

Microscopically positive (R1) resections do not affect survival in pancreatic head cancer



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BACKGROUND: Obtaining negative microscopic resection margins (R0) in cephalic duodenopancreatectomy (CDP) is the gold standard. Resection line involvement at microscopic histopathological examination (R1) could change prognostic unfavorable. Regarding R1 resections in CDP (data from the literature show rates between 20-80%), we considered it necessary to perform a study in Regional Institute of Gastroenterology and Hepatology "Prof. Dr. O. Fodor" Cluj-Napoca.

METHODS: Here we present the results of a retrospective study carried out between January 2012 - December 2013 in our Institute. This study includes 63 patients with pancreatic head resections for pancreatic cancer. The circumferential soft tissue margin, the pancreatic transection margin, the bile duct and duodenum/stomach margins were analyzed. We investigated the incidence of R1 and its impact on the survival rates after oncologic pancreatic resections using a non-standardized pathologic routine protocol. R1 status was defined as the distance of the tumor from the resection margin of ≤ 1 mm.

RESULTS: Pancreatic ductal adenocarcinoma (PDAC) was diagnosed in 93.65 %. The R1 rate was 36.5 % (23 cases). The circumferential margins were most commonly involved as R1 (91.3%). No statistically significant differences were found between patients with R1 to those with R0 ($p \geq 0.1$) regarding 3-year survival.

CONCLUSIONS: Survival for pancreatic head cancer at 3 years is not influenced by the margins of resection (R1/R0). Microscopic resection margin involvement is not an independent marker of survival.

KEY WORDS: Circumferential margins, Nonstandardized pathologic protocol, Pancreatic ductal adenocarcinoma, Positive margins R1 Survival

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with a 5-year survival rate of less than 5% by the time of diagnosis, being one of the most lethal

diseases¹ and is the fourth most common cause of cancer death in Europe and the USA².

The only potentially curative treatment still remains resection, despite improved multimodal cancer treatment protocols, including chemo, radio and immunotherapy³. By the time the diagnosis is established most patients are inoperable. Even in cases where a curative resection can be performed the 5-year survival rates are approximately 20%, with a median survival of approximately 18 months⁴⁻⁶ with an additional benefit in patients receiving adjuvant treatment⁷⁻⁹. Unfortunately most patients develop local or distant metastasis after resection¹⁰, which

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could reflect the presence of microscopic residual disease at the time of resection^{11,12}. Resection status is one of the major factors influencing patient survival rates, therefore, complete surgical resection of the primary tumor (as we mentioned before) represents the only curative treatment option.

Obtaining negative microscopic resection margins (R0) in cephalic duodenopancreatectomy (CDP) is the gold standard. Unfortunately, data from the literature show an incidence between 20-80% of R1 (positive microscopical margins)^{5,9,13-23}. The lack of standardized pathology reports for pancreatic cancer is a possible reason for this discrepancy. Detailed accepted standardized protocols are still lacking, even though general guidelines for the processing of pancreatic specimens have been established¹³.

The definition of R1 is a continuing problem. R1 was defined by the International Union Against Cancer (UICC) as a microscopic tumor at the edges of the surgical specimen²⁴. However the more recent protocols of the British Royal College of Pathologists²⁵ consider the presence of tumor cells ≤ 1 mm from a circumferential margin or surface of the resected specimen as an involved margin.

Regarding the differences of R1 in the different studies, we considered it necessary to perform a study in our Institute to evaluate the rate of R1 and the its impact on survival.

Materials and Methods

Here we present a single center experience with 63 cases of pancreaticoduodenectomies for pancreatic cancer carried out between January 2012 - December 2013.

Data was collected retrospectively from our Institute's electronic database. We included only patients with pancreatic head cancer revealed at the histopathological examination, while patients with pancreaticoduodenectomies for duodenal tumors, ampullary tumors or tumors of inferior main biliary duct were excluded from the study. The assessment of resection margins (RM) included the circumferential soft tissue margins, pancreatic transection margin, the bile duct margins and duodenum/stomach margins.

All these resection margins were analyzed. Examinations of the entire surgical specimens were carried out under the supervision of senior pathologists following non-standardized protocols. The location, histological tumor type, tumor size, and also the number and site of lymph node involvement were defined. Vascular, lymphatic, and perineural invasion were reported as well.

R1 was defined when the distance of the tumor from the resection margin was ≤ 1 mm. A curative R0 resection was defined as a surgical RM or organ surface without tumor cell infiltration.

PATHOLOGICAL EXAMINATION OF RESECTED SPECIMENS

The macroscopic and histological examinations of the surgical specimens were carried out in the anatomopathological department following nonstandardized protocols. The specimen of cephalic duodenopancreatectomy consists of stomach, duodenum, head of the pancreas, and part of the common bile duct \pm the gallbladder. When the specimen is unfixed, it is opened along the greater curvature of the stomach, across the anterior wall of the pylorus and down the outer curvature of the duodenum.

After the specimen is fixed, each component of the specimen is measured. The mucosa of the stomach, duodenum and papilla are carefully inspected. Next, the margins are identified: bile duct margin, proximal margin (gastric or duodenal), distal margin (distal duodenal), pancreatic neck resection margin and uncinate process/retroperitoneal margin (nonperitonealized surface of the uncinate process). Before cutting the specimen, a section of each margin (shave section) is submitted. Particularly, the uncinate process margin is submitted entirely, making perpendicular sections.

Next, the common bile duct is opened using scissors, extending the incision longitudinally down through the ampulla of Vater and noting any strictures or exophytic masses in the bile duct and in the ampulla of Vater. The mucosa of the common bile duct is inked with a distinct color because without painting the bile duct, it can be almost impossible to distinguish the bile duct from the pancreatic duct microscopically. Then the pathologist identifies the main pancreatic duct and places a probe into it. After that a section is made along the plane of both pancreatic duct and bile duct margins, so the ampulla is bisected and the relationship of any mass with the ampulla, common bile duct, main pancreatic duct, duodenal wall and pancreas can be observed.

If any mass is identified, the lesion is described: size, color, consistency, cyst and the relationships with anatomic sites. Sections that demonstrate the relationships of the mass with each component of the specimen are included. Usually one section of the tumor for each 1 cm of maximum dimension is submitted. Non-lesional pancreatic parenchyma is examined and submitted. Next, each identified regional lymph node is included.

Results

CLINICAL DATA

A total of 63 patients including 37 men (58.73%) and 26 women (41.27%), with the youngest of 35 and the oldest of 84 years of age, were included in a cohort study.

54 patients (85.71%) underwent a standard Kausch-Whipple CDP, 3 (4.76%) pylorus-preserving CDP, and 6 patients (9.52%) a total pancreatectomy. In 7 patients

(11.11%), a resection of the portal vein and/or the superior mesenteric vein was performed.

In 40 cases (63.49%) a biliary drainage was made before pancreatic head resection: 15 cases (37.5) with endoscopic biliary stenting; 14 cases (35%) a laparoscopic cholecystostomy was performed; 10 cases (25%) with biliodigestive by-pass; 1 case (0.25%) with an ultrasound guided percutaneous transhepatic bile duct drainage.

In 20 cases (31.7%) a jejunostomy feeding tube was used to provide hyperproteic nutrition for the patients on the first day after surgery.

PATHOLOGICAL DATA

PDAC was diagnosed in 59 patients (93.65 %), the remaining 4 (6.35 %) were pancreatic neuroendocrine tumors. The median tumor size was 3 cm (IQR, 2–8). 50 cases (79.36%) were pT3, 10 cases (15.87%) were pT2 and 3 cases (4.76%) were pT1. Forty patients (63.5%) had metastases in regional lymph nodes (pN1), thirty-five (55.55%) displayed lymphatic invasion and 15 (23.8%) perineural invasion (Table I).

According to AJCC 7th ed., 2010, 40 (63.5%) cases was stage II B, 16 (25.39%) cases stage IIA, 4 (6.34%) cases IB and 3 (4.76%) cases IA (Table II).

Resection Margin Status

Positive microscopic resection margin involvement (R1) was present in 23 cases (36.5%), with the most commonly involved margin being the circumferential margin

TABLE I - Pathological data.

Pathological Data	Value	Percent
pT1	3	4.76%
pT2	10	15.87%
pT3	50	79.36%
pN0	23	36.50%
pN1	40	63.50%
Lymphatic Invasion	35	55.55%
Vascular Invasion	15	23.80%
Median tumor size (cm)	3	
Range tumor size (cm)	2-8	

TABLE II - Staging according to AJCC 7th ed., 2010.

Stage	Patients
IA	3
IB	4
IIA	16
IIB	40

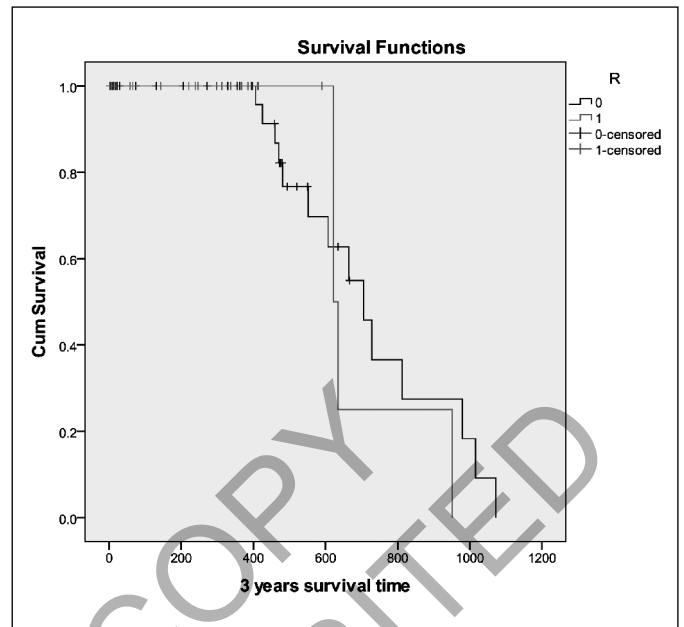


Fig. 1: The Kaplan-Meier survival function R0/R1 at 3 years.

(21 cases; 91.3%) and 2 (8.7%) cases with positive microscopic pancreatic transection margin.

Table 3 present survival rate at 3 years; in order to see whether important differences exist between patients with R0 and R1 in terms of survival probability we have applied the Kaplan-Meier survival analysis. Fig. 1 shows the Kaplan-Meier survival function for the two groups of patients. As it can be seen, the type of R does not really significantly influence the probability of survival of the patients in the sample. For a better assessment of this aspect we have also run some comparison analyses between the two groups. Table IV presents the comparative descriptive statistics for the two groups.

Based on these results we can conclude that no significance difference exists in terms of average values between the two groups. Table IV, V also present statistics related to the median value, again higher values being found in the case of the R0 group. Based on this parameter, half of the R0 patients have survived at maximum 706 days, while the same share of R1 patients have survived at the very most 622 days.

In order to be sure that no significant statistical difference exists between the survival probabilities of the two

Table III - Survival rate at 3 years.

Type R	Patients	Patients alive	Patients deceased	
			Number	Percent
R0	40	14	26	65.0%
R1	23	4	19	82.6%
Overall	63	18	45	71.4%

TABLE IV - Mean and median survival for the two groups.

R	Estimate	Std. Error	Meana 95% Confidence Interval		Estimate	Std. Error	Median 95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
0	724.111	56.786	612.811	835.411	706.000	62.043	584.395	827.605
1	707.500	81.224	548.300	866.700	622.000	.	.	.
Overall	724.081	46.716	632.514	815.643	665.000	61.665	544.137	785.863

TABLE V - Percentiles values for the two groups.

R	25.0%		50.0%		75.0%	
	Estimate	Std. Error	Estimate	Std. Error	Estimate	Std. Error
0	979.000	155.913	706.000	62.043	552.000	70.468
1	635.000	142.461	622.000	.	622.000	.
Overall	951.000	124.136	665.000	61.665	607.000	61.957

TABLE VI - The overall comparison test.

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.083	1	.773
Breslow (Generalized Wilcoxon)	.299	1	.584
Tarone-Ware	.031	1	.860

groups, we have also applied the overall comparison test. The three tests in table 6 all have very high significance values (0.773, 0.584 and 0.860). As they are all much higher than 0.1, we can conclude that results found in Tables IV, V are true. There is no significant difference between the survival curves of the two groups of patients. Based on the present sample we can conclude that the R type is not a significant factor of influence for the survival of the patient. The fact of having R0 or R1 is not significantly affecting the probability of survival for the analyzed sample of patients. Other more important factors can interfere, like lymph node metastasis, tumor grading, advanced T stage, vascular and perineural invasion.

Discussion

For a long time, pancreatic surgeons have considered R1 as a key index for poor technical performance, being not aggressive and meticulous enough to achieve complete tumor clearance^{3,26-28}. Recent studies^{3,13,29,30} have shown that a high rate of R1 resections in pancreatic cancer is a marker of high-quality pathology and not a low-quality surgery. Since Royal College of Pathologists (RCP) suggested to declare R1 when tumor cells are found within 1 mm of the RM, in contrast with international Union Against Cancer (UICC) (defined R1 as the microscopic presence of tumor cells at the surface of the

resection margin), this lead to the development of standardized protocols where the margins of pancreas were redefined, increasing the rates of R1 from around 20% to 80%. In this study we present the results of a non-standardized protocol for specimens of the CDP; to test the hypothesis that a standardized histopathological examination increases the rate of R1, we consider that a new study (prospective) should be propose, with a standardized histopathological protocol where the entire resection margins of the specimens to be inked and analyzed (along with the pancreatic transection margin, the bile duct, stomach/duodenum margins, and the circumferential soft tissue margins which will be divided in medial, anterior surface, superior, and posterior). The impact of margin status on the outcome is still controversial. In our study we put the accent on survival, and the data was comparable with other studies (no differences between R1 and R0)^{5,9,13-23}. It seems that microscopic margins involvement is not an independent marker for survival. Other pathological factors could play an important role in survival; like advanced T stage, lymph node metastasis, tumor grading, and vascular and perineural invasion²⁹. Still, the assessment of R1/R0 is important as some studies demonstrated that in cases of R1, radiochemotherapy could be useful³¹.

Conclusion

We can conclude that survival for pancreatic head cancer at 3 years is not influenced by the margins of resection (R1/R0), and that microscopic margin involvement is not an independent marker of survival. New protocol with standardized histopathological must be adopted to develop a new study in order to test the hypothesis if standardized examination increases the rate of R1.

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Riassunto

Il "gold standard" prognostico della duodenocefalopancreasectomia (CDP) è rappresentato dal raggiungimento di margini di resezione microscopicamente esenti da cellule neoplastiche (R0). La presenza di cellule neoplastiche sulla linea di resezione a livello microscopico (R1) può rendere sfavorevole la prognosi. Per quanto concerne le resezioni R1 nella CDP (ed i dati della letteratura mostrano un'incidenza tra il 20 e 80%) ci hanno fatto considerare necessario uno studio presso il Regional Institute of Gastroenterology and Hepatology "Prof. Dr. O. Fodor" Cluj-Napoca.

Vengono qui presentati i risultati di uno studio retrospettivo condotto tra Gennaio 2012 e Dicembre 2013 nel nostro istituto.

Lo studio ha riguardato 63 pazienti sottoposti a resezione pancreatica per cancro, analizzando i margini circostanti dei tessuti, il margine di transezione pancreatica, i margini del dotto biliare, del duodeno e dello stomaco, alla ricerca dell'incidenza di R1 e il relativo impatto sulla sopravvivenza dopo resezione oncologica del pancreas usando un protocollo anatomopatologico non standardizzato. La condizione di R1 è stata definita come la distanza del tumore dal margine di resezione ≤ 1 mm. L'adenocarcinoma duttale del pancreas (PDAC) è stato diagnosticato nel 93,65% dei casi. L'incidenza di R1 è stata del 36,5% (23 casi). I margini circostanti erano maggiormente coinvolti come R1 (91,3%). Non è stata riscontrata alcuna differenza statisticamente significativa tra pazienti R1 ed R0 ($p \geq 0,1$) riguardo una sopravvivenza di 3 anni.

Si conclude che la sopravvivenza a 3 anni per un carcinoma della testa pancreatica non è influenzata dai margini di resezione (R1/R0), e dunque il coinvolgimento microscopico dei margini di resezione non è un marker indipendente riguardo alla sopravvivenza.

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