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# HBXIP protein overexpression predicts the poor prognosis of pancreatic ductal adenocarcinomas

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ABSTRACT

Background: Hepatitis B virus X-interacting protein (HBXIP) is associated with a variety of tumors. The purpose of this study was to investigate the clinicopathological significance of HBXIP expression in pancreatic ductal adenocarcinoma (PDAC) and to explore its potential as a biomarker for PDAC.

Methods: Immunohistochemical (IHC) staining was performed on 126 PDAC tissues, 36 paraneoplastic tissues and 22 normal pancreatic tissues. The relationship between high levels of HBXIP expression and pathological features of PDAC patients was evaluated by chi-squared values.

Results:The positive rate of HBXIP protein in PDAC tissues was 85.7% (108/126), which was significantly higher than that of adjacent pancreatic tissue (41.7%, 15/36) and normal pancreas (18.2%, 4/22). In addition, strong positive expression of HBXIP was associated with tumor size, positive lymph node metastasis, clinical stage and 80-month overall survival. Patient's age, gender, degree of differentiation, Ki-67 expression index, and calcification were, however, not associated with high levels of HBXIP expression.

Conclusions:We present association between HBXIP expression and the pathological features of patients with PDAC.

## 1. Introduction

The treatments for some cancers achieve satisfactory results. However, there are still many obstacles to the diagnosis and treatment of pancreatic cancer. From 1930 to 2014, the mortality rate of pancreatic cancer showed an upward trend, and the 5-year survival rate was only 8% [1]. In addition, according to the National Cancer Center of China, from 2000 to 2011 the mortality rate of male patients with pancreatic cancer increased by 1.2%, the mortality rate was almost equal to the incidence rate, and the 5-year survival rate was 4.1% [2,3]. Accurate pancreatic cancer staging is very important for treatment [4]; however, the 5-year survival rate of patients after surgery is still less than 20% [5]. Therefore, accurate prognosis for postoperative patients will contribute to improved follow-up treatment and improved survival.

The sensitivity and specificity of biomarkers play a very important role in the field of biomedical research and diagnostics [6]. Recently reported biomarkers, such as PD1/PD-L1, MZB1 and FM83B, have shown promising results in the diagnosis of cancer [7–9]. At present, carbohydrate antigen 19-9 (CA19-9) is a commonly used biomarker for diagnosing pancreatic cancer, and its sensitivity for pancreatic cancer is 75.4% [10]. Pancreatitis, biliary inflammation, tract obstruction and other digestive cancers can, however, significantly increase the level of CA19-9 expression to produce false positive results. In addition, Lewis-negative individuals can produce false negative results, which have limited the clinical application of CA19-9 [11–14]. Therefore, new biomarkers need to be explored for assessing cancer risk. HBXIP is a 19 kDa cellular protein originally identified as capable of binding to the hepatitis B virus X protein [15]. HBXIP is widely involved in the development of many cancers. HBXIP promotes tumor cell proliferation and collaborates with survivin to inhibit apoptosis in tumor cells. It also inhibits gluconeogenesis through the miR-135a/FOXO1 axis and the PI3K/Akt pathway, resulting in the promotion of hepatocellular carcinoma [16]. Currently, HBXIP is a useful biomarker for various cancers, such as breast, ovarian, and cervical cancers [17–19].

In this study, we investigated the relationship between HBXIP expression and the clinicopathological features of PDAC. We determined

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**Table 1**
HBXIP protein expression in PDAC, adjacent tissue samples and normal pancreas tissue samples.

| Diagnosis | No. of cases | HBXIP expression - + ++ +++ | Positive rate (%) | Strongly positive rate (%) |
|---|---|---|---|---|
| Pancreatic cancers | 126 | 18 27 43 38 | 85.7%*** | 64.3%*** |
| Adjacent tissues | 36 | 21 12 3 0 | 41.7% | 8.3% |
| Normal pancreas | 22 | 18 4 0 0 | 18.2% | 0% |

*** $P < 0.001$, compared with normal pancreas. Positive rate: percentage of positive cases with '+', '++', and '+++' staining score; Strongly positive rate: percentage of positive cases with '++' and '+++' staining score.

the relationship between poor prognosis of PDAC patients and HBXIP levels. We evaluated the expression of HBXIP in PDAC tissues by IHC and demonstrated the prognostic value of strongly positive HBXIP expression. These results contribute to understanding the role of HBXIP in PDAC pathology.

## 2. Materials and methods

### 2.1. Patients and tissue samples

A total of 126 samples were collected from Shanghai core biological technology co., Ltd and Xinhua hospital affiliated to Dalian University. The samples were routinely processed by 10% buffered-formalin fixation and paraffin embedding. The pathological parameters considered in this study are summarized in Table 1. Two experienced pathologists reviewed the IHC-stained slides.

This research complied with the Helsinki Declaration. It has been approved by the Human Ethics Committee and the Research Ethics Committee of Dalian University. Patients were informed that hospital would store the resect specimens and potentially for scientific research, and their privacy would be protected. Follow-up survival data were collected retrospectively through medical record analyses.

### 2.2. Immunohistochemistry

IHC was performed using a 2-step plus poly-HRP anti rabbit/mouse IgG detection kit (Elabscience Biotechnology Co., Ltd, Wuhan, China). After slides were dewaxed and washed in phosphate buffered saline, antigens were retrieved by immersing the slides in 0.01 M sodium citrate buffer at 80 °C and then allowing the slides to cool to room temperature for 1 h. After rinsing in PBS, slides were covered with 3% hydrogen peroxide for 15 min at room temperature in a humid chamber. The slides were then incubated with an HBXIP antibody (1:400, #14492-1-AP, Proteintech, USA) in a humid chamber overnight at 4 °C. After washing with PBS, the slides were incubated with a secondary antibody for 1 h, stained with 3,3′-diaminobenzidine tetrahydrochloride (DAB; Zhongshanjinqiao Biological Technology Ltd., Beijing, China) and then counterstained with Mayer's hematoxylin. Rabbit IgG isotype was used as a control to show negative results. The staining of the entire tissue sample was evaluated at low magnification (×4) and areas further examined at high magnification (×10 and ×20).

### 2.3. Interpretation of IHC staining

All slides were evaluated independently by two pathologists (Liu S and Ren X). The interpretation criteria were described previously [20]. Briefly, the IHC staining for HBXIP was scored semi-quantitatively as '-' (negative) (no or less than 5% positive cells), '+' (5–25% positive cells), '++' (26–50% positive cells) and '+++' (more than 50% positive cells). Cytoplasmic and membranous expression patterns were considered as positive staining, indicated by '++' and strongly positive staining indicated by '+++'.

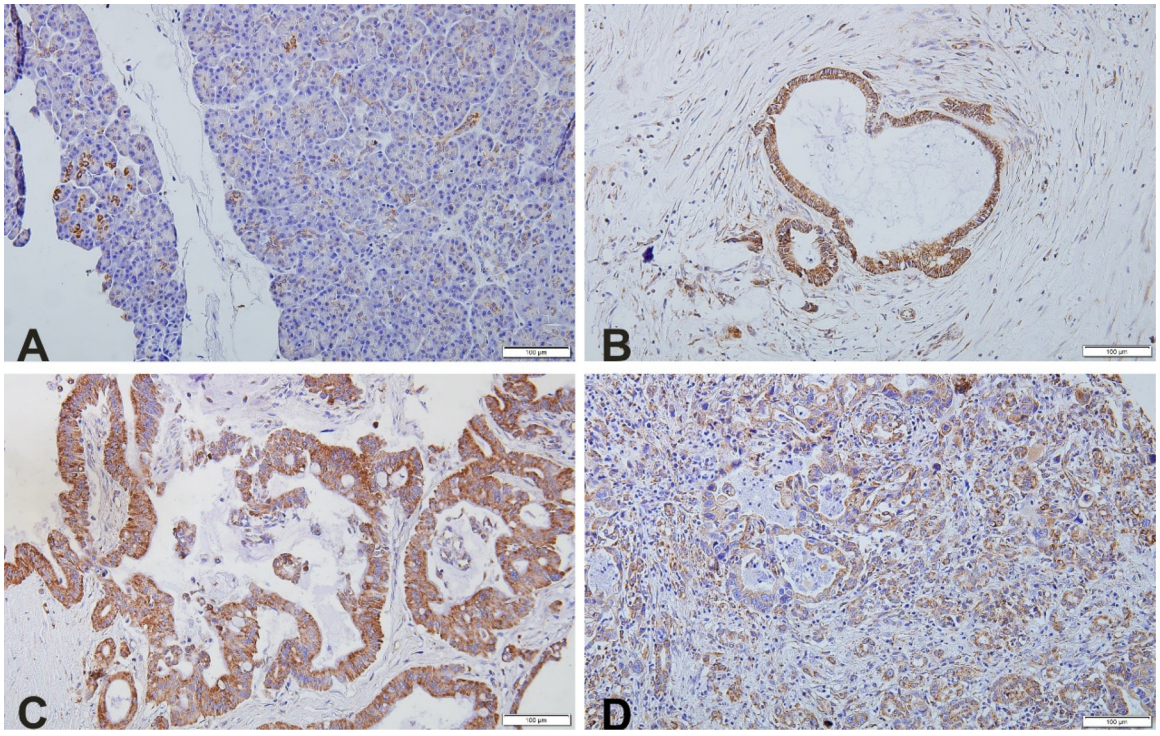


**Fig. 1.** The expression of HBXIP protein in PDAC. (A) Negative expression of HBXIP in normal pancreatic tissues. (B) HBXIP expression was strongly positive in the formation of ductal structures in pancreatic cancer. (C) Strongly positive HBXIP protein was detected in the cytoplasm/perinucleus of pancreatic cancer. (D) HBXIP protein was focally positive in pancreatic cancer with lymph node metastasis.

### 2.4. Statistical analysis

SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The statistical significance between HBXIP expression and various clinicopathological parameters was evaluated by chi-square or Fisher's tests. The overall survival was calculated using the Kaplan-Meier method. $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. HBXIP is upregulated in PDAC

Strongly positive IHC signals for HBXIP could be detected in the cytoplasm and on membranes of PDAC samples (Fig. 1). HBXIP showed a higher positive rate in PDAC (85.7%, 108/126) ($P < 0.001$) compared with adjacent tissues (41.7%, 15/36) and normal pancreatic tissues (18.2%, 4/22). Furthermore, the level of HBXIP staining was strongly positive in PDAC tissues (64.3%, 81/126) ($P < 0.001$), and was significantly higher compared with that in adjacent tissues (8.3%, 3/36) and normal pancreas (0.0%, 0/22) (Table 1).

### 3.2. Correlation between HBXIP overexpression and clinical parameters of PDAC

HBXIP overexpression was significantly correlated with tumor size, lymph node metastasis, and clinical stage of PDAC. Strongly positive rates of HBXIP were 52.3% (45/86) and 90.0% (36/40) in non-metastatic and metastatic PDAC ($P < 0.001$), respectively. HBXIP was weakly positive in non-metastatic PDAC, while it was strongly positive in metastatic PDAC. Clinicopathological clinical TNM stages were determined according to the Staging Manual of the American Joint Committee on Cancer (AJCC), 8th edition [21]. The HBXIP positive rate was only 43.5% (30/69) in stage I-II PDAC, but was significantly higher in stage III-IV cases (89.5%, 51/57) ($P < 0.001$). The strongly positive rate of HBXIP expression was significantly higher in cases with tumor size $\geq$ 3 cm (75.3%, 58/77) compared with cases with tumor size < 3 cm (53.1%, 26/49) ($P < 0.01$). However, HBXIP expression level was not correlated with patient age, gender, differentiation, Ki-67 protein expression, or pancreatic calcification point status ($P > 0.05$) (Table 2).

### 3.3. HBXIP expression levels influence overall survival rates of PDAC

To further confirm the role of HBXIP expression in PDAC progression, we analyzed the overall survival rates of 126 PDAC cases using the Kaplan-Meier method. We found that PDAC with high HBXIP expression had a shorter survival time than PDAC with low HBXIP expression ($P < 0.001$) (Fig. 2).

## 4. Discussion

PDAC is the fourth most lethal cancer in the United States [1]. Although chemotherapy can prolong the survival of patients with pancreatic cancer, surgical resection is still considered to be a more effective treatment [22–25]. However, because of the difficulties of early diagnosis, only about 20% of patients are treated by surgery [26]. Another first-line treatment, gemcitabine monotherapy, is limited because of patient resistance and therefore the objective response rate is only 9.4% [27]. In addition, the lack of a specific test means early detection of pancreatic cancer remains a huge challenge. We have, therefore, tried to find new biomarkers to diagnose pancreatic cancer and to evaluate prognosis to facilitate optimal treatment for patients.

To determine the relationship between HBXIP expression and clinicopathological features, we performed IHC staining of HBXIP in 126 PDAC cases, 36 adjacent pancreatic tissue samples, and 22 normal pancreatic tissue samples. We found that HBXIP showed higher positivity in PDAC (85.7%, 108/126) ($P < 0.001$) compared with adjacent non-tumor tissues (41.7%, 15/36) and normal pancreas (18.2%, 4/22). In addition, HBXIP was strongly positive in PDAC (64.3%, 81/126) ($P < 0.001$), indicating that HBXIP is frequently upregulated in PDAC tissue compared with normal pancreatic tissue. These results revealed that HBXIP may be closely related to the progression of PDAC, and might also be a potential biomarker for PDAC diagnosis.

We show here that HBXIP is associated with many clinicopathological features. Cheng et al. found that HBXIP overexpression correlated with TNM stage, lymph node metastasis, and Ki67 status in breast cancer [17]. In our previous work, we similarly found that HBXIP protein expression correlated with lymph node metastasis and clinical stage in cervical cancer and ovarian cancer [18,19]. Consistent with the results of Cheng et al and our previous work, the current study showed that HBXIP expression was associated with tumor size, lymph node metastasis and TNM stage; however, it was not associated with patient

**Table 2**
Relationship between HBXIP overexpression and the clinicopathological features in PDAC.

| Characteristic | No. of cases | Strongly positive cases (%) | χ2 | *P* value |
|---|---|---|---|---|
| Gender | | | 0.026 | 0.871 |
| Male | 74 | 48 (64.9%) | | |
| Female | 52 | 33 (63.7%) | | |
| Age (years old) | | | 0.516 | 0.472 |
| ≤50 | 59 | 36 (61.0%) | | |
| > 50 | 67 | 45 (67.2%) | | |
| Differentiation | | | 4.483 | 0.106 |
| Well diff. | 35 | 20 (57.1%) | | |
| Mod. diff. | 51 | 30 (58.8%) | | |
| Poorly diff. | 40 | 31 (77.5%) | | |
| Tumor size (cm) | | | 6.679 | 0.010** |
| < 3 | 49 | 26 (53.1%) | | |
| ≥3 | 77 | 58 (75.3%) | | |
| Lymph node metastasis | | | 16.878 | 0.000*** |
| + | 40 | 36 (90.0%) | | |
| – | 86 | 45 (52.3%) | | |
| TNM Clinical Stage | | | 28.762 | 0.000*** |
| I-II | 69 | 30 (43.5%) | | |
| III-IV | 57 | 51 (89.5%) | | |
| Ki67 protein | | | 0.218 | 0.641 |
| + | 47 | 29 (61.7%) | | |
| – | 79 | 52 (65.8%) | | |
| Calcification point | | | 0.130 | 0.719 |
| + | 81 | 53 (65.4%) | | |
| – | 45 | 28 (62.2%) | | |
| Overall Survival | | | | |
| + | 26 | 12 (46.2%) | 18.955 | 0.000*** |
| – | 100 | 86 (86.0%) | | |

** $P < 0.01$.
*** $P < 0.001$.

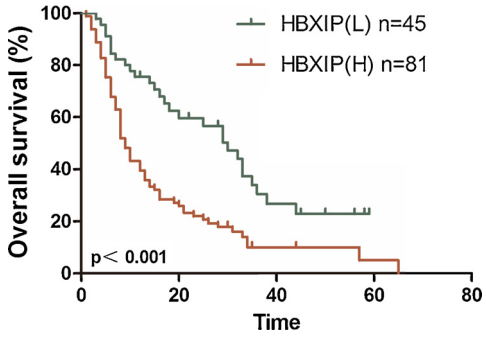


**Fig. 2.** The OS curve of high and low HBXIP expression in PDAC patients. Patients with high HBXIP expression of PDAC had lower OS than patients with HBXIP expression (P < 0.001).

age, gender, differentiation, Ki-67 protein expression, or calcification point status (a pathological phenomenon associated with cancer) [28]. The current results indicate that HBXIP overexpression was associated with the acquisition of invasive and metastatic potential.

We further evaluated the association between HBXIP expression and prognosis in patients with PDAC. PDAC patients with high-level HBXIP expression had lower survival rates than patients with low-level HBXIP expression. The intensity of HBXIP expression may be an indicator for evaluating the progression of PDAC and HBXIP may be a novel biomarker for poor overall survival of PDAC patients.

## 5. Conclusions

In summary, HBXIP may play a key role in the progression of PDAC. The high proportion of PDAC patients that express HBXIP and the prognostic value of HBXIP suggests that HBXIP may be a significant biomarker and a potential therapeutic target for patients with PDAC.

## Disclosure

The author has no conflicts of interest.

## Authors contributions

XZ Zhou and XY Wang contributed to this article equally. XZ Zhou and XY Wang participated in the study conception, design, case selection and experiments. DJ, SW, ZC, LQ, OZ and JG carried out data collection. XZ, RX and LS performed the data analysis and wrote the manuscript.

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## References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2017, Ca A Cancer J. Clin. 67 (1) (2017) 7–30.
[2] W. Chen, R. Zheng, D. Baade, S.W. Zhang, H.M. Zeng, F. Bray, A. Jemal, X.Q. Yu, J. He, Cancer statistics in China, 2015, CA Cancer J. Clin. 66 (2) (2016) 115–132.
[3] J.F. Luo, L.H. Xiao, C.X. Wu, Y. Zhang, N.Q. Zhao, The incidence and survival rate of population-based pancreatic cancer patients: Shanghai cancer registry 2004-2009, PLoS One 8 (10) (2013) e76052.
[4] C.L. Wolfgang, J.M. Herman, D.A.Laheru JM, A.P. Klein, M.A. Erdek, E.K. Fishman, R.H. Hruban, Recent progress in pancreatic cancer, Ca A Cancer J. Clin. 63 (5) (2013) 318–348.
[5] B. Zhou, J.W. Xu, Y.G. Cheng, J.Y. Gao, S.Y. Hu, L. Wang, H.X. Zhan, Early detection of pancreatic cancer: where are we now and where are we going? Int. J. Cancer 141 (2) (2017) 231–241.
[6] H. Kitano, Systems biology: a brief overview, Science 295 (5560) (2002) 1662–1664.
[7] Y. Wang, J. Lin, J. Cui, T. Han, F. Jiao, Z. Meng, L.W. Wang, Prognostic value and clinicopathological features of PD-1/PD-L1 expression with mismatch repair status and desmoplastic stroma in Chinese patients with pancreatic cancer, Oncotarget 8 (6) (2017) 9354–9365.
[8] K. Miyake, R. Mori, Y. Homma, R. Matsuyama, A. Okayama, T. Murakami, H. Hirano, I. Endo, MZB1 in borderline resectable pancreatic cancer resected after neoadjuvant chemoradiotherapy, J. Surg. Res. 220 (2017) 391–401.
[9] C. Shen, T. Yan, W. Liu, X.Q. Zhu, X.L. Tian, X.L. Fu, R. Hua, J.F. Zhang, Y.M. Huo, D.J. Liu, J.Y. Yang, Y.W. Sun, J.Y. Fang, H.Y. Chen, J. Hong, High expression of FAM83B predicts poor prognosis in patients with pancreatic ductal adenocarcinoma and correlates with cell cycle and cell proliferation, J. Cancer 8 (16) (2017) 3154–3165.
[10] D. Reitz, A. Gerger, J. Seidel, P. Kornprat, H. Samonigg, M. Stotz, J. Szkandera, M. Pichler, Combination of tumour markers CEA and CA19-9 improves the prognostic prediction in patients with pancreatic cancer, J. Clin. Pathol. 68 (6) (2015) 427–433.
[11] J. Xu, Z. Cao, W. Liu, L. You, L. Zhou, C.Y. Wang, W.H. Lou, B. Sun, Y. Miao, X.B. Liu, T.P. Zhang, Y.P. Zhao, Plasma miRNAs effectively distinguish patients with pancreatic cancer from controls: a multicenter study, Ann. Surg. 263 (6) (2016) 1173–1179.
[12] G. Lu, Z. Xiao, J. Long, Z.Q. Liu, L. Liu, C. Liu, J. Xu, Q.X. Ni, X.J. Yu, CA125 is superior to CA19-9 in predicting the resectability of pancreatic cancer, J. Gastrointest. Surg. 17 (12) (2013) 2092–2098.
[13] A. Chan, I. Prassas, A. Dimitromanolakis, R.E. Brand, S. Serra, E.P. Diamandis, I.M. Blasutig, Validation of biomarkers that complement CA19.9 in detecting early pancreatic cancer, Clin. Cancer Res. 20 (22) (2014) 5787–5795.
[14] D.P. O'Brien, N.S. Sandanayake, C. Jenkinson, A. Gentry-Maharaj, S. Apostolidou, E.O. Fourkala, S. Camuzeaux, O. Blyuss, R. Gunu, A. Dawnay, A. Zaikin, R.C. Smith, I.J. Jacobs, U. Menon, E. Costello, S.P. Pereira, J.F. Timms, Serum CA19-9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection, Clin. Cancer Res. 21 (3) (2015) 622–631.
[15] M. Melegari, P.P. Scaglioni, J.R. Wands, Cloning and characterization of a novel hepatitis B virus x binding protein that inhibits viral replication, J. Virol. 72 (3) (1998) 1737–1743.
[16] H. Shi, R. Fang, Y. Li, L.L. Li, W.Y. Zhang, H.W. Wang, F.Q. Chen, S.Q. Zhang, X.D. Zhang, L.H. Ye, The oncoprotein HBXIP suppresses gluconeogenesis through modulating PCK1 to enhance the growth of hepatoma cells, Cancer Lett. 382 (2) (2016) 147–156.
[17] D. Cheng, B. Liang, Y. Li, HBXIP expression predicts patient prognosis in breast cancer, Med. Oncol. 31 (10) (2014) 210.
[18] Y. Wang, J. Sun, N. Li, S.L. Che, T.F. Jin, S.P. Liu, Z.H. Lin, HBXIP overexpression is correlated with the clinical features and survival outcome of ovarian cancer, J. Ovarian Res. 10 (1) (2017) 26.
[19] N. Li, Y. Wang, S. Che, Y. Yang, J.J. Piao, S.P. Liu, Z.H. Lin, HBXIP over expression as an independent biomarker for cervical cancer, Exp. Mol. Pathol. 102 (1) (2017) 133–137.
[20] Q. Wu, Z. Li, H. Lin, L.Z. Han, S.P. Liu, Z.H. Lin, DEK overexpression in uterine cervical cancers, Pathol. Int. 58 (6) (2008) 378–382.
[21] M.B. Amin, S. Edge, F. Greene, D.R. Byrd, R.K. Brookland, M.K. Washington, J.E. Gershenwald, C.C. Compton, K.R. Hess, D.C. Sullivan, J.M. Jessup, J.D. Brierley, L.E. Gaspar, R.L. Schilsky, C.M. Balch, D.P. Winchester, E.A. Asare, M. Madera, D.M. Gress, L.R. Meyer, AJCC Cancer Staging Manual, eighth ed., Springer, New York, 2016.
[22] J. Péron, J.P. Roy, T. Conroy, F. Desseigne, M. Ychou, S. Gourgou-Bourgade, T. Stanbury, L. Roche, B. Ozenne, M. Buyse, An assessment of the benefit-risk balance of FOLFIRINOX in metastatic pancreatic adenocarcinoma, Oncotarget 7 (50) (2016) 82953–82960.
[23] T. Conroy, F. Desseigne, M. Ychou, O. Bouché, R. Guimbaud, Y. Bécouarn, A. Adenis, J.L. Raoul, S. Gourgou-Bourgade, C. de la Fouchardière, J. Bennouna, J.B. Bachet, F. Khemissa-Akouz, D. Péré-Vergé, C. Delbaldo, E. Assenat, B. Chauffert, P. Michel, C. Montoto-Grillot, M. Ducreux, Groupe tumeurs digestives of unicancer, PRODIGE intergroup, FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, New Engl. J. Med. 364 (19) (2011) 1817–1825.
[24] D.D. Von Hoff, T. Ervin, F.P. Arena, E.G. Chiorean, J. Infante, M. Moore, T. Seay, S.A. Tjulandin, W.W. Ma, M.N. Saleh, M. Harris, M. Reni, S. Dowden, D. Laheru, N. Bahary, R.K. Ramanathan, J. Tabernero, M. Hidalgo, D. Goldstein, E. Van Cutsem, X. Wei, J. Iglesias, M.F. Renschler, Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine, New Engl. J. Med. 369 (18) (2013) 1691–1703.
[25] H. Oettle, P. Neuhaus, A. Hochhaus, J.T. Hartmann, K. Gellert, K. Ridwelski, M. Niedergethmann, C. Zülke, J. Fahlke, M.B. Arning, M. Sinn, A. Hinke, H. Riess, Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial, JAMA 310 (14) (2013) 1473–1481.
[26] A. Vincent, J. Herman, R. Schulick, R.H. Hruban, M. Goggins, Pancreatic cancer, Lancet 378 (9791) (2011) 607–620.
[27] D.P. Ryan, T.S. Hong, N. Bardeesy, Pancreatic adenocarcinoma, New Engl. J. Med. 371 (11) (2014) 1039–1049.
[28] A. Mohamed, A. Ayav, A. Belle, X. Orry, J.B. Chevaux, V. Laurent, Pancreatic cancer in patients with chronic calcifying pancreatitis: computed tomography findings-a retrospective analysis of 48 patients, Eur. J. Radiol. 86 (2017) 206–212.