



Clinical trial results:

ESPAC-5F: European Study Group for Pancreatic Cancer - Trial 5F
Four arm, prospective, multicentre, randomised feasibility trial of
immediate surgery compared with neoadjuvant chemotherapies and
neoadjuvant chemoradiotherapy.

Summary

EudraCT number	2013-003932-56
Trial protocol	GB DE IE FI
Global end of trial date	03 February 2021

Results information

Result version number	v1 (current)
This version publication date	12 February 2022
First version publication date	12 February 2022

Trial information

Trial identification

Sponsor protocol code	UoL000726
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Additional study identifiers

ISRCTN number	ISRCTN89500674
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	1-3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
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Scientific contact	Professor Paula Ghaneh, University of Liverpool, +44 1517064062, paula@liverpool.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2019
Global end of trial reached?	Yes
Global end of trial date	03 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Recruitment Rate: Is it feasible to recruit and randomise patients with borderline resectable pancreatic cancer to receive immediate surgical exploration versus neoadjuvant chemotherapies or chemoradiotherapy?
2. Resection Rate: Resection rate will be measured using the total number of patients in the arm as baseline and, secondly, using the number of patients having explorative surgery. R0 (resection margins free of tumour) and R1 (Tumour within 1 mm of resection margin) resection margins will be included in the resection rate but not R2 resection (tumour present at resection margin).

Protection of trial subjects:

Surgery

Immediate surgery is standard practice and the risks to the patient are as expected for that treatment. Mortality rate is < 5% in specialist centres. The overall complication rate even in specialist centres is 18-54%. Reviews of large series of pancreatic resections shows an incidence of common complications of 10.4% for fistula, 9.9% for delayed gastric emptying, 4.8% for bleeding, 4.8% for wound infection and 3.8% for intra-abdominal abscess. The median hospital stay is 13-18 days in different series. The re-operation rate varies from 4 to 9% with a mortality rate of 23 to 67%. Major complications are a significant factor in post-operative mortality, especially if they require re-operation. The use of octreotide or somatostatin to prevent complications is supported by several multicentre, double-blind, randomized controlled trials. The best way to improve outcome is to concentrate pancreatic cancer care in regional specialist centre as was implemented in this trial.

Gemcitabine and Capecitabine and Folinic acid, 5-Fluorouracil, Oxaliplatin and Irinotecan

The planned chemotherapy used in the study has a well described toxicity profile when used within the terms of its marketing authorisation and administered in experienced tertiary care centres

Radiotherapy

The risks of upper abdominal radiotherapy are significant because of the proximity of gross tumour volume (GTV) to several critical structures. The optimum balance between efficacy and toxicity will be achieved by employing strict protocol defined target definition and strict CRT QA and will be carefully documented.

Background therapy:

Arm A: Immediate surgery: Patients will undergo a pylorus preserving or classical Kausch Whipple resection with standard lymphadenectomy. Total pancreatectomy will be accepted if clinically indicated.

Surgery alone with no neoadjuvant chemotherapy or chemoradiotherapy was the established standard of care in the UK for this group of patients at the point of study commencement.

Evidence for comparator:

At the point of designing this study there was no clear evidence to indicate if either neoadjuvant chemotherapy (CT) or chemoradiotherapy (CRT) is superior. At this stage a randomized neoadjuvant trial should include both CT and CRT arms to evaluate the relative merits/demerits of either modality. The proposed CT and CRT arms have demonstrated the best survival and response rates in Phase III trials +/- meta-analyses.

Arm B: Gemcitabine plus capecitabine (GEMCAP): GEMCAP versus gemcitabine demonstrated significantly improved objective response rate (19.1% v 12.4%; P = .034) and progression-free survival (hazard ratio [HR], 0.78; 95% CI, 0.66 to 0.93; P = .004) in patients with advanced pancreatic cancer.

Meta-analysis of two additional studies involving 935 patients showed a significant survival benefit in favour of GEM-CAP (HR, 0.86; 95% CI, 0.75 to 0.98; P = .02) versus gemcitabine. Neoadjuvant GEMCAP has been used in forty-three patients (18 with BR disease and 25 with LA disease). The radiologic response rate was 18.6%, median overall survival was 23.1 months in patients who underwent surgery and 13.2 months in patients unable to complete surgery (P = .017).

Arm C: Oxaliplatin, irinotecan, fluorouracil, and Folinic acid (FOLFIRINOX): A Phase III trial of patients with metastatic pancreatic cancer comparing FOLFIRINOX with gemcitabine; demonstrated median overall survival of 11.1 months with FOLFIRINOX versus 6.8 months with gemcitabine (HR, 0.57; 95% [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 6.4 months with FOLFIRINOX versus 3.3 months with gemcitabine (HR, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate was 31.6% with FOLFIRINOX versus 9.4% with gemcitabine (P<0.001) [29]. The majority of patients in this trial had body and tail tumours and good performance status.

Arm D: Capecitabine based chemoradiotherapy (CRT): Chemoradiotherapy [CRT] has been the commonest modality tested in neoadjuvant therapy to date.

Actual start date of recruitment	01 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	44
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The aim was to recruit 100 patients in a ratio of 2:1:1:1 between surgery and the three neoadjuvant interventions. The minimum acceptable sample size was 75, 30 for Arm A, 15 for Arms B, C and D. The minimum acceptable sample size was achieved, with 90 patients randomised in the ratio 33:20:20:17.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	542 ^[1]
Intermediate milestone: Number of subjects	Central Review: 158
Number of subjects completed	90

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Patients deemed unsuitable at screening: 384
Reason: Number of subjects	Patients unsuitable at central review: 68

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The majority of patients presenting with pancreatic cancer are not suitable for surgery (~80%), thus while 542 patients were screened, only 90 were deemed to be suitable. Of those 90, 86 started treatment.

Period 1

Period 1 title	Treatment Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Immediate Surgery

Arm description:

Patients will undergo a pylorus preserving or classical Kausch Whipple resection with standard lymphadenectomy. Total pancreatectomy will be accepted if clinically indicated.

Surgery alone with no neoadjuvant chemotherapy or chemoradiotherapy was the established standard of care in the UK for this group of patients at the point of study commencement.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	GEMCAP

Arm description:

Within two weeks of randomisation, eligible patients will commence neoadjuvant gemcitabine, 1000mg/m² iv infusion over 30 minutes, days 1, 8 and 15 of a 28 day cycle and capecitabine 830mg/m² BD PO for 21 out of 28 days (one cycle) for 2 cycles i.e. 8 weeks. Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)

Arm type	Experimental
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Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	SUB02324MIG
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
1000mg/m ² iv infusion over 30 minutes, days 1, 8 and 15 of a 28 day cycle for 2 cycles, i.e. 8 weeks.	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	SUB12474MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
capecitabine 830mg/m ² BD orally for 21 out of 28 day (one cycle) for 2 cycles, i.e. 8 weeks	
Arm title	FOLFIRINOX
Arm description:	
Within two weeks of randomisation, eligible patients will commence neoadjuvant oxaliplatin 85mg/m ² , irinotecan 180mg/m ² , folinic acid given according to local practice for both the drug and the dose, 5-FU 400mg/m ² bolus injection followed by 2400mg/m ² 46 hour infusion, repeated every 2 weeks for 4 cycles i.e. 8 weeks. Growth factor support may be administered at the investigator's discretion. Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)	
Arm type	Experimental
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	SUB09490MIG
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
85mg/m ² IV infusion over 2 hours on day one repeated every 2 weeks (1 cycle) for 4 cycles. i.e. 8 weeks	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	SUB02772MIG
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
180mg/m ² IV over 30 to -90 minutes on day 1 repeated every 2 weeks (one cycle) for 4 cycles. i.e. 8 weeks.	
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	SUB27520
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous bolus use
Dosage and administration details:	
400mg/m ² bolus injection followed by 2400mg/m ² infusion over 46 hours. Repeated every 2 weeks for 4 cycles. i.e. 8 weeks	
Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

400mg/m² IV on day 1 repeated every 2 weeks for 4 cycles. i.e. 8 weeks

Arm title	ChemoRadiotherapy
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Arm description:

Within two weeks of randomisation, eligible patients will commence neoadjuvant chemoradiotherapy (CRT) delivering a total dose of 50.4Gy in 28 daily fractions over 5 1/2 weeks (1.8Gy/fraction, Mon to Fri) with capecitabine 830mg/m² BD PO (Mon to Fri) throughout radiotherapy. Four to six weeks after completion of CRT patients will undergo a staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	SUB12474MIG
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 830mg/m² twice daily orally on days of radiotherapy only. i.e. total of 28 days

Number of subjects in period 1	Immediate Surgery	GEMCAP	FOLFIRINOX
Started	33	20	20
Total number started treatment	31	19	20
Completed all treatment	30	17	15
Completed	9	13	15
Not completed	24	7	5
Physician decision	2	-	1
Consent withdrawn by subject	-	1	-
Advanced illness	-	-	1
Death	18	4	3
Did not start treatment	2	1	-
Withdrawn from surgery	1	-	-
Lost to follow-up	1	-	-
Refused chemotherapy during trial period	-	1	-

Number of subjects in period 1	ChemoRadiotherapy
Started	17
Total number started treatment	16
Completed all treatment	11

Completed	9
Not completed	8
Physician decision	2
Consent withdrawn by subject	-
Advanced illness	-
Death	5
Did not start treatment	1
Withdrawn from surgery	-
Lost to follow-up	-
Refused chemotherapy during trial period	-

Baseline characteristics

Reporting groups

Reporting group title	Immediate Surgery
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Reporting group description:

Patients will undergo a pylorus preserving or classical Kausch Whipple resection with standard lymphadenectomy. Total pancreatectomy will be accepted if clinically indicated.

Surgery alone with no neoadjuvant chemotherapy or chemoradiotherapy was the established standard of care in the UK for this group of patients at the point of study commencement.

Reporting group title	GEMCAP
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Reporting group description:

Within two weeks of randomisation, eligible patients will commence neoadjuvant gemcitabine, 1000mg/m² iv infusion over 30 minutes, days 1, 8 and 15 of a 28 day cycle and capecitabine 830mg/m² BD PO for 21 out of 28 days (one cycle) for 2 cycles i.e. 8 weeks. Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)

Reporting group title	FOLFIRINOX
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Reporting group description:

Within two weeks of randomisation, eligible patients will commence neoadjuvant oxaliplatin 85mg/m², irinotecan 180mg/m², folinic acid given according to local practice for both the drug and the dose, 5-FU 400mg/m² bolus injection followed by 2400mg/m² 46 hour infusion, repeated every 2 weeks for 4 cycles i.e. 8 weeks. Growth factor support may be administered at the investigator's discretion. Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)

Reporting group title	ChemoRadiotherapy
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Reporting group description:

Within two weeks of randomisation, eligible patients will commence neoadjuvant chemoradiotherapy (CRT) delivering a total dose of 50.4Gy in 28 daily fractions over 5 1/2 weeks (1.8Gy/fraction, Mon to Fri) with capecitabine 830mg/m² BD PO (Mon to Fri) throughout radiotherapy. Four to six weeks after completion of CRT patients will undergo a staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)

Reporting group values	Immediate Surgery	GEMCAP	FOLFIRINOX
Number of subjects	33	20	20
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median	61	63	64

inter-quartile range (Q1-Q3)	54 to 66	58 to 70	63 to 70
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Gender categorical Units: Subjects			
Female	19	10	10
Male	12	9	10
Not recorded	2	1	0
Diabetic Status Units: Subjects			
No	23	13	7
Type II	4	4	8
Type II (on insulin)	4	2	5
Not recorded	2	1	0
Smoking Status Units: Subjects			
Current	7	4	2
Past	10	7	3
Never	14	8	15
Not recorded	2	1	0
WHO Performance Status Units: Subjects			
Zero	16	6	8
One	15	13	12
Not recorded	2	1	0
T Stage Units: Subjects			
T1	0	0	1
T2	2	4	4
T3	24	12	13
T4	5	3	2
Not recorded	2	1	0
N Stage Units: Subjects			
N0	11	10	10
N1	18	9	9
nX	2	0	1
Not recorded	2	1	0
Cytology/EUS Biopsy Units: Subjects			
Adenocarcinoma	31	19	20
Not recorded	2	1	0
Surgical characteristic- Operation type Units: Subjects			
Pylorus preserving Whipples	15	5	11
Standard Whipples	2	5	0
Total pancreatectomy	4	1	0
Bypass	6	0	5
Open and Close	1	2	1
No Surgery	3	6	3
Not recorded	2	1	0

Extent of resection			
Within 51 resected patients			
Units: Subjects			
Resection with extended lymphadenectomy	5	5	1
Standard resection	16	6	10
Not recorded	12	9	9
Vein resection			
Within 51 resected patients			
Units: Subjects			
No	7	5	5
Yes	14	6	6
Not recorded	12	9	9
Tumour Stage			
From 51 resected patients			
Units: Subjects			
pT1	0	0	3
pT2	4	3	0
pT3	17	8	8
Not recorded	12	9	9
Nodes			
Units: Subjects			
Negative	2	4	3
Positive	19	7	8
Not recorded	12	9	9
Metastases			
Units: Subjects			
M0	21	11	11
Not recorded	12	9	9
R Status			
Units: Subjects			
R0	3	2	2
R1	18	9	9
Not recorded	12	9	9
Differentiation			
Units: Subjects			
Undifferentiated	0	1	0
Poor	6	1	4
Moderate	15	4	6
Well	0	2	1
Not assessed	0	3	0
Not recorded	12	9	9
Total lymph nodes			
Units: Subjects			
0-9	0	0	1
10-19	9	3	5
20+	12	8	5
Not recorded	12	9	9
Positive lymph nodes			
Units: Subjects			
Zero	2	4	3

One	7	3	2
Two or more	12	4	6
Not recorded	12	9	9
Resection Margin			
More than one resection margin can refer to the same patient. For the purposes of presenting the correct data in a format the website will accept, 4 subject analysis sets are defined as "Armname for resection margin". The data presented in the four overall reporting groups are meaningless for this variable.			
Units: Subjects			
Posterior	0	0	0
Anterior	0	0	0
SMV Groove	0	0	0
Pancreatic Neck	0	0	0
Bile Duct	0	0	0
Duodenal Resection	0	0	0
Gastric Resection	0	0	0
Other	33	20	20
CA19-9			
Data available for 82 patients split 29:18:19:16.			
Units: kU/L			
median	802.0	503.6	622.5
inter-quartile range (Q1-Q3)	183 to 1854.7	234.2 to 1364.8	75.5 to 1294.5
Haemoglobin			
Data available for 85 patients split 31:18:20:16.			
Units: g/L			
median	124.0	129.0	123.0
inter-quartile range (Q1-Q3)	115.5 to 130.0	124.5 to 144.5	119.8 to 128.8
Platelets			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	272.0	268.0	296.5
inter-quartile range (Q1-Q3)	229.5 to 390.0	201.0 to 321.0	214.5 to 321.0
Absolute Neutrophil Count			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	5.1	4.8	5.0
inter-quartile range (Q1-Q3)	4.0 to 6.7	4.2 to 6.5	4.1 to 5.8
White Blood Cell Count			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	7.7	8.1	7.6
inter-quartile range (Q1-Q3)	6.2 to 10.1	7.0 to 8.8	6.3 to 8.4
Lymphocytes			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	1.7	1.8	1.8
inter-quartile range (Q1-Q3)	1.3 to 2.3	1.4 to 2.2	1.4 to 2.1
Sodium			
Data available for 85 patients split 30:19:20:16.			
Units: mmol/L			
median	139	137.0	137.0
inter-quartile range (Q1-Q3)	136.2 to 140.0	135.0 to 138.5	133.8 to 141.0

Potassium			
Data available for 84 patients split 30:19:20:15.			
Units: mmol/L			
median	4.3	4.4	4.1
inter-quartile range (Q1-Q3)	4.1 to 4.6	4.0 to 4.8	3.6 to 4.4
Calcium			
Data available for 83 patients split 30:19:19:15.			
Units: mmol/L			
median	2.4	2.4	2.4
inter-quartile range (Q1-Q3)	2.3 to 2.5	2.3 to 2.4	2.4 to 2.4
Urea			
Data available for 84 patients split 30:18:20:16.			
Units: mmol/L			
median	4.0	4.2	4.5
inter-quartile range (Q1-Q3)	3.6 to 5.2	3.2 to 5.5	3.9 to 5.5
Creatinine			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L			
median	65.0	64.0	67.6
inter-quartile range (Q1-Q3)	51.6 to 70.4	54.0 to 68.5	61.8 to 74.5
Albumin			
Data available for 70 patients split 24:15:18:13.			
Units: g/L			
median	40.0	42.0	39.0
inter-quartile range (Q1-Q3)	38.0 to 44.2	37.0 to 43.0	35.0 to 44.8
Bilirubin			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L			
median	15.0	17.0	19.8
inter-quartile range (Q1-Q3)	9.0 to 26.0	12.5 to 24.0	11.5 to 28.0
AST			
Either AST or ALT were required, all patients had at least one of the two. 70 patients had AST, split 24:15:18:13.			
Units: IU/L			
median	30.5	28.0	42.5
inter-quartile range (Q1-Q3)	23.8 to 61.2	24.0 to 42.5	21.2 to 76.8
ALT			
Either AST or ALT were required. All patients had at least one of the two. 60 patients had ALT, split 23:14:12:11.			
Units: IU/L			
median	26.0	26.5	28.5
inter-quartile range (Q1-Q3)	19.5 to 41.5	22.0 to 41.5	18.2 to 53.5
ALK Phosphatase			
Units: IU/L			
median	145.0	136.0	180.0
inter-quartile range (Q1-Q3)	111.5 to 213.5	105.5 to 194.5	111.0 to 238.0
Maximum Tumour Dimension			
Units: mm			
median	36	30	30
inter-quartile range (Q1-Q3)	32 to 45	30 to 42	22 to 35
Reporting group values	ChemoRadiotherapy	Total	

Number of subjects	17	90	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	66		
inter-quartile range (Q1-Q3)	59 to 69	-	
Gender categorical			
Units: Subjects			
Female	9	48	
Male	7	38	
Not recorded	1	4	
Diabetic Status			
Units: Subjects			
No	12	55	
Type II	3	19	
Type II (on insulin)	1	12	
Not recorded	1	4	
Smoking Status			
Units: Subjects			
Current	3	16	
Past	8	28	
Never	5	42	
Not recorded	1	4	
WHO Performance Status			
Units: Subjects			
Zero	9	39	
One	7	47	
Not recorded	1	4	
T Stage			
Units: Subjects			
T1	0	1	
T2	0	10	
T3	16	65	
T4	0	10	
Not recorded	1	4	
N Stage			
Units: Subjects			
N0	5	36	
N1	11	47	
nX	0	3	

Not recorded	1	4	
Cytology/EUS Biopsy			
Units: Subjects			
Adenocarcinoma	16	86	
Not recorded	1	4	
Surgical characteristic- Operation type			
Units: Subjects			
Pylorus preserving Whipples	6	37	
Standard Whipples	1	8	
Total pancreatectomy	1	6	
Bypass	2	13	
Open and Close	0	4	
No Surgery	6	18	
Not recorded	1	4	
Extent of resection			
Within 51 resected patients			
Units: Subjects			
Resection with extended lyphadenectomy	2	13	
Standard resection	6	38	
Not recorded	9	39	
Vein resection			
Within 51 resected patients			
Units: Subjects			
No	2	19	
Yes	6	32	
Not recorded	9	39	
Tumour Stage			
From 51 resected patients			
Units: Subjects			
pT1	2	5	
pT2	2	9	
pT3	4	37	
Not recorded	9	39	
Nodes			
Units: Subjects			
Negative	6	15	
Positive	2	36	
Not recorded	9	39	
Metastases			
Units: Subjects			
M0	8	51	
Not recorded	9	39	
R Status			
Units: Subjects			
R0	3	10	
R1	5	41	
Not recorded	9	39	
Differentiation			
Units: Subjects			
Undifferentiated	0	1	

Poor	2	13	
Moderate	2	27	
Well	1	4	
Not assessed	3	6	
Not recorded	9	39	
Total lymph nodes			
Units: Subjects			
0-9	2	3	
10-19	1	18	
20+	5	30	
Not recorded	9	39	
Positive lymph nodes			
Units: Subjects			
Zero	6	15	
One	2	14	
Two or more	0	22	
Not recorded	9	39	
Resection Margin			
More than one resection margin can refer to the same patient. For the purposes of presenting the correct data in a format the website will accept, 4 subject analysis sets are defined as "Armname for resection margin". The data presented in the four overall reporting groups are meaningless for this variable.			
Units: Subjects			
Posterior	0	0	
Anterior	0	0	
SMV Groove	0	0	
Pancreatic Neck	0	0	
Bile Duct	0	0	
Duodenal Resection	0	0	
Gastric Resection	0	0	
Other	17	90	
CA19-9			
Data available for 82 patients split 29:18:19:16.			
Units: kU/L			
median	321.5		
inter-quartile range (Q1-Q3)	67.4 to 717.0	-	
Haemoglobin			
Data available for 85 patients split 31:18:20:16.			
Units: g/L			
median	137.0		
inter-quartile range (Q1-Q3)	122.8 to 142.0	-	
Platelets			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	279.0		
inter-quartile range (Q1-Q3)	219.5 to 340.0	-	
Absolute Neutrophil Count			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	4.8		
inter-quartile range (Q1-Q3)	4.2 to 5.4	-	
White Blood Cell Count			

Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	8.1		
inter-quartile range (Q1-Q3)	6.9 to 9.3	-	
Lymphocytes			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L			
median	2.3		
inter-quartile range (Q1-Q3)	1.8 to 2.9	-	
Sodium			
Data available for 85 patients split 30:19:20:16.			
Units: mmol/L			
median	138.5		
inter-quartile range (Q1-Q3)	136.8 to 139.2	-	
Potassium			
Data available for 84 patients split 30:19:20:15.			
Units: mmol/L			
median	4.5		
inter-quartile range (Q1-Q3)	4.3 to 4.7	-	
Calcium			
Data available for 83 patients split 30:19:19:15.			
Units: mmol/L			
median	2.4		
inter-quartile range (Q1-Q3)	2.3 to 2.5	-	
Urea			
Data available for 84 patients split 30:18:20:16.			
Units: mmol/L			
median	5.0		
inter-quartile range (Q1-Q3)	4.3 to 5.3	-	
Creatinine			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L			
median	61.5		
inter-quartile range (Q1-Q3)	54.8 to 69.5	-	
Albumin			
Data available for 70 patients split 24:15:18:13.			
Units: g/L			
median	42.5		
inter-quartile range (Q1-Q3)	37.6 to 44.1	-	
Bilirubin			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L			
median	19.5		
inter-quartile range (Q1-Q3)	8.8 to 26.8	-	
AST			
Either AST or ALT were required, all patients had at least one of the two. 70 patients had AST, split 24:15:18:13.			
Units: IU/L			
median	31.0		
inter-quartile range (Q1-Q3)	26.0 to 85.0	-	
ALT			
Either AST or ALT were required. All patients had at least one of the two. 60 patients had ALT, split 23:			

14:12:11.			
Units: IU/L			
median	29.0		
inter-quartile range (Q1-Q3)	25.0 to 36.5	-	
ALK Phosphatase			
Units: IU/L			
median	149.5		
inter-quartile range (Q1-Q3)	106.2 to 207.0	-	
Maximum Tumour Dimension			
Units: mm			
median	32		
inter-quartile range (Q1-Q3)	22 to 43	-	

Subject analysis sets

Subject analysis set title	Centre
Subject analysis set type	Per protocol
Subject analysis set description: Recruitment to randomisation, split by site.	
Subject analysis set title	Baseline Patients
Subject analysis set type	Per protocol
Subject analysis set description: Full dataset incorporating all four arms	
Subject analysis set title	Explorative Surgery Patients
Subject analysis set type	Per protocol
Subject analysis set description: Patients who had undergone explorative surgery	
Subject analysis set title	Immediate Surgery for Resection Margin
Subject analysis set type	Per protocol
Subject analysis set description: Immediate surgery including repeated patients	
Subject analysis set title	GEMCAP for resection margin
Subject analysis set type	Per protocol
Subject analysis set description: GEMCAP with repeated patients	
Subject analysis set title	FOLFIRINOX for resection margin
Subject analysis set type	Per protocol
Subject analysis set description: FOLFIRINOX with repeated patients	
Subject analysis set title	Chemoradiotherapy for resection margin
Subject analysis set type	Per protocol
Subject analysis set description: Chemoradiotherapy with repeated patients	
Subject analysis set title	Baseline Patients Immediate Surgery
Subject analysis set type	Per protocol
Subject analysis set description: Baseline patients randomised to immediate surgery	
Subject analysis set title	Baseline Patients Neoadjuvant Therapies
Subject analysis set type	Per protocol
Subject analysis set description: Baseline patients randomised to neoadjuvant therapies	
Subject analysis set title	Explorative Surgery Immediate Surgery

Subject analysis set type	Per protocol
Subject analysis set description:	
Patients that underwent exploratory surgery who were randomised to immediate surgery	
Subject analysis set title	Explorative Surgery Neoadjuvant Therapies
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients that underwent explorative surgery who were randomised to neoadjuvant therapies	

Reporting group values	Centre	Baseline Patients	Explorative Surgery Patients
Number of subjects	90	86	68
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female			
Male			
Not recorded			
Diabetic Status			
Units: Subjects			
No			
Type II			
Type II (on insulin)			
Not recorded			
Smoking Status			
Units: Subjects			
Current			
Past			
Never			
Not recorded			
WHO Performance Status			
Units: Subjects			
Zero			
One			
Not recorded			
T Stage			
Units: Subjects			

T1 T2 T3 T4 Not recorded			
N Stage Units: Subjects			
N0 N1 nX Not recorded			
Cytology/EUS Biopsy Units: Subjects			
Adenocarcinoma Not recorded			
Surgical characteristic- Operation type Units: Subjects			
Pylorus preserving Whipples Standard Whipples Total pancreatectomy Bypass Open and Close No Surgery Not recorded			
Extent of resection			
Within 51 resected patients			
Units: Subjects			
Resection with extended lyphadenectomy Standard resection Not recorded			
Vein resection			
Within 51 resected patients			
Units: Subjects			
No Yes Not recorded			
Tumour Stage			
From 51 resected patients			
Units: Subjects			
pT1 pT2 pT3 Not recorded			
Nodes Units: Subjects			
Negative Positive Not recorded			
Metastases Units: Subjects			

M0 Not recorded			
R Status Units: Subjects			
R0 R1 Not recorded			
Differentiation Units: Subjects			
Undifferentiated Poor Moderate Well Not assessed Not recorded			
Total lymph nodes Units: Subjects			
0-9 10-19 20+ Not recorded			
Positive lymph nodes Units: Subjects			
Zero One Two or more Not recorded			
Resection Margin			
More than one resection margin can refer to the same patient. For the purposes of presenting the correct data in a format the website will accept, 4 subject analysis sets are defined as "Armname for resection margin". The data presented in the four overall reporting groups are meaningless for this variable.			
Units: Subjects			
Posterior Anterior SMV Groove Pancreatic Neck Bile Duct Duodenal Resection Gastric Resection Other			
CA19-9			
Data available for 82 patients split 29:18:19:16.			
Units: kU/L median inter-quartile range (Q1-Q3)			
Haemoglobin			
Data available for 85 patients split 31:18:20:16.			
Units: g/L median inter-quartile range (Q1-Q3)			
Platelets			

Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$ median inter-quartile range (Q1-Q3)			
Absolute Neutrophil Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$ median inter-quartile range (Q1-Q3)			
White Blood Cell Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$ median inter-quartile range (Q1-Q3)			
Lymphocytes			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$ median inter-quartile range (Q1-Q3)			
Sodium			
Data available for 85 patients split 30:19:20:16.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Potassium			
Data available for 84 patients split 30:19:20:15.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Calcium			
Data available for 83 patients split 30:19:19:15.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Urea			
Data available for 84 patients split 30:18:20:16.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Creatinine			
Data available for 70 patients split 24:15:18:13.			
Units: $\mu\text{mol}/L$ median inter-quartile range (Q1-Q3)			
Albumin			
Data available for 70 patients split 24:15:18:13.			
Units: g/L median inter-quartile range (Q1-Q3)			
Bilirubin			
Data available for 70 patients split 24:15:18:13.			
Units: $\mu\text{mol}/L$			

median			
inter-quartile range (Q1-Q3)			
AST			
Either AST or ALT were required, all patients had at least one of the two. 70 patients had AST, split 24:15:18:13.			
Units: IU/L			
median			
inter-quartile range (Q1-Q3)			
ALT			
Either AST or ALT were required. All patients had at least one of the two. 60 patients had ALT, split 23:14:12:11.			
Units: IU/L			
median			
inter-quartile range (Q1-Q3)			
ALK Phosphatase			
Units: IU/L			
median			
inter-quartile range (Q1-Q3)			
Maximum Tumour Dimension			
Units: mm			
median			
inter-quartile range (Q1-Q3)			

Reporting group values	Immediate Surgery for Resection Margin	GEMCAP for resection margin	FOLFIRINOX for resection margin
Number of subjects	40	17	15
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female			
Male			
Not recorded			
Diabetic Status			
Units: Subjects			
No			
Type II			
Type II (on insulin)			

Not recorded			
Smoking Status			
Units: Subjects			
Current			
Past			
Never			
Not recorded			
WHO Performance Status			
Units: Subjects			
Zero			
One			
Not recorded			
T Stage			
Units: Subjects			
T1			
T2			
T3			
T4			
Not recorded			
N Stage			
Units: Subjects			
N0			
N1			
nX			
Not recorded			
Cytology/EUS Biopsy			
Units: Subjects			
Adenocarcinoma			
Not recorded			
Surgical characteristic- Operation type			
Units: Subjects			
Pylorus preserving Whipples			
Standard Whipples			
Total pancreatectomy			
Bypass			
Open and Close			
No Surgery			
Not recorded			
Extent of resection			
Within 51 resected patients			
Units: Subjects			
Resection with extended lyphadenectomy			
Standard resection			
Not recorded			
Vein resection			
Within 51 resected patients			
Units: Subjects			
No			
Yes			
Not recorded			

Tumour Stage			
From 51 resected patients			
Units: Subjects			
pT1			
pT2			
pT3			
Not recorded			
Nodes			
Units: Subjects			
Negative			
Positive			
Not recorded			
Metastases			
Units: Subjects			
M0			
Not recorded			
R Status			
Units: Subjects			
R0			
R1			
Not recorded			
Differentiation			
Units: Subjects			
Undifferentiated			
Poor			
Moderate			
Well			
Not assessed			
Not recorded			
Total lymph nodes			
Units: Subjects			
0-9			
10-19			
20+			
Not recorded			
Positive lymph nodes			
Units: Subjects			
Zero			
One			
Two or more			
Not recorded			
Resection Margin			
More than one resection margin can refer to the same patient. For the purposes of presenting the correct data in a format the website will accept, 4 subject analysis sets are defined as "Armname for resection margin". The data presented in the four overall reporting groups are meaningless for this variable.			
Units: Subjects			
Posterior	12	3	2
Anterior	8	3	2
SMV Groove	13	6	5
Pancreatic Neck	4	3	3
Bile Duct	0	1	1

Duodenal Resection	1	1	0
Gastric Resection	0	0	0
Other	2	0	2
CA19-9			
Data available for 82 patients split 29:18:19:16.			
Units: kU/L			
median			
inter-quartile range (Q1-Q3)			
Haemoglobin			
Data available for 85 patients split 31:18:20:16.			
Units: g/L			
median			
inter-quartile range (Q1-Q3)			
Platelets			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
Absolute Neutrophil Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
White Blood Cell Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
Lymphocytes			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
Sodium			
Data available for 85 patients split 30:19:20:16.			
Units: mmol/L			
median			
inter-quartile range (Q1-Q3)			
Potassium			
Data available for 84 patients split 30:19:20:15.			
Units: mmol/L			
median			
inter-quartile range (Q1-Q3)			
Calcium			
Data available for 83 patients split 30:19:19:15.			
Units: mmol/L			
median			
inter-quartile range (Q1-Q3)			
Urea			
Data available for 84 patients split 30:18:20:16.			
Units: mmol/L			

median			
inter-quartile range (Q1-Q3)			
Creatinine			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L			
median			
inter-quartile range (Q1-Q3)			
Albumin			
Data available for 70 patients split 24:15:18:13.			
Units: g/L			
median			
inter-quartile range (Q1-Q3)			
Bilirubin			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L			
median			
inter-quartile range (Q1-Q3)			
AST			
Either AST or ALT were required, all patients had at least one of the two. 70 patients had AST, split 24:15:18:13.			
Units: IU/L			
median			
inter-quartile range (Q1-Q3)			
ALT			
Either AST or ALT were required. All patients had at least one of the two. 60 patients had ALT, split 23:14:12:11.			
Units: IU/L			
median			
inter-quartile range (Q1-Q3)			
ALK Phosphatase			
Units: IU/L			
median			
inter-quartile range (Q1-Q3)			
Maximum Tumour Dimension			
Units: mm			
median			
inter-quartile range (Q1-Q3)			

Reporting group values	Chemoradiotherapy for resection margin	Baseline Patients Immediate Surgery	Baseline Patients Neoadjuvant Therapies
Number of subjects	7	31	55
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			

85 years and over			
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Age continuous Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female Male Not recorded			
Diabetic Status Units: Subjects			
No Type II Type II (on insulin) Not recorded			
Smoking Status Units: Subjects			
Current Past Never Not recorded			
WHO Performance Status Units: Subjects			
Zero One Not recorded			
T Stage Units: Subjects			
T1 T2 T3 T4 Not recorded			
N Stage Units: Subjects			
N0 N1 nX Not recorded			
Cytology/EUS Biopsy Units: Subjects			
Adenocarcinoma Not recorded			
Surgical characteristic- Operation type Units: Subjects			
Pylorus preserving Whipples Standard Whipples Total pancreatectomy			

Bypass Open and Close No Surgery Not recorded			
Extent of resection			
Within 51 resected patients			
Units: Subjects			
Resection with extended lymphadenectomy Standard resection Not recorded			
Vein resection			
Within 51 resected patients			
Units: Subjects			
No Yes Not recorded			
Tumour Stage			
From 51 resected patients			
Units: Subjects			
pT1 pT2 pT3 Not recorded			
Nodes			
Units: Subjects			
Negative Positive Not recorded			
Metastases			
Units: Subjects			
M0 Not recorded			
R Status			
Units: Subjects			
R0 R1 Not recorded			
Differentiation			
Units: Subjects			
Undifferentiated Poor Moderate Well Not assessed Not recorded			
Total lymph nodes			
Units: Subjects			
0-9 10-19 20+			

Not recorded			
Positive lymph nodes			
Units: Subjects			
Zero			
One			
Two or more			
Not recorded			
Resection Margin			
More than one resection margin can refer to the same patient. For the purposes of presenting the correct data in a format the website will accept, 4 subject analysis sets are defined as "Armname for resection margin". The data presented in the four overall reporting groups are meaningless for this variable.			
Units: Subjects			
Posterior	2		
Anterior	0		
SMV Groove	3		
Pancreatic Neck	0		
Bile Duct	0		
Duodenal Resection	2		
Gastric Resection	0		
Other	0		
CA19-9			
Data available for 82 patients split 29:18:19:16.			
Units: kU/L			
median			
inter-quartile range (Q1-Q3)			
Haemoglobin			
Data available for 85 patients split 31:18:20:16.			
Units: g/L			
median			
inter-quartile range (Q1-Q3)			
Platelets			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
Absolute Neutrophil Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
White Blood Cell Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
Lymphocytes			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$			
median			
inter-quartile range (Q1-Q3)			
Sodium			

Data available for 85 patients split 30:19:20:16.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Potassium			
Data available for 84 patients split 30:19:20:15.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Calcium			
Data available for 83 patients split 30:19:19:15.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Urea			
Data available for 84 patients split 30:18:20:16.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Creatinine			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L median inter-quartile range (Q1-Q3)			
Albumin			
Data available for 70 patients split 24:15:18:13.			
Units: g/L median inter-quartile range (Q1-Q3)			
Bilirubin			
Data available for 70 patients split 24:15:18:13.			
Units: µmol/L median inter-quartile range (Q1-Q3)			
AST			
Either AST or ALT were required, all patients had at least one of the two. 70 patients had AST, split 24:15:18:13.			
Units: IU/L median inter-quartile range (Q1-Q3)			
ALT			
Either AST or ALT were required. All patients had at least one of the two. 60 patients had ALT, split 23:14:12:11.			
Units: IU/L median inter-quartile range (Q1-Q3)			
ALK Phosphatase Units: IU/L median inter-quartile range (Q1-Q3)			
Maximum Tumour Dimension Units: mm			

median			
inter-quartile range (Q1-Q3)			

Reporting group values	Explorative Surgery Immediate Surgery	Explorative Surgery Neoadjuvant Therapies	
Number of subjects	28	40	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female Male Not recorded			
Diabetic Status Units: Subjects			
No Type II Type II (on insulin) Not recorded			
Smoking Status Units: Subjects			
Current Past Never Not recorded			
WHO Performance Status Units: Subjects			
Zero One Not recorded			
T Stage Units: Subjects			
T1 T2 T3 T4			

Not recorded			
N Stage			
Units: Subjects			
N0			
N1			
nX			
Not recorded			
Cytology/EUS Biopsy			
Units: Subjects			
Adenocarcinoma			
Not recorded			
Surgical characteristic- Operation type			
Units: Subjects			
Pylorus preserving Whipples			
Standard Whipples			
Total pancreatectomy			
Bypass			
Open and Close			
No Surgery			
Not recorded			
Extent of resection			
Within 51 resected patients			
Units: Subjects			
Resection with extended lyphadenectomy			
Standard resection			
Not recorded			
Vein resection			
Within 51 resected patients			
Units: Subjects			
No			
Yes			
Not recorded			
Tumour Stage			
From 51 resected patients			
Units: Subjects			
pT1			
pT2			
pT3			
Not recorded			
Nodes			
Units: Subjects			
Negative			
Positive			
Not recorded			
Metastases			
Units: Subjects			
M0			
Not recorded			
R Status			
Units: Subjects			

R0 R1 Not recorded			
Differentiation Units: Subjects			
Undifferentiated Poor Moderate Well Not assessed Not recorded			
Total lymph nodes Units: Subjects			
0-9 10-19 20+ Not recorded			
Positive lymph nodes Units: Subjects			
Zero One Two or more Not recorded			
Resection Margin			
More than one resection margin can refer to the same patient. For the purposes of presenting the correct data in a format the website will accept, 4 subject analysis sets are defined as "Armname for resection margin". The data presented in the four overall reporting groups are meaningless for this variable.			
Units: Subjects			
Posterior Anterior SMV Groove Pancreatic Neck Bile Duct Duodenal Resection Gastric Resection Other			
CA19-9			
Data available for 82 patients split 29:18:19:16.			
Units: kU/L median inter-quartile range (Q1-Q3)			
Haemoglobin			
Data available for 85 patients split 31:18:20:16.			
Units: g/L median inter-quartile range (Q1-Q3)			
Platelets			
Data available for 85 patients split 31:18:20:16.			
Units: x10 ⁹ /L median inter-quartile range (Q1-Q3)			

Absolute Neutrophil Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$ median inter-quartile range (Q1-Q3)			
White Blood Cell Count			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$ median inter-quartile range (Q1-Q3)			
Lymphocytes			
Data available for 85 patients split 31:18:20:16.			
Units: $\times 10^9/L$ median inter-quartile range (Q1-Q3)			
Sodium			
Data available for 85 patients split 30:19:20:16.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Potassium			
Data available for 84 patients split 30:19:20:15.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Calcium			
Data available for 83 patients split 30:19:19:15.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Urea			
Data available for 84 patients split 30:18:20:16.			
Units: mmol/L median inter-quartile range (Q1-Q3)			
Creatinine			
Data available for 70 patients split 24:15:18:13.			
Units: $\mu\text{mol}/L$ median inter-quartile range (Q1-Q3)			
Albumin			
Data available for 70 patients split 24:15:18:13.			
Units: g/L median inter-quartile range (Q1-Q3)			
Bilirubin			
Data available for 70 patients split 24:15:18:13.			
Units: $\mu\text{mol}/L$ median inter-quartile range (Q1-Q3)			
AST			
Either AST or ALT were required, all patients had at least one of the two. 70 patients had AST, split 24:			

15:18:13.			
Units: IU/L median inter-quartile range (Q1-Q3)			
ALT			
Either AST or ALT were required. All patients had at least one of the two. 60 patients had ALT, split 23:14:12:11.			
Units: IU/L median inter-quartile range (Q1-Q3)			
ALK Phosphatase Units: IU/L median inter-quartile range (Q1-Q3)			
Maximum Tumour Dimension Units: mm median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Immediate Surgery
Reporting group description:	
Patients will undergo a pylorus preserving or classical Kausch Whipple resection with standard lymphadenectomy. Total pancreatectomy will be accepted if clinically indicated.	
Surgery alone with no neoadjuvant chemotherapy or chemoradiotherapy was the established standard of care in the Uk for this group of patients at the point of study commencement.	
Reporting group title	GEMCAP
Reporting group description:	
Within two weeks of randomisation, eligible patients will commence neoadjuvant gemcitabine, 1000mg/m2 iv infusion over 30 minutes, days 1, 8 and 15 of a 28 day cycle and capecitabine 830mg/m2 BD PO for 21 out of 28 days (one cycle) for 2 cycles i.e. 8 weeks. Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)	
Reporting group title	FOLFIRINOX
Reporting group description:	
Within two weeks of randomisation, eligible patients will commence neoadjuvant oxaliplatin 85mg/m2 , irinotecan 180mg/m2 , folinic acid given according to local practice for both the drug and the dose, 5-FU 400mg/m2 bolus injection followed by 2400mg/m2 46 hour infusion, repeated every 2 weeks for 4 cycles i.e. 8 weeks. Growth factor support may be administered at the investigator's discretion. Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)	
Reporting group title	ChemoRadiotherapy
Reporting group description:	
Within two weeks of randomisation, eligible patients will commence neoadjuvant chemoradiotherapy (CRT) delivering a total dose of 50.4Gy in 28 daily fractions over 5 1/2 weeks (1.8Gy/fraction, Mon to Fri) with capecitabine 830mg/m2 BD PO (Mon to Fri) throughout radiotherapy. Four to six weeks after completion of CRT patients will undergo a staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A (surgery alone)	
Subject analysis set title	Centre
Subject analysis set type	Per protocol
Subject analysis set description:	
Recruitment to randomisation, split by site.	
Subject analysis set title	Baseline Patients
Subject analysis set type	Per protocol
Subject analysis set description:	
Full dataset incorporating all four arms	
Subject analysis set title	Explorative Surgery Patients
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who had undergone explorative surgery	
Subject analysis set title	Immediate Surgery for Resection Margin
Subject analysis set type	Per protocol
Subject analysis set description:	
Immediate surgery including repeated patients	
Subject analysis set title	GEMCAP for resection margin
Subject analysis set type	Per protocol
Subject analysis set description:	
GEMCAP with repeated patients	

Subject analysis set title	FOLFIRINOX for resection margin
Subject analysis set type	Per protocol
Subject analysis set description: FOLFIRINOX with repeated patients	
Subject analysis set title	Chemoradiotherapy for resection margin
Subject analysis set type	Per protocol
Subject analysis set description: Chemoradiotherapy with repeated patients	
Subject analysis set title	Baseline Patients Immediate Surgery
Subject analysis set type	Per protocol
Subject analysis set description: Baseline patients randomised to immediate surgery	
Subject analysis set title	Baseline Patients Neoadjuvant Therapies
Subject analysis set type	Per protocol
Subject analysis set description: Baseline patients randomised to neoadjuvant therapies	
Subject analysis set title	Explorative Surgery Immediate Surgery
Subject analysis set type	Per protocol
Subject analysis set description: Patients that underwent exploratory surgery who were randomised to immediate surgery	
Subject analysis set title	Explorative Surgery Neoadjuvant Therapies
Subject analysis set type	Per protocol
Subject analysis set description: Patients that underwent explorative surgery who were randomised to neoadjuvant therapies	

Primary: Recruitment Rate

End point title	Recruitment Rate ^[1]
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End point description:

Recruitment rate will be measured by (i) recruitment rate by centre (ii) overall recruitment rate and (iii) a graph comparing expected versus actual cumulative recruitment. The recruitment target is 100 patients in 39 months.

Recruitment rate per site is defined as the number of patients recruited at a site divided by the amount of time the site has been open to recruit.

Recruitment rate (per site) = number of patients recruited in the site /
(date of data lock – site green light date)

Similarly, overall recruitment rate is defined as the number of patients recruited in the trial divided by the amount of the trial has been open to recruit.

Recruitment rate (overall) = total number of patients recruited in the trial /
(date of data lock –trial green light date)

End point type	Primary
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End point timeframe:

52 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was a feasibility trial, and thus this endpoint was analysed by whether it met its minimum recruitment target within the study-period.

End point values	Centre			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: Patients/unit time				
number (confidence interval 95%)				
Royal Liverpool and Clatterbridge	8.74 (6.18 to 11.99)			
University Hospital of Heidelberg	4.80 (2.48 to 8.38)			
Weston Park Hospital (Sheffield)	2.00 (0.80 to 4.12)			
Hammersmith Hospital (London)	1.36 (0.44 to 3.18)			
The Beatson WoSCC and Glasgow RI	1.55 (0.50 to 3.61)			
Ninewells Hospital (Dundee)	1.32 (0.36 to 3.37)			
The Christie and Manchester Royal Infirmary	1.40 (0.38 to 3.59)			
Velindre and Singleton and Morriston	1.28 (0.35 to 3.27)			
King's College and Guy's and St Thomas	0.92 (0.19 to 2.70)			
Aberdeen Royal Infirmary	0.59 (0.07 to 2.13)			
Queen Alexandra and Southampton General Hospital	0.68 (0.08 to 1.88)			
Royal Marsden Hospital (London and Sutton)	0.52 (0.06 to 1.88)			
Churchill and the Great Western Swindon	0.27 (0.01 to 1.52)			
Queen Elizabeth Hospital (Birmingham)	0.27 (0.01 to 1.48)			
Royal Free Hospital (London)	0.00 (0.00 to 2.18)			
University Hospital Coventry	0.00 (0.00 to 1.14)			
Overall	20.69 (16.64 to 25.43)			

Attachments (see zip file)	Observed Recruitment/Recruitment.docx
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Statistical analyses

No statistical analyses for this end point

Primary: Resection Rate

End point title	Resection Rate
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End point description:

An overall resection rate will be measured using the total number of patients at baseline. A second resection rate will also be measured using only the patients who undergo explorative surgery. R1 and R0 resection margins will be used when measuring the resection rate – R2 resection margins will be excluded.

Resection rate is thus defined as the total number of resected R0 or R1 patients divided by the total number of patients at baseline or the total number of patients undergone surgery (two rates will be

measured).

Resection Rate (baseline pts) = number of R0 or R1 resected patients /
number of patients at baseline

Resection Rate (surgery pts) = number of R0 or R1 resected patients /
number of patients undergone explorative surgery

End point type	Primary
End point timeframe:	
52 Months	

End point values	Baseline Patients	Explorative Surgery Patients	Baseline Patients Immediate Surgery	Baseline Patients Neoadjuvant Therapies
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	86	68	31	55
Units: Resection Rate				
number (confidence interval 95%)				
Overall	0.59 (0.48 to 0.70)	0.75 (0.63 to 0.85)	0.68 (0.49 to 0.83)	0.55 (0.41 to 0.68)

End point values	Explorative Surgery Immediate Surgery	Explorative Surgery Neoadjuvant Therapies		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	40		
Units: Resection Rate				
number (confidence interval 95%)				
Overall	0.75 (0.55 to 0.89)	0.75 (0.59 to 0.87)		

Statistical analyses

Statistical analysis title	Resection Rate (overall)
Statistical analysis description: A Chi-square test is performed to compare the resection rate of combined neoadjuvant therapies with that for immediate surgery.	
Comparison groups	Baseline Patients Immediate Surgery v Baseline Patients Neoadjuvant Therapies
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	> 0.05
Method	Chi-squared

Notes:

[2] - Investigation of recruitment to surgery, comparing immediate surgery with all neoadjuvant therapy arms.

Statistical analysis title	Resection rate (explorative surgery)
Statistical analysis description: A Chi-square test is performed to compare the resection rate of combined neoadjuvant therapies with that for immediate surgery, for patients who had undergone exploratory surgery.	
Comparison groups	Explorative Surgery Immediate Surgery v Explorative Surgery Neoadjuvant Therapies
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Chi-squared

Secondary: R0 Resection Rate

End point title	R0 Resection Rate
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End point description:

An overall R0 resection rate will be measured using the total number of patients at baseline. A second resection rate will also be measured using only the patients who undergo explorative surgery. The R0 resection margin is recorded according to the Royal College of Pathologists report on Standards and datasets for reporting cancers.

Resection rate is defined as the total number of resected R0 patients divided by the total number of patients recruited or the total number of patients undergone surgery (two rates will be measured).

R0 Resection Rate (baseline pts) = number of R0 resected patients / number of patients at baseline

R0 Resection Rate (surgery pts) = number of R0 resected patients / number of patients undergone explorative surgery

End point type	Secondary
End point timeframe: 52 months	

End point values	Baseline Patients	Explorative Surgery Patients	Baseline Patients Immediate Surgery	Baseline Patients Neoadjuvant Therapies
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	86	68	31	55
Units: Resection Rate				
number (confidence interval 95%)				
Overall	0.12 (0.06 to 0.20)	0.15 (0.07 to 0.25)	0.10 (0.02 to 0.26)	0.13 (0.05 to 0.24)

End point values	Explorative Surgery	Explorative Surgery		
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	Immediate Surgery	Neoadjuvant Therapies		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	40		
Units: Resection Rate				
number (confidence interval 95%)				
Overall	0.11 (0.02 to 0.28)	0.18 (0.07 to 0.33)		

Statistical analyses

Statistical analysis title	R0 Resection Rate (overall)
Statistical analysis description: A Fisher's exact test is performed to compare the rate of combined neoadjuvant therapies with that for immediate surgery.	
Comparison groups	Baseline Patients Neoadjuvant Therapies v Baseline Patients Immediate Surgery
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Chi-squared

Statistical analysis title	R0 Resection Rate (Explorative Surgery)
Statistical analysis description: A Fisher's exact test is performed to compare the rate of combined neoadjuvant therapies with that for immediate surgery, for patients who had undergone exploratory surgery.	
Comparison groups	Explorative Surgery Immediate Surgery v Explorative Surgery Neoadjuvant Therapies
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Chi-squared

Secondary: Post-operative complications rate

End point title	Post-operative complications rate
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End point description:

Post-operative complications will be measured using morbidity and mortality rates. Post-operative morbidity will be recorded following surgery and classified according to existing guidelines. Post-operative mortality will be recorded as the 30 day mortality rate.

Post-operative complications rates are defined as morbidity and 30-days mortality rates. The denominator of both measures will be the total number of patients undergone surgery.

Morbidity Rate = number of patients with complications /
number of patients undergone explorative surgery

30-days Mortality Rate = number of patients died within 30 days from surgery /

number of patients undergone explorative surgery

End point type	Secondary
End point timeframe:	
Morbidity- any patient deemed to have post-operative morbidity before censoring	
Mortality- 30 days post-operative	

End point values	Immediate Surgery	GEMCAP	FOLFIRINOX	ChemoRadiotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	13	17	10
Units: Complications Rate				
number (confidence interval 95%)				
Post-operative morbidity	0.50 (0.31 to 0.69)	0.38 (0.14 to 0.68)	0.29 (0.10 to 0.56)	0.50 (0.19 to 0.81)
Post-operative mortality (30 days)	0 (0 to 0.12)	0 (0 to 0.25)	0 (0 to 0.20)	0 (0 to 0.31)

Statistical analyses

Statistical analysis title	Morbidity
Statistical analysis description:	
A Chi-square test is performed to compare the rates on a regimen basis.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Chi-squared

Secondary: Response rate

End point title	Response rate ^[3]
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End point description:

An overall response rate will be measured using the number of patients at baseline. Response will be assessed in accordance with RECIST 1.1 guidelines (www.recist.com/files/Recist-1.1-Fanbook.pdf) and those patients achieving partial or complete response with disease control will be compared.

The response rate is defined as the number of complete response or partial response or stable disease or progression disease divided the total number of patients at baseline.

e.g.

Complete Response Rate = number of patients showing complete response at re-staging / number of patients at baseline

In the same way, the rates for partial response, stable disease and progression disease will be calculated.

Furthermore, an overall response rate will be measured pulling together complete and partial responders.

Overall Response Rate = number of complete responders + number of partial responders / number of patients at baseline

End point type	Secondary
End point timeframe:	
Diagnosis of response will occur at post-surgery restaging.	

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Response rate is reported for neo-adjuvant arms only.

End point values	GEMCAP	FOLFIRINOX	ChemoRadiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	12	
Units: Response Rate				
number (not applicable)				
Complete Response Rate	0.00	0.00	0.00	
Partial Response Rate	0.12	0.23	0.00	
Stable Disease Rate	0.70	0.71	0.75	
Disease Progression Rate	0.18	0.06	0.25	
Overall Response Rate (CR+PR)	0.12	0.24	0.00	

Statistical analyses

Statistical analysis title	Complete response
Statistical analysis description:	
A Fisher's exact test is performed to compare the rates on a regimen basis.	
Comparison groups	GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Partial Response
Statistical analysis description:	
A Fisher's exact test is performed to compare the rates on a regimen basis.	
Comparison groups	GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Fisher exact

Statistical analysis title	Stable Disease
Statistical analysis description: A Chi-square test is performed as appropriate to compare the rates on a regimen basis.	
Comparison groups	GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Chi-squared

Statistical analysis title	Disease Progression
Statistical analysis description: A Fisher's exact test is performed to compare the rates on a regimen basis.	
Comparison groups	GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Fisher exact

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival is defined as follow:

Overall survival (months) = (min(censoring data, date of death) – date of randomisation)/ 30.44

The final – administrative – censoring date (at which the trial terminates) will be the date of most recent randomisation + 12 month. Patients will otherwise be censored at the date last know alive.

End point type	Secondary
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End point timeframe:

Days between date of randomisation and date of death, 12 months from date of randomisation, or date of last follow-up if not followed up for a full 12 months.

End point values	Immediate Surgery	GEMCAP	FOLFIRINOX	ChemoRadiotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	19	20	16
Units: 12 month survival rate				
number (confidence interval 95%)	40 (25 to 63)	78 (60 to 100)	84 (70 to 100)	60 (37 to 97)

Attachments (see zip file)	Overall Survival Kaplan-Meier/Overall_Survival.docx
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Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
Log-rank test is applied to investigate the difference in survival outcomes among the arms. Kaplan-Meier curve is plotted to visualise any differences over time.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Logrank

Secondary: Disease or local disease-free survival

End point title	Disease or local disease-free survival
End point description:	
Disease and local disease free survival rate will be measured for the patients who undergo explorative surgery. Disease and local disease free survival are defined as the number of days between the date of surgery and disease or local disease recurrence, respectively.	
Disease and local disease free survival are defined as follow:	
Time to recurrence* (month) = (min(censoring date, date of recurrence) – date of surgery) / 30.44	
* Localised, metastatic or both	
Time to local recurrence (month) = (min(censoring date, date of recurrence) – date of surgery) / 30.44	
Patients who do not have confirmed recurrence at CT and patients who are not assessed by CT will be censored for recurrence at the later of current visit or last follow up. Patients who die without confirmed recurrence will be censored at their date of death.	
End point type	Secondary
End point timeframe:	
Date of surgery to disease recurrence, or date of most recent follow-up after surgery.	

End point values	Immediate Surgery	GEMCAP	FOLFIRINOX	ChemoRadiotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	12	17	10
Units: Disease-free survival rate				
number (confidence interval 95%)				
Disease-free survival	41 (24 to 69)	73 (51 to 100)	41 (24 to 69)	73 (51 to 100)
Local disease-free survival	91 (80 to 100)	100 (100 to 100)	91 (80 to 100)	100 (100 to 100)

Attachments (see zip file)	Disease-free survival Kaplan-Meier/Disease-free survival.docx
	Local disease-free survival K-M/Local disease-free survival.docx

Statistical analyses

Statistical analysis title	Disease-free survival
Statistical analysis description: Log-rank test is applied to investigate the difference in disease-free survival among arms. Kaplan-Meier curve is also plotted.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Logrank

Statistical analysis title	Local disease-free survival
Statistical analysis description: Log rank test is applied to investigate the difference in local disease-free survival among arms. Kaplan-Meier curve is also plotted.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Logrank

Secondary: Quality of Life 24 weeks

End point title	Quality of Life 24 weeks
End point description: Quality of life will be assessed for all patients with the EORTC Quality of Life Questionnaire version 3. The data will be scored according to the algorithm described in the EORTC scoring manual which linearly transforms the data from categorical scales to a score of 0-100. Summary measures of quality of life will be expressed as the direct difference in QoL scores between baseline and follow up assessment. EORTC questionnaire scores will be calculated in two steps, as described in the manual: $\text{Raw Score} = \text{RA} = (I1 + I2 + \dots + In) / n$ where $I1 + I2 + \dots + In$ are the component items Transformation into 0-100 score For Functional scales: $\text{Score} = 1 - ((RS-1))/\text{range} \times 100$ For Symptom scales / items and Global health status / QoL: $\text{Score} = ((RS-1))/\text{range} \times 100$ (dispersion parameter of difference is interquartile range)	
End point type	Secondary
End point timeframe: Baseline and 24 weeks follow-up	

End point values	Immediate Surgery	GEMCAP	FOLFIRINOX	ChemoRadiotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12 ^[4]	12 ^[5]	14	6
Units: EORTC QoL index difference				
number (confidence interval 50%)				
Overall QoL	4.2 (-10.4 to 10.4)	-8.3 (-16.7 to 16.7)	0.0 (0.0 to 12.5)	-4.2 (-20.8 to 12.5)
Physical functioning	-6.7 (-13.3 to 1.7)	-10 (-21.2 to 3.3)	-10.0 (-33.3 to 0.0)	-20.0 (-33.3 to -2.9)
Role functioning	0.0 (-16.7 to 16.7)	-8.3 (-37.5 to 16.7)	-16.7 (-33.3 to -4.2)	-41.7 (-50.0 to -33.3)
Emotional functioning	8.3 (-2.1 to 18.8)	2.8 (0.0 to 12.5)	0.0 (-8.3 to 8.3)	16.7 (0.0 to 31.3)
Cognitive functioning	0.0 (0.0 to 4.2)	0.0 (-25.0 to 0.0)	0.0 (-12.5 to 0.0)	0.0 (0.0 to 12.5)
Social functioning	0.0 (-20.8 to 16.7)	-16.7 (-25.0 to 0.0)	-8.3 (-33.3 to 0.0)	-41.7 (-50.0 to -8.3)
Fatigue	0.0 (-5.6 to 13.9)	5.6 (-16.7 to 13.9)	11.1 (0.0 to 19.4)	22.2 (11.1 to 33.3)
Nausea and vomiting	0.0 (-20.8 to 16.7)	0.0 (-4.2 to 0.0)	0.0 (-16.7 to 0.0)	0.0 (0.0 to 12.5)
Pain	-8.3 (-37.5 to 0.0)	0.0 (-16.7 to 20.8)	0.0 (-12.5 to 16.7)	8.3 (-37.5 to 29.2)
Dyspnoea	0.0 (0.0 to 33.3)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	16.7 (0.0 to 33.3)
Insomnia	0.0 (-33.3 to 0.0)	0.0 (-33.3 to 41.7)	0.0 (-33.3 to 33.3)	0.0 (-25.0 to 0.0)
Appetite loss	0.0 (-41.7 to 8.3)	0.0 (-8.3 to 0.0)	0.0 (0.0 to 33.3)	16.7 (0.0 to 58.3)
Constipation	0.0 (-8.3 to 0.0)	0.0 (0.0 to 0.0)	0.0 (-33.3 to 0.0)	0.0 (-75.0 to 0.0)
Diarrhoea	0.0 (-8.3 to 33.3)	0.0 (0.0 to 66.7)	0.0 (0.0 to 25.0)	0.0 (0.0 to 25.0)
Financial difficulties	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 58.3)	0.0 (0.0 to 25.0)

Notes:

[4] - For some categories, subjects available is reduced to 11

[5] - For some categories, subjects available is reduced to 11 or 10

Statistical analyses

Statistical analysis title	Overall QoL
Statistical analysis description:	
Wilcoxon test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Physical functioning
Statistical analysis description: Wilcoxon test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Role functioning
Statistical analysis description: Wilcoxon test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Emotional functioning
Statistical analysis description: Wilcoxon test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Cognitive functioning
Statistical analysis description: Wilcoxon test to assess the differences in QoL changes among the four arms.	
Comparison groups	GEMCAP v Immediate Surgery v FOLFIRINOX v ChemoRadiotherapy

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Social functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Fatigue
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Nausea and vomiting
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	GEMCAP v Immediate Surgery v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Pain
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Dyspnoea
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insomnia
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Appetite loss
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Constipation
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Diarrhoea
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Financial difficulties
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of Life 36 weeks

End point title	Quality of Life 36 weeks
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End point description:

Quality of life will be assessed for all patients with the EORTC Quality of Life Questionnaire version 3. The data will be scored according to the algorithm described in the EORTC scoring manual which linearly transforms the data from categorical scales to a score of 0-100.

Summary measures of quality of life will be expressed as the direct difference in QoL scores between baseline and follow up assessment.

EORTC questionnaire scores will be calculated in two steps, as described in the manual:

Raw Score = $RA = (I1 + I2 + \dots + In) / n$ where $I1 + I2 + \dots + In$ are the component items
Transformation into 0-100 score
For Functional scales: Score = $1 - ((RS-1))/range \times 100$
For Symptom scales / items and Global health status / QoL:

Score = ((RS-1))/range x 100

(dispersion parameter of difference is interquartile range)

End point type	Secondary
End point timeframe:	
Baseline and 36 weeks follow-up	

End point values	Immediate Surgery	GEMCAP	FOLFIRINOX	ChemoRadiotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10 ^[6]	12	7
Units: EORTC QoL index difference				
number (confidence interval 50%)				
Overall QoL	0.0 (-31.2 to 6.2)	-16.7 (-33.3 to 0.0)	-8.3 (-27.1 to 16.7)	-8.3 (-25.0 to 4.2)
Physical functioning	-3.3 (-18.3 to 0.0)	-20.0 (-30.4 to -13.3)	-13.3 (-35.0 to 0.0)	-6.7 (-21.7 to 0.8)
Role functioning	-8.3 (-45.8 to 12.5)	-25.0 (-33.3 to -4.2)	0.0 (-37.5 to 0.0)	-33.3 (-33.3 to -16.7)
Emotional functioning	-11.1 (-22.9 to 6.3)	0.0 (-8.3 to 0.0)	0.0 (-8.3 to 25.0)	25.0 (-5.6 to 37.5)
Cognitive functioning	0.0 (-29.2 to 0.0)	0.0 (-16.7 to 0.0)	0.0 (-33.3 to 0.0)	0.0 (-16.7 to 0.0)
Social functioning	0.0 (-12.5 to 12.5)	0.0 (-16.7 to 0.0)	-16.7 (-37.5 to 4.2)	-16.7 (-33.3 to -16.7)
Fatigue	16.7 (-16.7 to 30.6)	16.7 (-16.7 to 33.3)	0.0 (-13.9 to 38.9)	11.1 (0.0 to 22.2)
Nausea and vomiting	0.0 (-25.0 to 12.5)	8.3 (0.0 to 29.2)	0.0 (-16.7 to 0.0)	0.0 (-8.3 to 8.3)
Pain	8.3 (-29.2 to 58.3)	16.7 (0.0 to 33.3)	8.3 (-16.7 to 37.5)	0.0 (-25.0 to 8.3)
Dyspnoea	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 33.3)	0.0 (0.0 to 0.0)
Insomnia	16.7 (0.0 to 58.3)	0.0 (-25.0 to 0.0)	0.0 (-33.3 to 33.3)	0.0 (-16.7 to 16.7)
Appetite loss	0.0 (-33.3 to 25.0)	0.0 (-25.0 to 25.0)	0.0 (0.0 to 8.3)	0.0 (0.0 to 33.3)
Constipation	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (-8.3 to 0.0)	0.0 (-33.3 to 33.3)
Diarrhoea	0.0 (0.0 to 33.3)	0.0 (0.0 to 33.3)	0.0 (-8.3 to 8.3)	0.0 (0.0 to 16.7)
Financial difficulties	0.0 (0.0 to 25.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 41.7)	0.0 (0.0 to 16.7)

Notes:

[6] - For some categories, available subjects is reduced to 9

Statistical analyses

Statistical analysis title	Overall QoL
Statistical analysis description:	
Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Physical functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Role functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Emotional functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Cognitive functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Social functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Fatigue
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Nausea and vomiting
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Pain
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Dyspnoea
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insomnia
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Appetite loss
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Constipation
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Diarrhoea
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Financial difficulties
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of Life 48 weeks

End point title	Quality of Life 48 weeks
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End point description:

Quality of life will be assessed for all patients with the EORTC Quality of Life Questionnaire version 3. The data will be scored according to the algorithm described in the EORTC scoring manual which linearly transforms the data from categorical scales to a score of 0-100.

Summary measures of quality of life will be expressed as the direct difference in QoL scores between baseline and follow up assessment.

EORTC questionnaire scores will be calculated in two steps, as described in the manual:

Raw Score = RA = $(I1 + I2 + \dots + In) / n$ where $I1 + I2 + \dots + In$ are the component items
Transformation into 0-100 score

For Functional scales: $\text{Score} = 1 - ((\text{RS}-1))/\text{range} \times 100$
For Symptom scales / items and Global health status / QoL:
 $\text{Score} = ((\text{RS}-1))/\text{range} \times 100$

(dispersion parameter of difference is interquartile range)

End point type	Secondary
End point timeframe:	
Baseline and 48 weeks follow-up	

End point values	Immediate Surgery	GEMCAP	FOLFIRINOX	ChemoRadiotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7 ^[7]	10	4
Units: EORTC QoL index difference				
number (confidence interval 50%)				
Overall QoL	0.0 (-8.3 to 33.3)	8.3 (0.0 to 22.9)	0.0 (-8.3 to 16.7)	-8.3 (-18.8 to -4.2)
Physical functioning	-6.7 (-6.7 to 20.0)	-6.7 (-10.0 to 13.3)	0.0 (-11.7 to 0.0)	-23.3 (-26.7 to -16.7)
Role functioning	33.3 (0.0 to 33.3)	0.0 (-8.3 to 8.3)	-8.3 (-45.8 to 0.0)	-33.3 (-50.0 to -25.0)
Emotional functioning	8.3 (0.0 to 16.7)	8.3 (2.1 to 8.3)	0.0 (-12.5 to 25.0)	0.0 (-2.1 to 6.2)
Cognitive functioning	-16.7 (-16.7 to 16.7)	-16.7 (-16.7 to -4.2)	0.0 (-12.5 to 25.0)	-16.7 (-33.3 to 0.0)
Social functioning	33.3 (0.0 to 33.3)	16.7 (0.0 to 45.8)	0.0 (-25.0 to 16.7)	-33.3 (-41.7 to -29.2)
Fatigue	-11.1 (-33.3 to 0.0)	-11.1 (-27.8 to 22.2)	0.0 (-8.3 to 8.3)	38.9 (27.8 to 50.0)
Nausea and vomiting	-33.3 (-33.3 to -33.3)	0.0 (-16.7 to 0.0)	0.0 (-16.7 to 0.0)	8.3 (0.0 to 20.8)
Pain	-33.3 (-66.7 to -16.7)	0.0 (-33.3 to 8.3)	-16.7 (-16.7 to 0.0)	8.3 (-12.5 to 20.8)
Dyspnoea	0.0 (-66.7 to 0.0)	0.0 (-16.7 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Insomnia	0.0 (-33.3 to 0.0)	0.0 (-33.3 to 0.0)	0.0 (-25.0 to 0.0)	-50.0 (-66.7 to -16.7)
Appetite loss	-33.3 (-66.7 to -33.3)	0.0 (-50.0 to 0.0)	0.0 (0.0 to 33.3)	33.3 (25.0 to 41.7)
Constipation	0.0 (0.0 to 0.0)	0.0 (-50.0 to 0.0)	0.0 (-25.0 to 0.0)	-16.7 (-50.0 to 0.0)
Diarrhoea	0.0 (0.0 to 33.3)	0.0 (0.0 to 50.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Financial difficulties	0.0 (0.0 to 0.0)	0.0 (-25.0 to 0.0)	0.0 (0.0 to 33.3)	33.3 (0.0 to 66.7)

Notes:

[7] - For some categories, available subjects is reduced to 6

Statistical analyses

Statistical analysis title	Overall QoL
Statistical analysis description:	
Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Physical functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Role functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Emotional functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Cognitive functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Social functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Fatigue
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Nausea and vomiting
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Pain
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Dyspnoea
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insomnia
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Appetite loss
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Constipation
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Diarrhoea
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Financial difficulties
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of life 52 weeks

End point title	Quality of life 52 weeks
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End point description:

Quality of life will be assessed for all patients with the EORTC Quality of Life Questionnaire version 3. The data will be scored according to the algorithm described in the EORTC scoring manual which linearly transforms the data from categorical scales to a score of 0-100.

Summary measures of quality of life will be expressed as the direct difference in QoL scores between baseline and follow up assessment.

EORTC questionnaire scores will be calculated in two steps, as described in the manual:

Raw Score = RA = $(I1 + I2 + \dots + In) / n$ where $I1 + I2 + \dots + In$ are the component items
Transformation into 0-100 score

For Functional scales: $\text{Score} = 1 - ((\text{RS}-1))/\text{range} \times 100$
For Symptom scales / items and Global health status / QoL:
 $\text{Score} = ((\text{RS}-1))/\text{range} \times 100$

(dispersion parameter of difference is interquartile range)

End point type	Secondary
End point timeframe:	
Baseline and 52 weeks follow-up	

End point values	Immediate Surgery	GEMCAP	FOLFIRINOX	ChemoRadiotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[8]	7 ^[9]	6	2
Units: EORTC QoL index difference				
number (confidence interval 50%)				
Overall QoL	8.3 (4.2 to 10.4)	16.7 (4.2 to 29.2)	12.5 (2.1 to 47.9)	0.0 (0.0 to 0.0)
Physical functioning	10.0 (0.0 to 23.3)	-5.0 (-16.7 to 13.3)	-3.3 (-11.7 to 0.0)	-11.7 (-12.5 to -10.8)
Role functioning	41.7 (25.0 to 54.2)	0.0 (-33.3 to 33.3)	8.3 (-25.0 to 16.7)	-16.7 (-16.7 to -16.7)
Emotional functioning	8.3 (0.0 to 29.2)	12.5 (2.1 to 16.7)	16.7 (10.4 to 22.9)	15.3 (10.4 to 20.1)
Cognitive functioning	16.7 (12.5 to 20.8)	0.0 (-25.0 to 12.5)	0.0 (0.0 to 12.5)	0.0 (0.0 to 0.0)
Social functioning	33.3 (12.5 to 50.0)	16.7 (0.0 to 45.8)	16.7 (4.2 to 29.2)	-25.0 (-29.2 to -20.8)
Fatigue	-22.2 (-36.1 to -8.3)	0.0 (-22.2 to 11.1)	0.0 (0.0 to 8.3)	0.0 (0.0 to 0.0)
Nausea and vomiting	-33.3 (-41.7 to -25.0)	0.0 (-16.7 to 0.0)	0.0 (-12.5 to 0.0)	-8.3 (-12.5 to -4.2)
Pain	-25.0 (-50.0 to -12.5)	33.3 (-16.7 to 41.7)	-8.3 (-41.7 to 0.0)	8.3 (4.2 to 12.5)
Dyspnoea	-33.3 (-66.7 to 0.0)	0.0 (-16.7 to 0.0)	0.0 (0.0 to 0.0)	16.7 (8.3 to 25.0)
Insomnia	-33.3 (-66.7 to 8.3)	-33.3 (-33.3 to 16.7)	-16.7 (-33.3 to 25.0)	-50.0 (-58.3 to -41.7)
Appetite loss	-66.7 (-66.7 to -58.3)	-33.3 (-83.3 to -16.7)	-16.7 (-33.3 to 0.0)	0.0 (0.0 to 0.0)
Constipation	0.0 (-16.7 to 0.0)	-33.3 (-58.3 to -8.3)	0.0 (-25.0 to 0.0)	0.0 (0.0 to 0.0)
Diarrhoea	0.0 (0.0 to 8.3)	0.0 (0.0 to 25.0)	0.0 (0.0 to 0.0)	33.3 (16.7 to 50.0)
Financial difficulties	0.0 (-33.3 to 0.0)	0.0 (-25.0 to 0.0)	0.0 (0.0 to 25.0)	0.0 (0.0 to 0.0)

Notes:

[8] - For some categories, subjects available is reduced to 3.

[9] - For some categories, subjects available is reduced to 6.

Statistical analyses

Statistical analysis title	Overall QoL
Statistical analysis description:	
Wilcoxon test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Physical functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Role functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Emotional functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Cognitive functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Social functioning
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Fatigue
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Nausea and vomiting
Statistical analysis description: Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Pain
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Dyspnoea
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Insomnia
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Appetite loss
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Statistical analysis description:

Wilcox test to assess the differences in QoL changes among the four arms.

Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Constipation
Statistical analysis description:	
Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Diarrhoea
Statistical analysis description:	
Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Financial difficulties
Statistical analysis description:	
Wilcox test to assess the differences in QoL changes among the four arms.	
Comparison groups	Immediate Surgery v GEMCAP v FOLFIRINOX v ChemoRadiotherapy
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout treatment phase

Adverse event reporting additional description:

Overall, 1258 adverse events occurred during the course of the study (120, 401, 428 and 309 in the surgery, GEMCAP, FOLFIRINOX and ChemoRadiotherapy arms respectively). Adverse events were recorded at each visit and it is not possible to assess whether an event was ongoing from the previous visit or was a new one.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Immediate Surgery
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Reporting group description:

120 adverse events were recorded across patients

Reporting group title	GEMCAP
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Reporting group description:

401 adverse events were recorded across patients.

Reporting group title	FOLFIRINOX
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Reporting group description:

428 adverse events were recorded across patients.

Reporting group title	ChemoRadiotherapy
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Reporting group description:

309 adverse events were recorded across patients.

Serious adverse events	Immediate Surgery	GEMCAP	FOLFIRINOX
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 28 (10.71%)	2 / 17 (11.76%)	5 / 19 (26.32%)
number of deaths (all causes)	18	4	3
number of deaths resulting from adverse events			
Investigations			
Creatinine increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastric anastomotic leak			

subjects affected / exposed	1 / 28 (3.57%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 17 (5.88%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 28 (7.14%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	2 / 28 (7.14%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 17 (5.88%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 17 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ChemoRadiotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
Investigations			
Creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Gastric anastomotic leak			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Immediate Surgery	GEMCAP	FOLFIRINOX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)	17 / 17 (100.00%)	19 / 19 (100.00%)
Investigations			
All Events	Additional description: 1236 non-serious adverse events were reported across reporting groups. Granular data are not available but these events were split 117:399:423:305 by reporting group.		
subjects affected / exposed	28 / 28 (100.00%)	17 / 17 (100.00%)	19 / 19 (100.00%)
occurrences (all)	28	17	19

Non-serious adverse events	ChemoRadiotherapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
Investigations			
All Events	Additional description: 1236 non-serious adverse events were reported across reporting groups. Granular data are not available but these events were split 117:399:423:305 by reporting group.		
subjects affected / exposed	14 / 14 (100.00%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2014	<p>3. Protocol Updated to Version 3, dated 5 August 2014</p> <p>Summary of changes:</p> <ol style="list-style-type: none">1) Updated numbering of tables.2) Contact details updated.3) Inclusion criteria no. 8 modified from creatinine clearance to glomerular filtration rate.4) Exclusion criteria no. 4 to allow exceptions case by case, e.g. methotrexate for rheumatoid arthritis.5) Section 4: two additional procedures for the screening and randomisation process.6) Section 7.3.1: allow pre-prepared vials/bags of solution as well as powder, as gemcitabine is now generic.7) Section 7: clarification that there is a 2-day window for taking toxicity-assessment bloods.8) Section 7: clarification regarding the use of G-CSF.9) Section 7: clarification on managing patients with angina or angina-like pain.10) Section 7.3.2: clarification of dose banding procedures.11) Section 7.4.1, Arm C, FOLFIRINOX: folinic acid may now be either calcium or sodium folinate rather than Sodiofolin as previously specified.12) Section 7.4.2, Arm C, FOLFIRINOX: folinic acid administration changed from 400mg/m² to local practice.13) Section 7.5, Chemoradiotherapy: re-written for improved clarity and with more detail.14) Section 8.1: addition of pathology central core lab review to the schedules of procedures and other clarifications.15) Section 8.5, Translational study: re-written for clarity and to reflect laboratory SOPs.16) Section 8.6, Quality Assurance: further information added regarding the transfer of radiology images to the LCTU; radiotherapy paragraph also added.17) Section 9.2: minimisation specified as the method of randomisation.18) Section 12: regulatory approval details added.19) Section 17: additional information regarding the publication policy.20) Miscellaneous administrative changes.

28 April 2015	<p>Protocol Updated to Version 4, dated 28.04.2015</p> <ol style="list-style-type: none"> 1) Updated numbering of tables. 2) Contact details updated. 3) Exclusion Criteria No 2 modified to Previous or concurrent malignancy diagnoses, except: i) curatively treated basal cell carcinoma of skin, ii) carcinoma in situ of cervix, iii) previous cancers treated with curative intent, ending treatment ≥ 5 years ago. 4) Exclusion Criteria No 4 modified to Previous chemotherapy ending < 5 years ago (exceptions may be given case by case by the CI, such as methotrexate for rheumatoid arthritis). 5) Schematic of Study Design modified to show Review of staging MDCT scan by central laboratory will be included within the screening process. 6) Section 7.3.3 Dose Modifications: Information on treatment delays has been added to this section: Treatment delays should be avoided as far possible; the maximum allowable treatment omission is 3 weeks. Any patient whose treatment is omitted for longer than 3 weeks should discontinue therapy. All patients who withdraw from treatment should remain on followup within the trial. 7) Section 7.4.1 Active Ingredient Name /Dose for 5Fluorouracil modified typo to show correct 50 mg fluorouracil in 10 ml solution not 500mg. 8) Section 7.4.1 Irinotecan formulation modified to show Concentrate For Solution For Infusion not injection as per the approved SmPC for Irinotecan. 9) Section 7.4.3 Dose Modifications Information on treatment delays has been added to this section: Treatment delays should be avoided as far possible; the maximum allowable treatment omission is 3 weeks. Any patient whose treatment is omitted for longer than 3 weeks should discontinue therapy. All patients who withdraw from treatment should remain on followup within the trial. 10) Section 7.5.2 Optional PreRadiotherapy Investigations. Reworded to allow local standard of care using additional diagnostic assessments, as per institutional practice, may be of assistance in identifying disease not visible on CT
22 March 2016	<p>1 - Exclusion Criteria Change</p> <p>Exclusion criteria change from</p> <ul style="list-style-type: none"> • Previous or concurrent malignancy diagnoses, except: i) curatively-treated basal cell carcinoma of skin, ii) carcinoma in situ of cervix, iii) previous cancers treated with curative intent, ending treatment ≥ 5 years ago. <p>To new suggested text</p> <ul style="list-style-type: none"> • Previous or concurrent malignancy diagnoses, except curatively-treated (i) basal cell carcinoma of skin, ii) carcinoma in situ of cervix; breast; bladder; (iii) non muscle invasive transitional cell carcinoma of the bladder; iv) previous cancers treated with curative intent, ending treatment ≥ 3 years ago. <p>Exclusion criteria change from</p> <ul style="list-style-type: none"> • Previous chemotherapy ending < 5 years ago (exceptions may be given case by case by the CI, such as methotrexate for rheumatoid arthritis). <p>To new suggested text</p> <ul style="list-style-type: none"> • Previous chemotherapy ending < 3 years ago (exceptions may be given case by case by the CI, such as methotrexate for rheumatoid arthritis).
31 July 2017	<p>Update to Protocol Version 6.0</p> <ol style="list-style-type: none"> 1) Inserted additional information to section 5.1.2 'Ending Trial intervention Early' to clarify how patients should be followed up 2) Amendments to the table of assessments was necessary to avoid confusion for sites. The information was adjusted to make it clear for research nurses at site 3) Protocol was updated to state that SAEs related to surgery, although should be reported, they would not be classed as 'unexpected' as all complications in surgery are expected. These will not be included in expedited reporting to the MHRA 4) Patients with 1.0 absolute neutrophil count should have 100% of the gemcitabine dose and there was no need for a dose reduction 5) The initial recruitment projection has been reviewed during the course of the study by the trial management group due to difficulties in opening centres and randomising patients in the first months of the trial. This created a need for an extension to recruitment and the statistical considerations have been updated to reflect this

05 August 2020	<p>Update to Protocol Version 7</p> <p>Amendment 1:</p> <p>Protocol Amendment End of Trial definition need amending</p> <p>Old Wording Section 8.8 Protocol Version 6.0 Dated 27/01/2017:</p> <p>The trial is closed when the required number of events for the secondary endpoints, disease and local disease free survival rate and overall survival, as defined in section 9.3.2, is reached and the database has been fully cleaned and frozen for each of these two final analyses.:</p> <p>New Wording Section 8.0:</p> <p>'The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database']</p> <p>Amendment 2:</p> <p>Protocol Amendment Extension of visit window</p> <p>Addition of + 90 days visit window on the week 52 follow-up visit on all arms.</p> <p>Amendment to Table 16 – 19</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported