Pancreas

Impact of smoking on pancreatic cancer patients receiving current chemotherapy

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Abstract:

Objectives: Smoking may affect pharmacokinetics of chemotherapeutic agents and hemodynamics of the smokers, thereby influencing adverse events and efficacy of chemotherapy in pancreatic cancer (PC) patients. The aim of this study was to clarify how smoking totally affected on PC patients receiving current chemotherapy.
Methods: We evaluated the impact of smoking status on the performance of chemotherapy and survival in 262 patients with PC including 158 resectable and 104 unresectable PC.
Results: There were more male and younger patients in current smokers than in non-smokers. In unresectable PC, current smokers had more metastatic tumors than locally advanced tumors compared to non-smokers. In current smokers receiving chemotherapy, the baseline white blood cell count, neutrophil count, and hemoglobin concentration were significantly higher in current smokers than non-smokers. Furthermore, grade 3-4 neutropenia was observed more often in non-smokers than smokers. On the other hand, the performance and efficacy of the planned adjuvant chemotherapy was similar between smokers and non-smokers. More importantly, there was no significant difference in overall prognosis between smokers and non-smokers

receiving chemotherapy.
Conclusion: Smoking status has no significant impact on the efficacy of current chemotherapy for both resectable and unresectable PC.

Impact of smoking on pancreatic cancer patients receiving current chemotherapy

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Key words: chemotherapy, pancreatic cancer, prognosis, smoking, surgery

Pancreatic cancer (PC) is one of the most difficult malignancies to treat and cure. The disease is so aggressive that most patients are unresectable at the time of initial evaluation. The substantial progress, including new effective chemotherapeutic agents and regimens, has been made in the treatment for PC in the past several years.[1-5] Current clinical practice guidelines recommend the use of chemotherapy for most cases with unresectable tumors.[6,7] Although curative resection has been considered to be the most important factor for determining patient prognosis, recent randomized clinical trials have shown that adjuvant use of gemcitabine, the most widely used chemotherapeutic agent for unresectable PC, also prolonged postoperative survival.[8,9] Therefore, chemotherapy is undoubtedly a mainstay of treatment for both resectable and unresectable PC.

Smoking is a well-established risk factor for PC. Recent meta-analysis suggests that smoking is associated with significantly increased risk of PC, and contributes to diagnosis at significantly younger age.[10-12] Furthermore, the excess risk associated with smoking may persist for at least ten years. In addition, several studies have indicated that smoking also affects the performance and efficacy of chemotherapy by various pharmacokinetic and hematological effects. In fact, it has been reported that several constituents of cigarette smoke interact with drug metabolizing enzymes, thereby

possibly reducing the clinical efficacy of certain chemotherapeutic agents.[13-15] On the other hand, smoking is known to increase the proliferation rate of myeloid progenitor cells. It may prevent neutropenia induced by chemotherapy and bring a favorable impact on the prognosis of smoking patients who receive chemotherapy.[16] Therefore, smoking status may have both beneficial and unfavorable effects on PC patients with chemotherapy. Kanai et al have shown that smoking history is an independent inverse predictor of gemcitabine-induced neutropenia in PC patients who received gemcitabine monotherapy.[17] However, since the data for patient prognosis were not shown, total impact of smoking history on PC patients treated with chemotherapy remains unknown.

The aim of this study was to clarify how smoking totally affected on PC patients who receive current chemotherapy. We extensively evaluated patients with both resectable and unresectable PC, and focused on smoking history in association with clinicopathological characteristics, survival, and performance of chemotherapy.

MATERIALS AND METHODS

Patients

We reviewed the records of 262 patients who started to receive chemotherapy for PC at Nara Medical University Hospital from May 2003 to July 2012. All patients had

no history of chemotherapy before the treatment for PC. Based on pretreatment imaging, resectability status was defined according to the National Comprehensive Cancer Network (NCCN) Guidelines Version 2. 2013.[18] Patients found to be unresectable at laparotomy were included in unresectable PC. One hundred fifty-eight patients with resectable PC received chemotherapy as adjuvant treatment after pancreatic resection. Among them, 78 patients had received neoadjuvant chemotherapy or chemoradiotherapy. On the other hand, 104 patients were unresectable because of locally advanced or metastatic disease, and received chemotherapy as initial treatment for PC (Fig. 1). Patients with postoperative recurrence were excluded from this study. Patients were followed up until December 2013. Patients provided written informed consent before treatment according to the rules and regulations of our institutions.

Treatment

For resectable PC, 6 cycles of gemcitabine were usually employed for adjuvant chemotherapy. Each cycle consists of gemcitabine at 1000 mg/m^2 as an intravenous infusion over 30 min weekly for three consecutive weeks followed by a 1-week rest period.[8] Patients with unresectable PC received gemcitabine, S-1, or combination of both drugs as shown previously (Fig. 1).[5] Stage classification and the evaluation of

resected specimen were performed according to the 7th AJCC/UICC TNM classification.[19,20] Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 4.0.

Smoking history

We obtained information of smoking history by patient interviews. Interviews were conducted in the first consultation at our hospital. Patients were classified into current smoker and non-smoker. Current smoker was defined as one who had a habit of smoking at the time of interview. Non-smokers comprised both never and ex-smokers. Ex-smoker was defined as one who had stopped smoking for more than 20 years.

Statistical analysis

Data were compared between groups based on smoking status using the Student's t test, the chi-square test or Fisher's exact test as appropriate. The overall survival rates were estimated using the Kaplan-Meier method, and the difference was analyzed using the log-rank test. All statistical analyses were performed using STATVIEW version 5.0 (SAS Institute, Cary, NC). A $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

The clinicopathological characteristics of patients who received chemotherapy for PC are summarized in Table 1 and 2. In both resectable and unresectable PC, the proportion of males was significantly higher in current smokers compared to non-smokers. In resectable PC, the median age at diagnosis was significantly younger in smokers than that of non-smokers. Furthermore, there was a similar tendency in unresectable PC. In patients with resectable PC, there were no significant differences in diabetes, drinking behavior, and history of pancreatitis, distribution of operation type, tumor pathological factors, the neoadjuvant treatment, and residual tumor status between smokers and non-smokers (Table 1). In patients with unresectable PC, drinking behavior was seen more in current smoker than non-smoker. Furthermore, tumors were more metastatic than locally advanced in current smokers compared to non-smokers (Table 2). However, there was no difference in the metastatic sites between smokers and non-smokers. Furthermore, there were no significant differences in first-line chemotherapy regimen between current smokers and non-smokers.

Hematological findings

To evaluate the direct physiological effect of smoking status on patients receiving chemotherapy, we compared hematological findings before initiating chemotherapy and incidence of grade 3-4 hematologic toxicities during chemotherapy (Table 3). The baseline white blood cell count, neutrophil count, and hemoglobin concentration were significantly higher in current smokers than non-smokers. Furthermore, grade 3-4 neutropenia was observed more often in non-smokers than smokers.

Performance of adjuvant chemotherapy

In order to evaluate whether smoking status affects the performance of chemotherapy in PC patients, we then focused on patients receiving the planned adjuvant chemotherapy. Seventy-two patients, including 34 smokers, have completed the planned adjuvant chemotherapy of 6 cycles of gemcitabine therapy (Fig. 1). In these patients, the period to complete the planned adjuvant chemotherapy, total amount of gemcitabine as well as disease-free survival after surgery were compared between smokers and non-smokers (Table 4). As a result, smoking status did not significantly associate with the performance and efficacy of adjuvant chemotherapy in postoperative patients with PC.

Overall survival

Finally, to assess if smoking status influences the prognosis of PC patients receiving chemotherapy, Kaplan-Meier analysis was performed. In patients with resectable PC, median survival time (MST) was 35.1 months in current smokers and 32.6 months in non-smokers (P = 0.889, Fig. 2A). Furthermore, in unresectable PC, MST of current smokers was not significantly different from that of non-smokers (11.4 months vs 13.2 months, P = 0.565, Fig. 2B). Therefore, smoking status did not significantly correlate with overall survival in both resectable and unresectable PC.

Period of smoking cessation and pack-years

Among 133 non-smoker patients, 25 patients were ex-smokers. Twenty-three out of them (92%) were male and median age was 68 years old (54-82). Median period of smoking cessation was 10 years (range 1.5 months to 48 years), and median pack-years of smoking was 30 (range 1.5 to 80). Neither period of smoking cessation nor pack-years correlated overall survival of patients with both resectable and unresectable PC in this study (data not shown).

DISCUSSION

Smoking is a well-known risk factor of PC. Tobacco smoke contains many mutagenic and carcinogenic chemicals, and several mechanisms of smoking-associated carcinogenesis have been demonstrated. For instance, tobacco-specific carcinogens such as nicotine and 4-(methylnitrosamineo)-1-(3-pyridyl)-1-butanone (NNK) were reported to induce cell proliferation and migration in pancreatic ductal cells.[21,22] Furthermore, chronic exposure to NNK affects on neurotransmitter signaling in pancreatic adenocarcinoma cells, and disturbs the balance between cancer-stimulating and -inhibiting neurotransmitters, thereby contributing to development of cancer.[22,23] These data suggested that smoking-associated PC might have enhanced malignant potential including aggressive local invasion or early distant metastasis. In this study, there were more male in current smokers than non-smokers. Furthermore, the age was lower in current smokers than in non-smokers. Although the difference in gender may be based on the whole smoking population, the difference in age at diagnosis may reflect high malignancy of smoking-related PC. Furthermore, metastatic rather than locally advanced tumors were observed more often in current smokers than non-smokers in unresectable PC. Our clinical data may corroborate the above basic findings on smoking-associated PC. However, in contrast, there were no significant differences in various clinicopathological factors between current smokers and non-smokers in

resectable PC. This discrepancy may be explained by the aggressive behavior of PC. PC is so aggressive that approximately only 20-30% of whole PC is generally resectable. Therefore, resectable PC is at relatively early stage in the entire population. If smoking enhances the malignant potential of PC through various mechanisms as mentioned above, tumors may easily acquire the ability to metastasize, thereby resulting in unresectability.

Several studies have recently shown that smoking might affect the efficacy and performance of chemotherapy.[13-15] For example, it was reported that current smokers had less exposure of erlotinib during treatment compared to non-smokers, indicating that the pharmacokinetics of erlotinib is dependent on smoking status of patients.[15] In addition, the other study has shown that smoking patients had an almost 40% lower exposure of irinotecan and less hematologic toxicity compared to non-smoking patients, suggesting a potential risk of treatment failure.[13] These reagents have recently been approved for clinical use against PC.[2,3] Therefore, smoking may significantly influence the chemotherapeutic treatment and outcome in PC patients. Although the underlying mechanism is not completely understood, the effects of smoking on the pharmacokinetics of each chemotherapeutic agent are probably due to modulation of enzymes involved in the metabolism. On the other hand, it has been recognized that

smoking stimulates the bone marrow and induces leukocytosis in smokers. In fact, our data showed that baseline white blood cell and neutrophil counts were higher in current smokers than those of non-smokers, suggesting that smoking may influence the immunological state in patients receiving chemotherapy. At present, it is unclear how smoking practically and totally affects the performance of chemotherapy. Some studies reported that patients without smoking history might have a higher risk of developing gemcitabine-induced neutropenia.[17,24] Our data further corroborate the previous findings. On the other hand, when we investigated the performance of chemotherapy as adjuvant treatment in postoperative patients, there were no significant differences in period for completing the planned adjuvant gemcitabine treatment, total amount of gemcitabine and potential therapeutic benefit between smokers and non-smokers with resectable pancreatic cancer. Therefore, further studies are needed to clarify the influence of smoking status on the performance of chemotherapy in PC patients.

Finally, and most importantly, we evaluated the impact of smoking status on the prognosis of PC patients receiving chemotherapy. In fact, it is controversial whether smoking history is associated with patient prognosis of PC.[25-30] In particular, there are only a few studies to investigate the association of smoking status with chemotherapy in PC.[17,24] In addition, the overall survival in relation to smoking with chemotherapy was

not addressed in previous studies. Our study clarified that smoking status did not have impact on overall prognosis in both resectable and unresectable PC. Taken together, smoking history might contribute to high-potential malignancy of PC, while it has little impact on the overall efficacy of current chemotherapy for PC.

Whether smoking cessation can improve the prognosis of PC patients receiving chemotherapy is an important clinical question. It has been widely accepted that smoking cessation had certain effect on risk and survival of human cancer. In fact, several epidemiologic and public health analysis demonstrated that smoking cessation would substantially reduce the future incidence of PC in many countries that smoking population has decreased.[31-33] However, while smoking cessation may prevent the development of PC, it is still unknown whether smoking cessation inhibits the progression and metastasis of PC and improves the prognosis in patients receiving chemotherapy. In this study, neither period of smoking cessation nor pack-years correlated overall survival of PC patients. Furthermore, there was no significant difference in disease-free survival after pancreatic resection between smokers and non-smokers. These data suggested that smoking cessation might have no impact on PC patients when receiving chemotherapy. However, there are some caveats in drawing this conclusion. First, it is difficult how to define ex-smoker for analysis. This is because it

has been reported that the excess risk persists for a minimum of 10 years after smoking cessation.[10,12] Furthermore, smoking-induced leukocytosis also persists as long as 5-10 years after cessation.[34,35] In fact, the definition of ex-smokers differs in each previous study. Second, it is also difficult to evaluate the effect of smoking intensity on patient survival, since smoking intensity may depend on the kind of cigarettes and the living environments. In fact, this study failed to demonstrate the effect of pack-years on patient survival, although there are some reports showing the positive correlation between smoking intensity and poor prognosis of various tumors including PC.[26-28] Taken together, it may be difficult to assess the effect of smoking cessation on patients with chemotherapy for PC that is one of most aggressive human cancers.

In conclusion, our study may provide new insights into the impact of smoking status on PC patients receiving chemotherapy. Smoking status has little impact on the overall efficacy of current chemotherapy for both resectable and unresectable PC.

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FIGURE LEGEND

FIGURE 1. Study flow chart showing all pancreatic cancer patient cohorts.

FIGURE 2. Patient overall survival according to smoking status in resectable pancreatic cancer (A) and in unresectable pancreatic cancer (B).

Figure 1
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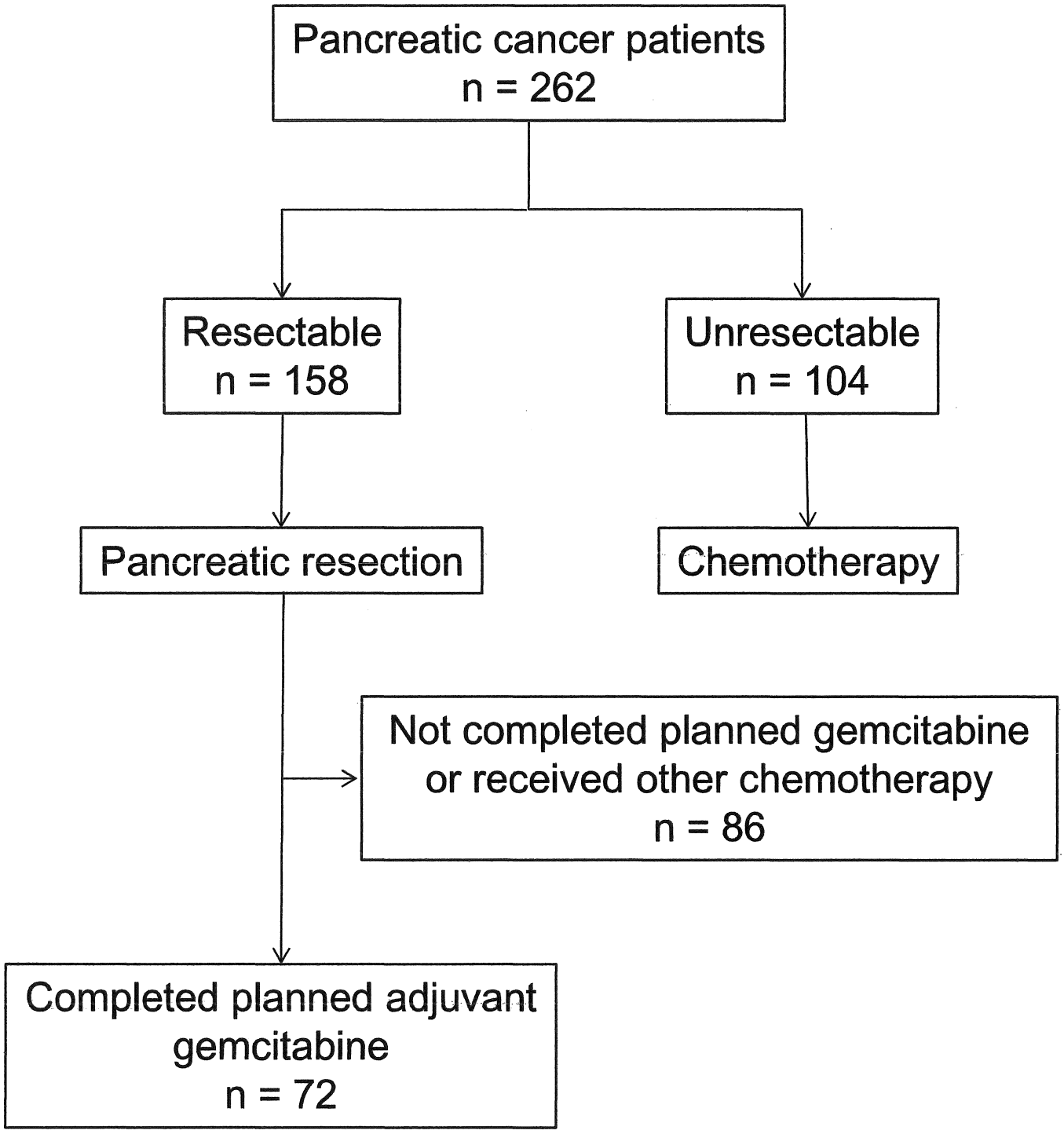

Figure 2
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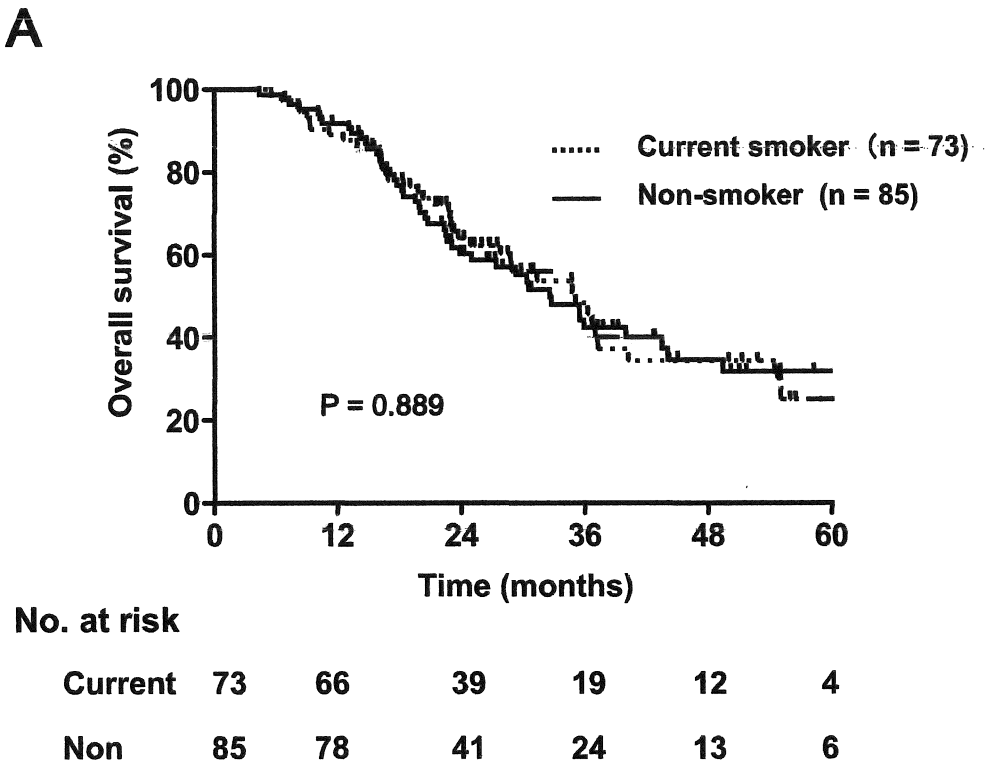
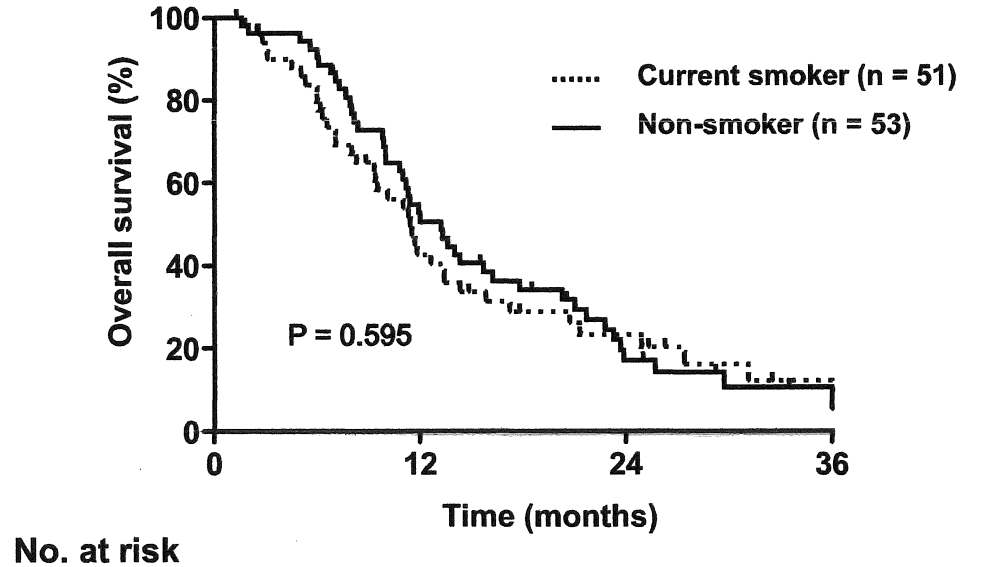


No. at risk

Current	73	66	39	19	12	4
Non	85	78	41	24	13	6



No. at risk

Current	51	20	9	3
Non	53	26	8	2

Table 1

TABLE 1. Clinicopathological Characteristics of Patients with Resectable Pancreatic Cancer

Characteristic	Current smoker (n=73)	Non-smoker (n=85)	*P*
Gender			<0.001
Male, n (%)	60 (82)	27 (32)	
Female, n (%)	13 (18)	58 (68)	
Age (years)			0.010
Median	66	68	
Range	40-80	32-82	
Diabetes			1.000
Present, n (%)	24 (33)	27 (32)	
None, n (%)	49 (67)	58 (68)	
Drinking behavior			0.508
Present, n (%)	45 (62)	57 (67)	
None, n (%)	28 (38)	28 (33)	
History of pancreatitis			0.082
Present, n (%)	7 (10)	2 (3)	
None, n (%)	66 (90)	83 (97)	
Operative procedures			0.614
Pancreatoduodenectomy, n (%)	43 (59)	50 (59)	
Distal pancreatectomy, n (%)	28 (38)	30 (35)	
Total pancreatectomy, n (%)	2 (3)	5 (6)	
UICC T stage			0.787
T1-2, n (%)	6 (8)	9 (8)	
T3-4, n (%)	67 (92)	76 (92)	
UICC N stage			0.628
N0, n (%)	44 (60)	47 (55)	
N1, n (%)	29 (40)	38 (45)	
Histological grade			0.619
G1, n (%)	36 (49)	31 (36)	
G2, n (%)	34 (47)	46 (54)	
G3/G4, n (%)	3 (4)	8 (10)	
Neoadjuvant treatment			0.079
Performed, n (%)	42 (68)	36 (42)	
None, n (%)	31 (32)	49 (58)	
Residual tumor states			0.111
R0, n (%)	69 (95)	73 (86)	
R1, n (%)	4 (5)	12 (14)	

Table 2

TABLE 2. Clinicopathological Characteristics of Patients with Unresectable Pancreatic Cancer

Characteristic	Current smoker (n=51)	Non-smoker (n=53)	*P*
Gender			<0.001
Male, n (%)	44 (86)	20 (38)	
Female, n (%)	7 (14)	33 (62)	
Age (years)			0.159
Median	63	68	
Range	44-79	40-80	
Diabetes			1.000
Present, n (%)	11 (22)	12 (23)	
None, n (%)	40 (78)	41 (77)	
Drinking behavior			0.019
Present, n (%)	34 (67)	23 (43)	
None, n (%)	17 (33)	30 (57)	
History of pacreatitis			1.000
Present, n (%)	1 (2)	2 (4)	
None, n (%)	50 (98)	51 (96)	
Unresectability			0.033
Locally advanced, n (%)	10 (20)	21 (40)	
Metastatic, n (%)	41 (80)	32 (60)	
Liver metastasis			0.051
Present, n (%)	34 (66)	25 (47)	
None, n (%)	17 (34)	28 (53)	
Peritoneal dissemination			0.776
Present, n (%)	6 (12)	8 (15)	
None, n (%)	45 (88)	45 (85)	
Lung metastasis			0.112
Present, n (%)	1 (2)	6 (11)	
None, n (%)	50 (98)	47 (89)	
First-line chemotherapy			0.142
Gemcitabine based, n (%)	34 (67)	26 (49)	
S-1 based, n (%)	3 (6)	3 (5)	
Gemcitabine + S-1, n (%)	12 (24)	16 (31)	
Gemcitabine + radiation, n (%)	2 (3)	8 (15)	

Table 3

TABLE 3. Baseline Hematological Findings and Grade 3-4 Hematologic Toxicities during Chemotherapy

Factor	Current smoker (n=124)	Non-smoker (n=138)	*P*
Hematological findings			
WBC count ($\times 10^9$/l)	6400	5400	<0.001
Neutrophil count ($\times 10^9$/l)	4100	3400	0.002
Hemoglobin concentration (g/dl)	12.7	11.9	0.004
Platelet count ($\times 10^8$/l)	23.1	22.1	0.325
Albumin concentration (g/dl)	4.1	4.0	0.935
AST concentration (IU/l)	25	25	0.823
ALT concentration (IU/l)	23	25	0.886
Total bilirubin concentration (mg/dl)	0.7	0.7	0.465
Creatinine concentration (mg/dl)	0.70	0.60	0.167
Incidence of grade 3-4 hematologic toxicities			
Neutrocytopenia, n (%)	54 (44)	84 (61)	0.006
Anemia, n (%)	9 (7)	15 (11)	0.393
Thrombocytopenia, n (%)	18 (15)	20 (15)	0.998

WBC, white blood cell; AST, asparate aminotransferase; ALT, alanine aminotransferase.

Table 4

TABLE 4 . Comparison of Planned Adjuvant Gemcitabine Treatment according to Smoking Status

Variable	Current smoker (n=34)	Non-smoker (n=38)	*P*
Period for completion of planned treatment (weeks)	28.8±0.97	29.3±1.58	0.815
Total amount of gemcitabine (g/m^2)	17.62 ± 0.21	17.92 ± 0.30	0.431
Disease free survival (median, months)	22.8	27.1	0.775