Diagnostic and intraoperative targeted molecular imaging for pancreatic cancer

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Chapter | 3

Tumor Characteristics and surgical technical aspects of R1 in pancreatic cancer surgery

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ABSTRACT

Background: The prognosis of patients with PDAC remains poor and selection of patients for potentially curative surgery is challenging. Here, we examined the impact of margin-positive (R1) resection on locoregional recurrence and overall survival (OS), tumor characteristics and/or surgical technical factors that determine R1 resection in PDAC surgery, and how these factors affect outcome.

Methods: This retrospective study included 470 patients who underwent surgery for PDAC. The effect of tumor margin status, patient characteristics, and tumor characteristics on locoregional recurrence, distant recurrence, and OS were assessed.

Results: R1 resection was associated with decreased OS ($p<0.001$) and reduced time until locoregional recurrence ($p<0.005$). In contrast, disease recurrence patterns were similar between R1 and R0 patients. The main risk factors for early recurrence were tumor stage, tumor-positive lymph nodes (N1), and perineural invasion. Among patients with tumor-negative lymph nodes (N0), those with R1 resections had significantly reduced OS compared to patients who underwent R0 (radical) resection.

Conclusion: For pancreatic cancer surgery, R1 status is determined largely by the tumor characteristics. Although R1 resection is a major contributor to reduced survival and early recurrence, overall recurrence patterns are similar between R0 and R1 patients. Finally, in N0 patients, surgical factors affect R1 status.

INTRODUCTION

The incidence of pancreatic ductal adenocarcinoma (PDAC) is increasing. Despite recent advances in cancer therapy, including improved chemotherapy regimens, overall survival (OS) among patients with PDAC remains poor.[1] Currently, radical surgical resection, combined with (neo)adjuvant chemotherapy, is the only potentially curative treatment. Unfortunately, among patients who undergo surgical resection, margin-positive resections (R1) and rate of recurrence are high.[2, 3] Several factors have been identified as potentially affecting outcome among patients who undergo surgical resection; these factors include resection margin status, tumor size, the presence of perineural and/or lymphangioinvasion, and lymph node status. Among these factors, margin status receives the most attention in literature, yet remains the most controversial and debatable factor.[4] More than two decades ago, Yeo et al. reported that patients who underwent a radical (R0) pancreatoduodenectomy had a 5-year survival rate of 26%, whereas patients who underwent an R1 resection had a 5-year survival rate of only 8%.[5] In addition, Ghaneh et al. recently reported the results of a large multicenter, randomized controlled trial in which they found a significant difference in median survival between R0 resection (24.9 months) and R1 direct positive margin resection (18.7 months).[6]

In contrast, a growing body of data has become available showing that resection margin status is not an independent risk factor for survival. [7-10] One reason suggested to explain this finding is the lack of a standard, international consensus for pathological evaluation and assessment, as well as the lack of a uniform definition of microscopic margin involvement.[11, 12] In addition to this lack of a clear definition, geographical differences have been observed. For example, in the US, a resection margin is considered to be positive if the tumor cells have reached the inked margin;[5, 13] in contrast, in Europe a resection is defined as R1 if the tumor is present within 1 mm of the resection margin.[11, 14, 15] This discrepancy has led to a wide range of reported rates of microscopic resection margin involvement (R1) from less than 20% to more than 75% of cases.[14, 16-20]

When using the R0 definition “absence of tumor tissue at the ink margin”, 50-80% of these patients will develop local recurrence.[21, 22] This finding indicates that this definition does not accurately represent clinically relevant outcomes such as disease-free survival (DFS). Recently, Osipov et al. reported an improved DFS when defining a R0 resection as tumor cells >2 mm from the margin; specifically, increasing the margin from 0.5 mm to 2 mm increased both OS and DFS, whereas further increasing the margin >2 mm did not significantly improve clinical outcome.[23] These results support reports by Chang et al.[24] and Gebauer et al.,[25] who recommend a resection margin definition of 1.5 mm or 2 mm. An alternative hypothesis suggests that recurrence following R1 resection is not due to residual tumor cells, but rather a more aggressive biology of the original tumor.[26, 27] This hypothesis is based on the finding that among patients with a recurrence, an isolated recurrence without distant metastases is relatively rare, occurring in only 10-25% of these patients.[7, 28]

In addition to a high rate of R1 resections, another major problem is the significant prevalence of early recurrence, either locoregional or at distant site, within six months following surgery. Although these patients underwent an extensive surgical procedure with high morbidity and a high risk of reduced quality of life, they received no oncologic benefit.

Here, we investigated a relatively large cohort of pancreatic cancer patients at a tertiary referral center in order to correlate microscopic margin status to survival, local control, and distance metastasis. In addition, we performed a subset analysis in order to investigate the impact of tumor biology characteristics and surgical technical aspects.

MATERIALS AND METHODS

Study design

This retrospective database study was approved by the Institutional Medical Ethics Committee at Leiden University Medical Center (LUMC) in Leiden, the Netherlands. Data were retrieved from the electronic patient records of all patients who underwent pancreatic cancer resection at LUMC from January 2006 through December 2016, and follow-up data were collected through October 2017. Patients were included in the study if the diagnosis of pancreaticobiliairy adenocarcinoma was confirmed by pathological examination; patients with any other histopathological diagnosis were excluded. The demographic information and patient characteristics collected in the database included the patient's age at the time of surgery, sex, and type of surgery. The tumor characteristics included pTNM stage, grade, histopathological diagnosis, lymph node involvement, and lymphangio- and/or perineural invasion.

For detailed information on the indications for surgery, adjuant therapy and follow-up plan, please see supplementary methods. Recurrence was defined as evidence of disease on an imaging scan. Local recurrence was defined as the presence of disease in the surgical bed. Regional recurrence was defined as presence in the mesentery, periaortic soft tissue, the pancreatojejunal anastomosis, or in the intracaval, periceliac, and/or retroperitoneal lymph nodes. Distant metastases were defined as the presence of disease in the omentum, peritoneum, solid organs, and/or pelvic lymph nodes. We defined early recurrence as recurrence that occurred within six months following surgery, based on the published definition.[29, 30]

Pathological assessment

Macroscopic and microscopic examination of the pancreatoduodenectomy specimen was performed using standardized methods in accordance with the guidelines established by the Dutch Pancreatic Cancer Group (DPCG), which followed the recommendations reported by Verbeke and colleagues.[11, 14] Before 2010, examination was performed by bi-valving of the specimen in accordance to Rosai and Ackerman's surgical pathology and Adsay et al. After the specimen is resected, the surgeon attaches colored beads to specific resection margins. Upon receiving the specimen, the pathologist then uses multicolor inking of the

specimen in order to clearly identify the margins. The following terms were used to define the margins: posterior margin, vascular margin (superior mesenteric vein or superior mesenteric artery), common bile duct margin, anterior margin, pancreatic neck margin, caudal margin, and circumferential margin.

Histological findings were reviewed to confirm the diagnosis, tumor characteristics, and R1 status of the margins. Staging was determined using the TNM cancer staging system, 7th edition (2010). For this study, we used the following definition for R1 resection in accordance with Dutch guidelines: a surgical margin with malignant cells identified ⩽1 mm from the inked margin was considered positive, per the guidelines of the British Royal College of Pathology (RCPath).

Statistical analyses

Data were analyzed using SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). For a detailed statistical plan, please see supplementary methods. Kaplan-Meier analysis and the log-rank test were used to analyze differences in survival between groups. Characteristics that were found to be correlated with either recurrence status or survival were included in a Cox proportional hazards regression analysis. Differences were considered statistically significant at $p<0.05$.

RESULTS

From January 2006 through December 2016, a total of 470 patients underwent surgery for pancreaticobiliairy adenocarcinoma at our center. Among these 470 patients, 322 patients underwent resection (68.5%); the remaining 148 patients (31.5%) underwent exploratory surgery only, either with or without palliative bypass surgery due to distant metastases or non-resectable disease. Of the resected patients, 299 underwent Whipple surgery or pylorus-preserving pancreaticoduodenectomy (PPPD), 35 patients distal pancreatectomy, and 12 total pancreatectomy. Among the 322 resected patients, 193 (59.9%) had an R0 resection, and 129 patients (40.1%) had an R1 resection; 161 of these 322 patients were men, and 161 were women, the mean age was 65.4 years, and the median survival time following resection was 18.0 months. Compared to the

R0 group, more patients in the R1 group received adjuvant therapy (49.2% vs. 59.7%, respectively; p=0.065). Prior to adopting the so-called Verbeke protocol for grossing of pancreas specimens (i.e., from 2006 through 2009), the R1 resection rate was 32.4%; in 2010 and later, the R1 resection was 42.1%; these rates did not differ significantly (p=0.144). Compared to the patients in the R0 group, the patients who underwent an R1 resection (Table 1) had significantly larger tumors (p<0.001), more tumor-positive lymph nodes (p=0.001), and a higher prevalence of perineural invasion (p<0.001).

Patients with R1 resection have increased risk of recurrence

Of all resected patients 60.9% of patients developed a form of recurrence at follow up after resection: 32.6% developed locoregional recurrence, 46.9% developed distant metastases. Time until locoregional recurrence was significantly shorter in the R1 resection group (median: 16 months; 95% CI: 12.5–19.5) compared to the R0 group (median: 36 months; 95% CI: 5.3–66.7; p<0.005) (Figure 1A). Interestingly, in the first 6 months following resection, the prevalence of locoregional recurrence was similar between the R1 and R0 groups (~8%) (Figure 1A). Time until distant metastases was also significantly shorter in the R1 group (median: 15 months; 95% CI: 10.6–19.4) compared to the R0 group (median: 20 months; 95% CI: 13.4–26.6; p<0.05) (Figure 1B). Among the patients who developed metastases, metastases developed more rapidly in the liver (median: 8 months; 95% CI: 6.8–9.2) compared to extrahepatic distant metastases (median: 13 months; 95% CI: 10.6–15.4; p<0.001) (Figure 1C). Finally, time until overall recurrence was significantly shorter in the R1 resection group (median: 13 months; 95% CI: 9.9–16.1) compared to the R0 resection group (median: 15 months; 95% CI: 12.2–17.9; p<0.001) (Figure 1D). Locoregional recurrence was significantly correlated with perineural invasion (HR: 1.62; p<0.04), and the only significant predictor of distant metastases was lymph node status (HR: 1.96; p<0.005) (Table S1).

R1 status of the vascular margin negatively influences outcome

Next, an in-depth analysis was performed of the technical aspects of pancreatic cancer surgery and found that among the various surgical margins, the vascular margin was affected in 46.5% of patients who underwent an R1 resection (Supplementary Table S2). The location of the R1 margin had little effect on surgical outcome. Among the various margins, only the vascular margin

Table 1. Patient characteristics categorized by R0 and R1 resection.

Variable	R0 (N=193)	R1 (N=129)	*p*-value
Age in years, mean SD)	66 (10)	64 (9)	0.172
Sex, M/F	95/98	66/63	0.733
Death, N (%)	130 (67.4)	101 (78.3)	0.033
Median survival in months (95% CI)	22 (17.2-26.8)	15 (12.6-17.4)	<0.001
Tumor size in mm, mean (SD)	26 (15)	33 (15)	<0.001
Adjuvant therapy, N (%)	95 (49.2%)	77 (59.7%)	0.065
Tumor differentiation, N (%)			0.564
Well	40 (20.7)	23 (17.8)	
Moderate	80 (41.5)	53 (41.1)	
Poor	71 (36.8)	53 (41.1)	
Undifferentiated	2 (1.0)	0 (0.0)	
Lymph node status positive, N (%)	122 (63.2)	100 (77.5)	0.007
Median number of positive lymph nodes (IQR)	1 (0-3)	3 (1-5)	0.001
Tumor stage, N (%)			<0.001
IA	23 (11.9)	4 (3.1)	
IB	9 (4.7)	2 (1.6)	
IIA	40 (20.7)	19 (14.7)	
IIB	118 (60.6)	89 (69.0)	
III	2 (1.0)	13 (10.1)	
IV	1 (0.5)	2 (1.6)	
Perineural invasion, N (%)	104 (53.9)	97 (75.2)	<0.001
Lymphangioinvasion, N (%)	35 (18.1)	35 (27.1)	0.055

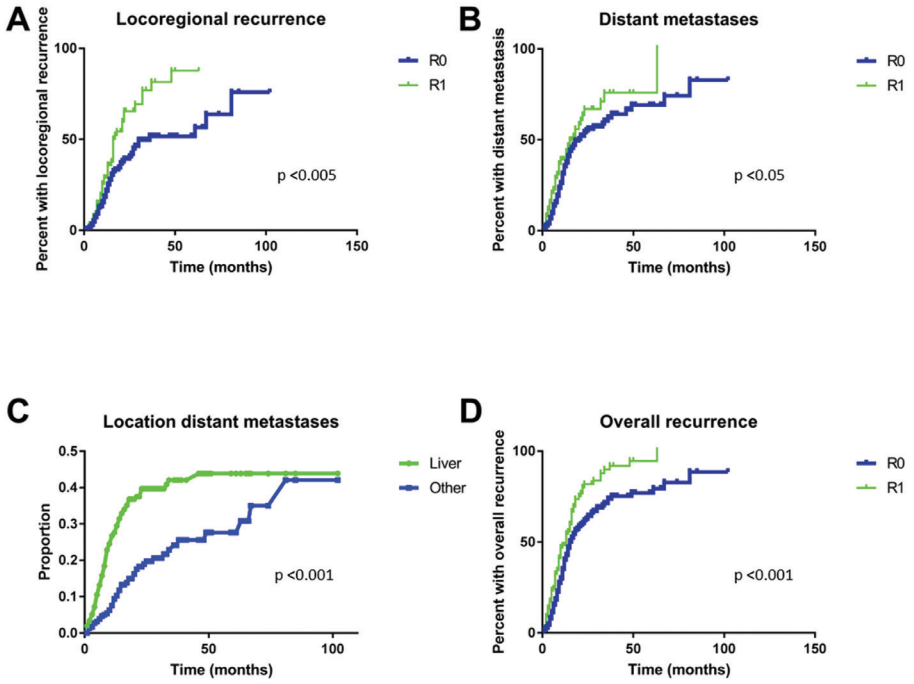

Figure 1. (A-B) Locoregional recurrence (A), and distant metastases (B) in patients who underwent R0 or R1 resection. (C) Time course of distant metastases in the liver or other locations. (D) Overall recurrence in patients who underwent R0 or R1 resection.

appeared to affect the clinically relevant outcome measures. Although the vascular margin did not affect OS (Figure S1A), performing an R1 resection at this margin increased the risk of local recurrence compared to other R1 margins, with a shorter amount of time until recurrence (median: 16 months; 95% CI: 14.5–17.5 vs. 28 months; 95% CI: 17.6–38.5; respectively; p=0.07) (Figure S1B). Other margins did not affect the time until local recurrence (Figure S1C). Lastly, distant metastases were not affected by the location of the R1 margin.

Among the 196 patients who had a recurrence, 55 (28.1%) had a recurrence within 6 months following surgery. The patients with early recurrence had a higher tumor stage, more tumor-positive lymph nodes, and a higher prevalence of perineural invasion compared to all other patients without a recurrence within 6 months following their resection, however none of these differences were significant (Table 2). Finally, among the patients who developed distant metastases, liver metastases were significantly more common in the early recurrence group compared to the patients in the late recurrence group (70.9% vs 22.5%, respectively; p<0.001).

Table 2. Patient characteristics categorized by time until recurrence.

Variable	<6 months recurrence (N=55)	All other patients (N=267)	*p*-value
Age in years, mean (SD)	64 (10)	66(10)	0.150
Sex, M/F	29/26	132/135	0.657
Death, N (%)	53 (96.4)	185 (64.5)	<0.001
Median survival in months	8	23	<0.001
Tumor size in mm, mean (SD)	32 (14)	28 (16)	0.083
Adjuvant therapy, N (%)	23 (41.8%)	149 (55.8%)	0.058
Tumor differentiation, N (%)			0.078
Well	6 (10.9)	57 (21.3)	
Moderate	20 (36.4)	113 (42.3)	
Poor	29 (52.7)	95 (35.6)	
Undifferentiated	0 (0.0)	2 (0.7)	
Lymph node status positive, N (%)	43 (78.2)	179 (67.0)	0.104
Median number of positive lymph nodes (IQR)	2 (0-4)	2 (1-5)	0.125
Tumor stage, N (%)			0.192
IA	2 (3.6)	25 (9.4)	
IB	1 (1.8)	10 (3.7)	
IIA	9 (16.4)	50 (18.7)	
IIB	38 (69.1)	169 (63.3)	
III	3 (5.5)	12 (4.5)	
IV	2 (3.6)	1 (0.4)	
Perineural invasion, N (%)	40 (72.7)	161 (60.3)	0.083
Lymphangio invasion, N (%)	15 (27.3)	55 (20.6)	0.275
Resection margin, N (%)			0.071
R0	27 (49.1)	166 (62.2)	
R1	28 (50.9)	101 (37.8)	

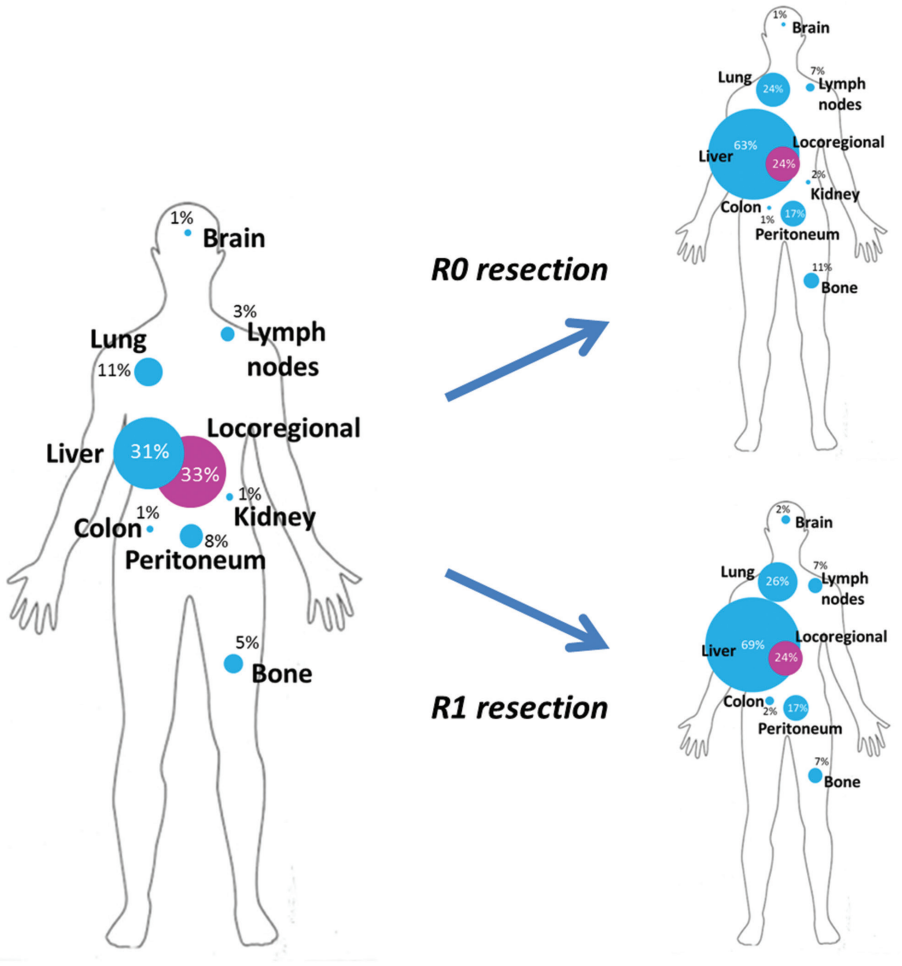

Figure 2. Spatial distribution of local recurrence (purple) and distant metastases (blue) following resection, for all patients (left) and only the patients with distant metastases sorted by R0 and R1 status (right).

Margin status does not affect long term patterns of recurrence

Among the patients who developed metastases, the majority of these patients (n = 99) developed liver metastases as the first site of distant spread, compared to only 52 patients with other distant metastases (primarily lung metastases). However, we found no difference in the pattern of metastases between the R0 and R1 resection groups (Figure 2). Interestingly, among our entire patient cohort, 14% presented with distant metastases within 5 months, and of the

patients who develop distant metastases, 26.3% of patients had liver metastases within 6 months after resection.

R1 resection reflects poor tumor characteristics and leads to decreased overall survival

The patients in the R1 resection group had significantly decreased OS time ($p<0.001$), with median survival of 15 months (95% CI: 12.6–17.4) compared to the patients in the R0 group (median OS: 22 months; 95% CI: 17.2–26.8) (Figure 3). Overall, the prognosis among the 55 patients with early recurrence was extremely poor, with overall survival similar to patients who underwent exploratory surgery without resection ($p=0.408$); the median survival time of these two groups was 8 and 5 months, respectively. Multivariable analyses revealed that perineural invasion, tumor-positive lymph node status (N1), and an R1 resection were significant predictors of OS, with hazard ratios (HR) of 1.44 ($p<0.02$), 2.15 ($p<0.001$), and 1.37 ($p<0.05$), respectively. Adjuvant chemotherapy had a protective effect on OS, with HR of 0.70 ($p<0.02$) (Table S3).

In node-negative (N0) patients surgical factors play a major role

Locoregional recurrence occurred significant earlier in the patients with R1 N0 (median: 17 months; 95% CI: 8.7–25.3) or R1 N1 status (median: 16 months; 95% CI: 12.3–19.8) compared to the patients with R0 N0 (median: 67 months) or R0 N1 (median: 27 months; 95% CI: 14.7–39.3) (Figure 4A). Finally, the patients with R0 N0 status had significantly longer interval until the development of distant metastases (median: 67 months; 95% CI: 17.0–117.0) compared to the patients in the R0 N1 (median: 14 months; 95% CI: 10.6–17.4), R1 N0 (median: 13 months; 95% CI: 6.1–19.9), and R1 N1 (median: 17 months; 95% CI: 12.7–21.3) groups (Figure 4B).

On average, the patients with R0 N0 status had significantly longer survival (median: 45 months; 95% CI: 0.00–95.3) compared to the patients with R0 N1 (median: 17 months; 95% CI: 14.7–19.3; $p<0.001$), the patients with R1 N0 status (median: 17 months; 95% CI: 10.4–23.6; $p<0.001$), and the patients with R1 N1 status (median: 14 months; 95% CI: 11.7–16.3; $p<0.001$). Moreover, the patients with R1 N1 status also had significantly longer survival than the patients who underwent exploratory surgery without resection (median: 5 months; 95% CI: 3.9–6.1; $p<0.001$ vs. the R1 N1 group) (Figure 4C). As discussed above, in the

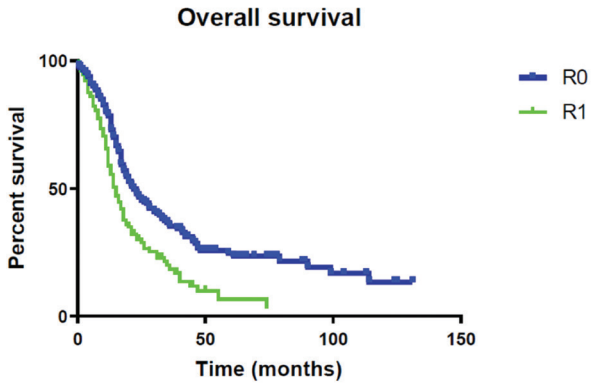

Figure 3. Subset analysis of the effect on overall survival of margin status

overall patient population tumor characteristics appears to affect outcome and local control more than performing an R1 resection. However, when we performed a subset analysis based on lymph node status, we found that survival was significantly worse in the N0 patients with an R1 resection, while tumor characteristics were similar (Table 3). Finally, we assessed the effect of adjuvant therapy on OS in node-negative and -positive patients (Figure 4D and 4E). All patient groups with adjuvant therapy show an improved OS, especially node-negative patients with R0 resection (figure 4D). Thus, for the node-negative patients performing a radical surgical resection will make a difference and, primary treatment should focus on getting the patient in an optimal condition to received adjuvant chemotherapy, to improve outcome.

Table 3. Effect of tumor biology.

	Lymph node status Negative (N0)			**Lymph node status Positive (N1)**		
	R0 N0	**R1 N0**	***p*-value**	**R0 N1**	**R1 N1**	***p*-value**
Perineural invasion, Y (%)	47.9%	55.2%	0.509	57.4%	81.0%	<0.001
Lymphangioinvasion, Y (%)	11.3%	20.7%	0.218	22.1%	29.0%	0.241
Tumor differentiation, N (%)			0.802			0.741
Well	22.5%	20.7%		19.7%	17.0%	
Moderate	35.2%	34.5%		45.1%	43.0%	
Poor	39.4%	44.8%		35.2%	40.0%	
Undifferentiated	2.8%	0%		0.0%	0%	
Mean tumor size in mm	27	27	0.933	26	34	<0.001

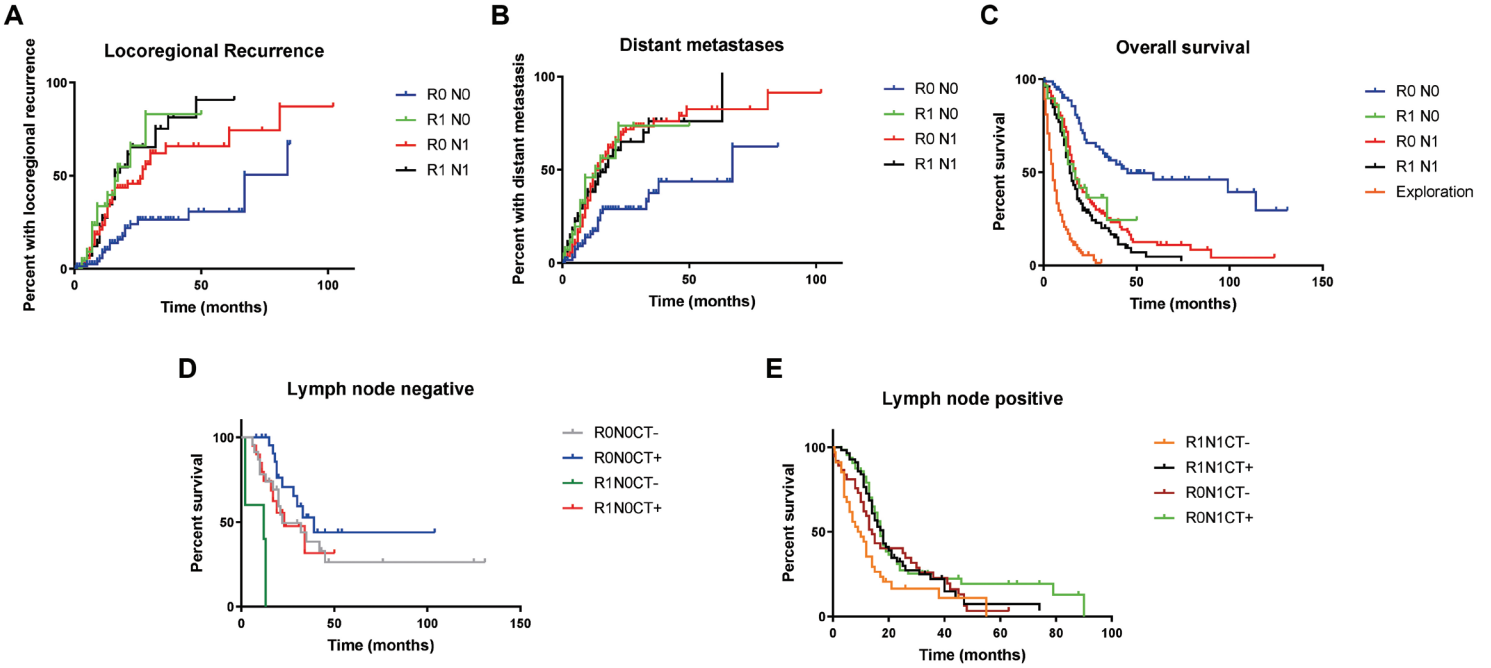

Figure 4. Subset analysis of the effect of margin status (R0 or R1) and lymph node status (N0 or N1) on (A) local recurrence, (B) distant metastases, (C) overall survival, and effect of adjuvant therapy on overall survival grouped by lymph node negative (D), and lymph node positive (E) patients. For comparison purposes, the overall survival of patients who underwent exploratory surgery only (without resection) is plotted in panel C.

DISCUSSION

Patient stratification in order to determine the optimal primary treatment modality with respect to pancreatic cancer surgery is challenging. Our results show a clear difference between R0 and R1 resection with respect to the clinically relevant outcomes OS and DFS. Several studies have gone one step further when defining clear margins, using a resection margin of ≥2 mm rather than >1 mm.[23-25] Potentially, the benefits associated with achieving an R0 resection in our study could have been even more robust if we had used a margin of ≥2 mm for R0 resections.

The posterior margin is often reported as the clinically relevant margin;[22, 23] however, this margin is the most challenging to clear.[4] In their recent study, Osipov et al., included the posterior surface, vascular groove, and uncinate margins in the posterior margin,[23] in accordance with criteria established by the American Joint Committee on Cancer. Their results are consistent with this study, in which the vascular margin was found to be the margin that has clinical consequences with respect to local recurrence. When we sorted the margins in a similar manner to that by Osipov et al., we found that 64.4% of R1 margins were posterior margins. In their recent study including 1151 patients, Ghaneh et al. found that an R1 direct posterior resection margin was associated with reduced overall survival and recurrence-free survival, whereas an R1 direct positive superior mesenteric margin was associated with local recurrence; for both of the margins, however, an R1 <1 mm did not affect clinically relevant outcomes.[6] On the other hand, other groups found that the transection margin of the pancreatic neck and the SMA-facing margin were the only significant R1 sites of R1 with respect to prognosis.[31] Although it is currently unclear why involvement of one margin would have higher prognostic value than another margin, the answer may lie in differences in the density of bloodvessels, nerves, and/or lymphatic vessels surrounding the pancreas. Another important factor to consider is that the resection commonly performed for pancreatic cancer is already quite an extensive procedure. Oftentimes, in order to resect more tumor the only option available to the surgeon is to perform a vascular resection. Therefore, a highly sensitive detection method for detecting the tumor's boundaries is essential, as the surgeon can still make a difference in the extent of the resection at the vascular margin and, according to this study, patient outcome.

A striking finding from our study is the relatively high recurrence rate within 6 months after surgery in both the R0 and R1 groups. This finding indicates that several lesions were not detected by preoperative imaging, possibly due to the use of conventional imaging modalities (i.e., computed tomography and MRI), which are currently not sufficiently sensitive for identifying small lesions. This issue is clinically relevant as mean OS of these patients was only 8 months compared to 11 months of OS in patients who receive palliative chemotherapy due to non-resectable or metastatic disease with FOLFIRINOX (leucovorin and fluorouracil combined with irinotecan and oxaliplatin). Thus, the patients with early recurrence often have a poorer prognosis following surgery.

We believe that focus should shift toward improving the detection of distant disease and determining the feasibility of local resection prior to performing pancreatic cancer surgery. For example, the development of detection methods with improved sensitivity will allow clinicians to select patients for the optimal primary treatment approach—i.e., direct surgery or neoadjuvant therapy—thereby resulting in improved outcome following resection. New molecular imaging modalities, such as fluorescence or photoacoustic imaging, could be used to improve the detection of tumor-positive lymph nodes and the resection at difficult margins such as the posterior margin.[32-34] These modalities provide both anatomical and molecular information. These imaging techniques, use an exogenous imaging agent directed against the tumor allowing the surgeon to image the tumor using a tumor-specific approach, providing important additional information during the resection. In addition, molecular imaging may be beneficial in terms of staging the disease. On the other hand contrast-enhanced ultrasound and/or tumor-specific PET imaging could be useful for preoperative detection of distant metastases and local staging. These methods can be used to detect disseminated disease in a specific manner, thereby increasing sensitivity and potentially improving early detection; alternatively, the surgeon may choose to stop a resection that is likely to have little or no oncological benefit.

Previous reports noted that R1 status can not only be a reflection of surgical quality, but can also be a reflection of the tumor's biological behavior.[26, 27] In our study, we found a significant difference in perineural invasion, tumor-positive lymph nodes, and tumor stage in our R1 patient group. These results are similar

to those reported by Kimbrough et al., who found a significantly higher lymph node ratio and more microvascular invasion in their R1 group.[35] This difference may also explain the difference in OS between our R1 and R0 patient groups.

Since the introduction of FOLFIRINOX for treating pancreatic cancer, chemotherapy has become an additional treatment modality that appears to improve resection rates and the outcome of patients with pancreatic cancer. In support of this notion, a recent study found that patients who undergo R1 resection followed by adjuvant therapy have similar OS compared to patients who undergo R0 resection.[23] Thus, if R0 and R1 are determined primarily by tumor biological behavior—e.g., lymphangioinvasion and lymph node status—then patients with tumors with aggressive biological behavior might reach the same improved prognosis as patients with tumors with less aggressive biological behavior after receiving (neo)adjuvant therapy.

Based on a subset analysis in our study, tumor biological behavior appears to have only a limited effect in N0 patients. Our results support the notion that the outcome of these patients is influenced primarily by margin status. Therefore, we suggest that in cases of suspected N0 disease based on preoperative—and possibly intraoperative—imaging, the surgeon should make every reasonable effort to achieve radical resection. Based on our results, involvement of the large vessels should be examined thoroughly during surgery, as the vascular margin is the margin at risk in nearly half of all R1 resections. Novel techniques such as fluorescence-guided surgery could aid the surgeon in these situations. In addition, these patients should receive adjuvant chemotherapy and/or local radiotherapy in order to improve an aggressive biological behaviour associated with potential R1 resection.

CONCLUSIONS

Here, we report the results of a large, single-hospital retrospective analysis of pancreatic cancer patients treated at a specialized pancreatic cancer center, in which we used a consistent R1 definition to examine the prognostic effect of specific positive margins. We found that patients with R0 resection have significantly longer survival, and a R1 vascular margin appears to be the most

clinically relevant margin. Furthermore, our data support the notion that R1 status is likely associated with more aggressive tumor biological behavior, thus identifying patients with a high risk of recurrence and who may benefit the most from adjuvant or neoadjuvant chemotherapy. Moreover, we found that achieving radical resection can change the outcome in lymph node-negative patients; therefore, involvement of the large vessels should be thoroughly examined intraoperative in patients with suspected N0 disease in order to achieve maximum local control.

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