Journal of Gastrointestinal Surgery (2019) 23:1984–1990
https://doi.org/10.1007/s11605-018-3939-y

ORIGINAL ARTICLE

Major Complications Independently Increase Long-Term Mortality After Pancreatoduodenectomy for Cancer

M. Sandini[1] · K. J. Ruscic[2] · C. R. Ferrone[1] · M. Qadan[1] · M. Eikermann[2] · A. L. Warshaw[1] · K. D. Lillemoe[1] · Carlos Fernández-del Castillo[1]

Received: 25 June 2018 / Accepted: 17 August 2018 / Published online: 17 September 2018

Abstract

Background Postoperative major morbidity has been associated with worse survival gastrointestinal tumors. This association remains controversial in pancreatic cancer (PC). We analyzed whether major complications after surgical resection affect long-term survival.

Methods Records of all PC patients resected from 2007 to 2015 were reviewed. Major morbidity was defined as any grade-3 or higher 30-day complications, per the Clavien-Dindo Classification. Patients who died within 90 days after surgery were excluded from survival analysis.

Results Of 616 patients, 81.7% underwent pancreatoduodenectomy (PD) and 18.3% distal pancreatectomy (DP). Major complications occurred in 19.1% after PD and 15.9% after DP. In patients who survived > 90 days, the likelihood of receiving adjuvant treatment was 43.9% if major complications had occurred, vs. 68.5% if not ($p < 0.001$), and those who received it started the treatment median 10 days later compared with uncomplicated patients (median 60 days (50–72) vs. 50 days (41–61), $p = 0.001$). By univariate analysis, in addition to the conventional pathology-related prognostic determinants and the receipt of adjuvant treatment, major complications worsened long-term survival after PD (median OS 26 months vs. 15, $p = 0.008$). A difference was also seen after DP, but it did not reach statistical significance, likely related to the small sample size (median OS 33 months vs. 18, $p = 0.189$). At multivariate analysis for PD, major postoperative complications remained independently associated with worse survival [HR 1.37, 95%CI (1.01–1.86)].

Conclusions Major surgical complications after pancreaticoduodenectomy are associated with worse long-term survival in pancreatic cancer. This effect is independent of the receipt of adjuvant treatment.

Keywords Major morbidity · Complications · Survival · Pancreatic cancer · Adjuvant treatment

Introduction

Although mortality from pancreatic resections has decreased markedly in high-volume centers, these operations are still fraught with complications. The overall burden of morbidity is reported to be around 50% for overall complications and up to 20% for major morbidity.[1,2]

Major morbidity after surgery has been shown to worsen long-term outcome in many types of cancers, though the underlying mechanisms are not completely understood.[3–6] Some authors have hypothesized that the occurrence of complications, or the lack of effort to thrive, may reflect a condition of impaired resilience in those patients who consequently experience early recurrence and death.[7] Others have posited that complications may be directly responsible for a long-standing

This paper has been presented at SSAT's 59th Annual Meeting, June 2–5, 2018 in Washington, D.C., during Digestive Disease Week.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-018-3939-y) contains supplementary material, which is available to authorized users.

✉ Carlos Fernández-del Castillo
cfernandez@mgh.harvard.edu

[1] Department of Surgery, Massachusetts General Hospital, Harvard Medical School, 15 Parkman ST, Boston, MA 02114-02115, USA

[2] Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

immune-suppressive effect, with consequent increased susceptibility to cancer recurrence and death.[8,9]

Several predictors of worse survival after surgical resection for pancreatic ductal cancer (PDAC) are well-recognized, and include advanced stage, positive resection margins, nodal involvement, perineural and lymphatic invasion, size of the tumor, high Ca19-9 levels and lack of adjuvant treatment (AT).[10–13] Whether major complications have an impact on long-term survival in pancreatic cancer patients is controversial. Overall, presence of any complication has been associated with delay in receiving adjuvant therapy, but not in the likelihood of receiving the treatment,[14] unless the complications are severe.[15] Several studies have indeed shown an association between the occurrence of major postoperative morbidity and impaired survival in PDAC[16–19]; however, in a recent analysis involving more than 500 resected pancreatic ductal adenocarcinomas, long-term survival was independent from the occurrence of high-grade complications.[20]

In this study, we sought to investigate in a large cohort of patients undergoing surgical resection for pancreatic ductal adenocarcinoma whether the occurrence of clinically relevant postoperative complications affected long-term survival and to assess if this effect is potentially mediated by an impairment in adjuvant treatment administration.

Methods

Patient Selection

After IRB approval, all consecutive patients who underwent resection for PDAC at the Massachusetts General Hospital from January 2007 to December 2015 were analyzed. Demographic and clinical data were retrieved from institutional prospective databases and patient medical records. Cases missing PDAC confirmation at the final pathology or with diagnosis of pancreatic adenocarcinoma arising from intraductal papillary mucinous neoplasm (IPMN) were excluded.

Preoperative Work-up and Definitions

All patients underwent preoperative staging by multiphase enhanced abdominal CT. According to our institutional practice, in cases of radiologic vascular involvement suggesting borderline or locally advanced disease, the patients were offered neoadjuvant treatment. The most commonly utlilized was FOLFIRINOX, followed by R gemcitabine in combination with nab-paclitaxel, with an 8:1 ratio.

Postoperative complications were considered as any 30-day deviation from the patient recovery, prolonging the length of hospitalization, requiring supplementary care or a new admission. The severity of complications was graded per the Clavien-Dindo classification.[21] Major complications were defined as any complication equal or more than grade 3. Pancreatic fistula was diagnosed and classified according to the ISGPS classification[22]; only clinically relevant pancreatic fistulae (grades B and C) were recorded.

Postoperative mortality was defined as death for any reason within 90 days after surgery; these patients were excluded from the survival analysis. An R0 resection was defined as the absence of cancer cells within 1 mm from the resection margin.[23] Follow-up time was calculated from the date of surgery to the patient death, or to the last available contact via office visit, hospital admission, or phone call.

Statistical Analysis

Continuous variables were evaluated for normal distribution with Kolmogorov-Smirnov test and are expressed as mean values and standard deviation (SD) or median and interquartile range (IQR). Categorical variables are presented as absolute numbers and percentages.

Nonrandom association was tested with the Fisher's exact test for categorical variables, while the Student's *t* test or the Mann-Whitney U-test were used to compare continuous data.

Survival analyses were performed through the log-rank (Mantel-Cox) test. Patients who did not die during the follow-up period were censored at the last available contact date.

To assess which variables were independently associated with OS, a Cox proportional hazard ratio model was built, based on the type of surgery (proximal or distal pancreatic resections), adjusted for need for vascular resection, occurrence of major complications, size of the tumor, nodal status, radical resection margins and receipt of adjuvant treatment. Hazard rates (HRs) are reported with the 95% confidence interval (CI).

For each test, a two-sided *p* value of 0.05 was considered significant. All statistical computations were performed using IBM SPSS, version 24 (IBM Corp., Armonk, NY).

Results

616 patients underwent surgical resection for PDAC at our institution from January 2007 to December 2015. The median age was 68 years, and 48.7% were ASA 3 or more. Neoadjuvant treatment was administered to 36.9% and most patients underwent pancreaticoduodenectomy (PD, 81.7%). Patient characteristics are depicted in Table 1.

As shown in Tables 2, 57.5% of patients experienced a postoperative complication. Major morbidity (Clavien-Dindo equal or more than grade 3) occurred in 114 (18.5%). Specifically, 38 patients (6.2%) had a clinically relevant postoperative pancreatic fistula, 40 (6.5%) had a septic complication and 20 (3.2%) needed a relaparotomy. Postoperative 30-

Table 1 General characteristics of included population ($n = 616$)

	n or mean	% or SD
Gender F	319	51.8%
Age	68	12
Neoadjuvant treatment	227	36.9%
ASA score 3 or more	300	48.7%
Charlson Comorbidity Index		
Risk class I (0)	6	61.0%
Risk class II (1, 2)	92	14.9%
Risk class III (3)	88	14.3%
Risk class IV (4–7)	79	12.8%
Risk class V (8–20)	343	55.7%
Operation		
Pancreatoduodenectomy	503	81.7%
Distal pancreatectomy	113	18.3%
Operation time (min)	349	123
EBL > 700 mL	207	33.6%
Vascular resection	84	13.6%
Extended resection	19	3.1%

ASA American Anesthesiology Association score, *EBL* estimated blood losses

Table 2 Postoperative outcomes

	n or mean/median	% or SD (IQR)
Overall complications	354	57.5%
Clavien-Dindo Classification ≥ 3	114	18.5%
B- and C-POPF	38	6.2%
DGE	81	13.1%
Biliary fistula	17	2.8%
Abscess	42	6.8%
Sepsis	40	6.5%
LOS (days)	7	6–9
Reoperation	20	3.2%
30-day mortality	14	2.3%
90-day mortality	21	3.4%
Size of the tumor	31	15
Readmission	116	18.8%
$T \geq 3$	529	85.9%
Grade ≥ 3	520	84.4%
N+	400	64.9%
Perineural invasion	525	85.2%
Lymphatic vascular invasion	348	56.5%
Margin involvement < 1 mm	203	33.0%
Receipt of adjuvant treatment	394	64.0%
Recurrence	383	62.2%
Median FU-time (months)	16	8–32

POPF postoperative pancreatic fistula, *LOS* length of hospital stay, *FU* follow-up

and 90-day mortality was 2.3 and 3.4%, respectively. Median follow-up was 16 months (IQR 8-32).

Baseline characteristics of patients with or without high-grade complications were similar, except for need for vascular resection. The prevalence of vascular resection was 27.3% in those who experienced severe postoperative morbidity, compared with 11.4%, in uncomplicated patients ($p = 0.001$) (Supplementary Table 1).

Adjuvant treatment was administered to 394 of 616 patients (64.0%), with a median time from surgery to the beginning of adjuvant treatment of 50 days, IQR (42–65). The likelihood of receiving adjuvant treatment was significantly reduced in patients who experienced major complications, with a rate of 43.9% vs. 68.5%, ($p < 0.001$). When excluding those patients who died within 90 days, the proportions were 55.8 and 71.4%, respectively ($p = 0.001$). Likewise, the time from surgery to the first dose of chemotherapy was longer in patients with severe complications when compared with those without (median 60 (50–72) vs. 50 days (41–61), $p = 0.001$), though, the rate of patients who began adjuvant treatment over 12 weeks after resection was similar in both groups [3 out of 42 (3.9%) vs. 20 out of 271 (5.2%), $p = 0.789$].

Kaplan-Meier curves for overall and disease-free survival after PD are shown in Fig. 1.

Predictors associated with overall survival, according to the type of surgical resection, are shown in Table 3. By univariate analysis, the median OS was nearly halved in PD patients who experienced major complications [15 months (IQR 8.2–21.8) vs. 26 months (IQR 21.8–30.2), $p = 0.007$]. Other predictors of poor survival were need for vascular resection, tumor size ≥ 30 mm, positive nodal status, non-R0 resection, and lack of adjuvant treatment ($p < 0.05$). Specifically for postoperative morbidity, infectious complications were associated with reduced OS in PD patients [18 m (11.3–24.7) vs. 27 m (22.6–31.4), $p = 0.023$]. At multivariate analysis, the occurrence of major morbidity remained independently associated with OS after pancreatoduodenectomy, with a HR of 1.37, 95%CI (1.01–1.87), $p = 0.041$, together with tumor size [HR 1.43, 95%CI (1.11–1.85), $p = 0.006$], positive nodes [HR 1.82, 95%CI (1.35–2.47), $p < 0.001$], R-status [HR 1.39, 95%CI (1.08–1.80), $p = 0.012$], and receipt of adjuvant treatment [HR 0.54, 95%CI (0.41–0.71), $p < 0.001$].

After distal pancreatectomy, only tumor size [HR 3.06, 95%CI (1.56–6.00), $p = 0.001$], nodal status [HR 2.06, 95%CI (1.03–4.13), $p = 0.041$], and lack of adjuvant treatment [HR 1.91, 95%CI (1.02–3.61), $p = 0.045$] were independently associated with OS.

We then compared the survival curves after combination of adjuvant treatment and major morbidity after PD (Fig. 2). We observed that 6-month, 1-, 2- and 5-year survival rates for patients who did not experience major complications and did not receive AT (group A) were similar to those of patients who had major complications and underwent AT (group D) (Table 4).

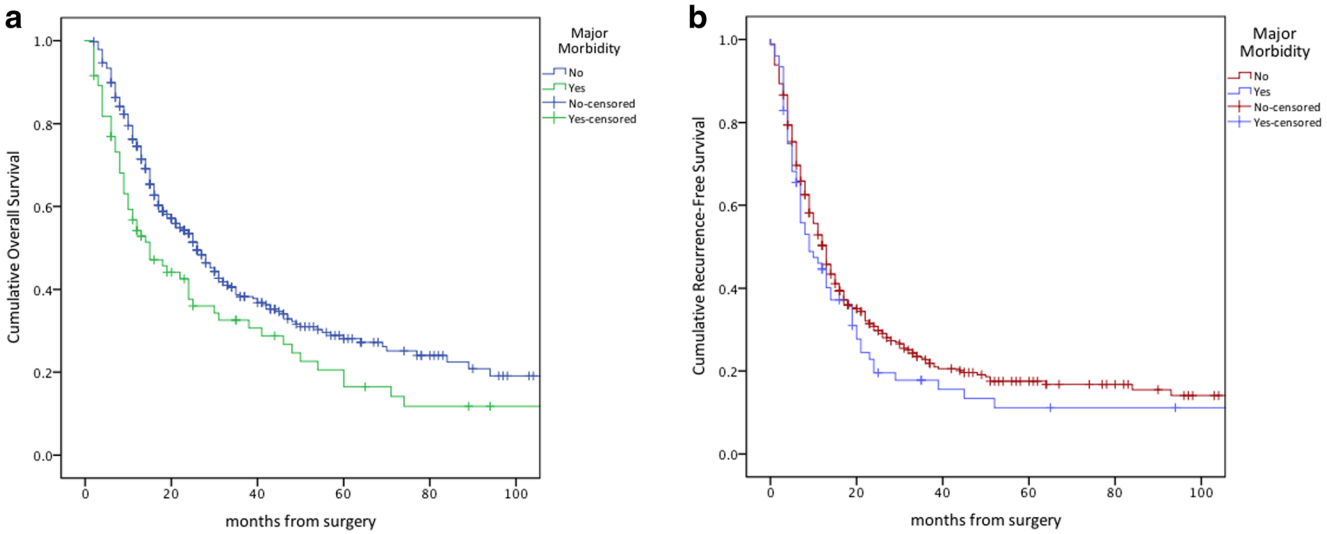

Fig. 1 The figure depicts Kaplan-Meyer analysis for overall survival (OS) and disease-free survival (DFS) in patients who either experienced or not major morbidity after pancreatoduodenectomy (**A**) or distal pancreatectomy (**B**). **A** Median OS was 26 months (21.8–30.2) and 15 months (7.9–22.1), $p = 0.007$, in uncomplicated and complicated patients, respectively. **B** Median DFS was 13 months (11.3–14.7) and 9 months (3.9–14.1), $p = 0.240$, in uncomplicated and complicated patients, respectively. 90-day mortality was not considered for survival analysis

Table 3 Univariate and multivariate analysis (adjusted for Charlson Comorbidity Index)

	PD		PD ($n = 418$)		DP		DP ($n = 98$)	
	Median survival time (months)	p	HR (95% CI)	p	Median survival time (months)	p	HR (95% CI)	p
Neoadjuvant treatment			–	–			–	–
No	24 (18.6–29.7)	0.353			25 (12.4–37.6)	0.423		
Yes	28 (22.4–33.6)				34 (23.9–34.1)			
Vascular resection								
No	26 (21.8–30.2)	0.026			29 (18.4–39.6)	0.623		
Yes	16 (7.5–24.6)		1.21 (0.87–1.68)	0.251	–		0.50 (0.06–4.25)	0.525
Overall complications			–	–			–	–
No	27 (21.4–32.6)	0.176			33 (11.9–54.1)	0.218		
Yes	25 (19.3–30.7)				25 (13.5–36.6)			
Clavien-Dindo 3 or more								
No	26 (21.8–30.2)	0.007			33 (18.6–47.4)	0.189		
Yes	15 (8.2–21.8)		1.37 (1.01–1.86)	0.041	18 (4.8–31.2)		1.26 (0.58–2.75)	0.556
Size of the tumor								
< 30 mm	30 (21.7–38.3)	0.001			88 (36.2–139.8)	<0.001		
30 mm or more	19 (13.9–24.1)		1.39 (1.08–1.78)	0.010	18 (13.7–22.3)		3.06 (1.56–6.00)	0.001
Nodal status								
N0	41 (25.1–56.9)	<0.001			46 (25.3–66.7)	0.001		
N1	20 (15.6–24.4)		1.85 (1.37–2.50)	< 0.001	18 (14.9–21.1)		2.06 (1.03–4.13)	0.041
Resection margins								
> 1 mm	31 (25.3–36.7)	<0.001			32 (22.1–41.9)	0.353		
< 1 mm	18 (12.5–23.5)		1.41 (1.09–1.81)	0.008	25 (0.2–49.8)		0.97 (0.54–1.75)	0.928
Adjuvant treatment								
No	15 (10.7–19.3)	<0.001			25 (11.1–38.9)	0.435		
Yes	28 (23.9–32.1)		1.86 (1.43–2.41)	< 0.001	32 (16.5–47.5)		1.91 (1.02–3.61)	0.045

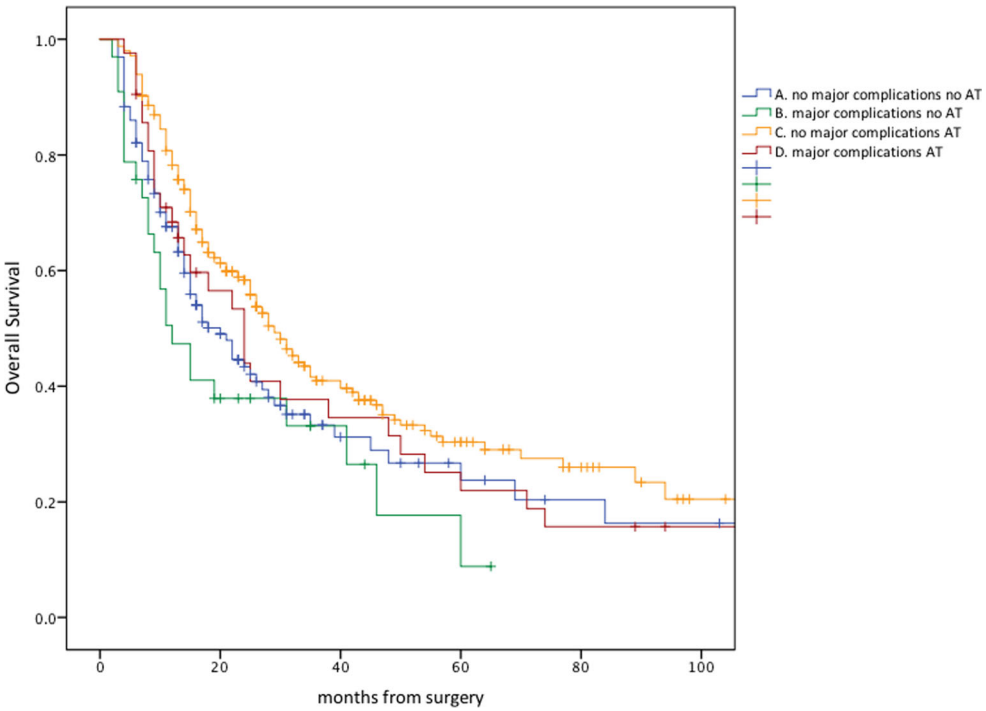

Fig. 2 Overall survival rates according to the occurrence of major complications and receipt of adjuvant treatment

Discussion

This retrospective analysis shows that major complications after pancreaticoduodenectomy for pancreatic cancer have a major impact on survival. Although a few of those patients die in the immediate postoperative period as a consequence of the complications, the impact of major complications is long-lasting, and in fact median survival is almost halved in these patients (15 months vs. 26 months). Patients with major complications are also less likely to receive adjuvant treatment (43.9% vs. 68.5%); however, this consequence cannot entirely explain the impact on long-term survival, since the effect is independent of the receipt of adjuvant treatment at the multivariate model.

Our results are not consistent with a recent large retrospective analysis reported by Pugalenthi et al., which concluded that there is no effect of complications on survival after PD for cancer.[20] It is important to highlight, however, that the authors analyzed an old cohort (PD were performed on average 10 years previous than in our population), and did not provide any information concerning the receipt of adjuvant treatment.

In patients undergoing surgery for pancreatic cancer, the best expectation for long-term survival and cure is a combination of margin-negative resection and systemic chemotherapy.[24] Other studies have found that occurrence of complications after surgery for PC reduce the likelihood of receiving systemic treatment and delay its onset, thus potentially explaining the detrimental effect of complications on survival.[25,26] Similarly, we noticed that the probability of receiving AT was significantly lower after major complications and the interval between surgery and the first dose of chemotherapy was a median of 10 days longer than in uncomplicated patients. However, our data suggest that major complications also play an intrinsic role in affecting overall survival. First, by multivariate analysis, we observed an independent effect of severe morbidity on survival, with a HR of 1.37, $p = 0.041$; second, despite being statistically significant, the 10-day delay in initiating adjuvant treatment is clinically meaningless; and finally, the rate of patients who started treatment within 12 weeks did not vary between the groups, which on a post-hoc analysis of the ESPAC3 trial cohort was the time-point below which no differences in outcomes were shown.[27]

Table 4 Effect of both major morbidity and receipt of adjuvant treatment on overall survival after pancretoduodenectomy

Group	Median OS (95% CI)	6-month OS (%)	1-year OS (%)	3-year OS (%)	5-year OS (%)
A. No adjuvant, CDC < 3 ($n = 129$)	20 (14.3–25.7)	80	65	33	23
B. No adjuvant, CDC ≥ 3 ($n = 33$)	12 (6.5–17.5)	76	47	27	8
C. Adjuvant, CDC < 3 ($n = 246$)	29 (24.5–33.5)	94	78	40	30
D. Adjuvant, CDC ≥ 3 ($n = 42$)	24 (16.2–31.8)	88	66	35	22

CDC Clavien-Dindo Classification

A biological explanation of our results can rely in the intimate relationship between inflammation and pancreatic cancer. Not only can inflammation promote oncogenesis and cancer development,[28,29] but also inflammatory events are able to stimulate cancer growth and dissemination.[30,31] Uncomplicated surgery represents per se an inflammatory stimulus, whose burden is proportional to the invasiveness of the surgical procedure.[32] In addition, postoperative morbidity directly activates the systemic inflammatory response (SIR), leading to secretion of oncogenic cytokines and to immune-suppressive activity.[33,34]

This synergism between cancer-promoting and immune-suppressive activity is a possible explanation for the poor outcome observed in surgical cancer patients who experience postoperative complications. In fact, overall survival has also been found to be reduced in patients undergoing major surgical resections for esophageal, gastric, and liver cancer who had a postoperative course complicated by sepsis.[35] Postoperative complications have also been associated with decreased long-term survival in patients undergoing curative surgery for colorectal and lung cancer.[36,37] In our analysis, patients in the "complication/no adjuvant therapy" group had the worst survival, with a median of 12 months, which is comparable with that of unresectable PC patients undergoing palliative treatment with gemcitabine.[38]

Our study has some limitations. We did not observe the same effect on survival after distal pancreatectomy. Although the median overall survival of patients with major complications was lower (18 vs. 33 months), this was not statistically significant. Even if it is not possible to exclude a priori that severe morbidity does not affect survival after DP, the lack of significance could be attributed to a type II error. Second, given the retrospective nature of the study, we were not able to retrieve accurate information on potential interruptions or suspensions of AT, since a large proportion of patients had their adjuvant treatment elsewhere. Thus, adjustment for such confounders could not be analyzed in this study.

In conclusion, our findings suggest that major morbidity not only negatively affects the likelihood of receiving adjuvant treatment in pancreatic cancer, but has also an independent harmful effect on the survival of those patients undergoing pancreatoduodenectomy. This adds further emphasis to the overarching goal of preventing major complications in pancreatic surgery.

Author's contribution Drs. Sandini, Ruscic, Ferrone, Qadan, Eikermann, Warshaw, Lillemoe, and Fernández provided substantial contributions to the conception and design of the work, or the acquisition, analysis, or interpretation of data for the work.

Dr. Sandini and Dr. Fernández drafted the work, Drs. Qadan, Warshaw, and Lillemoe revised it critically for important intellectual content. All authors gave final approval of the version to be published. All authors give their agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Fernandez-del Castillo C, Morales-Oyarvide V, McGrath D, Wargo JA, Ferrone CR, Thayer SP, et al. Evolution of the Whipple procedure at the Massachusetts General Hospital. Surgery. 2012;152(3 Suppl 1):S56–63.
2. Kimura W, Miyata H, Gotoh M, Hirai I, Kenjo A, Kitagawa Y, et al. A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. Annals of surgery. 2014;259(4):773–80.
3. Chok KS, Ng KK, Poon RT, Lo CM, Fan ST. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. The British journal of surgery. 2009;96(1):81–7.
4. Odermatt M, Miskovic D, Flashman K, Khan J, Senapati A, O'Leary D, et al. Major postoperative complications following elective resection for colorectal cancer decrease long-term survival but not the time to recurrence. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2015;17(2):141–9.
5. Rueth NM, Parsons HM, Habermann EB, Groth SS, Virnig BA, Tuttle TM, et al. The long-term impact of surgical complications after resection of stage I nonsmall cell lung cancer: a population-based survival analysis. Annals of surgery. 2011;254(2):368–74.
6. Ito H, Are C, Gonen M, D'Angelica M, Dematteo RP, Kemeny NE, et al. Effect of postoperative morbidity on long-term survival after hepatic resection for metastatic colorectal cancer. Annals of surgery. 2008;247(6):994–1002.
7. Brown JC, Harhay MO, Harhay MN. The Prognostic Importance of Frailty in Cancer Survivors. Journal of the American Geriatrics Society. 2015;63(12):2538–43.
8. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Annals of surgery. 2005;242(3):326–41; **discussion 41-3**.
9. Tirkes T, Hollar MA, Tann M, Kohli MD, Akisik F, Sandrasegaran K. Response criteria in oncologic imaging: review of traditional and new criteria. Radiographics: a review publication of the Radiological Society of North America, Inc. 2013;33(5):1323–41.
10. Wentz SC, Zhao ZG, Shyr Y, Shi CJ, Merchant NB, Washington K, et al. Lymph node ratio and preoperative CA 19-9 levels predict overall survival and recurrence-free survival in patients with resected pancreatic adenocarcinoma. World journal of gastrointestinal oncology. 2012;4(10):207–15.
11. Hirai I, Kimura W, Ozawa K, Kudo S, Suto K, Kuzu H, et al. Perineural invasion in pancreatic cancer. Pancreas. 2002;24(1):15–25.
12. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607–20.
13. Moghanaki D, Mick R, Furth EE, Sohal D, Salmon PM, Behbahani A, et al. Resection status, age and nodal involvement determine survival among patients receiving adjuvant chemoradiotherapy in pancreatic adenocarcinoma. JOP: Journal of the pancreas. 2011;12(5):438–44.
14. Wu W, He J, Cameron JL, Makary M, Soares K, Ahuja N, et al. The impact of postoperative complications on the administration of adjuvant therapy following pancreaticoduodenectomy for adenocarcinoma. Annals of surgical oncology. 2014;21(9):2873–81.
15. Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Annals of surgery. 2014;260(2):372–7.

16. Aahlin EK, Olsen F, Uleberg B, Jacobsen BK, Lassen K. Major postoperative complications are associated with impaired long-term survival after gastro-esophageal and pancreatic cancer surgery: a complete national cohort study. BMC surgery. 2016;16(1):32.
17. Aoyama T, Murakawa M, Katayama Y, Yamaoku K, Kanazawa A, Higuchi A, et al. Impact of postoperative complications on survival and recurrence in pancreatic cancer. Anticancer research. 2015;35(4):2401–9.
18. Kamphues C, Bova R, Schricke D, Hippler-Benscheidt M, Klauschen F, Stenzinger A, et al. Postoperative complications deteriorate long-term outcome in pancreatic cancer patients. Annals of surgical oncology. 2012;19(3):856–63.
19. van der Gaag NA, Harmsen K, Eshuis WJ, Busch OR, van Gulik TM, Gouma DJ. Pancreatoduodenectomy associated complications influence cancer recurrence and time interval to death. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2014;40(5):551–8.
20. Pugalenthi A, Protic M, Gonen M, Kingham TP, Angelica MI, Dematteo RP, et al. Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. Journal of surgical oncology. 2016;113(2):188–93.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205–13.
22. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, et al. Pancreatic fistula rate after pancreatic resection. The importance of definitions. Digestive surgery. 2004;21(1):54–9.
23. Menon KV, Gomez D, Smith AM, Anthoney A, Verbeke CS. Impact of margin status on survival following pancreatoduodenectomy for cancer: the Leeds Pathology Protocol (LEEPP). HPB: the official journal of the International Hepato Pancreato Biliary Association. 2009;11(1):18–24.
24. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010 Sep 8;304(10):1073–81
25. Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, Ko CY, Bentrem DJ. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg. 2014 Aug;260(2):372–7
26. Wu W, He J, Cameron JL, Makary M, Soares K, Ahuja N, Rezaee N, Herman J, Zheng L, Laheru D, Choti MA, Hruban RH, Pawlik TM, Wolfgang CL, Weiss MJ. The impact of postoperative complications on the administration of adjuvant therapy following pancreaticoduodenectomy for adenocarcinoma. Ann Surg Oncol. 2014 Sep;21(9):2873–81
27. Valle JW, Palmer D, Jackson R, Cox T, Neoptolemos JP, Ghaneh P, Rawcliffe CL, Bassi C, Stocken DD, Cunningham D, O'Reilly D, Goldstein D, Robinson BA, Karapetis C, Scarfe A, Lacaine F, Sand J, Izbicki JR, Mayerle J, Dervenis C, Oláh A, Butturini G, Lind PA, Middleton MR, Anthoney A, Sumpter K, Carter R, Büchler MW. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014 Feb 20;32(6):504–12
28. Löhr M, Klöppel G, Maisonneuve P, Lowenfels AB, Lüttges J. Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: a meta-analysis. Neoplasia. 2005 Jan; 7(1):17–23
29. Ancrile BB, O'Hayer KM, Counter CM. Oncogenic ras-induced expression of cytokines: a new target of anti-cancer therapeutics. Mol Interv. 2008 Feb; 8(1):22–7.
30. Fukuda A, Wang SC, Morris JP 4th, Folias AE, Liou A, Kim GE, Akira S, Boucher KM, Firpo MA, Mulvihill SJ, Hebrok M. Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression. Cancer Cell. 2011 Apr 12; 19(4):441–55
31. Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, Reichert M, Beatty GL, Rustgi AK, Vonderheide RH, Leach SD, Stanger BZ. EMT and dissemination precede pancreatic tumor formation. Cell. 2012 Jan 20;148(1–2):349–61
32. Biro P, Gurman G. Proposal for a surrogate surgical invasiveness score to obtain a 'post hoc' quantification of surgical stress and tissue trauma in the context of postoperative outcome assessments. Br J Anaesth. 2014 May;112(5):951–3
33. Haga Y, Beppu T, Doi K, Nozawa F, Mugita N, Ikei S, Ogawa M. Systemic inflammatory response syndrome and organ dysfunction following gastrointestinal surgery. Crit Care Med. 1997 Dec;25(12):1994–2000
34. Walton AH, Muenzer JT, Rasche D, Boomer JS, Sato B, Brownstein BH, et al. Reactivation of multiple viruses in patients with sepsis. PLoS One 2014;9:e98819.
35. Mokart D, Giaoui E, Barbier L, Lambert J, Sannini A, Chow-Chine L, Brun JP, Faucher M, Guiramand J, Ewald J, Bisbal M, Blache JL, Delpero JR, Leone M, Turrini O. Postoperative sepsis in cancer patients undergoing major elective digestive surgery is associated with increased long-term mortality. J Crit Care. 2016 Feb;31(1):48–53
36. Artinyan A, Orcutt ST, Anaya DA, Richardson P, Chen GJ, Berger DH. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. Ann Surg.2015 Mar;261(3):497–505
37. Andalib A, Ramana-Kumar AV, Bartlett G, Franco EL, Ferri LE. Influence of postoperative infectious complications on long-term survival of lung cancer patients: a population-based cohort study. J Thorac Oncol. 2013 May;8(5):554–61
38. Hamada T, Nakai Y, Yasunaga H, Isayama H, Matsui H, Takahara N, Sasaki T, Takagi K, Watanabe T, Yagioka H, Kogure H, Arizumi T, Yamamoto N, Ito Y, Hirano K, Tsujino T, Tada M, Koike K. Prognostic nomogram for nonresectable pancreatic cancer treated with gemcitabine-based chemotherapy. Br J Cancer. 2014 Apr 15;110(8):1943–9