

Impact on Long-term Survival of a Standardized Histopathological Protocol on the R1 Incidence in Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma

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Abbreviations:

PDAC: Pancreatic Ductal

Adenocarcinoma;

PD: Pancreatoduodenectomy;

TP: Total Pancreatectomy;

OS: Overall Survival;

R1: microscopic positive resection
margins;

R0: negative resection margin;

G: Grading;

IQR: Interquartile Range;

HR: Hazard Ratio;

TNM: Tumor Node Metastasis;

UICC: International Union Against
Cancer;

Rezumat

Impactul asupra supraviețuirii pe termen lung a unui protocol histopatologic standardizat asupra incidenței R1 în duodenopancreatectomie cefalică pentru adenocarcinomul ductal pancreatic

Introducere: Adenocarcinomul ductal cefalo-pancreatic este o patologie cu un prognostic extrem de infaust, având ca singură opțiune terapeutică cu scop curativ rezecția chirurgicală, în asociere cu chimioterapia. Scopul acestui studiu este de a evalua influența utilizării unui raport histopatologic standardizat în duodenopancreatectomie cefalică (DPC) asupra incidenței marginilor R1 și impactul acestora asupra supraviețuirii pe termen lung.

Material și Metode: Am inclus 116 pacienți internați la Institutul Regional de Gastroenterologie și Hepatologie Prof. Dr. O. Fodor Cluj Napoca, care au beneficiat de duodenopancreatectomie cefalică pentru adenocarcinom ductal cefalo-pancreatic în perioada ianuarie 2012 – mai 2017. Pacienții au fost împărțiți în două grupuri: 59 de pacienți pentru care a fost utilizat un protocol histopatologic nestandardizat și 57 de pacienți pentru care a fost implementat un protocol standardizat. O margine a fost considerată microscopic pozitivă (R1) atunci când celulele tumorale erau prezente la ≤ 1 mm de marginea de rezecție.

Rezultate: Procentul de margini R1 în primul grup de pacienți a fost de 39%, în timp ce în al doilea grup a fost de 68,4%. Rata medie

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AJCC: American Joint Committee on Cancer;
RCP: British Royal College of Pathologists;
SMA: Superior Mesenteric Artery;
SMV: Superior Mesenteric Vein;
PV: Portal Vein.

de supraviețuire a fost asemănătoare în cele două grupuri, fără diferențe semnificative statistice, dar în studiul prospectiv pacienții cu margini R1 au avut o supraviețuire general semnificativ statistic mai mică comparativ cu pacienții cu margini de rezecție R0 (p-value = 0,03).

Concluzie: Folosirea unui protocol standardizat histopatologic în DPC pentru adenocarcinomul ductal cefalo-pancreatic duce la o creștere semnificativă statistic a marginilor de rezecție R1, iar atunci când se folosește un protocol standardizat histopatologic aceste margini (R1) influențează negativ supraviețuirea pe termen lung. Mezopancreeasul este marginea de rezecție cea mai des R1 atunci când se folosește un protocol standardizat histopatologic.

Cuvinte cheie: adenocarcinom ductal pancreatic, duodenopancreatctomie cefalică, margini de rezecție R1, raport histopatologic standardizat, supraviețuire

Abstract

Background: Pancreatic Ductal Adenocarcinoma (PDAC) is a pathology with a very poor prognostic, the only curative treatment option being surgery, in association with chemotherapy. This study aims to assess the influence that the use of a standardized pathology report after a pancreaticoduodenectomy (PD) has on the R1 margins rate and the impact that this has on long term survival.

Material and Methods: We included 116 patients admitted to the Regional Institute of Gastroenterology and Hepatology Prof. Dr. O. Fodor Cluj Napoca, who underwent PD for PDAC (Pancreatic Ductal Adenocarcinoma) between January 2012 and May 2017. We divided them in two groups: 59 patients for which a non-standardized histopathological protocol was used and 57 patients for which a standardized protocol was implemented. We considered a margin to be R1 when there were tumor cells at ≤ 1 mm from the resection margin.

Results: The R1 percentage in the first group of patients was of 39%, while the R1 resection rate in the second group was of 68.4%. The median survival rate was similar in the two groups, with no statistically significant difference between them, but in the prospective study when comparing R0 vs R1 margins there was a statistically differences in 5 year OS with a p-value = 0.03.

Conclusion: The use of a standardized pathology report reveals a significant increase in R1 resection rates. Also study revealed not only increasing R1 incidence when using a standardized histopathology report, but also that those margins (R1) playing a determinant role in 5-year OS. The mesopancreeas is the most frequently R1 resection margin.

Key words: pancreatic ductal adenocarcinoma, pancreatoduodenectomy, R1 resection margins, standardized histopathology report, survival

Introduction

According to the American Cancer Society in 2023 pancreatic cancer is estimated as the 10th most frequent cancer in men and the 8th most frequent in women in the USA. It is also known to be one of the most aggressive malignant tumors, occupying the 7th place in the cancer related deaths worldwide (1,2).

The 5-year survival rate for pancreatic cancer is estimated at 12%, for all stages and histopathological types, but only at 9% for the pancreatic ductal adenocarcinoma (PDAC), which represents approximately 90% of the malignant tumors of the pancreas (3-6).

PDAC is therefore an extremely lethal disease, with a poor prognosis and a complex management. The only treatment with curative intent for the pancreatic adenocarcinoma continues to be surgery, with a 10-25% five-year survival rate and an overall survival (OS) of 11-20 months (slightly higher with adjuvant therapy)(7,8).

Only 15-20% of the diagnosed PDAC of the head of the pancreas are considered resectable, the golden standard procedure being pancreaticoduodenectomy (PD) with or without vascular reconstruction, alongside chemotherapy. An oncologic surgeon's desideratum will always be to obtain a R0 resection margin. One of the most discussed topics in the case of pancreatic surgery is how this influences the overall survival and local recurrence rates (8).

Multiple studies have been conducted in order to assess this, but the results vary a lot. There are multiple factors that influence these variations. One of them is the difference in the definition of R0/R1 margins. While some specialists consider a microscopic positive resection margin (R1) when malignant cells are present at the edge of the resection margin (R1 = 0 mm), others consider a margin to be R1 when there are malignant cells at 1 mm or at less than 1 mm from the tumor (R1 ≤ 1 mm)(6,9,10).

Other important factors while assessing the radicality of the procedure are which of the resection margins are taken into

consideration, as well as the protocol used by the pathologists to examine the specimen.

In our study, the aim was to assess if a standardized pathology report increases the percentage of R1 resection in PD performed for PDAC, as Verbeke et al. have suggested for the first time in 2006 and to evaluate the impact that R1 resection margin has on the overall survival (11). A second objective was to identify the factors that lead to R1 resection margins.

Materials and Methods

Patients enrolled in our institute's electronic database who underwent PD or total pancreatectomy (TP) for cancer of the head of the pancreas between January 2012 and May 2017 were identified. From these, we included the 116 patients which had a histopathological confirmation of PDAC, while any other pathologies, like tumors of the ampulla of Vater, duodenum or main biliary duct, were excluded.

We then divided the 116 patients in two groups. The first group consists of 59 patients who underwent PD between January 2012 and May 2014, for which the histopathological report was not based on a standardized examination protocol and the data was collected retrospectively. The second group is represented by 57 patients who underwent PD between June 2014 and May 2017, for which a standardized protocol of examination was implemented, as follows: right after the procedure each resection margin was identified and inked as shown in *Fig. 1* and *Fig. 2*. The following margins were assessed: transection margins (pancreatic neck/duct, bile duct, proximal duodenal/stomach and jejunal margin), vascular resection margins (for cases in which a venous resection was performed) and circumferential margins. The latter included the anterior, posterior, superior and medial (mesopancreas) margins. The medial margin involved the tissue lying posteriorly to the superior mesenteric vein and to the right of the superior mesenteric artery. The resection margins are highlighted in *Fig. 3*



Figure 1. Inked resection margins (anterior view).

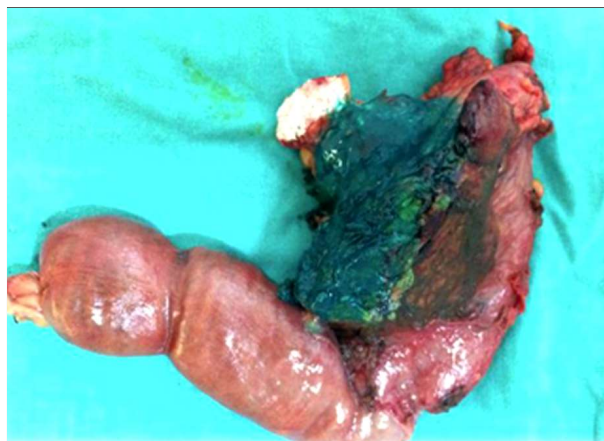


Figure 2. Inked resection margins (posterior view).

and *Fig. 4*. The data for the second group of patients was collected prospectively.

From the lot of 116 patients only one received neoadjuvant therapy, while post-operatively a recommendation for adjuvant therapy was made for all of the patients, according to the UICC indications (7th edition) (12)

Most of the patients underwent Whipple or Traverso-Longmire procedure, but in a few cases, it was also necessary to perform a TP. The pancreato-digestive reconstruction was

based on the surgical team's preference (pancreato-jejunal or pancreato-gastric anastomosis). For the cases with venous invasion, a tangential or segmentary vascular resection was performed. Lymphadenectomy was conducted according to the standards in all cases and it included the following lymph node stations: anterior, posterior, celiac trunk, common hepatic artery and the mesopancreas up to the right border of the superior mesenteric artery.

We considered a margin to be positive (R1)

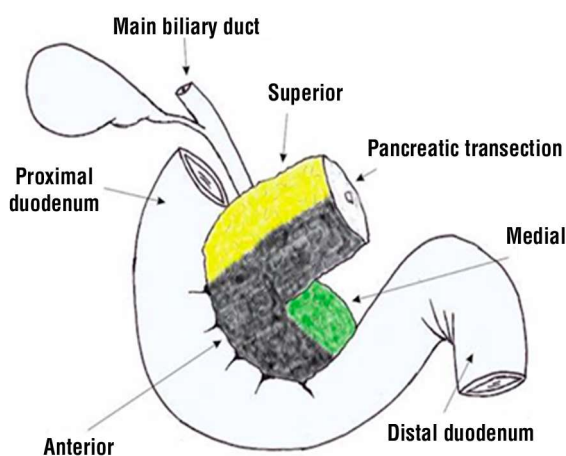


Figure 3. Schematic representation of the resection margins (anterior view)

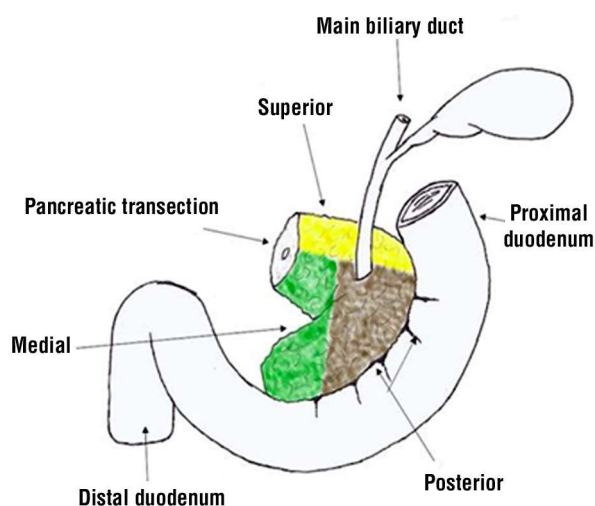


Figure 4. Schematic representation of the resection margins (posterior view).

when cancer cells were identified at ≤ 1 mm from the resection margin. A negative (R0) margin was defined as the lack of tumor cells within 1 mm of the resection margins.

Tumor location, grading and size were reported. The TNM stage was then established, according to the 8th edition of the AJCC. We also reported the vascular, lymphatic and perineural invasion (13).

Variables were collected in a Microsoft Excel database. Comparisons between the groups and within the groups were performed using the IBM SPSS v26.0 software. Qualitative values were analyzed using the Pearson Chi-Squared test. Quantitative values were addressed regarding the normality of the distribution, which was tested using the

Shapiro-Wilk test. Normally distributed values were compared using the T-test for independent variables. Non-normally distributed values were compared using Mann-Whitney U test. Survival rates were evaluated using the Kaplan-Meier curve and compared using the log-rank tests. Multivariate analysis was performed using Cox Regression. The value of statistical significance was $p < 0.05$.

Results

Patients and Tumor Characteristics

Demographic data, tumor related characteristics, as well as a comparison between the two groups were highlighted in *Table 1*. In the

Table 1. Association between clinicopathological parameters and resection margin status for the two groups of evaluated patients.

Parameters	Resection margins						Between groups
	Standardized protocol			Non-Standardized protocol			
	R0	R1	p-value	R0	R1	p-value	
Number of patients	18 31.60%	39 68.40%	-	36 61%	23 39%	-	0.001
Mean age	63.28 (±8.63)	62.03 (±9.04)	0.624	66.25 (±9.54)	61.48 (±8.17)	0.123	0.418
Age group							
< 65	9	23	0.528	19	14	0.538	0.928
≥ 65	9	16		17	9		
Tumor diameter (cm)	2.4 (± 0.68)	3.01 (±0.83)	0.008	3.2 (±1.21)	3.09 (±0.99)	0.834	0.068
Tumor diameter in the two groups							
< 2 cm	7	6	0.085	10	7	0.954	0.721
2-5 cm	12	32		24	15		
> 5 cm	-	-		1	1		
Gender							
Male	8	22	0.4	23	12	0.373	0.467
Female	10	17		13	11		
T stage							
1	2	0	0.394	2	0	0.311	0.736
2	3	5		6	3		
3	12	34		28	20		
4	1	0		0	0		
N stage							
0	7	7	0.113	18	3	0.001	0.192
1	11	32		18	20		
L stage							
0	7	4	0.02	20	5	0.005	0.005
1	11	35		16	18		
V stage							
0	11	20	0.484	33	11	0	0.02
1	7	19		3	12		
Grading (G)							
1	7	8	0.139	7	1	0.031	0.013
2	9	21		18	10		
3	3	9		8	11		
4	0	0		1	3		

R0 – negative resection margin; R1 – microscopic positive resection margin. Statistically significant results are highlighted.

standardized protocol group, tumor size and lymphatic invasion were factors that independently influenced the occurrence of R1 resection margins. In the non-standardized group N stage, lymphatic invasion, vascular invasion and tumor grading were identified to increase the percentage of R1 resection margins (*Table 1*). The comparison between the two groups showed three statistically significant factors that influence the R1 incidence: the vascular invasion ($p = 0.02$), lymphatic invasion ($p = 0.005$) and the tumor grading ($p = 0.01$).

Resection Margins

There were statistically significant differences in the incidence rate of R1 resections between the standardized and non-standardized protocol (39 patients - 68.4% vs. 23 patients - 39%, $p = 0.001$) as presented in *Table 1*. Overall, there were 62 patients with R1 margins: 39 (63%) cases with only one positive margin and 23 (37%) cases with two or more R1 margins. The involved margins are highlighted in *Table 2*. In the standardized group, most of the cases presented with invasion of the medial margin, followed by the pancreatic margin, then more than 1/6th with a positive anterior margin.

In the non-standardized group, there were 20 patients with only one positive margin and 3 patients with two or more R1 margins, while in the standardized group there were 19 patients with one positive margin and 20 patients with more R1 margins, with a statistically significant difference ($p = 0.003$).

Out of the 13 cases in which a venous resection was performed (7 tangential portal resections, 2 segmentary portal resections, 1 tangential SMV - superior mesenteric vein resection and 3 segmentary SMV resections), 5 cases had R0 margins and 8 had tumor invaded margins, the difference being not statistically significant ($p = 0.43$).

Survival Data

The 1, 3 and 5-years survival rates were analyzed, as well as median survival rates

Table 2. R1 resection margin localization (*only for the non-standardized protocol).

R1 resection margins	Non-Standardized Protocol	Standardized Protocol
Pancreatic transection	3 (5.7%)	13 (22.8%)
Medial	-	29 (50.9%)
Posterior	2 (3.8%)	8 (14%)
Anterior	-	10 (17.5%)
Superior	-	2 (3.5%)
Circumferential *	20 (38.4%)	-
Bile duct	1 (1.9%)	2 (3.5%)

* Circumferential resection margin was divided in the prospective group: anterior, posterior, superior and medial (mesopancreas) margins.

regarding resection margins status, the number of positive resection margins, T stage, N stage, the presence of lymphatic or vascular invasion and tumoral grading, as highlighted in *Table 3*. Overall survival rate was 7.8% with a median survival duration of 15 months (IQR – interquartile range, 12.32 – 17.6).

Table 3. Overall survival rate based on multiple parameters

Parameters	OS/Events (%)	P-value (log-rank)	Median survival (months)
T stage			
T1	1/4 (25%)	0.56	16
T2	1/17 (5.9%)		13
T3	7/94 (8.4%)		15
T4	0/1 (0%)		16
N stage			
N0	6/35 (17.1%)	0.27	22
N+	3/81 (3.7%)		13
L status			
L0	5/36 (13.9%)	0.04	16
L1	4/80 (5.0%)		13
V status			
V0	5/75 (6.7%)	0.81	16
V1	4/41 (9.8%)		15
G status			
G1-2	9/81 (11.1%)	0.001	18
G3-4	0/30 (0%)		16
R status			
R0	7/62 (11.3%)	0.16	16
R1	2/52 (3.7%)		13
Number of margins			
0	7/57 (13.0%)	0.07	16
1	2/39 (5.1%)		14
2+	0/23 (0%)		13
Staging			
IA	2/6 (33.3%)	0.03	16
IB	0/5 (0%)		14
IIA	4/23 (17.4%)		22
IIIB	3/82 (3.7%)		13

Statistically significant results are highlighted.

Table 3 highlights the overall survival rates based on the histopathological parameters, as well as the tumoral staging. When accounting for independent analysis, the only statistically significant factors influencing the overall survival are the lymphatic invasion (16 vs. 13 months, $p=0.01$), the tumoral staging (14 vs. 22 vs. 13 months, $p=0.03$) and tumoral grading (18 vs.

16 months, $p=0.001$). The median survival rate in patients with R0 was 16 months (IQR, 12.6 – 18.8), whereas in R1 patients, it was 13 months (9.6 – 16.03), with no statistically significant difference being recorded ($p=0.17$). Figs. 5, 6 and 7 exhibit the overall survival curves (5-year survival) of each group and respectively of the whole lot of 116 patients, depending on the resection margin status.

Figure 5. Overall survival of the whole lot of patients with R0 vs. R1 resections (p -value = 0.171).

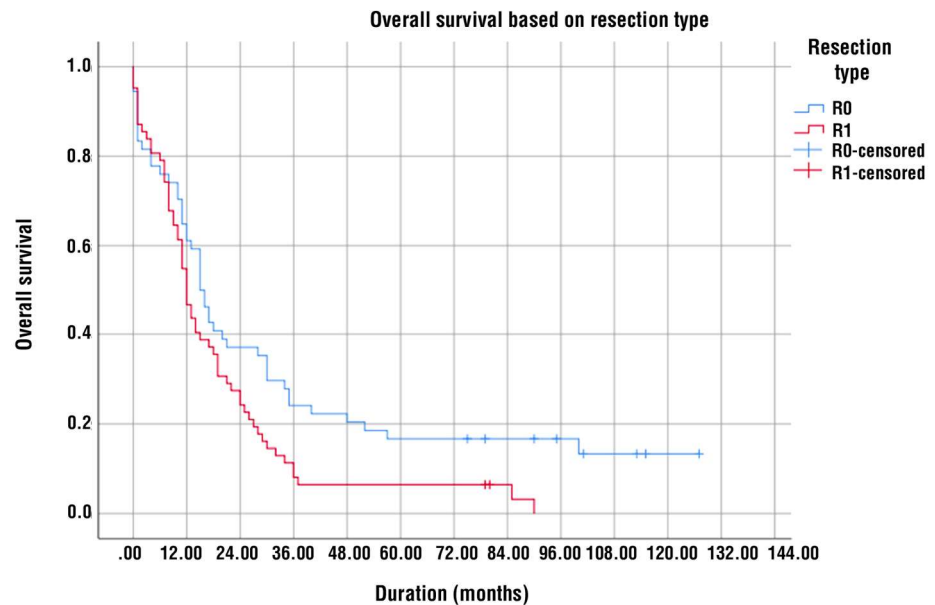


Figure 6. Overall survival for the standardized group (prospective analysis) with R0 vs. R1 resections (p -value = 0.03).

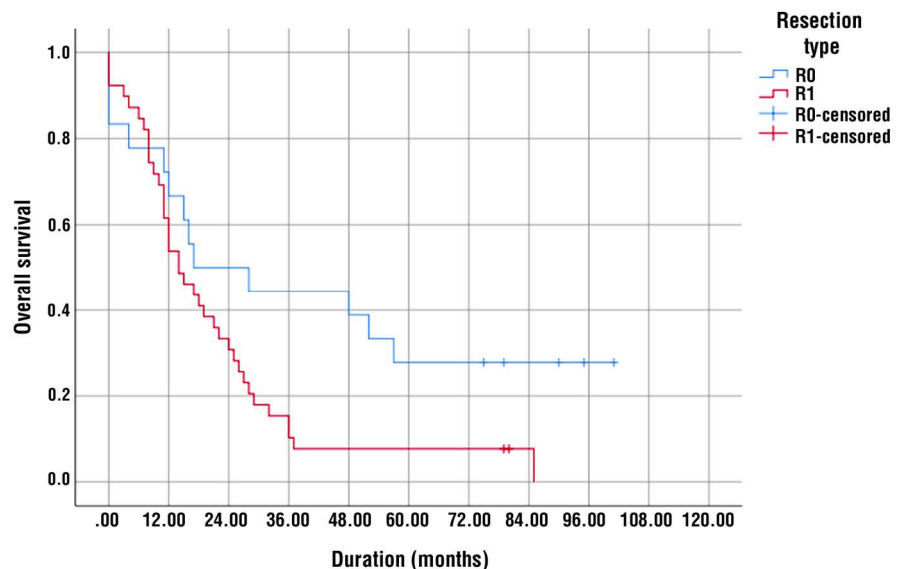
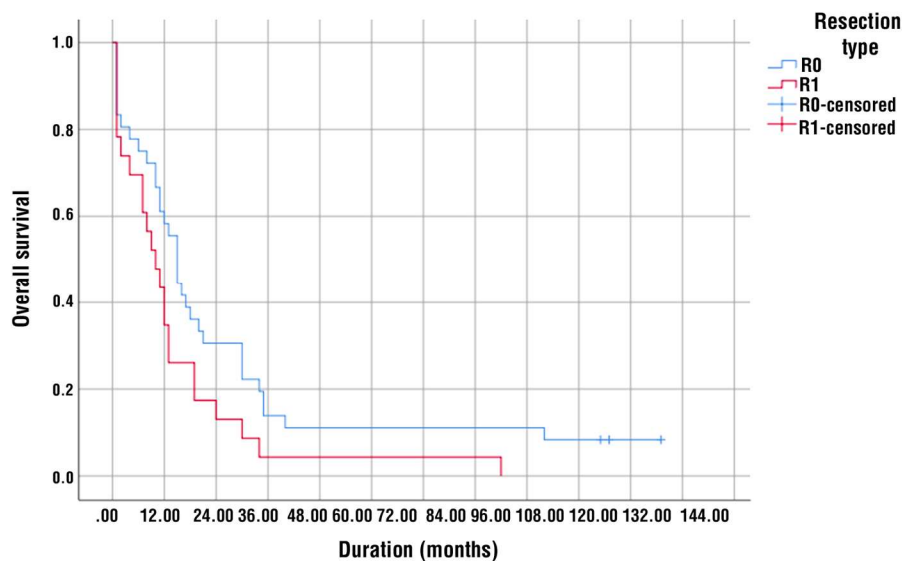


Figure 7. Overall survival for the non-standardized group (retrospective analysis) with R0 vs. R1 resections (p-value= 0.309).



When comparing R0 vs R1 margins in the entire cohort (116 patients) we found no statistically differences between the groups regarding OS (p-value = 0.171, *Fig. 5*). The same results was in the retrospective study when comparing R0 vs R1 margins groups (p-value =). But in the prospective study there was a statistically differences between R0 and R1 margins regarding OS with a p-value = 0.03 (*Fig. 6*).

A comparison between the most frequently discovered positive resection margins within the standardized group was performed regarding the overall survival. Statistically significant differences were found between the patients with positive medial margin compared to the rest of the group (p=0.02). In comparison, there were no statistically significant differences between the patients with positive pancreatic margin and the rest of the group (p=0.93). When comparing within the patients with at least 1 positive margin, there were no statistically significant differences between the patients with one of the positive margins mentioned above or both margins (p=0.20).

Among the patients with a R1 resection we also analyzed if the overall survival is influenced by the number of involved margins.

For the cases in which only one margin was positive the median survival rate was of 14 months, while for those with two or more positive margins it was of 13, with no statistically significant difference (p = 0.834).

When accounting for the multivariate analysis, the statistically significant factors highlighted were N staging (HR = 5.19, CI 95% = 1.17 - 23.00, p=0.03), number of positive margins (HR = 2.65, CI 95% = 1.28 - 5.49, p = 0.01) and tumoral grading (HR = 2.50, CI 95% = 1.09 - 5.72, p = 0.03). Details are highlighted in *Table 4*. The overall survival of the patients with only one positive margin in comparison to the ones with two or more positive margins is presented in *Fig. 8* and *Fig. 9*.

Discussion

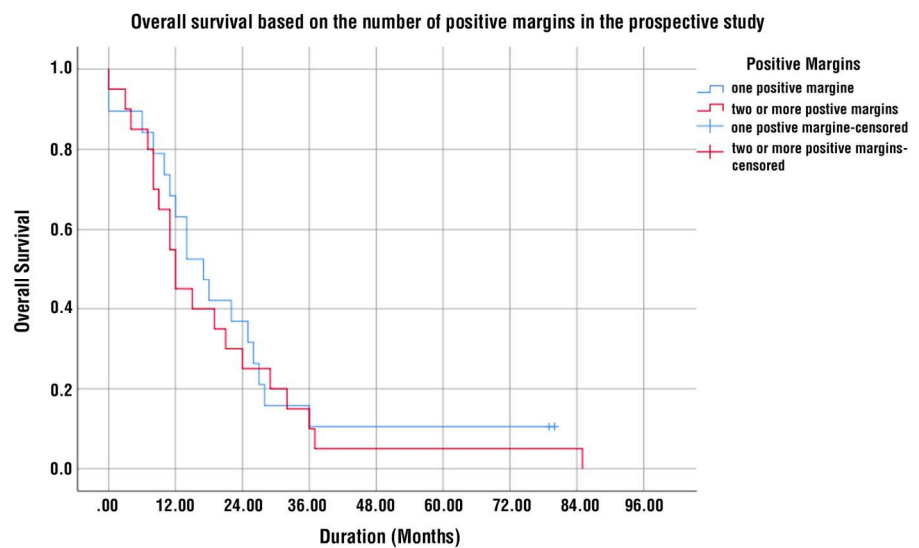
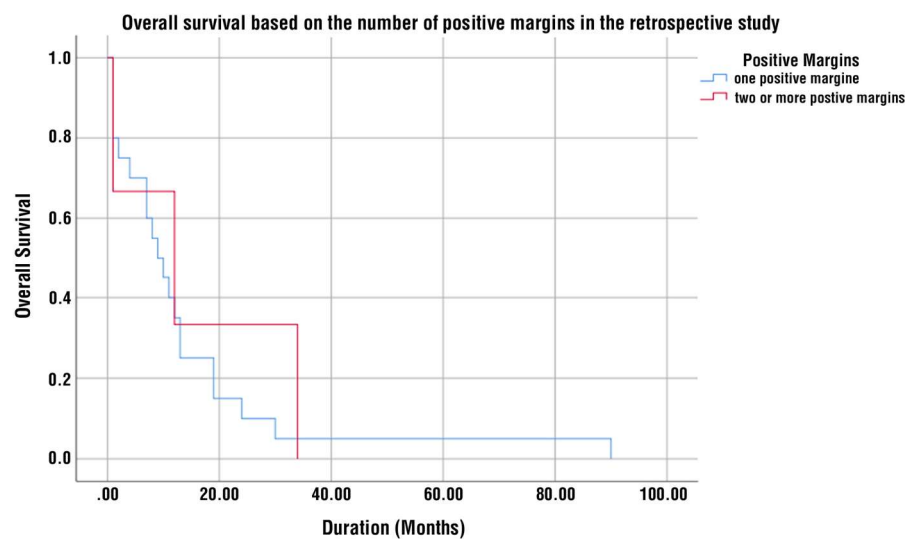
Overall survival, local recurrence and distant metastatic rates of patients diagnosed with PDAC can be influenced by a variety of factors. Among these, of most significance are the tumor characteristics (size, location and grading), the number of involved lymph nodes and the presence of vascular/perineural invasion, as several studies have showed in the last few years. When it comes to the

Table 4. Multivariate analysis regarding overall survival using Cox-Regression

Parameters	HR*	95% CI		p value
		Lower	Upper	
R status	0.51	0.14	1.84	0.03
Tumor Stage (I vs. II)	0.41	0.04	4.74	0.048
Tumoral Grading (G12 vs. G34)	2.5	1.09	5.72	0.003
Lymphatic invasion	0.36	0.08	1.49	0.016
N staging (0 vs. 1+)	5.19	1.17	23	0.003
T staging (1 vs. 2 vs. 3 vs. 4)	1.14	0.32	4.08	0.084
Positive Margins (1 vs. 2+)	2.65	1.28	5.49	0.001
Vascular resections	0.63	0.24	1.65	0.035

*Adjusted with Bonferroni correction.

Statistically significant results are highlighted.

Figure 8. Overall survival of patients with one vs. patients with two or more positive margins in the standardized group (prospective analysis)(p-value = 0.619)**Figure 9.** Overall survival of patients with one vs. patients with two or more positive margins in the non-standardized group (retrospective analysis) (p-value = 0,594).

resection margin status, opinions are divided (14-24).

According to Verbeke et al. the percentage of positive resection margins (R1) varies a lot between centers and studies (from less than 20% to more than 80%), due to differences in the definition of the margin involvement and the absence of an international consensus regarding a standardized pathology examination protocol (6).

After Verbeke proposed the introduction of a standardized protocol, Esposito et al. conducted the first study to test and, in the end, confirm this theory on a group of 111 patients. Since then, multiple studies have proven this theory, whether they analyzed all types of periampullary tumors or focused just on the pancreatic ductal adenocarcinoma (11,13,25-32). Our study has focused entirely on the pancreatic ductal adenocarcinoma patients in order to minimize the bias. The histopathological protocol that we used was based on the one suggested by Verbeke et al., the only difference being that we did not divide the medial margin into two, one corresponding to the SMV - superior mesenteric vein/PV - portal vein and one to the SMA - superior mesenteric artery, as reported by Verbeke (11). Our research has shown a statistically significant increase in the percentage of positive resection margins by almost 30% in the standardized protocol group, which reinforces the idea that a standardized analysis of the PD specimen should be implemented in the high-volume centers.

The other constantly discussed aspect in the research on pancreatic adenocarcinoma is the definition of a R1 margin. In the past, a positive resection margin (R1) was defined as direct microscopic tumor involvement of any surgical margin, by both the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), while the British Royal College of Pathologists (RCP) considered a margin to be positive when there were tumor cells less than 1 mm from the surgical resection margin. In the 8th edition of the AJCC guidelines, the definition has changed and is now in consensus with the

one recommended by the RCP (this being the reference point for most of the European centers). Meanwhile the definition remains unchanged in the 8th edition of the UICC guidelines (13). Since the 1 mm clearance rule for assessing the resection margins is the one adopted by most of the European countries and strongly recommended by the International Study Group of Pancreatic Surgery, it is the definition that we also adopted in our study (10,33). There were also several publications which aimed to prove that a minimum distance of 1.5 or 2 mm from the tumor bed in defining a R0 resection is more suitable for pancreatic cancer because of its dispersed pattern in tumor growth (15,25,26,34).

It is generally known that for any type of oncologic resection a positive resection margin has a negative impact on the long-term survival, but according to our analysis, only when using a standardized histopathological report R1 play a determinant role in 5-years OS. Our team has previously published an article regarding this matter, in which we studied the 3-year survival rates, while now we extended our research to reveal the 5-year survival rates of the same group of patients (35). Therefore, our study sustain the hypothesis sustained by other publications, that positive resection margins alone have an impact on overall survival in PDAC when using a standardized histopathological report and a R1 < 1 mm definition (16,36,37). This is in contradictory with the findings of several studies conducted over the last 20 years (19-24,38). Among the first studies that also indicated this, was the one carried out by Neoptolemos et al. in 2001 in the ESPAC-1 trial. They have suggested that the occurrence of R1 is directly linked to the tumor's biology and the presence of lymph node invasion and not to the surgical technique (38). This was also confirmed in the research conducted by Hernandez et al. in 2009 (39). More recent data on the subject can be found in a meta-analysis conducted by Demir et al. in 2017, who also propose to view R1 margin as a reflection of an aggressive tumor biology and emphasize the importance of factors like

vascular and perineural invasion, as well as tumor grading (17). These findings are consistent with the ones in our study, which demonstrates a correlation between R1 margins and higher tumor grading, as well as vascular and lymphatic invasion.

In 2013, Raut et al. have proven that a R1 resection margin was associated with tumor size and operative blood loss and was therefore not an independent factor in determining lower survival rates. They also pointed up that in most cases (88.3%) the involved margin was the SMA one. In our study the medial margin (involving the tissue in the proximity of the SMA and SMV) was also the most frequent positive margin (50.9%). Several other publications confirm that this margin is the one with the greatest chance of being implicated, with a poor prognostic for the patients (14,19,40). We have also noticed that when comparing the patients with a positive medial margin to the rest of the group, the overall survival is negatively influenced. The question of therapeutical options in this particular situation arises. Regarding this matter, several publications have studied the impact that extensive surgery has on the long-term survival in case of initially positive resection margins (18,20,36,39). According to the findings of Schmidt et al., reexcision could have a beneficial impact in the case of a positive transection margins (36). When it comes to the SMA margin though, where the local anatomy does not really permit a more extensive excision, a reintervention does probably not bring any advantages for the patients (20,21,27,39). The protocol of PD in our center includes a total mesopancreatic excision, so we believe that, unfortunately, in the case of positive resection margins at this level extensive surgery would not change the course of the disease. We consider that only a closer follow-up or a different approach when it comes to adjuvant therapy could benefit these patients and that more research has to be carried out on this subject.

However, when it comes to multifocal positive margins, according to the multivariate analysis in our research an increasing

number of margins does reduce the overall survival. This is one of the conclusions that was also reached by Ghaneh et al. in 2017 (14). Pine et al. similarly proved that when it comes to R1 < 1 mm margins, the factors with the greatest influence on overall survival are the presence of a medial positive margin and the implication of multiple margins (19).

Conclusions

The use of a standardized histopathology report not only that reveals a significant increase in R1 resection margins rates it also increase the number of R1 margins (it is more likely to have more than two R1 resection margins/specimen). Also when it comes to use a standardized histopathology report the R1 resection margins play a determinant role in 5-year OS. The factors that we found to have an influence on the occurrence of R1 are the tumoral grading and the vascular and lymphatic invasion. The most frequently involved margin is the medial one (the mesopancreas), which in comparison to other margins, has a negative impact on the overall survival. In our opinion, the cases in which this margin is positive should therefore benefit of a closer postoperative follow-up and maybe more aggressive adjuvant therapy, since a more extensive resection in this particular region is not feasible (without arterial resection).

Author's Contributions

Conceptualization, E.M., F.G., N.A.H., C.P., A.P., F.Z., C.I., R.B. and C.P.; Data collection, I.V., S.M., V.-I.N., P.U. and D.V.; Formal analysis, L.F., R.B., D.V., V.-I.N., S.M. and P.U.; Funding acquisition, E.M., C.P., N.A.H. and F.G.; Investigation, L.F., R.B., I.R. D.V., A.P., V.-I.N., I.V. and S.M.; Methodology, E.M., N.A.H., F.G., F.Z., C.I., C.P. and L.F.; Project administration, E.M., N.A.H., F.G., F.Z., C.P. and A.P.; Resources, E.M., C.P., A.P., F.G., F.Z., R.B., I.R. and L.F.; Software, D.V., V.I.N., I.V., P.U. and S.M.; Supervision, N.A.H., C.P., C.I. and F.G.; Validation, N.A.H., F.G., R.B., A.P.,

E.M. and L.F.; Writing—original draft, L.F., I.R., S.M., I.V., P.U., V.I.N. and R.B.; Writing—review and editing, N.A.H., F.G., E.M., A.P., C.P., F.Z. and C.I. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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For this study, the approval of Iuliu Hațieganu University of Medicine and Pharmacy Ethics Committee (number 384/10.11.2014) was received.

Data Availability Statement

Not applicable.

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