

1 **The Impact of Diabetes Mellitus on Survival Following Resection and Adjuvant Chemotherapy for**  
2 **Pancreatic Cancer**

3

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46

48 **ABSTRACT**

49 **Background.** Diabetes mellitus is frequently observed in pancreatic cancer patients and is both a risk  
50 factor and an early manifestation of the disease.

51 **Methods.** We analyzed the prognostic impact of diabetes on the outcome of pancreatic cancer  
52 following resection and adjuvant chemotherapy using individual patient data from three European  
53 Study Group for Pancreatic Cancer (ESPAC) randomized controlled trials. Analyses were carried out  
54 to assess the association between clinical characteristics and the presence of pre-operative diabetes  
55 as well as the effect of diabetic status on overall survival.

56 **Results.** 1105 patients were included in the analysis, of whom 257 (23%) had confirmed diabetes  
57 and 848 (77%) did not. Median (95% confidence interval) unadjusted overall survival in non-diabetic  
58 patients was 22.3 (20.8 - 24.1) months compared to 18.8 (16.9 - 22.1) months for diabetic patients  
59 ( $p=0.24$ ). Diabetic patients were older, had increased weight and more co-morbidities. Following  
60 adjustment, multivariable analysis demonstrated that diabetic patients had an increased risk of  
61 death (HR: 1.19 (95%CI 1.01, 1.40),  $P=0.034$ ). Maximum tumor size (MTS) of diabetic patients was  
62 larger at randomization (33.6mm vs 29.7mm,  $p=0.026$ ).

63 **Conclusions.** Diabetes mellitus was associated with increased tumor size and reduced survival  
64 following pancreatic cancer resection and adjuvant chemotherapy.

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68 **KEYWORDS:** pancreas cancer, diabetes mellitus, prognosis, resection, adjuvant therapy

69

70 **INTRODUCTION**

71 Pancreatic cancer is currently the fourth most common cause of cancer related mortality in  
72 developed countries (Siegel *et al*, 2015) and is predicted to be the second leading cause within the  
73 next decade (Rahib *et al*, 2014). Most patients are diagnosed at an advanced stage with distant  
74 metastasis and/or locally advanced unresectable tumors (Hidalgo *et al*, 2015). Together with limited  
75 and often ineffective treatment options, this results in an overall low 5-year survival rate of less than  
76 7%. Surgery, the only chance for cure, can be offered to only 15-20% of patients resulting in  
77 approximately 20% 5-year survival rates (Kleeff *et al*, 2016).

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78  
79 Risk factors that have been identified for pancreatic cancer include tobacco smoking, diabetes  
80 mellitus, and others (Bosetti *et al*, 2012; Kleeff *et al*, 2016). Several studies have established that  
81 diabetes mellitus has a higher prevalence in patients with pancreatic cancer than other cancers or  
82 control subjects especially in patients with a more recent diagnosis (Aggarwal *et al*, 2013; Chari *et al*,  
83 2008; Pannala *et al*, 2008). Systematic reviews and meta-analyses have confirmed that diabetes is a  
84 risk factor for pancreatic cancer with risk ratios of around 1.8-2.1 (Ansary-Moghaddam *et al*, 2006;  
85 Ben *et al*, 2011; Huxley *et al*, 2005; Stevens *et al*, 2007). The risk is higher with recent onset diabetes  
86 (Ben *et al*, 2011; Calle *et al*, 1998; Huxley *et al*, 2005), possibly as an early manifestation of pancreatic  
87 cancer. In contrast to an earlier report (Gullo *et al*, 1994) long standing diabetes mellitus (> 5 years)  
88 has also been shown to have an increased risk of pancreatic cancer of 1.5-2.0 (Everhart & Wright,  
89 1995; Huxley *et al*, 2005; Li *et al*, 2011). There is still an excess risk of pancreatic cancer even with a  
90 long standing diagnosis of diabetes of 20 years or more but at a lower level with an odds ratio of 1.3  
91 (Bosetti *et al*, 2014). There is some evidence that diabetes mellitus may resolve after pancreatic  
92 cancer resection in a proportion of new-onset cases, whereas it remains unchanged in patients with  
93 long standing diabetes (Pannala *et al*, 2008; Permert *et al*, 1993), which appears to be specific for  
94 pancreatic cancer, as resection for chronic pancreatitis does not improve pre-existing diabetes  
95 (Litwin *et al*, 2008). While diabetes mellitus increases the risk of pancreatic cancer, there is also

98 evidence that pancreatic cancer itself induces diabetes (type 3c). Potential mechanisms include the  
99 release of adrenomedullin, a potential mediator of beta cell dysfunction (Aggarwal *et al*, 2012) or by  
100 beta cell apoptosis induced by pancreatic stellate cells (Kikuta *et al*, 2013). Thus, diabetes is both  
101 causal and consequential to pancreatic cancer, the latter offering a window for screening, early  
102 tumor detection and therapy (Jenkinson *et al*, 2015).

103 The survival of diabetic cancer patients compared with normoglycemic individuals across all cancer  
104 types seems to be less with risk ratios of around 1.4 (Barone *et al*, 2008; van de Poll-Franse *et al*,  
105 2007), but not for pancreatic cancer, possibly because of the limited cohort size (Park *et al*, 2006).

106 Analysis of diabetes as covariate on survival outcome in advanced pancreatic is difficult due to the  
107 large number of variables and the very short survival. Preoperative diabetes found in 275 (56.3%) of  
108 488 patients with pancreatic cancer that had resection also did not influence survival although tumor  
109 size was significantly larger (mean=36 mm) compared to the non-diabetics (mean=33 mm) (Hart *et*  
110 *al*, 2014). In another study, 93 (45.4%) of 209 patients with pancreatic cancer and preoperative  
111 diabetes had a median survival of 15 months, which was less compared to 17 months in non-  
112 diabetics with a hazard ratio of 1.55 (Chu *et al*, 2010). The risk of survival was even less in new onset  
113 diabetics (<2 years duration) compared to the longstanding diabetics with a hazard ratio of 1.75 (Chu  
114 *et al*, 2010). Diabetics also had a larger tumor size (mean = 38 mm) compared to non-diabetics  
115 (mean= 32 mm).

116

117 Thus, the prognostic effect of diabetes mellitus in patients with pancreatic cancer is uncertain. The  
118 purpose of this study was to analyze the prognostic effect of clinically revealed diabetes on long term  
119 survival in pancreatic cancer patients following resection and adjuvant chemotherapy from three  
120 randomized controlled trials of the European Study Group for Pancreatic Cancer (ESPAC) trials,  
121 namely ESPAC-1Plus, ESPAC-1, and ESPAC-3 (Neoptolemos *et al*, 2001; Neoptolemos *et al*, 2010;  
122 Neoptolemos *et al*, 2004; Neoptolemos *et al*, 2009),

Gelöscht: Thus

Gelöscht: using individual patient data

126 **METHODS**127 **Patients**

128 Patients with pancreatic ductal adenocarcinoma were identified from the ESPAC-1Plus, ESPAC-1 and  
129 ESPAC-3 trials (Neoptolemos *et al*, 2001; Neoptolemos *et al*, 2010; Neoptolemos *et al*, 2004;  
130 Neoptolemos *et al*, 2009). These were open label, international, randomized phase III studies. In  
131 order to improve homogeneity patients randomized to receive chemotherapy only were selected for  
132 this analysis. Patients were excluded if they had been randomized to either chemoradiation or to  
133 observation. There were 541 patients randomized together in ESPAC-1Plus and ESPAC-1 of whom  
134 164 patients were randomized to chemotherapy alone. There were 25 (15%) of these 164 patients  
135 with diabetes. There were 941 patients with ductal adenocarcinoma randomized in ESPAC-3 to either  
136 of two adjuvant chemotherapy regimens. There were 232 (25%) of these 941 patients with diabetes.

137 [The diabetes mellitus status was prospectively obtained by the principal investigator at each of the](#)  
138 [referring sites according to the best available clinical evidence and guidelines at that time and site.](#)

Gelöscht: Diabetes mellitus was prospectively obtained by clinical status

139 and categorized as no diabetes, insulin-dependent or non-insulin dependent diabetes. Glucose  
140 tolerance testing or fasting glucose measurements were not routinely carried out, and data regarding  
141 duration of diabetes were not recorded (Neoptolemos *et al*, 2001; Neoptolemos *et al*, 2010;  
142 Neoptolemos *et al*, 2004; Neoptolemos *et al*, 2009).

143

144 **Statistical Analysis**

145 Clinical characteristics were compared across diabetic groups using two-sided Mann-Whitney U  
146 statistics for continuous characteristics and the Chi-Squared test for categorical variables.  
147 Multivariable regression using logistic regression was used to assess the relationship between clinical  
148 characteristics and diabetic status. The primary outcome of interest was overall survival measured as  
149 the time from surgery until death by any cause. Survival estimates are calculated using the method of  
150 Kaplan and Meier (Kaplan & Meier, 1958) and compared across biological groups using Log-Rank  
151 tests (Peto & Peto, 1972). Median follow-up is calculated using the reverse Kaplan Meier approach

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154 (Schemper & Smith, 1996). Multivariable analyses are carried out using Cox proportional hazards  
 155 models (Cox, 1972) and are constructed using forward selection based on Akaike's Information  
 156 Criterion (AIC). The effects for trial and country are both included as stratification factors. Only  
 157 covariates with a univariate significance of  $P < 0.25$  are considered for selection in the multivariable  
 158 model. Assessment of maximum tumor size carried out using a  $\log(x+1)$  transformation on  
 159 continuous covariate. Proportional hazards assumptions are evaluated via assessment of Schoenfeld's  
 160 residuals (Schoenfeld, 1982). Further sensitivity analyses are carried out using a landmark method,  
 161 excluding patients who died within 30, 60, and 90 days of randomisation. All analyses were carried  
 162 out using R (v 3.2.1) (R-Development-Core-Team, 2011) on an intention to treat basis, retaining  
 163 patients in their randomized treatment groups and including protocol violators and ineligible  
 164 patients. A two-sided significance of  $P < 0.05$  was used throughout.

Gelöscht: Proportional

Gelöscht: effect of trial is included as a frailty term.

Gelöscht: Porportional

Gelöscht: assesment

Gelöscht:

Gelöscht: sesitivity

Gelöscht: 6, 9 and 12 months

## 166 RESULTS

### 167 Clinical and Pathological Variables

168 A total of 1105 patients were included in the analysis, 164 (15%) patients from the ESPAC-1 studies  
 169 and 941 (85%) patients from the ESPAC-3 study. There were 25 (15%) and 232 (25%) diabetics  
 170 respectively from these studies. Together there were 257 (23%) patients with clinically revealed  
 171 diabetes mellitus and 848 (77%) who were non-diabetic at the point of randomization. Patient  
 172 characteristics at baseline and univariate analyses are presented to identify patient characteristics  
 173 associated with diabetes (Table 1). Patients with diabetes were significantly older with a median  
 174 (interquartile range) age of 65 (57-71) years versus 63 (56-69) years for non-diabetics ( $p=0.04$ ), and  
 175 had an increased median (interquartile range) weight at presentation of 72 (62, 80) kg versus 66 (58,  
 176 75) kg for non-diabetics ( $p < 0.001$ ). Diabetic patients were also more likely to have concurrent  
 177 medical conditions other than diabetes (64% versus 42%;  $p < 0.001$ ). 146 of 257 (57%) diabetic  
 178 patients completed all six cycles of adjuvant therapy, which was not significantly different from the  
 179 458 of 848 (54%) non diabetic patients ( $p=0.47$ ). The mean (sd) maximum tumor size (MTS), was  
 180 33.59 (20.64) mm in diabetic patients and 29.67 (14.53) mm in non-diabetic patients with

Gelöscht: 60

189 significantly larger tumors in diabetic patients ( $p=0.026$ , MTS compared on the log scale). Diabetic  
190 patients had proportionally larger resections in the form of total pancreatectomy (12%) compared to  
191 non-diabetics (1%;  $p<0.001$ ) although the distribution of tumor location was not significantly  
192 different between diabetic and non-diabetic patients ( $p=0.216$ ). There were no significant  
193 preoperative or postoperative differences between insulin dependent and non-insulin dependent  
194 patients. Multivariable analysis identified increased age and increased weight as clinical  
195 characteristics independently associated with pre-operative diabetes (Table 2). Further, increased  
196 maximum tumor size but also a lower proportion of positive lymph nodes, were independently  
197 associated with pre-operative diabetes.

198

### 199 **Overall Survival**

200 Eight hundred and sixty two patients (78%) died during the course of both trial sets. The median  
201 (95% confidence interval) overall survival was 21.4 (20.2, 23.4) months. The median (95% confidence  
202 interval) overall survival for non-diabetics was 22.3 (20.8 - 24.1) months compared to 18.8 (16.9 -  
203 22.1) months for diabetic patients. Analysis of the overall survival by diabetic status obtained  $X^2LR$

204 ( $_{1DF}$ ) = 1.39 ( $p=0.238$ ). Multivariable model analysis for overall survival identified World Health

205 Organization (WHO) performance status and smoking status as independent prognostic clinical  
206 indicators and resection margin status, tumor differentiation and lymph node involvement as  
207 independent prognostic pathological indicators (Table 3). Following adjustment of other terms,

208 diabetic status was significantly associated with survival, with diabetic patients having an increased  
209 risk of death (Hazard Ratio: 1.19 (95% confidence interval: 1.01, 1.40),  $p=0.034$ ). The fitted effect of

210 diabetic status is given in Figure 1. Assessment of Schoenfeld residuals did not identify any

211 prognostic factors, which may be associated with non-proportional hazards.

212

213 Of the 257 patients who were diabetic, insulin status was missing in two patients. One hundred and  
214 forty four (56%) of these 255 patients were insulin-dependent and the remainder ( $n=111$ ) were non-  
215 insulin dependent received either oral antidiabetics or were controlled by diet alone. At least 13

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220 patients were receiving oral antidiabetic therapy (seven taking metformin) but specific information  
221 was not available for the remaining 98 non-insulin dependent diabetics. The median (95% confidence  
222 interval) overall survival estimates was 18.0 (16.5, 21.1) months for patients who used insulin and  
223 20.5 (16.0, 26.6) months for patients who did not use insulin. The unadjusted overall survival by  
224 diabetic status was not significant ( $X^2_{LR(1DF)} = 0.03$ ,  $p=0.857$ ). The unadjusted overall survival for  
225 diabetics in those using insulin versus metformin versus other oral diabetic medication was not  
226 significant ( $X^2_{LR(2DF)} = 0.80$ ,  $p=0.371$ ). The median (95% confidence interval) overall survival estimates  
227 was 18.0 (16.5, 21.1) months for patients who used insulin ( $n=144$ ) and 22.2 (20.7, 23.9) months for  
228 patients who were not diabetic or who were non-insulin dependent ( $n=959$ ) ( $X^2_{LR(1DF)} = 0.4$ ,  $p=0.527$ ).

229 In insulin-dependent diabetic patients the median (95% confidence interval) overall survival  
230 estimates with a maximum tumor diameter  $> 30$ mm was 17.0 (15.2-22.7) months compared to 18.5  
231 (15.9-26.1) months for patients a maximum tumor diameter  $\leq 30$ mm (Hazard ratio [95% confidence  
232 interval] =0.96 (0.65,1.4);  $p=0.823$ ). In non-insulin diabetic dependent patients with a maximum  
233 tumor diameter  $> 30$ mm was 14.6 (9.51-21.9) months compared to 32.0 (22.11-41.4) months for  
234 patients a maximum tumor diameter  $\leq 30$ mm (Hazard ratio [95% confidence interval] =1.99 [1.30,  
235 3.03];  $p<0.001$ ). The overall survival difference was significant ( $X^2_{LR(3DF)} = 10.37$ ,  $p=0.016$ ) (Figure 2).

236 A multivariable analysis was carried out of factors independently associated with overall survival  
237 specifically in the 257 diabetic patients. Due to the interaction between insulin status and maximum  
238 tumor size, we included the latter as a nested effect within insulin status, allowing for separate  
239 hazard ratios for insulin dependent and non-dependent groups. This showed that lymph node  
240 metastasis remained an independent prognostic factor (Table 4). There was also a significant effect  
241 of maximum tumor size for non-insulin dependent patients but not for patients who were insulin-  
242 dependent. Landmark analyses, removing patients who died within the first 30, 60 and 90 days  
243 respectively showed that the magnitude and direction of all treatment effects remained consistent  
244 showing that the effects reported are not overly effected by early deaths. Details are included in

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247 [supplementary table 1. Further to this, assessment of Schoenfeld residuals did not identify any](#)  
248 [prognostic factors, which may be associated with non-proportional hazards.](#)

Gelöscht: supplementary

## 250 DISCUSSION

251  
252 The present study shows that diabetes mellitus is associated with increased tumor size and a small  
253 but significant increased overall risk of death with a hazard ratio of 1.19. There was a significant  
254 effect of maximum tumor size on survival for non-insulin dependent but not for insulin dependent

255 [diabetic](#) patients. Two specific smaller studies also showed increased tumor size with diabetes with  
256 only one of these found a worse prognosis for diabetic patients following tumor resection (Chu *et al*,  
257 2010; Hart *et al*, 2014). A meta-analysis of retrospective studies demonstrated worse prognosis in  
258 diabetic patients following resection with a hazard ratio of 1.32 (Walter *et al*, 2014).

Gelöscht: This is by far the largest study to date on this topic and relied on clinical data collected in prospectively randomized controlled trials of patients with histological proven ductal adenocarcinoma involving a total of 1105 patients of whom 257 (23%) were diabetic (Neoptolemos *et al*, 2001; Neoptolemos *et al*, 2010; Neoptolemos *et al*, 2004; Neoptolemos *et al*, 2009). ¶

259  
260 Taken together, there is now solid evidence that the diabetic state at the time of resection influences  
261 outcome. There are several concepts on how diabetes mellitus might impact on prognosis of  
262 pancreatic cancer patients. Patients with long standing type II diabetes exhibit insulin resistance and  
263 hypersecretion of insulin (Fisher *et al*, 1996; Li, 2012). In addition, elevated insulin levels result in  
264 increased bioavailability of IGFs and pancreatic cancer cells highly express high-affinity insulin and  
265 IGF receptors (Li, 2012). Insulin has been shown to act as a mitogen for pancreatic cancer cells (Ding  
266 *et al*, 2000; Fisher *et al*, 1996), and IGF-1 -besides its mitogenic effects, induces angiogenesis and  
267 increases invasion and blocks apoptosis of pancreatic cancer cells, thereby promoting tumor growth  
268 (Li, 2012). In line with this hypothesis, this and two other mentioned studies (Chu *et al*, 2010; Hart *et*  
269 *al*, 2014) have shown that diabetic patients have larger tumors at the time of resection. The present  
270 study has also demonstrated that the effects of diabetes on outcome were independent from tumor  
271 size, suggesting that other mechanisms are responsible for the worse prognosis of diabetic patients.  
272 It is conceivable that in the adjuvant setting, hyperinsulinemia supports growth of occult pancreatic

282 cancer cells, resulting in worsened prognosis. This might further be augmented by related obesity,  
283 leading to enhanced oxidative stress and inflammatory responses (Li, 2012). Indeed, the median  
284 weight of diabetic patients was significantly higher than of non-diabetic patients in the present  
285 analysis.

Gelöscht: contributing to the increased risk of pancreatic cancer

286  
287 The association between diabetes and tumor size has been substantiated from three large trials.  
288 Here, we show in addition, that in the group of diabetic patients, tumor size was an important  
289 prognostic indicator in non-insulin dependent, but not in insulin dependent patients. This suggests  
290 that in non-insulin dependent diabetes mellitus, tumor size has a predominant effect on prognosis  
291 whereas insulin dependent diabetes mellitus has a stronger, likely systemic effect on survival. There  
292 is evidence that therapies that increase insulin levels such as exogenous insulin or sulfonylurea could  
293 increase cancer risk. Therapies that decrease insulin levels by decreasing insulin resistance such as  
294 metformin, which also inhibits mTOR activity (Gong *et al*, 2014), would decrease the risk. Long  
295 duration ( $\geq 15$  years) of oral antidiabetics is associated with a decreased pancreatic cancer risk (OR  
296 0.31), whereas insulin use (<5 years) is associated with increased cancer risk (OR 5.6) (Bosetti *et al*,  
297 2014). A case control study has shown that diabetic patients on metformin had a significantly  
298 reduced risk of pancreatic cancer compared to patients not on metformin. In contrast, patients on  
299 insulin or insulin secretagogues had a significantly higher risk (Li *et al*, 2009), whilst a meta-analysis  
300 showed a reduced pancreatic cancer risk for patients on metformin but not sulfonylurea (Soranna *et*  
301 *al*, 2012). Another recent meta-analysis could not verify these associations between metformin or  
302 insulin and pancreatic cancer risk (Singh *et al*, 2013).

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303  
304 A previous study has shown that the effect on survival was especially pronounced for recent onset  
305 diabetes (Chu *et al*, 2010). Tumors that induce diabetes might constitute a more aggressive subtype.  
306 Alternatively, symptoms of diabetes may mask symptoms of a developing tumor and contribute to  
307 delayed diagnosis. Our data on this aspect are conflicting, in as much as tumors of diabetic patients

312 were significantly larger, but had significantly less lymph node involvement and did not display  
313 differences in tumor differentiation. Furthermore, diabetic patients might have been treated less  
314 aggressively than non-diabetic patients, as it has been shown for other tumor entities (van de Poll-  
315 Franse *et al*, 2007), although there was no difference in surgery and adjuvant therapy (including  
316 completion of therapy) in our series. On the other hand, it is also conceivable that cancer-induced  
317 diabetes results in earlier diagnosis, and thus in potentially better outcome. It could be speculated  
318 that all of these effects might play a role and that our data reflect the sum of these effects.

319  
320 [This study relied on clinical data collected in prospectively randomized controlled trials of patients](#)  
321 [with histological proven ductal adenocarcinoma involving a total of 1105 patients of whom 257 \(23%\)](#)  
322 [were diabetic \(Neoptolemos \*et al\*, 2001; Neoptolemos \*et al\*, 2010; Neoptolemos \*et al\*, 2004;](#)  
323 [Neoptolemos \*et al\*, 2009\). Diabetes mellitus status was determined by the principal investigator at](#)  
324 [each of the referring sites according to the best available clinical evidence and guidelines at that time](#)  
325 [and site. This is a limitation of the present study, as no clear definition or test was utilized. Diagnosis](#)  
326 [reflected actual clinical care at the different sites and under-diagnosis is a likely issue, as routine use](#)  
327 [of specific tests \(e.g. glucose tolerance test\) was not mandatory within the ESPAC study protocols.](#)  
328 [Thus, it is possible that some of the patients were actually diabetic, but had not been formally](#)  
329 [assessed prior to therapy.](#)

330  
331 In conclusion, diabetic patients that undergo resection for pancreatic cancer and adjuvant therapy  
332 present with larger tumors and have a small but significantly higher risk of death than non-diabetic  
333 patients. There seem to be important differences in patients with pancreatic cancer between those  
334 with insulin and non-insulin dependent diabetes mellitus and from previous studies between those  
335 with new onset and established diabetes mellitus. Understanding the biological mechanisms behind  
336 these observations may offer new opportunities for diagnosis and therapy.

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339 **Figure legends:**

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341 [Figure 1: Fitted effect of diabetic status on overall survival in 1105 pancreatic cancer patients](#)  
342 [following resection and adjuvant chemotherapy. Yes: diabetic patients; No: non-diabetic patients](#)

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343

344 [Figure 2: Overall survival analysis in diabetic patients stratified according to whether patients were](#)  
345 [insulin-dependent \(Yes\) versus non-insulin-dependent \(No\), and maximum tumor diameter > 30 mm](#)  
346 [versus < 30 mm.](#)

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