-9 levels were associated with an increased risk (odds ratio 0.666, 95% confidence interval 0.5- 1.01; □ = 0.04).

Table 3. Multivariate logistic regression analysis for preoperative factors associated with severe complications

Variable	Odds ratio (95% confidence interval)	P value
Hb	1.632 (0.42-6.123)	0.55
CEA	0.711 (0.11-1.59)	0.19
CA19-9	0.666 (0.5- 1.01)	0.04

Discussions

According to data in literature, more than 80% of patients presenting with pancreatic cancer will have unresectable disease at the moment of the initial diagnosis (7). While the aim of this paper is not to evaluate this aspect, it shows the importance of the issue and this reiterates the main problem of this disease, that is resectability. Furthermore, the majority of patients undergoing curative resection will present with local and distant recurrence (8). Thus, these two issues raise the question whether or not surgical resection can be obtained with a chance of microscopically negative resection, given the important morbidity and mortality associated with major pancreatic surgery. This is a problem to be taken into discussion in future studies on the issue.

Postoperative mortality following pancreaticoduodenectomy has decreased over years from values up to 25% to as low as 5% (9). This is especially due to cases being directed towards high-volume centres, in which optimised operative management of pancreatic cancer is performed; in addition, relationship between hospital and surgeon volume and outcomes in pancreatic surgery has been well established (10), especially in pancreaticoduodenectomy from as early as 1999 (11). Our study shows a low 30-day mortality of 3.4%, with no statistically significant difference between localised

tumours (3.1%) and advanced tumours (3.8%); this is an important aspect, showing that surgical outcome in terms of mortality is not as much associated with tumour staging, but with surgical technique and postoperative management of complications.

Taking into consideration that pancreatic surgery is associated with high morbidity, of up to 40% of cases (12), we can say that the evolution of pancreatic cancer patients undergoing major surgery relies very much on successful management of complications. In accordance to data in the literature, this study shows an occurrence of 39.5% of minor complications and 22.4% of major complications, according to Dindo-Clavien classification of surgical complications (13). Notably, there is no significant difference between localised tumours and advanced tumours in terms of postoperative complications. This matter may emerge from a standardised surgical technique that is undertaken whether the surgeon is faced with low-stage or locally advanced tumours. As a result, we may say that surgical resection is of choice when faced with potentially resectable disease.

Perioperative local complications mostly associated with pancreatic cancer surgery are pancreatic fistula, delayed gastric emptying and postoperative haemorrhage. Although pancreatic fistula is more prevalent in the advanced cancer group, there is no significant difference between the two groups. There is no data in this matter in the literature up to date. On the other hand, standardization in the definition of postoperative pancreatic fistula is needed, in order to obtain homogenous results; in literature, leak rates vary from as low as 2% to more than 35% (10). Remarkably, there were no significant differences in variations of amylase levels between the two groups. Thus, serum amylase, correlated with the extension of the tumour does not accurately predict the risk of postoperative pancreatic fistula development. Unfortunately, drainage fluid amylase levels were not recorded in this study. In addition, a weak point of this study resides in the absence of fistula grading according to the International Study Group of Pancreatic Fistula classification (14).

Moreover, postoperative haemorrhage showed no significant difference in our study, which is somewhat explainable by the fact that surgical technique and the extent of resection is the same in both early tumours and advanced ones. Both values, of 6.25% and 7.69% are within the limits cited in literature, between 1% and 10% (9,15). Early haemorrhage is best managed through embolization or stenting (12), which was not the case in any of the studied cases.

Delayed gastric emptying is an important issue in pancreatic cancer surgery, and is seen in 19% to 57% of cases (10), but was, unfortunately, not quantified in this study.

When talking about complication management following pancreatic surgery, data in literature shows that an adequate approach makes the difference between low-mortality and high-mortality hospitals (12). Furthermore, it is reported that a well-trained interventional radiology department at a hospital is associated with lower perioperative mortality in pancreatic cancer surgery (16).

A weak point of this study is not taking into consideration the localisation, thus the type of surgical procedure undertaken, when comparing the postoperative complications in the two studied batches of patients.

An interesting fact that resulted from the present study is the difference in oncological outcome between the two studied groups, that was observed through the number of positive lymph nodes. As expected, the advanced cancer group had significantly more positive lymphnodes and a more frequent lymphovascular invasion, as compared to the localised tumour subgroup.

An original element in this study is the evaluation of predictive markers for postoperative complications. Carbohydrated antigen 19-9 (CA 19-9) was, thus, seen to most accurately predict postoperative complications; this aspect may result from the fact that in advanced disease, with a more elevated CA 19-9, the resection is more difficult and, in addition, positive margin resection is more frequent in said cases.

All in all, this study showed a significant difference in terms of oncological outcome between the localised and more advanced tumours. Interestingly, no significant differences were seen in terms of postoperative complications between the two subgroups. CA 19-9 is an accurate biomarker for the prediction of post-operative complications.

Conflicts of Interests

The authors declare that they have no conflict of interest.

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