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Research

Pancreatic Cancer: Emerging Trends In Diagnosis, Treatment And Future Directions

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Abstract

Pancreatic cancer stands as one of the most daunting challenges in oncology, characterized by high mortality rates and limited progress in treatment outcomes over decades. A critical barrier to improving survival lies in the difficulty of early detection and prevention: symptoms often do not manifest until the disease has reached an advanced stage and reliable screening methods are lacking. This delayed diagnosis contributes significantly to the poor prognosis associated with pancreatic cancer. Genetically, pancreatic tumors exhibit a limited repertoire of frequently mutated genes, including KRAS, CDKN2A (p16), TP53, and SMAD4. Neoadjuvant therapies are being explored to downstage tumors and increase the likelihood of successful surgery. Despite advancements in treatment strategies, including novel drug combinations and multimodal approaches, disease recurrence following surgery remains common, highlighting the urgent need for innovative therapeutic approaches. We summarize the existing knowledge on the critical pathophysiological, molecular, translational, and clinical aspects of pancreatic cancer. Additionally, we outline potential future directions for research and patient management in this challenging disease.

Keywords: Pancreas, Pancreatic cancer, Biomarker, Treatment.

INTRODUCTION

Pancreatic cancer is a type of cancer where malignant cells develop within the pancreas tissue, posing a significant threat globally as a leading cause of cancer-related deaths. It ranks seventh in both men and women worldwide according to 2012 data from Worldwide Cancer Statistics.[1] Developed nations like Australia, East Asia, North America, and Europe face higher risks of this disease.[2] Without treatment, advanced stages typically result in a survival time of about three months, with only a 9% chance of recovery.[3] Current effective treatments include adjuvant chemotherapy, immunotherapy, and surgery, particularly surgical resection as the primary approach[4]. However, due to the invasive nature of the tumor, only 15%–20% of patients are eligible for surgery, highlighting the urgent need for effective medicinal therapies[5]

Anatomy of pancreas

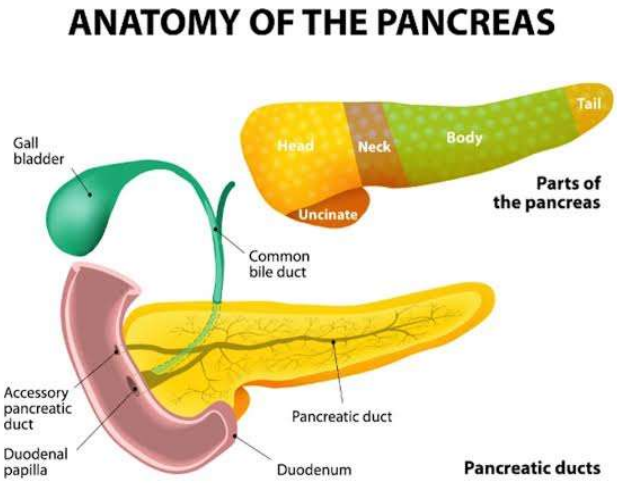

Fig 1: Anatomy of pancreas

The pancreas, situated in the retroperitoneum behind the stomach's greater curvature within the lesser sac, is anatomically partitioned into four regions: the head, neck, body, and tail. The pancreatic head is positioned medially to the C-loop of the duodenum, behind the transverse mesocolon, and is anterior to the vena cava, right renal artery, and renal veins.

Overlying the portal vein, the neck of the pancreas marks the juncture where the superior mesenteric vein converges with the splenic vein, eventually forming the portal vein. The body of the pancreas lies in front of the splenic artery and vein, while the tail, situated within the splenic hilum, is anterior to the left kidney. Unlike its anterior border, the pancreas lacks a peritoneal covering along its posterior border, thereby exposing the pancreatic lymphatics to the retroperitoneum.

Blood supply to the pancreas originates from branches of the celiac and superior mesenteric arteries (SMA). The head receives arterial blood from an arcade formed by the gastro-duodenal artery (GDA) and SMA branches, specifically the superior pancreaticoduodenal artery (dividing into anterior and posterior branches) and the inferior pancreaticoduodenal artery. Supply to the body and tail is provided by branches of the splenic artery. The SMA also branches into the inferior pancreatic artery, running along the pancreas's lower border. Anatomically parallel, the splenic artery and inferior pancreatic artery are interconnected by lateral, dorsal, and transverse pancreatic arteries. Venous drainage mirrors arterial supply, with veins running anterior to arteries.

Lymphatic drainage throughout the pancreas is extensive and diffuse, with lymphatic vessels draining into five primary groups of nodes: superior nodes along the pancreas's upper border and the celiac trunk, anterior lymphatics to prepyloric and infrapyloric nodes, inferior nodes to superior mesenteric and periaortic nodes along the pancreas's lower border, posterior pancreaticoduodenal nodes to right periaortic nodes including lymphatics from the distal common bile duct and ampulla, and splenic nodes draining the tail along the splenic vessels to interceliomesenteric lymph nodes.[6]

Pathophysiology

Genetic mutations play a crucial role in the development of adenocarcinomas in the pancreas. These mutations involve the activation of oncogenes, inactivation of tumor suppressor genes, and disruptions in genome maintenance genes.[7] The majority of pancreatic malignancies are associated with activation of the ras oncogene, often through point mutations and gene amplification. Up to 90% of these cancers exhibit point mutations at codons 12, 13, and 61 in the Kirsten rat sarcoma viral oncogene homolog (K-ras) .[8] Additionally, various types of notch genes and their ligands have been implicated as potential oncogenes in pancreatic carcinogenesis.[9]

A significant pathological feature of these cancers is the inactivation of tumor suppressor genes. A high percentage of pancreatic cancers show inactivation of p16, which plays a critical role in inhibiting tumor growth. Approximately half of pancreatic carcinomas also exhibit inactivation of another crucial apoptotic factor, tumor protein p53, which contributes to enhanced cancer cell proliferation and survival . Another common mutation involves the tumor suppressor gene.[10] Deleted in Pancreatic Cancer-4 (DPC4), which is deactivated in half of patients. DPC4 is important for suppressing vascular growth and tumor proliferation.[11]

Other significant factors contributing to the pathology of pancreatic carcinoma include the dysregulation of epidermal growth factor receptor (EGFR) signaling, which promotes tumor cell proliferation, invasion, and

metastasis .[12] Aberrations in protein kinase B (Akt) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activity also inhibit tumor cell apoptosis, thereby promoting tumor survival and invasion.[13]
Embryogenic factors also play a role in the progression of pancreatic carcinoma. Pancreatic growth during fetal development depends on hedgehog signaling, which is critical for normal tissue morphogenesis and organogenesis in the digestive system. Dysregulation of this pathway, leading to its increased expression, is associated with many cancers, including pancreatic adenocarcinomas .[14] Several other signaling pathways, such as mitogen-activated protein kinases (MAPK), insulin-like growth factor (IGF), and signal transducer and activator of transcription 3 (STAT3), are also implicated in the pathogenesis of pancreatic carcinomas.[15]

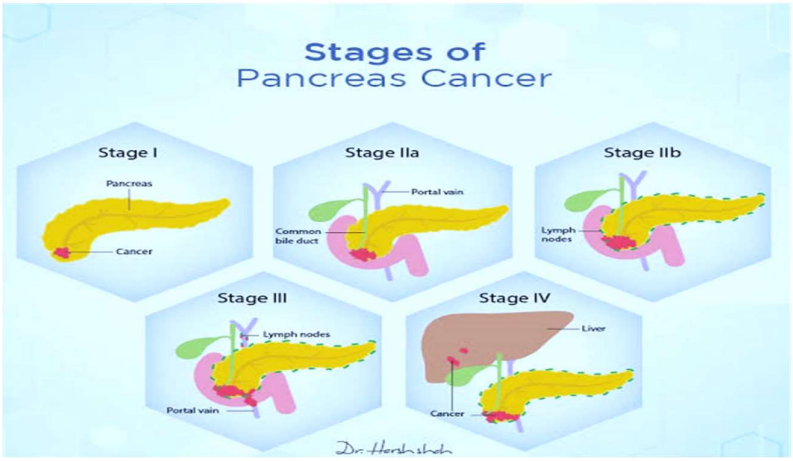

Fig 2: illustrates various stages of pancreatic cancer

Risk factors
The risk factors for this disease are classified into two categories:
1. Modifiable risk factors
- ✓ Overweight,
- ✓ smoking,
- ✓ alcohol consumption,
- ✓ occupational exposure,
- ✓ and dietary factors.

Studies indicate that smoking can significantly increase the risk of this cancer, especially with prolonged exposure or passive smoking .[16]Being overweight is also associated with an increased risk of pancreatic carcinoma .[17]Certain dietary choices have been shown to influence the risk of pancreatic cancer in about half of all cases .[18] Alcohol consumption, particularly at levels of 60 grams per day, has been linked causally to the development of pancreatic cancer .[19] Certain occupations exposing individuals to carcinogenic agents, such as nickel, are also implicated in the etiology of this malignancy .[20]
2. Non-modifiable factors
- ✓ sex
- ✓ age
- ✓ positive family history
- ✓ diabetes mellitus
- ✓ infections
- ✓ genetic disorders

Men have a higher incidence rate of pancreatic cancer compared to women .[29] The risk increases with age, particularly above fifty years old, according to SEER statistics.[21] Diabetes mellitus, both Type I and II, predisposes individuals to a higher risk of developing this cancer .[22] Having a positive family history, especially in first-degree relatives, significantly increases the likelihood of occurrence .[23-25]

Chemotherapy for pancreatic cancer is typically administered either before surgery (neoadjuvant chemotherapy) or after surgery (adjuvant chemotherapy) [26]. Various chemotherapeutic agents used include Gemcitabine (GEM), 5-fluorouracil (5-FU), Doxorubicin (DOX), Oxaliplatin, Paclitaxel (PTX), Capecitabine (Cap), Cisplatin, Irinotecan, and immunomodulators. These agents are combined in different protocols depending on the specific treatment plan.[27,28]

Epidemeology

Pancreatic cancer ranks as the fourth leading cause of cancer-related deaths in the United States and results in approximately 227,000 deaths annually worldwide.[29] Various risk factors contribute to this disease, including smoking, a family history[30] of chronic pancreatitis, advancing age, male gender, diabetes mellitus, obesity, non-O blood group,[31] occupational exposures to certain chemicals like chlorinated hydrocarbon solvents and nickel, [32]African-American ethnicity, diets high in fat and meat but low in vegetables and folate, and possibly infections such as Helicobacter pylori and periodontal disease.[29] Notably, coffee intake is not associated with an increased risk of pancreatic cancer.

The etiology of pancreatic cancer is complex and multifaceted, with smoking and family history being prominent factors. Approximately 20% of pancreatic tumors are attributed to smoking, and these cancers tend to harbor more genetic mutations compared to non-smokers.[32] A family history of pancreatic cancer significantly elevates individual risk, affecting about 7-10% of affected individuals.[33]Familial pancreatic cancer is typically defined as cases where first-degree relatives (e.g., parents, siblings) have been diagnosed with pancreatic tumors.[30] First-degree relatives of individuals with familial pancreatic cancer carry a ninefold increased risk of developing the disease compared to the general population, which escalates to a 32-fold greater risk in families with three or more affected first-degree relatives.

Young-onset pancreatic cancer (occurring before age 50) in a family further increases the risk.[34] Patients with familial pancreatic cancer tend to exhibit more precancerous lesions[35] and face an augmented risk of developing cancers outside of the pancreas.[36]

Genetic testing plays a crucial role in identifying cancer predisposition genes within families affected by pancreatic cancer. However, it is underutilized due to insufficient recognition of familial cancer syndromes based on incomplete family history documentation. Even without genetic testing, detailed cancer family histories can help predict clinical risk. Current guidelines do not universally recommend genetic testing for inherited susceptibility to pancreatic cancer due to many aspects of genetic predisposition remaining poorly understood.[37] For individuals with specific risk factors (e.g., Jewish ethnicity, strong family history of breast cancer, multiple first-degree relatives with pancreatic cancer), BRCA2 and CDKN2A genetic testing may be considered after appropriate genetic counseling. Mendelian risk-prediction programs have also been evaluated to aid in managing familial pancreatic cancer risk. [38]

Symptoms

Approximately 70-80% of patients with pancreatic cancer experience pain in the epigastrium, which is the upper central part of the abdomen. This pain may radiate to the sides and back. The pain is typically relieved by sitting still or bending forward. Other common symptoms include jaundice, which presents as yellowing of the skin and eyes due to bile duct obstruction, leading to cholestasis (buildup of bile in the bloodstream). Patients often report a loss of appetite, unexplained weight loss, and may experience depression. Some individuals also develop diarrhea or steatorrhea (fatty stools).

Pancreatic cancers located in the head of the pancreas can cause progressive and dark jaundice due to bile duct obstruction by the tumor. When examining a patient, physicians should consider pancreatic cancer if they present with persistent abdominal pain around the abdomen, navel, and stomach, along with symptoms such as indigestion, swelling, significant weight loss, and loss of appetite.

In cases where the tumor obstructs the bile ducts sufficiently, the gallbladder may become palpably enlarged, a finding known as vesicle hydrops, which is characteristic of Courvoisier-Terrier sign. This sign suggests the obstruction of bile ducts is likely due to a non-inflammatory process such as pancreatic cancer.[39]

Diagnosis and screening

Diagnosing pancreatic cancer is notably challenging, often resulting in late-stage detection where the disease has already progressed to locally advanced or metastatic stages. This delay stems from various factors, including the nonspecific nature of symptoms associated with pancreatic cancer and its tendency to invade nearby major blood vessels early on, making many tumors unresectable (80%-85%) upon presentation. [40,41]Surgical resection remains the sole potential cure, albeit with high recurrence rates and generally poor long-term survival outcomes.

Given the relatively low lifetime risk of pancreatic cancer (around 1%), there is no recommendation for population-wide screening of asymptomatic individuals. There is some debate on the optimal age to commence screening among high-risk populations, with a slight majority suggesting initiation at age 50. Surveillance intervals vary based on findings, with non-suspicious cysts requiring repeat imaging every 6-12 months and solid lesions or main pancreatic duct strictures needing reassessment after three months.

While a high-risk population for screening has been identified, there is still ambiguity regarding the optimal diagnostic imaging modalities and specific lesions to target. Secretin-enhanced MRI and MRCP have demonstrated strong concordance with EUS findings as a one-time screening modality, avoiding the risks associated with ionizing radiation. However, EUS exhibits higher sensitivity for detecting small solid pancreatic

lesions (<2cm) compared to CT and MRI, and it can characterize pancreatic cysts using fine needle aspiration cytology.

Previously, PanIN (pancreatic intraepithelial neoplasia) was thought challenging to identify on imaging, but emerging evidence suggests associations with lobulocentric atrophy that mimics chronic pancreatitis on EUS. For high-risk populations recommended by the International Cancer of the Pancreas Screening Consortium, a combination of EUS and MRI/MRCP is recommended for screening.[42]

Despite advancements in screening technology, managing identified abnormalities remains a subject of ongoing study.[43] While screening programs in high-risk populations show promise in improving rates of curative resection and survival, these benefits must be weighed against potential concerns such as heightened anxiety among those screened.[44,45,46]

Although general population-based screening is not advised, raising awareness about the vague symptoms of pancreatic cancer through various campaigns is crucial. Many individuals diagnosed with pancreatic cancer had previously ignored intermittent symptoms, emphasizing the need for heightened awareness among primary care physicians to ensure timely investigation and management when relevant symptoms arise.[47,48]

Biomarkers for early detection

Research focused on identifying biomarkers, such as through liquid biopsy, to assist in the screening, diagnosis, and treatment of pancreatic cancer has been vigorously pursued. Various approaches to detect biomarkers in blood, breath, and pancreatic juice have all been explored in this endeavor.

CA 19-9 is currently the only biomarker approved by the FDA for routine management of pancreatic cancer.[49] However, its limited ability to accurately predict disease presence makes it unsuitable for mass screening of asymptomatic individuals. Instead, it is more appropriate for monitoring treatment response and detecting disease recurrence.[50] Recent studies using mass spectrometry have found higher levels of specific metabolic by-products in early-stage pancreatic adenocarcinoma compared to controls.[43] Nevertheless, discrepancies between levels found in tumor tissue and plasma samples highlight the necessity for further research if a blood-based biomarker is to be developed.[43]

Efforts have also focused on metabolites detected via mass spectrometry in tumor tissue, showing potential for early-stage pancreatic adenocarcinoma diagnosis. However, discrepancies between tumor tissue and plasma samples suggest the need for further investigation before a blood-based biomarker can be developed.[51] Recent studies on plasma-based metabolite panels have shown promise in early diagnosis, particularly in populations at higher risk due to chronic pancreatitis.[52]

Genetic mutations like KRAS have prompted investigation into cell-free DNA and circulating tumor cells for screening, yet current findings indicate insufficient sensitivity and specificity for widespread use. Meanwhile, volatile organic compounds (VOCs) in exhaled air have shown potential as non-invasive biomarkers, demonstrating elevated levels in pancreatic cancer patients compared to healthy controls.[53]

In pancreatic juice, mutant P53 and other mutated DNA markers have been identified in individuals with various stages of pancreatic lesions, suggesting potential for early detection using next-generation sequencing techniques.[54] However, the lack of validated and specific biomarkers remains a significant challenge in the field, underscoring the need for continued research and validation efforts.[55]

Treatment

Surgical resection stands as the primary curative option for pancreatic cancer, with chemotherapy in the adjuvant setting demonstrating improved survival rates. Recent studies have shown encouraging results with the addition of chemo-radiotherapy in the neo-adjuvant setting, although further research is necessary to determine which patient groups would benefit most from this approach. Here, we review the latest evidence supporting these treatment strategies.[56]

Surgical management

Pancreatico-duodenectomy (Whipple's procedure), distal pancreatectomy, or total pancreatectomy are the surgical options available depending on the tumor's anatomical location. Centralization of these procedures in high-volume centers has led to improved outcomes as surgical expertise increases. [56]Technological advancements and refined operative techniques aim to minimize adverse events and enhance survival. The goal of surgical resection is to achieve an R0 resection, significantly associated with improved survival compared to R1 resections. Debate persists regarding the definition of an R1 resection, with differing criteria among international pathology organizations.[57,58]

Pre-operative biliary drainage

A significant number of pancreatic cancer patients present with jaundice, which can complicate peri-operative management. Traditionally, obstructive jaundice is relieved prior to surgery to mitigate coagulation issues and infection risks. Recent trials comparing pre-operative biliary drainage methods have suggested that

some patients may benefit more from expedited surgery rather than drainage followed by resection, owing to higher peri-operative complication rates in the drainage group.[59,60,61]

Anastomotic techniques

Post-Whipple procedure, pancreatic anastomotic leakage and pancreatic fistula formation are major sources of morbidity. Various techniques for reconstructing the digestive tract after Whipple's procedure have been explored, including anastomosing the pancreatic remnant to the stomach or jejunum. However, studies have not shown significant differences in outcomes between these techniques or variations within them.[62,63]

Minimally invasive surgery

Interest in minimally invasive techniques for pancreatic surgery has grown, with laparoscopic distal pancreatectomy showing comparable morbidity and mortality to open procedures, along with reduced blood loss and hospital stay. Although initial studies are promising, further high-quality evidence is needed to establish superiority over open surgery.[64,65]

Robotic surgery

Robotic-assisted Whipple's procedure has been investigated for its potential benefits, including lower complication rates and reduced margin involvement compared to open surgery in retrospective cohort studies. However, the lack of randomized controlled trials introduces potential selection bias, and the significant cost of robotic systems requires further evaluation of cost-effectiveness.[66,67]

Vascular resection

Resection of pancreatic tumors involving surrounding vasculature remains controversial. While resection of invaded mesenteric and portal vessels is technically feasible, studies have shown higher peri-operative mortality and poorer outcomes at one and three years with arterial reconstruction. In contrast, venous resection during pancreatectomy may offer more promising outcomes, with comparable perioperative morbidity and survival rates to non-intervention cases, albeit with increased operative time and blood loss.

In conclusion, while surgical resection remains the cornerstone of potentially curative treatment for pancreatic cancer, ongoing research into peri-operative management, anastomotic techniques, minimally invasive approaches, robotic surgery, and vascular resection aims to optimize outcomes and expand treatment options for this challenging disease.[68-70]

Medical management

Adjuvant treatment

Adjuvant chemotherapy has been validated by the landmark CONKO-001 trial, which compared adjuvant gemcitabine following complete surgical resection versus surgery alone. This study demonstrated a significant improvement in median disease-free survival (13.4 months vs 6.7 months) and overall survival, with five-year survival rates of 20.7% versus 10.4%, and ten-year survival rates of 12.2% versus 7.7%. Despite these promising outcomes, the median overall survival improvement was modest (20 to 23 months, $P = 0.01$).[71]

Further research has focused on identifying optimal chemotherapy regimens. The ESPAC-3 trial established gemcitabine as the preferred agent over 5-fluorouracil due to better tolerability. Building on dual therapy success in advanced disease, the ESPAC-4 trial by Neoptolemos et al. demonstrated that combining capecitabine with gemcitabine in resected pancreatic cancer patients improved median overall survival to 28 months compared to 25.5 months with gemcitabine alone (HR: 0.82, $P = 0.032$).[72]

Other chemotherapy approaches have also been explored. For instance, the PRODIGE24/CCTG trial compared gemcitabine with mFOLFIRINOX (a combination of oxaliplatin, irinotecan, and leucovorin) in patients with R1 or R0 resection of pancreatic adenocarcinoma. Results at a median follow-up of 33.6 months showed significantly improved disease-free survival (21.6 months vs 12.8 months) and overall survival (54.4 months vs 35 months) with mFOLFIRINOX, albeit with a higher risk of complications.[73-75]

Neo-adjuvant treatment

Despite the benefits of adjuvant therapy, a substantial proportion (71-76%) of patients experience relapse within two years, and up to 40% are unfit for adjuvant therapy due to surgical complications. Given the success of neo-adjuvant therapy in other cancers, there is growing interest in its potential benefits for pancreatic cancer. Theoretical advantages include micro-metastasis elimination and primary tumor shrinkage, which may reduce recurrence rates. However, complications from neo-adjuvant treatment can delay surgery or render tumors unresponsive, potentially converting resectable disease to unresectable. Additionally, chemoradiotherapy-induced pancreatic fibrosis may complicate subsequent pancreatectomy.

Studies investigating neo-adjuvant therapy have focused on resectable or borderline resectable disease. Meta-analyses, including the recent work by Versteijne et al., have shown that neo-adjuvant treatment prolongs

median overall survival (26.1 months vs 14.8 months) and increases R0 resection rates compared to upfront surgery.

Ongoing trials like Preopanc-1 are evaluating the role of pre-operative chemoradiotherapy versus immediate surgery in improving resection rates and survival outcomes for resectable or borderline resectable disease.[76-81]

Treatment in metastatic patients

For metastatic pancreatic cancer, management primarily aims at symptom control, jaundice management, and palliative chemotherapy. FOLFIRINOX has emerged as the preferred regimen over gemcitabine, based on trials like those by Conroy et al., which demonstrated superior median overall survival (11.1 months vs 6.8 months) despite increased adverse effects.[81,83]

Future Directions for Pancreatic Cancer Treatment

Given the limitations of current therapies, ongoing research is essential to explore novel therapeutic avenues. Promising areas include oncolytic viral therapy and gene editing technologies, which have shown potential in pre-clinical and early clinical trials.

CONCLUSION

In conclusion, while adjuvant chemotherapy remains pivotal in managing resected pancreatic cancer, the potential benefits of neo-adjuvant therapy and advancements in metastatic disease treatment underscore the need for continued research to improve outcomes in this challenging disease.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
3. Tempero MA. NCCN guidelines updates: pancreatic cancer. J Natl Compr Cancer Netw. 2019;17(5.5):603-605.
4. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6):977-988.
5. Saha SK, Khuda-Bukhsh AR. Molecular approaches towards development of purified natural products and their structurally known derivatives as efficient anti-cancer drugs: current trends. Eur J Pharmacol. 2013;714(1-3):239-248.
6. Narcis Octavian Zarnescu, Isam W Nasr, Mario Lora, A James Moser. Pancreatic Cancer. Textbook of Surgical Oncology. 2011;488-502
7. T.J. Grant, K. Hua, A. Singh, Molecular pathogenesis of pancreatic cancer, Prog. Mol. Biol. Transl. Sci. 144 (2016) 241–275.
8. C. Almoguera, D. Shibata, K. Forrester, J. Martin, N. Arnheim, M. Perucho, Most human carcinomas of the exocrine pancreas contain mutant cK-ras genes, Cell 53 (1988) 549–554.
9. Y. Miyamoto, A. Maitra, B. Ghosh, U. Zechner, P. Argani, C.A. IacobuzioDonahue, V. Sriuranpong, T. Iso, I.M. Meszoely, M.S. Wolfe, R.H. Hruban, D. U. Hani et al. Journal of Drug Delivery Science and Technology 63 (2021) 102539 16 W. Ball, R.M. Schmid, S.D. Leach, Notch mediates TGFα-induced changes in epithelial differentiation during pancreatic tumorigenesis, Canc. Cell 3 (2003) 565–576.
10. J. Zinczuk, ´ K. Zaręba, K. Guzinska-Ustymowicz, ´ B. Kędra, A. Kemona, A. Pryczynicz, p16, p21, and p53 proteins play an important role in development of pancreatic intraepithelial neoplastic, Ir. J. Med. Sci. 187 (2018) 629–637.
11. J.Z. Xu, W.Q. Wang, W.H. Zhang, H.X. Xu, H.L. Gao, S.R. Zhang, C.T. Wu, S. Li, H. Li, J. Xu, X.J. Yu, L. Liu, The loss of SMAD4/DPC4 expression associated with a strongly activated hedgehog signaling pathway predicts poor prognosis in resected pancreatic cancer, J. Canc. 10 (2019) 4123.
12. J.B. Fagman, D. Ljungman, P. Falk, B.M. Iresjo, ¨ C. Engstrom, ¨ P. Naredi, K. Lundholmet, EGFR, but not COX-2, protein in resected pancreatic ductal adenocarcinoma is associated with poor survival, Oncol. Lett. 17 (2019) 5361–5368.
13. D. Murthy, K.S. Attri, P.K. Singh, Phosphoinositide 3-kinase signaling pathway in pancreatic ductal adenocarcinoma progression, pathogenesis, and therapeutics, Front. Physiol. 9 (2018) 335.
14. Y. Bai, Y. Bai, J. Dong, Q. Li, Y. Jin, B. Chen, M. Zhou, Hedgehog signaling in pancreatic fibrosis and cancer, Medicine 95 (2016).

15. F.H. Sarkar, S. Banerjee, Y. Li, Pancreatic cancer: pathogenesis, prevention and treatment, Toxicol. Appl. Pharmacol. 224 (2007) 326–336.
16. I. Kuzmickiene, R. Everatt, D. Virviciute, A. Tamosiunas, R. Radisauskas, R. Reklaitiene, E. Milinaviciene, Smoking and other risk factors for pancreatic cancer: a cohort study in men in Lithuania, Cancer Epidemiol. 37 (2013) 133–139.
17. M. Xu, X. Jung, O.J. Hines, G. Eibl, Y. Chen, Obesity and pancreatic cancer: overview of epidemiology and potential prevention by weight loss, Pancreas 47 (2018) 158.
18. P.Y. Lu, L. Shu, S.-S. Shen, X.-J. Chen, X.-Y. Zhang, Dietary patterns and pancreatic cancer risk: a meta-analysis, Nutrients 9 (2017) 38.
19. D.S. Michaud, A. Vrieling, L. Jiao, J.B. Mendelsohn, E. Steplowski, S.M. Lynch, J. Wactawski-Wende, A.A. Arslan, H.B. Bueno-de-Mesquita, C.S. Fuchs, Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan), Cancer Causes Control 21 (2010) 1213–1225.
20. I.A. Ojajarvi, ¨ T.J. Partanen, A. Ahlbom, P. Boffetta, T. Hakulinen, N. Jourenkova, T.P. Kauppinen, M. Kogevinas, M. Porta, H.U. Vainio, E. Weiderpass, C. H. Wesseling, Occupational exposures and pancreatic cancer: a meta-analysis, Occup. Environ. Med. 57 (2000) 316–324.
21. N. Howlader, A.M. Noone, M. Krapcho, D. Miller, A. Brest, M. Yu, J. Ruhl, Z. Tatalovich, A. Mariotto, D.R. Lewis, H.S. Chen, E.J. Feuer, K.A. Cronin, SEER Cancer Statistics Review 1975-2015 4, National Cancer Institute, Bethesda, MD, 2018, p. 2016.
22. D.K. Andersen, M. Korc, G.M. Petersen, G. Eibl, D. Li, M.R. Rickels, S.T. Chari, J. L. Abbruzzese, Diabetes, pancreatogenic diabetes, and pancreatic cancer, Diabetes 66 (2017) 1103–1110.
23. S.H. Olson, R.C. Kurtz, Epidemiology of pancreatic cancer and the role of family history, J. Surg. Oncol. 107 (2013) 1–7.
24. R.A. Osmani, P.K. Kulkarni, D.V. Gowda, U. Hani, V.K. Gupta, M. Prerana, C. Saha, Cyclodextrin-based nanosponges in drug delivery and cancer therapeutics: new perspectives for old problems, in: Applications of Nanocomposite Materials in Drug Delivery, Woodhead Publishing, 2018, pp. 97–147.
25. R.A.Osmani, U. Hani, R.R. Bhosale, P.K. Kulkarni, S. Shanmuganathan, Nanosponge carriers- an archetype swing in cancer therapy: a comprehensive review, Curr. Drug Targets 18 (2017) 108–118. [26] M. Ghosn, T. Ibrahim, T. Assi, E. El Rassy, H.R. Kourie, J. Kattan, Dilemma of first line regimens in metastatic pancreatic adenocarcinoma, World J. Gastroenterol. 22 (2016) 10124.
26. T.J. Hobday, R. Qin, D. Reidy-Lagunes, M.J. Moore, J. Strosberg, A. Kaubisch, et al., Multicenter phase II trial of temsirolimus and bevacizumab in pancreatic neuroendocrine tumors, J. Clin. Oncol. 33 (2015) 1551.
27. R.R. Bhosale, H.V. Gangadharappa, D.V. Gowda, R.A. Osmani, R. Vaghela, P. K. Kulkarni, K.V. Sairam, B. Gurupadayya, Current perspectives on novel drug carrier systems and therapies for management of pancreatic cancer: an updated inclusive review, Crit. Rev. Ther. Drug Carrier Syst. 35 (2018).
28. F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 68 (2018) 394–424
29. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 2009; 6: 699–708.
30. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004; 64: 2634–38.
31. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifi es variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet 2009; 41: 986–90.
32. Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst 2009; 101: 424–31.
33. Ojajärvi IA, Partanen TJ, Ahlbom A, et al. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med 2000; 57: 316–24.
34. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies aff ect risk of pancreatic cancer. Gastroenterology 2009; 137: 482–88.
35. Blackford A, Parmigiani G, Kensler TW, et al. Genetic mutations associated with cigarette smoking in pancreatic cancer. Cancer Res 2009; 69: 3681–88.
36. Grover S, Stoff el EM, Bussone L, Syngal S. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004; 2: 813–19.
37. Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol 2007; 25: 1417–22.
38. Vedat Goral, Pancreatic Cancer: Pathogenesis and Diagnosis, Asian Pacific Journal of Cancer Prevention, Vol 16, 2015;5619-5624

39. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, Nio Y, Schulick RS, Bassi C, Kluijt I, Levy MJ, Chak A, Fockens P, Goggins M, Bruno M; Consortium. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013; 62: 339-347 [PMID: 23135763 DOI: 10.1136/ gutjnl-2012-303108]
40. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011; 378: 607-620 [PMID: 21620466 DOI: 10.1016/S0140-6736(10)62307-0
41. Unger K, Mehta KY, Kaur P, Wang Y, Menon SS, Jain SK, Moonjelly RA, Suman S, Datta K, Singh R, Fogel P, Cheema AK. Metabolomics based predictive classifier for early detection of pancreatic ductal adenocarcinoma. Oncotarget 2018; 9: 23078-23090 [PMID: 29796173 DOI: 10.18632/oncotarget.25212]
42. Poley JW, Kluijt I, Gouma DJ, Harinck F, Wagner A, Aalfs C, van Eijck CH, Cats A, Kuipers EJ, Nio Y, Fockens P, Bruno MJ. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. Am J Gastroenterol 2009; 104: 2175-2181 [PMID: 19491823 DOI: 10.1038/ajg.2009.276]
43. Zamboni G, Hirabayashi K, Castelli P, Lennon AM. Precancerous lesions of the pancreas. Best Pract Res Clin Gastroenterol 2013; 27: 299-322 [PMID: 23809247 DOI: 10.1016/j.bpg.2013.04.001]
44. Lu C, Xu CF, Wan XY, Zhu HT, Yu CH, Li YM. Screening for pancreatic cancer in familial high-risk individuals: A systematic review. World J Gastroenterol 2015; 21: 8678-8686 [PMID: 26229410 DOI: 10.3748/wjg.v21.i28.8678]
45. Mills K, Birt L, Emery JD, Hall N, Banks J, Johnson M, Lancaster J, Hamilton W, Rubin GP, Walter FM. Understanding symptom appraisal and help-seeking in people with symptoms suggestive of pancreatic cancer: a qualitative study. BMJ Open 2017; 7: e015682 [PMID: 28871013 DOI: 10.1136/bmjopen-2016-015682]
46. Keane MG, Horsfall L, Rait G, Pereira SP. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. BMJ Open 2014; 4: e005720 [PMID: 25410605 DOI: 10.1136/bmjopen-2014-005720]
47. Xu J, Cao Z, Liu W, You L, Zhou L, Wang C, Lou W, Sun B, Miao Y, Liu X, Zhang T, Zhao Y. Plasma miRNAs Effectively Distinguish Patients With Pancreatic Cancer From Controls: A Multicenter Study. Ann Surg 2016; 263: 1173-1179 [PMID: 26114496 DOI: 10.1097/SLA.0000000000001345]
48. Kim JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. J Gastroenterol Hepatol 2004; 19: 182-186 [PMID: 14731128 DOI: 10.1111/ j.1440-1746.2004.03219.x]
49. Fahrmann JF, Bantis LE, Capello M, Scelo G, Dennison JB, Patel N, Murage E, etal. A Plasma-Derived Protein-Metabolite Multiplexed Panel for Early-Stage Pancreatic Cancer. J Natl Cancer Inst 2018 [PMID: 30137376 DOI: 10.1093/jnci/djy126]
50. Mayerle J, Kalthoff H, Reszka R, Kamlage B, Peter E, Schniewind B, González Maldonado S, Pilarsky C, Heidecke CD, Schatz P, Distler M, Scheiber JA, Mahajan UM, Weiss FU, Grützmann R, Lerch MM. Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis. Gut 2018; 67: 128-137 [PMID: 28108468 DOI: 10.1136/ gutjnl-2016-312432]
51. Riva F, Dronov OI, Khomenko DI, Huguet F, Louvet C, Mariani P, Stern MH, Lantz O, Proudhon C, Pierga JY, Bidard FC. Clinical applications of circulating tumor DNA and circulating tumor cells in pancreatic cancer. Mol Oncol 2016; 10: 481-493 [PMID: 26856794 DOI: 10.1016/j.molonc.2016.01.006]
52. Princivalle A, Monasta L, Butturini G, Bassi C, Perbellini L. Pancreatic ductal adenocarcinoma can be detected by analysis of volatile organic compounds (VOCs) in alveolar air. BMC Cancer 2018; 18: 529 [PMID: 29728093 DOI: 10.1186/ s12885-018-4452-0]
53. Kanda M, Sadakari Y, Borges M, Topazian M, Farrell J, Syngal S, Lee J, Kamel I, Lennon AM, Knight S, Fujiwara S, Hruban RH, Canto MI, Goggins M. Mutant TP53 in duodenal samples of pancreatic juice from patients with pancreatic cancer or high-grade dysplasia. Clin Gastroenterol Hepatol 2013; 11: 719-30.e5 [PMID: 23200980 DOI: 10.1016/j.cgh.2012.11.016]
54. Zhou B, Xu JW, Cheng YG, Gao JY, Hu SY, Wang L, Zhan HX. Early detection of pancreatic cancer: Where are we now and where are we going? Int J Cancer 2017; 141: 231-241 [PMID: 28240774 DOI: 10.1002/ijc.30670]
55. Lynch SM, Vrieling A, Lubin JH, Kraft P, etal. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009; 170: 403-413 [PMID: 19561064 DOI: 10.1093/aje/kwp134]
56. Demir IE, Jäger C, Schlitter AM, Konukiewitz B, Stecher L, Schorn S, Tieftrunk E, Scheufele F, Calavrezos L, Schirren R, Esposito I, Weichert W, Friess H, Ceyhan GO. R0 Versus R1 Resection Matters after Pancreaticoduodenectomy, and Less after Distal or Total Pancreatectomy for Pancreatic Cancer. Ann Surg 2017 [PMID: 28692477 DOI: 10.1097/SLA.0000000000002345]

57. Kim KS, Kwon J, Kim K, Chie EK. Impact of Resection Margin Distance on Survival of Pancreatic Cancer: A Systematic Review and Meta-Analysis. Cancer Res Treat 2017; 49: 824-833 [PMID: 27561314 DOI: 10.4143/crt.2016.336]
58. Blamey SL, Fearon KC, Gilmour WH, Osborne DH, Carter DC. Prediction of risk in biliary surgery. Br J Surg 1983; 70: 535-538 [PMID: 6616158 DOI: 10.1002/bjs.1800700910]
59. Wang Q, Gurusamy KS, Lin H, Xie X, Wang C. Preoperative biliary drainage for obstructive jaundice. Cochrane Database Syst Rev 2008; CD005444 [PMID: 18677779 DOI: 10.1002/14651858. CD005444.pub2]
60. Van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010; 362: 129-137 [PMID: 20071702 DOI: 10.1056/NEJMoa0903230]
61. 6Hua J, He Z, Qian D, Meng H, Zhou B, Song Z. Duct-toMucosa Versus Invagination Pancreaticojejunostomy Following Pancreaticoduodenectomy: a Systematic Review and Meta Analysis. J Gastrointest Surg 2015; 19: 1900-1909 [PMID: 26264363 DOI: 10.1007/s11605-015-2913-1]
62. Cheng Y, Briarava M, Lai M, Wang X, Tu B, Cheng N, Gong J, Yuan Y, Pilati P, Mocellin S. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction for the prevention of postoperative pancreatic fistula following pancreaticoduodenectomy. Cochrane Database Syst Rev 2017; 9: CD012257 [PMID: 28898386 DOI: 10.1002/14651858.CD012257.pub2]
63. Venkat R, Edil BH, Schulick RD, Lidor AO, Makary MA, Wolfgang CL. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. Ann Surg 2012; 255: 1048-1059 [PMID: 22511003 DOI: 10.1097/ SLA.0b013e318251ee09]
64. Pericleous S, Middleton N, McKay SC, Bowers KA, Hutchins RR. Systematic review and meta-analysis of case-matched studies comparing open and laparoscopic distal pancreatectomy: is it a safe procedure? Pancreas 2012; 41: 993-1000 [PMID: 22836858
65. Zhang J, Wu WM, You L, Zhao YP. Robotic versus open pancreatectomy: a systematic review and meta-analysis. Ann Surg Oncol 2013; 20: 1774-80 [PMID:23504140 DOI: 10.1245/ s10434-012-2823-3]
66. Buchs NC, Chilcott M, Poletti PA, Buhler LH, Morel P. Vascular invasion in pancreatic cancer: Imaging modalities, preoperative diagnosis and surgical management. World J Gastroenterol 2010; 16: 818-831 [PMID: 20143460]
67. Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J. Arterial resection during pancreatectomy for pancreatic cancer. Ann Surg 2011; 254: 882-93 [PMID: 22064622 DOI: 10.1097/SLA.0b013e31823ac299]
68. Yu XZ, Li J, Fu DL, Di Y, Yang F, Hao SJ, Jin C. Benefit from synchronous portal-superior mesenteric vein resection during pancreaticoduodenectomy for cancer: a meta-analysis. Eur J Surg Oncol 2014; 40: 371-378 [PMID: 24560302 DOI: 10.1016/ j.ejso.2014.01.010]
69. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013; 310: 1473-1481 [PMID: 24104372 DOI: 10.1001/ jama.2013.279201]
70. Neoptolemos JP, Stocken DD, Bassi C, etal. European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010; 304: 1073-1081 [PMID: 20823433 DOI: 10.1001/jama.2010.1275]
71. Neoptolemos JP, Palmer DH, etal; European Study Group for Pancreatic Cancer. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017; 389: 1011-1024 [PMID: 28129987 DOI: 10.1016/ S0140-6736(16)32409-6]
72. . Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, Chone L, Francois E, Artru P, Biagi JJ, Lecomte T, Assenat E, Faroux R, Ychou M, Volet J, Sauvanet A, JouffroyZeller C, Rat P, Castan F, Bachet JB. A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. J Clin Oncol 2018; 36: LBA4001-LBA4001 [DOI: 10.1200/JCO.2018.36.18_suppl.LBA4001]
73. Ghosn M, Kourie HR, El Rassy E, Haddad FG, Hanna C, El Karak F, Nasr D. Where does chemotherapy stands in the treatment of ampullary carcinoma? A review of literature. World J Gastrointest Oncol 2016; 8: 745-750 [PMID: 27795814 DOI: 10.4251/wjgo. v8.i10.745]
74. Altorki N, Harrison S. What is the role of neoadjuvant chemotherapy, radiation, and adjuvant treatment in resectable esophageal cancer? Ann Cardiothorac Surg 2017; 6: 167-174 [PMID: 28447006 DOI: 10.21037/acs.2017.03.16]

75. Labori KJ, Lassen K, Hoem D, Grønbech JE, Søreide JA, Mortensen K, Smaaland R, Sorbye H, Verbeke C, Dueland S. Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial. BMC Surg 2017; 17: 94 DOI: 10.1186/ s12893-017-0291-1]
76. Zhan HX, Xu JW, Wu D, Wu ZY, Wang L, Hu SY, Zhang GY. Neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of prospective studies. Cancer Med 2017; 6: 1201-1219 [PMID: 28544758 DOI: 10.1002/cam4.1071]
77. Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. World J Gastroenterol 2014; 20: 10740-10751 [PMID: 25152577 DOI: 10.3748/wjg.v20.i31.10740]
78. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, van Eijck CHJ, Groot Koerkamp B, Rasch CRN, van Tienhoven G; Dutch Pancreatic Cancer Group. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg 2018; 105: 946-958 [PMID: 29708592 DOI: 10.1002/ bjs.10870]
79. Van Tienhoven G, Versteijne E, Suker M, Groothuis KBC, Busch OR, Bonsing BA, de Hingh IHJT, Festen S, Patijn GA, de VosGeelen J, Zwinderman AH, Punt CJA, van Eijck CHJ. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): A randomized, controlled, multicenter phase III trial. J Clin Oncol 2018; 36: LBA4002-LBA4002 [DOI: 10.1200/JCO.2018.36.18_suppl. LBA4002]
80. Conroy T, Desseigne F, Ychou M, Bouché O, etal; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
81. Mahaseth H, Brutcher E, Kauh J, Hawk N, Kim S, Chen Z, Kooby DA, Maithel SK, Landry J, El-Rayes BF. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas 2013; 42: 1311-1315 [PMID: 24152956 DOI: 10.1097/MPA.0b013e31829e2006]
82. Chu QD, Sun G, Pope M, Luraguiz N, Curiel DT, Kim R, Li BD, Mathis JM. Virotherapy using a novel chimeric oncolytic adenovirus prolongs survival in a human pancreatic cancer xenograft model. Surgery 2012; 152: 441-448 [PMID: 22853858 DOI: 10.1016/j.surg.2012.05.040]