CURRENT AND FUTURE STRATEGIES FOR THERAPY OF PANCREATIC CANCER

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ABSTRACT
Pancreatic cancer is a difficult and unsolved surgical problem pancreatic cancer is the fourth leading cause of cancer mortality in both men and women. Surgical resection is the only potential curative treatment. The median survival of this disease is between three and four months for untreated patients. However, in spite of treatment, less than 5% of patients are alive for five years. Because clinical symptoms are usually absent or aseptic in the early stage, it is frequently discovered at advanced or metastatic stage, only around 15–20% of tumors are resectable. In the majority of patients the chemotherapy offers a prolongation of life. Combination of various cytostatics did not produce a significant improvement either. For that reason, continuous search for other agents is mandatory. Nowadays, in the era of molecular-targeted oncotherapeutic approaches, pancreatic cancer is also a subject of trials such as: epidermal growth factor receptor blockade (EGFR), inhibition of angiogenesis, modulation of tumor response through the extracellular matrix, inhibition of cyclooxygenase-2, fernery transferees inhibitors, signal transduction inhibitors, ablation of the hormonal impudence and some other aspects have all been studied, but to date, no breakthrough in the treatment of pancreatic carcinoma is proven. Trials on adjuvant and neo-adjuvant therapy of pancreatic cancer are also ongoing. This review presents the recent developments with newer chemotherapeutic and molecular-targeted agents, identifying the efforts for individualized treatment strategies. The ability to predict which patients would benefit most from surgical intervention and/or chemotherapy would be a great clinical asset.

Keywords: Pancreatitis, diagnosis, Targeted therapies.

INTRODUCTION
Pancreatic cancer (PC) is a devastating disease. As a whole, every patient diagnosed with a PC will die within 12 months, including the vast majority of those that underwent a potential curative surgery. Pancreatic cancer is the fourth most common cause of adult cancer death, accounting for an estimated 37,680 new cases and 34,290 deaths in USA for 2008. The high mortality rate is due to the high incidence of metastatic disease at initial diagnosis, the aggressive clinical course and the failure of systemic therapies. In only 5–25% of the patients presenting with pancreatic cancer will the tumor be operable. The median disease-free survival following complete resection of pancreatic cancer and adjuvant administration of gemcitabine is 13.4 months and 6.9 months for untreated patients. However, the longer disease-free survival has not translated in any advantage in overall survival. In addition, the median survival in locally advanced disease (40% of the patients at diagnosis) is 8–12 months and 3–6 months for those patients presenting with metastatic disease (40–45%). The administration of cytotoxic agents for the treatment of advanced disease has had...
disappointing results and currently, research focuses on the understanding of molecular pathways in order to evaluate the role of targeted therapy, while trials on combinations of newer chemotherapeutic drugs in metastatic disease and adjuvant therapy of pancreatic cancer are ongoing.

Symptoms
- Pain in the upper abdomen from the tumor pushing against nerves
- A painless yellowing of the skin and eyes and darkening of the urine called jaundice, created when the cancer interferes with the bile duct and the liver.
- Loss of appetite, nausea, and vomiting
- Significant weight loss and weakness
- Alcoholic stool (pale or grey stool) and steatorrhea (excess fat in stool) [6,7]
- Signs and symptoms of pancreatic cancer often don’t occur in initial stages and are observed only after the disease has progressed. When signs and symptoms do appear, they may include: upper abdominal pain that may radiate to back, yellowing of skin and the whites of eyes (jaundice), loss of appetite, weight loss and depression.

Causes
Pancreatic cancer occurs when cells of pancreas develop genetic mutations. These mutations cause the cells to grow uncontrollably and to continue living after normal cells would die. These accumulating cells can form a tumor. Factors that may increase the risk of pancreatic cancer include: smoking, being overweight or obese, personal or family history of chronic inflammation of the pancreas (pancreatitis), personal or family history of pancreatic cancer, family history of genetic syndromes that can increase cancer risk, including a BRCA2 gene mutation, peutz-Jeghers syndrome, Lynch syndrome and familial atypical mole-malignant melanoma (FAMMM), older age [8]

Risk factors
Exocrine pancreas includes
Familial atypical mole-multiple melanoma (FAMMM) [9]
- Melanoma-pancreatic cancer syndrome
- Peutz-Jeghers syndrome (PJS) [10]
- Familial/hereditary pancreatitis [11]
- Cystic fibrosis (CF) [12]
- Lynch syndrome (human non-polyposis colorectal cancer) [13]
- Familial breast-ovarian cancer [14]
- Li-Fraumeni syndrome [15]
- Familial adenomatous polyposis (FAP) [16]

Endocrine pancreas includes
- Multiple endocrine neoplasia (MEN) [17]
- Von Hippel-Lindau syndrome (VHL) [18]

Other possible risk factors
- Diabetes [19]
- Pancreatitis [20]
- Nutrition [21]
- Smoking habit and alcohol and coffee drinking

Diagnosis

CT SCAN
Computerized tomography (CT) has become the imaging modality of choice for the evaluation of pancreatic disease. Freeny et al. initially evaluated the diagnosis and staging of pancreatic ductal adenocarcinoma with dynamic CT imaging in 1988 and found it to be superior to standard imaging studies in assessing respectability [22]. Furthermore, the development of helical or spiral CT in 1989 has resulted in dramatic refinements in CT technology, and has further enhanced our abilities to accurately assess the respectability of pancreatic cancer. With spiral CT technology, the patient undergoes continuous scanning of complete organs within the same breath hold. The acquisition time is 24 s thus limiting radiation exposure as well as intravenous contrast material [23]. Spiral CT allows the pancreas to be imaged during the phase of maximal vascular enhancement of the pancreatic parenchyma and adjacent vasculature providing extremely high quality images with a single breath hold [24,25].

MAGNETIC RESONANCE IMAGING (MRI)
Magnetic resonance imaging of the pancreas has developed over the last 1.5 years into an effective and powerful imaging modality for the evaluation of pancreatic disorders [26]. The signal intensity of tumors is variable on TZ-weighting relative to the normal pancreas sometimes making detection difficult [27]. The normal pancreas enhances rapidly and intensely on dynamic gadolinium-enhanced images leaving a hypo intense tumor visible [28,29]. 189 patients with pancreatic adenocarcinoma in terms of prediction of respectability, vascular invasion, nodal metastasis and liver metastasis [30].

POSITRON EMISSION TOMOGRAPHY (PET)
Recent technological advances have allowed positron emission tomography (PET) with labeled fluorodeoxyglucose (FDG) to become an established noninvasive imaging method
for the early detection and diagnosis of various malignancies\textsuperscript{[31]}. PET imaging with FDG has shown a very high sensitivity in the detection of pancreatic cancer. Recently showed that PET imaging correctly identified 12 patients as having pancreatic cancer who had indeterminate mass lesions on CT scan \textsuperscript{[32]}. There are many conflicting reports as to the utility of FDG-PET in the identification and localization of regional lymph node metastases and small liver metastases\textsuperscript{[33,34]}

**ENDOSCOPIC ULTRASOUND (EUS)**

Endoscopic ultrasonography (EUS) has a well established utility in staging gastric cancer and is currently being applied for the preoperative diagnosis and staging assessment of pancreatic carcinoma. An endoscope with an ultrasound probe is placed into the duodenum, and as a result of its close proximity to the pancreas EUS is able to produce great detail of the pancreatic parenchyma and regional lymph nodes. It is especially sensitive in the detection of small pancreatic masses which cannot be imaged with other modalities. EUS has the additional advantage of directing transduodenal fine-needle aspiration biopsies\textsuperscript{[35]}. The overall positive predictive value was 83\% for EUS, 100\% for US, and 89\% for CT. The negative predictive values were 100\%, 41\%, and 63\%, respectively, and the overall accuracy was 87\%, 47\%, and 76\%. Yasuda et al. compared EUS to US and CT in the local staging of patients with pancreatic adenocarcinoma\textsuperscript{[36]}

**LAPAROSCOPY**

Diagnostic laparoscopy has developed over the last 10 years into an established method in the preoperative assessment and staging of many solid tumor malignancies. Its main advantage lies in the detection of small (\textless{} 1 cm) liver metastasis and peritoneal implants of tumor which cannot be visualized by any other modality. It also provides the means to biopsy suspicious areas (including peripancreatic lymph nodes) under direct vision and can assess local invasion of the primary tumor. The value of minimal access surgery in the staging of patients with potentially resectable per pancreatic malignancies was recently evaluated by Conlon\textsuperscript{[37]}

**FINE-NEEDLE ASPIRATION CYTOLOGY**

Percutaneous fine-needle aspiration (FNA) biopsy of the pancreas is a safe and effective technique for the diagnosis of pancreatic cancer\textsuperscript{[38]}. Early experience with FNA of pancreatic masses yielded a false negative rate of up to 36\% with an overall accuracy of 87-100\%\textsuperscript{[39]}

**ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) AND BRUSH CYTOLOGY**

Endoscopic retrograde cholangiopancreatography (ERCP) in combination with ductal brush cytology is an established technique for the diagnosis of pancreaticobiliary malignancies\textsuperscript{[40]}. Layfield et al. examined 108 pancreatic and biliary duct brushings and found a diagnostic sensitivity for carcinoma of 44\% with a specificity of 98\%\textsuperscript{[41]}. These results are similar to that of nine related studies on the accuracy of pancreatic and biliary duct cytology with a sensitivity ranging from 33\%-85\% and a specificity of 83-100\%. Several reports suggest that brush cytology is more sensitive in the diagnosis of pancreatic cancer compared to bile cytology\textsuperscript{[42,43]}

**CARBOHYDRATE ANTIGEN 19-9 (CA 19-9)**

CA 19-9 is a mucin-type glycoprotein expressed on the surface of pancreatic cancer cells first discovered in the early 1980s. The majority of patients with pancreatic cancer have been found to have increased serum levels of CA 19-9. One of the first studies by Fariniet al. Demonstrated that a CA 19-9 value greater than 17 U/ml had a sensitivity of 86\%, a specificity of 62\%, and an overall accuracy of 49\% for the diagnosis of pancreatic cancer\textsuperscript{[44]}

**SCREENING FOR MUTATED RAS ONCOGENE**

The most common gene abnormality in patients with pancreatic cancer is the K-ras gene mutation. Numerous studies have evaluated this mutation at codon 12, and its estimated prevalence in pancreatic adenocarcinoma ranges from 70-90\% \textsuperscript{[45,46]}. The K-ras gene encodes a 21-kD guanosine triphosphatase protein involved in cellular signal transduction; specifically tyrosine kinase mediated signals important in the regulation of cell proliferation and differentiation\textsuperscript{[47]}

**SCREENING FOR MUTATED p53 ONCOGENE**

Mutations of the p53 tumor suppressor gene are the most common genetic alterations identified in human neoplasia with germline mutations contributing to the development of a variety of cancers in the Li-Fraumeni cancer family syndrome. The p53 gene has been shown to have multiple cellular functions, playing a major role in the inhibition of oncogeneinduced cell transformation. It is
important in blocking the progression of the cell cycle through the G1-phase and thereby induces apoptosis in damaged cells. Mutations of this 53 kD DNA binding protein can result in the permanent loss of the negative regulatory process of cell growth and proliferation. Mutated p53 proteins are over expressed in cells. Over expression of the gene leads to persistently high steady state levels, which unlike the wild type protein, is readily detectable by immuno-histochemical staining.

Treatment of Pancreatic Cancer
Treatment for pancreatic cancer depends on the stage and location of the cancer as well as on age, overall health and personal preferences. The first goal of pancreatic cancer treatment is to eliminate the cancer, when possible. When that isn’t an option, the focus may be on preventing the pancreatic cancer from rowing or causing more harm.

Surgery
Only a small portion of pancreatic cancers are considered respectable - that is, hey have a good chance of being removed completely with surgery. Once the cancer has spread beyond the pancreas to other organs, lymph nodes or blood easels, surgery is usually no longer an option.

Radiation therapy
Radiation therapy uses high-energy beams to destroy cancer cells. One may deceive radiation treatments before or after cancer surgery, often in combination it chemotherapy. Or, sometimes it is recommended as a combination of radiation chemotherapy treatments when cancer can’t be treated surgically. Radiation therapy can come from a machine outside the body (external beam radiation), or it can be placed inside the body near the cancer (brachytherapy). Radiation therapy can also be used during surgery (intraoperative radiation).

Chemotherapy for metastatic disease
The goal of systemic chemotherapy is to minimize the patients’ disease-related symptoms and to prolong survival. 5-Fluorouracil (5-FU) combinations compared with no chemotherapy or best supportive care provided a survival advantage [33 weeks for the treated group compared with 15 weeks in the untreated group (P < 0.002)] for pancreatic cancer patients, but a meta-analysis demonstrated no survival benefit among 5-FU combinations and 5-FU alone. Data for 5365 patients from 43 randomized controlled trials were included in this meta-analysis. Survival benefit over best supportive care was demonstrated in 5-FU-based chemotherapy in 9 randomized trials. However, trials comparing 5-FU alone vs. 5-FU-based combinations did not show any statistical differences, nor did various 5-FU combinations compared among themselves.

Adjuvant therapy
Adjuvant chemo radiation
Brief review of adjuvant therapy is included as it impacts the rationale for neoadjuvant therapy. The first trial of adjuvant therapy for pancreatic cancer was a study conducted by the Gastrointestinal Tumor Study Group (GITSG).

Adjuvant chemotherapy
The more recent European Study Group for Pancreatic Cancer (ESPAC-1) trial demonstrated a survival benefit with the use of 6 months of bolus fluorouracil (FU) with leucovorin chemotherapy for resected pancreatic cancer, but rather surprisingly an inferior survival in patients who received radiation with concurrent chemotherapy.

Potential reasons for this reduced survival have been proposed including the radiotherapy techniques which involved low doses to large volume fields, possibly reducing the chance of tumor control and increasing the risk of late toxicity.

Rationale for neoadjuvant therapy
Although by definition neoadjuvant therapy is intended to be delivered to patients with resectable disease, patients with unresectable disease have been included in several series of ‘neoadjuvant therapy’ in pancreatic cancer, as there is motivation to change patients from an unresectable state to resectable, with the hope that their prognosis will improve. Neoadjuvant therapy has some theoretical advantages and disadvantages when compared to adjuvant therapy in pancreatic tumors. First, more patients will be able to receive full-dose chemotherapy and radiotherapy if treatment is given prior to surgery. In the context of post-operative treatment, up to 20–30% of patients are unable to complete the course of adjuvant treatment usually because of protracted recovery periods after surgery.

Unresectable or borderline resectable pancreatic Cancer
Locally advanced disease
Locally advanced disease is defined as unresectable disease but without evidence of distant metastases. Patients who only undergo palliative gastric or biliary bypass have a
median survival of only 3–6 months the use of chemoradiation treatment has been demonstrated to be superior to single modality chemotherapy or radiotherapy treatment in a number of trials and can improve median survival rates to 9–11 months, but the chance of longer-term survival remains very low.

Tumor downstaging
The interest in ‘neoadjuvant’ therapy for locally advanced disease comes from the poor outcome of these patients and the potential for longer-term survival if the disease can be resected. In this setting downstaging is the primary goal and so combinations of both radiotherapy and chemotherapy are used. Doses of radiotherapy that can be administered to the upper abdomen is limited by normal tissue tolerance of structures surrounding the pancreas (for example, spinal cord, duodenum, bowel, kidney). Therefore doses given are typically no higher than the range of 45–60 Gy. Pilepich et al. first reported on the use of radiotherapy alone to allow sufficient downstaging of tumors to allow resection in patients with initial locally advanced disease on presentation. Seventeen patients were administered 40–50 Gy radiotherapy alone. Five patients had radiographic response and six were able to have resection. None of the patients had a complete response and the overall median survival was only 8 months. White et al. from Duke University reports on 25 patients who received 45–50.4 Gy radiotherapy (1.8 Gy/fraction, 5 days a week) with 5-FU. Some also received cisplatin or mitomycin or a combination. Eight patients proceed to surgery after chemoradiation, five were able to have resection although only one patient had complete resection with negative margins and lymph nodes.

Borderline resectable disease
The definition for resectable disease has been discussed but there has been a recent proposal by Varadhachary et al. to define the category of borderline-resectable pancreatic carcinoma and determine optimal management for this group. They define borderline resectability as encasement of a short segment of the hepatic artery without evidence of tumor extension to the celiac axis, tumor abutment of the superior mesenteric artery involving less than 180° of the artery circumference and short-segment occlusion of the superior mesenteric vein/portal vein confluence beneath the neck of the pancreas. As prognosis for resection margin-positive

Targeted therapies
VEGF inhibitors
Recent developments in molecular therapy have opened up many potential new treatments for pancreatic carcinoma. Vascular endothelial growth factor (VEGF) and its receptors are expressed in pancreatic cancer and play an important role in the growth and dissemination of the cancer. It is known to stimulate cell growth in pancreatic cancer cell lines and in animal models, inhibitors of the VEGF tyrosine kinase (and anti-VEGF antibodies) inhibit growth and angiogenesis associated with pancreatic cancer cells. Bevacizumab (Avastin, Genentech, San Francisco, CA) is a recombinant humanized anti-VEGF monoclonal antibody which has been investigated in a number of trials for treatment of advanced (metastatic) pancreatic carcinoma. Kindler et al. report on a phase II trial where 52 patients with untreated advanced pancreatic cancer were given gemcitabine (1000 mg/m2 i.v. days 1, 8, 15 every 28 days) with bevacizumab (10 mg/kg days 1 and 15). Eleven (21%) patients had PR and 24 (46%) had SD. Six-month survival was 77%, 1-year survival 29%, median survival 8.8 months and median PFS 5.4 months. However it was recently reported that the phase III study of gemcitabine±bevacizumab did not show a survival benefit in advanced disease.

EGFR inhibitors
Pancreatic cancers frequently over express epidermal growth factor (EGFR)—this is thought to lead to activation of its downstream signaling molecules with eventual change in proliferation, angiogenesis, apoptosis and the potential for metastasis. Erlotinib (Tarceva, Genentech, San Francisco, CA) is an oral reversible inhibitor of EGFR tyrosine kinase. A recent randomized study of gemcitabine±erlotinib in advanced disease revealed a significant survival and progression free survival benefit in favour of the erlotinib arm.

New agents
Gemcitabine is considered to be the most active agent in the treatment of metastatic pancreatic cancer. Although most studies have used gemcitabine combinations with rather disappointing results, studies have also begun to evaluate the role of new agents in the treatment of metastatic pancreatic cancer. In addition, advances in the treatment of
metastatic pancreatic cancer might be achieved by investigating strategies of matching each individual's cancer with the most effective available drugs. A novel micellar formulation of paclitaxel in a low molecular weight biodegradable synthetic polymer has been developed. The substitution of cremophor EL by bioabsorbable polymer results in higher maximally tolerated dose and lower toxicity. In a phase II study, 56 chemotherapy-naive pancreatic cancer patients were treated with 3 h infusion of the new formulation of paclitaxel at a dose of 300–435 mg/m² every 21 days. The overall response rate was 6.7%, the median time to progression was 3 months and the median overall survival was 6.2 months. The most common grade 3 toxicities were neutropenia (18%), fatigue (18%), infection (13%) and peripheral sensory neuropathy (11%). These results suggest that the new formulation of paclitaxel was well tolerated and resulted in progression-free survival similar to that seen historically with gemcitabine. Telomerase is expressed in 85–90% of pancreatic cancer and immunogenic telomerase peptides have been characterised. A phase I/II study was conducted to investigate the safety, tolerability, and immunogenecity of telomerase peptide vaccination. Survival of the patients was also recorded. Forty-eight patients with non-resectable pancreatic cancer received intradermal injections of the telomerase peptide GV1001 at three dose levels, in combination with granulocyte–macrophage colony-stimulating factor. The treatment period was 10 weeks. Monthly booster vaccinations were offered as follow-up treatment. The vaccine was well tolerated and 1-year survival for the evaluable patients in the intermediate dose group was 25%. These data indicate that induction of an immune response is correlated with prolonged survival, and the vaccine may offer a new treatment option for pancreatic cancer patients, encouraging further clinical studies. Also, the identification of new targets will hopefully provide with promising strategies for individualized treatment. Such a new target is S100P, which has been found to be overexpressed in pancreatic, lung and breast cancer. The overexpression leads to tumour growth and metastasis and high levels of S100P has shown resistance to cytotoxic drugs in vitro and gemcitabine in vivo. Cromolyn binds S100P and increases chemosensitivity of gemcitabine in experimental models. Additionally, preclinical testing has shown that patients with BRCA-2 germline mutations are sensitive to mitomycin-C and this is being tested in pancreatic cancer patients (7% are associated) Finally, studies have shown that the overexpression of a gemcitabine transporter in pancreatic cancer cells (hENT-1, human equilibrative nucleoside transporter 1) is associated with longer overall survival in patients treated with gemcitabine.

INHIBITION OF ANGIogenesis

Angiogenesis is a critical step in the development, progression and metastasis formation of malignant tumors, thus, control of new vessel formation could be another approach to the management of pancreatic carcinoma. High expression of VEGF (vascular endothelial growth factor) is also a predictor of early recurrence after surgery and associated with shorter survival. Based on promising preclinical studies, a recombinant humanized anti-VEGF monoclonal antibody bevacizumab (Avastin) was also tested in patients with pancreatic cancer. Demonstrated beneath of this compound was reported in 2005 in a stage IV patient who had received combined chemotherapy earlier without any improvement. Administration of bevacizumab resulted in a CT-proven objective response in this patient. Adding bevacizumab (10 mg/kg) to gemcitabine, in stage IV pancreatic cancer has also shown promising effects: partial responses were seen in 19% of patients, with a further 48% having stable disease. More potent antitumor response can be achieved through the concomitant inhibition of both the EGFR/ErbB-2 and VEGF receptors. An interesting novel molecule, the AEE788 has such a dual mode of effect: it inhibits both EGFR and VEGF receptor tyrosine kinesis, its ant proliferative activity was demonstrated against EGFR-overexpressing cell lines and VEGF-stimulated human umbilical vein endothelial cells, as well. In orthotopic pancreatic cancer xenograft model AEE788 given in combination with gemcitabine resulted a very strong (nearly 95%) inhibition of tumor growth, an increased apoptotic activity, a decreased micro vessel density, and prolongation of survival of the animals.

EXTRACELLULAR MATRIX AS A TARGET FOR THERAPY

Since the tumor stoma seems to play an important role in the invasiveness of the malignant tumors, novel strategies are being evaluated targeting this component of carcinomas. The matrix metalloproteases (MMPs) consisting of more than 20 family members have a complex effect on the tumor cells: in addition to the extracellular matrix degradation they play an important role in the
initiation process, the growth, migration, invasion, metastasis formation, angiogenesis or selection of apoptosis resistant clones within the cancer. Great number of MMP inhibitors have been synthesized and tested in experimental model systems with variable success, and some of them were investigated in clinical studies. Marimastat, an orally available compound, for example, failed to show any beneficial effect in different (gastric, breast, ovarian, and lung) cancer patients, but promising results were seen in pancreatic cancer.\textsuperscript{77,78}

CYCLOOXYGENASE-2 (COX-2) INHIBITION
Several lines of data suggest that cyclooxygenase (especially COX-2), a key enzyme in the arachidonic acid metabolism, contributes to the growth of pancreatic cancer. Frequent COX-2 overexpression (54–67\%) was found in different cell lines (at mRNA and protein level) and also in human tumors. The expression was up-regulated by EGF. The non-steroidal anti-inflammatory drugs resulted in an inhibition of cell proliferation in vitro at a dose-dependent fashion and induced a marked apoptosis. Clinical studies, however, showed modest and sometimes intriguing effects. Celecoxib (Celebrex), a COX-2 inhibitor, was found to strongly enhance the antitumor efficacy of chemo irradiation in locally advanced pancreatic cancer patients, but it also resulted in a more toxicity of the cytostatic drug (gemcitabine)\textsuperscript{79,80}

FARNESYL TRANSFERASE INHIBITORS
The K-ras proto-oncogene is activated (mutated) in a majority of pancreatic cancer and it contributes to continuous growth. The key enzyme catalyzing the synthesis of ras-protein is the farnesyl transferase, and theoretically, inhibition of this enzyme may have a clinical importance in the treatment of this tumor. Several such molecules have been synthesized and after promising preclinical experiments they were under clinical trials. The most intensively studies compound is the tipifarnib (R11577, Zarnestra), however, the results were disappointing. Administered as mono therapy to advanced or metastatic cancer patients, no objective response was observed, the median time to progression was 4.9 weeks, median survival times were 2.6–5 months, and Grade 3/4 toxicities were seen in more than 50\% of the patients. Another compound (BMS-214662) has also failed to show any objective response, although one patient received it more than 3.5 years.\textsuperscript{81,82}

CONCLUSION
Pancreatic cancer remains a major therapeutic challenge with the majority of patients having advanced disease at the time of diagnosis and consequently a dismal prognosis. Out of all the molecular targets determined EGF receptor has been found to be the most promising and several clinical trials are been carried out to exploit this particular site in order to obtain a potential treatment for pancreatic cancer. Other clinical trials are been carried out with the hope to find a combination that can effectively treat pancreatic cancer. Pancreatic cancer remains a dismal disease with poor prognosis, even after curative resection without nodal involvement or metastasis. Complete surgical resection remains the only option for cure, and the rate of loco regional recurrence makes adjuvant therapy vital.

Fig. 1: This figure was discussed about the pancreatic cell was effected by the cancer and this disease was effected nearly (40-50\%) yearly
Fig. 2: This figure was discussed about the symptoms of pancreatic cancer.

Fig. 3: This figure was discussed about the smoking is one of the causes of pancreatic cancer.

Fig. 4: This figure was discussed about the pancreatic cancer was treated with using radiation therapy.
Fig. 5: was discussed about the pancreatic cancer was treated with using chemotherapy

ABBREVIATIONS
1. (EGFR): pancreatic cancer diagnosis epidermal growth factor receptor blockade
2. (PC): Pancreatic cancer
3. (FAMMM): Familial atypical multiple melanoma
4. (PJS): Peutz-Jeghers syndrome
5. (CF): Cystic fibrosis
6. (FAP): Familial adenomatous polyposis
7. (MEN): Multiple endocrine neoplasia
8. (VHL): Von Hippel-Lindau syndrome
9. (CT): Computerized tomography
10. (PET): Positron emission tomography
11. (FDG): Fluorodeoxy glucose
12. (EUS): Endoscopic ultrasonography
13. (FNA): Percutaneous fine-needle aspiration
14. (ERCP): Endoscopic retrograde cholangiopancreatography
15. Gastrointestinal Tumor Study Group (GITSG)
16. European Study Group for Pancreatic Cancer (ESPAC)
17. Vascular endothelial growth factor (VEGF)
18. Matrix metalloproteases (MMPs)

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