Title: Five-year recurrence/survival after pancreatoduodenectomy for pancreatic adenocarcinoma: does pre-existing diabetes matter? Results from the Recurrence After Whipple's (RAW) study

Running Head: Diabetes mellitus and outcomes of pancreatoduodenectomy

Authors:

[1]Ashray Rajagopalan, [2]Somaiah Aroori, [2]Thomas B. Russell, [2]Peter L. Labib, [3]Fabio Ausania, [4]Elizabeth Pando, [5]Keith J. Roberts, [6]Ambareen Kausar, [7]Vasileios K. Mavroeidis, [8]Gabriele Marangoni, [9]Sarah C. Thomasset, [10]Adam E. Frampton, [11]Pavlos Lykoudis, [12]Manuel Maglione, [13]Nassir Alhaboob, [14]Hassaan Bari, [15]Andrew M. Smith, [16]Duncan Spalding, [17]Parthi Srinivasan, [18]Brian R. Davidson, [19]Ricky H. Bhogal, [20]Ismael Dominguez, [21]Rohan Thakkar, [22]Dhanny Gomez, [23]Michael A. Silva, [24]Pierfrancesco Lapolla, [24]Andrea Mingoli, [25]Alberto Porcu, [26]Nehal S. Shah, [27]Zaed Z. R. Hamady, [28]Bilal Al-Sarrieh, [29]Alejandro Serrablo, [1]Daniel Croagh on behalf of *RAW Study Collaborators,

*See **Appendix 1** for a full list of authors comprising the Recurrence After Whipple's (RAW) study team. All are required to be PubMed citable and should be included in the online version of the manuscript.

Corresponding Author:

Dr Daniel Croagh

Monash Health

246 Clayton Road,

Clayton VIC 3168

Australia

Daniel.Croagh@monashhealth.org

(03) 9594 6666

Author affiliations:

[1]Monash Health, Melbourne, Australia, [2]University Hospitals Plymouth NHS Trust, Plymouth, UK, [3]Hospital Clinic de Barcelona, Barcelona, Spain, [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [5]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [6]East Lancashire Hospitals NHS Trust, Blackburn, UK, [7]University Hospitals Bristol NHS Foundation Trust, Bristol, UK, [8]University Hospital Coventry & Warwickshire, Coventry, UK, [9]NHS Lothian, Edinburgh, UK, [10]Royal Surrey NHS Foundation Trust, Guildford, UK, [11]Hull University Teaching Hospitals NHS Trust, Hull, UK, [12]Medical University of Innsbruck, Innsbruck, Austria, [13]Ibn Sina Specialized Hospital, Khartoum, Sudan, [14]Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan, [15]Leeds Teaching Hospitals NHS Trust, Leeds, UK, [16]Imperial College Healthcare NHS Trust, London, UK, [17]King's College Hospital NHS Foundation Trust, London, UK, [18]Royal Free London NHS Foundation Trust, London, UK, [19]The Royal Marsden NHS Foundation Trust, London, UK, [20]Salvador Zubiran National Institute of Health Sciences and Nutrition, Mexico City, Mexico, [21]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK, [22]Nottingham University Hospitals NHS Trust, Nottingham, UK, [23]Oxford University Hospitals NHS Foundation Trust, Oxford, UK, [24]Policlinico Umberto I University Hospital Sapienza, Rome, Italy, [25]Azienda Ospedaliero Universitaria di Sassari, Sassari, Italy, [26]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, [27]University Hospital Southampton NHS Foundation Trust,

Southampton, UK, [28]Swansea Bay University Health Board, Swansea, UK and [29]Hospital Universitario Miguel Servet, Zaragoza, Spain

Tables:	2
Figures:	3
Word count (Abstract):	204
Word count (Main Text):	3111

Keywords: Pancreatic Neoplasms, Prognosis, Diabetes Mellitus, Pancreaticoduodenectomy**.**

Disclosure Statement

The authors have no conflicts of interest to declare.

Abstract

Objectives

Diabetes mellitus (DM) has a complex relationship with pancreatic cancer. This study examines the impact of preoperative DM, both recent-onset and pre-existing, on long-term outcomes following pancreatoduodenectomy (PD for pancreatic ductal adenocarcinoma (PDAC).

Methods

Data were extracted from the Recurrence After Whipple's (RAW) study, a multi-centre cohort of PD performed for pancreatic head malignancy (2012-2015). Recurrence and five-year survival rates of patients with DM were compared to those without. A subgroup analysis was also performed to compare patients with recent-onset DM (less than one year) to patients with established DM.

Results

Out of 758 patients that were included, 187 (24.7%) had DM, of whom, 47 of the 187 (25.1%) had recent-onset DM. There was no difference in the rate of postoperative pancreatic fistula (DM: 5.9% vs no DM 9.8%; p=0.11), five-year survival (DM: 24.1% vs no DM: 22.9%; p=0.77) or five-year recurrence (DM: 71.7% vs no DM: 67.4%; p=0.32). There was also no difference between patients with recent-onset DM and patients with established DM in postoperative outcomes, recurrence, or survival.

Conclusions

We found no difference in five-year recurrence and survival between diabetic patients and those without diabetes. Patients with pre-existing DM should be evaluated for PD on a comparable basis to non-diabetic patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is diagnosed in approximately half a million patients annually and is associated with high mortality rates.[1] Pancreatoduodenectomy (PD) is the only potentially curative treatment, but this major operation is associated with high morbidity rates and poor long-term survival.[2-4]

Diabetes mellitus (DM) has a complex relationship with pancreatic cancer, as both a systemic metabolic disease and a potential modulator of oncologic outcomes, with pancreatogenic DM suggested to reflect more aggressive tumour biology.[5] Pancreatogenic DM has been previously associated with decreased overall survival,[5,6] as well as increased tumour size.[7] This may be due to both the proliferative effect of hyperglycaemia on pancreatic tumour growth, and that larger tumours are more likely to produce factors which promote insulin resistance.[7,8]

DM is also associated with increased risk of pancreatic cancer, which is more pronounced in new-onset than pre-existing DM.[9-12] Recognition of new-onset diabetes as a potential presenting symptom of pancreatic cancer is essential for early diagnosis, and differentiation of pancreatic cancer-induced diabetes from the more common type 2 DM has been a topic of interest in recent years.[13-17] Despite large-scale epidemiological evidence that new-onset diabetes, particularly in the context of weight loss, has been associated with an increased risk of pancreatic cancer,[18] the screening of asymptomatic adults with new-onset diabetes for pancreatic cancer is controversial. Currently, the US Preventive Service Task Force recommends against screening individuals with new-onset diabetes for pancreatic cancer, in the absence of a high risk family history or genetic syndrome.[19] However, in these high risk

individuals, new-onset diabetes is an accepted trigger for further workup or more intensive surveillance.[20]

Diabetes mellitus may also influence postoperative outcomes of PD. In particular, there is conflicting evidence to date regarding the rate of postoperative pancreatic fistula (POPF). One single centre analysis of 251 PD patients showed a statistically significant increase of POPF rate in diabetic patients, independent of other risk factors (OR 4.3; p=0.027).[21] In contrast, other studies have instead shown a protective effect of DM which has been attributed to a lower rate of high-risk pancreatic gland features.[22-24]

Clarifying the prognostic implications of DM in patients presenting with resectable PDAC is essential for patient counselling and developing postoperative surveillance protocols with a view to earlier diagnosis of any recurrence. The study aimed to examine the impact of preoperative DM, both recent-onset and pre-existing, on long-term recurrence and survival following PD for PDAC.

Materials and Methods

Patient recruitment

We performed a retrospective cohort study using data from the Recurrence After Whipple's (RAW) study database.[25] Patients were included if they underwent PD for a histopathological diagnosis of PDAC at one of twenty-nine participating centres from 1st June 2012 to 31st May 2015. Patients with five-year follow-up data were included in the study. Patients lost to

follow-up were excluded from the study. Other missing data were handled by exclusion from the relevant analysis.

The diagnosis, grading and definitions of postoperative pancreatic fistula (POPF; grade A, B and C) was as per the 2016 international study group in pancreatic surgery (ISGPS).[26] R1 was defined as any specimen margin reported as having tumour <1mm from the margin/surface. Recurrence was defined as postoperative cross-sectional imaging reports diagnosing cancer recurrence, and the time of recurrence was defined as the date of the diagnostic imaging. Data were entered into a purpose-built REDCap electronic data collection tool.[27,28]

The following aspects of study design aimed to mitigate against potential sources of bias:

- Sampling bias: Multiple centres participated in the study to aim for a cohort representative of patients undergoing PD for PDAC.
- Selection bias: All consecutive eligible patients in the research window were included.
- Recall bias: Data were extracted from medical records documented contemporaneously.
- Attrition bias: Regional cancer registries, primary care data requests and regional radiology systems were used to determine if patients had developed recurrence or died.

Ethical approval

Data were collected from the Recurrence After Whipple's (RAW) study (ClinicalTrials.gov NCT04596865). Ethical approval was granted by Northwest – Greater Manchester South

Research Ethics Committee (20/NW/0397) and the study was sponsored by University Hospitals Plymouth NHS Trust. In addition, the study was approved by the research and development departments of all collaborating units and adhered to the standards laid down in the Declaration of Helsinki (revised 2013).

Data sources and storage

Data were collected by each participating unit from the medical records and supplemented by follow-up data from referring hospitals, if not available at the treating unit. A REDCap (version 11.0.3) electronic database was utilised to collect and store the data.

Data collected included demographic data, type and onset of diabetes, radiological stage, neoadjuvant and adjuvant treatment, histology, postoperative complications, recurrence, and survival. Radiological and histopathological staging were performed using the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours 7th edition, which was current at the time of patient assessment.

Statistical analysis

Data were analysed with IBM SPSS version 29 and GraphPad Prism version 9. Cases were divided into two cohorts based on the preoperative diagnosis of DM. A subgroup analysis was subsequently conducted on the patients with preoperative DM to compare those patients with recent-onset DM (within twelve months prior to presentation) to patients with established or unknown onset of DM. The primary outcomes were survival, recurrence, and occurrence of POPF. Secondary outcomes were the length of hospital stay, 30-day readmission, 90-day mortality, and unplanned return to theatre.

Non-parametric variables were expressed as medians with interquartile ranges, and categorical variables as numbers with percentages. Chi-Square and Kruskal Wallis tests evaluated differences between the cohorts. Bonferroni correction for multiple comparisons was conducted for outcomes which were not predetermined. Backwards Wald (multivariable) logistic regression was then performed to evaluate factors associated with POPF, five-year survival and five-year recurrence. The least predictive variables were removed from the model in a stepwise fashion. Results from this analysis were reported as classification accuracy and odds ratios (ORs) with 95% confidence intervals (CIs).

Overall survival, disease-free survival (DFS), and recurrence were also estimated by the Kaplan-Meier method, comparing patients who did not have diabetes to patients with recent-onset DM (within 12 months) and patients with established or unknown onset of DM. The log-rank (Mantel-Cox) test was performed to test the difference in survival curves between groups. A two-tailed p-value < 0.05 was considered statistically significant for all analyses.

Results

Baseline characteristics

Our study included 758 patients. In total, 187 patients (24.7%) had diabetes (cases, group 1), and 47 of these 187 patients (25.1%) had recent-onset DM. There was no statistically significant difference in age, sex, radiological TNM stage, or the number of patients with neoadjuvant or adjuvant treatment between the diabetic and non-diabetic groups. There was no significant difference in the maximum histological tumour dimension (DM: median 30.0

mm, IQR 25.0-40.0 mm vs no DM: median 30.0 mm, IQR 22.0-35.5 mm; p=0.48). The baseline characteristics and histological data of the patient cohort are provided in **Table 1**.

Timing of death was not available for one of the 582 patients who died, and timing of recurrence was unknown for 54 of 519 patients who were known to have had a recurrence within the five-year follow-up period. As a result, these patients could not be included in the Kaplan-Meier analysis, one-year and three-year statistics, though they were included in the five-year analysis.

Postoperative outcome data

The rate of POPF was not significantly different between diabetic and non-diabetic patients (DM: 5.9 vs no DM: 9.8%; p=0.11). Preoperative DM was also not a significant predictor of POPF on multivariate analysis [(Odds Ratio (OR): 0.61, 95% CI 0.30-1.23); p=0.17; **Supplementary Table 1**).

There was also no difference in the rates of length of stay, unplanned return to theatre, 30-day readmission (DM: 9.6% vs no DM: 10.5%; p=0.89) or 90-day mortality (DM: 5.3% vs no DM: 3.9%; p=0.40) between groups. The details of postoperative outcomes are provided in **Table 1**.

Characteristics and postoperative outcomes between recent-onset diabetes and patients with long-term diabetes

Demographic, preoperative and adjuvant treatment was similar between groups. In the subgroup analysis, the TNM stage of the tumour was similar between patients with recent-

onset diabetes and long-term diabetes. There was also no difference in maximum histological tumour dimension (recent DM: median 32.0 mm, IQR 24.0-40.0 mm vs established DM: median 30.0 mm, IQR 25.0-38.0 mm; p=1.00). Stage and R status were also similar between both groups. The subgroup demographic, preoperative, adjuvant treatment and postoperative histology data are provided in **Table 2**.

There was no difference in the rate of POPF (recent DM: 8.5% vs. established DM: 5.0%; p=0.47), including on multivariate analysis (OR: 1.66, 95% CI 0.39-7.04); p=0.50; **Supplementary Table 1**). The median length of hospital stay and unplanned return to the theatre was also not different between patients with recent-onset DM and those with established DM.

We found no difference in the rates of 30-day readmission (recent DM: 6.4% vs established DM: 10.7%; p=0.57) or 90-day mortality (recent DM: 6.4% vs established DM: 5.0%; p=0.71) between both groups. The subgroup analysis of postoperative outcomes is provided in **Table 2**.

Recurrence & survival details

The rate of five-year recurrence was comparable between diabetic and non-diabetic patients (DM: 71.7% vs no DM: 67.4%; p=0.32) and between patients with recent-onset DM and patients with established DM (recent DM: 75.5% vs established DM: 70.7%; p=0.71). There was no difference in recurrence rate at one-year or three-year endpoints on univariate analysis. Multivariate analysis of risk factors for five-year recurrence did not show any

predictive value of either preoperative diabetes (OR 1.23 (95% CI 0.82-1.84); p=0.32) or recent-onset diabetes precisely (OR 0.94 (95% CI 0.41-2.17); p=0.89).

We found no difference in five-year survival between diabetic and non-diabetic patients (DM: 24.1% vs no DM: 22.9%; p=0.77). There was also no difference in five-year survival between patients with recent-onset DM and patients with established DM (recent DM: 27.7% vs established DM 22.9%; p=0.56). Multivariate analysis showed that neither preoperative diabetes (OR 1.07 (95% CI 0.64-1.76); p=0.81) nor recent-onset diabetes (OR 1.20 (95% CI 0.55-2.62); p=0.65) were significant predictors of five-year survival. Kaplan-Meier analysis did not demonstrate any difference between non-diabetic, recent-onset diabetic and patients with established or unknown onset of diabetes concerning overall survival (p=0.47; **Figure 1**), recurrence (p=0.47; **Figure 2**) or disease-free survival (p=0.77; **Figure 3**).

The details of recurrence and survival rates are provided in **Table 1**, while a subgroup analysis of these outcomes between recent and established DM is provided in **Table 2**. The multivariate analysis of risk factors for 5-year recurrence is provided in **Supplementary Table 2,** and the multivariate analysis of risk factors for 5-year survival is provided in **Supplementary Table 3.**

Discussion

The RAW study was set up to identify predictive factors of recurrence following PD for PDAC, lower common bile duct cholangiocarcinoma, and ampullary adenocarcinoma. For this sub-study, we examined the impact of preoperative diabetes on short-and long-term outcomes of PD performed for histologically confirmed PDAC. The strength of our study is the large

cohort size, availability of detailed information on pre-, intra- and post-op variables, and actual long-term follow-up data, which enables us to accurately analyse the long-term recurrence and survival.

DM is known to have a high prevalence in patients with PDAC. Chari et al. found a prevalence of 40% DM in a single institution analysis of 736 PDAC cases.[12] The reported prevalence in several cohorts of post-resection PDAC patients ranges from approximately 20-50%, including a finding by Malleo et al. of 19.9% (n=602), Chu et al. of 46% (n=251),[21] by Dandona et al. of 32.7% (n=355),[29] by Terasaki et al. of 32.4% (n=373).[30] The prevalence of DM in our analysis is comparable to that reported previously.

Our reported 90-day post-operative mortality rates are also comparable with other large studies, with a 3.7% 90-day mortality rate reported in one study of 596 patients at a single-centre in the United States,[31] while a large analysis of 8490 patients following PD from a registry in Taiwan demonstrated an 8.4% 90-day mortality rate.[32]

DM and POPF rates

To date, the influence of preoperative DM on occurrence of POPF has been unclear. Previous evidence has produced conflicting results. Chu et al., in a study of 251 PD patients with PDAC from a prospective database at a single centre in the United States, demonstrated a 6.8% rate of POPF and found that this was higher in diabetic patients (DM: 10.3% vs no DM: 3.7%; p=0.04).[21] This was found to be significant on multivariate analysis controlling for age, comorbidity, nutritional status, operative type and time, and pancreatic quality (OR 4.3;

p=0.027).[21] In this cohort, acute kidney injury was also more prevalent in diabetic patients (DM: 23.3% vs no DM: 12.6%; p=0.03), though other complications, length of stay and overall mortality, were not significantly different.[21] In contrast, Hu et al. observed a lower rate of POPF (DM: 39.19% vs no DM: 51.61%; p=0.047) in diabetic patients in a retrospective single centre study of 539 PD cases. However, DM was no longer a significant predictor of POPF on multivariate analysis (p=0.268). Instead, male sex (OR 1.784 (95% CI 1.214-2.622); p=0.003), body mass index greater than 25 (OR 1.679 (95% CI 1.107-2.546); p=0.015), double-layer mucosa-to-mucosa pancreatico-jejunostomy (OR 2.102 (95% CI 1.374-3.216); p=0.001), pancreatic duct diameter of 3mm or less (OR 2.062 (95% CI 1.416-3.003); p<0.001) and soft pancreatic texture (OR 3.048 (95% CI 1.953-4.757); p<0.001) were identified as risk factors.[24]

In another large cohort study of 602 patients undergoing PDAC resection (predominantly PD) at a single institution in Italy, Malleo et al. reported decreased incidence of clinically relevant POPF (CR-POPF) in diabetic patients (DM: 5.0% vs no DM: 11.8%; p=0.043) with an overall CR-POPF rate of 10.5%.[22] Multivariate analysis showed that male sex (OR 3.48 (95% CI 1.62-7.48); p=0.002), diabetes mellitus (OR 0.53 (95% CI 0.22-0.95); p=0.047), soft pancreatic texture (OR 2.19 (95% CI 1.36-4.12); p=0.008), pancreatic duct diameter of less than 3mm (OR 1.79 (95% CI 1.23-3.31); p=0.045) were statistically significant predictors of CR-POPF.[22] Diabetic patients were also less likely to have a soft pancreatic texture (DM: 46.0% vs no DM: 79.5%; p=0.001).[22] The authors concluded that preoperative DM is not a significant risk factor for POPF, but is likely protective due to a reduced frequency of high-risk pancreatic gland features.[22] This finding was also supported by a meta-analysis by Xia et al. of ten studies including 1251 patients, which found a reduced incidence of POPF in diabetic patients (DM: 19.1% vs no DM: 29.1%; OR 0.64 (95% CI 0.45-0.90); p=0.01).[23] This was also attributed to decreased frequency

of high-risk gland features, including soft pancreatic texture.[23] Another meta-analysis by Zhang et al., including 24,740 patients from 27 studies, did not show a statistically significant association between DM and CR-POPF (OR 0.6 (95% CI 0.40-1.08); p=0.10).[33] However, both of these meta-analyses were limited by the heterogeneity of included studies.[23,33]

There is a high degree of variability in the reported POPF rate of the cited single-centre studies, which may be partly due to the inclusion in some studies of patients with all grades of POPF,[24] while others exclude biochemical leaks (Grade A POPF) and consider only CR-POPF[22] in keeping with updated grading which recognises that solely biochemical leaks do not adversely affect the postoperative pathway.[26]

Our results do not demonstrate any statistically significant difference in the rate of POPF, and tend towards a lower incidence of POPF in diabetic patients. This supports the conclusion that DM does not increase the risk of POPF, although a larger sample size may be required to determine whether there is a statistically significant protective effect.

Recurrence and survival

Our finding that preoperative DM, including recent-onset DM, is not adversely associated with either recurrence or overall or disease-free survival. This result is discordant with some existing evidence. In a retrospective study by Lee et al. of 288 PD patients with confirmed PDAC from a single institution in Korea, new-onset DM was associated with early recurrence (Hazard ratio (HR) 1.451 (95% CI 1.054-1.999); p=0.022), as well as poorer overall survival (recent DM: 22 months vs. no DM: 33 months; p=0.039).[5] The authors suggested that these

findings likely reflect patients with new-onset DM having more aggressive tumour characteristics.[5]

A study by Chu et al. of 209 patients with resected PDAC from a single institution in the United States also demonstrated poorer overall survival in both recent and established onset diabetic patients (recent DM: 15 months vs established DM: 15 months vs no DM: 17 months; p=0.04).[7] However, in this study, only new-onset DM was a statistically significant predictor of reduced post-resection survival on Cox regression analysis (HR 1.75 (95% CI 1.10-2.78); p=0.017), with long-standing DM no longer significant as a risk factor (HR 1.30 (95% CI 0.75-2.25, p=0.36).[7] However, other existing literature is conflicting in this area. In a cohort of 355 patients who underwent PD for PDAC, Dandona et al. demonstrated no adverse impact of DM on overall survival (HR 0.87 (95% CI 0.66-1.14); p=0.31).[29] In another study including 373 patients who underwent curative resection of PDAC at a single centre in Japan, Terasaki et al. found no difference in 5-year survival between diabetic and non-diabetic patients (DM: 29.7% vs. no DM: 30.6%; p=0.766).[30] Our findings suggest that pre-existing DM, including recent-onset DM, does not adversely influence long-term recurrence or survival in patients undergoing PD for PDAC.

Limitations of the study

Although our study utilised a large multi-centre cohort, it is a retrospective study with its associated weaknesses, including heterogeneity of treatment and incomplete data requiring some patients to be excluded from relevant sub-analyses. The study was also not set up to examine the impact of DM on outcomes of PD performed for histologically confirmed PDAC. As a result, patients were classified as having DM according to the medical record, and not

according to a consistent biochemical or clinical definition. In addition, we did not collect information on diabetic control in the peri-operative period and medication status; consequently, we could not analyse the influence of diabetic medication on peri-operative complications and survival outcomes. This is potentially relevant as some studies have found a survival benefit from using metformin following pancreatic cancer resection, possibly due to an anti-neoplastic effect.[30,34] However, recent randomised trial evidence has not shown any benefit to adding metformin to standard systemic therapy for pancreatic cancer.[35,36] Glycated haemoglobin (HbA1c) level was also unavailable, which has been of prognostic interest in pancreatic cancer as well.[37,38] Future prospective research, including data on glycaemic control, DM treatment and metformin use, would be of interest to validate and extend our findings.

Conclusion

In our international multi-centre study of patients who underwent PD for histologically confirmed PDAC, a preoperative diagnosis of DM, including recent-onset DM, did not influence the stage at presentation, perioperative outcomes, long-term recurrence, or survival. The presence of diabetes mellitus, either recent-onset or long-term, should not factor into decision-making when considering patients with suspected pancreatic cancer for resection.

Author Contributions

Conceptualisation: AR, TR, PL, SA, DC; **Data curation:** all authors; **Formal analysis:** AR, DC; **Funding acquisition:** N/A; **Investigation:** AR, DC; **Methodology:** AR, TR, PL, SA, DC; **Project administration:** AR, TR, PL; **Resources:** AR, TR, PL; **Software:** AR, DC; **Supervision:** SA, DC;

Validation: SA, DC; **Visualisation:** all authors; **Writing – original draft:** AR; **Writing – review and editing:** all authors.

Acknowledgements

We would like to thank all those who contributed towards the Recurrence After Whipple's (RAW) study.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021;71(3):209-249.

2. Mathur A, Ross SB, Luberice K, et al. Margin Status Impacts Survival after Pancreaticoduodenectomy but Negative Margins Should Not be Pursued. The American Surgeon™. 2014/04/01 2014;80(4):353-360.

3. Pugalenthi A, Protic M, Gonen M, et al. Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. Journal of Surgical Oncology. 2016/02/01 2016;113(2):188-193.

4. Chen S-C, Shyr Y-M, Wang S-E. Longterm survival after pancreaticoduodenectomy for periampullary adenocarcinomas. HPB. 2013/12/01/ 2013;15(12):951-957.

5. Lee S, Hwang HK, Kang CM, Lee WJ. Adverse Oncologic Impact of New-Onset Diabetes Mellitus on Recurrence in Resected Pancreatic Ductal Adenocarcinoma: A Comparison With Long-standing and Non–Diabetes Mellitus Patients. Pancreas. 2018;47(7).

6. Shen H, Zhan M, Wang W, et al. Impact of diabetes mellitus on the survival of pancreatic cancer: a meta-analysis. OncoTargets and Therapy. 2016/03/22 2016;9:1679-1688.

7. Chu CK, Mazo AE, Goodman M, et al. Preoperative Diabetes Mellitus and Long-Term Survival After Resection of Pancreatic Adenocarcinoma. Annals of Surgical Oncology. 2010/02/01 2010;17(2):502-513.

8. Basso D, Greco E, Fogar P, et al. Pancreatic cancer-derived S-100A8 N-terminal peptide: A diabetes cause? Clinica Chimica Acta. 2006/10/01/ 2006;372(1):120-128.

9. Lee HS, Chae W, Sung MJ, et al. Difference of Risk of Pancreatic Cancer in New-Onset Diabetes and Long-standing Diabetes: A Population-based Cohort Study. The Journal of Clinical Endocrinology & Metabolism. 2023;108(6):1338-1347.

10. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. European Journal of Cancer. 2011/09/01/ 2011;47(13):1928-1937.

11. Chari ST, Leibson CL, Rabe KG, et al. Probability of Pancreatic Cancer Following Diabetes: A Population-Based Study. Gastroenterology. 2005/08/01/ 2005;129(2):504-511.

12. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology. Jan 2008;134(1):95-101.

13. Pereira SP, Oldfield L, Ney A, et al. Early detection of pancreatic cancer. Lancet Gastroenterol Hepatol. Jul 2020;5(7):698-710.

14. Sharma A, Kandlakunta H, Nagpal SJS, et al. Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes. Gastroenterology. Sep 2018;155(3):730-739.e733.

15. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. Nat Rev Gastroenterol Hepatol. Jul 2013;10(7):423-433.

16. Hart PA, Kudva YC, Yadav D, et al. A Reduced Pancreatic Polypeptide Response is Associated With New-onset Pancreatogenic Diabetes Versus Type 2 Diabetes. The Journal of Clinical Endocrinology & Metabolism. 2023;108(5):e120-e128.

17. Popovic K, Smolović B, Martinović M, Vučković L. The Relationship between Diabetes Mellitus and Pancreatic Cancer—Diabetes Mellitus as a Red Flag for Pancreatic Cancer. Cancer Epidemiology, Biomarkers & Prevention. 2023;32(3):298-305.

18. Yuan C, Babic A, Khalaf N, et al. Diabetes, Weight Change, and Pancreatic Cancer Risk. JAMA Oncol. Oct 1 2020;6(10):e202948.

19. Force UPST. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. JAMA. 2019;322(5):438-444.

20. Aslanian HR, Lee JH, Canto MI. AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review. Gastroenterology. 2020;159(1):358-362.

21. Chu CK, Mazo AE, Sarmiento JM, et al. Impact of Diabetes Mellitus on Perioperative Outcomes after Resection for Pancreatic Adenocarcinoma. Journal of the American College of Surgeons. 2010;210(4).

22. Malleo G, Mazzarella F, Malpaga A, et al. Diabetes mellitus does not impact on clinically relevant pancreatic fistula after partial pancreatic resection for ductal adenocarcinoma. Surgery. May 2013;153(5):641-650.

23. Xia X, Huang C, Cen G, Qiu Z-J. Preoperative diabetes as a protective factor for pancreatic fistula after pancreaticoduodenectomy: a meta-analysis. Hepatobiliary & Pancreatic Diseases International. 2015/04/15/ 2015;14(2):132-138.

24. Hu BY, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: Analysis of 539 successive cases of pancreaticoduodenectomy. World J Gastroenterol. Sep 14 2016;22(34):7797-7805.

25. Russell TB, Labib PL, Ausania F, et al. Serious complications of pancreatoduodenectomy correlate with lower rates of adjuvant chemotherapy: Results from the recurrence after Whipple's (RAW) study. European Journal of Surgical Oncology. 2023/09/01/ 2023;49(9):106919.

26. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. Mar 2017;161(3):584-591.

27. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. Jul 2019;95:103208.

28. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. Apr 2009;42(2):377-381.

29. Dandona M, Linehan D, Hawkins W, et al. Influence of Obesity and Other Risk Factors on Survival Outcomes in Patients Undergoing Pancreaticoduodenectomy for Pancreatic Cancer. Pancreas. 2011;40(6).

30. Terasaki F, Sugiura T, Okamura Y, et al. Oncological benefit of metformin in patients with pancreatic ductal adenocarcinoma and comorbid diabetes mellitus. Langenbeck's Archives of Surgery. 2020;405:313-324.

31. Pugalenthi A, Protic M, Gonen M, et al. Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. J Surg Oncol. Feb 2016;113(2):188-193.

32. Shia BC, Qin L, Lin KC, et al. Age comorbidity scores as risk factors for 90-day mortality in patients with a pancreatic head adenocarcinoma receiving a pancreaticoduodenectomy: A National Population-Based Study. Cancer Med. Jan 2020;9(2):562-574.

33. Zhang B, Yuan Q, Li S, et al. Risk factors of clinically relevant postoperative pancreatic fistula after pancreaticoduodenectomy: A systematic review and meta-analysis. Medicine (Baltimore). Jul 1 2022;101(26):e29757.

34. Cerullo M, Gani F, Chen SY, et al. Metformin Use Is Associated with Improved Survival in Patients Undergoing Resection for Pancreatic Cancer. Journal of Gastrointestinal Surgery. 2016/09/01 2016;20(9):1572-1580.

35. Reni M, Dugnani E, Cereda S, et al. (Ir)relevance of Metformin Treatment in Patients with Metastatic Pancreatic Cancer: An Open-Label, Randomized Phase II Trial. Clinical Cancer Research. 2016;22(5):1076-1085.

36. Kordes S, Pollak MN, Zwinderman AH, et al. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. Jul 2015;16(7):839-847.

37. Lemanska A, Price CA, Jeffreys N, et al. BMI and HbA1c are metabolic markers for pancreatic cancer: Matched case-control study using a UK primary care database. PLOS ONE. 2022;17(10):e0275369.

38. Ling S, Sweeting M, Zaccardi F, et al. Glycosylated haemoglobin and prognosis in 10,536 people with cancer and pre-existing diabetes: a meta-analysis with dose-response analysis. BMC Cancer. 2022/10/06 2022;22(1):1048.

Tables

Factor	No diabetes	Diabetes	p-value
Number of patients	571	187	
Type of diabetes (%)			
Type 1	N/A	10 (5.3)	
Type 2	N/A	177 (94.7)	
Onset of diabetes			
Recent	N/A	47 (25.1)	
Established	N/A	79 (42.2)	
Unknown / not recorded	N/A	51 (27.3)	
Demographic, preoperative and adjuvant treatment data			
Age, median (IQR)	67 (67-73)	69 (61-74)	0.78
Gender (%)			1.00
Male	298 (52.2)	103 (55.1)	
Female	273 (47.8)	84 (44.9)	
Radiological T stage (%)			1.00
T1	112 (19.6)	38 (20.3)	
T2	185 (32.4)	61 (32.6)	
T3	142 (24.9)	50 (26.7)	
T4	17 (3.0)	6 (3.2)	
Tx	103 (18.0)	27 (14.4)	
Radiological N stage (%)			1.00
N0	348 (60.9)	118 (63.1)	
N1	157 (27.5)	51 (27.3)	
Nx	57 (10.0)	13 (7.0)	
Radiological M stage (%)			0.91
M0	498 (87.2)	169 (90.4)	
M1	7 (1.2)	4 (2.1)	
Mx	57 (10.0)	9 (4.8)	
Neoadjuvant chemotherapy (%)	34 (6.0)	11 (5.9)	1.00
Neoadjuvant chemoradiation (%)	14 (2.5)	6 (3.2)	1.00
Adjuvant chemotherapy (%)	371 (65.0)	125 (66.8)	1.00
Adjuvant radiotherapy (%)	21 (3.7)	8 (4.3)	1.00
Postoperative histology			
Histological maximum tumour dimension (mm), median (IQR)	30.0 (22.0-35.5)	30.0 (25.0-40.0)	0.48

Histological T stage (%)			1.00
T1	35 (6.1)	10 (5.3)	
T2	54 (9.5)	17 (9.1)	
T3	462 (80.9)	150 (80.2)	
T4	16 (2.8)	7 (3.7)	
Tx	2 (0.4)	2 (1.1)	
Histological N stage (%)			1.00
N0	126 (22.1)	41 (21.9)	
N1	442 (77.4)	144 (77.0)	
Nx	2 (0.4)	2 (1.1)	
R status (%)			1.00
R0	228 (39.9)	79 (42.2)	
R1	279 (48.9)	89 (47.6)	
R2	20 (3.5)	5 (2.7)	
Postoperative outcomes			
Length of stay, median (IQR)	13 (9-18)	13 (10-17)	0.85
30-day readmission (%)	60 (10.5)	18 (9.6)	0.89
90-day mortality (%)	22 (3.9)	10 (5.3)	0.40
Postoperative pancreatic fistula (%)	56 (9.8)	11 (5.9)	0.11
Return to theatre (%)	35 (6.1)	6 (3.2)	0.19
Recurrence (%)			
1 year	185 (35.3)	68 (37.8)	0.59
3 years	325 (62.0)	116 (64.4)	0.59
5 years	385 (67.4)	134 (71.7)	0.32
Survival (%)			
1 year	427 (74.9)	145 (77.5)	0.49
3 years	182 (31.9)	75 (40.1)	0.050
5 years	131 (22.9)	45 (24.1)	0.77

Table 1: Baseline, treatment and outcomes data

Factor	Recent-onset diabetes	Established or unknown onset diabetes	p value
Number of patients	47	140	
Demographic, preoperative and adjuvant treatment data			
Age, median (IQR)	69 (58-73)	70 (62-75)	1.00
Gender (%)			1.00
Male	26 (55.3)	77 (55.0)	
Female	21 (44.7)	63 (45.0)	
Radiological T stage (%)			1.00
T1	6 (12.8)	32 (22.9)	
T2	19 (40.4)	42 (30.0)	
T3	13 (27.7)	37 (26.4)	
T4	2 (4.3)	4 (2.9)	
Tx	4 (8.5)	23 (16.4)	
Radiological N stage (%)			1.00
N0	24 (51.1)	94 (67.1)	
N1	18 (38.3)	33 (23.6)	
Nx	2 (4.3)	11 (7.9)	
Radiological M stage (%)			1.00
M0	42 (89.4)	127 (90.7)	
M1	2 (4.3)	2 (1.4)	
Mx	0	9 (6.4)	
Neoadjuvant chemotherapy (%)	2 (4.3)	9 (6.4)	1.00
Neoadjuvant chemoradiation (%)	1 (2.1)	5 (3.6)	1.00
Adjuvant chemotherapy (%)	37 (78.7)	88 (62.9)	0.57
Adjuvant radiotherapy (%)	1 (2.1)	7 (5.0)	1.00
Postoperative histology			
Histological maximum tumour dimension (mm), median (IQR)	32.0 (24.0-40.0)	30.0 (25.0-38.0)	1.00
Histological T stage (%)			1.00
T1	2 (4.3)	8 (5.7)	
T2	3 (6.4)	14 (10.0)	
T3	39 (83.0)	111 (79.3)	
T4	1 (2.1)	6 (4.3)	
Tx	1 (2.1)	1 (0.7)	
Histological N stage (%)			1.00

N0	11 (23.4)	30 (21.4)	
N1	36 (76.6)	108 (77.1)	
Nx	0	2 (1.4)	
R status (%)			1.00
R0	18 (38.3)	61 (43.6)	
R1	25 (53.2)	64 (45.7)	
R2	1 (2.1)	4 (2.9)	
Postoperative outcomes			
Length of stay, median (IQR)	13 (9-18)	13 (10-16)	0.54
30-day readmission (%)	3 (6.4)	15 (10.7)	0.57
90-day mortality (%)	3 (6.4)	7 (5.0)	0.71
Postoperative pancreatic fistula (%)	4 (8.5)	7 (5.0)	0.47
Unplanned return to theatre (%)	1 (2.1)	5 (3.6)	1.00
Recurrence (%)			
1 year	16 (37.2)	52 (38.0)	1.00
3 years	28 (65.1)	88 (64.2)	1.00
5 years	35 (74.5)	99 (70.7)	0.71
Survival (%)			
1 year	39 (83.0)	106 (75.7)	0.42
3 years	21 (44.7)	54 (38.6)	0.49
5 years	13 (27.7)	32 (22.9)	0.56

Table 2: Subgroup baseline, treatment and outcomes data of diabetic patients

Figures

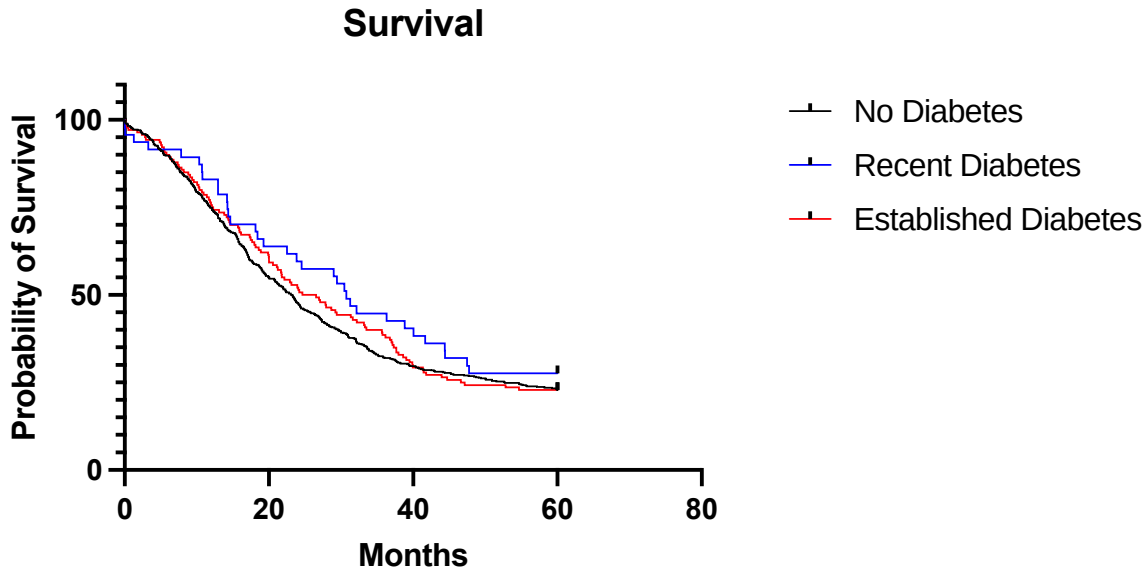

Figure 1

Kaplan-Meier curve for survival grouped into three cohorts (not diabetic vs. recent-onset diabetes vs. diabetic established or unknown onset) (p=0.47)

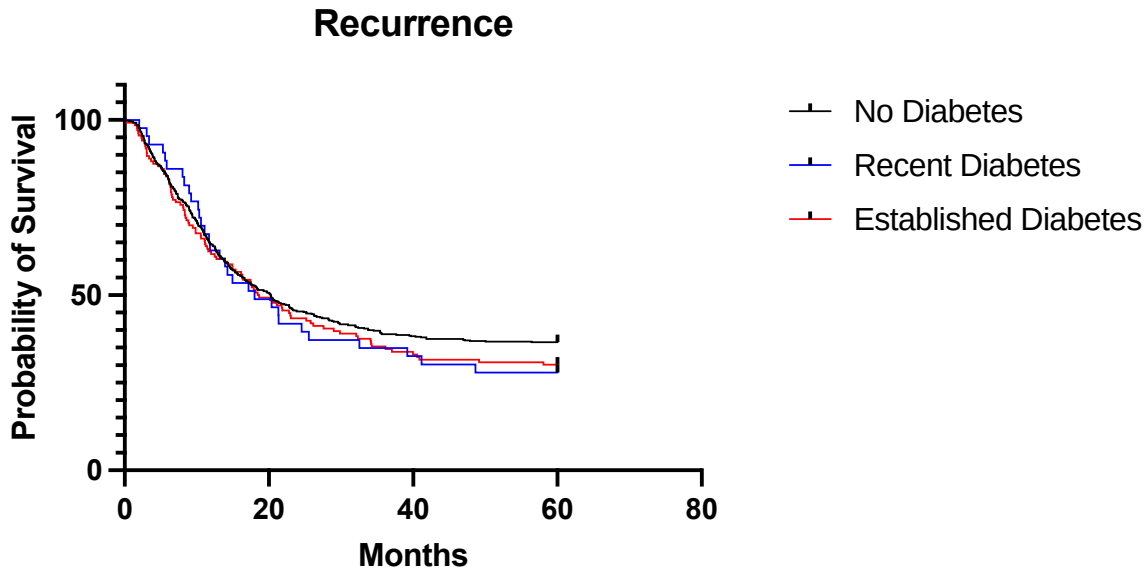

Figure 2

Kaplan-Meier curve for recurrence grouped into three cohorts (not diabetic vs. recent-onset diabetes vs. diabetic established or unknown onset) (p=0.47)

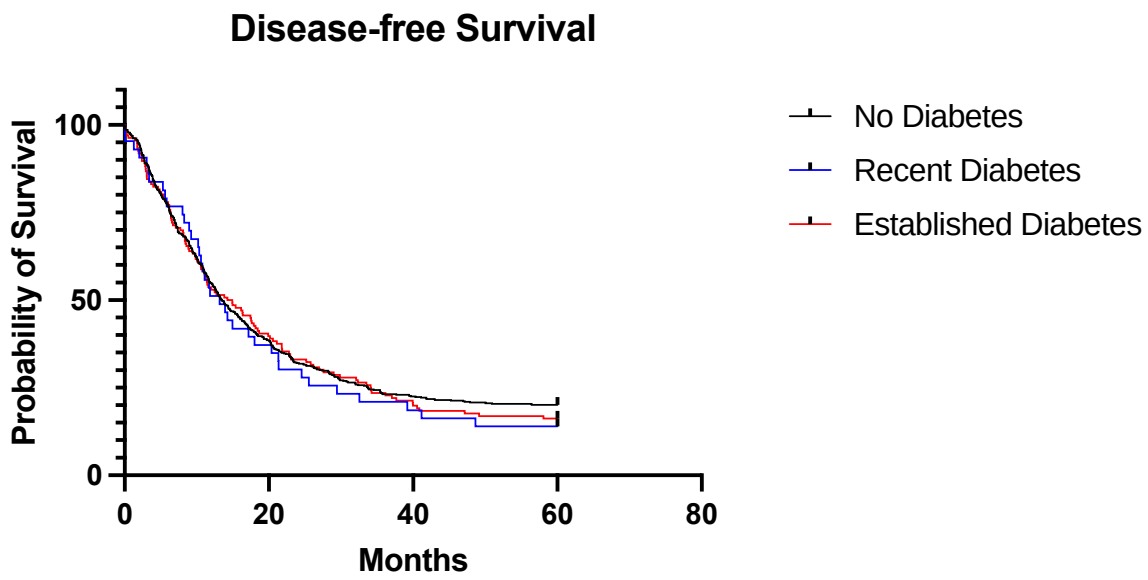

Figure 3

Kaplan-Meier curve for disease-free survival grouped into three cohorts (not diabetic vs. recent-onset diabetes vs. diabetic established or unknown onset) (p=0.77)

Supplementary Tables

	Step 1		Step 12		Step 14	
Parameters	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Preoperative diabetes	0.54 (0.23-1.25)	0.15	0.61 (0.30-1.23)	0.17		
Recent-onset diabetes	1.66 (0.39-7.04)	0.50				
Age	0.99 (0.97-1.02)	0.66				
Gender						
Male	Ref.	-	Ref.	-	Ref.	-
Female	0.64 (0.37-1.13)	0.13	0.61 (0.35-1.06)	0.079	0.62 (0.36-1.07)	0.087
Radiological T stage						
T1	Ref.	-	Ref.	-		
T2	0.45 (0.22-0.92)	**0.028***	0.51 (0.25-1.02)	0.056		
T3	0.39 (0.17-0.91)	**0.030***	0.42 (0.19-0.91)	**0.028***		
T4	N/A		N/A			
Tx	1.18 (0.48-2.88)	0.72	0.85 (0.39-1.84)	0.68		
Radiological N stage						
N0	Ref.	-				
N1	1.14 (0.58-2.24)	0.70				
Nx	0.48 (0.12-1.83(	0.28				
Radiological M stage						
M0	Ref.	-				
M1	N/A					
Mx	0.82 (0.24-2.75)	0.74				
Neoadjuvant chemotherapy	0.68 (0.08-5.48)	0.72				
Neoadjuvant chemoradiation	N/A					
Adjuvant chemotherapy	0.65 (0.36-1.18)	0.15				

Adjuvant radiotherapy	0.84 (0.18-3.85)	0.82				
Histological T stage						
T1	Ref.	-				
T2	1.48 (0.31-7.02)	0.62				
T3	2.29 (0.60-8.75)	0.23				
T4	N/A					
Tx	N/A					
Histological N stage						
N0	Ref.	-				
N1	0.76 (0.37-1.54)	0.44				
Nx	N/A	N/A				
R status						
R0	Ref.	-				
R1	0.76 (0.42-1.39)	0.37				
R2	1.01 (0.21-4.80)	0.99				

Notes: Classification Accuracy: M_0 = 91.4; M_1 = 91.4; M_{12} = 91.4; M_{14} = 91.4 (0% improvement).
Final model $\chi^2(1)=3.019$, $p=0.082$.
Multivariable analysis conducted using Backwards Wald to 14 steps. Steps shown to most predictive model including either preoperative diabetes or recent-onset diabetes, and final step.

Supplementary Table 1: Multivariate analysis of risk factors for postoperative pancreatic fistula.

	Step 1		Step 7		Step 11	
Parameters	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Preoperative diabetes	1.23 (0.78-1.94)	0.37	1.23 (0.82-1.84)	0.32		
Recent-onset diabetes	0.94 (0.41-2.17)	0.89				
Age	0.99 (0.97-1.01)	0.30	0.99 (0.97-1.01)	0.30		
Gender						
Male	Ref.	-				
Female	1.24 (0.88-1.75)	0.22	1.23 (0.88-1.73)	0.23		
Radiological T stage						
T1	Ref.	-				
T2	0.78 (0.48-1.27)	0.33				
T3	1.11 (0.64-1.92)	0.72				
T4	0.70 (0.24-2.04)	0.51				
Tx	0.93 (0.47-1.83)	0.83				
Radiological N stage						
N0	Ref.	-				
N1	1.03 (0.67-1.58)	0.89				
Nx	0.89 (0.42-1.91)	0.77				
Radiological M stage						
M0	Ref.	-				
M1	1.57 (0.32-7.77)	0.58				
Mx	0.98 (0.50-1.93)	0.95				
Neoadjuvant chemotherapy	0.80 (0.32-1.93)	0.64				
Neoadjuvant chemoradiation	2.51 (0.62-10.20)	0.20	1.94 (0.68-5.60)	0.22		
Adjuvant chemotherapy	1.59 (1.10-2.31)	**0.014***	1.60 (1.11-2.30)	**0.011***	1.59 (1.12-2.26)	**0.010***

Adjuvant radiotherapy	0.83 (0.35-1.99)	0.67				
Histological T stage						
T1	Ref.	-	Ref.	-	Ref.	-
T2	1.82 (0.79-4.21)	0.16	1.70 (0.75-3.85)	0.20	1.62 (0.72-3.63)	0.24
T3	3.06 (1.46-6.42)	**0.003***	2.94 (1.43-6.01)	**0.003***	2.68 (1.33-5.41)	**0.006***
T4	2.09 (0.63-6.92)	0.23	1.88 (0.59-6.05)	0.29	1.68 (0.53-5.31)	0.38
Tx	5.09 (0.43-60.32)	0.20	5.33 (0.46-62.43)	0.18	4.81 (0.44-53.10)	0.20
Histological N stage						
N0	Ref.	-	Ref.	-	Ref.	-
N1	1.91 (1.23-2.95)	**0.004***	1.95 (1.28-2.99)	**0.002***	1.85 (1.22-2.81)	**0.004***
Nx	N/A					
R status						
R0	Ref.	-	Ref.	-	Ref.	-
R1	1.36 (1.00-2.12)	**0.048***	1.48 (1.02-2.14)	**0.037***	1.48 (1.02-2.13)	**0.037***
R2	0.66 (0.27-1.59)	0.36	0.71 (0.30-1.67)	0.43	0.69 (0.29-1.64)	0.41

Notes: Classification Accuracy: M_0 = 68.8; M_1 = 72.0; M_3 = 71.2; M_{12} = 71.3 (4% improvement).
Final model $\chi^2(10)=54.31$, $p<0.001$.
Multivariable analysis conducted using Backwards Wald to 10 steps. Steps shown to most predictive model including either preoperative diabetes or recent-onset diabetes, and final step.

Supplementary Table 2: Multivariate analysis of risk factors for 5-year recurrence.

	Step 1		Step 3		Step 12	
Parameters	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Preoperative diabetes	1.07 (0.64-1.76)	0.81				
Recent-onset diabetes	1.14 (0.47-2.75)	0.77	1.20 (0.55-2.62)	0.65		
Age	1.00 (0.98-1.02)	0.78				
Gender						
Male	Ref.	-				
Female	0.85 (0.58-1.25)	0.41	0.85 (0.58-1.25)	0.40		
Radiological T stage						
T1	Ref.	-				
T2	1.95 (1.12-3.41)	**0.019***	1.95 (1.11-3.41)	**0.019***		
T3	1.27 (0.67-2.41)	0.47	1.27 (0.67-2.41)	0.47		
T4	3.14 (0.97-10.14)	0.056	3.15 (0.98-10.17)	0.055		
Tx	2.14 (1.00-4.59)	0.050	2.14 (1.00-4.58)	0.051		
Radiological N stage						
N0	Ref.	-				
N1	0.87 (0.54-1.42)	0.58	0.87 (0.54-1.42)	0.58		
Nx	0.46 (0.18-1.18)	0.11	0.46 (0.18-1.17)	0.10		
Radiological M stage						
M0	Ref.	-				
M1	N/A					
Mx	1.83 (0.86-3.94)	0.12	1.83 (0.85-3.93)	0.12		
Neoadjuvant chemotherapy	2.31 (0.88-6.09)	0.091	2.30 (0.88-6.07)	0.091		
Neoadjuvant chemoradiation	0.25 (0.057-1.10)	0.067	0.26 (0.059-1.12)	0.071		
Adjuvant chemotherapy	1.93 (1.22-3.05)	**0.005***	1.95 (1.24-3.05)	**0.004***	2.89 (1.24-2.89)	**0.003***

Adjuvant radiotherapy	1.41 (0.55-3.59)	0.47	1.42 (0.56-3.61)	0.46		
Histological T stage						
T1	Ref.	-	Ref.	-	Ref.	-
T2	0.69 (0.30-1.62)	0.40	0.69 (0.30-1.62)	0.40	0.78 (0.35-1.73)	0.53
T3	0.22 (0.10-0.46)	**<0.001***	0.21 (0.10-0.46)	**<0.001***	0.25 (0.13-0.51)	**<0.001***
T4	0.56 (0.16-2.02)	0.38	0.56 (0.16-2.00)	0.37	0.69 (0.22-2.21)	0.53
Tx	0.13 (0.011-1.67)	0.12	0.14 (0.011-1.70)	0.12	0.20 (0.018-2.16)	0.18
Histological N stage						
N0	Ref.	-	Ref.	-	Ref.	-
N1	0.41 (0.26-0.66)	**<0.001***	0.41 (0.26-0.66)	**<0.001***	0.35 (0.23-0.54)	**<0.001***
Nx	N/A					
R status						
R0	Ref.	-	Ref.	-		
R1	0.71 (0.47-1.08)	0.11	0.71 (0.47-1.08)	0.11		
R2	0.65 (0.20-2.15)	0.48	0.65 (0.20-2.14)	0.48		

Notes: Classification Accuracy: M_0 = 76.1; M_1 = 78.3; M_3 = 78.2; M_{12} = 77.6 (2% improvement).
Final model $\chi^2(8)=73.78$, $p<0.001$.
Multivariable analysis conducted using Backwards Wald to 10 steps. Steps shown to most predictive model including either preoperative diabetes or recent-onset diabetes, and final step.

Supplementary Table 3: Multivariate analysis of risk factors for 5-year survival.

Declarations of interest: none