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Evaluation of the MDACC clinical classification system for pancreatic cancer patients in an European multicenter cohort

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ABSTRACT

Background: The MDACC group recommends to extend the current borderline classification for pancreatic cancer into three groups: type A patients with resectable/borderline tumor anatomy, type B with resectable/borderline resectable tumor anatomy and clinical findings suspicious for extrapancreatic disease and type C with borderline resectable and marginal performance status/severe pre-existing comorbidity profile or age>80. This study intents to evaluate the proposed borderline classification system in a multicenter patient cohort without neoadjuvant treatment.

Methods: Evaluation was based on a multicenter database of pancreatic cancer patients undergoing surgery from 2005 to 2016 ($n = 1020$). Complications were classified based on the Clavien-Dindo classification. χ^2-test, Kaplan–Meier estimator and Cox regression hazard model were used for statistical analysis.

Results: Most patients (55.1%) were assigned as type A patients, followed by type C (35.8%) and type B patients (9.1%). Neither the complication rate, nor the mortality rate revealed a correlation to any subgroup. Type B patients had a significant worse progression free ($p < 0.001$) and overall survival ($p = 0.005$). Type B classification was identified as an independent prognostic marker for progression free survival ($p = 0.005$, HR 1.47).

Conclusion: The evaluation of the proposed classification in a cohort without neoadjuvant treatment did not justify an additional medical borderline subgroup. A new subgroup based on prognostic borderline patients might be the main target group for neoadjuvant protocols in future.

Introduction

Surgical advances have been made during the past decades in pancreatic cancer surgery; the combination of improved surgical experience, standardized operative techniques, technical advances of intensive-care medicine and centralization has reduced the mortality to a low single-digit rate, but patients operated with curative intent still have a median overall survival of only two years, despite modern chemotherapeutic regimes [1,2]. Implementation of neoadjuvant chemotherapy protocols such as FOLFIRINOX for high-risk patients could be a way forward. Borderline resectability (BR) based on anatomic tumor characteristics has been defined previously [3–5]. Also individual patient factors and tumor biology were shown to be important and might help understand patient prognosis. Since 2008, the MD Anderson Cancer Center (MDACC) pancreatic group is proposing to extend the solely anatomic

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definition of resectability to a clinical borderline resectable classification (CBRC) system (type A: resectable/anatomically BR, type B: prognostic BR, type C: medically BR) [6]. This CBRC system was evaluated in patients prior to the administration of neoadjuvant therapy in institutional cohorts and national databases including all patients, which underwent resection, by the MDACC group. Despite numerous publications from MDACC, the CBRC system has not found acceptance in daily practice [7,8]. One explanation could be that the classification system is mainly based on patients treated with neoadjuvant protocols - which is so far not representative for current clinical practice. Based on their survival data of type B patients and the higher morbidity risk profile in type C patients, the MDACC group promotes neoadjuvant therapy for all patients, which are classified as borderline resectable due to anatomic, prognostic or medical reasons. In contrast, the ISGPS does not recommend neoadjuvant treatment for anatomic borderline resectable patients, especially if this allocation is solely based on mesentericoportal axis involvement [5]. We therefore aimed to evaluate if the outcome of high-risk prognostic or medical patients after surgery without neoadjuvant treatment justifies medical optimization or neoadjuvant treatment prior to surgery and respectively the extension of the borderline resectable criteria.

Patients and methods

Patients

This retrospective analysis is based on prospectively collected European multicenter database of patients undergoing pancreatic surgery for PDAC from 2005 to 2016. Patients had to meet resectable or borderline resectable criteria based on the NCCN guidelines Version 2.2016, patients with neoadjuvant treatment were excluded [9]. In each center, patients signed an informed consent, declaring their agreement to collect clinical information. All participating centers obtained approval from their institutional review board.

Clinical and histopathological data

The primary endpoints of the study were perioperative morbidity and mortality, as well as progression-free (PFS) and overall survival (OS). Secondary endpoints were resection margin status, administration and completion of adjuvant therapy. The following parameters were included: clinical and pathological data (sex, age at time of surgery, comorbidities, weight loss, Ca 19-9 prior to surgery, tumor specific pre- and postoperative treatments, operative procedure, clinical/pathological TNM and UICC stage, resection margins based on the Leeds Pathology Protocol), reports of outside medical records, and communication with patients and their attending physicians [10–12]. Postoperative morbidity was defined using the Clavien-Dindo classification [13,14]. Complications graded as III to V were defined as surgically relevant major complications. Mortality was defined as death occurring within 90 days postoperatively.

Statistical analysis

Associations between categorical variables were assessed by χ^2-test. The OS was computed as the period from the date of surgery to either the date of death or last follow-up, whichever occurred first within 60 months. The PFS was defined as the period from the date of surgery to the date of recurrence or death, if details on time of progression were not available. Patients alive without recurrence at the last follow-up date or after 60 months were censored. For univariate survival analysis, the Kaplan-Meier method was used to generate survival curves and the log-rank test was used to assess differences between survival curves. Results are presented as median survival in months with 95% confidence interval. Cox regression model was used for multivariate analyses. Significant statements refer to P values of two-tailed tests that were <0.05. SPSS Version 22 was used for statistical analyses.

Results

Study cohort

The study cohort consisted of 1020 patients. If clinical findings warranted inclusion in more than one subgroup, patients were classified in priority of type C > B > A, 55.1% (n = 562) of all patients were classified as type A, 9.1% (n = 93) as type B and 35.8% (n = 365) as type C (Fig. 1).

Clinicopathological characteristics

The median age of the study population was 68 years (range 27–91). Due to the classification criteria (age ≥80), the type C subgroup had a significant higher percentage of patients older than 67 years (p = 0.010). The gender distribution showed no relevant correlations between the three subgroups (p = 0.224). All patients did not receive neoadjuvant treatment. The distribution of anatomically borderline resectable patients did not reveal a significant correlation with any subgroup (p = 0.837). No significant correlation of a specific procedure to any of the subgroups was evident (p = 0.817). Type B patients were found to have more often stage IV cancer (p < 0.001). Negative resection margins were achieved in 53.2% of patients. Type B patient status was significantly associated with positive resection margins (p = 0.020). Surgically relevant major complications (CD III-V) were seen in 21.1% (n = 215) of the study cohort. No statistically relevant correlation to any subgroup was evident (p = 0.124). Exclusion of all anatomically borderline patients did not reveal any correlation of major complications to any subgroup either (p = 0.236, type A:19.5% vs. type B:21.4% vs. type C:15.2). Including only anatomically borderline resectable patients, did not reveal any further correlations (p = 0.628, 43.5% vs. 33.0% and 33.9% in type A and C patients, respectively). The 90-day mortality rate was 4.0% (n = 41) within the whole study without association to any subgroup (p = 0.594). The presence of anatomical borderline characteristics in patients without prognostic or medical borderline characteristics revealed an association with positive resection margins (39.0% vs. 60.2%, p < 0.001), major complications (20.0% vs. 30.1%, p = 0.021) and mortality (3.3% vs. 8.0%, p = 0.030). The presence of anatomical borderline characteristics in addition to prognostic borderline characteristics revealed similar results (51.4% vs. 76.2%, p = 0.043; 1.4% vs. 19.0%, p = 0.002; 20.8% vs. 47.6%, p = 0.015). In patients with anatomical borderline characteristics in addition to medical borderline characteristics only the mortality rate was higher (2.1% vs. 7.8%, p = 0.013). An overview of the clinicopathological results is given in Table 1 and Table 2.

Postoperative regime characteristics

Postoperative adjuvant therapy was administered in 82.8% (n = 838) of all patients, 17.2% (n = 174) did not receive adjuvant therapy due to morbidity related delay, mortality, advanced age, malnutrition/impaired general condition or refuse of further therapy. Data of 0.8% (n = 8) of patients was not available.

Out of the 949 patients who were administered adjuvant therapy, the majority (68.5%, n = 573) received gemcitabine mono or combinations. Adjuvant radiochemotherapy was administered in

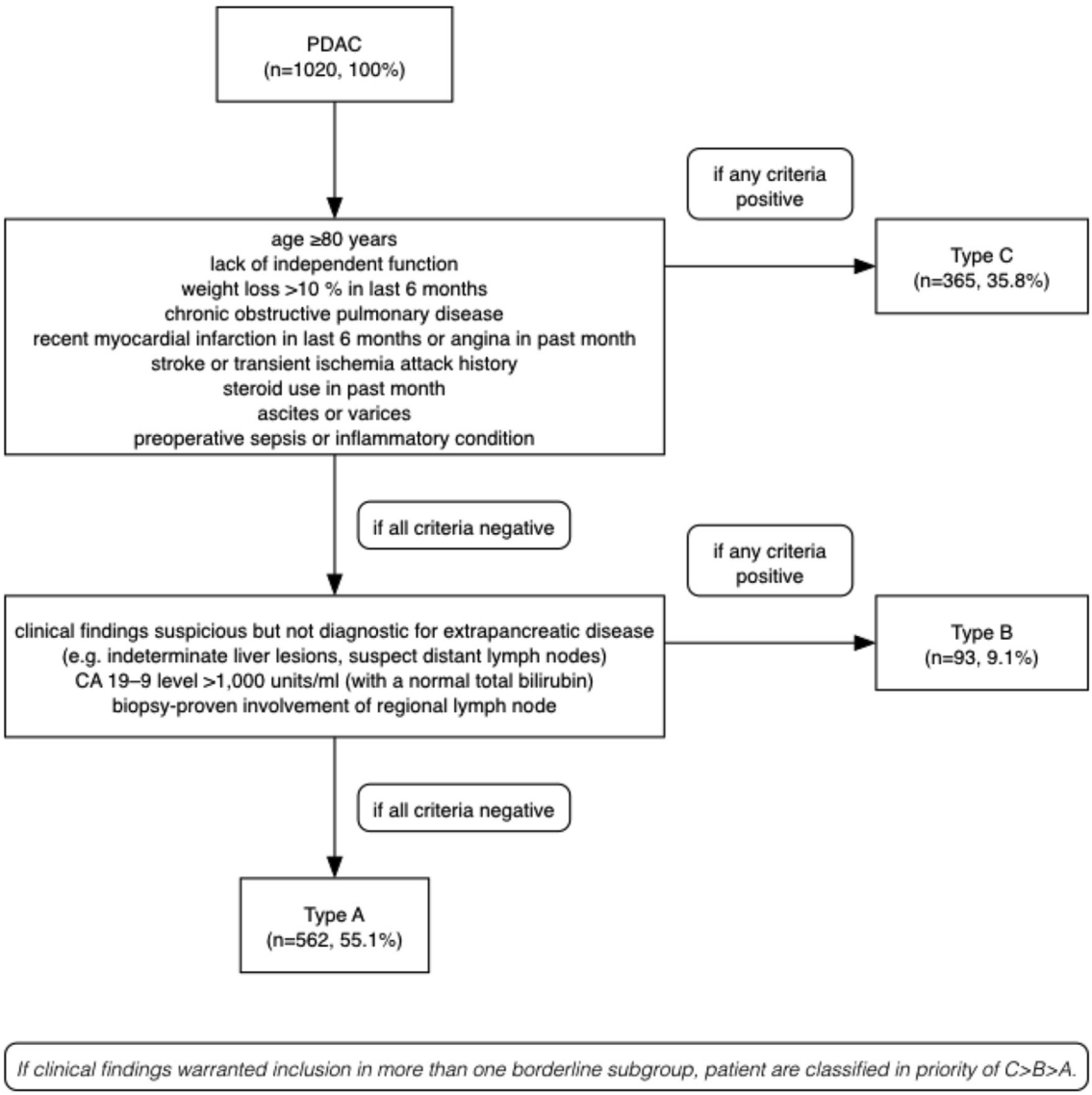

Fig. 1. Flow Chart. Flow chart of patient allocation to borderline subgroups A (resectable/anatomically borderline resectable), B (prognostic±anatomically borderline) and C (medical±anatomically borderline).

1.9% (n = 16) of the study cohort. Detailed data on adjuvant therapeutic regimes was not available in 27.9% (n = 234).

Analysis of postoperative regimes in relation to the three subgroups did not show any difference regarding the completeness of adjuvant therapeutic regimes but the percentage of type B and type C patients who did not receive adjuvant therapy at all was higher (p = 0.030, 21.5% and 20.4% vs. 14.4%, Table 1; 8 patients excluded due to missing data).

Survival analysis

Overall survival analysis was based on 965 patients (94.6%), 41 patients were excluded due to perioperative mortality (4.0%), data for 14 patients (1.4%) was missing. The median OS was 30.0 month (95% CI 27.2–32.9). Overall survival analysis in relation to the three subgroups revealed a significant shorter median OS in type B patients with 25.4 month (95% CI 20.0–30.8) compared to type A patients with 32.6 month (95% CI 28.2–37.1, p = 0.005). Compared to type C patients, a tendency was seen (28.1 month, 95% CI 22.6–33.6, p = 0.094). No significant difference was evident between type A and type C patients (p = 0.167, Fig. 2A). We carried out two different models of multivariate analyses. Model 1 analyzed the three subgroups independent of anatomically borderline patient characteristics. No significant difference was seen. In model 2, the three borderline subgroups were subdivided in six subgroups (type A/B/C±anatomically borderline characteristics). The presence of additional anatomically borderline characteristics did not show any relevant impact on OS (Table 3).

Progression free survival was based on 923 patients (92.3%), 41 patients were excluded due to perioperative mortality (4.0%), data on 56 patients was missing (3.7%). The median PFS was 16.4 month (95% CI 15.2–17.6). PFS analysis in relation to the three subgroups revealed a significant shorter median PFS in type B patients with 11.9 month (95% CI 8.3–15.5) in relation to type A patients (16.9 month [95% CI 14.9–18.9], p < 0.001) and type C patients (17.1 month [95% CI 15.3–18.9], p = 0.014). A tendency towards difference between type A and C patients was seen (p = 0.053, Fig. 2B). In multivariate analyses using model 1 the type B subgroup was identified as an independent prognostic marker for poor PFS (p = 0.005, HR 1.47). Model 2 revealed that type B patients with

Table 1
Clinicopathologicgal characteristics.

	All (n = 1020)	TYPE A (n = 562)	TYPE B (n = 93)	TYPE C (n = 365)	P
Age, years					
>67	519 (50.9)	263 (46.8)	48 (51.6)	208 (57.0)	0.010
Gender					
Male	537 (52.6)	283 (50.4)	49 (52.7)	205 (56.2)	0.224
Anatomical borderline					
Yes	211 (20.7)	113 (20.1)	21 (22.6)	77 (21.1)	0.837
Type of surgery					
PD/PPPD	765 (75.0)	428 (76.2)	67 (72.0)	270 (74.0)	0.817
TP	152 (14.9)	78 (13.9)	17 (18.3)	57 (15.6)	
DP	103 (10.1)	56 (10.0)	9 (9.7)	38 (10.4)	
Tumor stage					
I	41 (4.0)	34 (6.0)	1 (1.1)	6 (1.6)	<0.001
II	907 (88.9)	504 (89.7)	69 (74.2)	334 (91.5)	
III	29 (2.8)	11 (2.0)	5 (5.4)	13 (3.6)	
IV	43 (4.2)	13 (2.3)	18 (19.4)	12 (3.3)	
Resection margins[a]					
Positive	476 (46.8)	243 (43.2)	53 (57.0)	180 (49.6)	0.020
Clavien Dindo					
≥III	215 (21.1)	124 (22.1)	25 (26.9)	66 (18.1)	0.124
90 days mortality					
Yes	41 (4.0)	24 (4.3)	5 (5.4)	12 (3.3)	0.594
Adjuvant therapy[b]					
complete	746 (74.5)	424 (77.5)	66 (71.0)	256 (70.9)	0.139
incomplete	81 (8.1)	43 (7.9)	7 (7.5)	31 (8.6)	
no therapy	174 (17.4)	80 (14.6)	20 (21.5)	74 (20.5)	

PD: pancreaticoduodenectomy; PPPD: Pylorus preserving pancreaticoduodenectomy, TP: Total pancreatectomy, DP: Distal pancreatectomy.
[a] No data in 2 patients.
[b] No data in 8 patients.

Table 2
Impact of anatomical borderline characteristics.

	Resectable (n = 449)	Anatomical BR (n = 113)	P	Prognostic BR (n = 72)	Prognostic and anatomical BR (n = 21)	P	Medical BR (n = 287)	Medical and anatomical BR (n = 76)	P
Resection margins*									
Positive	175 (39.0)	68 (60.2)	<0.001	37 (51.4)	16 (76.2)	0.043	141 (49.1)	39 (51.3)	0.735
Clavien Dindo									
≥III	90 (20.0)	34 (30.1)	0.021	15 (20.8)	10 (47.6)	0.015	50 (17.4)	16 (20.8)	0.489
90 days mortality									
Yes	15 (3.3)	9 (8.0)	0.030	1 (1.4)	4 (19.0)	0.002	6 (2.1)	6 (7.8)	0.013

BR: borderline resectable; *no data in 2 patients; values in brackets: %.

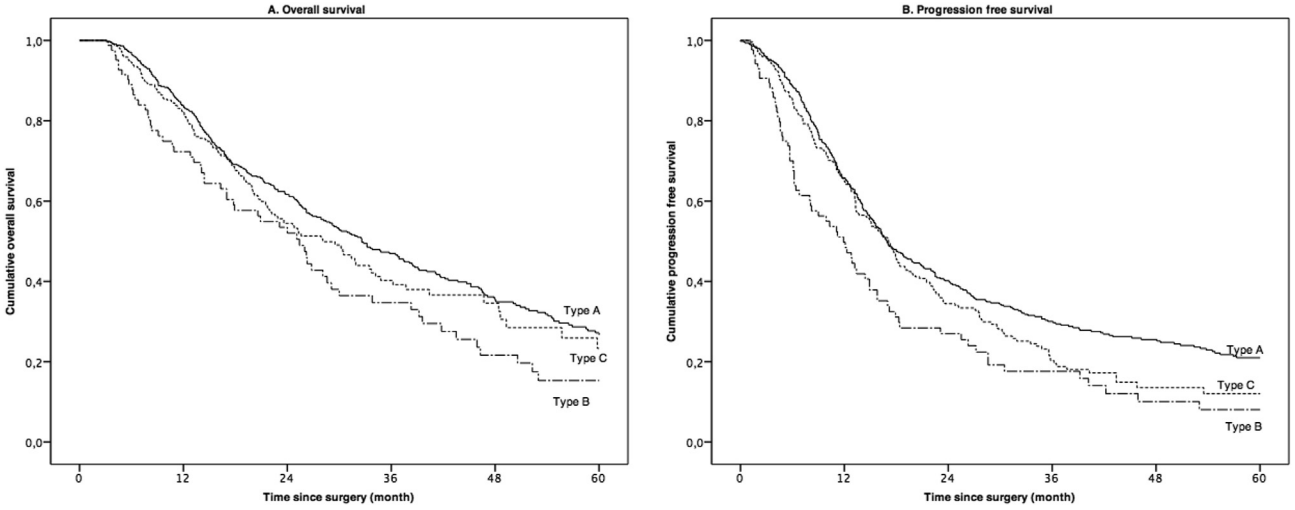

Fig. 2. Survival. A. Overall survival: type B vs. type A (25.4 month vs. 32.6 month, p = 0.005), type B vs. type C (25.4 month vs. 28.1 month, p = 0.094). B. Progression free survival: type B vs. type A (11.9 month vs. 16.9 month, p < 0.001), type B vs. type C (11.9 month vs. 17.1 month, p = 0.014).

Table 3
Multivariate analyses.

	PFS Model 1		PFS Model 2		OS Model 1		OS Model 2	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, years								
≤67	reference		reference		reference		reference	
>76	0.98 (0.83–1.15)	0.821	0.99 (0.84–1.17)	0.902	1.09 (0.90–1.30)	0.389	1.09 (0.90–1.31)	0.367
Gender								
Male	reference		reference		reference		reference	
Female	0.89 (0.76–1.04)	0.150	0.88 (0.75–1.03)	0.111	0.77 (0.64–0.92)	0.05	0.76 (0.63–0.91)	0.04
Type of surgery								
PD/PPPD	reference		reference		reference		reference	
TP	1.09 (0.86–1.37)	0.479	1.09 (0.87–1.37)	0.472	1.00 (0.78–1.30)	0.983	1.00 (0.77–1.29)	0.984
DP	0.96 (0.72–1.28)	0.786	0.96 (0.72–1.23)	0.786	0.85 (0.60–1.19)	0.334	0.84 (0.60–1.18)	0.317
Tumor stage								
I	reference		reference		reference		reference	
II	2.63 (1.62–4.25)	<0.001	2.63 (1.62–4.25)	<0.001	2.51 (1.50–4.19)	<0.001	2.52 (1.51–4.21)	<0.001
III	2.85 (1.44–5.63)	0.003	2.88 (1.45–5.73)	0.003	3.46 (1.67–7.16)	0.001	3.61 (1.74–7.50)	0.001
IV	4.11 (2.25–7.50)	<0.001	4.12 (2.25–7.53)	<0.001	4.44 (2.33–8.45)	<0.001	4.46 (2.34–8.51)	<0.001
Resection margins								
Negative	reference		reference		reference		reference	
Positive	1.73 (1.47–2.04)	<0.001	1.71 (1.45–2.02)	<0.001	1.65 (1.37–1.99)	<0.001	1.63 (1.35–1.97)	<0.001
Adjuvant therapy								
Yes	reference		reference		reference		reference	
No	0.54 (0.43–0.67)	<0.001	0.55 (0.44–0.68)	<0.001	0.49 (0.38–0.62)	<0.001	0.50 (0.39–0.63)	<0.001
Borderline								
No	reference		–		reference		–	
yes	0.99 (0.82–1.21)	0.947	–		1.00 (0.80–1.26)	0.984	–	
MDACC type								
Type A	reference		reference		reference		reference	
Type AB	–	–	1.11 (0.86–1.44)	0.429	–	–	1.14 (0.85–1.53)	0.368
Type B	1.47 (1.12–1.94)	0.005	1.43 (1.05–2.00)	0.022	1.29 (0.96–1.73)	0.097	1.30 (0.93–1.81)	0.131
Type BB	–	–	1.83 (1.08–3.11)	0.024	–	–	1.42 (0.81–2.48)	0.224
Type C	1.09 (0.92–1.30)	0.318	1.19 (0.97–1.44)	0.089	1.03 (0.84–1.27)	0.760	1.13 (0.90–1.42)	0.307
Type CB	–	–	0.91 (0.65–1.27)	0.567	–	–	0.84 (0.55–1.28)	0.407

Cox regression hazard model was used for multivariate analysis. HR, hazard ratio; CI, confidence interval; .PFS: Progression free survival; OS: Overall survival; PD: Pancreaticoduodenectomy; PPPD: Pylorus preserving pancreaticoduodenectomy; TP: Total pancreatectomy, DP: Distal pancreatectomy.
Two models of multivariate analyses to take account of potential confounding effects by anatomically borderline characteristics MDACC Type A: anatomically resectable, Type AB: anatomically borderline resectable, Type B: prognostic borderline±anatomically borderline resectable, Type BB: prognostic borderline and anatomically borderline, Type C: medical borderline±anatomically borderline resectable, Type CB: medical borderline and anatomically borderline resectable.

additional anatomically borderline characteristics were at a higher risk to develop relapse with a HR of 1.83 ($p = 0.024$; Table 3).

Discussion

This is the first attempt of external evaluation of the MDACC CBRC system. The intention of this study was to evaluate, if the use of the extended borderline classification in a cohort without neoadjuvant treatment reveals worse morbidity and mortality rates as well as worse survival in type B and C patients compared to (borderline-) resectable patients. Such results would justify the extension of the current purely anatomic definition of borderline resectable in upfront surgery patients for the first time - with potential impact on future treatment protocols, including neoadjuvant therapy, especially in Europe.

Our data revealed that the presence of anatomical borderline characteristics was the main factor for major complications and mortality in patients who did not present themselves with prognostic or medical borderline characteristics at the same time. The solely presence of prognostic borderline characteristics was not associated with a higher morbidity and mortality rate, whereas the combination of prognostic and anatomical borderline characteristics was indeed associated with higher morbidity and mortality rates. The solely presence of medical borderline characteristics was not associated with a higher mortality rate, whereas patients who presented themselves with medical and anatomical borderline characteristics at the same time, had a significant higher mortality rate.

In terms of survival, the type B status was an independent prognostic marker for a worse PFS (HR 1.43, $p = 0.022$). This was even more evident in patients with prognostic and anatomical borderline characteristics at the same time (HR 1.83, $p = 0.024$) The presence of medical borderline characteristics with or without anatomical borderline characteristics at the same time had no impact on the PFS or OS in the multivariate analysis.

The available data for medical borderline patients, especially without anatomical borderline characteristics at the same time, does not justify neoadjuvant treatment protocols for these patients in terms of survival. However, a new subgroup based on prognostic borderline characteristics might be a target group for neoadjuvant protocols. Despite these partially divergent results, some disputable questions regarding the MDACC study designs, the choice and allocation of risk factors to the three borderline resectable groups appeared, which needs to be discussed.

The first descriptive report introducing the CBRC system was published in 2008 [6]. Three cohorts undergoing neoadjuvant therapy were compared: patients with anatomically borderline resectable disease (type A) vs. patients with possible extrapancreatic disease (type B) vs. patients with marginal performance status/severe preexisting comorbidity profile (type C). In contrast to group A, anatomically resectable patients were included in group B and C too, which leads to an imbalance of risk profiles within and between the subgroups and accounts for potential risk of biased results, as we were able to show in our study and which is underlined in the most recent meta-analysis, which shows an increased postoperative mortality, higher rates of non-radical surgery and worse survival after pancreatic resection in anatomically borderline resectable PDAC patients [15]. However, the survival data of the

index study was actually supporting the extension of the borderline classification with a median survival of 29 month in type B patients in contrast to 39 and 40 month in type C and type A patients, respectively. Of note, the median survival in each group of the index study was better than our survival rates, but based on the cohort differences (e.g. index study with a smaller study cohort and only anatomically resectable patients in group A) the true impact of the neoadjuvant treatment cannot be assessed.

The second study with a better uniformity regarding the risk profiles was published in 2012 [7]. Only patients with resectable tumor anatomy (no tumor extension to the superior mesenteric artery or celiac axis, no occlusion of the superior mesenteric vein or superior mesenteric vein-portal confluence) were included. Of note, this definition is slightly divergent to the current NCCN definition of resectable patients, since patients with venous tumor contact of >180° were not excluded. In contrast to the index study, the overall survival of the study population did not reveal a difference between the three subgroups. Again, all patients received neoadjuvant therapy.

Our survival data is in line with the data published in the index study. Type B patients had a significant worse prognostic outcome compared to type A and C patients. Although we tried to avoid an imbalance of risk profiles by including anatomically resectable and borderline resectable patients in group A as well, and carried out two models of multivariate analyses to factor in anatomic borderline characteristics, our data needs to be evaluated with caution, since 18.3% of our type B study cohort had stage IV pancreatic cancer in the final histopathological results and had significantly more often a positive resection margin, especially when anatomical borderline characeteristics were evident at the same time. Having these facts in mind, the type B cohort might still most likely profit from a neoadjuvant approach with restaging prior surgery. The interval detection of metastases during or after completion of preoperative therapy was the most common contraindication to resection in the MDACC group. This seems to be compatible with our hypothesis.

The third MDACC study, designed to evaluate postoperative morbidity and mortality in type C versus non-type C patients, was published in 2014 [8]. Based on the ACS-NSQIP (American College of Surgeons National Surgical Quality Improvement Program) database 3033 patients were identified as type C and were evaluated against remaining 5233 patients. Similar to our results, about one third of the study population were type C patients. Therefore, we do believe that we have captured most of medically high risk patients that received surgery within our study period. The major complication and mortality rate (30 days or in hospital death later) in the MDACC study was significantly higher in type C patients with 31.3% vs. 26.2% and 4.2% vs. 2.3%, respectively. Although clinical experience indicates that type C patients should have a higher risk for major complications and mortality, our data does not support this assumption. This assumption was only evident in terms of mortality in patients with medical and anatomical borderline characteristics. These divergent results might be caused by our smaller study cohort compared to the ACS-NSQIP based MDACC study. Nevertheless, the reader should be reminded that the comparison of major complications is limited due to the different definitions (e.g. pneumonia, reintubation, sepsis vs. Clavien Dindo ≥ III). Besides that, the divergent findings may be the result of multiple factors related to the classification design. First, inclusion or exclusion of anatomically borderline resectable patients were variable among the publications and subgroups. Second, the criteria for allocation of patients to the subgroups B and C were partially unassertive within the three publications, e.g. weight loss of >10% was a criterion for inclusion into the type C subgroup only in the most recent MDACC study, which might be based on the ACS-NSQIP database limitations. Third, clinical findings that warranted inclusion in more than one subgroup, had to be classified in priority of C > B > A. Not only but especially regarding the age of patients this guideline is arguable. A recently published nationwide analysis of pancreatic surgery in Germany has shown, that the absolute number of surgeries has risen significantly from 2009 to 2013 due to a rising number of patients aged 70 years and older. At the same time, a trend analysis of the annual mortality rates revealed a significant decline in patients aged 70 years and older [16]. Therefore, the authors are at least questioning the age of a patient as a criterion for inclusion into the medically borderline subgroup, which is additionally overruling prognostic criterions of group B and therefore potentially falsifying the outcome of both groups. Furthermore, the criterion weight loss ≥10% within 6 month might be seen more as an indicator for aggressive tumor biology with minor impact on the medical risk profile.

However, our study has limitations as well: the database did not allow us to analyze patients that did not receive surgery after evaluation and preoperative supportive treatment protocols were not recorded. The patient's assignment was done in a retrospective manner. Details on postoperative therapeutic regimes, recurrence and survival were partially incomplete due to loss of follow-up. Most patients for whom data on adjuvant therapy is missing, did most likely received adjuvant gemcitabine based chemotherapy, since gemcitabine was the predominant standard of care during the study period [17]. However, some of these limitations are valid for the MDACC studies as well.

Based on their results, the MDACC group proposes a preoperative multidisciplinary management, including neoadjuvant therapeutic regimes, for type C patients [18]. The authors believe that preoperative optimization of patient's comorbidities is practiced throughout a long time whenever possible, without the need of labeling patients as high-risk. However, due to the natural limitations of “surgical” databases, type C patients are difficult to fully assess. It is likely that there are many patients with resectable pancreatic tumors who did not receive pancreatectomy due to comorbidities without an attempt of optimization or reevaluation. Nevertheless, our data does not support an additional borderline subgroup based on the presence of purely medical borderline criteria to promote neoadjuvant treatment, especially since hospitalization for complications associated with neoadjuvant treatment was an independent factor associated with not being selected for resection by the MDACC group [7].

Conclusion

The evaluation of the proposed classification showed that the presence of borderline anatomical characteristics is still the main reason for labelling a patient as borderline resectable. The presence of prognostic borderline characteristics as defined by the MDACC group justifies the extension of the purely anatomical definition of borderline respectability.

Despite anatomical borderline resectable patients, prognostic borderline patients might most likely profit from neoadjuvant protocols. Based on the available data, the presence of purely medical borderline characteristics does not seem be an adequate criterion for assignment of patients to neaoadjuvant treatment protocols.

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