Title: Serious complications of pancreatoduodenectomy correlate with lower rates of adjuvant chemotherapy: results from the Recurrence After Whipple's (RAW) study

Short title: Pancreatoduodenectomy: complications and adjuvant therapy

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Abstract

Introduction: Adjuvant chemotherapy (AC) can prolong overall survival (OS) after pancreatoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC). However, fitness for AC may be influenced by postoperative recovery. We aimed to investigate if serious (Clavien-Dindo grade ≥IIIa) postoperative complications affected AC rates, disease recurrence and OS. **Materials and methods:** Data were extracted from the Recurrence After Whipple's (RAW) study (n=1484), a retrospective study of PD outcomes (29 centres from eight countries). Patients who died within 90-days of PD were excluded. The Kaplan-Meier method was used to compare OS in those receiving or not receiving AC, and those with and without serious postoperative complications. The groups were then compared using univariable and multivariable tests. **Results:** Patients who commenced AC (vs no AC) had improved OS (median difference: (MD): 201 days), as did those who completed their planned course of AC (MD: 291 days, p<0.0001). Those who commenced AC were younger (mean difference: 2.7 years, p=0.0002), more often (preoperative) American Society of Anesthesiologists (ASA) grade I-II (74% vs 63%, p=0.004) and had less often experienced a serious postoperative complication (10% vs 18%, p=0.002). Patients who developed a serious postoperative complication were less often ASA grade I-II (52% vs 73%, p=0.0004) and less often commenced AC (58% vs 74%, p=0.002). **Conclusion:** In our multicentre study of PD outcomes, PDAC patients who received AC had improved OS, and those who experienced a serious postoperative complication commenced AC less frequently. Selected high-risk patients may benefit from targeted preoperative optimisation and/or neoadjuvant chemotherapy.

Keywords: Adjuvant Chemotherapy; Neoadjuvant Therapy; Morbidity; Pancreatic Ductal Carcinoma; Pancreaticoduodenectomy; Postoperative Complications.

1. Introduction

Pancreatoduodenectomy (PD) followed by adjuvant chemotherapy (AC) is recommended in fit patients with a resectable pancreatic head ductal adenocarcinoma (PDAC). PD remains the only curative-intent treatment option for this group and AC has been shown to provide a significant survival benefit[1, 2]. Around half of the patients who undergo PD experience at least one postoperative complication[3]. Those who develop no complications, or only minor complications, are likely to make a timely recovery. However, patients who develop a serious complication may have a prolonged recovery and some do not recover to their preoperative baseline level of fitness. This can affect their suitability for AC[4, 5]. Hence, the preoperative identification of high-risk patients is important as there may be a group that would benefit from targeted preoperative optimisation and/or a course of neoadjuvant chemotherapy. The latter is not currently recommended in the UK (and many other countries) in patients with resectable disease. This study aimed to investigate the impact of serious PD complications on AC rates, disease recurrence and overall survival (OS). This information will guide patient selection and the consenting process, and could help to identify patients that might benefit from a tailored management approach. This article has been written in accordance with the STROBE checklist.

2. Materials and methods

Patients were included if they underwent PD for histologically confirmed PDAC at one of twenty-nine participating units between June 1st, 2012 and May 31st, 2015. The study involved nineteen units from the UK, three from Spain, two from Italy, and one from Australia, Austria, Mexico, Pakistan and Sudan (see **Appendix A** for full details). The end date was selected so that five-year follow-up data was available for all patients. Those lost to follow-up before five-years were excluded. Data were collected locally at each participating unit from physical and electronic patient records. If not available locally, follow-up data were collected from referring

hospitals to reduce attrition bias. A purpose-built electronic database was created using REDCap (v11.0.3, Nashville, TN) to collect and store the data. This was uploaded locally by the participating units. Information on the following were collected: patient demographics, comorbidities, preoperative imaging and staging, neoadjuvant therapy (NAT), preoperative blood results, procedure and intraoperative findings, postoperative management and complications, histology results, adjuvant treatment, five-year disease recurrence, palliative treatment, and five-year survival. Data on race/ethnicity were not collected.

Complication definitions were as follows (see **Appendix B** for full definitions): postoperative pancreatic fistula (POPF) was categorised as per the International Study Group of Pancreatic Surgery (ISGPS) 2016 definitions[6] as biochemical leak (formerly grade A POPF) or clinically relevant (CR)-POPF (grade B and grade C POPF)[6]. Post-pancreatectomy haemorrhage (PPH)[7] and delayed gastric emptying (DGE)[8] were defined as per the ISGPS 2007 definitions (grade A, B and C). All complications were graded using the Clavien-Dindo (CD) classification of surgical complications[9]. For the purposes of this study, a “serious” complication included any CD grade ≥IIIa complication. Cancer recurrence, if not confirmed radiologically, was assumed if a patient had a raised CA 19-9 and/or relevant signs/symptoms, or confirmed intraoperatively. AC was defined as any chemotherapy received postoperatively within 120 days of PD which was intended to treat PDAC, where recurrent disease/metastases had not been diagnosed and were not suspected.

This study was approved by North West - Greater Manchester South Research Ethics Committee as part of the Recurrence After Whipple’s (RAW) study (20/NW/0397) and University Hospitals Plymouth NHS Trust Research and Development Department. 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).

2.1. Statistical methods

Categorical data are presented as frequency counts and associated percentages, and continuous data are presented as means, with standard deviation (SD), or medians, with interquartile range (IQR). After patients who died within 90 days of PD were excluded (from all analyses), the Kaplan-Meier method was used to compare survival between those who commenced AC and those who did not, those who completed AC and those who did not (including those who did not commence AC), and those who developed a serious (CD grade ≥IIIa) complication and those who did not. If patients did not have data available on their postoperative complications (if any), they were excluded from the latter only (see **Figure S1** and **Table 1**). Univariable tests were then performed to compare these groups. Means were compared using Student's *t*-test, medians were compared using the Mann Whitney *U* test, and percentages were compared using Pearson's χ^2 test. If one or both of the samples being compared was <30, Fisher's exact test was used in place of Pearson's χ^2 test. Results were considered significant if a *p*-value of <0.05 was obtained. Following the univariable tests, the Holm and Hochberg step methods were used to determine which variables remained significant. These are step-down and step-up versions of the Bonferroni test, respectively[10]. The statistical methods were discussed with a statistician. The analyses were performed using Microsoft Excel (v2103, Redmond, WA), GraphPad Prism (v9.3.1, San Diego, CA) and IBM SPSS Statistics (v25, Chicago, IL).

3. Results

A total of 3705 records were screened by the collaborating centres and 2212 were excluded as they did not meet the inclusion criteria, leaving 1493 records (**Figure S1**). A further 685 cases were excluded by the lead centre. This included 599 patients who did not have histologically confirmed PDAC, nine records which were incomplete, 38 patients who died within 90 days of PD, and 39 patients who did not have AC data available (if any). Therefore, the final analysis included 808 patients. The mean patient age was 67 years (SD:

9), 47% were female and the mean body mass index (BMI) was 25.4 kg/m^2 (SD: 4.6) (**Table 1**). The vast majority of patients (94%) were ASA grade I-II and 47% had undergone a classic Whipple procedure, with the remainder undergoing a pylorus-preserving PD. The median length of stay was thirteen days (IQR: 9.0) and 11% of patients had an unplanned readmission within 30 days of discharge. CR-POPF, PPH and DGE affected 6%, 5% and 13% of patients, respectively. Concerning major morbidity, 12% of patients experienced a serious complication (CD grade ≥IIIa). Five-year recurrence was 69% and actual five-year survival was 24%.

In total, 71% of patients commenced AC; the median number of cycles was six (IQR: 2) and the majority of patients (78%) received gemcitabine only (**Figure 1**). Of those who commenced AC, 63% completed the planned course. The median time to administration (TTA) of the first AC dose was 69 days (IQR: 35). Those who completed the planned course had a shorter median TTA (66 days, IQR: 32) than those who did not (77 days, IQR: 30, p=0.006). Among those who received AC, patients who developed a serious postoperative complication had a longer median TTA of the first AC dose (73 days, IQR: 49) than those who did not (69 days, IQR: 34) but this difference was not significant (p=0.4).

Among the patients that died within five years of PD (n=615, 76%), the median OS was 569 days (19.0 months). Among those who developed recurrence within five years, the median time to recurrence was 339 days (11.3 months). Patients who commenced AC had longer disease-free survival (DFS, MD: 176 days, p=0.001) and OS (MD: 201 days, p<0.0001) than those who did not (**Figure 2**). The same pattern was observed when patients who completed AC were compared to those who did not. Patients who experienced a serious postoperative complication had similar DFS (MD: 27 days, p=0.5) and OS (MD: 52 days, p=0.3) to those who did not. The univariable tests (**Table 2**) demonstrated that the patients who commenced AC were younger (mean difference: 2.7 years, p=0.0002) and more often ASA grade I-II (74% vs 63%, p=0.004). In addition, these patients had less often experienced PPH (4% vs 9%, p=0.02), a serious complication (10% vs 18%, p=0.002), or readmission (9% vs 14%, p=0.04). Those who completed AC were younger (mean difference: 2.2 years, p=0.0009), less often

had positive nodes on preoperative imaging (33% vs 42%, p=0.01) and were more often ASA grade I-II (76% vs 66%, p=0.003). In addition, CR-POPF (4% vs 8%, p=0.047) and an unplanned readmission (8% vs 14%, p=0.03) were less common in this group.

The patients who experienced a serious complication were less often ASA I-II (52% vs 73%, p=0.0004), and more frequently experienced readmission (24% vs 9%, p<0.0001). Those who experienced a serious complication commenced AC less frequently (58% vs 74%, p=0.002). Following the application of the Holm and Hochberg step methods (**Table 3**), only younger age remained a significant association of commencing (mean difference: 2.7 years) and completing (mean difference: 2.2 years) AC. Serious complications correlated with readmission (OR: 3.3). Patients who experienced a serious postoperative complication were less often ASA I-II (OR: 0.4) and commenced AC less frequently (OR: 0.5).

4. Discussion

In our multicentre study of PD patients with histologically confirmed PDAC, those who commenced AC had improved DFS and OS compared to those who did not. Patients who commenced AC were younger, were more likely to be ASA grade I-II and had less often experienced a serious postoperative complication. Whilst serious complications correlated inversely with commencing AC, a serious complication alone did not significantly affect DFS or OS (patients who died within 90 days of PD were excluded). Our study is comparable to that of Wu et al. (n=1144) who studied PD outcomes at a single Chinese institution (PDAC only). The median age was 68 years (vs mean: 67 years in our study), 48% of patients were female (vs 47%), and 19% developed a complication which was CD grade ≥IIIa (vs 12%)[11]. Overall, 54% of patients received AC (vs 71%) and the median TTA was 60 days (vs 69 days)[11]. Age >68 years (p<0.001) and length of stay >9 days (p=0.002) both correlated with not receiving AC[11]. Whilst the presence of any complication correlated with not receiving AC, this effect did not increase with increasing complication grade[11]. Unlike in our study,

those who experienced a complication had reduced survival compared to those who did not (16.1 vs 19.5 months, p=0.001)[11]. The authors found that patients who did not experience a complication and received AC survived longer than those who experienced a complication and received no AC (22.5 vs 10.7 months, p<0.001)[11]. Both complications (HR: 1.2, p=0.02) and AC (HR: 0.7, p<0.001) were independently related to survival[11]. The authors concluded that both complications and a lack of AC are common following PD for PDAC, and that patients who experience a serious complication have increased TTA of the first AC dose, and are less likely to receive multimodal treatment.

Our study can also be compared to that of Mackay et al. (n=1306) which used Dutch national data. In the overall cohort, the median age was 67 years, 45% of patients were female and 24% developed a complication which was CD grade ≥IIIa[12]. A total of 67% received AC and the median TTA was 48 days[12]. Among other factors, major complications were shown to be an independent predictor of not receiving AC (OR: 0.4, p<0.001)[12]. Unlike in the Chinese study, patients with major complications received AC less frequently (52% vs 27%, p<0.001) and the median TTA was also longer in this group (56 vs 47 days, p<0.001)[12]. The authors concluded that serious complications were the most important factor in patients not receiving AC.

In a smaller Norwegian study which also included patients who had undergone distal pancreatectomy (median age: 67 years, 47% females), Labori et al. (n=203) found that 20% of patients experienced a serious postoperative complication[3]. A total of 62% commenced AC and 33% of these did not complete the planned course[3]. The primary reasons for not initiating AC were recurrent disease (35%), postoperative complications/poor performance status (32%) and advanced age (25%)[3]. OS was significantly longer in those who completed AC (25.0 vs 12.0 months, p<0.001). Patients who experienced serious complications (CD grade ≥IIIa) were less likely to commence AC (p<0.001), less likely to complete AC (p=0.007) and had reduced OS (11.0 months vs 19.0 months, p=0.03)[3]. The authors argued that strategies are required to improve patient selection and reduce surgical morbidity as early

recurrence, major postoperative complications and poor postoperative performance status together result in more than a third of patients not completing their planned adjuvant treatment[3].

Postoperative AC has been offered to fit PD patients with PDAC since the 1990s[13]. The findings of studies such as the European Study Group of Pancreatic Cancer (ESPAC) studies have confirmed that AC can provide a significant survival benefit so this is now the standard of care[1]. Our study would support the benefits of AC with time to recurrence and time to death being significantly longer in those who commenced AC (**Figure 2**). Time to recurrence and time to death were also significantly longer in those who completed AC. Whilst DFS and OS were longer in those who did not experience a serious complication, these differences were not significant (patients who died within 90 days of PD were excluded). A recent randomised controlled trial showed that combination AC could increase median OS to 54.4 months in some patients[14]. Other studies[1] have also shown that AC correlates with increased five-year survival but our data did not suggest this. This may be due to the relatively small number of patients that achieved five-year survival and the fact that patients who died within 90 days of PD were excluded.

Our results suggest patients are less likely to receive AC if they are older, are ASA grade ≥III, or if they experience a serious postoperative complication. It may be that some patients who experienced a serious complication had a prolonged recovery as a result. Some of these might have never returned to their preoperative baseline level of fitness, or a level of fitness which is required to undergo AC. Furthermore, they may have developed early disease recurrence during their prolonged recovery and missed their window of opportunity to commence AC. However, we acknowledge that some patients diagnosed with early recurrence will likely have had radiographically occult or persistent disease. Postoperative complications (of any grade) did not affect whether patients completed AC or not. This is likely as, whilst a prolonged recovery might affect commencing AC, it is unlikely to result in treatment being terminated. The optimal timing for AC is debated and some authors argue that it is the

completion of AC which is more important[15]. However, Sung et al. (n=7548) found patients who started AC before 60 days post-PD had the greatest survival advantage[16].

In our study, patients who experienced a serious postoperative complication were less likely to commence AC. They were also less likely to complete AC but this difference was not significant, possibly due to the low number of patients in this group. Currently, there are no models which can accurately predict which PD patients are likely to develop serious complications. This information would be useful as those who are high-risk may benefit from NAT. These patients would then complete a course of systemic therapy and undergo repeat imaging. Those with a good response would likely have a chemosensitive tumour and be appropriate surgical candidates. Those who do not have a good response, or those who develop metastases, may not have been appropriate candidates[17]. These patients would arguably have a better quality of life if they received palliative chemotherapy rather than an aggressive surgical resection[18]. This is particularly relevant in older patients, those with positive nodes on preoperative imaging and those who are not ASA grade I-II. Whilst neoadjuvant therapy is often given to patients with resectable disease in the USA[19], guidelines from many other countries do not advise this[20]. Future research which focusses on developing predictive models could be very helpful for patient selection.

Our study has several limitations. Firstly, it is retrospective so may have been affected by recall bias and incomplete clinical documentation. Secondly, we excluded patients who died within 90 days of PD but some of these may have already commenced AC. Thirdly, since our study spanned a considerable length of time, it is likely that practice evolved during this period e.g., the vast majority of patients that commenced AC received gemcitabine only whereas multimodal therapy is now the standard of care. However, this does not detract from our key finding that the patients who experienced a serious postoperative complication less frequently commenced or completed AC, irrespective of the AC given. Fourth, whilst our results suggested there was an inverse relationship between serious complications and commencing AC, we accept that there are confounding factors. Although the patients who commenced (and

completed) AC may have represented a less comorbid cohort, they were similar in terms of sex, BMI, preoperative comorbidities, staging, preoperative treatment and preoperative blood tests. Fifth, the RAW study was originally set up to study recurrence patterns in PD patients with PDAC, AA and distal CC. Hence, the power calculation we performed had limited relevance to this sub-study which had different inclusion criteria.

The RAW study was advertised via Twitter and also via “word of mouth” at various British meetings (hence, the relatively high number of UK centres involved). Two centres which originally expressed an interest in the study had to drop out due to difficulties associated with the coronavirus pandemic. Whilst we accept that treatment guidelines may alter slightly between the included countries, we feel our results are still generalisable due to our strict inclusion criteria. Also, although robust, our dataset was not 100% complete and some patients had to be excluded from some sub-analyses. Wherever data were missing, we have stated the number of patients this involves (see Table 1) and excluded these from the relevant sub-analyses. A not insignificant number of patients were lost to follow-up before five years and these had to be excluded for practical reasons (289 out of 3705 potentially eligible patients). Finally, as is inevitable with large multicentre studies, the larger high-volume centres provided a higher number of cases then the smaller, low-volume centres. We acknowledge that this a further potential source of bias.

5. Conclusion

In our multicentre study of patients who underwent PD for PDAC, both commencing and completing AC correlated with a significant survival advantage. Furthermore, the patients who commenced AC had less often experienced a serious postoperative complication. Although a serious complication alone did not affect long-term survival (patients who died within 90 days of PD were excluded), patients in this group were less likely to commence AC. The preoperative identification of patients who are high-risk for a serious complication may have

implications for management planning. Selected older patients who are not ASA grade I-II might benefit from neoadjuvant treatment. Future studies should investigate this.

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Tables

Mean age in years (SD)	66.6 (9.4)
Female sex	383 (47.4%)
Mean BMI in kg/m^2 (SD)	25.4 (4.6) Unknown: 268 (33.2%)
Preoperative diabetes	176 (27.8%) Unknown: 87*
Preoperative cardiovascular comorbidity	320 (39.7%) Unknown: 1
Preoperative respiratory comorbidity	83 (10.3%)
Median tumour size on pre-op CT in mm (IQR)	26 (13) Unable to assess/unknown: 324 (40.1%)
Radiological T stage	T1: 148 (21.0%) T2: 239 (33.9%) T3: 187 (26.5%) T4: 22 (3.1%) TX: 110 (27.1%) Unknown: 102*
Radiological N stage	N0: 439 (61.9%) N1: 205 (28.9%) NX: 65 (9.2%) Unknown: 99*
Preoperative biliary stent	522 (64.7%) Unknown: 1
Neoadjuvant chemotherapy received	46 (5.7%)
Median preoperative serum bilirubin in µmol/L (IQR)	21 (48) Unknown: 1 (0.1%)
Median preoperative serum albumin in g/L (IQR)	38 (IQR: 10) Unknown: 141 (17.5%)
Median preoperative serum neutrophils in x10^9/L (IQR)	4.7 (2.9) Unknown: 99 (12.3%)
Median preoperative serum lymphocytes in x10^9/L (IQR)	1.7 (1.3) Unknown: 99 (12.3%)
ASA grade I-II	536 (94.1%) Unknown: 48*
Surgical approach	Classic Whipple: 375 (46.5%) PPPD: 432 (53.5%) Unknown: 1*
Pancreatic anastomosis	P-J: 655 (82.9%) P-G: 135 (17.1%) Not performed/unknown: 18*
Concomitant venous resection	165 (22.9%) Unknown: 86*
Concomitant arterial resection	19 (2.6%) Unknown: 86*
Median length of stay in days (IQR)	13 (9) Unknown: 20 (2.5%)
30-day readmission	76 (10.6%) Unknown: 88*
CR-POPF**	41 (5.7%)
Post-pancreatectomy haemorrhage**	39 (5.4%)

Delayed gastric emptying**	93 (12.9%)
Any Clavien-Dindo grade ≥IIIa complication**	88 (12.2%)
Median tumour size on histology in mm (IQR)	30 (13) Unknown: 81 (10.0%)
Histological T stage	T1: 51 (6.3%) T2: 81 (10.0%) T3: 648 (80.5%) T4: 21 (2.6%) TX: 4 (0.5%) Unknown: 3*
Histological N stage	N0: 188 (23.4%) N1: 615 (76.2%) NX: 4 (0.5%) Unknown: 1*
Resection margin status	R0: 368 (48.1%) R1: 374 (48.9%) R2: 23 (3.0%) Unknown: 43*
Median number of positive nodes (IQR)	2 (4) Unknown: 27 (3.3%)
Median number of resected nodes (IQR)	17 (10.5) Unknown: 27 (3.3%)
Commenced adjuvant chemotherapy	576 (71.3%)
Completed planned adjuvant chemotherapy course	362 (44.8%)
Five-year PDAC recurrence	560 (69.3%) • Of these, 226 (40.4%) received palliative chemotherapy
Five-year actual survival	193 (23.9%)

Table 1: Key information on the included patients. Patients who died within 90 days of pancreatoduodenectomy (PD) excluded. *Not included in percentages. **Data on postoperative complications unknown/not recorded in 88 cases (excluded from relevant sub-analyses). BMI = body mass index, CR-POPF = clinically relevant postoperative pancreatic fistula, CT = computed tomography, IQR = interquartile range, P-G = pancreato-gastrostomy, P-J = pancreato-jejunostomy, PP = pylorus-preserving, SD = standard deviation.

Variable	Commenced AC (n=576)	Did not commence AC (n=232)	p-value
Mean age in years (SD)	65.8 (9.5)	68.5 (8.9)	**0.0002***
Female sex	266 (46.2%)	117 (50.4%)	0.274
Mean BMI in kg/m^2 (SD)	25.6 (4.5)	24.8 (4.6)	0.078
Preoperative diabetes	129 (25.0%)	47 (23.0%)	0.590
Preoperative cardiovascular comorbidity	221 (38.4%)	99 (42.9%)	0.239
Preoperative respiratory comorbidity	58 (11.2%)	25 (10.8%)	0.765
Median tumour size on pre-op CT in mm (IQR)	27 (13.5)	25 (13)	0.595
Radiological T stage I-II	284 (56.0%)	103 (51.8%)	0.307
No regional lymph nodes on preoperative CT	326 (69.5%)	113 (64.6%)	0.231
Preoperative biliary stent	384 (66.8%)	138 (59.7%)	0.058
Median pre-op serum bilirubin in µmol/L (IQR)	22 (51)	20 (39)	0.592
Median pre-op serum albumin in g/L (IQR)	37 (9)	39 (11)	0.119
Median pre-op serum neutrophils in x10^9/L (IQR)	4.7 (2.9)	4.9 (2.7)	0.513
Median pre-op serum lymphocytes in x10^9/L (IQR)	1.8 (1.3)	1.6 (1.4)	0.092
ASA grade I-II	400 (73.5%)	136 (63.0%)	**0.004***
Classic Whipple (vs PPPD)	262 (45.5%)	113 (48.9%)	0.406
P-J anastomosis (vs P-G)	479 (84.5%)	176 (78.9%)	0.062
Concomitant venous resection	123 (23.7%)	42 (20.8%)	0.676
Concomitant arterial resection	10 (1.9%)	10 (5.0%)	**0.040***
CR-POPF**	25 (4.8%)	16 (7.9%)	0.158
Post-pancreatectomy haemorrhage**	21 (4.1%)	18 (8.9%)	**0.016***
Delayed gastric emptying**	63 (12.2%)	30 (14.9%)	0.326
Any Clavien-Dindo grade ≥IIIa complication	51 (9.8%)	37 (18.3%)	**0.002***
Median length of stay in days (IQR)	13 (9)	14 (10)	0.092
30-day readmission	47 (9.1%)	29 (14.4%)	**0.043***
Five-year recurrence	416 (72.2%)	144 (62.1%)	**0.005***
Five-year survival	139 (24.1%)	54 (23.3%)	0.796
Variable	**Completed AC (n=362)**	**Did not complete AC or no AC (n=380)**	**p-value**
Mean age in years (SD)	65.5 (9.2)	67.7 (9.3)	**0.0009***
Female sex	179 (49.4%)	178 (46.8%)	0.478
Mean BMI in kg/m^2 (SD)	25.6 (4.4)	25.1 (4.7)	0.246
Preoperative diabetes	81 (24.7%)	82 (24.4%)	0.931
Preoperative cardiovascular comorbidity	133 (36.7%)	163 (43.0%)	0.082
Preoperative respiratory comorbidity	36 (9.9%)	40 (10.5%)	0.794
Median tumour size on pre-op CT in mm (IQR)	26 (12)	26 (13)	0.939
Radiological T stage I-II	188 (58.6%)	169 (51.2%)	0.059
No regional lymph nodes on preoperative CT	218 (67.5%)	191 (57.7%)	**0.010***
Preoperative biliary stent	232 (64.2%)	242 (63.9%)	0.907
Median pre-op serum bilirubin in µmol/L (IQR)	24 (50)	22 (50)	0.468
Median pre-op serum albumin in g/L (IQR)	37 (10)	38 (10)	0.245
Median pre-op serum neutrophils in x10^9/L (IQR)	4.6 (2.8)	4.9 (3.0)	0.182
Median pre-op serum lymphocytes in x10^9/L (IQR)	1.6 (1.2)	1.8 (1.5)	0.467
ASA grade I-II	260 (75.8%)	234 (65.5%)	**0.003***
Classic Whipple (vs PPPD)	177 (48.9%)	180 (47.5%)	0.703
P-J anastomosis (vs P-G)	296 (82.7%)	304 (82.4%)	0.916
Concomitant venous resection	72 (21.8%)	81 (24.3%)	0.444
Concomitant arterial resection	6 (1.8%)	13 (3.9%)	0.161
CR-POPF**	13 (4.0%)	26 (7.8%)	**0.047***
Post-pancreatectomy haemorrhage**	13 (4.0%)	24 (7.2%)	0.090
Delayed gastric emptying**	47 (14.3%)	44 (13.2%)	0.666
Any Clavien-Dindo grade ≥IIIa complication	34 (10.4%)	51 (15.3%)	0.079
Median length of stay in days (IQR)	13 (10)	13 (10)	0.973

30-day readmission	27 (8.2%)	46 (13.7%)	**0.026***
Median time to first AC dose in days (IQR)	66 (32)	77 (30)	**0.006***
Five-year recurrence	256 (70.7%)	260 (68.4%)	0.497
Five-year survival	107 (29.6%)	71 (18.7%)	**0.0005***
Variable	**CD ≥IIIa comp. (n=88)**	**No CD ≥IIIa comp. (n=632)**	**p-value**
Mean age in years (SD)	65.8 (9.6)	66.5 (9.5)	0.518
Female sex	42 (47.4%)	294 (46.5%)	0.831
Mean BMI in kg/m^2 (SD)	25.5 (4.0)	25.3 (4.5)	0.737
Preoperative diabetes	17 (19.3%)	159 (25.2%)	0.289
Preoperative cardiovascular comorbidity	33 (37.5%)	287 (45.4%)	0.171
Preoperative respiratory comorbidity	7 (8.0%)	76 (12.0%)	0.372
Median tumour size on pre-op CT in mm (IQR)	24.5 (17)	27 (12.5)	0.274
Radiological T stage I-II	51 (89.5%)	336 (54.3%)	0.446
No regional lymph nodes on preoperative CT	57 (65.5%)	382 (61.4%)	0.460
Preoperative biliary stent	51 (58.0%)	398 (63.0%)	0.343
Median pre-op serum bilirubin in µmol/L (IQR)	23.5 (73)	22 (48)	0.402
Median pre-op serum albumin in g/L (IQR)	36 (11.5)	38 (10)	0.547
Median pre-op serum neutrophils in x10^9/L (IQR)	4.5 (2.6)	4.8 (2.9)	0.183
Median pre-op serum lymphocytes in x10^9/L (IQR)	1.8 (1.6)	1.7 (1.2)	0.804
ASA grade I-II	43 (52.4%)	434 (73.4%)	**0.0004***
Classic Whipple (vs PPPD)	48 (54.5%)	327 (51.8%)	0.632
P-J anastomosis (vs P-G)	65 (75.6%)	502 (81.5%)	0.193
Concomitant venous resection	23 (26.4%)	142 (22.9%)	0.471
Concomitant arterial resection	4 (4.6%)	16 (2.6%)	0.295
Median length of stay in days (IQR)	14 (12)	12 (9)	0.611
30-day readmission	21 (23.9%)	55 (8.7%)	**<0.0001***
Commenced AC	51 (58.0%)	467 (73.9%)	**0.002***
Completed AC	34 (40%)	294 (50.9%)	0.061
Median time to first AC dose in days (IQR)	73 (49)	69 (34)	0.359
Five-year recurrence	69 (78.4%)	437 (69.1%)	0.075
Five-year survival	22 (25.0%)	160 (25.3%)	1.00

Table 2: Comparing patients who commenced adjuvant chemotherapy (AC) to those who did not, those who completed AC to those who did not, and those who developed a Clavien-Dindo (CD) grade >IIIa complication to those who did not. Patients who died within 90 days of pancreatoduodenectomy (PD) were excluded from all analyses. *Denotes statistical significance. **Data on postoperative complications unknown/not recorded in 88 cases (excluded from the relevant sub-analyses). Statistical methods: means were compared using Student's *t*-test, medians were compared using the Mann Whitney *U* test, percentages were compared using Pearson's χ^2 test unless one or both of the sample sizes was <30 (in which case, Fisher's exact test was used). BMI = body mass index, CR-POPF = clinically relevant postoperative pancreatic fistula, CT = computed tomography, IQR = interquartile range, P-G = pancreato-gastrostomy, P-J = pancreato-jejunostomy, PP = pylorus-preserving, SD = standard deviation.

Commenced AC vs did not	
Age	Mean difference: 2.7 years
Completed AC vs did not (or did not commence AC)	
Age	Mean difference: 2.2 years
Major complication (Clavien-Dindo grade ≥IIIa) vs none	
30-day readmission	OR: 3.3 (95% CI: 1.9-5.8)
American Society of Anesthiologists grade I-II	OR: 0.4 (95% CI: 0.2-0.6)
Commenced adjuvant chemotherapy	OR: 0.5 (95% CI: 0.3-0.8)

Table 3: Multivariable analysis. Variables that remained significant following both the Holm and Hochberg step methods. CI = confidence interval, OR = odds ratio.

Figures and legends

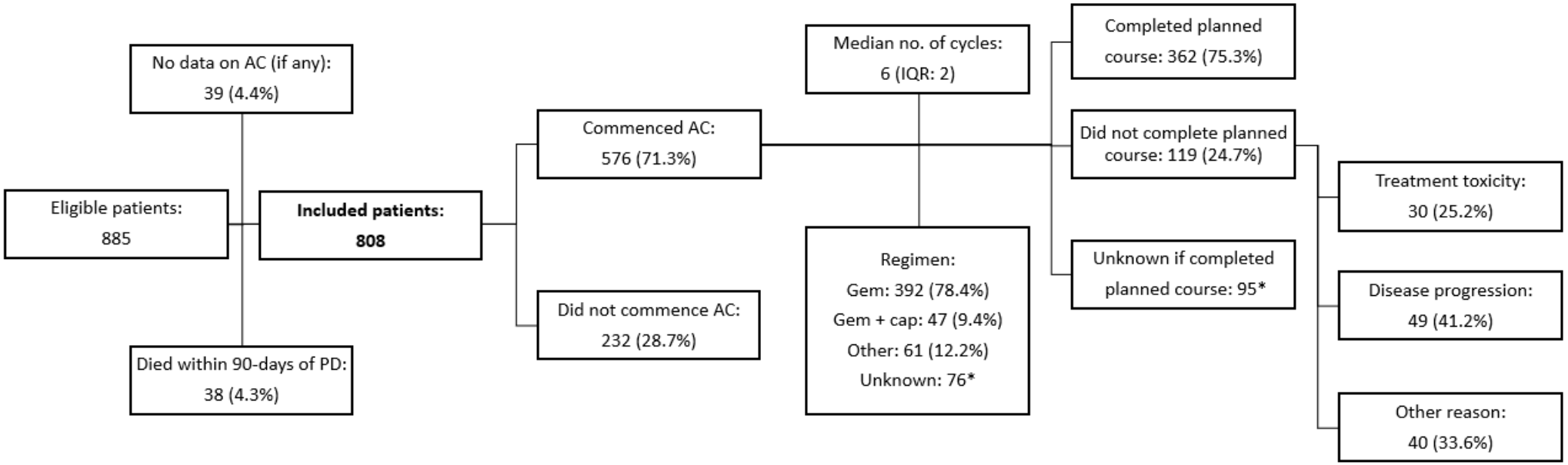
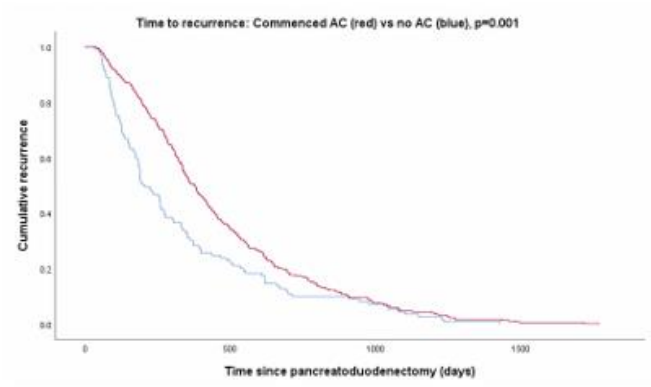
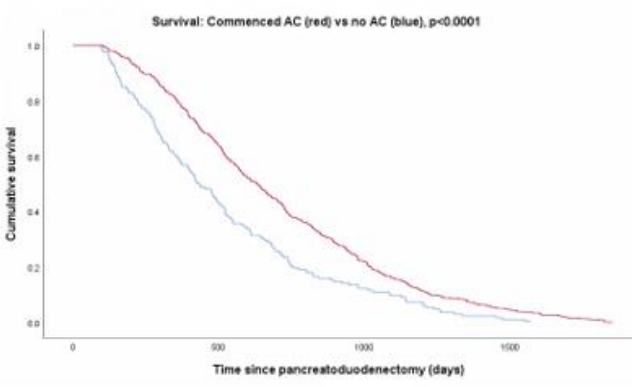


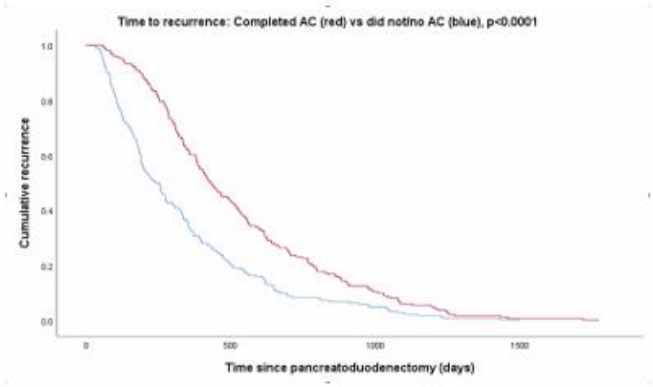
Figure 1: Adjuvant chemotherapy (AC) flow diagram. Cap = capecitabine, Gem = gemcitabine, IQR = interquartile range, PD = pancreatoduodenectomy. *Excluded from percentages.


Time to recurrence: Commenced AC (red) vs no AC (blue), p=0.001
Cumulative recurrence
Time since pancreatoduodenectomy (days)

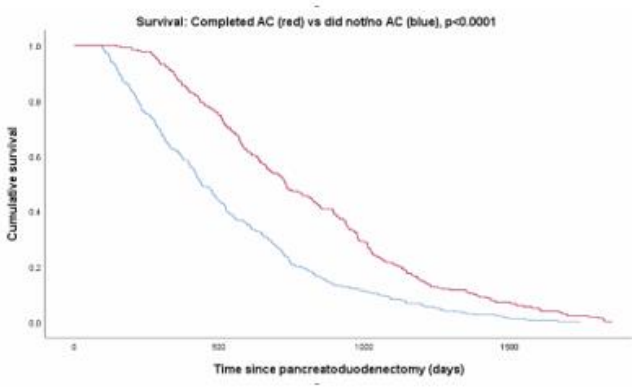
A


Survival: Commenced AC (red) vs no AC (blue), p<0.0001
Cumulative survival
Time since pancreatoduodenectomy (days)

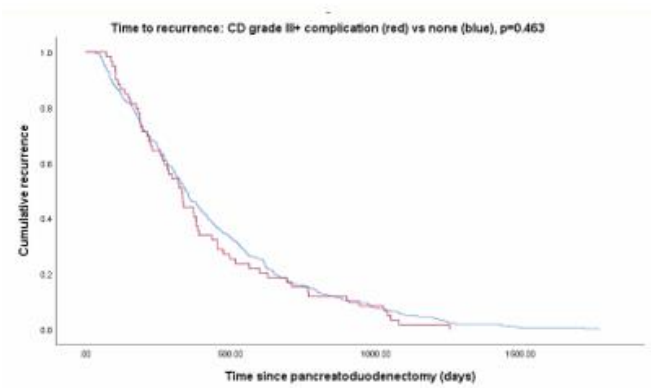
B


Time to recurrence: Completed AC (red) vs did notno AC (blue), p<0.0001
Cumulative recurrence
Time since pancreatoduodenectomy (days)

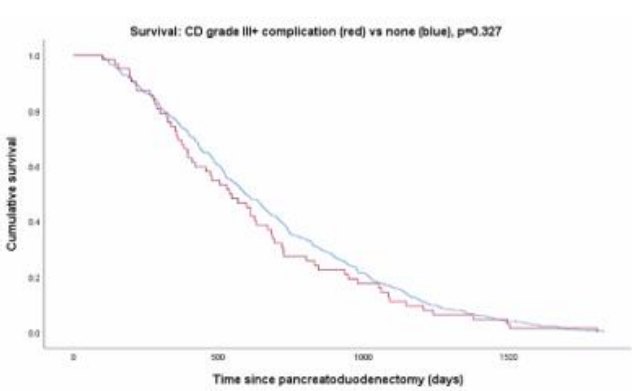
C


Survival: Completed AC (red) vs did notno AC (blue), p<0.0001
Cumulative survival
Time since pancreatoduodenectomy (days)

D


Time to recurrence: CD grade III+ complication (red) vs none (blue), p=0.463
Cumulative recurrence
Time since pancreatoduodenectomy (days)

E


Survival: CD grade III+ complication (red) vs none (blue), p=0.327
Cumulative survival
Time since pancreatoduodenectomy (days)

F

G	Mean				Median			
	Estimate	Std. Error	95% CI		Estimate	Std. Error	95% CI	
Time to recurrence (days)			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Commenced AC	458.4	17.7	423.8	493.1	380.0	19.3	342.2	417.8
No AC	336.7	30.1	277.8	395.6	204.0	30.5	144.3	263.7
Overall	428.3	15.4	398.1	458.6	339.0	14.7	310.2	367.8
Completed AC	525.3	23.0	480.1	570.4	433.0	30.7	372.9	493.1
Did not complete AC/no AC	334.9	20.5	294.8	375.0	240.0	24.0	193.0	287.0
Overall	432.0	16.1	400.3	463.6	345.0	17.0	311.7	378.3
CD grade ≥IIIa complication	407.1	38.3	332.2	482.1	332.0	28.0	277.2	386.8
No CD grade ≥IIIa complication	434.3	17.1	400.9	467.8	346.0	18.1	310.5	381.5
Overall	430.6	15.6	400.0	461.3	342.0	16.0	310.7	373.3
Time to death (days)								
Commenced AC	703.8	19.2	666.2	741.3	632.0	26.6	579.8	684.2
No AC	525.4	27.5	471.6	579.2	431.0	34.3	363.8	498.2
Overall	654.3	16.1	622.7	685.9	569.0	22.6	524.7	613.3
Completed AC	801.4	25.0	752.4	850.3	729.0	43.9	643.0	815.0
Did not complete AC/no AC	529.9	20.7	489.4	570.4	438.0	23.4	392.1	483.9
Overall	656.0	17.1	622.6	689.4	572.0	24.0	524.9	619.1
CD grade ≥IIIa complication	624.1	48.5	529.1	719.0	538.0	59.9	420.5	655.5
No CD grade ≥IIIa complication	676.5	18.9	639.6	713.5	593.0	27.3	539.5	646.5
Overall	670.1	17.6	635.7	704.6	586.0	26.0	535.0	637.0

Figure 2: Kaplan-Meier curves. Commenced adjuvant chemotherapy (AC) vs did not: time to recurrence (A) and time to death (B). Completed AC vs did not/did not commence AC: time to recurrence (C) and time to death (D). Experienced a Clavien-Dindo (CD) ≥IIIa complication vs did not: time to recurrence (E) and time to death (F). Mean and median time to recurrence/death figures (G). P-values obtained using the log-rank test. Patients who died within 90 days of PD were excluded from all analyses. AC = adjuvant chemotherapy, CI = confidence interval.

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Disclosure statement

All authors declare that there are no conflicts of interest.

Authorship statement

Conceptualisation: TR, PL, SA; Data curation: all authors; Formal analysis: TR, AS, Funding acquisition: N/A; Investigation: TR, PL; Methodology: TR, PL; Project administration: TR, PL; Resources: TR, PL; Software: TR, SA; Supervision: AS, SA; Validation: AS, SA; Visualisation: all authors; Writing – original draft: TR; Writing – review and editing: all authors.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.