**The Impact of Positive Resection Margins on Survival and Recurrence Following Resection and Adjuvant Chemotherapy for Pancreatic Ductal Adenocarcinoma**

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**MINI ABSTRACT**

We analysed the prognostic survival value of positive resection margins following pancreatic cancer resection and adjuvant chemotherapy. Margin involvement is associated with reduced overall and recurrence free survival. The knowledge of increased risk of local recurrence and specific margin involvement will aid tailored therapies.

**STRUCTRED ABSTRACT**

**Objective and Summary background data**

 Local and distant disease recurrence are frequently observed following pancreatic cancer resection but an improved understanding of resection margin assessment is required to aid tailored therapies.

**Methods**

Analyses were carried out to assess the association between clinical characteristics and margin involvement as well as the effects of individual margin involvement on site of recurrence and overall and recurrence free survival using individual patient data from the European Study Group for Pancreatic Cancer (ESPAC)-3 randomized controlled trial.

**Results**

There were 1151 patients, of whom 505 (43.9%) had an R1 resection. The median and 95% confidence interval (CI) overall survival was 24.9 (22.9, 27.2) months for 646 (56.1%) patients with resection margin negative (R0>1mm) tumors, 25.4 (21.6, 30.4) months for 146 (12.7%) patients with R1<1mm positive resection margins and 18.7 (17.2, 21.1) months for 359 (31.2%) patients with R1-direct positive margins (P < 0.001). In multivariable analysis, overall R1-direct tumor margins, poor tumor differentiation, positive lymph node status, WHO performance status >1, maximum tumor size, and R1-direct posterior resection margin were all independently significantly associated with reduced overall and recurrence free survival. Competing Risks analysis showed that overall R1-direct positive resection margin status, positive lymph node status, WHO performance status 1 and R1-direct positive superior mesenteric/medial margin resection status were all significantly associated with local recurrence.

**Conclusions**

R1-direct resections were associated with significantly reduced overall and recurrence free survival following pancreatic cancer resection. Resection margin involvement was also associated with increased risk for local recurrence.

**INTRODUCTION**

Pancreatic cancer treatment remains a challenge and only a relatively small percentage of around 15% of patients are candidates to undergo potentially curative surgery 1. Long-term survival after resection with adjuvant therapies has increased considerably in recent years approaching 30% 2. At least 70% of patients ultimately die of disease recurrence following resection. Predicting the pattern of disease recurrence has implications for optimizing therapy such as systemic therapy for distant metastasis or chemoradiation for local recurrence. It is now generally accepted that margin analysis has to be protocol-based, analyzing not only the four transection margins of pancreas, bile duct, proximal gastric or duodenum, and jejunum, but also the anterior surface, and the posterior, superior mesenteric vein and portal vein (SMV/PV), and the superior mesenteric artery (SMA) resection margins 3, 4.

Previously, both the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM Classifications had defined a positive resection (R1) as direct microscopic involvement by one or more malignant cells at any surface or margin (R1-direct) and a clear resection (R0) if otherwise 5, 6. In the current 8th edition UICC guidelines, this definition remains unchanged 7, whereas the 8th edition of the AJCC now defines R1 as cancer cells within 1-mm of the margin 8. Several institutions 9-12 and guidelines 3, 13 have also endorsed an R1 positive margin as one or more cancer cells within 1-mm of any surface or margin (R1<1mm). A clear (R0) resection margin is then defined as tumor cells > 1-mm away from any margin or surface (R0>1mm). Differences in survival have emerged in recent studies comparing R0 with R1-direct and R1<1mm. A single center study from Heidelberg of 561 patients with resected pancreatic cancer found 112 (20.0%) patients had R0 and 449 (80.0%) patients had R1 resections, of which 123 (21.9%) R1<1mm and 326 (58.1%) had R1-direct) resections. Multivariable analysis showed that margin status was an independent prognostic factor 14.

Increased distances of 1.5-mm and 2-mm have also been proposed as being prognostically valid 15, 16. A recent meta-analysis 17 compared different sampling techniques. The pooled R0 rate (95% CI%) was 29 (26-32)% in studies using an axial slicing technique and a R1<1mm margin, 49 (47-52)% in studies using other slicing techniques and an R1<1mm margin, and 72 (70-74)% in studies using an R1-direct margin definition.

Although there are several studies describing the prognostic relevance of positive resection margins, there are no prospective studies on the prognostic role of specific resection margin involvement in pancreatic cancer and the association with local disease recurrence. The purpose of this study was to analyse the prognostic effect of margin involvement on disease recurrence and long-term survival in pancreatic cancer patients following resection and adjuvant chemotherapy from the ESPAC-3(v1) and ESPAC-3(v2) randomized controlled trial of the European Study Group for Pancreatic Cancer 18, 19 using individual patient data.

**METHODS**

Data were collected from patients with pancreatic ductal adenocarcinoma enrolled into the ESPAC-3(v1) three-arm randomized controlled trial comparing adjuvant gemcitabine against 5-fluorouracil (5-FU) with folinic acid (FA) and against observation and the ESPAC-3(v2) two-armed randomized controlled trial comparing adjuvant gemcitabine against 5-FU/FA 18, 19. The trial was conducted at the Liverpool Cancer Research UK and Clinical Trials Unit, University of Liverpool, UK. The ESPAC-3 trial was initially introduced as a three-arm study (the first patient recruited on July 7th, 2000) that included an arm with observation only after resection but this observation arm was dropped (June 20th, 2003) following the definitive results from the ESPAC-1 trial on the recommendation of the independent data and safety monitoring committee 20.

Patients were randomly assigned to each treatment arm on a 1:1 basis using a computer-generated variable-size blocked randomization method. The primary outcome measure was length of survival and the secondary endpoints were toxicity, quality of life and 5-year survival. There were 159 centers that contributed patients to the trial from 17 countries. Patients were stratified at randomization by country and resection margin status (R0 versus R1). The clinicaltrials.gov identifier was NCT00058201. The full protocol is available online at:

[https://www.lctu.org.uk/Public/SSES3\_PROTOCOL.11-ESPAC-3(v2)\_Protocol.pdf](https://www.lctu.org.uk/Public/SSES3_PROTOCOL.11-ESPAC-3%28v2%29_Protocol.pdf)

Histopathological information was collected prospectively and was conditional for registration into the trial prior to randomization. Patients had to have histologically proven ductal adenocarcinoma of the pancreas that had been macroscopically resected (R0 or R1). Resection margin positivity was defined as one or more cancer cells within one millimeter of any surface or margin (R1<1mm) or at the surface (R1-direct). Anatomical positive sites were identified. A clear resection margin was defined as one or more cancer cells more than one millimeter from any surface or margin (R0>1mm). Minimum registration data included maximum 2-dimensional tumor size, tumor differentiation (as well, moderate or poor) and the number of involved lymph nodes and the total number of lymph nodes. TNM staging was also recorded using the UICC (1997) TNM Rules for the Classification of Pancreatic Cancer (ICD-o C25.0-2, 8) 21.

In addition, all histopathological reports had to be transmitted to the Liverpool Cancer Research UK and Clinical Trials Unit for registration and prior to randomization. Initial patient histology reports were re-assessed retrospectively using a more detailed proforma, which was sent to all contributing sites. This included the transection margins of pancreas, bile duct, proximal gastric or duodenum, and jejunum, and the anterior surface, and the posterior, superior mesenteric vein and portal vein, and the superior mesenteric artery resection margins. Each margin was classified as R0>1mm, R1<1mm and R1-direct. The margin was also defined as positive if there was an involved lymph node at any surface or margin (R1-LN). Tumor recurrence was categorized as either local, distant or ‘other’ where further information was not available.

**Statistical Methodology**

The main outcomes were overall survival measured as the time from randomization until death by any cause and recurrence free survival measured as the time from randomization until disease recurrence or death by any cause. Survival estimates were obtained using the method of Kaplan and Meier 22 and compared across subgroups using log-rank test 23. Multivariable regression were carried out using Cox proportional hazards models 24 with the assumption of proportional hazards assessed via inspection of Schoenfelds residuals 25. With respect to multivariable models, the effect of individual margins was only considered of interest if they provide extra information over the basic negative/positive resection margin status that has previously been shown 9, 19. Due to this, the effect of individual margins was only included in models which also adjust for the overall resection margin status. Terms were included in the multivariable model with Akaikes Information Criterion (AIC) 26 using a backwards selection process. Data on local or distant tumor recurrence and death are presented in terms of a cumulative incidence plot and analyses were carried out using a competing risks approach with multivariable modelling applied using the sub-distribution modelling approach of Fine and Gray 27.

**RESULTS**

The last of the 1151 patients recruited was randomized on January 8, 2007 and the database was locked on March 18, 2009 for survival analyses of the primary and secondary endpoints. Patient demographics have been previously reported (suppl. Table 1) 18, 19, 28. 551 (48%) patients were randomized to receive 5-FU/FA, 538 (47%) to receive gemcitabine and 62 (5%) were randomized to observation only. The CONSORT diagram is shown in suppl. Figure 1. The median (95% CI) survival was 23.0 (21.1-25.0) months for patients treated with 5-FU/FA and 23.6 (21.4-26.4) months for those treated with gemcitabine (hazard ratio = 0.94; 95% CI, 0.81-1.08; P=0.39). There was no difference in overall survival, progression-free survival or global quality-of-life, but there was less toxicity using adjuvant gemcitabine compared to 5FU/FA 18, 19. The five year (95% CI) overall survival estimates for ESPAC-3(v2) have recently been analyzed and showed this was 15.9 (12.7 – 19.4) % for 5FU/FA and 17.5 (14.0 – 21.2) % for gemcitabine (stratified log-rank χ2=7·40; P=0·390) 2.

There were 646 (56.1%) patients with R0>1mm tumor resections, 146 (12.7%) with R1<1mm margins and 359 (31.2%) with R1-direct margins (Table 1). There were 334 (66.1%) of 505 patients with a positive resection tumor margin (either R1-drect or R1<1mm), that had a single positive margin, and 120 (23.8%) that had two, 27 (5%) that had three and 4 (1%) that had four involved margins.

The overall survival (95% CI) estimates were 23.0 (21.6, 24.8) months for the full patient cohort, 24.9 (22.9, 27.2) months for patients with R0>1mm margins, 25.4 (21.6, 30.4) months for patients with an R1<1mm margin and 18.7 (17.2, 21.1) months for patients with an R1-direct margin (X2LR = 35.28; P <0.001, Figure 1a). Recurrence free survival (95% CI) estimates were 14.0 (13.3, 14.9) months for the full patient cohort, 15.7 (14.3, 17.0) months for patients with R0>1mm resection margins, 14.5 (12.8, 17.1) months for patients with an R1<1mm margin and 11.9 (10.9, 13.3) for patients with an R1-direct margin (X2LR = 34.77; P <0.001, Figure 1b).

The overall survival and recurrence free survival estimates for patients based on the number of involved margins is shown in Figure 2. One involved margin was associated with significantly reduced overall survival with hazard ratio (95% CI)=1.29 (1.11, 1.5; P = 0.001) and recurrence free survival with a hazard ratio (95% CI)=1.31 (1.14, 1.52; P < 0.001). There was a consistent decrease in prognosis in both overall and recurrence free survival with an increasing number of margins being involved (Table 2 and Figure 2). Multivariable analyses showed that patients with involved lymph nodes were more likely to have positive R1 resection margins (either an R1-direct or an R1<1mm margin). The effect of tumor maximum diameter was not significant at the 5% level (suppl. Table 2). Total pancreatectomies were associated with a high risk of positive margins whereas distal pancreatectomies were associated with a lower risk of positive margins.

Univariate analysis showed that patients with tumor involvement of the anterior surface were not associated with significantly worse overall survival and recurrence free survival than patients with clear R0>1mm tumor margins (Table 2 and suppl. Figure 2). Patients with an R1<1mm margin at the anterior surface, pancreatic transection margin or the superior mesenteric/medial margin had similar survival to patients with an R0>1mm margin (suppl. Figures 3-5). In contrast patients with an R1<1mm posterior margin tended to have a worse survival than patients with an R0>1mm margin (Figure 3). There were too few patients with positive lymph nodes at any margin (R1-LN) to permit a separate analysis.

Multivariable models were constructed including overall resection margin status (R0 versus R1), randomized intervention arm (gemcitabine, 5-FU/FA, observation), tumor differentiation (well, moderate, poor), World Health Organization (WHO) performance status (0, 1, 2) and maximum tumor size (measured on the log scale). Further included were covariates for the posterior and superior mesenteric/medial pancreatic margins and give the additional effect of these specific margins above the overall resection margin status. The final selected model included a term for the posterior resection margin but not the superior mesenteric/medial margin as it did not improve the model based on the Akaikes Information Criterion 26. The results of the models for both overall and recurrence free survival are shown in Supplementary Table 3.R1-direct tumor margins, tumor differentiation, lymph node status, WHO performance status, maximum tumor size, and R1-direct posterior resection margin were all associated with overall and recurrence free survival.

Competing risk analysis is based on the first reported event and was undertaken in the 532 (45%) patients who had reported tumor recurrence. The first reported event was local recurrence in 388 (34%) patients, distant recurrence in 77 (7%) patients, and recurrence not further specified in 67 (6%); there were also 407 (35%) patients who died prior to any disease recurrence being reported and 212 (18%) of patients were censored without death or recurrence being reported during the study. The cumulative incidence plot for each type of event shows that the accumulation of each type of event occurs proportionally over the course of the study (~~suppl.~~ Figure ~~6~~ 4). Competing Risks analysis showed that overall R1-direct margin status, positive lymph node status, WHO performance status 1 and R1-direct medial margin resection status were all associated with local recurrence (Table 3). Death was associated with poor tumor differentiation and positive lymph node status.

**DISCUSSION**

Histopathological assessment of pancreatic cancer resection specimens should include the transection margins, the circumferential posterior and superior mesenteric/medial margins and the anterior surface 3, 13.In this study the posterior and the superior mesenteric/medial margins were the most commonly involved margins as previously shown 9-12, 17. Studies performed before current standardized pathological reporting was introduced 13 sometimes failed to show survival differences between R0 and R1 resections 29. A study of 360 consecutive patients from the M. D. Anderson Cancer Centre found that lymph node metastases, major perioperative complications, and blood loss adversely independently affected survival but not resection margin status 30. In the ESPAC-1 trial, there were 101 (19%) out of 541 patients with an R1<1mm tumor resection with a significantly shortened ~~survival~~ median survival compared to patients with an R0>1mm resection. As in the present study of ESPAC-3 patients this was not independently significant taking the other significant factors of tumor grade and lymph node status into account 31. A study of 448 patients from Florida found longer survival with R0 resections compared to R1 resections but extending resections to achieve negative margins did not improve survival beyond R1 resections 32. In a study of 365 patients, margin stratification by 0.5-mm increments found that >1.5 mm clearance produced the optimal survival 15. In a study of 208 patients from Japan, the median survival in patients with an R0>1mm resection was 26 months, 30.4 months in patients with an R1<1mm resection and 22.9 months in patients with an R1-direct resection. However, only lymph node metastases and poor differentiation were independently associated with survival 33.

An earlier study from Heidelberg showed that R1<1mm was significantly associated with survival compared to R0 34, but a more recent update showed significant hazard ratios for survival between R0>1mm and R1-direct and between R1<1mm and R1-direct 14. A study of 411 patients following neoadjuvant therapy from the MD Anderson Cancer Center found that patients with a medial margin R0> 5.0 mm had better survival than those with positive margins defined by R1-direct, R1<1mm and R1-1.0-5.0 mm. Medial margin distance of involvement, tumor differentiation, lymph node metastasis, and histopathologic tumor response grade, were all independent prognostic factors for survival. The authors recommended the use of medial margin R0>1 mm for defining an R0 resection in post-therapy pancreaticoduodenectomy specimens 35.

In the present study, patients with R1 resections had a significantly reduced median overall survival compared to patients with R0>1mm resections. The dominant positive resection margin was R1-direct in the multivariable analysis, which independently predicted overall and progression free survival along with poor tumor differentiation, positive lymph node status, WHO performance status >1, maximum tumor size, and R1-direct posterior resection margin. There is now growing evidence that resection measures should be expanded beyond the UICC recommendation of R1-direct and R0 to include margin distance of involvement 14, 35, and indeed, the AJCC has now adopted to define R1 as cancer cells within 1-mm of the margin 8. Ideally future reporting should consider including information on R0>1mm, R1<1mm, and R1-direct as a minimum data set.

A retrospective study from Glasgow of 109 (74%) out of 148 pancreatic cancer patients with an R1<1mm resection margin found a significantly worse prognosis if the pancreatic (neck) transection and medial margins were involved, with a median survival of 11.1 months compared to 18.9 months if the anterior surface and posterior margin were involved 12. A study of 150 patients from Marseille, reported reduced survival for patients with medial margin R1-direct resections but not posterior margin involvement 36. In the present study, we have shown that R1-direct involvement of the posterior, medial and pancreatic transection margins are all associated with reduced overall and recurrence free survival. If only a single margin is positive, direct involvement of the posterior and pancreatic transection margins are significant factors predicting survival. The transection margin is of considerable interest in this context, since there has been a debate whether routine frozen section of this margin is relevant, with one argument being that converting an R1-direct resection after positive frozen section to a R0 resection would not change overall prognosis 37. Our data rather support the argument that achieving tumor free margin is important for the pancreatic transection margin 38. It is unclear whether margin positivity based only on a positive lymph node at the margin without any direct tumor involvement is of any survival significance and whether it should be called R1. There were very few patients with positive lymph nodes at any margin in the present study to permit a separate analysis. This question remains unanswered but we do know that that is a very uncommon event.

There is an increasing armamentarium of strategies that could be used for reducing the risk of local recurrence that includes targeted chemoradiotherapy and aggressive chemotherapy. A better understanding of patients specifically at high risk of early local recurrence following resection would be important. An autopsy study on 24 patients who had had potentially curative resection showed local recurrence in 75%, liver, peritoneal or lung metastasis in 88% and both in 71% 33. The cause of death was local recurrence in 17% and metastatic disease in 67% 39. A study of the pattern of recurrence of pancreatic cancer in 208 patients from a single center in Japan, found local recurrence in 8% of R0>1mm cases, in 20% of R1<1mm cases and in 50% of R1-direct cases 33. On the other hand, the study from Marseille found that 16 (11%) of the 150 patients who had had a resection had isolated local recurrence yet eight of these patients had also had an R0 resection 36. In the present study competing risks analysis showed that local recurrence was significantly associated with overall R1-direct positive resection margin status, positive lymph node status, WHO performance status 1 and R1-direct positive medial margin resection status. Death was significantly associated with poor tumor differentiation and positive lymph node status. The analysis was based on the 532 (45%) of the 1151 patients in whom disease relapse was reported as well as the 407 (35%) patients who died prior to any disease recurrence and the 212 (18%) patients without death or recurrence. The first event was local recurrence in 388 (34%) patients, distant recurrence in 77 (7%) patients, and unspecified recurrence in 67 (6%). In the more recent ESPAC-4 trial, relapse was reported in 479 (66%) of 730 patients and death without relapse occurred in 78 (11%) patients 2. Although the reported relapse rate in the present study was lower than in ESPAC-4, any bias in the results and conclusions was minimized by the fact that ESPAC-3 was a large, prospective, multicentre, randomized controlled trial, and so the conclusions essentially remain valid. The association between reduced performance status and increased local recurrence may be related to the ability to receive full dose chemotherapy with all six cycles, which is linked to overall and progression free survival in the adjuvant setting 28. Poor performance status is also a key negative survival factor in the advanced setting 40, which may be related to micro-metastatic disease not detectable by imaging methods 41,42.

In conclusion, we found that overall R1-direct tumor margins and R1-direct posterior resection margins were each independently associated with reduced overall and recurrence free survival. We also showed that overall R1-direct positive resection margins and R1-direct positive superior mesenteric/medial margin resection status were each significantly associated with local recurrence. Death was significantly associated with poor tumor differentiation and positive lymph node status. This improved understanding should be reflected in improved reporting of pancreatic cancer studies and help to inform future trials in this field.

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**FIGURE LEGENDS**

**Figure 1**: a) Overall survival and b) Recurrence free survival for the full patient cohort by resection margin by R0, R1<1mm and R1-direct status.

**Figure 2**: a) Overall and b) Recurrence free survival for the number of involved margins.

**Figure 3**: a) Overall survival and b) Recurrence free survival by R0, R1<1mm and R1-direct status for the posterior margin.

**Figure 4:** Competing Risks analyses for local distant and other recurrence and death.

**TABLES**

**Table 1**: Distribution of margins.

**Table 2**: Univariate analysis of pancreatic transection margins on overall survival and recurrence free survival.

**Table 3**: Competing Risks analysis for local recurrence and death.

**FIGURE LEGENDS FOR SUPPLEMENTARY FIGURES (APPENDIX 1)**

**Suppl. Figure 1: CONSORT diagram.**

**Suppl. Figure 2:** a) Overall survival and b) Recurrence free survival based on a single involved margin only.

**Suppl. Figure 3**: a) Overall and b) recurrence free survival by R0, R1<1mm and R1-direct status for the anterior surface.

**Suppl. Figure 4**: a) Overall and b) recurrence free survival by R0, R1<1mm and R1-direct status for the pancreatic transection margin.

**Suppl. Figure 5**: a) Overall survival and b) Recurrence free survival by R0, R1<1mm and R1-direct status for the medial margin.

**TITLES FOR SUPPLEMENTARY TABLES (APPENDIX 2)**

**Suppl. Table 1**: Patient demographics.

**Suppl. Table 2**: Multivariable regression of factors associated with positive R1 resection margins including both R1-direct and R1<1mm margins.

**Suppl. Table 3**: Multivariable Cox model for overall and recurrence free survival.

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