Immediate surgery compared with short-course neoadjuvant gemcitabine plus capecitabine, FOLFIRINOX, or chemoradiotherapy in patients with borderline resectable pancreatic cancer (ESPAC5): a four-arm, multicentre, randomised, phase 2 trial

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Summary

Background Patients with borderline resectable pancreatic ductal adenocarcinoma have relatively low resection rates and poor survival despite the use of adjuvant chemotherapy. The aim of our study was to establish the feasibility and efficacy of three different types of short-course neoadjuvant therapy compared with immediate surgery.

Methods ESPAC5 (formerly known as ESPAC-5f) was a multicentre, open label, randomised controlled trial done in 16 pancreatic centres in two countries (UK and Germany). Eligible patients were aged 18 years or older, with a WHO performance status of 0 or 1, biopsy proven pancreatic ductal adenocarcinoma in the pancreatic head, and were staged as having a borderline resectable tumour by contrast-enhanced CT following central review. Participants were randomly assigned by means of minimisation to one of four groups: immediate surgery; neoadjuvant gemcitabine and capecitabine (gemcitabine 1000 mg/m² on days 1, 8, and 15, and oral capecitabine 830 mg/m² twice a day on days 1–21 of a 28-day cycle for two cycles); neoadjuvant FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², 5-fluorouracil 400 mg/m² bolus injection on days 1 and 15 followed by 2400 mg/m² 46 h intravenous infusion given on days 1 and 15, repeated every 2 weeks for four cycles); or neoadjuvant capecitabine-based chemoradiation (total dose 50.4 Gy in 28 daily fractions over 5.5 weeks [1.8 Gy per fraction, Monday to Friday] with capecitabine 830 mg/m² twice daily [Monday to Friday] throughout radiotherapy). Patients underwent restaging contrast-enhanced CT at 4–6 weeks after neoadjuvant therapy and underwent surgical exploration if the tumour was still at least borderline resectable. All patients who had their tumour resected received adjuvant therapy at the oncologist’s discretion. Primary endpoints were recruitment rate and resection rate. Analyses were done on an intention-to-treat basis. This trial is registered with ISRCTN, 89500674, and is complete.

Findings Between Sept 3, 2014, and Dec 20, 2018, from 478 patients screened, 90 were randomly assigned to a group (33 to immediate surgery, 20 to gemcitabine plus capecitabine, 20 to FOLFIRINOX, and 17 to capecitabine-based chemoradiation); four patients were excluded from the intention-to-treat analysis (one in the capecitabine-based chemoradiotherapy withdrew consent before starting therapy and three [two in the immediate surgery group and one in the gemcitabine plus capecitabine group] were found to be ineligible after randomisation). 44 (80%) of 55 patients completed neoadjuvant therapy. The recruitment rate was 25–92 patients per year from 16 sites; 21 (68%) of 31 patients in the immediate surgery and 30 (55%) of 55 patients in the combined neoadjuvant therapy groups underwent resection (p=0.33). R0 resection was achieved in three (14%) of 21 patients in the immediate surgery group and seven (23%) of 30 in the neoadjuvant therapy group (p=0.49). Surgical complications were observed in 29 (43%) of 68 patients who underwent surgery; no patients died within 30 days. 46 (84%) of 55 patients receiving neoadjuvant therapy were available for restaging. Six (13%) of 46 had a partial response. Median follow-up time was 12.2 months (95% CI 12.0–12.4). 1-year overall survival was 39% (95% CI 24–61) for immediate surgery, 78% (60–100) for gemcitabine plus capecitabine, 84% (70–100) for FOLFIRINOX, and 60% (37–97) for capecitabine-based chemoradiotherapy (p=0.0028). 1-year disease-free survival from surgery was 33% (95% CI 19–58) for immediate surgery and 59% (46–74) for the combined neoadjuvant therapies (hazard ratio 0.53 [95% CI 0.28–0.98], p=0.016). Three patients reported local disease recurrence (two in the immediate surgery group and one in the FOLFIRINOX group). 78% (91%) patients were included in the safety set and assessed for toxicity events. 19 (24%) of 78 patients reported a grade 3 or worse adverse event (two [7%] of 28 patients in the immediate surgery group and 17 [34%] of 50 patients in the neoadjuvant therapy groups combined), the most common of which were neutropenia, infection, and hyperglycaemia.
Interpretation Recruitment was challenging. There was no significant difference in resection rates between patients who underwent immediate surgery and those who underwent neoadjuvant therapy. Short-course (8 week) neoadjuvant therapy had a significant survival benefit compared with immediate surgery. Neoadjuvant chemotherapy with either gemcitabine plus capcitabine or FOLFIRINOX had the best survival compared with immediate surgery. These findings support the use of short-course neoadjuvant chemotherapy in patients with borderline resectable pancreatic ductal adenocarcinoma.

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Introduction Pancreatic ductal adenocarcinoma remains a highly challenging cancer to treat. In 2020 the International Agency for Research on Cancer reported 495773 new cases with 466003 deaths globally. In the USA there has been improvement in 5-year overall survival with pancreatic ductal adenocarcinoma from less than 5% to 11% over the past three decades but this is poor compared with other tumour types, and it now ranks as the third most common cause of cancer death in the USA. The most important determinants of survival are surgical resection (owing to improved morbidity and mortality rates) combined with postoperative adjuvant chemotherapy. For upfront locally resectable pancreatic ductal adenocarcinoma (about 20% of all cases), single-agent adjuvant chemotherapy improves 5-year overall survival from 8% for surgery alone to 16–21% with adjuvant therapy. A further step forward has been the use of combination chemotherapy, with 3-year overall survival of 63–4% and a median overall survival of 54–4 months reported with modified FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) in selected patients aged less than 79 years old; and a 5-year overall survival of 28–8%, and a median overall survival of 28–0 months with gemcitabine plus capcitabine in unselected patients including those aged older than 80 years.

Resections are being increasingly offered to patients with borderline locally resectable pancreatic ductal adenocarcinoma or unresectable disease, altogether some 30% of pancreatic cancer cases. One approach has been to use preoperative neoadjuvant therapy to increase resectability rates, and thus improve overall survival. However, there have been no proof-of-concept randomised controlled trials of neoadjuvant therapy with immediate surgery as a control group. A secondary question is the optimal type of neoadjuvant therapy to be used. Two chemotherapy regimens—modified FOLFIRINOX and gemcitabine plus capcitabine—are efficacious in both the advanced and the adjuvant settings, but with differing degrees of toxicity. To the best of our knowledge, these two regimens have never been compared head to head. Although modified FOLFIRINOX

Research in context

Evidence before this study The standard of care for resectable and borderline resectable pancreatic ductal adenocarcinoma at the time of conception of this study was resection followed by adjuvant chemotherapy. Patients with borderline resectable disease had relatively low resection rates of around 50% and poor overall survival. The addition of neoadjuvant therapy might improve tumour resectability and survival. Before the start of this trial there were numerous cohort studies of neoadjuvant therapy in pancreatic cancer, but very little randomised evidence. We searched PubMed for randomised trials comparing immediate surgery versus neoadjuvant therapy up to 2013 published in English. We used search terms “neoadjuvant”, “pancreatic cancer”, “clinical trial”, “randomised”, “adenocarcinoma”, and “neoadjuvant therapy”. The search did not identify a completed randomised trial comparing immediate surgery with neoadjuvant therapy.

Added value of this study ESPAC5 is, we believe, the first randomised trial to compare different types of short-course neoadjuvant therapy with immediate surgery in patients with borderline resectable pancreatic ductal adenocarcinoma. Considering challenging recruitment conditions and a short follow-up of 12 months, the 1-year survival benefit with neoadjuvant therapy was significantly better than immediate surgery. Neoadjuvant chemotherapy was more effective than neoadjuvant chemoradiotherapy.

Implications of all the available evidence Since the start of the ESPAC5 trial there have been several randomised trials of immediate surgery versus neoadjuvant therapy in pancreatic cancer. None have compared different short-course regimens, and none have included detailed quality assurance of surgery, pathology, and radiotherapy. The outcomes have been mixed, and while they have provided evidence for the use of neoadjuvant therapy in borderline resectable pancreatic ductal adenocarcinoma, none have shown such a clear survival difference between groups. Even in the context of this feasibility study, the results of this trial provide evidence for short-course neoadjuvant chemotherapy in borderline resectable pancreatic ductal adenocarcinoma.
appears to provide a better tumour response and longer survival than gemcitabine plus capecitabine, the eligibility criteria for receiving this regimen are prognostically more favourable. Although modified FOLFIRINOX might provide a better tumour response in the locally advanced setting, potentially leading to more resections, its greater toxicity relative to gemcitabine plus capecitabine might lead to fewer attempted resections. Chemoradiation in the neoadjuvant setting remains an open question.\(^{1,3,12,14}\)

A previous randomised phase 2 trial of chemotherapy (either capecitabine or gemcitabine) followed by consolidation with either capecitabine-based or gemcitabine-based chemoradiotherapy regimens, for patients with locally advanced pancreatic cancer, found that capecitabine-based chemotherapy and chemoradiotherapy was the clinically more efficacious regimen.\(^{13}\)

Median overall survival was 15.2 months in the capecitabine group and 13.4 months in the gemcitabine group, and more patients in the gemcitabine group had grade 3–4 haematological toxic effects.\(^{17}\)

At the time we conceived the ESPAC5 trial, there was little information from the UK, Germany, or elsewhere on which to base our study, which aimed to explore whether short-course neoadjuvant therapy, followed by resection and then adjuvant therapy, might be superior to immediate surgery and adjuvant treatment in patients with borderline pancreatic ductal adenocarcinoma. We decided that a feasibility and efficacy trial was the best way to test this hypothesis in a pragmatic fashion, using recruitment rate and resection rate as a guide for establishing power calculations for the trial.

**Methods**

**Study design and participants**

ESPAC5 was a multicentre, randomised, open-label, controlled, phase 2 feasibility trial. The trial was done in 16 pancreatic centres in the UK and Germany.

The planned population comprised patients with borderline resectable pancreatic ductal adenocarcinoma. Inclusion criteria were a borderline resectable mass in the pancreatic head defined by contrast-enhanced CT scan criteria (based on the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology;\(^{11}\) appendix p 2); histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants); ability to undergo biliary drainage by means of a covered, partially covered self-expanding, or uncovered metal stent; age 18 years or older; a WHO performance status of 0 or 1; platelet concentration of more than 100×10\(^9\)/L; white cell count more than 3×10\(^9\)/cells per L; neutrophil count more than 1.5×10\(^9\)/cells per L; serum bilirubin less than 1.5 times upper limit of normal; glomerular filtration rate estimated to be greater than 50 mL/min; ability to comply with protocol requirements and fit for surgical resection, chemotherapy, and radiotherapy; and written informed consent. Exclusion criteria were distant metastatic disease; previous or concurrent malignancy diagnoses (except curatively treated basal cell carcinoma of skin, carcinoma in situ of cervix, or previous cancers treated with curative intent for which treatment ended at least 3 years ago); serious medical or psychological condition precluding neoadjuvant treatment and surgical resection; previous chemoradiotherapy ending more than 3 years ago; pregnancy; a New York Heart Association Classification grade III or IV; and uncontrolled angina or ischaemic heart disease.

Participants were identified at multidisciplinary team meetings and recruited at participating hospitals by principal investigators. All participants were required to give written informed consent before entering the trial. Sex and gender data were collected at clinical review.

The trial was co-ordinated by the Liverpool Clinical Trials Centre, UK, and reported in line with the CONSORT (2010) guidelines. Ethical approval was given by the North West Research Ethics Committee in 2014. The study protocol is available online. The study protocol underwent five amendments (Dec 20, 2013, Feb 24, 2014, Aug 5, 2014, April 28, 2015, and Jan 27, 2016). An independent data and safety monitoring committee was responsible for reviewing recruitment, monitoring of safety, effectiveness, trial conduct, and external data. The trial steering committee provided supervision and advice.

**Randomisation and masking**

Participants were randomly assigned to one of the following groups (2:1:1:1): immediate surgery; neoadjuvant gemcitabine plus capecitabine; neoadjuvant FOLFIRINOX; or neoadjuvant capecitabine-based chemoradiotherapy. Randomisation was done with minimisation, developed by a statistician independent of the study and included a random element of 20% with centre as the sole stratification factor. Randomisation was done centrally by trained authorised staff within the Liverpool Clinical Trials Centre. Participants were assigned to interventions by a web-based allocation system. This was an open-label study with participants and investigators not masked to treatment allocation.

**Procedures**

Treatment was planned to start within 2 weeks of randomisation. Patients assigned to the immediate surgery group underwent surgical exploration and resection if possible. Patients assigned to the neoadjuvant gemcitabine and capecitabine group received gemcitabine 1000 mg/m\(^2\) intravenous infusion over 30 min on days 1, 8, and 15, and capecitabine 830 mg/m\(^2\) twice a day orally on days 1–21 of a 28-day cycle for two cycles. Those assigned to the neoadjuvant FOLFIRINOX group received oxaliplatin 85 mg/m\(^2\), irinotecan 180 mg/m\(^2\), folinic acid given according to local practice for both the drug and the dose, and fluorouracil 400 mg/m\(^2\) bolus injection on days 1 and 15 followed by 2400 mg/m\(^2\) 46 h infusion on days 1 and 15, repeated every 2 weeks for four cycles. Those assigned to...
the neoadjuvant chemoradiotherapy group received radiotherapy at a total dose of 30·4 Gy in 28 daily fractions over 5·5 weeks (1·8 Gy per fraction, Monday to Friday) with capcitabine 830 mg/m² twice a day orally (Monday to Friday) throughout radiotherapy. Dose reductions for gemcitabine, capcitabine, and FOLFIRINOX were permitted and are detailed in the protocol. Following a dose reduction for FOLFIRINOX, no re-escalation was permitted. If the same grade 4 toxicity occurred despite dose reductions, FOLFIRINOX was discontinued. The maximum allowable treatment omission was 3 weeks. If treatment was omitted for longer than 3 weeks then therapy was discontinued.

4–6 weeks after completion of neoadjuvant therapy, all participants who had received neoadjuvant treatment underwent restaging with a contrast-enhanced CT scan; if there was no progression then participants underwent surgical exploration within 2 weeks. For all groups of the trial, following successful surgical resection, participants were considered for adjuvant chemotherapy. The choice of adjuvant therapy was at the clinicians’ discretion after discussion with each patient. At the start of the trial, the standard of care in the UK and Germany was adjuvant gemcitabine; combination adjuvant therapy only became available towards the end of the trial and was dependent on patient fitness. If participants did not undergo resection, further therapy was decided by the patient and clinician. Follow-up visits were every 3 months for 12 months following randomisation. Assessments at each 3-month visit included clinical examination, CA19-9, haematology, biochemistry, and contrast-enhanced CT scan. Patients could withdraw consent at any point during the study.

Central review of the baseline contrast-enhanced CT scans was done at the core central radiology laboratory, located at the Department of Radiology, Royal Liverpool and Broadgreen University Hospital NHS Trust, Liverpool, UK. CT scan images were electronically transferred to the core laboratory then reviewed by a masked radiologist and surgeon, to ensure borderline resectability of the tumour.

Minimum surgical quality standards were applied, as agreed by the ESPAC5 surgical working party, and incorporated into the ESPAC5 surgical handbook (details are available in the protocol). All investigators attended workshops run from the coordinating centre in Liverpool. Photographs were taken of the operative field and a surgical proforma was completed.

Developed in collaboration with the National Cancer Research Institute Radiotherapy Trials Quality Assurance team (NCRI RTTQA), the protocol and guidance document development involved a wide group of radiation oncologists, physicists, radiographers, and the SCALOP radiation protocol development team. The detailed ESPAC5 radiotherapy planning and delivery guideline document is available on the NCRI RTTQA website.

Central pathology review was done at the core laboratory at the Royal Liverpool and Broadgreen University Hospitals NHS Trust. Diagnostic specimens and histology slides of resection specimens were reviewed to confirm the local site assessment.

Safety was assessed through the reporting of adverse events. Formal toxicity assessments were done at each study visit. Adverse events were described by means of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.19 All new serious adverse events were reported from the start of preoperative care for patients who underwent immediate surgery until 28 days after the operation, and for patients in the other groups from the start of neoadjuvant treatment until 28 days following the last dose of neoadjuvant treatment. All non-serious adverse events, whether expected or not, were recorded and updated at each study visit. All events judged by the investigator to be related to the investigational medicinal product and graded as serious and unexpected were reported as a suspected unexpected serious adverse reaction. All serious adverse events that were related to surgery were not assessed as unexpected and therefore were not reported as suspected unexpected serious adverse reactions. Central and site monitoring was done throughout the trial.

Outcomes

The primary outcome measures were patient recruitment and surgical resection. Recruitment rate was measured as the number of patients randomly assigned relative to the time (in months) each centre was open to recruitment. Resection was defined as the number of patients with an R1 and R0 resection margin. R1 was defined as any cancer cell within 1 mm of any surface of the resected specimen, as per the Royal College of Pathologists (RCP) report on standards and datasets for reporting cancers.18

Secondary outcome measures were R0 resection margin rate, measured according to the RCP report on standards and datasets for reporting cancers; toxicity, graded according to the NCI-CTCAE version 4;19 post-operative complication rate recorded following surgery, classified according to Dindo and colleagues;20 post-operative mortality rate, recorded as 30-day mortality; response rate, reported according to Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1);21 disease-free survival, measured as the time between date of surgery and date of disease recurrence (CT scan, with or without clinical assessment and with or without CA19-9) or date of last follow-up if alive and disease free; local disease-free survival, measured as the time between date of surgery and date of local disease recurrence (CT scan) or date of last follow-up if alive and local disease free; overall survival, measured as the time between date of randomisation and date of death from any cause or date of last follow-up if alive; quality of life, assessed by the EORTC quality-of-life for cancer patients...
Statistical analysis
We aimed to recruit a total of 100 patients, with 40 patients being allocated to immediate surgery and 20 to each of the neoadjuvant therapy groups. The primary clinical outcome is resection rate; however, this study was not powered to compare resection rates between all available treatment groups. The sample size was large enough to compare the resection rate of all patients receiving neoadjuvant therapy versus immediate surgery with a power of 82% (one-sided \( \alpha=0.2 \), \( p_0=0.35 \), \( p_1=0.55 \)); however, as this was a feasibility study, no clinical criteria were set to establish the overall success of the study.

The overall rate of recruitment was reported as the number of patients recruited per site per month for all sites and overall. The success criteria for the study were based on showing that target recruitment of 100 patients was met. Resection rates were reported by means of both the total number of patients randomly assigned to the group and the number who underwent explorative surgery as denominators. Results are presented as proportions across treatment groups and compared with Fisher’s exact tests. Further binary secondary endpoints (R0 resection rates, post-operative complication rates, and response rates) are reported as proportions for each treatment group and compared across groups with Fisher’s exact tests.

Time-to-event endpoints were estimated with the Kaplan-Meier method. For both overall survival and distant recurrence-free survival, patients not having an event were censored at the date last known to be event-free. 1-year survival estimates are presented with 95% CIs. Differences across treatment groups were explored by means of Cox proportional hazards model stratified by centre and reported in terms of hazard ratios (HRs; 95% CIs). Assumptions of proportionality are assessed via inspection of Schoenfeld residuals. The median follow-up time (95% CI) was calculated with the reverse Kaplan-Meier method. Toxicity data are summarised as adverse events and serious adverse events. Any adverse event, either grade 3 and higher or any adverse event (of grade 1 or 2), which were reported in at least 10% of patients are included. All serious adverse events are reported with data presented as rates across treatment groups. Quality of life was assessed longitudinally at baseline and at four follow-up timepoints. The number of patients receiving allocated treatment, the treatment duration, and the range of total doses received are summarised. The number of patients receiving adjuvant therapy after resection and the type of treatment received are also reported.

Analyses were done on an intention-to-treat basis retaining all patients in their initially randomised allocation irrespective of any protocol deviations, with the exception of patients who withdrew consent before starting therapy and patients who were found to be ineligible after random assignment (the full analysis set).

Analyses of R0 resection rates were done on a modified intention-to-treat population, restricted to only those patients who underwent surgery. Toxicity analyses were done on the safety-set population, including patients who received allocated trial treatment.

All statistical analyses were done with R version 3.6.1. A two-sided significance level of \( p \) value of less than 0.05 was used throughout for any explorative comparison.

The end of the trial was defined as the date on which data for all participants was frozen and data entry privileges were withdrawn from the trial database (Feb 3, 2021). This trial is registered with ISRCTN, 89500674.

Role of the funding source
The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Sept 3, 2014, and Dec 20, 2018, 478 patients were screened and 90 were randomly assigned to a study group (figure 1). 33 patients were assigned to proceed immediately to surgery, 20 to receive neoadjuvant gemcitabine plus capecitabine, 20 to receive neoadjuvant FOLFIRINOX, and 17 to receive neoadjuvant chemoradiotherapy (figure 1). Four patients were excluded from the full analysis set (one in the neoadjuvant chemoradiotherapy group withdrew consent before starting therapy and three [two in the immediate surgery group and one in the neoadjuvant gemcitabine plus capecitabine group] were found to be ineligible after randomisation owing to incorrect histology and staging: figure 1). Thus, our original target of recruiting 100 patients was not reached. The last patient visit was on the Dec 23, 2019. The overall recruitment rate for the study was 2.16 patients per month (25.92 per year; range 0.0-73 patients per site per month for each individual site; appendix pp 3, 18). Two sites recruited no patients; of the remaining 14, 12 (86%) centres enrolled fewer than two patients per year. The median age of the patients was 63 years (IQR 57–69); 48 (56%) of the 86 patients in the full analysis set were female and 38 (44%) were male. Further baseline patient characteristics are shown in table 1.

Five patients (two in the neoadjuvant gemcitabine plus capecitabine group, one in the neoadjuvant FOLFIRINOX group, and two in the neoadjuvant chemoradiotherapy group) did not start their allocated neoadjuvant treatment. Planned therapy was completed by all 17 patients who started it in the neoadjuvant gemcitabine plus capecitabine group, 15 (79%) of 19 patients in the neoadjuvant FOLFIRINOX group and 12 (86%) of 14 in the neoadjuvant chemoradiotherapy. In the neoadjuvant gemcitabine plus...
capcitabine group, the median dose received of gemcitabine was 94% (IQR 70–99) and that for capecitabine was 90% (IQR 80–99) of the specified protocol dose. In the neoadjuvant FOLFIRINOX group, the median percentage of the protocol specified doses were 96% (IQR 75–99) for oxaliplatin, 96% (IQR 77–100) for irinotecan, and 98% (IQR 82–100) for fluorouracil. In the neoadjuvant chemoradiotherapy group, the median
percentage of the protocol specified radiotherapy dose was 100% (IQR 100–100) and the median percentage of the protocol specified capecitabine dose was 84% (IQR 53–93).

Details on patient delays, reductions, and omissions are included in the appendix (p 19). Patients receiving neoadjuvant therapy displayed significant reductions in CA19-9 between random assignment and surgery (appendix p 15). The median follow-up time was 12-2 months (95% CI 12.0–12.4). Of the 86 patients in the full analysis set, 68 (79%) underwent surgery: 28 (90%) of 31 patients in the immediate surgery group, 13 (68%) of 19 in the neoadjuvant gemcitabine plus capecitabine group, 17 (85%) of 20 in the neoadjuvant FOLFIRINOX group, and 10 (63%) of 16 in the neoadjuvant chemoradiotherapy group.

51 (59%) of 86 patients underwent resection—21 (68%) of 31 patients in the immediate surgery group and 30 (55%) of 55 in the pooled neoadjuvant therapy groups (p=0.33). Three (14%) of 21 patients in the immediate surgery group had an R0 resection, as did seven (23%) of 30 patients in the combined neoadjuvant therapy groups (p=0.49). Two (18%) of 11 in the neoadjuvant gemcitabine plus capecitabine group, two (18%) of 11 patients in the neoadjuvant FOLFIRINOX group and three (37%) of eight in the neoadjuvant chemoradiotherapy group had an R0 resection. 36 (71%) of 51 patients had positive lymph nodes: 19 (90%) of 21 in the immediate surgery group, seven (64%) of 11 in the neoadjuvant gemcitabine plus capecitabine group, eight (73%) of 11 in the neoadjuvant FOLFIRINOX group and two (25%) of eight in the neoadjuvant chemoradiotherapy group. Details of surgical procedures are described in table 1 and surgical characteristics in the appendix (pp 4, 5).

Surgical complications were observed in 29 (43%) of 68 patients: 14 (50%) of 28 in the immediate surgery group and 15 (38%) of 40 for neoadjuvant therapies combined (p=0.54; appendix p 6). There were no deaths within 30 days of surgery. The overall 90-day mortality rate following surgery was 7% (five of 68 patients, four were unresectable at the time of surgery and underwent bypass surgery consisting of gastrojejunostomy with or without hepatico-jejunostomy). There were two deaths in the surgery group and 17 (85%) of 20 in the neoadjuvant FOLFIRINOX group, and 10 (63%) of 16 in the neoadjuvant chemoradiotherapy group.

46 (84%) of 55 patients receiving neoadjuvant therapy were available for restaging. No patients had a complete response, six (13%) of 46 had a partial response (two in the neoadjuvant gemcitabine plus capecitabine group and four in the neoadjuvant FOLFIRINOX group), 33 (72%) of 46 had confirmed stable disease (12 in the neoadjuvant gemcitabine plus capecitabine group, 12 in the neoadjuvant FOLFIRINOX group, and nine in the neoadjuvant chemoradiotherapy group) and seven (15%) of 46 had progressive disease (three in the neoadjuvant gemcitabine plus capecitabine group, one in the neoadjuvant FOLFIRINOX group, and three in the neoadjuvant chemoradiotherapy group; appendix p 7).

Details for time-to-event endpoints are shown in the appendix (p 8). 19 patients in the immediate surgery group had died at the time of data lock, as had four in the neoadjuvant gemcitabine plus capecitabine group, three in the neoadjuvant FOLFIRINOX group, and five in the neoadjuvant chemoradiotherapy group. 1-year overall survival was 39% (95% CI 24–61) for immediate surgery and 76% (65–89) for the combined neoadjuvant therapy groups (HR 0·29 [95% CI 0·14–0·60], p=0·0052; figure 2A, B). 1-year overall survival was 78% (60–100) for the neoadjuvant

| Table 1: Baseline characteristics in the full analysis set |

<table>
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<th>Surgery group (n=31)</th>
<th>Gemcitabine plus capecitabine group (n=19)</th>
<th>FOLFIRINOX group (n=20)</th>
<th>Chemoradiotherapy group (n=16)</th>
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<tr>
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<td>15 (48%)</td>
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<td>20 (100%)</td>
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<td>Pylorus preserving Whipple’s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 (48%)</td>
<td>5 (26%)</td>
<td>11 (55%)</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>Standard Whipple’s</td>
<td>2 (6%)</td>
<td>5 (26%)</td>
<td>0 (1%)</td>
</tr>
<tr>
<td>Total pancreatectomy</td>
<td>4 (13%)</td>
<td>1 (5%)</td>
<td>0 (1%)</td>
</tr>
<tr>
<td>Bypass</td>
<td>6 (19%)</td>
<td>0 (0%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Open and close</td>
<td>1 (3%)</td>
<td>2 (11%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>No surgery</td>
<td>3 (10%)</td>
<td>6 (32%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Reason no surgery attempted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>3 (10%)</td>
<td>5 (26%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Death*</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Days between baseline CT scan and surgery</td>
<td>42 (29–58)</td>
<td>116 (105–121)</td>
<td>128 (105–147)</td>
</tr>
</tbody>
</table>

Data are median [IQR], or n (%). *Cause of death for all three patients was disease progression. Also included in cause of death was cardiogenic shock, liver function dysfunction probably due to cytotoxic chemotherapy, neutropenic sepsis, or other pancreatic cancer.
Overall survival for each treatment group (A) and for neoadjuvant therapy vs surgery alone (B).

Figure 2: Kaplan-Meier plots of overall survival

Overall survival for each treatment group (A) and for neoadjuvant therapy vs surgery alone (B).

78 (91%) patients were included in the safety set and assessed for toxicity events: 28 in the immediate surgery group, 17 in the neoadjuvant gemcitabine plus capecitabine group, 19 in the neoadjuvant FOLFIRINOX group, and 14 in the neoadjuvant chemoradiotherapy group (table 2). 14 (18%) patients reported at least one serious adverse event: three (11%) of 28 patients reported five events in the surgery group and 11 (22%) of 50 patients reported 17 events in the neoadjuvant therapy groups. Details on serious adverse events are included in the appendix (p 12).

34 grade 3 and higher adverse events were reported by 19 (24%) of 78 patients. This included two grade 3 and higher adverse events reported by two (7%) of 28 patients in the immediate surgery group, and 32 grade 3 and higher adverse events reported by 17 (34%) of 50 patients in the adjuvant therapy groups (five [29%] of 17 patients in the neoadjuvant gemcitabine plus capecitabine group reported seven events; eight [42%] of 19 in the neoadjuvant FOLFIRINOX group reported 14 events; four [29%] of 14 patients in the neoadjuvant chemoradiotherapy group reported 11 events). The most common adverse events were fatigue, nausea, and abdominal pain, which were mostly of grade 1 and 2.

Details of all grade 3 and higher adverse events and of grade 1 or 2 adverse events that occurred in more than 10% of patients are shown in table 2.

Overall quality-of-life questionnaire scores were available for 78 patients at baseline: 29 in the immediate surgery group, 15 in the neoadjuvant gemcitabine plus capecitabine group, 19 in the neoadjuvant FOLFIRINOX group, and 15 in the neoadjuvant chemoradiotherapy group. Scores were also completed at 24, 36, 48, and 52 weeks. However, no clinically significant differences in quality of life between baseline and follow-up visits were shown (appendix p 14).

Adjuvant therapy was administered to 43 (84%) of 51 patients following tumour resection. In the immediate surgery group 17 (81%) of 21 patients received adjuvant therapy. Adjuvant therapy was given to ten (91%) of 11 patients in the neoadjuvant gemcitabine plus capecitabine group, nine (82%) of 11 patients in the neoadjuvant FOLFIRINOX group, and seven (88%) of eight patients in the neoadjuvant chemoradiotherapy group. Gemcitabine or gemcitabine plus capecitabine was given to 41 (95%) of 43 patients who received adjuvant therapy and modified FOLFIRINOX was given to the remaining two (5%) patients (appendix p 13). Treatment following recurrence is detailed in the appendix (p 17).

Discussion

Overall, we were able to recruit 90 patients at a rate of 2.16 patients per month, but not to the original target. In some centres, fewer than two patients were recruited per year, mainly due to challenges in site set up and recruitment. At the time of study inception, the standard of care for borderline resectable disease was immediate...
surgery with adjuvant chemotherapy both in the UK and Germany. Initially, patients preferred immediate surgery, but this changed during the course of the trial as neoadjuvant therapy became more acceptable to patients.

There were logistical challenges at the start and a desire for investigators to not delay surgery. The overall resection rate and R0 resection rate for neoadjuvant therapy versus upfront surgery varied, but were not
significantly different, as the study was not powered to detect a difference between treatment groups. This variation, however, might be of clinical interest when considering neoadjuvant approaches for patients. The low R0 resection rates might partly be due to differences in definitions of borderline tumour resectability and R0 between studies. We used less than 1 mm as the definition for R0 and this could result in a lower R0 rate compared with other studies. The R0 rate for the ESPAC-4 adjuvant trial was 40%. Our lower R0 rate might also reflect the anticipated outcome for patients with borderline resectable tumours compared with patients with resectable tumours.

The neoadjuvant therapies could be delivered with acceptable side-effects and without increase in perioperative complications. There was a significant reduction in baseline CA19-9 following neoadjuvant therapy. Although survival was a secondary outcome measure, there were significant survival differences in favour of patients randomly assigned to neoadjuvant therapy compared with those in the immediate surgery group and improvements in post-hoc analysis of event-free survival. The principal hypothesis behind neoadjuvant therapy for borderline pancreatic ductal adenocarcinoma is to improve the rate of resection, the R0 resection rate, and as a consequence improve overall survival. None of these concepts have ever been adequately established. A meta-analysis of neoadjuvant response rates and resection rates from 111 cohort series showed that neoadjuvant therapy was unlikely to be of benefit in patients with resectable pancreatic cancer, but that around a third of patients with non-resectable tumours could be expected to have a resectable tumour following neoadjuvant therapy, with similar survival to those with primary resectable tumours. As there was no other trial on which to base power calculations for a significant effect on clinical outcome, we opted for a sample size that was large enough to compare the resection rate (R0 + R1) of immediate surgery compared with the neoadjuvant groups combined. It is of interest that significantly improved overall survival was found in favour of short-course neoadjuvant therapy that was unrelated to the resection rate in this context. This supports the fundamental biological feature of pancreatic ductal adenocarcinoma as a systemic disease driven by inherent biological characteristics; treatments need to be directed to systemic micrometastases as well as removing their primary source. Neoadjuvant systemic chemotherapy with either gemcitabine plus capecitabine or FOLFIRINOX in this study caused less grade 3–4 toxicity than seen in studies of patients with locally advanced disease or metastases or following surgery in the adjuvant setting, probably because the patients received only 2 months of therapy. We might speculate that chemotherapy is more tolerable with less toxicity before surgery than after resection. The higher R0 resection rate and lower positive lymph node rate observed with chemoradiotherapy compared with the other neoadjuvant therapy arms of the ESPAC5 trial might indicate a degree of local control.

The strengths of the current study are derived from the rigorous application of the trial design and the quality control systems including central independent review of borderline tumour resectability, and quality assurance for surgery, chemoradiotherapy, and pathology, and a comparison of three different neoadjuvant regimens. As a feasibility study with low numbers, there are methodological limitations and the possible chance for random confounding due to imbalances in the reported results, notably owing to the potential of bias that might be caused by non-adherence to treatment and the nature of the study design, which compares surgical intervention with neoadjuvant therapy. Furthermore, as a study with relatively small numbers per group, and a short minimum follow-up of period 12 months, some caution should be given to the estimated HRs. The capped follow-up rate and low overall event rate make it difficult to establish whether HRs display any non-proportional tendencies, indicating longer term effects of neoadjuvant therapy, and decreasing the precision about the reported results. Although the survival data should therefore be interpreted with caution, the survival differences were striking. These differences could be ascribed to the stringency of the study and the efficacy of this approach.

There have been several neoadjuvant therapy trials in borderline resectable pancreatic cancer. The PREOPANC1 trial, which included patients with both resectable and borderline pancreatic ductal adenocarcinoma, failed to reach its primary survival endpoint, but on longer follow-up found a significant survival benefit for neoadjuvant chemoradiotherapy (induction gemcitabine followed by gemcitabine-based 36 Gy chemoradiation, followed by surgery and then four adjuvant cycles of gemcitabine) compared with upfront surgery and six cycles of adjuvant gemcitabine. The survival effect in favour of neoadjuvant therapy derived from the patients with borderline resectable tumours (HR 0·67, 95% CI 0·42–0·99; p=0·045) rather than the patients with resectable tumours (HR 0·79, 0·54–1·16; p=0·23). The adjuvant chemotherapy in the PREOPANC1 study (gemcitabine monotherapy) is no longer state-of-the-art, and studies, including ESPAC5, show that the use of radiation in neoadjuvant pancreatic ductal adenocarcinoma therapy is less effective than chemotherapy. The PACT 15 study in resectable pancreatic cancer showed an event free advantage at 1 year for neoadjuvant therapy. The neoadjuvant therapy was cisplatin, etoposide, gemcitabine, and capecitabine and this combination is no longer standard of care. The JASP-05 randomised trial compared neoadjuvant S-1 plus gemcitabine with immediate surgery in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma. There was a modest survival
advantage for the neoadjuvant therapy group. The SWOG/NCI S1505 phase 2 study randomly assigned patients with resectable pancreatic ductal adenocarcinoma to neoadjuvant FOLFIRINOX or gemcitabine with nab-paclitaxel and showed a 2-year overall survival of 47% and 48% respectively. This trial did not show an improved overall survival with neoadjuvant chemotherapy, compared with adjacent trials in resectable pancreatic cancer, although direct comparison is difficult owing to the different patient populations analysed.

In 2022, the PANACHE01-PRODIGE48 trial reported on patients with resectable disease who were randomly assigned to neoadjuvant modified FOLFIRINOX (n=70), folinic acid, fluorouracil, and oxaliplatin (FOLFOX; n=50), or upfront surgery (n=26) with 12-month survival rates of 84.1% for modified FOLFIRINOX, 71.8% with FOLFOX, and 80.8% with upfront surgery, with no significant differences between groups. There was a 10% increase in 1-year event-free survival rate (51.4% vs 41.7%) and a median event-free survival improvement of 3 months (12.4 months vs 9.2 months) with neoadjuvant FOLFIRINOX compared with upfront surgery. The evidence points to adjuvant chemotherapy remaining the standard of care for resectable pancreatic ductal adenocarcinoma with growing evidence supporting neoadjuvant chemotherapy for patients with borderline resectable pancreatic cancer.

An outstanding issue is the use of radiotherapy in addition to chemotherapy in the neoadjuvant setting, although no longer used in the adjuvant setting. The Alliance A021501 randomly assigned patients with borderline resectable pancreatic ductal adenocarcinoma to neoadjuvant modified FOLFIRINOX (n=54) or to modified FOLFIRINOX plus hypofractionated radiation (n=56) with 18-month overall survival of 66.4% versus 47.3%, median event-free survival 15.0 months versus 10.2 months, resection rates of 49% versus 35%, and adverse events of grade 3 and higher of 57% versus 64%, respectively. It was concluded that modified FOLFIRINOX was efficacious whereas the combination of modified FOLFIRINOX plus chemoradiation was rejected. In the CONKO 007 phase 3 trial, which randomly assigned patients with non-resectable locally advanced pancreatic ductal adenocarcinoma to induction chemotherapy alone (n=167) or chemotherapy followed by chemoradiotherapy (n=168), 12-month overall survival was 71.3% with chemotherapy alone versus 71.1% with chemotherapy plus chemoradiotherapy. Tumour resectability did not translate into a significant progression-free or overall survival benefit. Grade 3 and higher toxicity was significantly greater in the chemoradiotherapy group at 79%, compared with 40% in the chemotherapy only group.

When the ESPAC5 trial was first designed, randomised evidence for neoadjuvant therapy was scarce. We originally designed an exploratory study with the possibility of a follow-on phase 3 study. Now the evidence for neoadjuvant therapy in borderline resectable pancreatic ductal adenocarcinoma is much more compelling. Neoadjuvant therapy is now becoming standard in the UK, Germany, and internationally for borderline resectable pancreatic ductal adenocarcinoma, and it is therefore difficult to justify a follow-on trial for these patients with an immediate surgery group.

In conclusion, accepting the limitations of small patient numbers and a short follow-up time, the results of ESPAC5 show that neoadjuvant short-course combination chemotherapy was more effective than immediate surgery with adjuvant therapy in the setting of borderline resectable pancreatic ductal adenocarcinoma, and favoured neoadjuvant chemotherapy rather than neoadjuvant chemoradiotherapy. The survival advantage of neoadjuvant therapy was seen despite no significant difference being noted in resection rate. The results of this trial provide evidence for neoadjuvant short-course chemotherapy in borderline resectable pancreatic ductal adenocarcinoma.

**Contributors**

PG, DP, RS, SM, JPN, SC, and RJ conceived and designed the trial. PG, RS, DP, CS, SC, JPN, SM, and CR supervised trial conduct, participated in data analysis and interpretation, and prepared and wrote the report. CR managed the trial and contributed to writing of the manuscript. PG, DP, CMH, RS, SM, ZS, JW, AA, ED, IG, LJ, HSW, IST, DA, AP, PR, JWV, DAO’R, BAS, SG, IA, K-LY, DC, TA, KC, CA, KR, YTM, CS, CT, TH, MWB, and JPN participated in patient recruitment and trial conduct. CR, SC, and RJ were responsible for onsite monitoring. SC and RJ participated in trial design, data analysis, and data interpretation. CS provided independent critical review of the data and drafts. All authors have verified the data. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

**Declaration of interests**

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December, 2022, with no specific end date. Applications will be reviewed by the sponsor involving all applicable parties in their decision-making outcome (e.g., chief investigator, joint data controllers, and pharmaceutical companies). New projects that result in data sharing should meet the high standards (quality, ethical, and financial) maintained by the sponsor. All data sharing will require a review of consent parameters and a data access agreement before sending data.

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References