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TOPIC HIGHLIGHT

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Prognostic factors related with survival in patients with pancreatic adenocarcinoma

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Abstract

The prognosis in patients with pancreatic cancer is poor and this cancer is the fourth leading cause of cancer-related death worldwide. Although surgical resection is the only curative treatment of choice for pancreatic cancer, the majority of patients are diagnosed at an advanced stage, thus only 10%-15% of them are suitable for curative resection and the overall survival is less than 5%. Chemotherapy for metastatic disease is to palliate symptoms of patients and to improve survival. Therefore, prognostic factors are important and a correct definition of poor prognostic factors may help to guide more aggressive adjuvant or aggressive treatment protocols in patients with pancreatic cancer. This article reviews the prognostic factors affecting survival of patients with pancreatic cancer in the light of recent advances in the literature.

Key words: Pancreatic cancer; Prognostic factors; Survival; Carbohydrate antigen 19-9; Treatment

Core tip: The overall prognosis associated with pancreatic cancer has not improved over the last 20 years, even if new diagnostic and therapeutic strategies have emerged. Thus, investigations on predictive factors in pancreatic cancer are needed because these factors should have predictive value in relation to longer survival after surgery than after palliative treatment. Prognostic factors are important and a correct definition of poor prognostic factors may help to guide more aggressive adjuvant or aggressive treatment protocols in patients with pancreatic cancer.

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INTRODUCTION

Pancreatic adenocarcinoma still remains a major public health issue and is the fourth leading cause of cancer-related death worldwide[1]. Although surgical resection is the only curative treatment of choice for pancreatic cancer, unfortunately, the majority of patients are diagnosed at an advanced stage, and thus only 10%-15% of them are suitable for curative resection and the overall survival is less than 5%[2,3]. Chemotherapy is used in the adjuvant setting and in the treatment of locally advanced inoperable and metastatic disease.

The primary goals of chemotherapy for metastatic disease are palliation and improved survival[4,5]. Therefore, identifying poor prognostic factors that may predict the tumor recurrence and prognosis of patients is important for selecting appropriate treatment protocols. So it is important to determine new biological or pathological indicators related to survival in addition to well-

known prognostic factors such as clinical and pathological stage, performance status, and surgical margin[6]. In this article, the prognostic factors affecting survival of patients with pancreatic cancer were reviewed.

SURGICAL AND PATHOLOGICAL FACTORS

The primary surgical or pathological factors that influence prognosis are whether the tumor is localized at the pancreas and whether the tumor has spread to lymph nodes or distant organs[1] because the highest cure rate occurs if the tumor is truly localized to the pancreas. In the present TNM staging system, tumor size, peripancreatic extension, and vascular involvement are used. Traditionally, TNM staging, especially in the presence of metastasis (advanced stage), has been found to be an important prognostic factor in patients with pancreatic cancer for survival[7-9].

Surgical margin

Surgical resection is the only potentially curative option for treatment of pancreatic cancer and the nature of surgery for resectable tumors depends on the tumor localization and size. The incidence of R1 resection has been indicated as being 20% in the literature, but the improvement of pathological work-up procedures has increased the rate of R1 resection up to 80%[10,11]. Menon *et al*[12] reported that of 27 patients with pancreatic cancer, 22 patients underwent R1 resection and the median survival rate for patients with R1 resection was significantly worse than that of patients with R0 resection (14 mo *vs* not reached). In a study performed by Raut *et al*[13], they reported that the rate of R1 resection was 16.7% and patients who underwent an R1 resection had a median overall survival (OS) of 21.5 mo compared with 27.8 mo in patients who underwent an R0 resection. In addition, multivariate analysis showed that high mean operative blood loss and large tumor size were independent predictors of an R1 resection, but margin status did not independently influence survival.

Another study including 265 pancreatic carcinoma patients who had undergone surgical resection reported that R1 resection in 49 patients (51%) and R2 resection in four patients (4%) were performed[14]. The R1-positive margin was localized at the retroperitoneal resection margin in 76% and at the trans-section margin in 14% of tumors. Median survival time was better in R0-resected patients compared with R1-resected patients (22 mo *vs* 15 mo). A positive resection margin after pancreatic resection is considered to be a poor prognostic factor, and some have proposed that an R1 margin may be a biologic predictor of more aggressive disease. On the other hand, whether these patients with pancreatic carcinoma who underwent margin-positive resection have to be managed with aggressive treatment modalities has not been described.

Lymph nodes status and lymph node ratio

Lymph node ratio (LNR) may be more useful than nodal (N) status in prognostic subclassification of pancreatic adenocarcinomas after pancreatoduodenectomy. Recent studies have suggested that LNR may also be an important prognostic factor in pancreatic cancer[15-17]. In the TNM staging system, the number of resected lymph nodes may be very important, but node-positive patients are not a homogenous group, because stage migration may occur in resected pancreatic cancer patients. To resolve these limitations, recently LNR was proposed as a new prognostic factor by several authors to prevent the 'stage migration' phenomenon[15-17]. Riediger *et al*[17], in 204 resected patients, reported that LNR was the strongest predictor of survival and they concluded that the routine estimation of the LNR may be helpful not only for the individual prediction of prognosis but also for the indication of adjuvant therapy. The analysis of Surveillance, Epidemiology, and End Results and MGH (Massachusetts General Hospital) in 10254 and 827 resected patients, respectively, showed that higher LNR (> 0.2) was associated with worse survival by univariate analysis, and in addition the hazard ratio (HR) raised proportionally when more lymph nodes were examined in multivariate analysis. This study concluded that while the contribution of the number of positive nodes to survival was relatively small, LNR was strongly associated with survival, and thus, LNR provided a stronger and more accurate predictor of survival than the number of positive nodes[18].

Perineural and blood vessel invasion

Both perineural (PNI) and blood vessel invasion (BVI) have been previously investigated in patients with pancreatic cancer and found to be important prognostic indicators for survival[14,19,20]. Lee *et al*[19] showed that PNI was an important adverse prognostic factor for patients with surgical resection, as was pN stage. In a study performed by Chatterjee *et al*[21], PNI and BVI were found to be associated with the OS and lymph node status in patients who were treated with neoadjuvant treatment. The median OS for patients with PNI was worse than that of patients without PNI (22 mo *vs* 36 mo). Moreover, the median OS was better in patients without BVI compared with patients with BVI (34 mo *vs* 22 mo). They detected that retroperitoneal resection margin was correlated with the presence of both BVI and PNI. The authors concluded that PNI and BVI were significantly poor prognostic indicators.

Tumor localization

Some studies have investigated the prognostic significance of tumor localization in pancreatic cancer patients, but there is currently no consensus[7-9,19,22]. In a study performed by Park *et al*[8], univariate analysis indicated that tumor location was an important prognostic factor for

Table 1 Surgical and pathological factors in pancreatic cancer

Ref.	No. of patients	Results
Surgical margin/resection (R1 *vs* R0)		
Menon *et al*[12]	27	mOS, 14 mo *vs* NR
Raut *et al*[13]	360	mOS, 21.5 mo *vs* 27.8 mo
Lymph nodes status and lymph node ratio		
Riediger *et al*[17]	204	LNR was an independent prognostic factor
Valsangkar *et al*[18]	14907	LNR was strongly correlated with survival
Perineural and blood vessel invasion		
Chatterjee *et al*[21]	86	mOS, 34 mo for BVI (-) *vs* 22 mo for BVI (+); mOS, 32 mo for PNI (-) *vs* 22 mo for PNI (+)
Tumor localization		
Park *et al*[8]	340	It was an important prognostic factor by univariate analysis
Zhang *et al*[7]	302	It was an independent prognostic indicator
Operative factors		
Nagai *et al*[23]	271	OBL greater than 2000 mL was an independent prognostic factor for OS
Keck *et al*[24]	270	PBT was an independent prognostic indicator for survival

mOS: Median overall survival; NR: Not reach; LNR: Lymph node ratio; BVI: Blood vessel invasion; PNI: Perineural invasion; OBL: Operative blood loss; PBT; Perioperative blood transfusion.

OS, but the significance of tumor site as an independent prognostic indicator could not be proved in the multivariate analysis. Lee *et al*[22] showed that high CEA level was significantly correlated with tumor location. In the patients with elevated CEA level, tumors were located mostly at the pancreas body and tail. The authors could not show that tumor location was a prognostic factor by multivariate analysis, although in the univariate analysis it was detected as being a prognostic factor. However, in another study carried out by Zhang *et al*[7], localization of the primary tumor was found to be an independent prognostic factor. In other words, the mortality risk was increased for tumors located at the body and tail of the pancreas compared to the tumors located at the head and neck of the pancreas.

Operative factors

An influence of operative blood loss (OBL) on survival in patients with pancreatic cancer after curative resection has been investigated. Nagai *et al*[23] retrospectively analyzed 271 patients and found that the OS was significantly affected by the amount of OBL. The median survival times were 26.0, 15.3, and 8.7 mo for OBL less than 1000, 1000 to 2000, and greater than 2000 mL, respectively (< 1000 mL *vs* 1000-2000 mL, $P = 0.019$; 1000-2000 mL *vs* > 2000 mL, $P < 0.0001$). Moreover, OBL greater than 2000 mL was also detected to be an independent prognostic factor in multivariate analysis (HR = 2.55) and OBL of 2010 mL was found to be an appropriate cut-off level to predict early mortality within 6 mo after resection. Male sex, year of resection, and plexus invasion were independently associated with OBL greater than 2000 mL. In light of these results, the authors concluded that excessive OBL was found to be a prognostic determinant of survival and it can be used to stratify the risk for pancreatic cancer mortality after surgery for pancreatic cancer. On the other hand, prognostic significance of perioperative blood transfusion (PBT) has also been reported. In a study performed by Keck *et al*[24], PBTs were given in 46% of 270 pancreatic cancer patients. Univariate analysis showed that PBT was related with poorer survival, as were positive margins, more than one involved node, and poorer grading. In addition, they found that PBT was an independent prognostic indicator for survival by multivariate analysis after resection. The authors thought that impact of PBT was independent of the perioperative complications or resection type. Table 1 shows selected trials of surgical and pathological prognostic factors in pancreatic cancer.

CLINICAL FACTORS

Performance status

Some studies have evaluated the impact of performance status (PS) on survival for patients with pancreatic adenocarcinoma, but the results are conflicting. In a study carried out by Sezgin *et al*[25], the authors reported that only PS was an independent prognostic factor for OS in patients with advanced pancreatic cancer. Similarly, Tas *et al*[26] found that initial poor PS (PS 2-4) was significantly associated with worse survival for patients with all stages of pancreatic cancer. In addition, poor PS remained as an independent prognostic indicator for survival by multivariate analysis and in patients with poor PS, severe weight loss (> 10%), large tumor diameter (> 3 cm), and especially metastatic disease was related with significantly shorter OS. On the other hand, in another study, although an influence of PS on survival was detected in the univariate analysis, its prognostic significance was lost in multivariate analysis[8]. Lee *et al*[22] showed that in the elevated CA19-9 level group (≥ 37 U/mL), PS was significantly higher compared with the normal CA19-9 group. Furthermore, PS (0 *vs* 1-2) was found to be an important prognostic factor in the univariate analysis for OS.

Diabetes mellitus, obesity and jaundice

Diabetes mellitus (DM) is commonly diagnosed in pancreatic cancer patients, but the significance of new-onset DM as a cause of underlying pancreatic cancer is unknown. Some studies have investigated the prognostic significance of DM in pancreatic cancer[8,25,27], but an impact of DM on survival could not be proved.

Cachexia is a known characteristic of pancreatic cancer with detects as 80% of patients cachexic at diagnosis. Therefore, measurement of body mass index (BMI) at

the time of diagnosis does not provide accurate representation of a patient's long-term exposure to obesity[28]. However, some studies have shown that high BMI is associated with increased risk of pancreatic cancer incidence and mortality[29,30]. On the other hand, studies of obesity and survival in patients with pancreatic cancer are notably controversial. In a population-based study including 510 patients with pancreatic cancer, Gong *et al*[31] indicated that elevated HR of 1.3 was detected for obese (BMI $\geqslant$ 30) compared with normal range BMI (< 25) patients. But, the relation between OS and BMI could not be found. Similarly, recent study evaluated the association of BMI with the risk of death from pancreatic cancer in a pooled analysis of data from Asia Cohort Consortium[32]. It did not support an relation between BMI and risk of death from pancreatic cancer. As a different these studies, in a study carried out by Yuan *et al*[33] the association of prediagnostic BMI with pancreatic cancer survival was analyzed. Higher prediagnostic BMI was associated with more advanced stage at diagnosis, with 72.5% of obese patients presenting with metastatic disease versus 59.4% of healthy-weight patients. Furthermore, higher baseline BMI was associated with reduced survival. HR for death was 1.53, comparing BMI $\geqslant$ 35 kg/m^2 with BMI < 25 kg/m^2 (P = 0.001).

In a study performed by Smith *et al*[34], the presence of preoperative jaundice was found to be associated with poor survival in patients with pancreatic cancer. Another study showed that preoperative jaundice was the only independent prognostic factor for pancreatic cancer patients[19]. On the other hand, Perini *et al*[35] demonstrated that both preoperative DM and jaundice had no adverse effect on survival for curative resection in pancreatic cancer patients. Recently, Strasberg *et al*[36] analyzed 400 patients with resected pancreatic cancer, and preoperative jaundice was found to be a significant indicator of poor outcome in the multivariate analysis. Moreover, the relationship was detected between jaundice and nodal status, and jaundiced patients who underwent preoperative stenting had a survival advantage. The underlying mechanism related with the influence of jaundice on survival is unknown and additional studies are required to determine the exact mechanism for this effect.

Treatment and gemcitabine

Chemotherapy is only modestly effective in advanced disease but has a significant impact in the adjuvant setting, with 5-fluorouracil and gemcitabine both having efficacy in a subgroup of patients and increasing 5-year survival from 10%-15% with surgery alone to 20%-25%[37-40]. Park *et al*[8] analyzed 340 patients with pancreatic cancer and of 141 stage Ⅲ patients, 57 received supportive care (BSC) only, 25 received chemotherapy (CT), and 59 received concurrent chemoradiotherapy (CCRT); of the 199 stage Ⅳ patients, 119 were treated with BSC only and 80 received CT. Univariate analysis showed that CT and CCRT were significant prognostic indicators for OS in stage Ⅲ patients compared with patients that received BSC only (11.3 mo *vs* 10.4 mo *vs* 6.4 mo, respectively; P < 0.001). Similarly, in stage Ⅳ patients, median OS for patients who were treated with CT was significantly better than that of patients who received BSC only (6.4 mo *vs* 3.1 mo, P < 0.001). In addition, initial treatment effect remained an independent prognostic factor compared to BSC only in the multivariate analysis[8].

In a study performed by Lee *et al*[19], gemcitabine chemotherapy was found to be the only independent prognostic indicator for OS in advanced or unresectable pancreatic cancer patients who had undergone palliative surgical by pass. Moreover, Zhang *et al*[7] evaluated 302 all-stage pancreatic cancer and found that the median OS of patients who did not receive any treatment or those treated with BSC only was 1.3 mo, while the median OS for patients who had undergone surgery, CT, biliary drainage therapy, arterial interventional CT, and comprehensive CT was 11.0, 7.3, 3.5, 9.0, and 11.0 mo, respectively (P < 0.05). In the multivariate analysis, the presence of treatment *vs* no therapy or BSC only was an independent prognostic factor (HR = 13.93, P = 0.000). However, platinum combination CT was significantly associated with improved OS compared to non-platinum CT regimen (HR = 0.56, P = 0.011). Selected trials related with clinical prognostic factors are summarized in Table 2.

LABORATORY AND MOLECULAR FACTORS

Prognostic role of carbohydrate antigen 19-9 levels

Serum carbohydrate antigen (CA) 19-9, the sialylated Lewis blood group antigen defined by the monoclonal antibody 1116 NS 19-9, is a tumor-associated antigen synthesized by normal pancreatic and ductal cells[41]. CA19-9 is considered to be the standard serum marker of pancreatic cancer due to its high sensitivity of 70%-90% and specificity of around 90%[42]. Serum CA19-9 levels have been found to be a useful tumor marker in differentiating benign from malignant pancreatic lesions, and to monitor tumor response to treatment[42,43]. Previous studies suggested that preoperative CA19-9 levels could predict the resectability of pancreatic cancer[44,45], and other studies reported that pretreatment CA19-9 level was an important prognostic factor in patients with pancreatic cancer who received CT or CCRT[8,9,45,46].

Park *et al*[8] reported that elevated CA19-9 levels (> 670 U/mL) were found to have prognostic significance for OS by univariate analysis, while it was an independent prognostic factor for OS in the multivariate analysis. Furthermore, another study found similar findings. The median OS time for patients with high CA19-9 level was worse than that of patients with normal CA19-9 level (3.8 *vs* 5.0 mo), which was not significant, but multivariate analysis indicated that it was an independent prognostic indicator for OS (HR = 4.54, P = 0.033)[7]. Recently, in a study by Humphris *et al*[47], low postoperative CA19-9 at 3 mo and before adjuvant chemotherapy were indepen-

Table 2 Clinical prognostic factors in pancreatic cancer in selected trials

Ref.	No. of patients	Results
Performance status		
Sezgin *et al*[25]	67	PS was an independent prognostic factor for OS
Tas *et al*[26]	335	Initial poor PS (2-4) was significantly associated with worse survival
DM, obesity and jaundice		
Gong *et al*[31]	510	HR = 1.3 for patients with BMI ⩾ 30 compare to those with BMI < 25. But no correlation was found between BMI and survival
Yuan *et al*[33]	902	Higher baseline BMI was associated with reduced survival
Smith *et al*[34]	155	The presence of jaundice at the time of surgery was a significant adverse predictor of early survival
Strasberg *et al*[36]	400	The preoperative jaundice was found to be a significant indicator of poor outcome
Treatment		
Park *et al*[8]	340	mOS, 11.3 *vs* 10.4 *vs* 6.4 mo for stage Ⅲ patients treated with CT, CCRT and BSC, respectively (P < 0.001) mOS, 6.4 *vs* 3.1 mo for patients with stage Ⅳ treated with CT or BSC, respectively (P < 0.001)
Lee *et al*[19]	82	Gemcitabine chemotherapy was found to be the only independent prognostic indicator for OS in advanced pancreatic cancer

DM: Diabetes mellitus; mOS: Median overall survival; PS:Performance status, BMI: Body mass index; CT: Chemotherapy; CCRT: Concurrent chemoradiotherapy; BSC: Best supportive care.

dent prognostic factors (median OS; 25.6 mo *vs* 14.8 mo, P = 0.0052) in 260 patients with pancreatic cancer who underwent surgical resection. Patients with postoperative CA19-9 levels > 90 U/mL did not benefit from adjuvant chemotherapy compared with those with a CA19-9 level of ⩽ 90 U/mL (median OS 26.0 mo *vs* 16.7 mo, P = 0.0108). Normalization of CA19-9 within 6 mo of resection was also an independent favorable prognostic factor (median OS: 29.9 mo *vs* 14.8 mo, P = 0.0004) and normal perioperative CA19-9 levels were identified as being a good prognostic group, which was associated with a 5-year survival of 42%.

Other tumor markers

Carcinoembryonic antigen (CEA) is the standard tumor marker and is commonly used for predicting treatment response and prognosis of patients with colorectal cancer[48]. In contrast to the CA19-9 level, an impact of CEA on survival of pancreatic cancer patients has not yet been determined, but CEA might be beneficial in predicting pancreatic cancer. Zhang *et al*[7] in their study including 302 patients with pancreatic cancer reported that the patients with high CEA levels had a median survival of 2.0 mo compared to patients with normal levels (5.0 mo). This difference was statistically significant (HR = 1.43, P = 0.030). However, the significance of CEA levels as an independent prognostic factor could not be proved in the multivariate analysis. In a study carried out by Lee *et al*[22], they retrospectively analyzed 187 pancreatic cancer patients, and reported that the median OS time for patients with normal CEA levels was significantly better than that of patients with high CEA levels (16.3 mo *vs* 10.2 mo, P = 0.004). In addition, elevated CEA levels were found to be an independent prognostic factor in the multivariate analysis.

Despite these findings, to detect whether CEA can be applicable as a prognostic marker of pancreatic cancer, it should be evaluated in a large number of patients with all stages of pancreatic cancer. Various tumor markers such as CA125, CA15-3, CA72-4, and CA242 have also been analyzed, but their importance as independent prognostic indicators could not be definitively demonstrated[7,49].

Hematological parameters

Platelet, lymphocyte, and neutrophil counts, mean platelet volume, and the ratios of various hematologic cells have been shown to be valuable prognostic factors in various malignancies, such as renal, gynecological, and colorectal cancers[50-53]. Schwarz *et al*[54] demonstrated that preoperative platelet count predicts survival after resection of pancreatic adenocarcinoma. On the other hand, in a study comprising 205 patients performed by Domínguez *et al*[55], there was no evidence to support preoperative platelet count as either an adverse or favorable prognostic factor in pancreatic ductal adenocarcinoma, which was not compatible with a study of Zhang *et al*[7]. Despite conflicting results regarding platelet counts, white blood cells (WBCs) were found to be an independent prognostic factor for OS in patients with pancreatic cancer in two studies[7,46]. Although low hemoglobin levels were associated with poorer OS time, the significance as an independent prognostic marker could not be proved by the multivariate analysis[7].

The prognostic value of pretreatment platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) in patients with pancreatic cancer has also been evaluated[56,57]. Preoperative PLR has been defined as an independent significant prognostic marker by Smith *et al*[58] in resected pancreatic ductal adenocarcinoma. In the same study, the median overall survival in patients with a PLR of 150 or less was 19.7 mo, 13.7 mo in those with a PLR of 151-300, and 5.8 mo in patients with a value of > 300. Aliustaoglu *et al*[57] showed that there was no statistically significant difference between cases with PLR values ⩽ 160 and > 160. However, they analyzed NLR in the same patients with pancreatic cancer. Patients with a NLR value of < 5 had a significantly higher median

Table 3 Selected trials of laboratory prognostic factors in pancreatic cancer

Ref.	No. of patients	Results
CA 19-9 levels		
Park *et al*[8]	340	Elevated CA19-9 levels (> 670 U/mL) were found to independent prognostic factor for OS
Zhang *et al*[7]	302	mOS, 3.8 mo for patients with high CA 19-9 levels *vs* 5.0 mo for those with normal CA 19-9 levels
Humphris *et al*[47]	260	mOS, 25.6 mo for low postoperative CA 19-9 levels *vs* 14.8 mo for high CA 19-9 levels Normalization of CA19-9 within 6 mo of resection was also an independent favorable prognostic factor
Other tumor markers		
Zhang *et al*[7]	302	mOS, 2.0 mo for patients with high CEA levels *vs* 5.0 mo for those with normal CEA levels
Lee *et al*[22]	187	mOS was 16.3 and 10.2 mo for patients with normal CEA *vs* high CEA levels, repsectively
Hematological factors		
Zhang *et al*[7]	302	WBCs were independent prognostic factor for OS
Smith *et al*[58]	110	mOS in patients with a preoperative PLR of 150 or less was 19.7 mo, 13.7 mo in those with a PLR of 151-300, and 5.8 mo in patients with a value of > 300
Aliustaoglu *et al*[57]	65	Patients with a NLR value of < 5 had a significantly higher median OS time compared to those with a NLR value of ⩾ 5
Stotz *et al*[56]	371	An increased NLR as an independent prognostic factor for inoperable and surgically resected patients
Biochemical parameters		
Zhang *et al*[7]	302	Serum albumin and BUN levels were found to be independent prognostic factors for prediction of OS
Stocken *et al*[46]	653	Albumin, ALP, LDH, BUN, and AST were independent prognostic indicators for survival of advanced pancreatic cancer
Haas *et al*[60]	291	Pretreatment LDH levels were significantly associated with TTP. Baseline LDH,CRP, and bilirubin were significant prognostic factors for OS

mOS: Median overall survival; WBC: White blood cell; PLR: Platelet to lymphocyte ratio; NLR: Neutrophil to lymphocyte ratio; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; TTP: Time to progression; CRP: C-reactive protein; CEA: Carcinoembryonic antigen.

OS time compared to those with a NLR value of ⩾ 5 (P = 0.015). Recently, Stotz *et al*[56] evaluated NLR in 371 patients with primary operable and inoperable pancreatic cancer. They reported that multivariate analysis identified increased NLR as an independent prognostic factor for inoperable PC patients (HR = 2.53, P < 0.001) and surgically resected pancreatic cancer patients (HR = 1.61, P = 0.039). Furthermore, in inoperable pancreatic cancer patients, the modified Glasgow prognostic score was associated with poor cancer-specific survival only in univariate analysis (HR = 1.44). In light of these findings, the authors concluded that risk prediction for cancer-related end points using NLR does add independent prognostic information to other well-established prognostic factors in patients with pancreatic cancer, regardless of the undergoing therapeutic modality. Thus, the NLR should be considered for future individual risk assessment in pancreatic cancer patients.

Biochemical parameters

Some serum chemistry markers such as albumin, lactate dehydrogenase (LDH), bilirubin, creatinine, and blood urea nitrogen (BUN) have previously been tested, but the prognostic role of these markers has not yet been fully defined. Serum albumin and BUN levels were found to be independent prognostic factors for prediction of survival in pancreatic cancer, while total bilirubin, direct bilirubin, glutamic-pyruvic transaminase, glutamic-oxalacetic transaminase, serum creatinine, and LDH were not[7]. However, the patients with high serum LDH levels had poor prognosis compared to those with normal levels (4.3 mo *vs* 7.0 mo) by univariate analysis. Tas *et al*[59] demonstrated that high serum LDH levels were significantly associated with tumor burden and reflected tumor growth and invasion potential in patients with pancreatic cancer. Similarly, Stocken *et al*[46], in their study including 653 pancreatic cancer patients, detected that albumin, alkaline phosphatase (ALP), LDH, BUN, and aspartate aminotransferase (AST) were independent prognostic indicators for survival in patients with advanced pancreatic cancer. A recent study conducted by Haas *et al*[60] showed that in univariate analysis, pretreatment LDH (HR = 2.04) levels were significantly associated with time-to progression (TTP). Regarding OS, baseline LDH (HR = 2.07), C-reactive protein (CRP) (HR = 1.69), and bilirubin (HR = 1.62) were significant prognostic factors. In the multivariate analyses, pre-treatment bilirubin and CRP for OS had an independent prognostic value. They concluded that CRP, LDH, and bilirubin can also provide prognostic information on TTP and OS. Table 3 indicates selected trials of laboratory factors in pancreatic cancer.

Molecular markers

Gemcitabine is transported into the cell mainly by human equilibrative nucleoside transporter 1 (hENT1) (also known as SLC29A1). hENT1 has been investigated as a predictive biomarker of gemcitabine efficacy, mostly in pancreatic cancer, and populations of cells with lower hENT1 expression may be relatively gemcitabine resistant due to reduced intracellular accumulation of the drug[61]. Previous studies suggest that hENT1 protein expression is associated with increased OS and DFS in pancreatic cancer patients who received gemcitabine[62,63]. Recently, in patients who were included in the ESPAC 1-3 trials and were treated with adjuvant gemcitabine or

5-fluorouracil (5-FU), the results of tissue microarrays for hENT1 was presented at the 2013 ASCO annual meeting[64]. The median OS time for patients with high hENT1 expression who received gemcitabine was significantly better than that of patients with low hENT1 expression (26.2 mo *vs* 17.1 mo, $P = 0.002$). However, there was no difference among patients treated with 5-FU with respect to hENT1 expression. The authors concluded that patients with high hENT1 expression might benefit more from gemcitabine treatment.

SPARC (secreted protein and rich in cysteine), a matricellular protein found to be under-expressed in certain cancers, has emerged as a multifunctional protein capable of inhibiting the growth of pancreatic, colorectal, and ovarian cancers[65,66]. The significance of expression of SPARC as a prognostic factor in the stroma of pancreatic tumors has been shown[67]. In a study performed by Sinn *et al*[68], immunohistochemistry in the tissue sample for expression of SPARC in the stroma around the tumor, but also in the tumor cell, of patients from the Charité Onkologie (CONKO)-001 study was carried out and their results were presented at the 2013 ASCO annual meeting. Patients who received gemcitabine as adjuvant treatment had a longer DFS and OS when stromal and cytoplasmic expression of SPARC was not-strong or negative, respectively, compared with strong expression of SPARC. Thus, SPARC expression estimation, both in the tumor or its stroma, seems to be a valuable prognostic factor in patients receiving gemcitabine as adjuvant therapy in patients with pancreatic cancer.

The prognostic significance of circulating tumor cells (CTCs) has been investigated and patients who had CTCs (more than 1 in 7.5 mL) before curative surgery, or after therapy initiation, has a trend towards poorer OS or PFS[69]. Bidard *et al*[70] prospectively analyzed patients with locally advanced unresectable pancreatic cancer before and after 2 mo of chemotherapy for CTCs. More than one tumor cell in 7.5 mL was considered as positive. Before treatment, 5% of patients had positive detection of CTCs and 9% at the end of 2 mo of therapy. This positivity was found to be associated with poor tumor differentiation and the OS was shorter in these positive patients. The determination of CTCs in patients with pancreatic cancer seems to have a negative prognostic role[71]. There is a significant relationship between the amount of peritumoral CD4+ and CD8+ T-cells and survival in patients with pancreatic cancer and it was found to be an independent prognostic factor for OS[71].

Transforming growth factor β (TGF-β) acts as suppressor and promoter of cancer progression. Intracellular Smad proteins (common mediator SMAD4) play a pivotal role in mediating antimitogenic and proapoptotic effects of TGF-β[72]. In 55% of pancreatic tumors SMAD4 alterations are found and *it* is inactivated in the majority of pancreatic adenocarcinoma with concurrent mutational inactivation of the *INK4A/ARF* tumor suppressor locus and activation of the *KRAS* oncogene[73]. Previous reports revealed unclear results related with SMAD4 as a predictor of survival in pancreatic cancer[74-76]. Blackford *et al*[76] reported that SMAD4 gene inactivation was associated with poorer prognosis in resected pancreatic adenocarcinoma. In other words, median survival time in patients without SMAD4 gene inactivation was significantly better than those with inactivation (14.2 mo *vs* 11.5 mo, $P = 0.006$). Recent study showed a significant relationship was found between SMAD4 expression and tumor size ($P = 0.006$), lymphatic invasion ($P = 0.033$), and lymph node metastasis ($P = 0.006$)[77]. Moreover, loss of SMAD4 expression was significantly associated with shorter OS and it was found to be an independent prognostic factor for both OS and DFS by multivariate analysis. Similarly, another study has confirmed these results[78].

Novel prognostic biomarkers

Hypoxia-inducible factor 1 alpha (HIF1α) has been found to be an unfavorable prognostic indicator in many cancers and is known to regulate some genes in the angiogenesis pathway[79]. Some studies have previously been showed that HIF1α had a strong impact on the prognosis of patients with pancreatic adenocarcinoma[80-82]. NEDD9, a focal adhesion scaffolding protein, has been recently proposed to regulate invasion and metastasis in some cancer types[83-85]. In a study performed by Xue *et al*[86], they investigated the expression and prognostic significance of NEDD9 in patients with pancreatic cancer. NEDD9 protein and mRNA levels were elevated in pancreatic carcinoma lesions compared with noncancerous tissues. A high NEDD9 expression level was significantly correlated with clinical staging, lymph node metastasis, and histological differentiation. The median survival time for patients with a higher NEDD9 expression was significantly shorter than that of patients with lower NEDD9 expression. In addition, the multivariate analysis revealed that NEDD9 was an independent factor of poor prognosis.

FOXM1 (Forkhead box M1) is a typical proliferation-related transcription factor and is also intimately involved in tumorigenesis. It induces cell proliferation and cell cycle progression by promoting the entry into S-phase and M-phase[87]. Xia *et al*[88] in their study, evaluated correlation between FoxM1 expression level and survival of patients with pancreatic adenocarcinoma. They showed that a high level of expression of FoxM1 was significantly correlated with clinical staging, lymph node metastasis, and histological differentiation. Furthermore, patients with a higher FoxM1 expression had a significantly shorter survival time compared to patients with lower FoxM1 expression and FoxM1 was found to be an independent factor for survival.

Recent study indicated that B7H4, HSP27 and DJ-1 protein expressions in the tissue specimens of 41 patients with resected pancreatic cancer were independently associated with a negative impact of chemotherapy with gemcitabine on patient's survival[89]. In addition, patients who overexpressed B7H4 had worse prognosis than patients without overexpression. In a study carried

Table 4 Molecular and novel biomarkers as prognostic factors in pancreatic cancer

References	No. of patients	Results
Molecular markers		
Neoptolemos *et al*[64]	48	mOS, 26.2 mo for patients with high hENT1 expression *vs* 17.1 for those with low hENT1 expression who treated with gemcitabine (P = 0.002)
Sinn *et al*[68]	160	Strong stromal SPARC expression was associated with worse DFS and OS (strong *vs* not-strong DFS 9.0 *vs* 12.6 mo, P = 0.005; OS 19.8 *vs* 26.6 mo (P = 0.033).Cytoplasmic SPARC expression was also associated with worse patient outcome (positive *vs* negative DFS 7.4 *vs* 12.1 mo, P = 0.041; OS 14.1 *vs* 25.6 mo, P = 0.011) in patients with pancreatic cancer who received gemcitabine as adjuvant CT
Blackford *et al*[76]	114	mOS,14.2 mo in patients without SMAD4 gene inactivation *vs* 11.5 mo for those with inactivation (P = 0.006)
Oshima *et al*[77]	106	Loss of SMAD4 expression was significantly associated with shorter OS and it was found to be an independent prognostic factor for both OS and DFS
Novel biomarkers		
Xue *et al*[86]	106	mOS for patients with a higher NEDD9 expression was significantly shorter than that of patients with lower NEDD9 expression. NEDD9 was an independent factor of poor prognosis
Xia *et al*[88]	80	A higher FoxM1 expression had a significantly shorter survival time compared to patients with lower FoxM1 expression and FoxM1 was found to be an independent factor for survival

mOS: Median overall survival; DFS: Disease-free survival; hENT1: Human equilibrative nucleoside transporter 1; SPARC: Secreted protein and rich in cysteine; CT: Chemotherapy; FOXM1: Forkhead box M1.

out by Perini *et al*[90], prognostic significance of epidermal growth factor receptor (EGFR) overexpression in pancreas cancer was investigated. Univariate analysis showed that positive EGFR expression in tumor tissue had worse survival, as were male gender, portal vein resection, perineural, lymphovascular and peri-pancreatic invasion, positive margins, however, prognostic significance of positive EGFR expression as an independent prognostic factor could not be confirmed in the multivariate analysis. Selected studies associated with molecular and novel biomarkers are listed in Table 4.

CONCLUSION

The overall prognosis associated with pancreatic cancer has not improved over the last 20 years, even if new diagnostic and therapeutic strategies have emerged. So, investigations on predictive factors in pancreatic cancer are needed because these factors should have predictive value in relation to longer survival after surgery than after palliative treatment. In addition to some well-known prognostic factors such as tumor stage, surgical margin, perineural invasion, PS, treatment effect, and CA19-9, recently new prognostic indicators that have an impact on survival of patients with pancreatic cancer have appeared. The prognostic value of operative factors including OBL and PBT, NLR, and molecular markers such as SPARC, hENT1, SMAD4, CTCs, HIF1α, NEDD9 and FOXM1 has recently been shown. Prognostic factors are important and a correct definition of poor prognostic factors may help to guide more aggressive adjuvant or aggressive treatment protocols in patients with pancreatic cancer.

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