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Pancreatic Adenocarcinoma Associated to Intraductal Papillary Mucinous Neoplasia: Histopathological Particularities and Clinical Implications

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Rezumat

Adenocarcinomul pancreatic asociat neoplasmului mucinos papilar intraductal: particularităţi histopatologice şi implicaţii clinice

Introducere: Adenocarcinomul ductal pancreatic (ADP) est cea mai comună tumoră pancreatică, fiind recunoscută pentru evoluţia sa agresivă. Neoplasmul mucinos papilar intraductal (IPMN) este o tumoră pancreatică rară, considerată leziune premalignă cu posibilitatea degenerescenţei maligne către ADP. Particularităţile clinice, chirurgicale şi histopatologice ale asocierii dintre ADP şi IPMN râmân în continuare necunoscute, cercetări adiţionale fiind necesare.
Metodologie: S-a realizat un studiu retrospectiv descriptiv, pe o perioadă de 9 ani (2012-2020), cu scopul comparării carcateristicilor pacienţilor care au urmat intervenţii chirurgicale cu intenţie curativă pentru ADP solitar, respectiv pentru ADP asociat IPMN.
Rezultate: Un număr de 15 pacienţi diagnosticaţi cu ADP asociat IPMN (Grupul 1) şi 386 de pacienţi diagnosticaţi cu ADP solitar (Grupul 2) au fost incluşi în studiu. Grupul 1 a înregistrat o vârstă medie mai mică (61.8 ani) comparativ cu Grupul 2 (63.89 ani). Duodenopancreatectomia totală a fost utilizată mai frecvent în Grupul 1 decât în Grupul 2 (33.33% versus 12.43%). Grupul 1 a înregistrat un proccent mai mare de cazuri cu invazie perineurală, perilimfatică şi perivasculară. Grupul 1 a înregistrat o supravieţuire atât de scurtă durată, cât şi de lungă durată mai scurtă, comparativ cu Grupul 2.

Concluzii: ADP asociat IPMN prezintă caracteristici epidemiologice, clinice şi histopatologice distincte comparativ cu ADP solitar.

Cuvinte cheie: cancer pancreatic, chirurgie pancreatică, adenocarcinom pancreatic, neoplasm mucinos papilar intraductal

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic tumor, known for an aggressive evolution. Intraductal papillary mucinous neoplasm (IPMN) is a rare pancreatic tumor, considered a premalignant lesion with the possibility of carcinogenesis towards PDAC. The clinical, surgical and histopathological particularities of the association between PDAC and IPMN are yet unknown, further research being needed.

Methods: We have conducted a retrospective descriptive study, on a nine-year period (2012-2020), with the aim of comparing the characteristics of patients that underwent curative surgical interventions for solitary PDAC and PDAC associated to IPMN.

Results: Fifteen patients with PDAC associated with IPMN (Group 1) and 386 patients with solitary PDAC (Group 2) were included in our study. Group 1 had a younger average age (61.8 years) compared to Group 2 (63.89 years). Total pancreatectomy was more frequently performed for Group 1 than Group 2 (33.33% vs 12.43%). Group 1 had a higher percentage of cases with positive perineural, perilymphatic and perivascular invasion. Group 1 registered a worse overall survival, as well as a worse short-time survival compared to Group 2.

Conclusions: PDAC associated to IPMN registers distinct epidemiological, clinical and histopathological characteristics compared to solitary PDAC.

Key words: pancreatic cancer, pancreatic surgery, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is reported as the most common tumor localized in the pancreas and is recognized for its aggressive evolution and a poor long-term prognosis (1-3).

Intraductal papillary mucinous neoplasm (IPMN) is a cystic tumor with a small incidence, of around 1 to 3% of all exocrine pancreatic tumors (1). The progression of IPMN towards PDAC is demonstrated, IPMN being considered a premalignant lesion; however, not all IPMNs progress toward adenocarcinoma. Around 30% of cases of IPMN are reported to progress towards PDAC (1). IPMNs can be classified based on their origin in main-duct (MD), branch-duct (BD), and mixed type; the risk of progression to invasive cancer is highest for MD IPMN (4-7).

Although the possible progression of IPMN to PDAC is well known and studied, there is not much discussion regarding the implication of the association between these two tumors on the evolution and overall prognosis of patients. IPMN is known to have a more indolent evolution compared to PDAC, but this difference fades in the cases in which histopathological stage of the disease is higher or lymphatic involvement is present (8-10). However, information is scarce regarding the evolution of patients and the histopathological characteristics of the association between the two tumor types.

Our study aimed to analyze the outcomes of patients diagnosed with concomitant IPMN

and PDAC and to compare them with the ones of the patients diagnosed solely with PDAC, in order to identify the particularities of this association and to underline the specific details that might influence clinical practice in these cases.

Material and Methods

The present study is a retrospective descriptive cohort study. We have included all patients diagnosed with pancreatic tumors operated in the Surgical Department of Regional Institute of Gastroenterology and Hepatology Prof. Dr. O. Fodor Cluj-Napoca in a nine-year period, between 2012 and 2020. The study was approved by our institution's ethical department (No 4584/01.04.2021).

The inclusion criteria were the following:

- Final histopathological diagnosis of PDAC associated to IPMN (Group 1) or PDAC (Group 2);
- Surgical intervention with curative intent (pancreatoduodenectomy, distal pancreatectomy or total pancreatectomy);
- Follow up of at least 6 months.

We excluded the following patients:

- Other histopathological tumor types;
- Palliative interventions or other types of interventions (enucleation, central pancreatectomy etc);
- Patients with distant metastasis;
- Insufficient data.

We have gathered the demographic characteristics of the included patients, the preoperative clinical and imagistic examinations, the operative data (resection and reconstruction method, operative time, intraoperative blood loss), the histopathological characteristics of the resection specimen, the postoperative data regarding follow-up and survival. The operating teams were different teams from our Institution, formed from surgeons with experience in hepatobiliopancreatic surgery.

Results

We screened the Institution's database, identifying 1948 records of pancreatic tumors in the above-mentioned period. After excluding patients with other histopathological diagnoses, patients not operated or who underwent palliative procedures and patients with distant metastasis, a total of 414 patients remained. Another 13 patients were excluded due to insufficient data. Therefore, 401 patients were included in our study.

A number of 15 patients with concomitant IPMN and PDAC were identified (Group 1). On the other hand, 386 patients with PDAC alone, not related to IPMN, were operated in our clinic in the respective time interval (Group 2).

Out of the 15 patients diagnosed with synchronous IPMN and PDAC, 12 patients had PDAC derived from the IPMN (80%), while 3 patients have concomitant IPMN with PDAC (20%), as separate tumors. Eight patients (53.33%) had branch-duct IPMNs, 1 patient had main-duct IPMN (6.66%), and 6 patients (40%) had mixed type IPMNs.

Demographic Data

The demographic characteristics of the included patients are presented in *Table 1.* Although in both groups, there is a predominance towards male patients, this is more evident for Group 1. The average age is also lower for patients within Group 1.

The final diagnosis of PDAC derived from IPMN was stated only on the final histopathological examination of the resection specimen. Preoperatively, 11 patients had a diagnosis of solid pancreatic tumor, without having a

Table 1. Demographic data of the study cohort

		IPMN + PDAC	PDAC
Number[a]		15	386
Sex[a]	Female	5 (33.33%)	168 (43.52%)
	Male	10 (66.66%)	218 (56.47%)
Age[b]		61.8	63.89
	Female	60	63
	Male	63	65

IPMN – intrapapillary mucinous neoplasia, PDAC – pancreatic ductal adenocarcinoma

[a]Results are presented as absolute number and in brackets, percentage out of total. [b]Results are presented as a mean.

concluding biopsy, 1 patient was diagnosed with pancreatic adenocarcinoma, 1 patient had an imagistic suspicion of cystadenoma, while 2 patients had an imagistic suspicion of IPMN.

Intraoperative Data

In both groups, pancreaticoduodenectomy (PD) was the main performed procedure; however, total pancreatectomy was performed in a higher percentage for Group 1. The reconstruction of the pancreatic remnant after PD was similar for both groups. The mean operative time is similar between groups, with a slightly higher operative time for Group 1. The intraoperative blood loss was lower for the first group, especially in the case of total pancreatectomy. Regarding the operative details, *Table 2* will present the important details for each of the 2 groups.

Table 2. The intraoperative data of the study cohort

		IPMN + PDAC	PDAC
Surgical intervention[a]	PD	9 (60%)	317 (82.12%)
	DP	1 (6.66%)	21 (5.44%)
	TP	5 (33.33%)	48 (12.43%)
Pancreatic anastomosis[a]	PG	7 (77.77%)	238 (75.07%)
	PJ	2 (22.22%)	79 (24.92%)
Mean operative time[b]	Total	274	260
	PD	281	267
	DP	80	193
	TP	299	294
Intraoperative blood loss[b]	Total	375	401
	PD	356	384
	DP	-	410
	TP	412	665
Reinterventions[a]		1 (6.66%)	33 (8.52%)

IPMN – intrapapillary mucinous neoplasia, PDAC – pancreatic ductal adenocarcinoma, PD – pancreatoduodenectomy, DP -distal pancreatectomy, TP – total pancreatectomy, PG – pancreatogastric anastomosis, PJ - pancreaticojejunal anastomosis.
[a]Results are presented as absolute number and in brackets, percentage out of total. [b]Results are presented as a mean.

Histopathological Characteristics

Regarding the histopathological characteristics, *Table 3* will present the important details for each of the 2 groups. *Fig. 1* shows the histological aspect of the PDAC associated to IPMN, will *Fig. 2* presents the histological aspect of solitary PDAC.

There were no stage I patients for the first group; other than that, the distribution of the patients between stages is similar between the two groups. Perineural, perilymphatic and perivascular invasion was present more frequent for patients in Group 1. For most patients in Group 1, the tumoral inflammatory infiltrate was mild, compared to Group 2, where most tumors had moderate inflammatory infiltrate.

Survival Data

The 90-day mortality rate was 20% (3 patients) for Group 1 and 10.62% (41 patients) for Group 2. For the PDAC associated with IPMN group, the overall survival time was 15.2 months, with a 60% survival year at 1 year after surgery, 13.33% survival rate at 2 years after surgery and 0% survival rate at 5 years after surgery. The overall survival time for the PDAC group was 20.48 months, with a 61.91% survival rate at 1 year, 29.53% survival rate at 2 years and 4.66% survival rate at 5 years.

IPMN Subgroup Analysis

We have analyzed the cases of IPMN associated

Table 3. The histopathological characteristics of the study cohort

		IPMN + PDAC	PDAC
Stage	IA	-	12 (3.1%)
	IB	-	48 (12.43%)
	IIA	4 (26.66%)	60 (15.54%)
	IIB	8 (53.33%)	205 (53.1%)
	III	3 (20%)	61 (15.8%)
Grade of differentiation	1	3 (20%)	91 (23.57%)
	2	11 (73.33%)	213 (55.18%)
	3	1 (6.66%)	82 (21.24%)
Perineural invasion	0	1 (6.66%)	79 (20.45%)
	1	14 (93.33%)	307 (79.53%)
Perivascular invasion	0	5 (33.33%)	233 (60.35%)
	1	10 (66.66%)	153 (39.63%)
Perilymphatic invasion	0	1 (6.66%)	126 (32.63%)
	1	14 (93.33%)	260 (67.35%)
Resection margin	0	13 (86.66%)	241 (62.43%)
	1	2 (13.33%)	145 (37.56%)
Tumoral inflammatory infiltrate	Mild	11 (73.33%)	147 (38.08%)
	Moderate	4 (26.66%)	231 (59.84%)
	Intense	-	8 (2.07%)

IPMN – intrapapillary mucinous neoplasia, PDAC – pancreatic ductal adenocarcinoma
[a]Results are presented as absolute number and in brackets, percentage out of total.

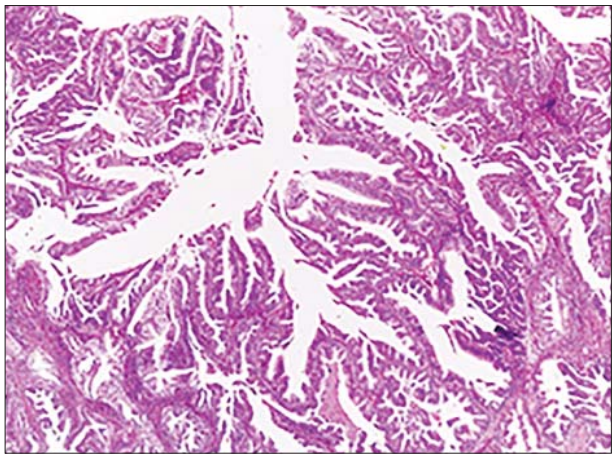

Figure 1. Histopathological image – PDAC derived from IPMN

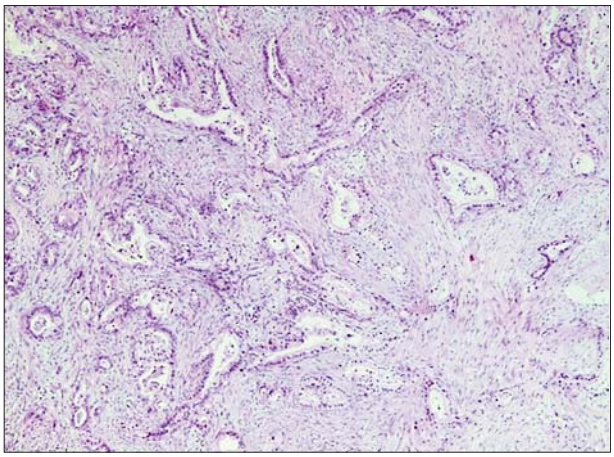

Figure 2. Histopathological image – solitary PDAC

with PDAC, based on the type of the IPMN (branch duct, main duct or mixed) and based on the relationship of the IPMN with the PDAC (IPMN concomitant with the PDAC or PDAC derived from the IPMN).

Branch-duct, main-duct, or mixed type IPMN

The age was highest for the BD IPMN group. No evident differences were observed in the choice of surgical intervention. The mean operative time and mean intraoperative blood loss was similar between groups. No evident differences were observed in the stage of the disease between groups. The grade of differentiation was mainly grade 2 for all subgroups. The inflammatory tumoral infiltrate seems to be higher for the mixed group. Details regarding the comparison will be provided in *Table 4*.

Table 4. Subgroup analysis depending on the type of IPMN

		MD IPMN + PDAC	BD IPMN + PDAC	Mixed type IPMN + PDAC
Number[a]		1	8	6
Age[b]		59	63	61
Sex[a]	Male		6 (75%)	4 (66.66%)
	Female	1 (100%)	2 (25%)	2 (33.33%)
Surgery[a]	PD	1 (100%)	5 (62.5%)	3 (50%)
	DP			1 (16.66%)
	TP		3 (37.5%)	2 (33.33%)
Mean operative time[b]		360	272	262
Mean blood loss[b]		400	362.5	400
Stage[a]	IIA	1 (100%)	1 (12.5%)	2 (33.33%)
	IIB		6 (75%)	2 (33.33%)
	III		1 (12.5%)	2 (33.33%)
Grade of differentiation[a]	1		3 (37.5%)	
	2	1 (100%)	5 (62.5%)	5(83.33%)
	3			1 (16.66%)
Inflammatory tumoral infiltrate[a]	Mild		8 (100%)	3 (50%)
	Moderate	1 (100%)		3 (50%)
	Intense			

IPMN – intrapapillary mucinous neoplasia, PDAC – pancreatic ductal adenocarcinoma, BD – branch-duct, MD – main duct, PD – pancreatoduodenectomy, DP – distal pancreatectomy, TP – total pancreatectomy.
[a]Results are presented as absolute number and in brackets, percentage out of total. [b]Results are presented as a mean.

Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN

The comparison between the 3 cases with PDAC concomitant with IPMN versus PDAC derived from IPMN is detailed in *Table 5*. For the first group, the patients are younger, all patients had total pancreatectomies, the mean intraoperative blood loss was higher, and all patients had mild inflammatory tumoral infiltrate.

Discussion

Pancreatic ductal adenocarcinoma can arise from different precursor lesions such as IPMN, pancreatic intraepithelial neoplasia or mucinous cystic neoplasm. Intraductal papillary mucinous neoplasm is a rare cystic tumor of the pancreas, recognized as a pre-malignant lesion. The association between PDAC and IPMN is considered as a biologically distinct entity, with few studies discussing its characteristics (8,9,11). We have aimed to address this issue through an exhaustive retrospective analysis of the cases operated in our institution. Since information is scarce regarding the association of PDAC and IPMN, we have analyzed and discussed our results in comparison to the studies who reported and compared outcomes for IPMN versus PDAC.

Demographic Data

Our study cohort shows a male preponderance in both groups, which is confirmed by the reports in medical literature (8,12). The first group, referring to PDAC associated to IPMN, has a younger average age, with an average of 61.8 years old. Medical literature suggests that the age of diagnosis is usually similar between patients diagnosed with IPMN and PDAC; however, some reports present IPMNs usually arising in older patients (10,13). On the other hand, in our cohort of patients, patients diagnosed with PDAC associated from IPMN were slightly younger.

Intraoperative Data

The main surgical intervention performed, in our reports, was pancreatoduodenectomy for both groups. For the first group, we can

Table 5. Subgroup analysis depending on the relationship between IPMN and PDAC

		PDAC derived from IPMN	PDAC concomitant with IPMN
Number[a]		3	12
Age[b]		57	63
Sex[a]	Male	2 (66.66%)	8 (66.66%)
	Female	1 (33.33%)	4 (33.33%)
Surgery[a]	PD		9 (75%)
	DP		1 (8.33%)
	TP	3 (100%)	2 (16.66%)
Mean operative time[b]		272	274
Mean blood loss[b]		517	328
Stage[a]	IIA		4 (33.33%)
	IIB	3 (100%)	5 (41.66%)
	III		3 (25%)
Grade of differentiation[a]	1		3 (25%)
	2	3 (100%)	8 (66.66%)
	3		1 (8.33%)
Inflammatory tumoral infiltrate[a]	Mild	3 (100%)	8 (66.66%)
	Moderate		4 (33.33%)
	Intense		

IPMN – intrapapillary mucinous neoplasia, PDAC – pancreatic ductal adenocarcinoma, PD – pancreatoduodenectomy, DP – distal pancreatectomy, TP – total pancreatectomy.
[a]Results are presented as absolute number and in brackets, percentage out of total. [b]Results are presented as a mean

observe an important percentage of total pancreatectomies being performed, in one third of the cases. Therefore, a preference towards performing total pancreatectomy is seen in cases of PDAC associated to IPMN, just as in the case of surgical resection of IPMN (8,14,15). No evident differences were observed between the two groups regarding the rest of the intraoperative parameters, such as the type of reconstruction after pancreatoduodenectomy, mean operative time, mean blood loss or reintervention rate. The studies that compare the surgical outcomes of PDAC and IPMN do not report any differences in these parameters, as well. We need to mention the fact that a shorter operative time has been identified in the case of total pancreatectomies performed for PDAC associated to IPMN than in the case of solitary PDAC. An explanation for this difference might be the indication of a total pancreatectomy in PDAC, that is needed in larger tumors or in the case of chronic pancreatitis with severe alterations of the pancreatic parenchyma, compared to the indication of a total pancreatectomy in IPMN, that is due to infiltrative or multicentric tumors.

Histopathological Characteristics

When discussing the stage of the disease in both groups, we can observe a clear prevalence of stage IIB, which can constitute a bias in our discussion; nonetheless, Group 1 contained patients of more advanced disease, since no stage I patients were identified. Most tumors were moderately differentiated (G2) in both groups, but in the first group we had only very few patients with high-grade tumors. Lower tumor grades are usually reported in the cases of IPMN, compared to PDAC (8).

Regarding the perineural, perivascular and perilymphatic tumoral invasion, higher rates of positivity were registered in Group 1. This shows that tumors in the first group might have a more aggressive biological behavior. In the case of IPMNs, medical literature mentions the fact that perineural, perivascular and perilymphatic invasion are less often present compared to PDAC. (8)

Based on the standard histopathological evaluation of pancreatic tumors, we were able to include in our analysis a parameter regarding the tumoral microenvironment: the immunoinflammatory infiltrate. A mild inflammatory infiltrate was predominant for the first group, while a moderate inflammatory infiltrate was apparent for the second group. Since the complex role of the tumoral microenvironment is yet unknown and a deeper analysis of the subtypes of cells that form this microenvironment is needed, we cannot speculate what are the implications of these findings.

Most tumors had negative resection margins for both groups, but the percentage of R0 resection was higher in Group 1. This finding is consistent with the report of higher percentages of R0 resection in IPMNs compared to PDACs (8,15).

Survival Data

Interestingly, we have found that in our cohort, short-term mortality rates (90-day mortality) are higher, almost doubled, for Group 1. Long-term survival was as well, poorer for the first group compared to the second group. This fact raises the problem that a PDAC derived from IPMN might have worse prognosis, with a more aggressive evolution, compared to solitary IPMN.

The conclusion of the medical literature review is that while the overall survival of IPMN seems to be better than for the PDAC, survival is highly dependent on the stage of the disease and lymphatic node spread (8,15-20). However, we need to take into consideration that the patients diagnosed with IPMN associated to PDAC included in our study had aggressive histopathological characteristics that are known to influence long-term survival.

IPMN Subgroup Analysis

Branch-duct, main-duct, or mixed type IPMN

Main-duct and mixed type IPMNs are known

to have a higher rate of malignant transformation, surgical resection being the treatment of choice. On the other hand, branch-duct IPMNs are reported to have a lower incidence of carcinogenesis and are usually referred to surveillance programs (21,22).

We have intended to analyze our small cohort of patients, based on the subtype of the IPMN. First, we must mention that the patient sample is small (15 patients), being an important limitation when trying to draw definitive conclusions. More than 50% of the patients had branch-duct IPMNs, which shows once again the possibility of carcinogenesis even in this subtype of IPMN. No clear differences were shown in the histopathological or surgical factors, but there is a tendency towards a more intense inflammatory infiltrate for mixed type tumors.

Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN

Information regarding the differences between these two entities: PDAC derived from IPMN and PDAC concomitant to IPMN is difficult to find, given the fact that the definition of the association of these two tumors are not always well presented or applied, and not many cases are presented (8).

Only three patients were diagnosed with PDAC concomitant to IPMN; therefore, an exhaustive analysis based on this characteristic is difficult to be done. However, some conclusions can be seen: these 3 patients were younger compared to the others and all had undergone total pancreatectomies (probably due to the multifocal character of the tumor). Also, in these cases, a mild inflammatory infiltrate was registered in all cases.

Conclusion

PDAC associated with IPMN should be discussed and treated as a separate entity since its epidemiological, surgical, and histopathological characteristics show slight, but important differences when compared to primary PDAC.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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