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

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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

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INTRODUCTION

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

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

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

The survival of diabetic cancer patients compared with normoglycemic individuals across all cancer types seems to be less with risk ratios of around 1.4 (Barone *et al*, 2008; van de Poll-Franse *et al*, 2007), but not for pancreatic cancer, possibly because of the limited cohort size (Park *et al*, 2006). Analysis of diabetes as covariate on survival outcome in advanced pancreatic is difficult due to the large number of variables and the very short survival. Preoperative diabetes found in 275 (56.3%) of 488 patients with pancreatic cancer that had resection also did not influence survival although tumor size was significantly larger (mean=36 mm) compared to the non-diabetics (mean=33 mm) (Hart *et al*, 2014). In another study, 93 (45.4%) of 209 patients with pancreatic cancer and preoperative diabetes had a median survival of 15 months, which was less compared to 17 months in non-diabetics with a hazard ratio of 1.55 (Chu *et al*, 2010). The risk of survival was even less in new onset diabetics (<2 years duration) compared to the longstanding diabetics with a hazard ratio of 1.75 (Chu *et al*, 2010). Diabetics also had a larger tumor size (mean = 38 mm) compared to non-diabetics (mean= 32 mm).

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

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METHODS

Patients

Patients with pancreatic ductal adenocarcinoma were identified from the ESPAC-1Plus, ESPAC-1 and ESPAC-3 trials (Neoptolemos *et al*, 2001; Neoptolemos *et al*, 2010; Neoptolemos *et al*, 2004; Neoptolemos *et al*, 2009). These were open label, international, randomized phase III studies. In order to improve homogeneity patients randomized to receive chemotherapy only were selected for this analysis. Patients were excluded if they had been randomized to either chemoradiation or to observation. There were 541 patients randomized together in ESPAC-1Plus and ESPAC-1 of whom 164 patients were randomized to chemotherapy alone. There were 25 (15%) of these 164 patients with diabetes. There were 941 patients with ductal adenocarcinoma randomized in ESPAC-3 to either of two adjuvant chemotherapy regimens. There were 232 (25%) of these 941 patients with diabetes. The diabetes mellitus status was prospectively obtained by the principal investigator at each of the referring sites according to the best available clinical evidence and guidelines at that time and site, and categorized as no diabetes, insulin-dependent or non-insulin dependent diabetes. Glucose tolerance testing or fasting glucose measurements were not routinely carried out, and data regarding duration of diabetes were not recorded (Neoptolemos *et al*, 2001; Neoptolemos *et al*, 2010; Neoptolemos *et al*, 2004; Neoptolemos *et al*, 2009).

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Statistical Analysis

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

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

RESULTS

Clinical and Pathological Variables

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

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

Overall Survival

Eight hundred and sixty two patients (78%) died during the course of both trial sets. The median (95% confidence interval) overall survival was 21.4 (20.2, 23.4) months. The median (95% confidence interval) overall survival for non-diabetics was 22.3 (20.8 - 24.1) months compared to 18.8 (16.9 - 22.1) months for diabetic patients. Analysis of the overall survival by diabetic status obtained $X^2_{LR\ (1DF)} = 1.39$ (p=0.238). Multivariable model analysis for overall survival identified World Health Organization (WHO) performance status and smoking status as independent prognostic clinical indicators and resection margin status, tumor differentiation and lymph node involvement as independent prognostic pathological indicators (Table 3). Following adjustment of other terms, diabetic status was significantly associated with survival, with diabetic patients having an increased risk of death (Hazard Ratio: 1.19 (95% confidence interval: 1.01, 1.40), p=0.034). The fitted effect of diabetic status is given in Figure 1. Assessment of Schoenfeld residuals did not identify any prognostic factors, which may be associated with non-proportional hazards.

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

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

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

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

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supplementary table 1. Further to this, assessment of Schoenfeld residuals did not identify any prognostic factors, which may be associated with non-proportional hazards.

DISCUSSION

The present study shows that diabetes mellitus is associated with increased tumor size and a small but significant increased overall risk of death with a hazard ratio of 1.19. There was a significant effect of maximum tumor size on survival for non-insulin dependent but not for insulin dependent diabetic patients. Two specific smaller studies also showed increased tumor size with diabetes with only one of these found a worse prognosis for diabetic patients following tumor resection (Chu *et al*, 2010; Hart *et al*, 2014). A meta-analysis of retrospective studies demonstrated worse prognosis in diabetic patients following resection with a hazard ratio of 1.32 (Walter *et al*, 2014).

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

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

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

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

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

This study 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). Diabetes mellitus status was determined by the principal investigator at each of the referring sites according to the best available clinical evidence and guidelines at that time and site. This is a limitation of the present study, as no clear definition or test was utilized. Diagnosis reflected actual clinical care at the different sites and under-diagnosis is a likely issue, as routine use of specific tests (e.g. glucose tolerance test) was not mandatory within the ESPAC study protocols. Thus, it is possible that some of the patients were actually diabetic, but had not been formally assessed prior to therapy.

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

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Figure legends:

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Figure 1: Fitted effect of diabetic status on overall survival in 1105 pancreatic cancer patients following resection and adjuvant chemotherapy. Yes: diabetic patients; No: non-diabetic patients

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

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