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ORIGINAL ARTICLE

Impact of margin status on survival following pancreatoduodenectomy for cancer: the Leeds Pathology Protocol (LEEPP)

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Abstract

Background: In a previous study we reported an 85% R1 rate for pancreatic cancer following the use of the rigorous, fully standardized Leeds Pathology Protocol (LEEPP). As this significantly exceeded R1 rates observed by others, we investigated the reproducibility of margin assessment using the LEEPP in a larger, prospective, observational cohort study and correlated clinicopathological data with survival.

Methods: Clinicopathological features, including exact site and multifocality of margin involvement, and survival were collated from a prospective series of 83 pancreatoduodenectomies for pancreatic (n = 27), ampullary (n = 24) and bile duct cancer (n = 32). Data were compared with those of the previous study in which the same pathology protocol, based on axial slicing and extensive tissue sampling from the circumferential margin, had been used.

Results: The R1 rate was high in pancreatic (82%) and bile duct (72%) cancer and significantly lower in ampullary cancer (25%). Margin positivity was often multifocal, the posterior margin being most frequently involved. Margin status correlated with survival in the entire cohort (P = 0.006) and the pancreatic subgroup (P = 0.046). These findings were consistent with observations in our previous study.

Conclusions: Margin involvement in pancreatic cancer is a frequent and prognostically significant finding when specimens are assessed using the LEEPP.

Keywords

pancreas, cancer, resection, margin, survival

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Introduction

The prognosis of patients with ductal adenocarcinoma of the pancreas is generally poor.[1] The majority of patients present with advanced disease, and only in just over 10% is the tumour amenable to surgical resection. However, after surgical resection, local recurrence is frequent and 5-year survival rates amount to only 7–25% of patients.[2] Although resection margin (RM) involvement is believed to be a critical prognostic factor in pancreatic cancer,[3–7] the R1 rates reported in the literature vary from as little as 16% to over 75%, and correlation with survival is observed in some, but not all, studies.[8–15]

By contrast with rectal cancer, in which the occurrence and prognostic significance of circumferential resection margin (CRM) involvement has been well recognized and pathological assessment standardized, there is currently no consensus on detailed guidance for margin examination in pancreatoduodenectomy specimens (PDEs).[16]

In a previous study, we reported an R1 rate of 85% for pancreatic cancer in a series of 54 PDEs, which had been subjected to a fully standardized pathology examination technique according to the Leeds Pathology Protocol (LEEPP).[17] As this observation significantly exceeded the R1 rates reported in the literature, we

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believed it important to assess whether this high R1 rate was also found in a larger prospective series, and thus investigate the reproducibility of margin status assessment according to the LEEPP. In addition, the survival outcome based on margin status was also determined.

Materials and methods

Patients

This was an observational study, prospective in terms of histopathology data recruitment, with retrospective data analysis. The case series consisted of 83 consecutive cancers arising in the pancreatic head that had been resected with curative intent between November 2003 and April 2007 by consultant specialist surgeons in a tertiary referral hospital. Only adenocarcinomas were included in the study; other tumour entities, including adenocarcinoma arising in the context of intraductal papillary-mucinous neoplasia or mucinous cystic neoplasia, were excluded. The technique used by the surgeons was that of a standard or pylorus preserving PDE with standard lymphadenectomy.

The Leeds Pathology Protocol (LEEPP)

The cases were reported by a gastrointestinal pathologist (CSV), using the LEEPP as previously described.[17] In brief, after multicolour inking of the posterior, superior mesenteric vein (SMV) groove and anterior surfaces of the pancreatic head, the specimen was serially sliced in an axial plane, perpendicular to the longitudinal duodenal axis (Fig. 1). The 3-dimensional tumour size, its relationship to the key anatomical structures and the CRM were recorded. Multiple tissue samples, including one whole mount block, were taken from the tumour where closest to the CRM. The trans-section margins of the duodenum/stomach, pancreatic neck and distal bile duct (DBD) were also sampled. Microscopic margin involvement (R1) was defined as tumour within one millimetre of a resection margin, independent of the mode of tumour spread.

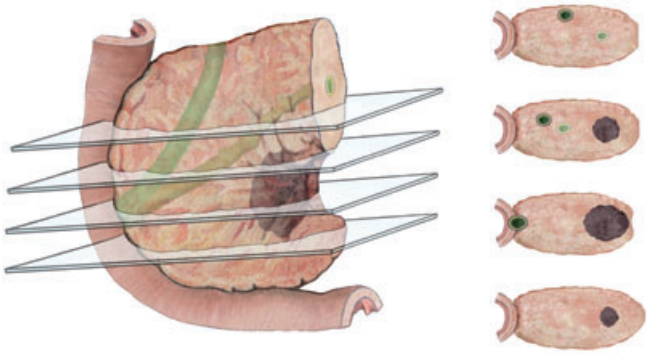


Figure 1 Specimen dissection according to the Leeds Pathology Protocol. Following multicolour-coded inking of the specimen surface, pancreatoduodenectomy specimens are sliced in an axial plane, providing a large number of specimen slices with good visualization of the tumour and its relationship to key anatomical structures and the anterior, posterior and superior mesenteric vein groove surfaces

Data collation

For each case the following data were collected: patient demographics; type of resection (standard or pylorus-preserving PDE); tumour size and origin (pancreatic, ampullary or DBD); pT stage; RM status; site of margin involvement; involvement of one or multiple RMs; pN stage; lymph node yield; number of positive lymph nodes, and positive lymph node rate (i.e. rate of positive to examined lymph nodes). Survival data were obtained from the hospital database.

Statistical analysis

Categorical data were presented as frequency and proportions, and analysed using Fisher's test and Pearson's chi-squared test. The Kaplan–Meier method was used to assess the actual survival rate, with the date of pancreatoduodenectomy as the starting point. Univariate analysis was performed to assess for a significant difference in clinicopathological characteristics that influenced overall survival following a potentially curative resection. A multivariate analysis was performed by Cox regression (stepwise forward model) for variables significant on univariate analysis. All statistical analyses were performed using SPSS for Windows™ Version 15.0 (SPSS, Inc., Chicago, IL, USA), and statistical significance was taken at the 5% level.

Results

Demographic, operative and histopathological data

During the study period, 83 patients underwent potentially curative resection for adenocarcinoma of the pancreatic head. They included 45 (54%) men. Median patient age at resection was 67 years (range 37–84 years). Of the 83 adenocarcinomas, 27 were primary pancreatic, 24 ampullary and 32 of DBD origin. Fifteen of the patients had undergone standard pancreatoduodenectomy and 68 had undergone a pylorus-preserving procedure. There was no significant difference in age, gender or surgical technique between the three cancer groups.

Pancreatic and DBD cancers were predominantly stage pT3, whereas a significant proportion of ampullary cancers were pT1 or pT2 (Table 1). Tumour size also differed significantly, with pancreatic cancers being larger (mean 3.3 cm, range 2.0–5.5 cm; $P < 0.001$) and ampullary cancers smaller (mean 1.9 cm, range 0.5–3.8 cm; $P = 0.006$) than DBD tumours (mean 2.5 cm, range 1.2–3.8 cm). The difference in size was significant when comparing pT3 ampullary cancers with pancreatic tumours ($P < 0.001$), but not when comparing either pancreatic or ampullary cancers with DBD cancers.

The pN stage was comparable between the three cancer groups, both for all pT stages and for the pT3 cancers (of 10 pT3 ampullary cancers, nine were pN1). However, the number of positive lymph nodes was significantly higher in the pancreatic cancer

Table 1 Clinicopathological data

	Pancreatic cancer		*P*	Ampullary cancer		*P*	DBD cancer		*P*
	R0 (*n* = 5)	R1 (*n* = 22)		R0 (*n* = 18)	R1 (*n* = 6)		R0 (*n* = 9)	R1 (*n* = 23)	
Age, years									
<65	2 (40%)	7 (32%)	1.000	7 (39%)	1 (17%)	0.621	3 (33%)	7 (30%)	1.000
≥65	3 (60%)	15 (68%)		11 (61%)	5 (83%)		6 (67%)	16 (70%)	
Gender									
Male	2 (40%)	8 (36%)	1.000	12 (67%)	3 (50%)	0.635	6 (67%)	14 (61%)	1.000
Female	3 (60%)	14 (64%)		6 (33%)	3 (50%)		3 (33%)	9 (39%)	
Tumour size									
<2.5 cm	1 (20%)	5 (23%)	1.000	13 (72%)	4 (67%)	1.000	6 (67%)	11 (48%)	0.444
≥2.5 cm	4 (80%)	17 (77%)		5 (28%)	2 (33%)		3 (33%)	12 (52%)	
pT stage[a]									
pT1	0	0	NA	2 (11%)	0	0.192	0	0	0.281
pT2	0	0		10 (56%)	2 (33%)		1 (11%)	0	
pT3	5 (100%)	22 (100%)		6 (33%)	4 (67%)		8 (89%)	23 (100%)	
pN stage									
N0	2 (40%)	2 (9%)	0.144	8 (44%)	0	0.066	5 (56%)	3 (13%)	**0.023**
N1	3 (60%)	20 (91%)		10 (56%)	6 (100%)		4 (44%)	20 (87%)	
Number of positive lymph nodes[b]	4 (80%)	11 (50%)	0.342	11 (61%)	1 (17%)	0.155	7 (78%)	9 (39%)	0.113
	1 (20%)	11 (50%)		7 (39%)	5 (83%)		2 (22%)	14 (61%)	
Positive lymph node rate[c]	4 (80%)	6 (27%)	**0.047**	10 (56%)	0	**0.024**	6 (67%)	5 (22%)	**0.035**
	1 (20%)	16 (73%)		8 (44%)	6 (100%)		3 (33%)	18 (78%)	
Margin involved[d]									
Posterior	NA	13	NA	NA	5	NA	NA	21	NA
SMVgroove		12			1			7	
Anterior		3			1			0	
Trans-section		3			0			0	
Multiple		8			1			5	

DBD, distal bile duct; NA, not applicable; SMV, superior mesenteric vein
[a]Analysis was performed comparing patients with pT1 or pT2 cancers with those with pT3 tumours
[b]Numbers of positive lymph nodes were compared between the R0 and R1 groups using the following cut-off values: pancreatic cancer (<5 vs. ≥5); ampullary cancer (≤1 vs. >1), and DBD cancer (≤2 vs. >2)
[c]Lymph node positivity rates were compared between the R0 and R1 groups using the following cut-off values: pancreatic cancer (≤0.1 vs. >0.1); ampullary cancer (≤0.05 vs. >0.05), and DBD cancer (≤0.05 vs. >0.05)
[d]Because of the multifocality of margin involvement in some cases, the number of involved margins exceeds the total number of R1 cases

group (mean 4.7, range 0–14) than in the ampullary (mean 1.5, range 0–4; $P < 0.001$) and DBD cancer groups (mean 2.8, range 0–7; $P = 0.015$). Similarly, the positive lymph node rate was significantly higher in pancreatic cancers (mean 0.282, range 0–0.85) than in ampullary (mean 0.097, range 0–0.30; $P < 0.001$) and DBD tumours (mean 0.157, range 0–0.54; $P = 0.015$). These differences remained significant when comparing pT3 cancers only. The lymph node yield was similar in the three cancer groups (mean 17.6, range 6–32).

Resection margin involvement

Rates of margin involvement in pancreatic (22 of 27, 82%) and DBD cancer (23 of 32, 72%) were comparable and significantly exceeded that in the ampullary cancer group (six of 24, 25%; $P < 0.001$). However, the R1 rate was higher in the pT3 subgroup of ampullary cancers (four of 10, 40%) than in tumours in stage pT1 or pT2 (two of 14, 14%; $P = 0.045$). The R1 rate pT3 ampullary cancers differed significantly from that in pancreatic cancer ($P = 0.013$), but showed only a trend towards divergence compared with DBD cancer ($P = 0.070$).

Of all the clinicopathological variables, pN stage differed significantly between R0 and R1 cases in the DBD cancer group, and the positive lymph node rate was significantly higher in R1 than R0 cases in all three cancer groups (Table 1).

Of the 27 pancreatic cancers, 22 were pT3N1 (81%); in the R1 subgroup the proportion of pT3N1 tumours amounted to 20 of

22 (91%). Near identical observations were made in the DBD group (24 of 32 were pT3N1, 75%) and the corresponding R1 subgroup (20 of 23, 87%).

In the three cancer groups, the posterior CRM was most frequently involved, followed by the SMV groove margin (Table 1). The anterior surface was involved in four of the total of 28 pancreatic and ampullary cancer cases with RM involvement, but in none of the DBD cancers. Involvement of the pancreatic transection margin was observed in only three pancreatic cancers, all of which also had a positive CRM.

Adjuvant treatment

All patients in the cohort were referred for consideration of adjuvant treatment, and 20 patients went on to receive chemotherapy (eight pancreatic, three ampullary, nine DBD cancers). Survival analysis for adjuvant chemotherapy was not performed because of the small number of patients in each cancer subgroup.

Survival

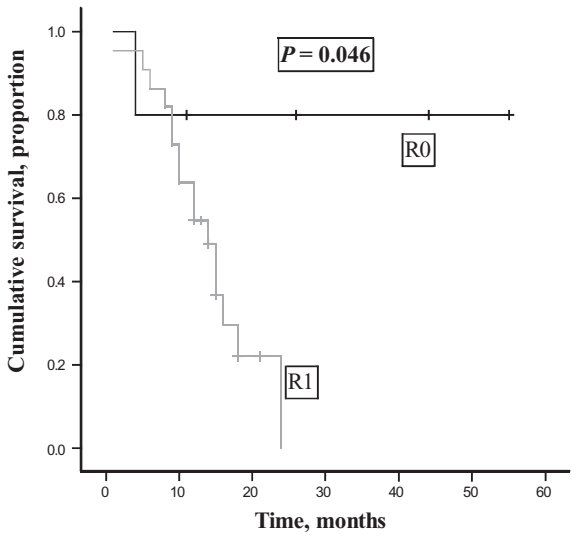
All patients were included in the survival analysis. The operative mortality rate (30 days) was 3.6% for the entire cohort. Median follow-up was 18 months (range 10–55 months), during which 42 patients died of recurrent disease. The overall 1-, 3- and 5-year actual survival rates for the entire cohort were 74%, 38% and 33%, respectively. The difference in survival following R0 and R1 resection was significant for the entire cohort ($P = 0.006$).

Of the 27 patients with pancreatic cancer, 17 died; none of these were postoperative deaths. The median follow-up of the remaining patients was 16.5 months (range 12–55 months). Overall 1-, 3- and 5-year survival rates following resection were 67%, 25% and 25%, respectively. There was a significant difference in survival between patients who underwent R0 resections compared with patients with tumour involvement of the RM ($P = 0.046$). The median survival of R1 pancreatic cancer patients was 14 months, whereas at 55-months follow-up, the median survival of the R0 pancreatic cancer group had not yet been identified (four of five patients were alive) (Fig. 2). No other clinicopathological variables achieved significance with respect to survival (Table 2).

Of the 24 patients with ampullary cancer, eight died; one of these represented a postoperative death. The remaining patients had a median follow-up of 25 months (range 11–50 months). The overall 1-, 3- and 5-year survival rates following resection were 79%, 69% and 55%, respectively. There were no clinicopathological variables that influenced overall survival (Table 2).

Of the 32 patients with DBD cancer, 17 died, two of which represented postoperative deaths. The median follow-up of the remaining patients was 13 months (range 10–49 months). Overall 1-, 3- and 5-year survival rates following resection were 75%, 24% and 24%, respectively. Similarly to the ampullary cancer group, none of the clinicopathological factors affected overall survival (Table 2).

In summary, based on the univariate analysis of these three subgroups, only RM status had an impact on survival in the pancreatic cancer group. None of the other clinicopathological factors influenced prognosis in the pancreatic, ampullary or DBD cancer subgroups and hence no multivariate analysis was performed.



Time, months	0	10	20	30	40	50	60
R0	5	4	3	2	2	1	0
R1	22	14	2	0	0	0	0

Figure 2 Survival of patients with pancreatic cancer. The actual survival curve for the 27 patients with pancreatic cancer shows that patients who underwent an R0 resection had a significantly better outcome than those in whom an R1 resection was performed ($P = 0.046$)

Discussion

Although RM involvement is recognized as an important prognostic factor in pancreatic cancer, there is currently no standardization of the histopathological examination technique and reporting of PDEs.[16] In a previous study, we demonstrated that standardization of the histopathological technique by implementing the LEEPP influences the reporting of RM status and allows a better correlation between histological staging and outcome in pancreatic cancer.[17] In the present study, the LEEPP was prospectively applied to a larger cohort to assess the reproducibility of findings.

The case series that formed the basis of the current study was comparable with that previously analysed in terms of patient age and gender, T-stage distribution in the pancreatic, ampullary and DBD cancer groups, and surgical technique.[17]

The R1 rate for pancreatic cancer in the current study was nearly identical (82%) to that previously reported, and a similar R1 rate was recorded for ampullary cancer (25%; 27% in the previous study).[17] A recent study from Heidelberg has shown similar results, with an R1 rate for pancreatic adenocarcinoma

Table 2 Univariate survival analysis

Clinicopathological factors	Survival analysis, *P*-value		
	Pancreatic cancer	Ampullary cancer	DBD cancer
Age ≥65 years	0.782	0.216	0.638
Male gender	0.177	0.871	0.812
Tumour size	0.908	0.753	0.784
pT stage[a]	NA	0.856	NA
pN stage	0.495	0.371	0.593
Number of positive lymph nodes[b]	0.499	0.945	0.384
Positive lymph node rate[c]	0.867	0.695	0.295
Resection margin status	**0.046**	0.252	0.871

DBD, distal bile duct
[a]Analysis was performed comparing patients with pT1 or pT2 cancers with those with pT3 tumours
[b]Analysis of the impact of the number of positive lymph nodes on survival was performed for the following cut-off values: pancreatic cancer (<5 vs. ≥5); ampullary cancer (≤1 vs. >1), and DBD cancer (≤2 vs. >2)
[c]Analysis of the impact of the positive lymph node rate on survival was performed for the following cut-off values: pancreatic cancer (≤0.1 vs. >0.1); ampullary cancer (≤0.05 vs. >0.05), and DBD cancer (≤0.05 vs. >0.05)

using a standardized protocol of 76%.[18] Interestingly, the R1 rate for DBD cancer (72%) exceeded that reported in the previous study (46%). The reason for this difference is not clear; however, two factors are likely to be responsible. Firstly, the previous study was based on a smaller series, which contained a lower number of DBD cancers (13 of 54, 24%) than the current cohort (32 of 83, 39%; $P = 0.07$). Secondly, the DBD tumours in the current series (mean 2.5 ± 0.7 cm) were significantly larger than in the previous series (mean 1.9 ± 0.6 cm; $P = 0.003$). The increase in relative incidence and size of DBD cancers is most likely attributable to chance because the selection criteria for surgery remained unaltered during both study periods.

Based on the current findings, the R1 rate in pancreatic cancer did not significantly differ from that in DBD cancer, despite the fact that tumour size was considerably smaller in the DBD cancer group. The high rate of margin involvement in DBD cancer, despite the smaller tumour size, probably results from the anatomical position of the DBD in PDEs, particularly its proximity to the posterior CRM and the propinquity of the proximal portion of the DBD to the SMV groove margin.

The R1 rate in ampullary carcinoma was significantly lower than that in pancreatic or DBD cancer. However, analysis of the ampullary cancer group showed that the rate of margin involvement in pT3 cancers differed only from that in pancreatic cancer ($P = 0.013$), not that in DBD tumours ($P = 0.069$). The latter finding may be explained by the similar size of pT3 ampullary cancers and DBD tumours.

The incidence of the site of margin involvement was also strikingly similar in both studies. In the current study, as in the previous series, the margins most commonly reported positive were the posterior (75% and 66%, respectively) and SMV groove CRM (39% and 44%, respectively), whereas the anterior surface was involved in only a limited number of cases (8% and 22%, respectively). The latter finding is in line with results from Japanese studies, which reported involvement of the anterior surface in 20% of cases and correlation with 5-year survival.[19,20] The observations in the current study indicate that the site of CRM involvement depended on the tumour origin and size. The SMV groove margin, which is anatomically the most remote from the ampullary region, was positive in only a single ampullary case, which was by far the largest tumour (3.8 cm) in the ampullary cancer group (median size 1.9 cm, range 0.5–3.8 cm). Similarly, the distances between the anterior and posterior surfaces of PDEs, which vary between 3.0 cm and 4.5 cm, and the different anatomical position and range of tumour sizes in the three cancer groups seem to explain why the anterior surface was involved in some of the pancreatic and ampullary cancers, but in none of the DBD tumours.

Similarly to findings in the previous study, a significant proportion of cases in the current series showed multifocal involvement of the CRM (28 vs. 44%; $P = 0.114$). The low rate of involvement of the trans-section margin at the pancreatic neck (6% in both series) may reflect the use of intraoperative frozen-section examination of that margin. Frozen-section examination of the pancreatic neck trans-section margin, although not performed routinely, was useful in tumours located close to the neck of the pancreas as, if the margin were positive, the resection could be extended more laterally to achieve a negative margin. However, in terms of other margins, particularly the CRM, frozen-section examination does not add any advantage, because even if the margin is positive there is no scope to resect any more tissue, as the limit of dissection has already been reached. Information on exactly which RM is involved allows for speculation on the probable R1 rate if only the pancreatic trans-section margin and the SMV groove CRM are examined, as is routine practice in some countries,[9] rather than the entire specimen surface, as stipulated in the LEEPP.

In addition to the fore-mentioned striking similarities in reported R1 rates for pancreatic and ampullary cancer and the

site of margin involvement, lymph node status in the current series was also found to be comparable with that observed in the previous study, both for the overall cohort and the three cancer groups. Compared with published data, the pN1 rate in this study is high, even if corrected for pT stage.[21,22] This may be related to the high lymph node yield from the PDEs in this study and the good visualization of peripancreatic lymph nodes facilitated by the axial slicing technique specified in the LEEPP. The positive lymph node rate, which is a more accurate indicator of the extent of metastatic lymph node spread,[23,24] correlated significantly with RM status, indicating that involvement of both lymph nodes and RMs is a feature of advanced tumour progression. The vast majority of pancreatic cancers were indeed pT3 tumours with a full house of prognostically adverse factors (83% pT3N1, 74% pT3N1R1).

Taken together, the results of this study indicate that standardization of the pathology examination technique results in the reproducible reporting of data related to margin involvement and lymph node metastasis in pancreatic head cancer. Most importantly, this study demonstrates that implementing the LEEPP results in a constant finding of a margin involvement rate of ≥80% in PDEs for pancreatic cancer. It is likely that a non-standardized approach accounts, at least in part, for the wide variation in R1 rates – 16–75% – that have been published for ductal adenocarcinoma of the pancreas.[8–15]

Critical review of survival data of pancreatic cancer patients reveals incongruence between the reported R1 rate and clinical outcome.[16] The high local recurrence rate of pancreatic cancer – usually reported at 67–86%[9,25–27] – seems to conflict with an R1 rate that, in the majority of published reports, lies below 30–40%. Survival figures in series with low R1 rates are not significantly different from those with higher R1 rates,[2,8,17,28] and the survival benefit of R0 vs. R1 resection is often small, at 4–8 months, and statistically non-significant.[5,8,9,11,14,29–32]

The overall survival rates for patients with pancreatic, ampullary and DBD cancer in this study are comparable with reported values, despite the higher R1 rate observed in this series.[1,2,6] Analysis of the entire cohort, irrespective of the site of cancer origin, demonstrated that patients with a clear RM (R0) had significantly better overall survival ($P = 0.006$). Analysis of the pancreatic cancer subgroup revealed margin status as the only significant prognostic factor influencing survival following surgical resection ($P = 0.046$). Although the number of R0 pancreatic cancer cases was small in this study, median survival had not yet been reached at 55 months follow-up and has exceeded that of other studies, in which the median survival of this particular subgroup has been reported as 8–32 months.[5,12,15,27,32–35] A similar survival benefit of R0 resection of pancreatic cancer was found in our previous study, which was based on the same pathological protocol.[17] In patients with ampullary or DBD cancer, none of the clinicopathological variables were found to influence survival.

The high R1 rate suggests that although these tumours are technically resectable, their more threatening biology cannot be resolved by more aggressive surgery, but requires, perhaps, newer targeted neoadjuvant therapies or better adjuvant treatment following surgery.

In conclusion, this study confirms that application of the LEEPP allows for accurate reporting of RM status, which correlates with a clear survival benefit for patients who undergo R0 resection of pancreatic cancer.

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Conflicts of interest

None declared.

References

1. Carpelan-Holmström M, Nordling S, Pukkala E, Sankila R, Lüttges J, Klöppel G *et al*. (2005) Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer registry. *Gut* 54:385–387.
2. Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. (2004) Current standards of surgery for pancreatic cancer. *Br J Surg* 91:1410–1427.
3. Matsuno S, Egawa S, Unno M. (2007) R0 resection for ductal pancreatic cancer – Japanese experience. *Am J Surg* 194:S110–S114.
4. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess HH, Büchler MW. (2004) Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 91:586–594.
5. Neoptolemos JP, Stocken DD, Dunn JA, Almond J, Beger HG, Pederzoli P *et al*. (2001) Influence of resection margin on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. *Ann Surg* 234:758–768.
6. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA *et al*. (1997) Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 226:248–260.
7. Allema JH, Reinders ME, van Gulik TM, Koelemay MJ, Van Leeuwen DJ, de Wit LT *et al*. (1995) Prognostic factors for survival after pancreaticoduodenectomy for patients with carcinoma of the pancreatic head region. *Cancer* 75:2069–2076.
8. Butturini G, Stocken DD, Wente MN, Jeekel H, Klinkenbijl JH, Bakkevold KE *et al*. (2008) Influence of resection margins and treatment on survival in patients with pancreatic cancer. Meta-analysis of randomized controlled trials. *Arch Surg* 143:75–83.
9. Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH *et al*. (2007) Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg* 246:52–60.
10. Pingpank JF, Hoffman JP, Ross EA, Cooper HS, Meropol NJ, Freedman G *et al*. (2001) Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. *J Gastrointest Surg* 5:121–130.
11. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA *et al*. (2000) Resected adenocarcinoma of the pancreas – 616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 4:567–579.

12. Benassai G, Mastrorilli M, Quarto G, Cappiello A, Giani U, Mosella G. (2000) Survival after pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas. *Chir Ital* 52:263–270.

13. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. (1996) Survival after resection for ductal adenocarcinoma of the pancreas. *Br J Surg* 83:625–631.

14. Nitecki SS, Sarr MG, Colby TV, van Heerden JA. (1995) Longterm survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg* 221:59–66.

15. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, Goodman SN *et al*. (1995) Pancreaticoduodenectomy for cancer of the head of the pancreas: 201 patients. *Ann Surg* 221:721–731.

16. Verbeke CS. (2008) Resection margins and R1 rates in pancreatic cancer – are we there yet? *Histopathology* 52:787–796.

17. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. (2006) Redefining the R1 resection in pancreatic cancer. *Br J Surg* 93:1232–1237.

18. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H *et al.* (2008) Most pancreatic cancer resections are R1 resections. *Ann Surg Oncol* 15:1651–1660.

19. Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T *et al.* (1996) Results of extensive surgery for pancreatic carcinoma. *Cancer* 77:640–645.

20. Tsuchiya R, Noda T, Harada N, Miyamoto T, Tomioka T, Yamamoto K *et al.* (1986) Collective review of small carcinomas of the pancreas. *Ann Surg* 203:77–81.

21. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. (1998) Periampullary adenocarcinoma: analysis of 5-year survivors. *Ann Surg* 227:821–831.

22. Van Geenen RCI, Van Gulik TM, Offerhaus GJA, De Wit LT, Busch ORC, Obertop H *et al.* (2001) Survival after pancreaticoduodenectomy for periampullary adenocarcinoma: an update. *Eur J Surg Oncol* 27:549–557.

23. Berger AC, Watson JC, Ross EA, Hoffman JP. (2004) The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am Surg* 70:235–240.

24. House MG, Gönen M, Jarnagin WR, D'Angelica M, DeMatteo RP, Fong Y *et al*. (2007) Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. *J Gastrointest Surg* 11:1549–1555.

25. Willett CG, Lewandrowski K, Warschaw AL, Efird J, Compton CC. (1993) Resection margins in carcinoma of the head of the pancreas. Implications for radiation therapy. *Ann Surg* 217:144–148.

26. Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. (1993) An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. *Cancer* 72:2118–2233.

27. Westerdahl J, Andren-Sandberg A, Ihse I. (1993) Recurrence of exocrine pancreatic cancer: local or hepatic? *Hepatogastroenterology* 40:384–387.

28. Takai S, Satoi S, Toyokawa H, Yanagimoto H, Sugimoto N, Tsuji K *et al*. (2003) Clinicopathologic evaluation after resection for ductal adenocarcinoma of the pancreas: a retrospective, single-institution experience. *Pancreas* 26:243–249.

29. Kuhlmann KF, de Castro SM, Wesseling JG, ten Kate FJ, Offerhaus GJ, Busch OR *et al*. (2004) Surgical treatment of pancreatic adenocarcinoma: actual survival and prognostic factors in 343 patients. *Eur J Cancer* 40:549–558.

30. Tseng JF, Raut CP, Lee JE, Pisters PW, Vanthey JN, Abdalla EK *et al*. (2004) Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg* 8:935–949.

31. Geer RJ, Brennan MF. (1993) Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg* 165:68–73.

32. Millikan KW, Deziel DJ, Silverstein JC, Kanjo TM, Christein JD, Doolas A *et al*. (1999) Prognostic factors associated with respectable adenocarcinoma of the head of the pancreas. *Am Surg* 65:618–623.

33. Nagakawa T, Sanada H, Inagaki M, Sugama J, Ueno K, Konishi I *et al*. (2004) Longterm survivors after resection of carcinoma of the head of the pancreas: significance of histologically curative resection. *J Hepatobiliary Pancreat Surg* 11:402–408.

34. Bouvet M, Gamagami RA, Gilpin EA, Romeo O, Sasson A, Easter DW *et al.* (2001) Factors influencing survival after resection for periampullary neoplasms. *Am J Surg* 180:13–17.

35. Moon HJ, An JY, Heo JS, Choi SH, Joh JW, Kim YI. (2006) Predicting survival after surgical resection for pancreatic ductal adenocarcinoma. *Pancreas* 32:37–43.