Influence of standardized histopathological workup on reporting of the resection margin status in pancreatic head cancer

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Background
Resection margin (RM) status in pancreatic head adenocarcinoma is assessed histologically, but pathological examination is not standardized. Our aim was to determine the influence of the 'standardized histopathological workup' of pancreaticoduodenectomy specimens on the reporting of the RM status using a 'surgical quality protocol'.

Patients and methods
Starting October 2009, 42 patients underwent pancreaticoduodenectomy using the 'surgical quality protocol' for pancreatic ductal adenocarcinoma and were examined using 'standardized histopathological workup'. We prospectively evaluated and validated its results for 50 months. We evaluated different sites of R1 at 0 and 1 mm resections according to the color code and determined the most frequent site of incomplete tumor resection.

Results
Patients included 14 women and 28 men. Their age ranged from 46 to 74 years, with a median of 60 years. Changing to 'standardized histopathological workup' from traditional pathological examination procedures resulted in an increase in the R1 rate from 14.3 to 64.3% in this prospective series. Fifteen percent of R1 resections showed multifocal margin involvement (i.e. more than one margin involved in a single specimen) for the 0 mm in contrast to 33% for the 1.0 mm margin. The uncinate margin represents the most frequent site with residual tumor mass by far (42% at 0 mm and 43% at 1 mm), followed by the posterior margin. When R1 resection was defined by a positive margin of 0 mm, 48% of the present patients achieved R1 resection. In contrast to when R1 resection was defined by the presence of tumor cells within 1.0 mm, 64% of the present patients achieved R1 resection.

Conclusion
Standardization of the histopathological examination of pancreaticoduodenectomy specimens influences the reporting of RM status. The RM involvement is significantly more frequent than commonly reported. Complete and meticulous surgical resection of the uncinate process *en bloc* with all the peripancreatic tissues between the artery and the pancreatic parenchyma must become the standard surgical approach in pancreatic head resection as it is the most frequent site for residual tumor by far.

Keywords:
histopathological workup, pancreatic cancer, R1 resection, resection margin, uncinate margin

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Introduction

Surgical resection with negative resection margins (RMs) (R0) remains the only potentially curative treatment for pancreatic ductal adenocarcinoma (PDAC). Because of its late presentation, aggressive tumor biology, and lack of early specific biological markers, only 10–15% of cases are resectable [1].

RM involvement (R1) is generally believed to be, among others (tumor size, degree of differentiation, nodal affection), a critical prognostic indicator to survival in those patients [2–6] and was reported to be an independent predictor of poor long-term survival in several studies [7–23]. However, even patients with tumor-free margins (R0 resection) frequently experience local recurrence and distant metastases. Consequently, more radical approaches have been evaluated, as described by Fortner [24]. Even though there was an initial indication of some survival benefit, follow-up studies have failed to confirm these promising results [25]. This raised the question as to whether such a discrepancy is caused, other than through incomplete lymphadenectomy and perineural invasion, by a misclassification of R1 resections as R0 resections [26]. Quoted R1 resection rates can vary significantly between individual specialist centers (14–85%) [5,6,20,27,28], and it is not known to what extent these differences reflect different pathological practices.

Because RM involvement is generally believed to be determined by the quality of surgery, a low R1 rate is often considered an indicator of high-quality surgery. Recent studies, however, have brought the pathologist as

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a second player into the field, on the basis of the growing awareness that standardization and meticulousness of the pathological examination have a significant impact on the accuracy of the reported RM status [20,27,28]. The R1 rate is therefore a performance measure not only for the surgeon but possibly also for the reporting pathologist.

The aim of this study was to determine the influence of the 'standardized histopathological workup' of pancreaticoduodenectomy (PD) specimens on the reporting of the RM status using a 'surgical quality protocol' to test prospectively the hypothesis that current histopathological reports underestimate the proportion of R1 pancreatic head resections.

Toward this goal, we first implemented color coding of the RMs and the organ surfaces. Second, we carefully re-evaluated the different sites of R1 resections according to the color code and found the most frequent site of incomplete tumor resection.

Patients and methods

To fulfill our aim and test our hypothesis, we first investigated our rates of curative resections by retrospectively identifying all patients who had undergone pancreatic head resection, either through pylorus-preserving pancreaticoduodenectomy (PPPD) or the Kausch–Whipple procedure because of malignant diseases (PDAC), in the Department of Surgery, Alexandria University, between 2004 and 2009. During this period, all the specimens were examined by the same experienced team of pathologists using conventional histopathological workup, where longitudinal opening of the main pancreatic duct and common bile duct was the preferred dissection method (mainly bivalve slicing). The following margins were examined: common bile duct margin, the proximal duodenal (gastric) margin, jejunal RM, pancreatic neck transaction margin, and the anterior and posterior surface. When present, vascular, lymphatic, and perineural invasion were reported. Histological classification [tumor type, grade of malignancy, pathological tumor–node–metastasis (TNM)] was carried out according to the current World Health Organization and Union for International Cancer Control (UICC) criteria [29]. According to the UICC criteria, the operation was considered potentially curative (R0) if the RMs and organ surfaces were free of tumor cells, whereas histopathologically verified tumor cell infiltration was defined as R1 resection. In cases of macroscopically visible tumor tissue, the resection was classified as R2.

Starting October 2009, we introduced the 'standardized histopathological workup' [27,30,31] to examine all PD specimens. We prospectively evaluated and validated its results for 50 months till December 2013. During this period, 54 consecutive patients with pancreatic head tumors underwent PD and provided an informed consent to their inclusion in the study before surgery. Forty-two out of the 54 patients with true macroscopic margin-free PDAC who underwent PD entered the present study, whereas 12 patients were excluded after surgery because of findings of macroscopic residual tumor (R2 resection), non adherence to the 'surgical quality protocol', and nonductal adenocarcinoma.

Standardized 'quality protocol' for pancreaticoduodenectomy

All of our studied patients received pancreatic head resection with curative intent. All resection procedures were performed by the same experienced surgical team. After a bilateral subcostal incision, assessment of resectability was performed by an examination of the abdominal cavity to exclude any contraindications for resection mainly liver metastases or peritoneal carcinomatosis. The duodenum was kocherized with the dissection plane developed. With extension of the Kocher maneuver, an adequate exposure of the aortocaval area was obtained. The superior mesenteric vein (SMV) was then identified as it passes anterior to the third part of the duodenum by ligating and dividing all the tributaries to the head of the pancreas. A plane is developed anterior to the SMV and portal vein by remaining in the periadventitial layer of the vein. All portal vein tributaries are ligated and divided individually until the portal vein is completely free from the pancreatic head.

The dissection of the retroperitoneal margin was performed by extending the excision of the perivascular neural plexus around the superior mesenteric artery (SMA). This was done by approaching the SMA after retracting the SMV with an eyelid ophthalmic retractor. A part of the inferior medial boundary of the uncinate process was defined by identifying the SMV and the partially exposed SMA and this plane was developed. This plane was extended posteriorly by dissecting the right meridian neural plexuses of the SMA. From there, the SMA was identified and the perivascular plexus on the lateral side was dissected laterally right up to the vessel, and all the tissues between the artery and the pancreatic parenchyma were resected (Fig. 1). The SMA was not dissected from the medial side and the perivascular neural plexus on the medial side was preserved to avoid postoperative diarrhea. The dissection was then extended superiorly along the SMA toward its origin. It was then possible to place the left hand just anterior to the inferior vena cava (IVC) and aorta and retract the uncinate process to the

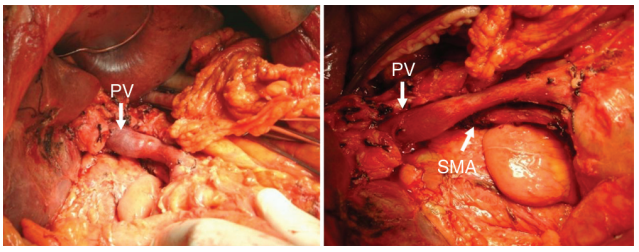
right of the patient, allowing the peripancreatic tissue around the uncinate process to be resected *en bloc*. The dissection of SMA continues along the plane of the adventitia up to the junction of the third and fourth parts of the duodenum. Standard lymphadenectomy plus resection of lymph nodes to the right of the celiac trunk, hepatic artery, and hepatoduodenal ligament were carried out in all patients [25]. After resection of the specimen, the posterior and retroperitoneal margin was grossly inspected for its integrity.

Standardized protocol for pathological examination

All surfaces and RMs of the pancreatic head resection specimen were stained according to a well-established five-color code (Fig. 2): the anterior (ventral) surface was painted yellow, the posterior (dorsal) surface green, the groove of the SMV blue, the pancreatic transection margin red, and the uncinate margin silver. Considerable emphasis was placed on clarifying the status of the RMs. Besides examining the status of RMs in the conventional technique, special attention was directed toward examining the circumferential resection margins (CRM) of the specimen including the anterior, posterior, and medial surfaces (SMV groove), with dedicated study of the status of the retroperitoneal uncinate margin. Isolated tumor involvement of the anterior surface of the pancreatic specimen was not considered an R1 resection in our patient cohort. No cases were classified as R1 exclusively on the basis of perineural invasion at a RM. Similarly, nodal involvement at a RM did not constitute an R1 classification in the absence of direct tumor involvement.

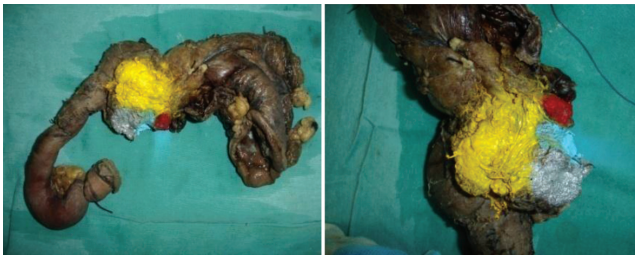
The uncinate process margin that extends along the proximal 3–4 cm of the SMA was identified immediately following resection (Fig. 3) as it was very difficult for the pathologist to identify, especially after formalin fixation, if it has not already been inked by the surgeon while the other parts were being colored after formalin fixation for 24–36 h. All staining procedures were performed by the operating surgeon or by a surgeon present during the procedure. The specimen was serially sliced (0.5–1-cm slices) in a single axial plane, that is, perpendicular to the longitudinal axis of the duodenum [20,27,28], according to the guidelines of the Royal College of Pathologists and the Leeds Pathology Protocol [27,30–32]. Therefore, large slices were obtained (median number 12), allowing the precise study of each colored margin at 0 and 1 mm. R1 resection rates were calculated twice: one with 'R1 resection' defined by a positive margin of 0 mm [33–35] and the other with 'R1 resection' defined by the presence of tumor cells within 1.0 mm [30,36]. Margin involvement (R1) was defined for the 0-mm margin if tumor cells were present at the inked margin; R1 was also defined for 1 mm margin width if tumor cells were present within the margin, independent of the mode of tumor spread. The pathological protocol also included the maximal transverse diameter of the tumor, the TNM classification, the grade of differentiation, the presence or absence of perineural, lymphatic, and/or vascular spread, and the number of lymph nodes retrieved from the specimen, enabling the calculation of the lymph node ratio. Several samples were taken from the tumor in relation to the anterior and posterior surface.

Figure 1



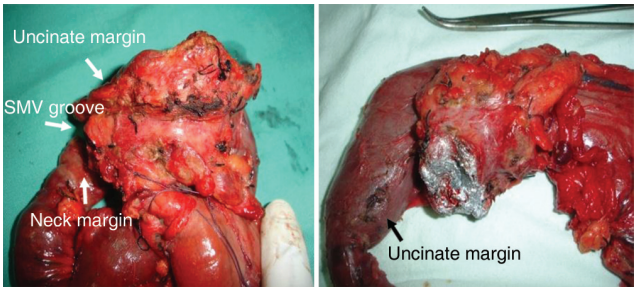
Operative pictures after resection of the pancreatic head showing the portal vein (PV) and superior mesenteric artery (SMA) after excision of the perivascular neural plexus on its lateral surface.

Figure 2



All surfaces and resection margins of the pancreatic head resection specimen were stained according a well-established five-color code: the anterior (ventral) surface was painted yellow, the posterior (dorsal) surface green, the groove of the superior mesenteric vein (SMV) blue, the pancreatic transection margin red, and the uncinate margin silver.

Figure 3



Pancreaticoduodenectomy fresh specimen showing the uncinate margin (silver), superior mesenteric vein superior mesenteric vein groove, and pancreatic neck transaction margin.

Results

To compare the rates of curative and noncurative resections in our department with the published data, we retrospectively identified 78 patients with malignant pancreatic head tumors (PDAC), excluding cases of distal bile duct cancer and ampullary carcinoma, who had undergone either PPPD or a Kausch – Whipple procedure over 5 years' duration. In 61 of these 78 (78%) patients, the operation could be considered potentially curative (R0), whereas the RMs in 17 cancer specimens was infiltrated (R1 = 22%). The most common site of infiltration was at the pancreatic neck transaction margin, followed by the posterior margin. The uncinate process margin was not assessed as a separate margin (Table 1).

Starting October 2009, we introduced the 'standardized histopathological workup' and applied it prospectively until December 2013. During this 50-month period, 42 consecutively resected pancreatic head specimens (PDAC) were processed according to this protocol. The patient population included 14 women and 28 men. Their age ranged from 46 to 74 years, with a median of 60 years. Eighteen patients underwent a Kausch–Whipple procedure, whereas the remaining 24 patients were treated by PPPD. None of our cases required partial or complete resection of the SMV. Clinicopathological data for the entire cohort showed that 81% were classified as T3 tumors (T1: 7%, T2: 12%). Sixty percent of the tumors were moderately differentiated (grade 1: 25%, grade 2: 58%, grade 3: 17%). None of our patients died within 30 days after surgery.

All 42 pancreatic head resections were invasive ductal adenocarcinoma on the final histopathological assessment after excluding those of distal bile duct cancer and ampullary adenocarcinoma. Applying our old conventional protocol for histopathological assessment, 36 cancers were curatively resected (R0 = 86%), whereas six (14%) cases turned out to be R1 resections. These six cases were classified as R1 on the basis of infiltration of the pancreatic neck margin. Applying the standardized histopathological workup and R1 resection at 0 mm, an additional set of 12 specimens had to be considered as R1 resections, resulting in a total percentage of 48% of noncurative operations (R1), reducing the rate of R0 resection to 52%. This is in contrast to when applying the 1 mm margin rule for R1 resection, a set of 21 specimens had to be considered R1 resections, resulting in a total percentage of 64% of noncurative operations (R1), reducing the rate of R0 resection to 36% (Table 1).

Tables 2 and 3 show the breakdown of RM involvement at 0 and 1.0 mm according to the number of involved margins per specimen and the distribution of margin involvement. Our results showed that 15% of R1 resections indicated multifocal margin

Table 1 Histopathological and resection classification data

	Prospective			Retrospective
	Conventional	Standard 0 mm	Standard 1 mm	
Resection [*n*/*n* (%)]				
R0	36/42 (86)	22/42 (52)	15/42 (36)	61/78 (78)
R1/2	6/42 (14)	20/42 (48)	27/42 (64)	17/78 (22)
Site of R1				
Uncinate	ND	10	18	ND
Posterior	0	6	12	6
Anterior	ND	0	3	2
Pancreatic transection	6	6	6	7
Groove SMV	0	1	3	ND
Distal duodenum	0	0	0	1
Proximal duodenal/gastric	0	0	0	2
Common bile duct	0	0	0	1
Number of affected sites				
1	6	17	18	17
2	0	2	3	0
3	0	1	6	0
Total	6	20	27	17
T1 [*n* (%)]		3 (7)		1 (1)
T2 [*n* (%)]		5 (12)		18 (23)
T3 [*n* (%)]		34 (81)		59 (76)
T4 [*n* (%)]		0 (0)		0 (0)
N0 [*n* (%)]		6 (14)		14 (18)
N1 [*n* (%)]		36 (86)		64 (82)

SMV, superior mesenteric vein; ND, not done.

Table 2 Breakdown of resection margin involvement according to the number of involved margins per specimen and the distribution of margin involvement

	Pancreas transaction margin		Anterior surface		Posterior surface		Groove of SMV		SMV		Bile duct		Duodenum		Uncinate	
	0 mm	1 mm	0 mm	1 mm	0 mm	1 mm	0 mm	1 mm	0 mm	1 mm	0 mm	1 mm	0 mm	1 mm	0 mm	1 mm
Case 1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Case 2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 3	–	–	–	–	+	+	+	+	–	–	–	–	–	–	–	+
Case 4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 5	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 6	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	+
Case 7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Case 8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 9	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 10	–	–	–	+	–	+	–	–	–	–	–	–	–	–	+	+
Case 11	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 12	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 13	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
Case 14	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Case 15	–	–	–	–	+	+	–	+	–	–	–	–	–	–	–	+
Case 16	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 17	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Case 18	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 19	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 20	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+
Case 21	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 22	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 23	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 24	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 25	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 26	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Case 27	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
Case 28	–	–	–	–	+	+	–	–	–	–	–	–	–	–	+	+
Case 29	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Case 30	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Case 31	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 32	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 33	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 34	–	–	–	+	–	+	–	–	–	–	–	–	–	–	+	+
Case 35	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Case 36	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 37	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Case 38	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	+
Case 39	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Case 40	–	–	–	–	+	+	+	+	–	–	–	–	–	–	+	+
Case 41	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–
Case 42	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–

SMV, superior mesenteric vein.

involvement (i.e. more than one margin involved in a single specimen) for the 0 mm in contrast to 33% for the 1.0 mm margin. The posterior and medial margins were the most commonly involved margin locations at 0 and 1 mm. Out of the total 20 cases of R1 resection at 0 mm, 17/20 R1 resections showed tumor infiltration at a single site (eight uncinate, six neck, three posterior surface), two patients had tumor infiltration in two stained areas and in one patient tumor infiltration was found in three stained areas.

Out of the total 27 cases of R1 resection at 1 mm, 18/27 R1 resections showed tumor infiltration at a single site (nine uncinate, six neck, three posterior surface), three patients had tumor infiltration in two stained areas, and in six patients, tumor infiltration was found in three stained areas. Interestingly, the uncinate margin was the most common site of infiltration in 10 and 18 of these R1 specimens at 0 and 1 mm, respectively. Uncinate margin infiltration was either alone (n = 8 at 0 mm and n = 9 at 1 mm) or in combination with the posterior surface

and SMV groove (n=1 at 0 mm and n = 3 at 1 mm), in combination with the posterior surface (n = 1 at 0 mm and n=3 at 1 mm), or in combination with the posterior and anterior surface (n = 0 at 0 mm and n = 3). In all, the uncinate margin was determined to be the most frequent site with residual tumor mass by far (n = 10, 42% at 0 mm) and (n = 18, 43% at 1 mm). Invasion of the uncinate margin was present in 42% of specimens at the 0-mm margin and 43% at the 1.0-mm margin.

In summary, if R1 resection is defined by a positive margin of 0 mm [33–35], 48% of the present patients achieved R1 resection. If R1 resection is defined by the presence of tumor cells within 1.0 mm [30,36], 64% of the present patients achieved R1 resection. Pancreatic neck transaction invasion resulted in an additional percentage of R1 resections for any definition of R1 on the inked margins. Thus, the rate of R1 resections was 48% when R1 was defined according to the 0-mm rule and 64% when R1 was defined according to the 1.00-mm rule (ratio: 2.2).

Discussion

RM status is an important prognostic factor in pancreatic cancer [2,37,38]. Although it is assessed histopathologically, there is currently no internationally recognized standard protocol for pathological examination and reporting of pancreatic head specimens, nor a universally accepted definition of CRM positivity. Meaningful comparison of R1 rates between individual centers is further complicated by the lack of standardized terminology for margins, which may explain the wide variation in published R1 rates. Increasing evidence exists to suggest that the standard of histopathological processing and reporting has a significant impact on R1 resection rates [20,27,28]. The hypothesis that R1 resections are commonly under-reported is also supported by the observation that 60–80% of cases with resected pancreatic cancer develop local recurrence [39–41], a finding that seems to be inconsistent with quoted R1 resection rates of less than 20%.

The Leeds [42] and Heidelberg [28] groups were the first to show that the standardization of histopathological study resulted in a significant increase in R1 resection rates, without requiring any change in surgical technique (respectively, from 53 to 85% [43] and 14 to 76% [28]). Thus, a high rate of R1 resection in PDAC is clearly a marker of high-quality pathology and depends, first, on the number of peripancreatic soft tissue RMs examined, second, on the number of blocks analyzed [30,31], and third, on the minimum clearance in millimeters used to define microscopic margin involvement (R1).

In a study published recently by Campbell *et al*. [44], tumor involvement within 1.0 mm of, but not directly reaching, one or more RMs represented 45% of the 79% of RMs identified as positive. In the most recent series, comparisons of R1 rates performed using the UICC criteria (R1: 0 mm definition), which are commonly used in North America [5,33,34], and those achieved using the UK Royal College of Pathologists criteria (R1: 1.0 mm definition) [30] show ratios ranging from 1.3 to 1.8 [28,44–46]. The ratio was 2.2 in the present study. Katz *et al*. [47] reported a ratio of 5.5 (4–22%) in a study in which only the superior mesenteric artery margin (SMAm) was assessed and in which 76% of patients had received preoperative radiochemotherapy; this study also showed that preoperative CT overestimated the SMAm in 73% of patients. Hartwig *et al*. [17] reported a maximum ratio of 8.4 in a study comparing the 0 mm definition with the revised 'R1=1.0 mm' definition (4.8–40.5%).

In our study, retrospective analyses of data from patients treated in our department between 2004 and 2009 with respect to the classification of the pancreatic head resections using the traditional dissection technique showed that the percentage of R1 resections was 21.7%, which is in agreement with the literature [8,11,48,49]. Shifting from traditional pathological examination procedures (mainly bivalving) to serial slicing of the specimen in a single axial plane, that is, perpendicular to the longitudinal axis of the duodenum as advocated in recent studies [27] resulted in an increase in the R1 rate from 14.3 to 64.3% in the prospective series. This is in agreement with a publication of the Heidelberg

Table 3 R1 resection rate for each margin increment (0 and 1.0 mm) and the proportion of patients with at least one, two, or three positive margins

Margin width (mm)	*n*/*n* (%)			
	R1 resection	One positive margin	Two positive margins	Three positive margins
0	20/42 (48)	17/20 (85)	2/20 (10)	1/20 (5)
1.0	27/42 (64)	18/27 (67)	3/27 (11)	6/27 (22)

Table 4 Resection margin status and R1 rates in our study compared with some published literature

References	Number of patients	RM status	R1 rate at 1 mm (%)
Nishimura *et al*. [50]	157	R1, R2	6
Sohn *et al*. [9]	616	R1	12
Neoptolemos *et al*. [7]	541	R1	11
Verbeke *et al*. [27]	26	R1	85
Westgaard *et al*. [14]	40	R1	45
Menon *et al*. [20]	27	R1	82
This study	43	R1	64

RM, resection margin.

group [28] (Table 4). The data also provide further evidence to indicate that robust pathological practice is a more important determinant of R1 classification in pancreatic cancer than operative expertise.

Longitudinal opening of the main pancreatic duct and common bile duct has traditionally been the preferred dissection method. This technique is of limited value for the assessment of the RMs, tumor origin, and tumor extension. Opening of the ducts disrupts the specimen surface along two tracks that run across the entire head of pancreas. This interferes with accurate evaluation of the CRM. As the common bile duct traverses the pancreatic head posteriorly, it is usually opened through the posterior surface, hence disrupting that part of the CRM that is frequently involved [27,51–54].

The axial slicing technique adopted in this study does not prescribe longitudinal opening of the pancreatic or bile duct; hence, the entire surface (or CRM) of the pancreatic head remains intact. Axial slicing is easy to perform, independent of the location and nature of the pathology encountered. A large number of slices are produced – usually between 10 and 13 – allowing extensive views of the lesion and its relation to the entire CRM and key anatomical structures [27]. Interestingly, axial slicing was the standardized dissection technique used in the recent studies that reported an unusually high R1 rate of over 75% [20,27,28]. The frequent identification of margin involvement reported in these studies is at least partially explained by the fact that all parts of the CRM can be inspected in each specimen slice obtained with this technique. This seems to indicate that the dissection and sampling technique has a significant impact on the assessment of the margin status in PD specimens.

Malignant pancreatic tumors often invade the retroperitoneal peripancreatic tissues. The retroperitoneal peripancreatic tissue surrounds the first 3–4 cm of the SMA origin behind the SMV [52,55,56]. Gockel *et al.* [57] have defined this anatomical structure as 'mesopancreas' similar to the mesorectum. Therefore, PD with curative intent should include complete clearance of the peripancreatic retroperitoneal tissue, which represents the most tedious step of PD, with an increased risk of intraoperative bleeding. The importance of the retroperitoneal RM was confirmed by Westgaard *et al.* [14].

When analyzing the distribution of margin involvement in R1 resections for pancreatic cancer and despite the current lack of consensus in terminology to denote the different CRMs, the finding that the uncinate margin represents the most frequently involved margin (42% at 0 mm and 43% at 1 mm), followed by the posterior margin is also consistent with the existing literature [20,27,28,58]. This was followed by the SMV groove CRM and anterior pancreatic surface. This pattern of CRM involvement is in line with Japanese studies [10,59]. Involvement of the pancreatic transection margin was observed in six cases of R1 specimens in the present study, a low rate that may be explained by the impact of intraoperative frozen-section examination of that margin.

The 'uncinate margin' is confusing as it is mainly used synonymously with the medial CRM, but occasionally refers to a true transection margin, produced by the surgeon when dividing the uncinate process as close to the SMA as possible [60,61]. With current standardized surgical procedures, however, the uncinate process remains intact and dissection of the SMA is performed in the soft tissue plane, which corresponds to the medial CRM of the specimen. Owing to morphological changes during formalin fixation, it is of utmost importance to color the uncinate RM directly after surgical resection. If the uncinate margin is not assessed separately, a positive margin here can be misinterpreted as a positive margin in the posterior or SMV groove CRM. We strongly believe that the complete and meticulous surgical resection of the uncinate margin as the structure to the right of the mesenteric artery must become the standard surgical approach in pancreatic head resection.

Although microscopic margin involvement is staged as 'R1' irrespective of which parts of the CRM are involved, detailed CRM mapping is important. It provides feedback both to the surgical and to the radiological teams, to enable improved preoperative assessment of resectability, identification of areas at risk of incomplete resection, and improved surgical technique. Further studies are needed to correlate the data from margin mapping and involvement to show the significance of involvement of each individual CRM in terms of survival and recurrence pattern.

Conclusion

Standardization of the histopathological examination of PD specimens influences the reporting of RM status and represents a more accurate assessment of curative and noncurative resection rates. Our study seems to indicate that RM involvement is significantly more frequent than reported commonly and the rates obviously depend on the definitions of microscopic invasion used. The uncinate margin is a frequent site for positive RMs, which has potential therapeutic implications. Owing to morphological changes during formalin fixation, it is of utmost importance to color

uncinate RM directly after surgical resection. We strongly believe that the complete and meticulous surgical resection of the uncinate process *en bloc* with all the peripancreatic tissues between the artery and the pancreatic parenchyma must become the standard surgical approach in pancreatic head resection. Meanwhile, the standardization of histological examination is not only necessary to provide accurate prognostic information, but may represent a significant step forward in the design of future randomized controlled trials and the optimization of adjuvant treatment strategies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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