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Original Article

Adjuvant chemotherapy for adenocarcinoma arising from intraductal papillary mucinous neoplasia: multicentre ADENO-IPMN study

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Abstract

Background: The clinical impact of adjuvant chemotherapy after resection for adenocarcinoma arising from intraductal papillary mucinous neoplasia is unclear. The aim of this study was to identify factors related to receipt of adjuvant chemotherapy and its impact on recurrence and survival.

Methods: This was a multicentre retrospective study of patients undergoing pancreatic resection for adenocarcinoma arising from intraductal papillary mucinous neoplasia between January 2010 and December 2020 at 18 centres. Recurrence and survival outcomes for patients who did and did not receive adjuvant chemotherapy were compared using propensity score matching.

Results: Of 459 patients who underwent pancreatic resection, 275 (59.9%) received adjuvant chemotherapy (gemcitabine 51.3%, gemcitabine–capecitabine 21.8%, FOLFIRINOX 8.0%, other 18.9%). Median follow-up was 78 months. The overall recurrence rate was 45.5% and the median time to recurrence was 33 months. In univariable analysis in the matched cohort, adjuvant chemotherapy was not associated with reduced overall ($P = 0.713$), locoregional ($P = 0.283$) or systemic ($P = 0.592$) recurrence, disease-free survival ($P = 0.284$) or overall survival ($P = 0.455$). Adjuvant chemotherapy was not associated with reduced site-specific recurrence. In multivariable analysis, there was no association between adjuvant chemotherapy and overall recurrence (HR 0.89, 95% c.i. 0.57 to

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1.40), disease-free survival (HR 0.86, 0.59 to 1.30) or overall survival (HR 0.77, 0.50 to 1.20). Adjuvant chemotherapy was not associated with reduced recurrence in any high-risk subgroup (for example, lymph node-positive, higher AJCC stage, poor differentiation). No particular chemotherapy regimen resulted in superior outcomes.

Conclusion: Chemotherapy following resection of adenocarcinoma arising from intraductal papillary mucinous neoplasia does not appear to influence recurrence rates, recurrence patterns or survival.

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) arise from mucin-producing cells in the main pancreatic duct and/or its branches. Adenocarcinoma may complicate IPMNs in 20% of cases, but make up approximately 5% of all pancreatic adenocarcinomas[1]. Following resection of adenocarcinoma arising from IPMN, patients are at significant risk of recurrence, which is estimated to occur in 32–43% of patients. Hence, adjuvant chemotherapy has been proposed along the lines of multimodal treatment for pancreatic cancer[2–6].

In patients with pancreatic ductal adenocarcinoma (PDAC), not associated with an underlying IPMN, the standard of care is surgical resection and adjuvant chemotherapy. More recently, the PREOPANC-1[7] and Prep-02JSAP05[8] trials have demonstrated the benefit of a neoadjuvant treatment strategy in PDAC. Trials that demonstrated the benefit of adjuvant therapy in pancreatic cancer included patients with primary PDAC without associated IPMN. As such, the benefit of adjuvant therapy is unclear in patients with adenocarcinoma arising from IPMN[6,9–14]. In particular, the effect of adjuvant chemotherapy on recurrence, its impact on site-specific recurrence, and the outcomes of different adjuvant chemotherapy regimens are largely unknown[3–6].

The aim of this study was to investigate the impact of adjuvant chemotherapy on recurrence and survival, its effect on site-specific recurrence, and to compare different chemotherapy regimens in a large, international, multicentre cohort of patients undergoing pancreatic resection for adenocarcinoma arising from IPMN.

Methods

This was a retrospective multicentre study of consecutive patients undergoing pancreatic resection for adenocarcinoma arising from IPMN between January 2010 and December 2020 at 18 academic pancreatic cancer centres in Europe, Asia, Australia, and New Zealand. The methods used to gather data on these patients were published previously in a study investigating the impact of treatment of recurrence on survival[15]. The presence of adenocarcinoma arising from IPMN was identified retrospectively based on histopathological specimens. Patients with PDAC with concomitant IPMN elsewhere in the specimen were excluded. A primary investigator was appointed for each centre and was responsible for leading data collection. The Research Electronic Data Capture (REDCap) system was used to store anonymized information (anonymized at the source), which was then maintained by Newcastle Joint Research Office. The institutional review board of each participating institution approved the study before initiation. The study was conducted according to the Declaration of Helsinki. Informed patient consent was not required given the retrospective nature of the study. STROBE recommendations were followed[16].

Data collection, outcomes and definitions

Adenocarcinoma arising from IPMN was defined as an invasive carcinoma derived from IPMN, in accordance with the WHO classification[17]. The type of adenocarcinoma was classified as either tubular or colloid, and the invasive component of the IPMN tumours were staged according to the TNM Classification of Malignant Tumours, 8th edition, published by the AJCC. Determination of R status was based on a cut-off distance from the tumour to the resection margin of less than 1 mm[18]. Where the underlying precursor epithelial lesion or subtype was not documented in the original reporting, the pathology slides were reviewed again by a pathologist with expertise in pancreatic cancer.

Duct type was classified as main duct type, branch duct type, or mixed type, according to consensus guidelines[19]. The type of surgical procedure and decision to administer adjuvant chemotherapy were at the discretion of each participating institution based on the location, degree, and extent of the tumour. The type and number of cycles of adjuvant chemotherapy were recorded.

In patients with resectable pancreatic cancer, upfront resection was performed and adjuvant chemotherapy was considered[19]. Patients underwent either Whipple's resection, pylorus-preserving pancreatoduodenectomy, distal pancreatectomy with splenectomy, distal pancreatectomy without splenectomy, or total pancreatectomy. In patients with borderline-resectable tumours portal or superior mesenteric vein resection was undertaken if infiltration was suspected.

Recurrence was diagnosed radiologically or histologically when available. Given the lack of current guidelines, follow-up was at the discretion of each centre. Overall recurrence was categorized as locoregional or systemic, and recurrence sites were reported. The overall rate and median time of overall (OS) and disease-free (DFS) survival were determined for the entire cohort. DFS was defined as survival in the absence of recurrence.

Statistical analysis

Clinicopathological variables associated with recurrence were identified using Kaplan–Meier (KM) analysis and the log rank test. In all statistical tests, $P < 0.050$ was considered significant.

The type of adjuvant chemotherapy used was compared between the pre-2017 and 2017-onwards groups using Pearson's χ^2 test to determine whether there had been a change in practice since the ESPAC-4 trial[14]. The administration rate of adjuvant chemotherapy between centres was compared using Pearson's χ^2 test. Clinicopathological variables associated with adjuvant chemotherapy use were identified by univariable analysis. Variables demonstrating statistical significance with a cut-off of $P < 0.100$ were included in a multivariable logistic regression model, with adjuvant chemotherapy as the dependent variable.

To allow for immortal time bias relating to administration of adjuvant chemotherapy, landmark analysis was performed at 6 months, whereby all patients who died before this time point were excluded. Postlandmark analysis propensity score matching (PSM) was performed to determine the impact of adjuvant chemotherapy on outcome; treatment (adjuvant chemotherapy) and control (no adjuvant chemotherapy) groups were matched for clinicopathological variables to decrease the effects of confounding. Propensity scores were calculated using

Table 1 Clinicopathological features of the overall cohort and predictors of recurrence

	Recurrence ($n = 209$)	No recurrence ($n = 250$)	P^*
Age (years), median (range)	70 (27–87)	70 (36–92)	0.653†
Sex			0.533
Male	110 (52.6)	140 (56.0)	
Female	99 (47.4)	110 (44.0)	
Charlson Co-morbidity Index score, median (range)	4 (0–9)	4 (0–9)	0.453†
Borderline resectable	15 (3.3)	6 (2.4)	0.651
Operation			0.190
Whipple's	78 (19.1)	94 (37.6)	
PPPD	45 (21.5)	45 (18.0)	
DPS	38 (9.3)	34 (13.6)	
DPNS	12 (2.9)	18 (7.2)	
TP	36 (8.8)	59 (23.6)	
Multivisceral resection	38 (9.3)	31 (12.4)	0.001
Duct location			0.006
Main duct	114 (27.9)	152 (60.8)	
Side	33 (8.1)	30 (12.0)	
Mixed	43 (10.5)	56 (22.4)	
Tumour location			0.390
Head	138 (33.7)	154 (61.6)	
Body	21 (5.1)	31 (12.4)	
Tail	32 (7.8)	37 (14.8)	
Tumour size (mm), median (i.q.r.)	28 (20–35)	20 (10–30)	< 0.001†
Cyst size (mm), median (i.q.r.)	30 (24–45)	33 (20–47.5)	0.817†
Precursor epithelium			0.256
Gastric	42 (10.3)	44 (17.6)	
Intestinal	35 (8.6)	62 (24.8)	
Pancreatobiliary	70 (17.1)	75 (30.0)	
IOPN	9 (4.3)	11 (4.2)	
Differentiation grade			< 0.001
Well	24 (11.5)	58 (23.2)	
Moderately	102 (48.8)	129 (51.6)	
Poor	76 (36.4)	42 (16.8)	
Invasive component			< 0.001
Ductal	170 (81.3)	173 (69.2)	
Colloid	19 (9.1)	50 (20.0)	
Lymphovascular invasion	129 (61.7)	107 (42.8)	< 0.001
Perineural invasion	143 (68.4)	113 (45.2)	< 0.001
R1 resection	102 (48.8)	75 (30.0)	< 0.001
Adjuvant chemotherapy	143 (68.4)	132 (52.8)	< 0.001
AJCC stage			< 0.001
Ia	16 (7.7)	75 (30.0)	
Ib	13 (6.2)	39 (15.6)	
IIa	29 (13.9)	40 (16.0)	
IIb	125 (59.8)	75 (30.0)	
III	26 (12.4)	21 (8.4)	

Values are *n* (%) unless otherwise indicated. PPPD, pylorus-preserving pancreaticoduodenectomy; DPS, distal pancreatectomy with splenectomy; DPNS, distal pancreatectomy without splenectomy; TP, total pancreatectomy; IOPN, intraductal oncocytic papillary neoplasm. *log rank test. †Continuous data split by median and recurrence rates compared using log rank test.

probit regression and patients in the treatment group were matched 1 : 1 using nearest-neighbour matching with patients in the control group. Groups were matched for age, sex, Charlson Co-morbidity Index score (split by median), differentiation, perineural invasion, lymphovascular invasion, AJCC stage, and R status. The caliper was used to impose a maximum distance in propensity scores between possible matches and was set to 0.05. Variable balancing was assessed using a standardized mean difference (SMD; less than 0.1 considered balanced) and the distance variance ratio (value close to 1.0 considered balanced). Matching without replacement was used to optimise precision, taken that matching was satisfactory. Jitter and Love plots were used to show the distribution of propensity scores and SMD respectively of unmatched and matched cohorts. KM curves were plotted for the treatment and control groups for each outcome (recurrence and OS) and the log rank test was used to compare groups. In the matched cohort, Cox proportional hazards models were developed to identify the effect of adjuvant chemotherapy on outcome. PSM was performed using the MatchIt package and graphs were displayed using the Cobalt package in R Studio 2022.02.1®. The PSM analysis was repeated in patients who received more contemporary chemotherapy regimens, specifically gemcitabine–capecitabine (GEM-CAP) or folinic acid, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX). The overall cohort was investigated to determine whether any particular high-risk subgroup (for example, poor differentiation, higher AJCC stage) would benefit from the administration of adjuvant chemotherapy. Treatment and control groups were compared using KM analysis and the log rank test.

Results

Study population

Of 459 patients who underwent pancreatic resection 275 (59.9%) received adjuvant chemotherapy. Chemotherapy regimens included gemcitabine (141, 51.3%), GEM-CAP (60, 21.8%), FOLFIRINOX (22, 8.0%), and other (52, 18.9%). Before 2017, 149 of

Table 2 Clinicopathological factors associated with adjuvant chemotherapy

	Adjuvant chemotherapy (*n* = 275)	No adjuvant chemotherapy (*n* = 184)	Univariable *P*	OR in multivariable analysis*
Age (years), median (i.q.r.)	70 (11.0)	71 (12.5)	0.546	
Male sex	152 (55.3)	98 (53.3)	0.671	
Median Charlson Co-morbidity score	4	4	0.324	
Borderline resectable	15 (5.5)	6 (3.3)	0.270	
Operation			0.167	
Whipple's	103 (37.5)	69 (37.5)		
PPPD	63 (22.9)	27 (14.7)		
DPS	39 (14.2)	33 (17.9)		
DPNS	20 (7.3)	10 (5.4)		
TP	50 (18.2)	45 (24.5)		
Multivisceral resection	41 (14.9)	28 (15.2)	0.928	
Duct location			0.785	
Main duct	161 (58.5)	105 (57.1)		
Side	36 (13.1)	27 (14.7)		
Mixed	62 (22.5)	37 (20.1)		
Tumour location			0.274	
Head	186 (67.6)	106 (57.6)		
Body	28 (10.2)	24 (13.0)		
Tail	39 (14.2)	30 (16.3)		
Tumour size (mm), median (i.q.r.)	23 (18)	22.5 (20)	0.565	
Cyst size (mm), median (i.q.r.)	30 (23.5)	35 (22.8)	0.035	0.94 (0.85, 1.04)
Precursor epithelium			0.706	
Gastric	51 (18.5)	35 (19.0)		
Intestinal	55 (20.0)	42 (22.8)		
Pancreatobiliary	90 (32.7)	55 (29.9)		
Differentiation			0.019	
Well	42 (15.3)	40 (21.7)		1.00 (reference)
Moderately	137 (49.8)	94 (51.1)		1.11 (0.98, 1.25)
Poor	83 (30.2)	35 (19.0)		1.70 (1.07, 2.69)
Invasive component			0.047	
Ductal	213 (77.5)	130 (70.7)		1.00 (reference)
Colloid	34 (12.4)	35 (19.0)		0.93 (0.80, 1.08)
Lymphovascular invasion	151 (54.9)	85 (46.2)	0.067	1.03 (0.91, 1.17)
Perineural invasion	166 (60.4)	90 (48.9)	< 0.001	1.07 (0.96, 1.19)
R1 resection	112 (40.7)	65 (35.3)	0.244	
N1 or N2	150 (54.5)	67 (36.4)	< 0.001	1.15 (0.96, 1.38)
AJCC stage			0.008	
Ia	44 (16.0)	47 (25.5)		1.00 (reference)
Ib	27 (9.8)	25 (13.6)		1.10 (0.91, 1.33)
IIa	37 (13.5)	32 (17.4)		1.06 (0.89, 1.26)
IIb	134 (48.7)	66 (35.9)		1.10 (0.88, 1.37)
III	33 (12.0)	14 (7.6)		1.18 (0.92, 1.51)
Complication CD II	83 (30.2)	46 (25.0)	0.226	
Complication CD ≥ III	27 (9.8)	43 (23.4)	< 0.001	1.02 (0.90, 1.15)

Values are *n* (%) unless otherwise indicated; *values in parentheses are 95% confidence intervals. PPPD, pylorus-preserving pancreaticoduodenectomy; DPS, distal pancreatectomy with splenectomy; DPNS, distal pancreatectomy without splenectomy; TP, total pancreatectomy; CD, Clavien–Dindo.

268 patients (55.6%) received adjuvant chemotherapy, and the most common regimen was gemcitabine (108, 72.5%) followed by GEM-CAP (13, 8.7%). From 2017, 126 of 191 patients (66.0%) received chemotherapy, and the most common regimens were GEM-CAP (47, 37.3%) followed by gemcitabine (33, 26.2%) and FOLFIRINOX (18, 14.3%). The proportion of patients receiving GEM-CAP and FOLFIRINOX increased in the cohort from 2017 onwards ($P < 0.001$). Gemcitabine was used less frequently compared with before 2017 ($P < 0.001$). The median number of chemotherapy cycles was 6 (i.q.r. 4–6). The proportion of patients who received adjuvant chemotherapy did not differ among the 18 pancreatic centres (*Table S1*).

Ten patients (2.2%) received adjuvant radiotherapy, nine of whom also received chemotherapy. Seventeen patients (3.7%) also received neoadjuvant chemotherapy with a median of 3 cycles. Of these, 13 also received adjuvant chemotherapy. The most common neoadjuvant chemotherapy regimen was FOLFIRINOX in eight patients. Only 1 of these 17 patients had a borderline resectable tumour.

Recurrence and survival

After a median follow-up of 78 months, the overall recurrence rate was 45.5% (209 of 459). Median time to recurrence was 33 months. Eighty-three patients (18.1%) developed locoregional recurrence after a median follow up of 34 months, including 39 (47.0%) who also developed systemic recurrence. Of these 83 patients, 51 (61.4%) had peripancreatic recurrence and 31 (37.3%) had lymph node recurrence. Some 164 patients (35.7%) developed systemic recurrence after a median follow up of 31 months. Sites of systemic recurrence were liver (66 of 164, 40.2%), lung (58 of 164, 35.4%), peritoneum (48 of 164, 29.3%), and other sites (33 of 164, 20.1%). Recurrence was proven histologically in 40 patients (19.1%). The diagnosis in the other patients was based on imaging. Clinicopathological features of the overall cohort and prognostic factors for recurrence are reported in *Table 1*.

Single-site recurrence occurred locoregionally in 44 patients (9.6%), in the liver in 38 (8.3%), lung in 30 (6.5%), peritoneum in 18 (3.9%), and at other sites in 15 (3.3%). Multisite recurrence occurred in 64 patients (13.9%).

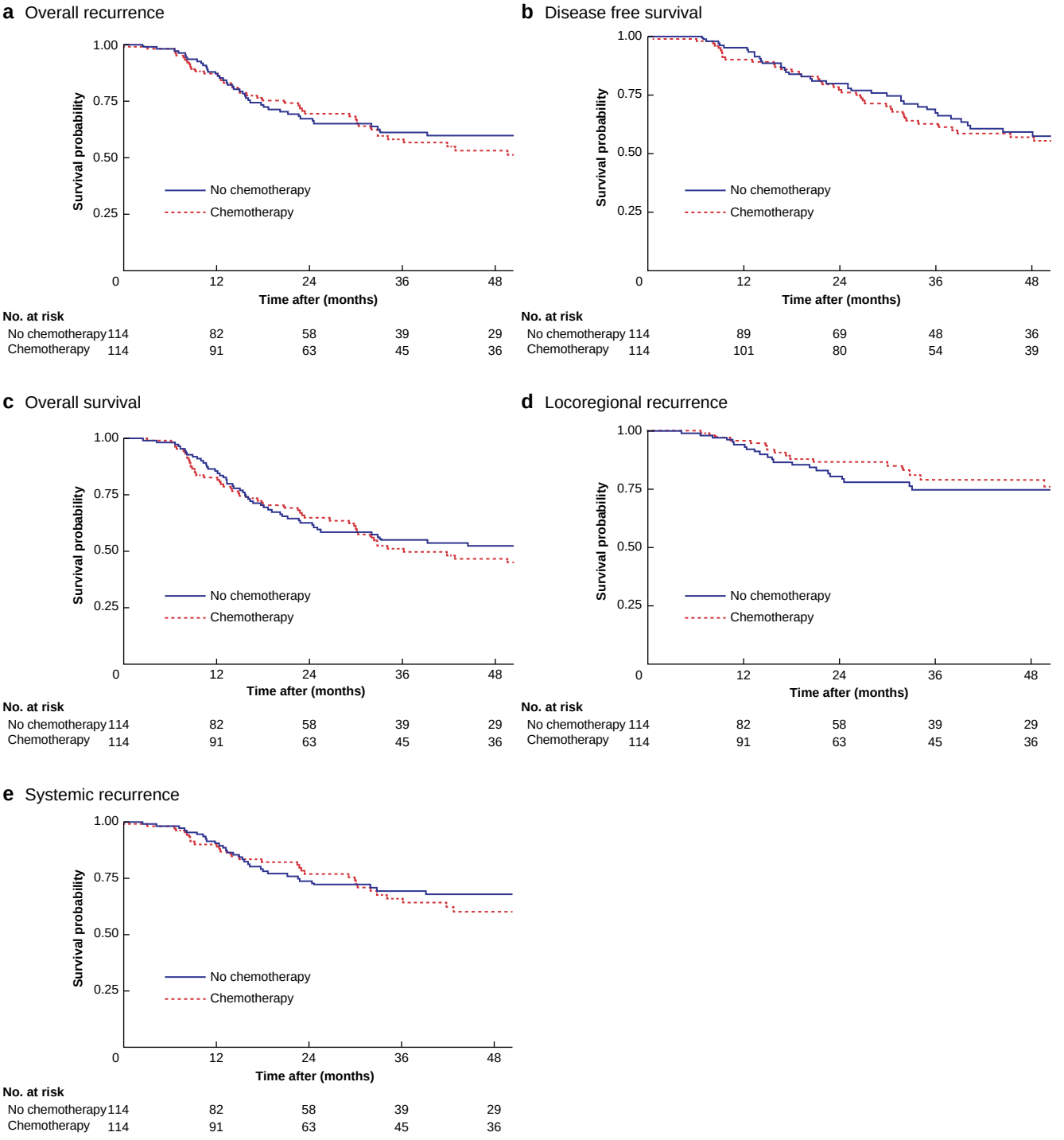

Fig. 1 Kaplan–Meier survival curves for patients who did or did not receive adjuvant chemotherapy in the matched cohorts

a Overall recurrence, **b** disease-free survival, **c** overall survival, **d** locoregional recurrence, and **e** systemic recurrence since resection: **a** $P = 0.713$, **b** $P = 0.284$, **c** $P = 0.455$, **d** $P = 0.283$, **e** $P = 0.592$ (log rank test).

Median OS for the entire cohort was 39 months, and median DFS was 23 months.

Factors associated with receipt of adjuvant chemotherapy

In univariable analysis, poor differentiation, larger cyst size, ductal invasive component, lymph node positivity, perineural invasion, and higher AJCC stage were positively associated with receipt of adjuvant chemotherapy (*Table 2*). Conversely, colloid invasive component and complication with a Clavien–Dindo grade of III or higher were negatively associated with adjuvant chemotherapy receipt. In multivariable analysis, only poor differentiation (OR 1.70; $P = 0.023$) was positively associated with the use of adjuvant chemotherapy (*Table 2*).

Impact of adjuvant chemotherapy on recurrence and survival

Thirty-one patients (6.8%) died in the first 6 months and were excluded from the landmark analysis. In the unmatched cohorts, 139 of 270 patients who received adjuvant

Table 3 Association between adjuvant chemotherapy and recurrence in high-risk subgroups

	Recurrence rate		P*
	Adjuvant chemotherapy	No adjuvant chemotherapy	
Poor differentiation	53 of 80 (66)	15 of 23 (65)	0.977
Lymphovascular invasion	83 of 146 (58.7)	34 of 63 (53)	0.622
Perineural invasion	96 of 162 (59.3)	36 of 68 (51)	0.673
R1	69 of 108 (63.9)	24 of 46 (52)	0.821
N1 or N2	101 of 149 (67.8)	27 of 49 (55)	0.790
AJCC stage			
Ia	11 of 43 (26)	4 of 47 (8)	0.036†
Ib	7 of 27 (26)	6 of 25 (24)	0.890
IIa	15 of 37 (41)	14 of 32 (42)	0.189
IIb	86 of 132 (65.2)	30 of 50 (60)	0.421
III	20 of 32 (63)	4 of 9 (44)	0.700

Values are *n* (%). *log rank test. †indicates higher rate of recurrence in adjuvant chemotherapy group.

chemotherapy (51.5%) developed recurrence compared with 58 of 158 (36.7%) who did not receive adjuvant chemotherapy. Among those receiving adjuvant chemotherapy, the 1-, 2-, and 5-year recurrence rates were 20.9% (56 of 268), 42.4% (111 of 262), and 50.3% (86 of 171) respectively. In the group without adjuvant chemotherapy, the rates were 16.5% (26 of 158), 29.1% (44 of 151), and 40.5% (45 of 111).

Before matching, the OS rate was 52.6% (142 of 270) in the adjuvant chemotherapy group compared with 53.8% (85 of 158) in the group without adjuvant chemotherapy. In the adjuvant chemotherapy group, 1-, 2-, and 5-year survival rates were 92.5% (248 of 268), 72.1% (189 of 262), and 51.5% (88 of 171) respectively. In the group without adjuvant chemotherapy the corresponding rates were 87.3% (138 of 158), 74.2% (112 of 151), and 50.5% (56 of 111).

In the adjuvant chemotherapy group, the DFS rate was 41.5% (112 of 270) compared with 50.0% (79 of 158) in the group without adjuvant chemotherapy. In the adjuvant chemotherapy group, 1-, 2-, and 5-year DFS rates were 77.6% (208 of 268), 53.8% (141 of 262), and 42.7% (73 of 171) respectively. Corresponding DFS rates in the group without adjuvant chemotherapy were 78.5% (124 of 158), 63.6% (96 of 151), and 44.1% (49 of 111).

Propensity score-matched analysis

In the PSM postlandmark analysis, 114 patients in the adjuvant chemotherapy group were matched with 114 in the group without adjuvant chemotherapy (*Table S2*). For all co-variables in the matched cohort, the SMD between treatment and control groups was less than 0.10. The variance ratio of the distance between propensity scores in the matched cohort was 1.01, demonstrating balanced co-variates. *Figure S1* illustrates the co-variate balance and *Fig. S2* the distribution of propensity scores in the unmatched and matched cohorts.

Univariable analysis in the matched cohort revealed that adjuvant chemotherapy was not associated with overall recurrence (*Fig. 1a*), DFS (*Fig. 1b*), OS (*Fig. 1c*), locoregional recurrence (*Fig. 1d*) or systemic recurrence (*Fig. 1e*). Adjuvant chemotherapy was not associated with reduced site-specific recurrence (liver $P = 0.275$; lung $P = 0.533$; peritoneum $P = 0.524$; other sites $P = 0.893$).

In the multivariable analysis of the matched cohort, adjuvant chemotherapy was not independently associated with reduced overall recurrence (HR 0.89, 95% c.i. 0.57 to1.40; $P = 0.584$) (*Fig. S3*), DFS (HR 0.86, 0.59 to 1.30; $P = 0.456$) (*Fig. S4*) or OS (HR 0.77, 0.50 to 1.20; $P = 0.236$) (*Fig. S5*). In the multivariable analysis, older age (age 60–70 years: HR 4.63, $P = 0.005$; age 71–80 years: HR 4.47, $P = 0.010$; age over 80 years: HR 5.71; $P = 0.007$); higher AJCC stage (IIb: HR 2.74; $P = 0.008$), and poor differentiation (HR 2.64; $P = 0.008$) were positively associated with overall recurrence.

Subgroup analyses

Table 3 shows the results of the subgroup analysis undertaken to determine whether any particular high-risk group defined by certain characteristics (for example N1–N2 status or AJCC stage) would benefit from adjuvant chemotherapy. In none of these groups were the recurrence rate lower among patients who received adjuvant chemotherapy compared with those who did not.

Type of adjuvant chemotherapy

The recurrence rate was 56.5% (median time to recurrence 32 months) for patients who received gemcitabine, 53.4% for those treated with GEM-CAP (median time to recurrence 23 months), and 54.5% in the FOLFIRINOX group (median time to recurrence 19 months). No particular adjuvant chemotherapy regimen (gemcitabine *versus* GEM-CAP *versus* FOLFIRINOX) was associated with a lower recurrence rate, superior DFS or superior OS (*Fig. 2*).

A separate PSM analysis was carried out for patients who received more contemporary chemotherapy regimens, specifically GEM-CAP or FOLFIRINOX. Fifty-five treated patients (42 GEM-CAP, 13 FOLFIRINOX) were matched with 55 controls (*Table S3*). In this matched cohort, adjuvant chemotherapy was not associated with reduced overall ($P = 0.752$), locoregional ($P = 0.346$), or systemic ($P = 0.694$) recurrence, or improved DFS ($P = 0.863$) or OS ($P = 0.823$) (log rank test).

Discussion

In this study, adjuvant chemotherapy did not influence recurrence rates, recurrence patterns or survival in patients with adenocarcinoma arising from IPMN. Among patients who received adjuvant chemotherapy, no particular regimen conferred superior outcomes.

Pancreatic resection followed by adjuvant chemotherapy for PDAC is considered the standard of care, with proven survival benefit in RCTs. Currently, a similar adjuvant treatment strategy is generally considered for patients with adenocarcinoma arising from IPMN, despite a lack of high-level evidence. The data that support adjuvant chemotherapy for adenocarcinoma arising from IPMN are extrapolated from smaller series or multi-institutional databases[20–24]. Two large institutional data sets published in the past few years have shown a survival benefit in patients with positive lymph node metastasis but not in patients with node-negative disease[20,23]. A recent systematic review[6] including 11 studies and comprising of 3393 patients showed that adjuvant chemotherapy was associated with improved OS in patients with node-positive adenocarcinomas arising from IPMN. Improved OS after adjuvant chemotherapy was also demonstrated in patients with stage III–IV disease, tumour size over 2 cm, node-positive status, grade 3 tumour differentiation, positive margin status, tubular carcinoma subtype, and presence of perineural or lymphovascular invasion. These findings were, however, limited by marked heterogeneity, lack of a consistent TNM staging system, and lack of data on chemotherapy regimens that prevented quantitative analysis.

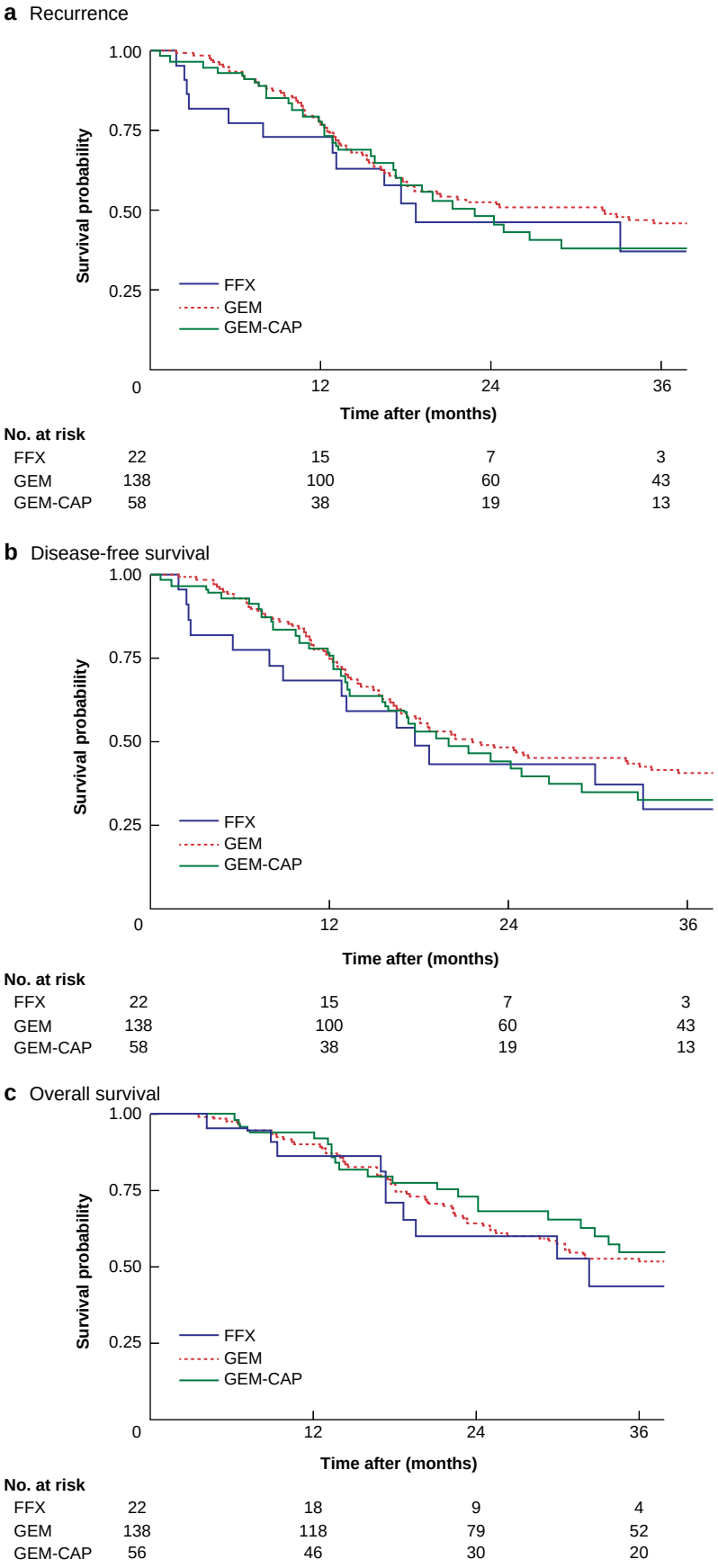

Fig. 2 Recurrence, disease-free survival, and overall survival according to type of chemotherapy

a Recurrence **b** disease-free survival, and **c** overall survival. FFX, FOLFIRINOX; GEM, gemcitabine; GEM-CAP, gemcitabine + capecitabine. **a** $P = 0.623$, **b** $P = 0.491$, **c** $P = 0.634$ (log rank test).

In the present study, the recurrence rates were higher in the adjuvant chemotherapy group than in the group without chemotherapy. This was likely related to the preponderance of adjuvant chemotherapy administration among those with adverse tumour factors such as poor differentiation, lymph node positivity, perineural invasion, and higher AJCC stage. After adjusting for confounding variables, there was no reduction in recurrence rate or survival benefit with adjuvant chemotherapy. In further analysis, there was no demonstrated benefit specifically in high-risk groups. Moreover, the type of adjuvant chemotherapy regimen did not affect the risk of recurrence, patterns of recurrence, both locoregional and systemic recurrence, or survival. These findings call into question the benefit of PDAC-derived adjuvant chemotherapy regimens for adenocarcinoma arising from IPMN, even in high-risk groups.

The results of the survival analysis were similar to those of a recent study from Heidelberg, among others[12,23]. Kaiser *et al.*[12] reported a trend towards better median OS and 5-year survival in patients not receiving chemotherapy with AJCC stage I–IIA disease, and comparable survival with and without chemotherapy in AJCC stage IIB–IV disease.

Since the ESPAC-4 trial[14], adjuvant GEM-CAP has been used routinely in the adjuvant setting and, more recently, FOLFIRINOX[25]. Interestingly, the ESPAC-4 trial[14] did not specifically include patients with adenocarcinoma arising from IPMN, similar to the more recent ESPAC-5F trial[26], which explored the benefits of neoadjuvant treatment in pancreatic adenocarcinoma. In the present study, the rates of GEM-CAP and FOLFIRINOX use increased significantly from 2017 (year of ESPAC-4 trial), with a concomitant reduction in the use of GEM. No particular regimen offered lower rates of recurrence or survival benefit, but it must be noted that the number of patients receiving FOLFIRINOX as monotherapy was small. There is currently no convincing guidance on the type of adjuvant chemotherapy to be used in this group and perhaps this is reflected in the rate of adjuvant chemotherapy across the cohort. The Fukuoka consensus statement[27] and the American College of Gastroenterology clinical guidelines[28] both make no recommendations on the role of adjuvant chemotherapy, and the recent European guidelines[29] recommend adjuvant chemotherapy for adenocarcinoma arising from IPMN with or without nodal disease in the absence of high-level evidence.

There are differences in tumour biology between adenocarcinoma arising from IPMN and PDAC which could explain the difference in response to adjuvant chemotherapy[30]. Kato *et al.*[31] performed organoid analyses and identified a distinct set of genetic mutations in adenocarcinoma arising from IPMN compared with PDAC. As well as differing chromatin profiles, they also found the MNX1–HNF1B axis to be critical in regulation of genes in IPMN lineages, unlike PDAC. Gentiluomo *et al.*[32] aimed to investigate whether the PDAC susceptibility polymorphisms would also be responsible for the progression to malignancy in IPMNs. In a sample of 345 patients, there was no commonality between 30 susceptibility polymorphisms, only a non-genetic link likely mediated by chronic inflammation through common risk factors (such as smoking and obesity)[33]. These inherent differences help explain the relatively indolent behaviour of adenocarcinoma arising from IPMN, reflected in higher survival rates and later recurrence after surgery[15,34]. These biological differences could explain why adjuvant chemotherapy may not confer any benefit in terms of recurrence or survival[19,20,35–38].

Limitations of the present study include the retrospective nature of the study. This introduced selection bias for consideration of adjuvant chemotherapy. Some clinicopathological features may not have been accounted for in the PSM analysis. A significant proportion of patients received mono-gemcitabine therapy, a now outdated adjuvant chemotherapy regimen. Only a small proportion of patients received FOLFIRINOX, so few conclusions can be drawn regarding the potential effect of adjuvant FOLFIRINOX in these patients.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Data will be available upon reasonable request.

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