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Pancreatoduodenectomy with venous resection for ductal adenocarcinoma rarely achieves complete (R0) resection

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Original article

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Abstract

Background: Pancreatoduodenectomy with venous resection is considered standard of care for patients with tumour involvement of the superior mesenteric/portal vein (SMV/PV) and deemed justified if an R0-resection can be achieved. The aim of this study was to provide a detailed pathology assessment of the site and extent of margin involvement in specimens resulting from pancreatoduodenectomy with venous resection.

Methods: Retrospective observational study including patients undergoing pancreatoduodenectomy with or without venous resection for pancreatic ductal adenocarcinoma between 2015 and 2017. Detailed histopathological mapping of the tumour and its relationship to the margins was undertaken.

Results: 98 patients met the inclusion criteria. An R0-resection, based on 1 mm clearance, was achieved in 16 of 73 patients without venous resection and in 1 of 25 patients with venous resection ($p=0.063$). The surface of the SMV-groove was the most frequently involved margin (23 of 25 patients with venous resection, 37 of 73 patients without venous resection; $p<0.001$). The broad invasive tumour front as well as the absence of peripancreatic fat at the SMV-groove were the reasons for these findings.

Discussion: An R0-resection following pancreatoduodenectomy with venous resection for ductal adenocarcinoma can rarely be achieved due to microscopically involvement of the SMV-groove.

INTRODUCTION

Vascular resections are increasingly being used during pancreatectomy for malignant disease[1]. This is the result of significant advances in surgical technique as well as the increased use of neoadjuvant treatment and the ensuing need to extend the concept of what is considered resectable disease[2-5]. Multivisceral surgical resection for pancreatic malignancy has been shown to be associated with an increase in morbidity, but not in mortality[5]. A resection leaving behind no microscopic residual disease (R0) and an uneventful postoperative course have previously been considered the main surgical objectives for the treatment of pancreatic cancer patients[6]. Consequently, it has been argued that venous resection during pancreatoduodenectomy is justified if an R0-resection can be achieved[7-9]. However, considering the ongoing dissensus regarding the evaluation of the margins and consequently, the wide variation of reported R0-resection rates[10], the impact of venous resection on the margin status is not precisely known.

The aim of this study was to map the relationship of the tumour to the resected vein and the specimen surfaces, in particular the surface of the superior mesenteric vein (SMV)-groove adjacent to the venous resection. It was hypothesized that even with venous resection, an R0-resection can rarely be achieved.

METHODS

Patients

All patients with pancreatic ductal adenocarcinoma (PDAC) in the head of the pancreas undergoing open pancreatoduodenectomy (pylorus-preserving or classic) with venous resection (PDVR) or without (PD) in the period 1.1.2015 – 12.31.2017 were identified from a prospectively maintained hospital database. Patients with primary resectable pancreatic cancer, as defined by the National Comprehensive Cancer Network (NCCN) criteria[11], were included in the study. Patients who had undergone types of resection other than pancreatoduodenectomy or were diagnosed with tumour entities other than pancreatic ductal adenocarcinoma (PDAC) were excluded. According to the national guidelines, all patients with borderline pancreatic cancer (BRPC) were recommended treatment with neoadjuvant chemotherapy, preferably FOLFIRINOX[12]. Accordingly, patients who received neoadjuvant chemotherapy and patients with BRPC or locally advanced pancreatic cancer, were excluded. However, in 2015 the NCCN panel consensus was to use a more liberal definition of borderline resectable disease[13]. For SMV/portal vein (PV) involvement, the definition on borderline resectable disease was changed from: "Venous involvement of the SMV or portal vein (PV) with *distortion or narrowing* of the vein or *occlusion* of the vein" in the 2012 guidelines to "solid tumour contact with the SMV or PV > 180˚, *contact of ≤ 180˚ with contour irregularity of the vein* or thrombosis of the vein"[14]. This latter definition was implemented in our hospital during the course of the study. Consequently, a minority of patients with SMV/PV tumour contact <180˚ and minimal contour irregularity underwent upfront surgery and were included in the study. The Hospital Review Board approved the study. Written informed consent was obtained from all patients. The manuscript was

completed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[15].

Surgical technique

All patients were evaluated preoperatively in a multidisciplinary setting. Preoperative work-up included computed tomography (CT) with a standard protocol optimized for imaging pancreatic tumours [16] and chest CT to evaluate primary or metastatic tumour sites. As a rule, time between last CT and surgery was no longer than six weeks. Depending on intraoperative findings, a pylorus-preserving or classical pancreatoduodenectomy was performed along with standard lymphadenectomy. Adhering to the principles of oncological surgery, an SMV/PV resection was performed if there was as suspicion of invasion of the venous wall. A trial dissection along the SMV/PV or shaving the tumour off the SMV/PV, approaches that could compromise the integrity of the tumour were avoided[17]. Venous resection and reconstruction were performed as proposed by the International Study Group of Pancreatic Surgery (ISGPS)[9] and as described elsewhere[18, 19]. In brief, the vein on either side of the tumor-involved segment was dissected free, securing in- and outflow. The decision on the reconstruction technique was based on intraoperative findings and the surgeon´s preference.

Pathology assessment

Macroscopic examination included multicolour inking of the specimen surfaces, serial axial specimen slicing and extensive tissue sampling. As previously described[20], all specimen surfaces were systematically embedded at multiple craniocaudal levels through the head of pancreas, rather than just where tumour was macroscopically suspected being close to a surface. In specimens with venous resection, the segment or wedge of resected vein was dissected en-bloc with the pancreatic head and embedded in its entirety. Tumour size was evaluated based on combined macro- and microscopical measurement. Local invasion (pT-stage) and regional lymph node metastasis were evaluated according to the UICC TNM 8th

edition[21]. The relationship of the tumour to the following specimen surfaces and margins was assessed: transection margins of the pancreatic neck, common bile duct, stomach and/or duodenum; the anterior surface and the posterior margin, the margin towards the superior mesenteric artery (SMA-margin) and the surface of the SMV-groove (SMV-margin)[22]. The presence of cancer cells less than 1 mm from any resection margin or specimen surface was reported as R1, except for the anterior, mesothelium-lined surface, where a clearance of 0 mm was reported as R1, according to pathology guidelines[22, 23]. All specimens were evaluated by an experienced pancreatic pathologist (C.S.V).

Statistical analysis

Continuous variables were presented as a median (range) or mean (s.d.), depending on data distribution. The χ^2 test, or Fisher's exact test when applicable, was used to compare frequencies. The Mann–Whitney *U* test was used for comparison of skewed continuous variables and two-sample *t* test for data with normal distribution. All statistical tests were two-tailed, and $p < 0.050$ was considered as significant. Data analysis was performed using SPSS version 25 for Windows® (IBM, Armonk, New York, USA).

RESULTS

During the study period, a total of 310 pancreatoduodenectomies were performed. Ninety-eight patients with pancreatic ductal adenocarcinoma met the inclusion criteria, of whom 25 had undergone pancreatoduodenectomy with venous resection (supplementary material, Figure 3). One-hundred and twenty-nine (42 %) patients underwent resection for pancreatic ductal adenocarcinoma. Thirty-one patients with borderline or locally advanced pancreatic tumours were excluded from the analysis. Of the patients who underwent venous resection and were included in the analysis, six had SMV/PV tumour contact <180˚ and minimal contour irregularity on preoperative imaging and were treated with upfront surgery. The remaining 19 patients had no signs of SMV/PV invasion on preoperative radiology. Median

time from last CT to surgery was 22 days (range 1 – 41, data not shown). In total, 34 patients were recruited during the first year of the study period, and some of the data on these patients have been published previously[24]. Baseline characteristics and histopathological data are shown in Table 1.

Involvement of the resected vein

In case of venous resection, segmental resection was more commonly performed than wedge resection. The median length of the resected vein was 15 mm (range 5-35 mm), measured after formalin fixation. Data on tumour involvement of the resected vein are shown in Table 2.

Margin involvement

There was no significant difference in R-status between the groups with and without venous resection (p=0.063; Table 1). Analysis of the site of margin involvement showed that the SMV-, SMA- and posterior margins were most frequently involved in both groups (Table 3). There was a significantly higher proportion of involvement of the SMV-groove in the group with venous resection: all but two patients with venous resection had microscopically involvement of the SMV-margin (23 of 25 versus 36 of 73, p<0.001). In both groups, more than half of the cases showed R1 at two or more margins (in 68% of cases with and 57% of those without venous resection, respectively), and the frequency of involvement of the various margins was similar (supplementary material, Table 4). Microscopical mapping revealed that in 10 of the 23 cases with VR and R1 at the SMV-margin, the latter was involved at a distance of more than 3 mm from the resected vein. In the remaining 13 cases, tumour involvement of the SMV-groove was contiguous to the VR (Figure 1). Involvement of the SMV-groove was found equally often to the lateral of the VR (4 cases) as at the SMV-surface immediately cranial or caudal to the area of attachment between the vein and SMV-groove (6 cases). In three cases, the SMV-groove was involved in both locations, i.e. both to the sides and

above/below the tethered vein. The reason for this “combined” involvement of the resected vein and the immediately adjoining surface of the SMV-groove was the fact that pancreatic ductal adenocarcinomas are of a large size at the time of surgery (Table 1) and therefore have a broad invasive front that more often than not encompasses both the vein and the adjacent SMV-groove (Figure 2). In contrast, a narrow, finger-like tumour extension that exclusively affected the adherent vein was hardly ever observed. The configuration of the invasive tumour front also explained why the surface of the SMV-groove immediately adjacent to the tethered vein was involved in 6 of the 8 patients with tumour growth close to the vein, but without microscopical involvement of the venous wall proper (Table 2). Indeed, in those cases the median distance between the tumour and tunica adventitia of the vein was only 1.1 mm (range 0-4 mm). The large size of most tumours compared to the size of the pancreatic head also explained why margins other than and in addition to the SMV-margin were frequently affected (Table 3).

DISCUSSION

This study demonstrates that pancreatoduodenectomy with SMV/PV resection results in a high rate of microscopic margin involvement (R1) that does not significantly differ from the one observed in patients undergoing pancreatoduodenectomy without the need for venous resection. In spite of surgical resection of a venous segment or wedge, the SMV-groove was found to be microscopically involved in 23 of 25 patients, i.e. tumour cells were present less than 1 mm from the bare surface of the SMV-groove. In over half of the cases, the latter was involved immediately adjacent to the tethered vein, either to the lateral sides of the vein, directly above or below, or both. In the remaining cases, the SMV-groove was involved at a distance (> 3 mm) from the resected vein. Detailed histopathological mapping revealed the two determining factors of this high rate of margin involvement at this particular site. First, the microanatomy at the SMV-groove is characterized by the absence of peripancreatic fat, such that the surface of the SMV-groove overlies directly the pancreatic parenchyma without a "buffer" of adipose tissue separating the pancreas from the specimen surface, as it is present e.g. at the posterior or SMA-facing margins. Furthermore, the layer of loose fibrose tissue that connects the surface of the SMV-groove with the overlying vein is exceedingly thin. Consequently, in the case of a pancreatic cancer that intraoperatively is suspected to involve the SMV/PV, the microscopic distances that distinguish between tumour growing *close to the vein*, *into the venous wall* (at least infiltration of the adventitial layer) or *within 1 mm to the SMV-groove* are minute, in the range of a few millimetres or less (Table 2). Keeping this in mind, it is self-evident that the large size of the resected tumours and correspondingly, the broad invasive front of these tumours, is a second determining factor of the high rate of SMV-groove involvement. Indeed, if the tumour infiltrates the vein, the surface of the SMV-groove, both contiguous to the tethered vein or at a distance from it, is most likely also involved, i.e.

227 tumour cells lie < 1 mm from the specimen surface (Figure 2).

228 While the surface of the SMV-groove is sometimes considered a free anatomical
229 surface, this is incorrect because it has no cellular (i.e. mesothelial) lining. Instead, it is
230 covered with a microscopically thin layer of loose connective tissue that is attached to the
231 adventitia of the SMV and becomes disrupted during blunt dissection of the vein from the
232 surface of the groove. It is presumably along this delicate soft tissue layer that tumour
233 extension occurs and eventually results in involvement of (part of) the circumference of the
234 vein. In view of the comparably small diameter of the SMV/PV (usually < 10 mm), exclusive
235 tumour infiltration of the resected vein *without* involvement of the adjacent SMV-groove
236 would imply a narrow, finger-like tumour extension, which is not commonly observed in
237 pancreatic cancer. Consequently, the results of this study show that an R0-resection can only
238 rarely be achieved, even when performing a venous resection. The reason for the likely failure
239 of an R0-resection lies primarily with the biology of pancreatic cancer, in particular its highly
240 infiltrative nature and dispersed growth pattern, and the regional microanatomy rather than
241 with the inadequacy of surgery[25, 26]. The results of this study imply that achieving an R0-
242 resection as a formal argument in support of undertaking a pancreatoduodenectomy with
243 venous resection may need reconsideration[7-9]. Performing this procedure is warranted if it can
244 be achieved with a short- and long-term outcome that is comparable to that of standard
245 pancreatoduodenectomy.

246 In this study, the surface of the SMV-groove was frequently involved, and this
247 observation is in accordance with other reports that provide a detailed description of margin
248 involvement[27-29]. However, in a recent multicenter series of 229 patients with both primary
249 resectable and borderline resectable pancreatic cancers undergoing pancreatoduodenectomy
250 with venous resection, the reported R1-rate at the SMV margin was remarkably low – 36.3 %
251 - compared to 92 % in the present study. The overall R0-status was 37.3 %, which is

considerably higher than in the current study (4 %) [28]. While the reasons for this divergence of findings have not been investigated, underreporting of microscopic margin involvement is a likely factor. Indeed, the detection rate of microscopic margin involvement is dependent on several aspects of the pathology examination procedure, in particular the specimen dissection technique and extent of sampling from the various specimen surfaces[20]. Unfortunately, studies do not always specify how specimens were evaluated[30-32], and particularly not how the margins of and around a venous resection were examined. Furthermore, in some studies the R1-rate is stated for series that included other histological tumour entities in addition to pancreatic ductal adenocarcinoma or patients who had undergone neoadjuvant therapy. These differences in composition of the study series make comparison with findings in the current study difficult. The results of a literature review of relevant studies that investigated the margin status following pancreatoduodenectomy with venous resection using the same stringent inclusion and exclusion criteria as in the current study, are presented in supplementary material (Table 5).

In the current study that aimed at histological tumour mapping, tissue sampling was extensive, in as far as all specimen surfaces were examined at multiple levels throughout the pancreatic head, and the venous resection was embedded in its entirety. However, as none of the current national pathology documents provides guidance for the examination of pancreatoduodenectomy specimens with venous resection, practice is likely to be of varying standard. At this point it should be mentioned that the detection of tumor cells within 1 mm to a margin is an irrefutable finding, whereas the lack of the detection of microscopic margin involvement is not, as it can be influenced by factors that determine the meticulousness of the examination. Another recent multicenter study reported R1 at the SMV-margin in only 42 % of the 36 patients undergoing PDVR, however, one fourth of the patients had received neoadjuvant chemotherapy[27]. The use of neoadjuvant therapy is a further factor that may lead

to incomparability of data. Indeed, as neoadjuvant therapy kills tumour cells seemingly haphazardly, the residual cancer often consists of scattered tumour foci that are separated by stretches of non-neoplastic tissue. Consequently, distances between remaining tumour cells increase, such that the R1-definition based on 1 mm clearance is no longer appropriate, making the evaluation of residual tumour beyond the resection margin even more troublesome[33]. This ambiguity was the reason for excluding from this study all patients who had undergone neoadjuvant treatment.

Of further consideration is the fact that margin involvement at the proximal or distal end of the resected vein was observed in only 3 patients, of whom 2 were also R1 at other margins. In fact, in only 7 (29 %) of the patients who underwent an R1 pancreatoduodenectomy with venous resection, a single margin was involved, while 17 patients (71 %) had involvement of two or more margins. This illustrates the fact that, in spite of resecting a substantial length of vein, the high likelihood of involvement of the SMV-margin and other margins precludes an R0-resection in most of these patients. Furthermore, all patients with involvement of the transection margin of the bile duct or pancreatic neck also had a positive SMV-margin, and the vast majority of these patients had in addition one or several other circumferential margins involved (supplementary material, Table 4). Taken together, these findings confirm that involvement of multiple margins is common, as it has been reported previously[34, 26, 35], and demonstrate that this is also the case if the SMV/PV is resected. The prognostic impact of the involvement of each individual margin of a pancreatoduodenectomy specimen is difficult to assess and a moot point in view of the fact that multiple margins are involved in most patients (60 % of the patients in the entire cohort had 2 or more margins involved (supplementary material, Table 4). While some studies suggest that a positive SMA-margin is prognostically more adverse than involvement of the SMV-margin[36], it is currently not clear whether the prognostic disadvantage of the former is

exclusively the result of microscopical residual tumour at that margin, or rather related to tumour growing into the peripancreatic soft tissue between the pancreatic head and SMA. The latter is notoriously rich in lymphatics, blood vessels and peripheral nerves and may as such contribute to increased tumour spread and, by implication, poorer patient outcome.

The high R1-rate observed in this study indicates that the traditional aim of achieving an R0-resection is in most cases unrealistic, even if the procedure is extended with a venous resection. Indeed, microscopically residual disease was still detected at the SMV-margin in 92 % of patients undergoing venous resection, indicating that R1 resection is determined by tumour biology rather than surgical technique. While this may at first seem disappointing, it is likely that without venous resection a considerably larger tumour burden would have been left behind at the site of tethering, akin an R2-resection, which is associated with a poorer survival[37]. Hence, the findings of this study do not advocate a change of practice regarding venous resection, but provide better insight into the degree of local oncological control that is achieved by venous resection during pancreatoduodenectomy for pancreatic ductal adenocarcinoma. While an R0-resection is unlikely, surgery achieves extensive tumour debulking that currently, for the vast majority of patients, remains unsurpassed by other treatment modalities. At the same time does the presence of multifocal microscopic margin involvement support the administration of neoadjuvant treatment, also in case of less advanced venous involvement.

A limitation of this study is its retrospective nature, although all data were collected prospectively and the study was hypothesis driven. A further limitation is the relatively small size of the study series of patients undergoing surgery with venous resection. However, the application of strict exclusion criteria such as neoadjuvant treatment, concomitant arterial resection and multivisceral resection ensured a relatively homogenous

patient cohort. This study does not include data on recurrence and post-resection survival, because microscopic margin involvement is only one of the many factors (incl. lymphovascular and perineurial tumour propagation) that determine these outcome measures. However, R1-status within the 1-mm margin rule was previously found to be associated with a decreased overall and disease-free survival for pancreatic head cancer [38, 39]

In conclusion, this study describes the tumour growth pattern at the SMV-groove in PDVR-specimens. Due to the peculiarities of the microanatomy at the SMV-groove and the broadly invasive growth pattern that is typically found in pancreatic cancer, an R0-resection can rarely be achieved with this surgical procedure. Underreporting of microscopic margin involvement in this complex micro-anatomical compartment likely contributes to the high R0-rates that have been reported previously. The findings seem to be in conflict with the prevailing opinion that PDVR is justified only if an R0-resection can be achieved. Based on our findings, we propose that achieving an R0/R1-resection is a more realistic aim. The obvious benefit of venous resection lies in the fact that it ensures the best possible reduction of the local residual tumour load, which inevitably would be larger should a venous resection not be performed. Hence, the study findings support the notion that surgery with venous resection is indicated, even in the light of (multifocal) microscopic margin involvement.

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495 **Table 1. Clinicopathological data of patient series with (+VR) and without (-VR) venous**

496 **resection**

	+VR (n=25)	-VR (n=73)	*p-value*
Age, years, mean (SD)	65.2 (10.4)	68.5 (9.6)	0.140 *
Sex Male Female	 14 11	 30 43	0.196**
Preoperative radiology Primary resectable Borderline	 19 6¶	 73 0	
pT-status≠ pT2 pT3	 13 12	 52 21	0.079**
pN-status≠ pN0 pN1 pN2	 2 9 14	 5 22 46	0.758 ∫
Tumor size, mm, median (range)	38 (23-58)	36 (21-61)	0.686§
Lymph nodes retrieved, median (range)	18 (9-29)	20 (8-48)	0.376§
Lymph node ratio, median (range)	0.19 (0-0.67)	0.24 (0-0.85)	0.935§
Extent of resection Pylorus-preserving+ Classic	 15 10	 47 26	0.695**
Perineural invasion Yes No	 25 0	 69 4	0.570∫

Lymphatic invasion Yes No	 24 1	 68 5	 1.000[∫]
Microvascular invasion Yes No	 21 4	 62 11	 1.000[∫]
Margin status R0 R1	 1 24	 16 57	 0.063[∫]

***Independent samples t-test, ** Chi-square – test, [∫] Fischer´s exact test, [§] Mann-Whitney U-test, [¶] tumour contact < 180 ° but minimal contour irregularity of the SMV/PV, [+] Pylorus-preserving pancreatoduodenectomy, [≠] TNM 8. edition**

Table 2. Venous resection: clinicopathological data (n=25).

Type of venous resection Segmental Wedge	 16 9
Length of venous resection, mm, median (range)	15 (5-35)
Proximal and/or distal margin of resected vein R0 R1	 22 3
Circumferential surface ("radial margin") of resected vein **R0** **R1**	 25 0
Depth of venous wall invasion No invasion Tunica adventitia Tunica media Tunica intima	 8 7 7 3
Distance from tumor to vein wall in patients without venous wall invasion, median (range), mm	1.1 (0-4)

Table 3. Rate of involvement of individual margins of pancreatoduodenectomy specimens with and without venous resection.

Margin	+VR (n=25)	-VR (n=73)	p-value
Bile duct margin R0 R1	25 0 (0%)	71 2 (2.7%)	1.000[∫]
Proximal gastric/duodenal margin R0 R1	25 0 (0%)	72 1 (1.4%)	1.000[∫]
Pancreatic neck margin R0 R1	21 4 (16%)	61 12 (16.4%)	1.000[∫]
Anterior surface R0 R1	20 5 (20%)	60 13 (17.8%)	0.773[∫]
Posterior surface R0 R1	15 10 (40%)	47 26 (35.6%)	0.695 [*]
SMV margin R0 R1	2 23 (92%)	36 37 (50.7%)	<0.001[∫]
SMA margin R0 R1	13 12 (48%)	38 35 (47.9%)	0.996 [*]

552 ∫ **Fischer´s exact test, * Chi-square – test**
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