Since 2002

The Future Perspectives of Redefining the Resection Margin Status in Different Cancers of Pancreas

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Abstract

BACKGROUND: The interest toward the assessment of circumferential resection margins (CRMs) in pancreatic cancers has been evolving over the past years. While several studies investigated the influence of R1 resections on survival, not many studies evaluated the prognostic value of each resection margin.

AIM: In this study, we examined the different resection margins to better understand their prognostic implications on overall survival.

METHODS: This prospective study included a cohort of patients who had pancreaticoduodenectomy for cancer purposes at our institution from 2008 till 2013. Median follow-up was 6 years. Involved margins in R1 resections were further classified into anatomical margins (anterior, posterior, and circumferential margins) and surgical margins (vascular/medial margins and transection margins). Overall survival was assessed for each specific resection margin.

RESULTS: A total of 134 patients were included with a median age of 66 years. R1 resection was done in 54% of patients (n = 72/134). Median survival of R0 resection group was 6.3 years, compared to 1.9 years for R1 resection group (p = 0.001). Vascular (surgical) margins had the lowest survival rate (1.7 years) compared to anatomical margins (anterior, posterior, and circumferential margins) with 3.6, 2.2, and 2.1 years, respectively (p = 0.02). On multivariate analysis; lymph node involvement and vascular resection were the only factors to correlate significantly with poor survival.

CONCLUSION: While the new pathological protocols advised to perform rigorous margin assessment of CRM, the prognostic value of each resection margin is still unclear. This study showed variation of survival across different resection margins with inferiority towards vascular (surgical) margins. This supported the need of redefining R1 margins in the future pathological classifications according to their different prognostic impacts.

Introduction

The incidence of pancreatic cancer increased 2–3 times over the past years and it represents now the seventh leading cause of cancer-related deaths worldwide [1]. Despite the advancement of multimodal therapy used nowadays in pancreatic cancer, the prognosis is still poor [2]. Several recent studies highlighted the impact of incomplete resection (R1 resection) on such poor prognosis. However, the appropriate R1 definition is still debatable, with a wide variation across studies between 0 mm (direct involvement), <1 mm, <1.5 mm, and <2 mm [3], [4], [5]. In their 8th edition, AJCC defined R1 as cancer cells <1 mm [6]. This is correlated to the standard definition stated previously by Royal College of Pathologists (RCP) [7].

This evolving interest toward better evaluation of R1 margins was grown up after standardization of axial slicing of pancreatic cancer specimens and evaluation of circumferential resection margins (CRMs) [8]. The notion was extensively examined in rectal and esophageal cancers.

This witness changes in CRM assessment led to a new era of understanding the prognostic role of not only the margin involvement but also the specific resection margins within CRM. Over the past decade, many studies analyzed the prognostic relevance of margin involvement (R1) on overall survival [9]; however, the data about the significance of each involved resection margins were scarce [10].

In this study, we analyzed the different resection margins of CRM in a prospectively collected database.

Methods

Patient cohort

This cohort study included patients underwent pancreaticoduodenectomy (PD) for cancer purposes at our institution between 2008 till 2013. The data were analyzed on retrospective basis. The exclusion criteria included patients who had resection for benign causes (as IPMN, pancreatic cysts, chronic pancreatitis, etc.)

or distal pancreatectomies. Patients who died within 90 days postoperatively on top of surgical complications were also excluded. Surgery was done by three specialist pancreatic consultant surgeons. All cases were discussed at our multidisciplinary teams (MDTs) at time of diagnosis and postoperatively with the final pathology data of the resected specimens. Adjuvant chemotherapy was offered to all patients with R1 margins. Most cases of R0 resections received adjuvant chemotherapy. However, patients with early cancer, node negative, and with favorable pathological prognostic features (as absence of lymphovascular invasion in a well-differentiated cancer) did not receive adjuvant chemotherapy. The agreement not to use adjuvant chemotherapy was decided after detailed discussion in MDT with final pathology. Ethical approval was obtained from the Research Ethics Committee at our institution.

Pathological work-up

All resected specimens were evaluated according to RCP recommendations with standardized axial slicing protocol [7]. Proper identification of the all seven resection margins described by RCP was essential to complete the pathological examination of the specimens [7]. On our analysis, we further divided these margins into surgical and anatomical margins based on the post-operative pathological examination: Surgical margins (which could be further resected), which included isolated vascular or medial margin (portal vein/superior mesenteric vein groove site) and transection margins which were bile duct, pancreatic neck, and enteric margins. However, anatomical margins (which named mobilization margins, and they could not be further resected) included anterior, posterior, and circumferential. We defined circumferential margins as those involved more than 1 margin (either anatomical or combined surgical and anatomical). In this study, we used RCP definition of R1 margins which is the microscopic evidence of tumor within 1 mm of a resection margin [7]. In this study, we analyzed R1 resection patients and compared between the different types of anatomical and surgical R1 resection margins.

Follow-up

Patients were followed up at our pancreatic clinic until their latest oncologic surveillance examination at 5 years postoperatively or until death. Data collection was also cross-checked with our hospital/national patients' electronic databases till end of 2019. Analysis was done retrospectively after completion of follow-up data.

Evaluation of predictors for overall survival (OS)

Factors which were analyzed to assess their impact on overall survival included age, sex, comorbidities, pathological types, R1 resection, tumors >4 cm (T4), vascular (SMV/PV) resection, and lymph node involvement.

Aim of study

The primary outcome of this study was to evaluate the prognostic value of each specific resection margin on overall survival. The secondary outcome was to assess other pathological factors affecting long-term survival after pancreatic resection.

Statistical analysis

SPSS software (SPSS Inc., IL, USA) was used for data analysis. For numerical variables, independent samples t-test was used to compare mean difference between two unpaired groups and Mann–Whitney U-test was used for non-normally distributed variables. Chi-square test was used to compare the categorical data. Kaplan–Meier survival analysis was used to analyze the overall survival from the time of surgery. Patients alive at the time of follow-up point were censored. Univariate and multivariate analyses were used to assess predictors of overall survival. Binary logistic regression was used in multivariate analysis for categorical outcomes and linear regression was used in multivariate analysis of numerical outcomes. $p < 0.05$ was considered statistically significant.

Results

During the study period, 225 pancreatectomies were performed at our institution. However, we found only 134 patients fulfilled the inclusion criteria (Figure 1). Median age was 66 (40–83) years. The majority were male (54%, n = 72). Median follow-up was 6 (1.8–11.5) years (Table 1).

Pathology data

In the whole cohort of patients, R1 resections represented the majority of resections (72/134 patients; 54%), while the rest showed R0 resections (62/134, 46%).

Pancreatic ductal adenocarcinoma (PDAC) represented the most common pathology (60%, n = 81), while ampullary cancers and cholangiocarcinoma were found in 36 (26%) and 17 (14%) cases, respectively. R1 resection was less observed in ampullary cancers in 12/36 patients (33%). Yet, it was more frequently seen in PDAC and cholangiocarcinoma resections (64% and 47%, respectively).

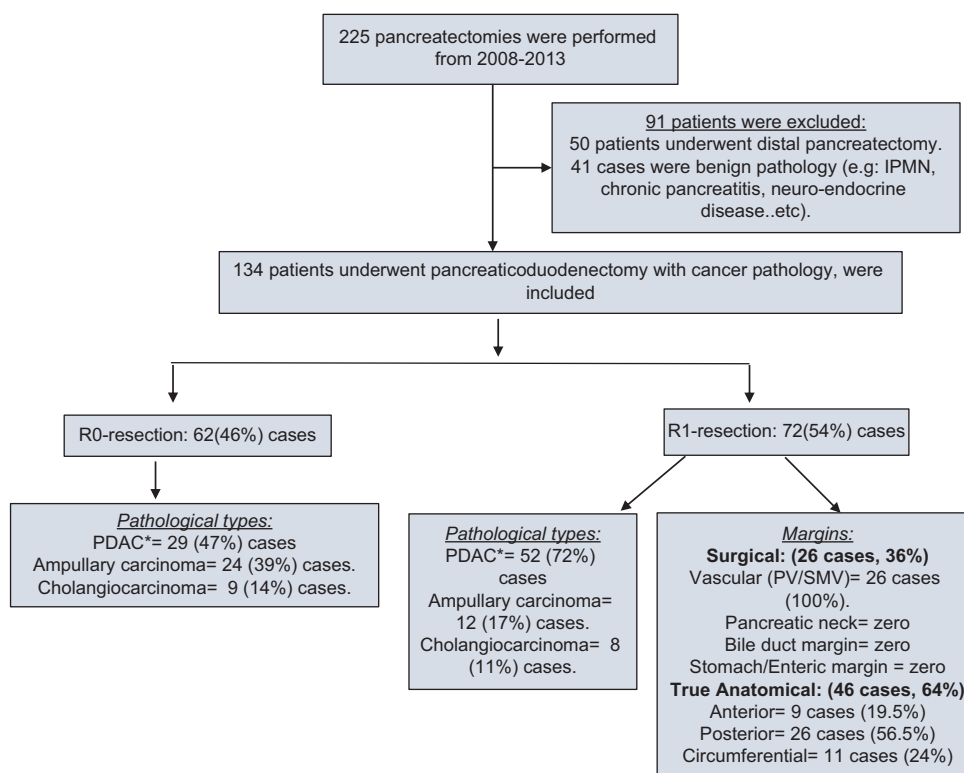Analysis of R1 margins showed that anatomical margins (64%, n = 46) were more common compared to

Figure 1: Flowchart of the patients underwent pancreatectomies from 2008 and 2013, with the pathological and resection margins characteristics.
*PDAC: Pancreatic ductal adenocarcinoma

the surgical margins (36%, n = 26). Posterior margins were the most common anatomical margins (56.5%, n = 26/46), while anterior and circumferential margins were detected in 9 (19.5%) and 11 (24%) cases, respectively. Vascular (SMV/PV) or medial margins were the only positive margins in the surgical margins group (26 cases).

Table 1: Demographic and pathological characteristics of 134 patients involved in this study

Characteristic	Number of patients (%)
Gender (M/F)	72 (54%)/62 (46%)
Tumor size (T-stage)	
T1/2	41 (31%)
T3/4	93 (69%)
Lymph node metastases (N-stage)	
N1	102 (76%)
N0	32 (24%)
SMV/PV vascular resection (yes/no)	46 (34%)/88 (66%)
Margins	
Surgical*	
Vascular/medial margins	26 cases
Transection margins	Zero cases
Anatomical**	
Anterior	9 cases
Posterior	26 cases
Circumferential	11 cases
Pathological type of tumor	
Pancreatic ductal adenocarcinoma	81 (60%)
Ampullary	36 (27%)
Cholangiocarcinoma	17 (13%)

*Surgical margins: Which could be further resected. **Anatomical margins (mobilization margins): Which could not be further resected.

Survival data (Figures 2 and 3)

R0 resections carried better survival compared to R1 resections, with median survival rates of 6.3 and 1.9 years, respectively (p = 0.001). This difference in survival rates continued also for each pathological type of cancers. However, on individual subgroup analysis to each pathological type, there was a significant difference in survival rates between R0 and R1 resections for ampullary cancers only (p = 0.002).

Ampullary tumors implicated the best median survival rate of 5.8 years (p = 0.02), while median survival rates for PAC and cholangiocarcinoma were 3.8 and 2 years, respectively. This favorable survival observed in ampullary cancers continued to be significant in R0 resection group, compared to PAC and cholangiocarcinoma (5.8, 4, and 1.7 years, respectively) with p = 0.002. Yet, it failed to be significant in R1 resection group across these pathological types (1.6, 2, and 1.8 years respectively, p = 0.5).

Median survival rate in patients with positive surgical (vascular) margins was 1.7 years, which was lower compared to anatomical margins (with median survival rate of 2.3 years) with a significant p = 0.02 (HR 0.7, CI 0.4–1.27). Anterior margins carried the best survival rate (3.6 years), however, posterior and circumferential margins had comparable survival rates at 2.2 and 2.1 years, respectively.

Univariate analysis of multiple factors (displayed in Table 2) showed that positive resection margins (R1), lymph nodes (LN) involvement, and PV/SMV resections were significantly associated with lower survival rate (p-values 0.09, 0.001, and 0.09, respectively). Although, when these factors were assessed on multivariate regression analysis, only LN involvement and vascular resections remained significant (p = 0.001 and p = 0.03, respectively).

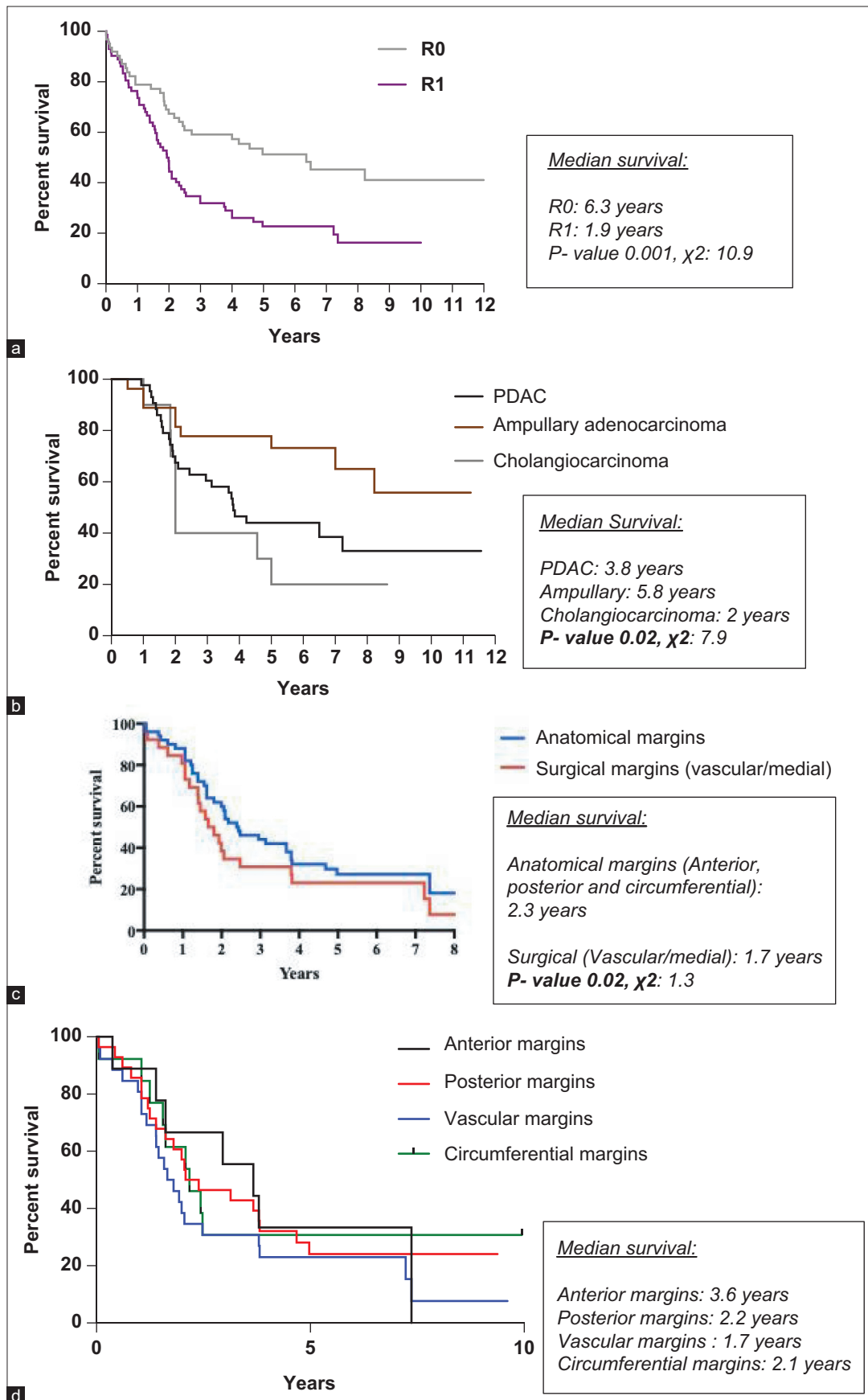Figure 2: Kaplan–Meier cumulative survival curves for all 134 patients categorized into three groups; (a) R0 versus R1 resections, (b) survival curves according to different pathological types, (c) survival curves of different involved resection margins, and (d) survival curves between all different margins. *R1 resections: Defined by microscopic evidence of tumor within 1 mm of a resection margin
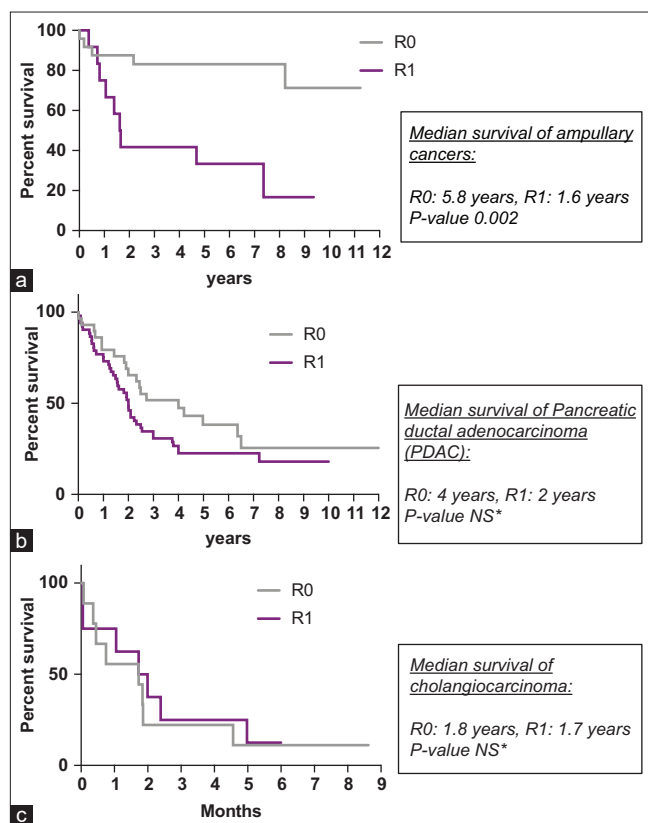
Figure 3: Kaplan–Meier cumulative survival curves for R0 versus R1 at each pathological type; (a) ampullary cancers, (b) pancreatic ductal adenocarcinoma, and (c) cholangiocarcinoma. *NS: Not significant

Discussion

The ongoing controversy in defining R1 resection margins led to difficult comparison across the studies with substantial underestimation of the frequency and survival rates of R1 resections. When standardized histological examination of PD specimens (based on axial specimen slicing technique) was used, the frequency of R1 resections (<1 mm) was reported as high as 60–84% [4], [5], [8], [11], [12]. Likewise, R1 resections represented the majority (54%) of our resections in the present study.

Table 2: Univariate and multivariate survival analysis for prognostic factors of overall survival.

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex	2.075 (0.84–5.08)	0.6		
Age	0.98 (0.94–1.029)	0.6		
Comorbidities				
IHD	1.17 (0.22–6.21)	0.5		
Respiratory diseases	0.62 (0.16–2.32)	0.8		
Pathology types				
PDAC	0.55 (0.22–1.35)	0.2		
Ampullary adenocarcinoma	3.57 (1.34–9.51)	0.2		
Cholangiocarcinoma	0.25 (0.05–1.26)	0.08		
Vascular (SMV/PV) resection	0.45 (0.1–1.89)	0.009	1.28 (0.19–8.4)	0.03
Resection positive margin (R1)	0.29 (0.11–0.72)	0.009	0.61 (0.19–1.95)	0.4
Lymph node involvement	0.17 (0.06–0.47)	0.0001	0.32 (0.98–1.08)	0.0001

The reported survival benefit between R0 and R1 margin status was highly heterogeneous across studies. The survival of R1 resections was significantly lower compared to R0 resections in most studies [5], [8], [9], [10], [13]. This was consistent with our results which showed a significant survival benefit in favor of R0 compared to R1 resections (6.3 vs. 1.9 years, respectively, p = 0.001). Nevertheless, other studies did not demonstrate any significant difference in survival despite the inferiority of survival period for R1 resections [4], [12].

Whilst these studies evaluated the prognostic relevance of R1 compared to R0 resections, the studies which assessed the prognostic role of each specific resection margin were scarce. The purpose of this study was to analyze the prognostic value of different types of involved resection margins in R1 resections.

In the present study, anatomical margins were more common than surgical margins (64% vs. 36%). This low number of surgical margins may be related to the high use of frozen sections, which avoided having any involved pancreatic neck, bile duct, or enteric margins in our final results. Hence, vascular/medial margins (PV/SMV) were the only representative for the surgical margins in this study.

Posterior and vascular/medial margins were the most involved margins (36% each). However, anterior margins were the least involved margins (19.5%). These results were similar to most published studies [5], [8], [9], [10], [11], [12], [14], [15].

The involved vascular margins carried the worst survival rate of 20.4 months in our study, which was inferior to all anatomical margins (p = 0.02). On the other hand, posterior margins (the most common anatomical margin) had a survival of 26.4 months. Thus, vascular resection in such advanced cases is favorable to avoid positive vascular margins. Of note, this low survival rate for vascular margins was observed despite adjuvant chemotherapy. The inferiority of survival rate seen in vascular margins was also comparable to the French multicenter prospective study which involved 150 patients, where the overall survival was significantly reduced with vascular margins but not with posterior margins (10.5 vs. 16.4 months, respectively) [4]. Furthermore, a study from Glasgow showed that survival rate of vascular margins was reduced to 11.1 months compared to 18.9 months for posterior margins [14].

On the contrary, Demir *et al.* concluded in their recently published meta-analysis that vascular margin involvement was associated with an improved overall median survival of 2.5 years when compared to posterior margin affection (1.2 years) with p = 0.02. However, in this meta-analysis, there was a lack of standardized examination of the resection specimens. Besides, there was no stratification of the surgical techniques used; with inclusion of different resections types as distal pancreatectomies, which would affect survival rates [9]. In another recent study, Ghaneh *et al.* emphasized that only posterior margins were significantly associated with reduced overall survival and higher local recurrence,

while vascular margins were associated with higher local recurrence only. However, these margins were meant for direct involvement (<0 mm), not < 1 mm margins which were used in this study [10].

It becomes clear in literature that isolated anterior margin involvement is very uncommon [10] and is considered in many studies as the only true anatomical margin with no clinical impact on transection [4], [12], [16]. Thereby, many centers do not assess it separately. However, it has been recommended recently by many pathologists' societies to be included as an integral part of examination protocols to ensure radicality; due to the data indicating its lower survival and higher local recurrence compared to R0 resections [7], [17], [18]. Interestingly, a recent study suggested that the lower part of anterior surface could be considered as a surgical margin, rather than a true anatomical margin. Their theory based on that direct infiltration of this part to the mesentery of transverse colon and small bowel could indicated further resection of the adipose tissue from the mesocolon or small intestine mesentery adherent to the anterior pancreatic surface [19].

In studies which examined the anterior margin separately, the associated survival rate was higher compared to other margins which reached 2 years [9], [14]. Similarly, in our study, it carried the best survival across all margins (3.6 years). It's noteworthy to mention that involvement of posterior margin together with the anterior margin (as in circumferential positive margins) dropped the survival rates significantly in our results (3.6–2.1 years). This was agreed by other studies which exhibited the same results when more than 1 margin was involved [5], [9], [10].

Given the high use of frozen section in most of our resections, we did not have any positive transection margins in final specimens. It's genuine in most studies that involved transection margin (particularly at pancreatic neck) carried worse prognosis compared to other different margins [9], [10], [11], [12], [14]. This highlights the importance of frozen section particularly in the advanced cases.

In the present study, margin involvement (R1) was observed less frequently in ampullary cancer (33%) compared to bile duct (47%) and pancreatic cancers (64%). This was consistent with many other studies [8], [13]. It may be explained by the early detection of ampullary tumors on top of early occlusion of bile or pancreatic ducts.

This low R1 incidence observed in ampullary tumors led subsequently to a higher 5-year survival of ampullary cancers in our study (61%) compared to PDAC and cholangiocarcinoma (26% and 12%, respectively). This was also observed in other published data which showed higher 5-year survival rates of ampullary cancer between 30 and 70% [13], [20].

This explicit higher survival rate shown in ampullary cancer can be also related to tumor biology not only the influence of higher R0 resections. Previous histological reports suggested that intestinal origin which was found in the majority of ampullary cancers had better survival rates compared to pancreaticobiliary origin exhibited in other cancer types [13], [21]. This may explain the results found on our further analysis to the completely resected tumors (R0). It revealed that ampullary cancers continued to have the best survival among the other pathological types, with significant p-value 0.02. Interestingly, in this study, survival rates of R1 resections for ampullary tumors did not show any significant differences compared to R1 resections of other pathological types. This may be explained by the general low survival rates in R1 resections in this study.

The presence of positive resection margins (R1) was an independent factor for survival in our univariate analysis, yet it failed to maintain its significance by multivariate analysis. This was agreed by many studies which emphasized on its significance either on univariate analysis only [8], [12] or combined with multivariate analysis [5], [9], [11]. While there was an agreement of its impact on survival in the above studies, other studies failed to show any prognostic significance of R1 on overall survival [22], [23]. This difference across studies may be related to the size of patient cohort, the different definitions of R1 resections, and the effect of other confounding factors as tumor differentiation and lymph nodes involvement.

On the other hand, lymph node involvement was the most powerful predictor of survival in our multivariate analysis, which was also observed in most studies [5], [9], [11].

It is noteworthy to highlight that the patients with SMV/PV resection had poor survival on our multivariate analysis, which indicated the poor survival of tumors with vascular invasion. This was also supported by many studies which suggested that vascular invasion was an independent factor of poor survival [4]. Therefore, it's intuitive to suggest the use of neoadjuvant therapy in advanced cases with venous involvement. This was supported recently in 2021 ASCO meeting by the long-term data of the PREOPANC trial, which resulted in an improvement of overall survival after neoadjuvant chemoradiotherapy [24].

There are many strengths of this study. First, it is one of the fewest prospective studies to evaluate the prognostic value of each specific resection margin after rigorous CRM assessment. Second, we included pancreaticoduodenectomy cases only with proved cancer pathology, hence, this avoided any heterogenicity in our results. In addition, this study provided a long follow-up data which reached a median of 6 years.

On the other side, one of the main limitations of this study is the lack of detailed information about the tumor biology or differentiation and the adjuvant chemotherapy cycles given to the studied patients.

Another limitation is that we were only able to assess overall survival, but not disease-free survival or pattern of disease recurrence.

Our study promotes a stimulus to perform a proper full histological examination of CRM in all specimens of pancreatic tumors. The variation of survival rates across different resection margins supports the need for redefinition of R1 according to margin sites. We advise that it should be involved in the future pathological classifications for better alignment with survival rates. Yet, more studies directed toward resection margins are still required.

Conclusion

Whilst the new pathological protocols advised to perform rigorous margin assessment of CRM, the prognostic value of each resection margin is still unclear. This study showed variation of survival across different resection margins with inferiority towards vascular (surgical) margins. This supported the need of redefining R1-margins in the future pathological classifications according to their different prognostic impacts.

Declarations

Ethics information

All the works in this study were in accordance with the ethical standards of our institution and with the 1964 Helsinki Declaration and its later amendments. Ethical approval was obtained from the Research Ethics Committee at our institution on January 14, 2019.

Authors' Contributions

AE and TE collected, interpreted the data, performed the statistical analysis, and drafted the manuscript. DD designed the study and revised the manuscript. All authors approved the final version to be published.

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