**Patterns of Recurrence after Resection of Pancreatic Ductal Adenocarcinoma in the ESPAC-4 Trial**

Robert P. Jones, Ph.D.1, Eftychia-Eirini Psarelli, M.Sc.2, Richard Jackson, Ph.D.,2 Paula Ghaneh, M.D.1,2, Christopher M. Halloran, M.D.1,2, Daniel H. Palmer, PhD.2,3, Fiona Campbell, M.D.1, Juan W. Valle, M.D.4, Olusola Faluyi, M.D.3, Derek A. O’Reilly, M.D.5, David Cunningham, M.D.6, Jonathan Wadsley, M.D.7, Suzanne Darby, M.D.7, Tim Meyer, M.D.8, Roopinder Gillmore, M.D.8, Alan Anthoney, M.D.9, Pehr Lind, M.D.10, Bengt Glimelius, M.D.11, Stephen Falk, M.D.12, Jakob R. Izbicki, M.D.13, Gary William Middleton M.D.14, Sebastian Cummins, M.D.14, Paul J. Ross, M.D.15, Harpreet Wasan, M.D.16, Alec McDonald, M.D.17, Tom Crosby, M.D.18, Yuk Ting Ma, M.D.19, Kinnari Patel, M.D.20, David Sherriff, F.R.C.R.21, Rubin Soomal, M.D.22, David Borg, M.D.23, Sharmila Sothi, M.D.24, Pascal Hammel, M.D.25, Markus M. Lerch, M.D26, Julia Mayerle, M.D.26 Oliver Strobel, M.D.27, Thilo Hackert, M.D.27, Markus W. Büchler, M.D.27, John P. Neoptolemos, M.D.27, for the European Study Group for Pancreatic Cancer.

**Addressees of Contributors:** 1The Royal Liverpool University Hospital, Liverpool, United Kingdom; 2University of Liverpool, Liverpool, United Kingdom; 3The Clatterbridge Cancer Centre, Wirral, United Kingdom; 4University of Manchester/The Christie, Manchester, United Kingdom; 5Manchester University Foundation Trust, Manchester, United Kingdom; 6Royal Marsden Hospital, London, United Kingdom; 7Weston Park Hospital, Sheffield, United Kingdom; 8 Royal Free Hospital, London, United Kingdom; 9 St. James's University Hospital, Leeds, United Kingdom; 10 Clinical Research Sörmland,Karolinska Institutet, Stockholm, Sweden; 11 Clinical Research Sörmland,University of Uppsala, Uppsala, Sweden; 12 Bristol Haematology and Oncology Centre, Bristol, United Kingdom; 13University of Hamburg Medical institutions UKE, Hamburg, Germany; 14 Royal Surrey County Hospital, Guildford, United Kingdom; 15Guy's Hospital, London, United Kingdom; 16Hammersmith Hospital, London, United Kingdom; 17 The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; 18Velindre Hospital, Cardiff, United Kingdom; 19Queen Elizabeth Hospital, Birmingham, United Kingdom; 20Churchill Hospital, Oxford, United Kingdom; 21 Derriford Hospital, Plymouth, United Kingdom; 22 Ipswich Hospital, Ipswich, United Kingdom; 23 Skåne University Hospital, Lund, Sweden; 24University Hospital Coventry, Coventry, United Kingdom; 25 Hôpital Beaujon, Clichy, France; 26Greifswald University, Medicine, Germany; 27University Hospital Munich, Ludwig-Maximilians-University Munich, Germany; 28University of Heidelberg, Heidelberg, Germany.

**Corresponding Author/requests for reprints**

Prof. Dr. med. John Neoptolemos

MA, MB, BChir, MD, FRCS, FMedSci

Professor of Surgery

Department of General Surgery

University of Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg

Germany

Tel: 0049 6221 56 32880

Fax: 0049 6221 56 5538

Email: john.neoptolemos@med.uni-heidelberg.de

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**KEY POINTS**

**Question:** What are the patterns of disease recurrence after resection of pancreatic cancer followed by systemic chemotherapy?

**Findings:** Local recurrence and distant metastases occurred with similar frequency. The median recurrence free survival, median survival after recurrence and the median overall survival were similar. Adjuvant gemcitabine plus capecitabine reduced the rate of local recurrence compared to gemcitabine monotherapy and improved overall survival.

**Meaning:** Pancreatic cancer can be regarded as a systemic disease, irrespective of site of recurrence, requiring adjuvant systemic therapy after resection for effective treatment.

**STRUCTURED ABSTRACT**

***Importance***

The patterns of disease recurrence after resection of pancreatic ductal adenocarcinoma with adjuvant chemotherapy remain unclear.

***Objective***

To define patterns of recurrence after adjuvant chemotherapy, and the association with survival.

***Design***

Prospectively collected data from the phase III ESPAC 4 adjuvant clinical trial.

***Setting***

International multicenter study.

***Participants***

730 patients who had resection and adjuvant chemotherapy for pancreatic cancer.

***Intervention***

Patients were randomized to receive adjuvant gemcitabine or gemcitabine plus capecitabine.

***Main outcomes***

The median (95% CI) follow-up time from randomization was 43.2 (39.7-45.5) months, with overall survival of 25.5 (22.7-27.9) months with gemcitabine and 28.0 (23.5-31.5) months with the combination (HR=0.82; 95% CI = 0.68-0.98; p=0.032). The 5-year (95% CI) survival estimates were 16.3 (10.2 - 23.7) % and 28.8 (22.9- 35.2)%. Recurrence occurred in 479 (65.6%) patients, local in 238 (49.7%) patients, distant only recurrence in 193 (40.3%), and simultaneous local and distant recurrence in 48 (10.0%) patients; a further 78 (10.7%) patients died without detectable recurrence. Local recurrence occurred at a median (95% CI) of 11.63 (10.05-12.19) months, statistically significantly different from those with distant recurrence with a median (95% CI) of 9.49 (8.44, 10.71) months (HR = 1.21; 95% CI=1.01-1.45; p=0.036). Following identification of recurrence, median (95% CI) survival was 9.36 (8.08-10.48) months for local recurrence and 8.94 (7.82, 11.17) months with distant recurrence (HR = 0.89; 95% CI=0.73-1.09; p=0.267). The median (95% CI) overall survival of patients with distant only (20.61 (18.12, 23.80) months) or local with distant recurrence (21.17 (18.51, 23.44) months) were not significantly different from those with only local recurrence (22.68 (21.33, 25.05) months) (p=0.828 and p=0.364 respectively). Independent determinates (HR, 95% CI) of local recurrence were N1 status (1.80, 1.199-2.689; p=0.005), N2 status (2.95 (1.95, 4.465); p<0.001), and adjuvant treatment allocation (0.77, 0.593-0.993; p=0.044). Gemcitabine plus capecitabine had a 21% reduction of death following recurrence compared to monotherapy (0.79, 0.64-0.98; p=0.034).

***Conclusions***

There were no significant differences between the time to recurrence and subsequent and overall survival between local and distant recurrence. Pancreatic cancer behaves as a systemic disease requiring effective systemic therapy after resection.

**Trial Registration:** EudraCT 2007-004299-38 and ISRCTN 96397434.

**INTRODUCTION**

The effective treatment of pancreatic ductal adenocarcinoma remains hugely challenging.1 However,there has also been considerable progress towards extending overall survival by improving surgical outcomes2-5 and the development of better adjuvant6-8 and neoadjuvant9-11 therapies. The incidence of pancreatic cancer is rising, and it is likely to be the second leading cause of cancer death by 2030.12,13

In specialized centers, resection rates of 15% can be achieved1,2 with a 5-year survival rate around 10% without adjuvant therapy,7,14,15 increasing to 16-18% with single agent adjuvant chemotherapy14-16 and 30% to 50% with combination gemcitabine and capecitabine or modified FOLFIRINOX respectively.7,8 The patterns of disease recurrence following resection include both loco-regional failure and distant metastases. Estimates of these patterns have been derived from several small post-mortem analyses, retrospective single center studies 3,17-23 and prospective data from the European Study Group for Pancreatic Cancer (ESPAC) 1 trial.15 In the large retrospective study from the Johns Hopkins Medical School, 692 (62.7%) of 1103 patients had sufficient data for analysis.3 Of these 531 (76.7%) had a recurrence, of whom 126 (23.7%) had local only recurrence, 307 (57.8%) had distant only metastases, and 98 (19%) had both local recurrence and distant metastases.3 Key findings were that liver-only recurrence, which was found in 134 (25.2%) patients, occurred relatively early after a median of 6.9 months while lung-only recurrence, which was found in 78 (15%) patients, occurred much later at a median of 18.6 months, and patients with a positive lymph node ratio >0.2 were most likely to develop distant metastatic disease.This and other retrospective series however are limited by a significant amount of missing data and other potential biases. 3,17-19 These limitations are minimized in large prospective multicenter studies. We therefore investigated the patterns of disease recurrence after resection of pancreatic ductal adenocarcinoma in the large multicenter randomized ESPAC4 adjuvant study. 7

**METHODS**

***Study Design***

The pattern of pancreatic cancer recurrence was recorded prospectively at the Liverpool Clinical and Cancer Research UK Trials Unit, University of Liverpool, as part of the ESPAC-4 Trial.7 This was an international phase III randomized controlled trial to compare overall survival after pancreatic adenocarcinoma resection followed by adjuvant gemcitabine (control arm) or combination gemcitabine plus capecitabine (experimental arm).

Patients were followed up every three months from surgery by standard practice and suspected recurrence was confirmed by cross-sectional imaging. Local recurrence was defined as radiological evidence of recurrent disease in the remnant pancreas, the surgical bed or in locoregional nodes. Distant recurrence was defined as radiological evidence of recurrence outside these areas. Distant recurrence was stratified by the organ of recurrence. Only the site or sites of first recurrence were analysed.

The primary outcome measure was a competing risk covariate that measured the time from randomization until either local recurrence, distant recurrence, synchronous local and distant recurrence or death without recurrence. Patients alive and without evidence of recurrence at the time of analysis were included as censored observations. Before randomization patients were stratified by country and R0 or R1 status.24 An R0 resection was defined as the absence of any cancer cells within 1mm of any cut surface of the resected specimen. An R1 resection was defined as at least one cancer cell within 1mm of any surface of the removed specimen. Evidence of ascites, intra-abdominal or distant metastasis precluded enrollment, as did an R2 resection. Patients who had received previous neoadjuvant therapy were not eligible for inclusion. A triple-phase contrast computerized tomography (CT) scan of chest, abdomen and pelvis was required in the three months before surgery to exclude pre-existing metastatic disease. Tumor staging was undertaken prospectively using the UICC TNM 7th edition classification of malignant tumors.25 Demographic and pathological variables for the study inclusion were pre-specified. A pathology proforma was completed and the full pathology report submitted to the Liverpool Clinical and Cancer Research UK Trials Unit before randomization could take place. For the purposes of this study, pathology reporting was re-examined and re-staged using the updated AJCC Cancer Staging Manual 8th Edition.26 The full trial protocol is available online at:

[**https://www.lctu.org.uk/Public/SSES4\_PROTOCOL.9-ESPAC-4\_Protocol.pdf**](https://www.lctu.org.uk/Public/SSES4_PROTOCOL.9-ESPAC-4_Protocol.pdf)

***Statistical Analysis***

Competing risks regression modeling was performed to assess the impact of clinical and demographic factors on the time to the first event of interest, local recurrence versus distant recurrence versus death without known recurrence as well as median and overall survival.Clinical and demographic covariates considered for inclusion were pre-specified and included those identified in the main trial analysis as predictive of overall survival.7 Further clinical and demographic factors with a significance level of p ≤ 0.25 on univariate modeling were considered for inclusion in the multivariable analysis with models constructed using backward selection and evaluated using Akaike’s Information Criterion (AIC).27,28 Key variables, such as treatment arm and resection margin status, were forced into all multivariable models. Proportionality of sub-hazards assumption was evaluated after fitting Schoenfeld residuals. Results are reported in terms of the cause-specific hazard ratios (HR) with 95% confidence intervals CI. Power analysis for the original clinical trial has been described previously.7 All analyses were conducted using two-sided significance tests at the 5% significance level. STATA v.15 (StatCorp LP, College Station, TX, USA) and R (Version 3.3.3) were used to perform all statistical analyses.

**RESULTS**

***Patient demographics***

Between November 2008 and September 2014, 732 patients were randomized, 367 patients (50.1%) to receive gemcitabine alone and 365 (49.9%) to receive combination gemcitabine plus capecitabine. Two patients were excluded from the full analysis set as they withdrew consent between randomization and starting therapy (one in each group); the CONSORT diagram is included in the original publication.7

***Overall survival***

The median (range) time from surgery to randomization was 65 (23–111) days in the gemcitabine group and 64 (21–111) days for the combination treatment arm. The median (95% CI) follow-up time from randomization was 43.2 (39.7-45.5) months. The median (95% CI) overall survival was 25.5 (22.7-27.9) months in the gemcitabine group and 28.0 (23.5-31.5) months in the gemcitabine plus capecitabine group (HR=0.82; 95% CI = 0.68-0.98; p=0.032). The 5-year (95% CI) survival estimates were 16.3 (10.2-23.7)% in the gemcitabine group and 28.8 (22.9-35.2)% in the gemcitabine plus capecitabine group.

***Patterns of recurrence***

Disease recurred in 479 (65.6%) of all 730 patients. Baseline clinical demographics and pathological variables are described in Table 1. Local recurrence occurred in 238 (49.7%) of these 479 patients, distant only recurrence in 193 (40.3%) patients, and simultaneous local and distant recurrence in 48 (10.0%) patients, whilst a further 78 (10.7%) patients died without any identifiable recurrence. The overall median time to recurrence was 15.6 (13.5 –17.9) months. Recurrence within 2 years of randomization occurred in 416 (86.8%) of all 479 patients with recurrences, in 202 (84.9%) of 238 patients with local recurrence, and in 214 (88.8%) of 241 patients with distant recurrence.Of the 458 patients who died, 380 (83.0%) had local recurrence and/or metastases prior to death. Patient groups were comparable, with no significant differences in the types and extent of surgical resection between groups.

Local recurrence occurred at a median (95% CI) of 11.63 (10.05-12.19) months and was statistically significantly different from those with distant recurrence with a median (95% CI) of 9.49 (8.44, 10.71) months (HR = 1.21; 95% CI=1.01-1.45; p=0.036). The commonest oligometastatic site amongst the 241 patients with distant recurrence was the liver found in 99 (41%) patients (or 20.7% of all recurrences), followed by lung-limited disease in 52 (22%) patients (or 10.9% of all recurrences) (Table 2). Liver metastatic disease occurred soonest with a median (95% CI) of 7.82 (6.37-8.90) months compared with lung metastases, which occurred at 12.78 (9.69-17.80) months (HR = 0.48; 95% CI 0.33-0.68; p<0.001).

Following identification of recurrence, median (95% CI) survival was 9.36 (8.08-10.48) months for local recurrence and 8.94 (7.82, 11.17) months with distant recurrence with no significant difference (HR = 0.89; 95% CI=0.73-1.09; p=0.267) (Figure 1a). Patients with lung-limited metastatic disease had a significantly longer survival from time of recurrence than those with liver-only metastases (HR = 0.60; 95% CI 0.40-0.90; p=0.014) (Figure 1b).

***Factors predictive of patterns of recurrence***

Univariate competing risks analyses of clinical and demographic factors on the risk of recurrence or death along with the forest plot are described in Figure 2. For local recurrence (HR, 95% CI) adjuvant treatment (0.77, 0.593-0.993, p=0.044), N1 status (1.8, 1.199-2.689, p=0.005), and N2 status (2.95, 1.95-4.465, p<0.001) were all significant, but not R-status; for distant recurrence, moderately differentiated grade (0.58, 0.443-0.763, p<0.001), well differentiated grade (0.56, 0.331-0.939, p=0.028), postoperative carbohydrate antigen (CA)19-9 levels (1.2, 1.108-1.305, p<0.001), and N2 stage (2.4, 1.593-3.63, p<0.001) were significant; for death without recurrence, postoperative CA19-9 levels (1.41, 1.226-1.628, p<0.001), and N2 status (3.25 (1.511-6.994, p=0.003) were significant; and for overall survival, adjuvant treatment (0.79, 0.66-0.96, p=0.16), R status (1.27, 1.04-1.55, p=0.016), moderately differentiated grade (0.67, 0.55-0.82, p<0.00.1], well differentiated grade (0.4, 0.262-0.616, p<0.001), maximum tumor size (1.11, 1.02-1.19, p=0.0030, postoperative CA19-9 levels (1.32, 1.23-1.43, p<0.001), N1 status (1.44, 1.056-1.96, p=0.036), and N2 status (2.10, 1.54-2.88, p<0.001] were all significant.

The cumulative incidence plot showing the accumulation of local and distant recurrence and deaths without recurrence, as well as the accumulation of distant recurrences stratified by organ is presented in Supplementary Figure SS1. The small number of patients with local with distant recurrence did not allow competing risk or cumulative incidence analysis to be performed.

Multivariable analyses showed that independent significant determinates of local recurrence were N1 status, N2 status, and adjuvant treatment allocation (Table 3). Independent determinates for distant recurrence were N1 status, postoperative CA19-9 levels, and moderately and well differentiated tumor grades. For death without recurrence the independent significant determinates were N2 status, and postoperative CA19-9 levels,

Independent factors associated with poorer survival following recurrence (HR, 95% CI) were resection margin status (1.39, 1.106-1.744, p=0.005), moderately (0.51, 0.406-0.64, p<0.001) and well differentiated tumor grades (0.47, 0.303-0.732, p <0.001), local invasion (1.26, 1.018-1.554, p=0.034), current smoking status (1.46, 1.087-1.957, p=0.012), and preoperative C-reactive protein (CRP) levels (1.22, 1.095-1.361, p<0.001) (Supplementary Table SS1). In this model patients who received combination gemcitabine plus capecitabine had a 21% reduction of death following recurrence compared to patients treated with gemcitabine alone (HR = 0.79; 95% CI = 0.64-0.98; p=0.034).

***Overall survival by patterns of recurrence***

The median overall survival of patients with distant only (p=0.828) or local with distant (p=0.364) recurrence were not significantly different from those with only local recurrence (Table 2; Supplementary Figure SS 2a). Using distant nodal disease as the reference between the distant metastasis subgroups there were no significant differences in overall median survival compared to patients with liver only (p=0.410), lung only (p=0.203), or other intra-abdominal (p=0.666) recurrence, but patients with combined liver and lung metastases had significantly shorter survival (p=0.024) (Table 2; Supplementary Figure SS 2b). The median (95% CI) survival of patients with lung only metastases was 31.03 (22.85, 45.71) months, which was significantly longer than this with liver only metastases, which was 18.58 (14.80, 21.73) months (HR=0.50, 95% CI=0.33-0.76, p<0.001).

**DISCUSSION**

This study showed a 23% reduction in the risk of developing local recurrence, a 21% reduction of death following recurrence, and an 18% increase in overall survival using the combination of gemcitabine with capecitabine compared to gemcitabine alone. There were no differences attributable to the combination regimen compared to gemcitabine monotherapy in either development of distant metastases or death without recurrence. Almost 90% of distant recurrences occurred within 2 years of surgery, with half of patients who developed liver metastases doing so within 12 months. This implies that the majority of patients had already developed distant metastases prior to resection,29-31 a finding consistent with the significant independent association of distant metastases with N2 lymph node involvement, elevated postoperative CA-19-9 levels, and poorly differentiated tumors. These findings are also supportive of the notion that micrometastases develop early in the pathogenesis of pancreatic ductal adenocarcinoma.29-31 Furthermore, this might explain why R-status correlates to survival but not to local recurrence. Previous studies have shown that even low-grade pancreatic intraepithelial neoplasms with oncogenic KRAS mutations can migrate away from the glandular pre-neoplasm into the surrounding tissue and circulatory system representong early epithelial-to-mesenchymal transition.30 Using autopsy and radiological data from 101 patients Haeno *et al* proposed that pancreatic cancer grows at an exponential rate, and that cells with high metastatic competency were generated during tumor expansion in the order of 1 in a million pancreatic cancer cells.31 From this modeling they predicted that even very small primary tumors frequently produced microscopic metastasis prior to surgical removal. The autopsy series also revealed that a small subset of patients died with only locally advanced disease, suggesting that some tumors may lack metastasis-promoting factors (or have metastasis suppressing factors), or have metastases that are especially sensitive to systemic therapy.31 In the present study we found that 78 (17.0%) of the 458 patients who died (or 10.7% of all 730 patients) did so without evidence of recurrence or metastases. This compares with 161 (23.3%) of 692 patients in the study by Groot *et al*.,3 and in 13 (16%) out of 81 subjects in four autopsy studies collectively.20-23

Of particular importance we found that there were no statistically significant differences between the time to recurrence and subsequent and overall survival between local and distant recurrence. It has been assumed that patients with local recurrence have apparently a less aggressive tumor biology and slower growing tendency than those with patients with distant metastases and might benefit from additional local treatment such as stereotactic body radiation therapy.3,32 The lack of survival differences between local and distant recurrence in this study does not support this hypothesis. In an autopsy study Iacobuzio-Donahue *et al.* found that 30% of patients died with localized pancreatic cancer, and 70% died with metastatic disease and that primary tumor DPC4 expression was associated with limited metastatic disease burden (<10 metastases) whilst loss of DPC4 expression was associated with widespread metastatic disease (>1,000 metastases).20 Although these observations suggest a degree of clonality to explain the divergent patterns of failure they were unrelated to clinical stage at initial presentation, treatment history, or histopathologic features. Similarly in this study we found variances in the determinates predicting local and distant recurrence and death without recurrence suggesting clonality, but without significant differences in survival patterns. Within the group of patients with distant metastases however there were significant survival differences. Patients with liver and lung metastases had the shortest survival of any group or subgroup. Lung metastases occurred much later than patients with liver only metastases. Patients with lung metastases also had longer survival from time of recurrence as well as longer overall survival than those with lung only metastases. This is in keeping with two clinical studies,3,33 and supported by recent experimental evidence.34,35 It now seems apparent that the large majority of lung and liver metastases from pancreatic cancer are monophyletic, with subclones giving rise to both liver and lung metastases in parallel.34 Nevertheless pancreatic cancer metastases often involve seeding by more than one clone and subsequent metastatic tumor growth may actually be more dependent on the stromal environment of the metastatic site.35

The updated AJCC 8th Edition staging system for pancreatic cancer makes a new distinction between N1 (<4 nodes) and N2 (≥4 nodes) disease.26 In this series, N2 disease was associated with more distant recurrence, but not more local recurrence, supporting the clinical utility of this updated staging system. A positive resection margin was strongly associated with poorer overall survival in the main study group. Point estimates (data not shown) suggest this effect is maintained in patients who develop local recurrence or death prior to recurrence but not in patients who develop distant recurrence. In the present study we found that N1 status and N2 status were each independent significant determinates of local recurrence along with adjuvant treatment allocation, whilst N1 status was also an Independent determinate for distant recurrence. Interestingly Honselmann *et al.* found that lymph node status was predictive of time to recurrence, but not location of recurrence.36

A number of potential confounders exist in this analysis. Because follow-up was performed according to local protocol, not all patients were routinely imaged in the same way but the detection rate for recurrence in patients who died (19.7%) approximated the rate in historical autopsy studies (16.1%).20-23  Additional treatment was given to 94 (39%) of 243 patients in the gemcitabine group with relapse and 77 (33%) of 236 patients in the gemcitabine plus capecitabine group7 but it is unclear whether early detection and treatment of recurrence confers an overall survival benefit. Trial data only captured site of first recurrence, which was subsequently stratified as local, distant or synchronous local and distant. Subsequent sites of recurrence were not recorded and so the patterns of progression from local recurrence to eventual distant recurrence and/or death were not evaluable. It may be that capturing only the first site of recurrence also partly explains the lower rates of combined local/distant recurrence seen in this series compared with others.3

In conclusion, pancreatic cancer can still be regarded as a systemic disease despite resection and irrespective of site of recurrence. This supports the further development of adjuvant systemic therapy after resection in order to increase the long-term survival rate.

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**REFERENCES**

1. Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. *Nat Rev Dis Primers*. 2016 Apr 21; 2: 16022. doi: 10.1038/nrdp.2016.22.
2. Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol. 2018 Oct 19. doi: 10.1038/s41571-018-0112-1.
3. Groot, V. P., Rezaee, N., Wu, W., et al. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. *Ann Surg* 2017.doi:10.1097/SLA.0000000000002234
4. Winter JM, Brennan MF, Tang LH et al. Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. *Ann Surg Oncol* 2012; 19: 169-175.
5. Konstantinidis IT, Warshaw AL, Allen JN et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? *Ann Surg* 2013; 257: 731-736.
6. Khorana, A. A., Mangu, P. B., Berlin, J., et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016; 35(20): 2324-2328.
7. Neoptolemos, J. P., Palmer, D. H., Ghaneh, P., et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet.* 2017;389(10073):1011-1024.
8. Conroy T, Hammel P, Hebbar M, et al and the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018; 20;379(25): 2395-2406.
9. Katz MH, Shi Q, Ahmad SA, Herman JM, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg.* 2016; 151(8):e161137. doi: 10.1001/jamasurg.2016.1137.
10. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced pancreatic cancer: neoadjuvant therapy with FOLFIRINOX results in resectability in 60% of the patients. *Ann Surg.* 2016; 264(3): 457-463.
11. Murphy JE, Wo JY, Ryan DP et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol* 2018; 4: 963-969.
12. Siegel R.L., Miller K.D., Jemal A. Cancer statistics 2019. *CA Cancer J Clin*. 2019 Jan 8. doi: 10.3322/caac.21551.
13. Rahib L, Smith BD, Aizenberg R, Rosenzweig AG, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014;74(11):2913-21.
14. Neoptolemos, J. P., Dunn, J. A., Stocken, D. D., et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001; 358(9293): 1576-1585.
15. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *New England Journal of Medicine* 2004; 350(12):1200-1210.
16. Neoptolemos JP, Stocken DD, Bassi C, et al. [Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial.](http://www.ncbi.nlm.nih.gov/pubmed/20823433) *JAMA*. 2010; 304(10): 1073-1081.
17. Johnstone PA, Sindelar WF. Patterns of disease recurrence following definitive therapy of adenocarcinoma of the pancreas using surgery and adjuvant radiotherapy: correlations of a clinical trial. *Int J Radiat Oncol Biol Phys.*1993;2(7):831–834.
18. Kayahara M, Nagakawa T, Ueno K, Ohta K, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. *Cancer.* 1993(7); 72: 2118–2123.
19. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg*. 2006; 10(4): 511–518.
20. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol.* 2009;27(11):1806–1813.
21. Schnelldorfer T, Ware AL, Sarr MG, et al. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma. *Ann Surg.* 2008;247(3):456–462.
22. Gnerlich JL, Luka SR, Deshpande AD, et al. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. *Arch Surg.* 2012;147(8):753–760.
23. Suenaga M, Fujii T, Kanda M, et al. Pattern of first recurrent lesions in pancreatic cancer: hepatic relapse is associated with dismal prognosis and portal vein invasion. *Hepatogastroenterology.* 2014;61(134):1756–1761.
24. Campbell F, Smith RA, Whelan P, et al. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathology* 2009; 55(3): 277–83.
25. Sobin LH, Gospodarowicz, MK, Wittekind C, eds. TNM classification of malignant tumours 7th edn. UICC, Oxford: Wiley-Blackwell, 2009.
26. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
27. Fine, J. P. and Gray, R. J. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical Association.* 1999; 94(446): 496-509 .
28. Akaike, H. A new look at the statistical model identification*. IEEE Transactions On Automatic Control.* 1974;19: 716-723.
29. Tuveson DA, Neoptolemos JP. Understanding metastasis in pancreatic cancer: a call for new clinical approaches. *Cell*. 2012;148(1-2):21-23.
30. Rhim AD, Mirek ET, Aiello NM, et al. EMT and dissemination precede pancreatic tumor formation. *Cell*. 2012; 148(1-2): 349-361.
31. Haeno H, Gonen M, Davis MB, et al. Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. *Cell*. 2012 ;1 48(1-2): 362-375.
32. Wild AT, Hiniker SM, Chang DT, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. J Gastrointest Oncol. 2013; 4(4): 343-51.
33. Van den Broeck A, Sergeant G, Ectors N, et al. Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. *Eur J Surg Oncol*. 2009;3 5: 600-604.
34. Reiter, J. G., Makohon-Moore, A. P., Gerold, J. M., et al. Reconstructing metastatic seeding patterns of human cancers. *Nat Commun* 2017; 8. 14114. doi:10.1038/ncomms14114.
35. Maddipati, R., Stanger, B. Z. Pancreatic cancer metastases harbor evidence of polyclonality. *Cancer Discov.* 2015; 5(10):1086–1097.
36. Honselmann KC, Pergolini I, Castillo CF, et al. Timing But Not Patterns of Recurrence Is Different Between Node-negative and Node-positive Resected Pancreatic Cancer. *Ann Surg.* 2019 Jan 18. doi: 10.1097/SLA.0000000000003123. [Epub ahead of print]

**TABLES and FIGURES**

**Table 1:** Demographic data of ESPAC-4 trial patients grouped according to site of initial recurrence. Disease recurrence was observed in 479 (65.6%) patients.

| **Characteristic** | **Alive without recurrence (n=173)** | **Local only recurrence (n=238)** | **Distant only recurrence (n=193)** | **Local/distant recurrence****(n=48)** | **Dead without recurrence (n=78)** | **Total (n=730)** |
| --- | --- | --- | --- | --- | --- | --- |
| Age | Median (IQR) | 63 (57, 68) | 63 (55, 68) | 66 (56, 70) | 66 (57, 70) | 64 (58, 71) | 64 (56, 69) |
| Gender | Female | 76 (24%) | 102 (32%) | 104 (33%) | 19 (6%) | 34 (11%) | 316 |
| Male | 97 (23%) | 136 (33%) | 137 (33%) | 29 (7%) | 44 (11%) | 414 |
| WHO Status | 0 | 80 (26%) | 97 (31%) | 103 (33%) | 17 (5%) | 28 (9%) | 308 |
| 1 | 88 (22%) | 134 (33%) | 132 (33%) | 30 (7%) | 47 (12%) | 401 |
| 2 | 5 (24%) | 7 (33%) | 6 (29%) | 1 (5%) | 3 (14%) | 21 |
| Treatment Allocation | Gemcitabine | 80 (22%) | 130 (36%) | 113 (31%) | 22 (6%) | 43 (12%) | 366 |
| Gemcitabine plus Capecitabine | 93 (26%) | 108 (30%) | 128 (35%) | 26 (7%) | 35 (10%) | 364 |
| T - Stage | T1  | 25 (42%) | 17 (29%) | 12 (20%) | 2 (3%) | 5 (8%) | 59 |
| T2 | 109 (23%) | 150 (32%) | 161 (34%) | 32 (7%) | 49 (10%) | 469 |
| T3 | 39 (19%) | 71 (35%) | 68 (34%) | 14 (7%) | 24 (12%) | 202 |
| N - Stage | N0 | 63 (46%) | 32 (23%) | 33 (24%) | 4 (3%) | 9 (7%) | 137 |
| N1 | 87 (28%) | 102 (33%) | 92 (29%) | 18 (6%) | 31 (10%) | 312 |
| N2 | 22 (8%) | 102 (37%) | 115 (42%) | 25 (9%) | 38 (14%) | 277 |
| Stage | I | 53 (43%) | 32 (26%) | 29 (24%) | 5 (4%) | 8 (7%) | 122 |
| II | 98 (30%) | 104 (31%) | 97 (29%) | 18 (5%) | 32 (10%) | 331 |
| III | 22 (8%) | 102 (37%) | 115 (42%) | 25 (9%) | 38 (14%) | 277 |
| Smoker | Never | 72 (24%) | 97 (33%) | 103 (35%) | 21 (7%) | 25 (8%) | 297 |
| Past | 77 (27%) | 88 (31%) | 88 (31%) | 17 (6%) | 31 (11%) | 284 |
| Present | 24 (20%) | 39 (32%) | 40 (33%) | 7 (5%) | 20 (16%) | 123 |
| Diabetes Mellitus | Insulin dependent | 24 (26%) | 37 (40%) | 23 (25%) | 3 (3%) | 9 (10%) | 93 |
| No | 121 (22%) | 171 (32%) | 186 (35%) | 32 (6%) | 60 (11%) | 538 |
| Non-insulin dependent | 28 (29%) | 29 (30%) | 31 (32%) | 13 (13%) | 9 (9%) | 97 |
| Tumor grade | Poor | 48 (17%) | 80 (28%) | 125 (44%) | 23 (8%) | 34 (12%) | 287 |
| Undifferentiated | 2 (50%) | 2 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 |
| Moderately | 101 (28%) | 127 (35%) | 98 (27%) | 19 (5%) | 41 (11%) | 367 |
| Well  | 20 (32%) | 23 (37%) | 17 (27%) | 6 (10%) | 2 (3%) | 62 |
| Maximum tumor size (mm) | Median (IQR) | 28 (21, 35) | 31 (25, 40) | 30 (24.5, 40) | 30 (25, 40) | 30 (25, 40) | 30 (24, 40) |
| Extent of lymph node resection | Extent lymph. | 10 (22%) | 17 (37%) | 15 (33%) | 3 (6%) | 4 (9%) | 46 |
| Radical | 26 (24%) | 35 (32%) | 39 (36%) | 10 (9%) | 9 (8%) | 109 |
| Standard | 136 (24%) | 183 (32%) | 185 (33%) | 34 (6%) | 64 (11%) | 568 |
| Portal vein resection | No | 154 (25%) | 198 (32%) | 206 (33%) | 45 (7%) | 63 (10%) | 621 |
| Yes | 16 (16%) | 38 (37%) | 34 (33%) | 3 (3%) | 14 (14%) | 102 |
| Local invasion | No | 101 (27%) | 117 (31%) | 125 (33%) | 25 (7%) | 35 (9%) | 378 |
| Yes | 71 (20%) | 121 (35%) | 115 (33%) | 23 (7%) | 42 (12%) | 349 |
| Post-operative complications | No | 124 (24%) | 171 (33%) | 170 (33%) | 34 (6%) | 56 (11%) | 521 |
| Yes | 47 (23%) | 66 (32%) | 71 (34%) | 14 (7%) | 22 (11%) | 206 |
| Operation type | Distal pancreatectomy | 19 (32%) | 20 (33%) | 17 (28%) | 5 (8%) | 4 (7%) | 60 |
| Pylorus preservingpancreatectomy | 60 (24%) | 79 (31%) | 81 (32%) | 17 (7%) | 31 (12%) | 251 |
| Total pancreatectomy | 17 (35%) | 20 (41%) | 10 (20%) | 2 (4%) | 2 (4%) | 49 |
| Classic Whipple | 77 (21%) | 119 (32%) | 133 (36%) | 24 (7%) | 41 (11%) | 370 |
| Resection margin | R0 | 88 (30%) | 83 (29%) | 93 (32%) | 22 (8%) | 26 (9%) | 290 |
| R1 | 85 (19%) | 155 (35%) | 148 (34%) | 26 (6%) | 52 (12%) | 440 |
| Toxicity ≥ Grade 3\* | No | 74 (24%) | 91 (29%) | 118 (38%) | 25 (8%) | 26 (8%) | 309 |
| Yes | 99 (24%) | 147 (35%) | 123 (29%) | 23 (5%) | 52 (12%) | 421 |
| Pre-operative CA19.9 level (KU/L) | <150 | 66 (29%) | 75 (33%) | 65 (29%) | 16 (7%) | 22 (10%) | 228 |
| ≥150 | 42 (18%) | 80 (35%) | 81 (35%) | 15 (7%) | 27 (12%) | 230 |
| Post-operative CA19.9 level (KL/L) | <18.7 | 107 (32%) | 102 (31%) | 93 (28%) | 18 (5%) | 29 (9%) | 331 |
| ≥18.7 | 51 (15%) | 115 (35%) | 121 (37%) | 22 (7%) | 44 (13%) | 331 |
| Pre-operative CRP level (mg/L) | <7 | 63 (24%) | 85 (32%) | 90 (34%) | 19 (7%) | 29 (11%) | 267 |
| ≥7 | 60 (22%) | 93 (33%) | 97 (35%) | 21 (8%) | 29 (10%) | 279 |
| Post-operative CRP level (mg/L) | <5 | 70 (23%) | 112 (37%) | 97 (32%) | 16 (5%) | 27 (9%) | 306 |
| ≥5 | 90 (23%) | 114 (30%) | 134 (35%) | 29 (8%) | 46 (12%) | 384 |

\*Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 4.03.

**Table 2.** Sites of first recurrence and median overall survival from randomization, and median survival after diagnosis of recurrence by site.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Site of recurrence | n | Median recurrence free survival, months (95% CI) | Median survival after recurrence, months (95% CI) | Median overall survival, months (95% CI) |
| Local only | 238 | 11.63 (10.05, 12.19) | 9.36 (8.08, 10.48) | 22.68 (21.33, 25.05) |
| Local and distant recurrence | 48 | 10.25 (7.75, 13.67) | 8.11 (5.22, 11.79) | 21.76 (15.09, 25.51) |
| Distant only | 193 | 8.90 (8.05, 10.22) | 9.23 (7.82, 11.43) | 20.61 (18.12, 23.80) |
| Patients with any distant recurrence | 241 | 9.49 (8.44, 10.71) | 8.94 (7.82, 11.17) | 21.17 (18.51, 23.44) |
|  *Oligometastatic* |  |  |  |  |
| -Bone | 6 |  |  |  |
| -Distant nodal | 16 | 8.21 (6.01, 12.61) | 13.17 (4.86, NE) | 22.71 (12.24, NE) |
| -Liver | 99 | 7.82 (6.37, 8.90) | 8.54 (7.03, 9.62) | 18.58 (14.80, 21.73) |
| -Lung | 52 | 12.78 (9.69, 17.80) | 15.04 (12.25, 23.65) | 31.03 (22.85, 45.71) |
| -Other intra-abdominal | 26 | 11.96 (5.98, 17.84) | 11.17 (5.85, 13.40) | 26.68 (18.22, 47.42) |
| -Ovarian | 2 |  |  |  |
|  *Polymetastatic* |  |  |  |  |
| -Distant nodal and bone | 1 |  |  |  |
| -Liver and bone | 1 |  |  |  |
| -Liver and lung | 18 | 9.13 (7.26, 11.23) | 4.53 (2.13, 6.41) | 12.96 (10.13, 19.56) |
| -Liver, lung and bone | 1 |  |  |  |
| -Liver, lung and nodal | 2 |  |  |  |
| -Liver and nodal | 2 |  |  |  |
| -Liver and peritoneal | 1 |  |  |  |
| -Lung and nodal | 7 |  |  |  |
| -Lung and peritoneal | 7 |  |  |  |

NE: not estimable

**Table 3.** Competing risks analysis for local recurrence versus distant recurrence versus death without recurrence. Where boxes are blank, the factor did not reach significance on univariate modeling for inclusion in the competing risks model.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Local Recurrence | Distant Recurrence | Death without Recurrence |
| Estimate (se) | Hazard ratio(95% CI) | P | Estimate (se) | Hazard ratio(95% CI) | P | Estimate (se) | Hazard ratio(95% CI) | P |
| Lymph node stage | 0 | Reference |
| 1 | 0.59 (0.206) | 1.80(1.199, 2.689) | 0.005 | 0.38 (0.207) | 1.47(0.977, 2.201) | 0.065 | 0.54 (0.388) | 1.72(0.806, 3.687) | 0.16 |
| 2 | 1.08 (0.211) | 2.95(1.95, 4.465) | <0.001 | 0.88 (0.21) | 2.4(1.593, 3.63) | <.001 | 1.18 (0.391) | 3.25(1.511, 6.994) | 0.003 |
| Maximum tumor diameter |    | 0.1 (0.056) | 1.11(0.993, 1.237) | 0.057 | - | - | - | - | - | - |
| Resection margin  | Negative | Reference |
| Positive | 0.18 (0.142) | 1.19(0.903, 1.575) | 0.22 | -0.01 (0.139) | 0.99(0.753, 1.299) | 0.94 | 0.19 (0.248) | 1.21(0.746, 1.976) | 0.44 |
| Treatment allocation | Gemcitabine | Reference |
| Gemcitabine plus capecitabine | -0.26 (0.131) | 0.77(0.593, 0.993) | 0.044 | 0.02 (0.131) | 1.02(0.79, 1.319) | 0.88 | -0.31 (0.229) | 0.73(0.466, 1.144) | 0.17 |
| Post operative CA19.9 level |  | - | - | - | 0.18 (0.042) | 1.2(1.108, 1.305) | <.001 | 0.35 (0.072) | 1.41(1.226, 1.628) |  <0.001 |
| Tumor differentiation | Poorly differentiated | Reference |
| Well differentiated | - | - | - | -0.58(0.266) | 0.56(0.331, 0.939) | 0.028 | - | - | - |
| Moderately Differentiated |  |  |  | -0.54 (0.139) | 0.58(0.443, 0.763) | <0.001 |  |  |   |

**Figure 1.** Kaplan – Meier curves showing survival from time of recurrence.

 (a) Recurrence stratified by local versus distant disease.



(b) Recurrence stratified by organ of recurrence



**Figure 2.** Forest Plot comparing competing risks results for local recurrence, distant recurrence and overall survival



**Supplementary Table 1.** Multivariable analysis of overall survival after identification of recurrence

| **Characteristic** | **Estimate (se)** | **Hazard ratio** **(95% CI)** | **P** |
| --- | --- | --- | --- |
| Resection margin | Negative |  |
| Positive | 0.33 (0.116) | 1.39 (1.106, 1.744) | 0.005 |
| Tumor grade | Poor | Reference |  |  |
| Moderate | -0.67 (0.116) | 0.51 (0.406, 0.64) | <0.001 |
| Well  | -0.75 (0.225) | 0.47 (0.303, 0.732) | <0.001 |
| Local invasion | No | Reference |
| Yes | 0.23 (0.108) | 1.26 (1.018, 1.554) | 0.034 |
| Smoking status | Never | Reference |
| Past | 0.11 (0.121) | 1.11 (0.878, 1.41) | 0.38 |
| Present | 0.38 (0.15) | 1.46 (1.087, 1.957) | 0.012 |
| Site of recurrence | Local | Reference |
| Distant | -0.21 (0.111) | 0.81 (0.649, 1.004) | 0.054 |
| Pre-operative CRP level |  | 0.2 (0.055) | 1.22 (1.095, 1.361) | <0.001 |
| Treatment arm | Gemcitabine | Reference |
| Gemcitabine plus capecitabine | -0.23 (0.11) | 0.79 (0.64, 0.982) | 0.034 |

**Supplementary Figure 1.** Post progression survival as cumulative incidence plots.

1. Local vs. distant recurrence vs. death without recurrence



1. Site of distant recurrence



**Supplementary Figure 2.** Post progression survival as cumulative incidence plots.

1. Local vs. distant recurrence vs. death without recurrence



1. Site of distant recurrence

