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Research Article

Enhanced Recovery after Surgery (ERAS) and Adjuvant Chemotherapy Completion Rates after Pancreaticoduodenectomy (PD): A Retrospective Analysis

Callum Fryer[1,2*], Sharnice Koek[2], Laurence Webber[2], John Tran[1,2], Wallace Hilary[1], Mayank Bhandari[1,2], Mohammed Ballal[1,2]

[1]Fiona Stanley Hospital (Western Australia Southern Metropolitan Health Service), Perth, Australia

[2]University of Notre Dame Fremantle, Perth, Australia

[*]**Corresponding author:** Callum Fryer, The Upper Gastrointestinal Surgical Unit, South Metropolitan Health Service, WA Fiona Stanley Hospital, Perth, Australia

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Abstract

Background: To compare adjuvant chemotherapy completion rates in patient's post-pancreaticoduodenectomy (PD) with and without exposure to the Enhanced Recovery After Surgery (ERAS) protocol.

Methods: A retrospective cohort study was conducted in all PD patients with adenocarcinomas, who commenced adjuvant chemotherapy and either had the pre-ERAS (n=19) or ERAS (n=66) protocol between 2009 and 2017. Data was analysed via Chi-square, logistic regression and Kaplan–Meier analysis.

Results: Pre-ERAS and ERAS patients displayed similar chemotherapy completion rates (79%). However, ERAS patients had higher America Society of Anaesthesiology (ASA) Physical Status scores (p=0.04) and Charlson Comorbidity Index (CCI) scores (p=0.004) as well as approaching statistical significantly different Clavien-Dindo (CD) scores (p=0.052), compared to pre-ERAS patients. CD score was the only independent variable that statistically influenced chemotherapy completion (p=0.02). Chi-square cross tabulation showed the ERAS group had a higher proportion of CD minor and major complications completing chemotherapy (86.4 and 63.6%, respectively), compared to non-completion (13.6% and 36.4%, respectively) (p=0.033). On Kaplan-Meier analysis, ERAS showed a trend of increased 5-year survival (56%) when compared to pre-ERAS (36%) (p=0.36).

Conclusions: This is the first study that shows ERAS patients displaying similar chemotherapy completion rates compared to the pre-ERAS group (79%), despite having higher ASA, CCI and CD scores. While CD score was found to be the only independent variable influencing chemotherapy completion, further studies are required. The ERAS protocol may help significantly more complex patients complete multimodal therapy including chemotherapy. Overall, the ERAS protocol implemented at FSH hospital is worth considering as a standardised protocol in future trials.

Keywords: Chemotherapy completion; ERAS; Pancreaticoduodenectomy

List of Abbreviations: **ASA:** American Society of Anaesthesiologists; **AJCC:** The American Joint Committee on Cancer; **BMI:** Body Mass Index; **CCI:** Charlson Comorbidity Index; **CD:** Clavien-Dindo Post-Operative Complications; **ERAS:** Enhance Recovery After Surgery; **PSC:** Physical Status Score; **PD:** Pancreaticoduodenectomy

Introduction

Pancreatic cancer is one of the leading causes of cancer relate death in Australia. In 2018 more than 3000 death occurred ranking 4th in all age groups [1]. The overall 5- year survival rate for all stages pancreatic malignancy is only 9 % [2]. Pancreaticoduodenectomy (PD) remains the only curative treatment option for head of pancreas lesions [3]. The survival advantage of Multimodal Therapy (MMT) which includes surgery, chemotherapy and in some cases, radiotherapy has been consistently demonstrated in multiple randomised trials and prospective analysis [4-12]. There are multiple factors precluding patients from completion of MMT. Postoperative complications and frailty are the leading causes for patients no initiating or completing chemotherapy [13-15]. Identification of modifiable factors that lower surgical morbidity, increase chemotherapy completion rates and potentially increase overall survival are a major focus in the field of pancreatic cancer surgery.

Enhanced Recovery After Surgery (ERAS) is a package of interventions aimed at decreasing surgical morbidity, lowering complication rates and decreasing length of stay in hospital. These protocols aim to minimize surgical trauma and postoperative pain, reduce complications, improve outcomes, and decrease LOS, while expediting recovery following elective procedures [16,17]. Currently, there is no unified ERAS protocol apart from general guidelines for PD patients [18]. Since ERAS aims to expedite recovery and reduce morbidity, this may aid in successful completion of adjuvant chemotherapy. We hypothesise that the FSH ERAS protocol may help patients post pancreaticoduodenectomy complete adjuvant chemotherapy.

Materials and Methods

The study was initiated by The Upper Gastrointestinal Surgical Unit, South Metropolitan Health Service, Perth, WA. Ethical approval was obtained from the Human Research Ethics Committees of the South Metropolitan Health Service (HREC Ref: 15-040-1) and University of Notre Dame Australia (HREC Ref: 018072F).

Patient Selection and Data Collection

A retrospective cohort study was conducted in all patients who underwent Pancreaticoduodenectomy (PD) through the Upper Gastrointestinal unit of the Western Australian South Metropolitan Health Service from 2009 to 2017 (n=169) across two sites (Fremantle hospital prior to 2015, and Fiona Stanley hospital form 2015 on wards). The pre-ERAS group (n=29) consisted of patients at Fremantle Hospital between January 2009 to December 2011. In accordance with the ERAS society guidelines (see Supplementary Figure S1, Kristoffer, 2013), the care of patients undergoing PD were modified and adapted as the early-ERAS programme. A total of 140 consecutive patients were included in the analysis (67 from Fremantle hospital and 73 from Fiona Stanley hospital). All operations were performed by the same team of pancreatic surgeons in these hospitals, comprising two fellowship-trained hepatobiliary consultant surgeons at Fremantle Hospital with the addition of a third hepatobiliary surgeon at Fiona Stanley Hospital.

Item	Summary and recommendations	Evidence level	Recommendation grade
Preoperative counselling	Patients should receive dedicated preoperative counselling routinely	Low	Strong
Perioperative biliary drainage	Preoperative endoscopic biliary drainage should not be undertaken routinely in patients with a serum bilirubin concentration <250 µmol/l	Moderate	Weak
Preoperative smoking and alcohol consumption	For alcohol abusers, 1 month of abstinence before surgery is beneficial and should be attempted. For daily smokers, 1 month of abstinence before surgery is beneficial. For appropriate groups, both should be attempted	Alcohol abstention: low Smoking cessation: moderate	Strong
Preoperative nutrition	Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition preoperatively	Very low	Weak
Perioperative oral immunonutrition (IN)	The balance of evidence suggests that IN for 5–7 days perioperatively should be considered because it may reduce the rate of infectious complications in patients undergoing major open abdominal surgery	Moderate	Weak
Oral bowel preparation	Extrapolation of data from studies on colonic surgery and retrospective studies in PD show that MBP has no proven benefit. MBP should not be used	Moderate	Strong
Preoperative fasting and preoperative treatment with carbohydrates	Intake of clear fluids up to 2 h before anaesthesia does not increase gastric residual volume and is recommended before elective surgery. Intake of solids should be withheld 6 h before anaesthesia. Data extrapolation from studies in major surgery suggests that preoperative oral carbohydrate treatment should be given in patients without diabetes	Fluid intake: high Solid intake: low Carbohydrate loading: low	Fasting: strong carbohydrate loading: strong
Preanaesthetic medication	Data from studies on abdominal surgery show no evidence of clinical benefit from pre-operative use of long-acting sedatives, and they should not be used routinely. Short-acting anxiolytics may be used for procedures such as insertion of epidural catheters	No long-acting sedatives: moderate	Weak
Anti-thrombotic prophylaxis	LMWH reduces the risk of thromboembolic complications, and administration should be continued for 4 weeks after hospital discharge. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk	High	Strong
Antimicrobial prophylaxis and skin preparation	Antimicrobial prophylaxis prevents surgical-site infections, and should be used in a single-dose manner initiated 30–60 min before skin incision. Repeated intraoperative doses may be necessary depending on the half-life of the drug and duration of procedure	High	Strong
Epidural analgesia	Mid-thoracic epidurals are recommended based on data from studies on major open abdominal surgery showing superior pain relief and fewer respiratory complications compared with intravenous opioids	Pain: high Reduced respiratory complications: moderate Overall morbidity: low	Weak
Intravenous analgesia	Some evidence supports the use of PCA or intravenous lidocaine analgesic methods. There is insufficient information on outcome after PD	PCA: very low I.V. Lidocaine: moderate	Weak
Wound catheters and transversus abdominis plane block	Some evidence supports the use of wound catheters or TAP blocks in abdominal surgery. Results are conflicting and variable, and mostly from studies on lower gastrointestinal surgery	Wound catheters: moderate TAP blocks: moderate	Weak
Audit	Systematic improves compliance and clinical outcomes	Low	Strong

Supplementary Figure S1 (continued)

Item	Summary and recommendations	Evidence level	Recommendation grade
Postoperative nausea and vomiting (PONV)	Data from the literature on gastrointestinal surgery in patients at risk of PONV show the benefits of using different pharmacological agents depending on the patient's PONV history, type of surgery and type of anaesthesia. Multimodal intervention during and after surgery is indicated	Low	Strong
Incision	The choice of incision is at the surgeon's discretion, and should be of a length sufficient to ensure good exposure	Very low	Strong
Avoiding hypothermia	Intraoperative hypothermia should be avoided by using cutaneous warming, i.e., forced-air or circulating-water garment systems	High	Strong
Postoperative glycaemic control	Insulin resistance and hyperglycaemia are strongly associated with postoperative morbidity and mortality. Treatment of hyperglycaemia with intravenous insulin in the ICU setting improves outcomes but hypoglycaemia remains a risk. Several ERAS protocol items attenuate insulin resistance and facilitate glycaemic control without the risk of hypoglycaemia. Hyperglycaemia should be avoided as far as possible without introducing the risk of hypoglycaemia	Low	Strong
Nasogastric intubation	Pre-emptive use of nasogastric tubes postoperatively does not improve outcomes, and their use is not warranted routinely	Moderate	Strong
Fluid balance	Near-zero fluid balance, avoiding overload of salt and water results in improved outcomes. Perioperative monitoring of stroke volume with transoesophageal Doppler to optimize cardiac output with fluid boluses improves outcomes. Balanced crystalloids should be preferred to 0.9 % saline	Fluid balance: high oesophageal doppler: moderate Balanced crystalloids vs. 0.9 % saline: moderate	Strong
Perianastomotic drain	Early removal of drains after 72 h may be advisable in patients at low risk (i.e., amylase content in drain <5,000 U/L) for developing a pancreatic fistula. There is insufficient evidence to recommend routine use of drains, but their use is based only on low-level evidence	Early removal: high	Early removal: strong
Somatostatin analogues	Somatostatin and its analogues have no beneficial effects on outcome after PD. In general, their use is not warranted. Subgroup analyses for variability in the texture and duct size of the pancreas are not available	Moderate	Strong
Urinary drainage	Suprapubic catheterisation is superior to transurethral catheterisation if used for >4 days. Transurethral catheters can be removed safely on postoperative day 1 or 2 unless otherwise indicated	High	For suprapubic: weak Transurethral catheter out POD 1–2: strong

Supplementary Figure S1: ERAS Society recommendations for Pancreaticoduodenectomy.

Only patients with resectable pancreatic adenocarcinoma were included in our study. Other histological variants were excluded such as pancreatic neuroendocrine tumours and intraductal papillary mucinous neoplasm. Other inclusion criteria included being referred and commencement adjuvant chemotherapy and being subject to the pre-ERAS or ERAS protocol (summarised in Table 1). Any chemotherapy agents were part of the inclusion criteria. These were categorised under Gemcitabine (Gemzar), 5-Fluorouracil (5-FU), oxaliplatin (Eloxatin), Albumin-bound paclitaxel (Abraxane), Capecitabine (Xeloda), Cisplatin, Paclitacel (Taxol), Leucovirin, Irinotecan (Onivyde), Folic acid or other. Patients who were not referred or referred but did not commence adjuvant chemotherapy were excluded.

Day	Intervention
Day of Surgery Admission	Oral PPI Octreotide 200mcg Fasted minimum 6 hours for food, 2 hours for clear fluids preOp® drinks complete (not for IDDM) No bowel preparation
Day of Surgery	Antimicrobial prophylaxis Insertion of NJ tube, urinary catheter, intra-abdominal drains Normothermia maintained ≥ 37°C Anti-embolic stockings or calf compression pumps in situ PCA analgesia and wound catheters Subcutaneous Octreotide Subcutaneous Heparin
Day 2	Cessation of IV antibiotics Commence clear fluids Nasojejunal feeds increased as per regime to target rate Out of bed minimum 1 hour BD, with assistance on ambulation BD Indwelling catheter removed
Day 3	Commence NF * Nasojejunal feeds at the target rate* Nasogastric spigotted * Cease PCA Drain bottles changed and sent for amylase and lipase
Day 4	Wound catheters removed APS oral protocol Nasojejunal feeds ceased Remove NJT/NGT
Day 5	Drain bottles changed and sent for amylase and lipase Removal of intra-abdominal drains if no evidence of POPF
Day 6 +	Once tolerating NF, diet progressed to 1 week pureed diet then 1 week soft diet

PPI: Proton Pump Inhibitor; IDDM: Insulin Dependent Diabetes Mellitus; NGT: Nasogastric Tube; NJT: Nasojejunal Tube; PCA: Patient-Controlled Analgesia; IV: Intravenous; CSL: Compound Sodium Lactate; HDU: High Dependency Unit; BD: Bis in Die (twice daily); NF: Nourishing Fluids; APS: Acute Pain Service; POPF: Postoperative Pancreatic Fistula. * If no sign of ileus [19].

Table 1: Summary of ERAS protocol.

Clinical factors were obtained and documented for each patient. These included age, gender, body mass index (BMI), American Society of Anaesthesiologists (ASA) physical status score [20], Charlson Comorbidity Index (CCI) score [21], and tumour histopathology. Neoadjuvant chemotherapy was not recorded in our analysis, however, there were limited numbers in both the pre-ERAS (n=0) and ERAS (n=12) groups.Postoperative variables were assessed for each patient, including Clavien-Dindo post-operative complications (CD) (Dindo + Clavien, 2004), the American Joint Committee on Cancer (AJCC) staging system [22,23], chemotherapy agents, chemotherapy completion rates and the adherence to the ERAS protocol (Supplementary Figure S1) based on the goals of care. A CD score of 3 or more was considered to be a major complication

Primary and Secondary Outcomes

The primary outcome was the completion of all cycles of chemotherapy. A cycle of chemotherapy was defined by type of chemotherapy protocol. The agents and number of doses which defined a chemotherapy cycle varied thorough the duration. This was due to evolving protocols based on evidence based medicine throughout the study. The secondary outcomes included factors relating to chemotherapy completion. These included ASA scores, CCI scores, CD scores, AJCC staging system, referral or non-referral for chemotherapy (including reasons and numbers of incomplete cycles). The reasons for incompletion include patient factors, physician factors, progression of disease and unknown. Post-operative complications were associated with physician and patient factors.

Statistical Analysis

Descriptive analyses were conducted including frequencies and percentages for categorical variables and mean and Standard Deviation (SD) for continuous variables. Patient demographics, clinical features and chemotherapy completion were compared between the pre-ERAS and ERAS groups. Continuous variables were compared by t-tests and categorical variables by Chi-square tests. Additional analysis (t-tests and Chi-square tests) for other factors associated with chemotherapy completion were performed. Logistic regression was performed to adjust for covariates and confounders between the chemotherapy completion and chemotherapy non-completion. The variables included were age, gender, ASA score, CCI score, CD score, AJCC classification and pre-ERAS or ERAS protocol. All variables were entered simultaneously. Survivability between pre-ERAS and ERAS was performed via Kaplan– Meier analyses.

All statistical tests were two-tailed and $P<0.05$ were considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences, version 16.0 (SPSS).

Results

A total of 169 patients had undergone pancreaticoduodenectomy between 2009 and 2017. Only 118 patients had pancreatic adenocarcinomas, with 23 in pre-ERAS and 95 in ERAS groups. Chemotherapy data was not available for 16 patients electing to have chemotherapy in out of district or private institutions or not at all due to side effects (Figure 1). The final patient data for analysis comprised 19 and 66 patients in the pre-ERAS and ERAS groups, respectively. Adjuvant chemotherapy completion rates were similar between pre-ERAS and ERAS groups, being 79%(p=0.98) (Figure 1). Compliance to the ERAS protocol in the ERAS group, was confirmed in a previous study [19]. The Pre ERAS group had a lower ASA grade as compared to the ERAS group. 15.8% of pre-ERAS patients had ASA scores of 3-4 as compared to 52% of ERAS patients (p=0.04). Furthermore, 31.58% of the pre-ERAS patients had CCI scores of 4-6, compared to 80.29% of ERAS patients (p=0.004) (Table 2).

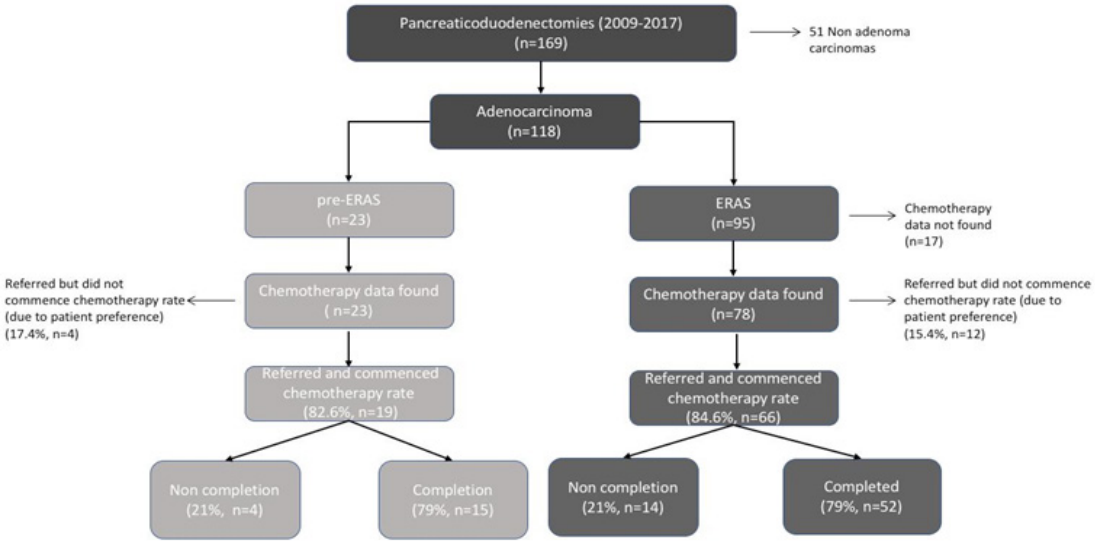

Figure 1: Flowchart representing patient pool, pre-ERAS and ERAS patient groups as well as chemotherapy completion rates

Figure 1: Flowchat representing patient pool, pre-ERAS and ERAS patient group as well as chemotherapy completion rates.

There was a lower rate of major complications in Pre ERAS group however this did not reach statistical significance (10.53% pre-ERAS, 33.33% of ERAS group, p=0.052) (Table 2). Patients who suffered a major post-operative complication had a lower chemotherapy completion rate (62.5%) as compared to those who had minor complication (85.3%) (p=0.02) (Table 3). Multivariable analysis using logistic regression found CD complications to be the only independent variable that statistically influenced chemotherapy completion (p=0.02) (Table 4). The ERAS protocol was not shown to influence chemotherapy completion, along with age, gender, ASA score and CCI score.

	Pre-ERAS	**ERAS**	**P value**
	(n=19)	**(n=66)**	
Age (SD)	62.3 (9.3)	64.9 (9.5)	0.8
BMI (SD)	26.2 (3.9)	27.3 (4.9)	0.34
Gender (%)			
F	9 (47.37)	26 (38.81)	
M	10 (52.63)	40 (61.19)	0.53
ASA score (%)			
1-2	16 (84.21)	32 (48)	
3-4	3 (15.79)	34 (52)	**.04***
Charlson score (%)			
1	1 (5.26)	2 (3.03)	
2	4 (21.05)	5 (7.58)	
3	8 (42.11)	6 (9.1)	
4	4 (21.05)	31 (46.97)	
5	2 (10.53)	14 (21.21)	
6	0 (0)	8 (12.11)	**.004***
AJCC (%)			
0	0 (0)	1 (1.52)	
1a	0 (0)	0 (0)	
1b	1 (5.26)	3 (4.55)	
2a	4 (21.05)	16 (24.24)	
2b	14 (73.68)	41 (62.12)	
3	0 (0)	5 (7.58)	0.72
Clavien-Dindo Complications (%)			
Minor (<3)	17 (89.47)	44 (66.67)	
Major (≥ 3)	2 (10.53)	22 (33.33)	0.052
Adjuvant Chemotherapy completion			
(%)			
Y	15 (78.95)	52 (78.79)	

N	4 (21.05)	14 (21.21)	0.98
Pearson Chi-square P<0.05 significant*; Y=Yes, N=NO; ASA: American Society of Anesthesiology Physical Status score; AJCC: American Joint Committee on Cancer Staging system; ERAS: Enhanced Recovery after Surgery			

Table 2: Pre-ERAS and ERAS patient demographics and clinical features.

	Adjuvant Chemotherapy non-completion (n=18)	**Adjuvant Chemotherapy completion (n=67)**	**P value**
Age (SD)	64 (SD12.88)	64 (SD8.49)	0.82
Gender (SD)			
F	5 (27.78)	30 (44.78)	
M	13 (72.22)	37 (55.22)	0.19
ASA score (%)			
2-Jan	9 (50)	39 (58.21)	
4-Mar	9 (50)	28 (41.79)	0.58
Charlson score (%)			
1	0 (0)	4 (5.97)	
2	4(22.22)	4 (5.97)	
3	2 (11.11)	12 (17.91)	
4	6 (33.33)	29 (43.28)	
5	2 (22.22)	14 (20.9)	
6	4 (22.22)	4 (5.97)	0.07
AJCC (%)			
0	1 (5.56)	0 (0)	
1a	0 (0)	0 (0)	
1b	0 (0)	4 (5.97)	
2a	6 (33.33)	14 (20.9)	
2b	9 (50.0)	46 (68.66)	
3	2 (11.11)	3 (4.48)	0.1
Clavien-Dindo Complications			
Minor (<3)	9 (50.0)	52 (77.61)	
Major (≥ 3)	9 (50.0)	15 (22.39)	**0.02***
ERAS Protocol (%)			
Y	14 (77.78)	52 (77.61)	
N	4 (22.22)	15 (22.39)	0.98
Pearson Chi-square P<0.05 significant*; Y=Yes, N=NO; ASA: American Society of Anaesthesiology Physical Status score; AJCC: American Joint Committee on Cancer Staging system; ERAS: Enhanced Recovery After Surgery			

Table 3: Adjuvant Chemotherapy completion vs non completion patient demographics and clinical features.

	Adjuvant Chemotherapy Completion Adjusted OR (95% CI)	P Value
Age	0.98 (0.89-1.1)	0.69
Gender	0.52 (0.15-1.7)	0.29
ASA	1.08 (0.39-2.9)	0.89
Charlson score	1.13 (0.5-2.5)	0.74
Clavien-Dindo Complications	0.59 (0.36-0.99)	**.04***
AJCC	1.29 (0.64-2.5)	0.47
ERAS	0.89 (0.21-3.8)	0.89
Pearson Chi-square P<0.05 significant*; ASA: American Society of Anesthesiology Physical Status score; AJCC: American Joint Committee on Cancer Staging system; ERAS: Enhanced Recovery after Surgery		

Table 4: Logistic Regression for Adjuvant chemotherapy completion as a variable.

On further analysis of CD complications, Chi-square cross tabulation showed a relationship between chemotherapy completion, ERAS and CD complication (Table 5). There was an association between the implementation of the ERAS protocol and higher chemotherapy completion rates, when comparing both the minor and major CD complication groups. The ERAS group had a higher proportion of CD minor and major complications completing chemotherapy (86.4 and 63.6%, respectively), compared to non-completion (13.6% and 36.4%, respectively) (p=0.033). Reasons for not completing chemotherapy are listed in Table 6. A high number of patients in the ERAS group declined further chemotherapy due to patient preference. Patient reasons were often variable (data not shown) however commonly involved side effects being intolerable.

Table 5: Cross tabulation of adjuvant chemotherapy completion, Clavien-Dindo Complications and pre-ERAS or ERAS protocol

Protocol	Adjuvant Chemotherapy non-completion	Adjuvant Chemotherapy Completion	P value	P Value (overall)
Pre-ERAS				
Clavien-Dindo Complications				
Minor (<3)	3 (17.6)	14 (84.4)		
Major (≥ 3)	1 (50.0)	1 (50.0)	.29	
ERAS				
Clavien-Dindo complications				
Minor (<3)	6 (13.6)	38 (86.4)		
Major (≥ 3)	8 (36.4)	14 (63.6)	**.033***	**.02***

Pearson Chi-Square P<0.05 significant*
ERAS: Enhanced Recovery After Surgery

Pearson Chi-Square P<0.05 significant*; ERAS: Enhanced Recovery after Surgery

Table 5: Cross tabulation of adjuvant chemotherapy completion, Clavien-Dindo Complications and pre-ERAS or ERAS protocol.

	Pre-ERAS	ERAS
Patient preference	1	8
Physician preference	0	1
Progressive disease	1	3
Unknown	2	2
ERAS: Enhanced Recovery after Surgery		

Table 6: Reasons for not completing adjuvant chemotherapy.

Recurrence before 3 months are displayed in Table 7. ERAS patients had lower levels of recurrence <3 months (p=0.001), when compared to the pre-ERAS group. The ERAS group showed a trend of increased 5-year (60 months) survival and median survival compared to the pre-ERAS group. The ERAS group 5-year survival and median survival were 56% and 4.36 years, respectively. This was compared to the pre-ERAS group 5-year survival and median survival of 36% and 3.99 years, respectively (displayed in Figure 2). These differences in survival were not shown to be statistically significant (p=0.37).

	Pre-ERAS (n=19)	ERAS (n=66)	P values
Recurrence (<3 months)			
(n=19)			
Y	9 (47.4)	8 (12.1)	
N	10 (57.6)	58 (87.9)	0.001*
Pearson Chi-square P<0.05 significant*; ERAS: Enhanced Recovery after Surgery			

Table 7: Recurrence rates for pre-ERAS and ERAS at <3months.

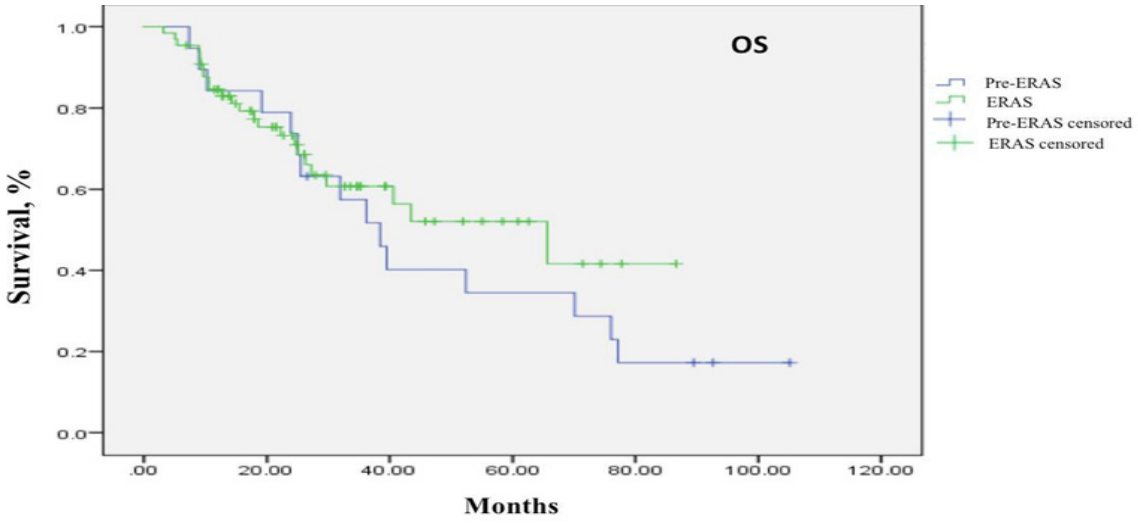

Figure 2: Overall survival analysis between pre-ERAS and ERAS in years
Kaplan-Meier plot of overall survival among all resected PD with ERAS (1, green line) and with pre-ERAS (2, blue line) (p=.36). Event reported as death. Median overall survival was 3.99 years (95% CI, 2.32-3.99) in the pre-ERAS group compared with 4.36 years (95% CI, 2.27-8.52) in the ERAS group (95% CI, 0.44-0.69)

Figure 2: Overall survival analysis between pre-ERAS and ERAS in years Kaplan-Meier plot of overall survival among all resected PD with ERAS (1, green line) and with pre-ERAS (2, blue line) (p=.36). Event reported as death. Median overall survival was 3.99 years (95% CI, 2.32-3.99) in the pre-ERAS group compared with 4.36 years (95% CI, 2.27-8.52) in the ERAS group (95% CI, 0.44- 0.69).

Discussion

With suboptimal 5-year survival rates post pancreaticoduodenectomy of 15-20% [24,25], multimodal therapy is the mainstay treatment of pancreatic cancer. These modalities include surgery, adjuvant chemotherapy, radiotherapy and a variety of other protocols. This study aimed to compare adjuvant chemotherapy completion rates in patients post-pancreaticoduodenectomy (PD) with and without exposure to the ERAS protocol. This is the first study to our knowledge that explores the relationship between ERAS and chemotherapy completion rates following PD.

ERAS protocol implements multimodal strategies that aim to maximise and restore functional capacity after surgery. Morbidity is minimised by reducing surgical stress, post-operative complications and post-operative pain as well as early oral diet and early mobilisation [16]. The beneficial effects of the ERAS protocol have been extensively studied in colorectal cancer and were associated with stepwise reductions in complication rates, LOS, readmissions, the surgical stress response and increased 5-year survivability [26-29]. While, the beneficial effects of the ERAS protocol have been demonstrated after pancreaticoduodenectomy in a number of studies [30-35] no unified protocol exists apart from general guidelines [18]. We hypothesised that our ERAS protocol improved adjuvant chemotherapy completion rates and thus overall survival (summarised in Table 1).

In our study, the pre-ERAS and ERAS chemotherapy completion rates were high (79%) in comparison to world standards (Table 2). The ESPAC-3 and CONKO-001 displayed completion rates of 68% and 62%, respectively [9,10,36]. Our high chemotherapy completion rates may reflect good case selection for pancreaticoduodenectomy. The pre-ERAS and ERAS groups displayed similar completion rates, despite ERAS patients being considerably more complicated as reflected in higher ASA scores, CCI scores and PD post-operative complications approaching statistical significance.

Numerous phase 3 clinical trials have demonstrated a clear relationship between completion of adjuvant chemotherapy and improved overall survival after pancreaticoduodenectomy. In 2013, the German CONKO-001 trial, demonstrated that among patients with macroscopic complete removal of pancreatic cancer, the use of adjuvant gemcitabine for 6 months compared with observation alone resulted in increased 5-year overall survival of 20.7% compared to 10.4%, respectively ($p=0.01$) [36]. The ESPAC-3 study showed that overall survival favoured patients who completed the full six courses of either gemcitabine or fluorouracil treatment versus those who did not ($p<0.001$) [9]. A Mayo Clinic clinical trial additionally showed overall survival was longer for recipients of adjuvant chemoradiotherapy versus surgery alone (OS 44.7 vs. 34.6%, $p<0.001$) [4].

Our study additionally displayed high initiation of chemotherapy rates, when compared to world standards. Pre-ERAS and ERAS initiation of chemotherapy rates were 82.6% and 84.6%, respectively (Figure 1). With the exception of a few centres of excellence with aggressive adjuvant chemotherapy initiation [37], in the majority of institutions, only 47-60 % of patients receive any adjuvant therapy after resection [15,38,39]. Reasons for this included advanced age, age-adjusted Charlson comorbidity index, side effects of chemotherapy and post-operative complications [13,14]. CD complications was the only independent variable that statistically influenced chemotherapy completion via logistic regression ($p=0.02$) (Table 4). Our findings are corroborated in a study by Labori et al which found major postoperative complications to negatively impact chemotherapy completion [14]. In that study, of patients with major postoperative complications (CD complication$\geq$3), only nine completed chemotherapy, with 32 not completing chemotherapy, and this was statistically significant. Major postoperative complications have been suggested to impair cellular immunity, increase the patient's predisposition to early cancer recurrence and reduced survival [40].

Interesting, Chi-square cross tabulation analysis found the ERAS protocol to influence CD post-operative complications and chemotherapy completion. The ERAS group had a higher proportion of CD minor and major complications completing chemotherapy compared to non-completion. This is opposite to the majority of studies, where high rates of post-operative complications correlate to lower initiation and completion of chemotherapy rates [13,40,41]. It could be deduced that ERAS significantly helps more complex patients with post-operative complications complete chemotherapy. The ERAS group has significantly lower cancer recurrence before 3 months, compared to the pre-ERAS group (Table 6). This may be due to improved patient selection as the ERAS protocol for pre-op evaluation has changed during this period involving routine use of PET scans and selective use of staging laparoscopy. However, greater than 3-month recurrence rates would be more meaningful results with data currently being collected. Implementation of the ERAS protocol showed a trend to improve 5-year survival, compared to pre-ERAS. Rates were approximately 56% and 36%, respectively between the two groups (Figure 2). This is considerably higher than 5-year survival world standards of 15-25% [24,25,36,42]. Interestingly, the presence of CD major complications has been shown to negatively influence long-term survival in PD patients [43,44]. Some studies have demonstrated the presence of a postoperative complication correlated with delays in time to initiate chemotherapy. It is possible that delayed recovery from surgery due to postoperative complications might influence whether a patient receives adjuvant therapy [41,45].

The need to identify and reduce PD patient risk of failing to initiate and complete chemotherapy is of paramount importance and thus the ERAS protocol continues to evolve and develop. While many studies focus on the short-term benefits of ERAS, more research is required to explore the potential long-term benefits of ERAS, such as chemotherapy completion rates. The ERAS protocol for PD patients is to a large extent unexplored. These findings support the continued development of ERAS in PD patients as an opportunity to standardise care, reduce morbidity and the potential to reduce health care burden.

The limitations of this study are related to its retrospective nature. Firstly, small sample size reduced statistical significance of our results. However, a tertiary centre completing five pancreaticoduodenectomies a year is considered to be a high output centre [46-49]. Secondly, incomplete data regarding adjuvant chemotherapy were omitted from our analysis. Thirdly, we were unable to control the adjuvant chemotherapy regimen including agents used, dose, route of delivery and duration between pre-ERAS and ERAS groups. Nevertheless, the optimal regimen of either gemcitabine or 5-FU based chemotherapy were most often used. Furthermore, our knowledge of best practice has changed over the years [10,36] and is currently still developing [12]. Additionally, we did not analyse the potential effects of neoadjuvant chemotherapy as well as radiotherapy on chemotherapy completion rates. Lastly, the ERAS protocol with closer consultant review may have increased the rate of detection, diagnosis and treatment of complications and thus lessen their impact.

Conclusion

This is the first study to our knowledge that has investigated the relationship between ERAS and chemotherapy completion rates. Our ERAS protocol has shown no deleterious effects on patient morbidity or mortality. Pre-ERAS and ERAS patients displayed similar chemotherapy completion rates of 79%, despite ERAS patients having higher ASA, CCI and CD postoperative scores. In the literature, higher postoperative complication rates correlate with lower chemotherapy completion and overall survival. In contrast, our study showed that high complication rates had higher chemotherapy completion rates, when the ERAS protocol was implemented. Overall, the ERAS protocol implemented at FSH hospital, is worth considering as a standardised protocol in future trials, with higher than world standard chemotherapy completion rates, despite significantly more complex patients.

References

1. Statistics ABS (2016) Australia's leading causes of death 2016.
2. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA: A Cancer Journal for Clinicians 63: 11-30.
3. Kamisawa TD, Wood LD, Itoi T, Takaori K (2016) Pancreatic cancer. Lancet, The 388: 73-85.
4. Hsu CC, Herman JM, Corsini MM, Winter JM, Callister MD, et al. (2010) Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Annals of surgical oncology 17: 981-990.
5. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Kondo N, et al. (2013) Early initiation of adjuvant chemotherapy improves survival of patients with pancreatic carcinoma after surgical resection. Cancer Chemotherapy and Pharmacology 71: 419-429.
6. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, et al. (2006) 1423 Pancreaticoduodenectomies for Pancreatic Cancer: A Single-Institution Experience. Journal of Gastrointestinal Surgery 10: 1199-211.
7. Katz MHGMD, Pisters PWTMDF, Evans DBMDF, Sun CCDMPH, Lee JEMDF, et al. (2008) Borderline Resectable Pancreatic Cancer: The Importance of This Emerging Stage of Disease. Journal of the American College of Surgeons 206: 833-846.
8. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, et al. (2004) A Randomized Trial of Chemoradiotherapy and Chemotherapy after Resection of Pancreatic Cancer. The New England Journal of Medicine 350: 1200-1210.
9. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, et al. (2010) Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid vs Gemcitabine Following Pancreatic Cancer Resection: A Randomized Controlled Trial. JAMA 304: 1073-1081.
10. Neoptolemos JPP, Palmer DHP, Ghaneh PP, Psarelli EEM, Valle JW, et al. (2017) Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet The 389: 1011-1024.
11. He J, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, et al. (2013) 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. HPB 16: 83-90.
12. Uesaka KMD, Boku ND, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. (2016) Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet, The 388: 248-257.
13. Labori KJ, Katz MH, Tzeng CW, Bjørnbeth BA, Cvancarova M, et al. (2016) Impact of early disease progression and surgical complications on adjuvant chemotherapy completion rates and survival in patients undergoing the surgery first approach for resectable pancreatic ductal adenocarcinoma - A population-based cohort study. Acta oncologica (Stockholm, Sweden) 55: 265-277.
14. Xia BT, Habib DA, Dhar VK, Levinsky NC, Kim Y, et al. (2016) Early Recurrence and Omission of Adjuvant Therapy after Pancreaticoduodenectomy Argue against a Surgery-First Approach. Annals of Surgical Oncology 23: 4156-4164.
15. Tzeng C-WD, Cao HST, Lee JE, Pisters PWT, Varadhachary GR, et al. (2014) Treatment Sequencing for Resectable Pancreatic Cancer: Influence of Early Metastases and Surgical Complications on Multimodality Therapy Completion and Survival. Journal of Gastrointestinal Surgery 18: 16-25.
16. Ricciardi R MGJG (2017) Enhanced Recovery After Colorectal Surgery 2017.

17. Ljungqvist O, Scott M, Fearon KC (2017) Enhanced Recovery After Surgery: A Review. JAMA surgery 152: 292-298.

18. Lassen K, Coolsen MME, Slim K, Carli F, de Aguilar-Nascimento JE, et al. (2012) Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clinical Nutrition 31: 817-830.

19. Koek S (2018) Implementation of Enhanced Recovery After Surgery (ERAS) in Pancreaticoduodenectomy. UWA Masters 2018.

20. Sankar A, Johnson SR, Beattie WS, Tait G, Wijeysundera DN (2014) Reliability of the American Society of Anesthesiologists physical status scale in clinical practice. British Journal of Anaesthesia 113: 424-432.

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases 40: 373.

22. Hamilton S AL (2010) Pathology and Genetics of Tumours of the Digestive System 2010.

23. (AJCC) AJCoC. TNM staging system 2013.

24. Kennedy EP, Rosato EL, Sauter PKRNA, Rosenberg LMBS, Doria CMD, et al. (2007) Initiation of a Critical Pathway for Pancreaticoduodenectomy at an Academic Institution-the First Step in Multidisciplinary Team Building. Journal of the American College of Surgeons 204: 917-923.

25. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, et al. (2000) Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. Journal of Gastrointestinal Surgery 4: 567-579.

26. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, et al. (2011) Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Archives of surgery 146: 571-577.

27. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O, et al. (2016) Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. World Journal of Surgery 40: 1741-1747.

28. Currie A, Burch J, Jenkins JT, Faiz O, Kennedy RH, et al. (2015) The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Annals of surgery 261: 1153-1159.

29. Gatt M, Khan S, MacFie J (2010) In response to: Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. Clin Nutr 29: 434-440.

30. Kennedy EP, Yeo CJ (2007) The case for routine use of adjuvant therapy in pancreatic cancer. Journal of Surgical Oncology 95: 597-603.

31. Wichmann MW, Roth M, Jauch KW, Bruns CJ (2006) A prospective clinical feasibility study for multimodal “fast track” rehabilitation in elective pancreatic cancer surgery. Rozhledy v chirurgii: mesicnik Ceskoslovenske chirurgicke spolecnosti 85: 169.

32. Berberat PO, Ingold H, Gulbinas A, Kleeff J, Müller MW, et al. (2007) Fast Track-Different Implications in Pancreatic Surgery. Journal of Gastrointestinal Surgery 11: 880-887.

33. Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, et al. (2008) Fast□track recovery programme after pancreatico□ duodenectomy reduces delayed gastric emptying. British Journal of Surgery 95: 1387-1393.

34. Montiel Casado MC, Pardo Sanchez F, Rotellar Sastre F, Marti Cruchaga P, Alvarez Cienfuegos FJ (2010) [Experience of a cephalic pancreatoduodenectomy fast-track program]. Cirugia espanola 87: 378-384.

35. di Sebastiano P, Festa L, De Bonis A, Ciuffreda A, Valvano MR, et al. (2011) A modified fast-track program for pancreatic surgery: a prospective single-center experience. Langenbeck’s Archives of Surgery. 396: 345-351.

36. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, et al. (2013) Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer: The CONKO-001 Randomized Trial. JAMA 310: 1473-1481.

37. Lewis R, Drebin JA, Callery MP, Fraker D, Kent TS, et al. (2013) A contemporary analysis of survival for resected pancreatic ductal adenocarcinoma. HPB 15: 49-60.

38. Ferrone CRMD, Pieretti-Vanmarcke RMD, Bloom JPMD, Zheng HP, Szymonifka JP, et al. (2012) Pancreatic ductal adenocarcinoma: Long-term survival does not equal cure. Surgery: Official Journal of the Society of University Surgeons, Central Surgical Association, and the American Association of Endocrine Surgeons 152: S43-S49.

39. Winter JM, Brennan MF, Tang LH, D’Angelica MI, DeMatteo RP, et al. (2012) Survival after Resection of Pancreatic Adenocarcinoma: Results from a Single Institution over Three Decades. Annals of Surgical Oncology 19: 169-175.

40. van der Gaag NA, Harmsen K, Eshuis WJ, Busch ORC, van Gulik TM, et al. (2013) Pancreatoduodenectomy associated complications influence cancer recurrence and time interval to death. European Journal of Surgical Oncology 40: 551-558.

41. Wu W, He J, Cameron JL, Makary M, Soares K, et al. (2014) The Impact of Postoperative Complications on the Administration of Adjuvant Therapy Following Pancreaticoduodenectomy for Adenocarcinoma. Annals of Surgical Oncology 21: 2873-2881.

42. Cameron JLMDF, He JMDP (2015) Two Thousand Consecutive Pancreaticoduodenectomies. Journal of the American College of Surgeons 220: 530-536.

43. Kamphues C, Bova R, Schricke D, Hippler-Benscheidt M, Klauschen F, et al. (2012) Postoperative Complications Deteriorate Long-Term Outcome in Pancreatic Cancer Patients. Annals of Surgical Oncology 19: 856-863.

44. Petermann D, Demartines N, Schäfer M (2013) Severe Postoperative Complications Adversely Affect Long-Term Survival After R1 Resection for Pancreatic Head Adenocarcinoma. World Journal of Surgery 37: 1901-1908.

45. Lima ISF, Yasui Y, Scarfe A, Winget M (2011) Association between receipt and timing of adjuvant chemotherapy and survival for patients with stage III colon cancer in Alberta, Canada. Cancer 117: 3833-3840.

46. Moesinger RC, Davis JW, Hill B, Johnston WC, Gray C, et al. (2011) Treatment of Pancreatic and Periampullary Cancers at a Community Hospital: Successful Application of Tertiary Care Treatment Standards. International Journal of Surgical Oncology 2011: 1-8.

47. Bilimoria KYMDMS, Talamonti MSMD, Sener SFMD, Bilimoria MMMD, Stewart AKMA, et al. (2008) Effect of Hospital Volume on Margin Status after Pancreaticoduodenectomy for Cancer. Journal of the American College of Surgeons 207: 510-519.

48. Reames BN, Ghaferi AA, Birkmeyer JD, Dimick JB (2014) Hospital volume and operative mortality in the modern era. Annals of surgery 260: 244-251.

49. Merrill AL, Jha AK, Dimick JB (2016) Clinical Effect of Surgical Volume. The New England journal of medicine 374: 1380-1382.