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Recent Achievements in Pancreatic Adenocarcinoma's Treatment

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INTRODUCTION

Pancreatic cancer is one of the most fearful pathologies, occupying the fourth most common cause of death by cancer in USA and the seventh worldwide [1,2]. Till this moment no treatment was found in order to cure this disease. The radical surgical treatment together with different chemotherapies will only prolong the survival of the patient by months/years but not too much. Unfortunately, it's incidence is increasing and it is expected that by 2030 it will be the second cause of death by cancer in USA [2]. The decision in regard to the therapeutic approach should be taken in a high volume center and involve a multidisciplinary meeting.

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The symptomatology of this pathology is very vague, usually the disease being discovered in its advanced stages because of the symptoms done by its complications (invasion of nearby structures). At the moment of diagnosis, 80% of the cases are not operable [2]. This is the reason why for only a few percent of the cases (10-20%) a radical surgery can be carried out [1]. As said previously, the survival rate is very low even with radical surgery, the expectancy of medial survival rate being of 19-24 months [1,2]. In case of locally advanced and metastatic tumor the rates are7-9 respectively 6-9 months [2].

Because of these poor data, the treatments for pancreatic cancer are a continuous challenge for surgeons, oncology physicians and pharmacologists.

These being said, we will discuss about the two therapeutic options: surgery and adjuvant therapy.

CURRENT TREATMENT PROTOCOL

According to the NCCN guidelines there are few options in regard with the treatment that has to be done in different situations [3].

If the tumor is resectable, a radical surgery should be performed followed by adjuvant therapy; in this case a few options are available:

1. Systemic gemcitabine or continuous intravenous infusion of5-FU for one cycle followed by continuous intravenous infusion of 5-FU/radiotherapy followed by maintenance gemcitabine or continuous intravenous infusion of 5-FU
2. Systemic gemcitabine or bolus of 5-FU/leucovorin or continuous intravenous infusion of 5-FU
3. Systemic gemcitabine or bolus of 5-FU/leucovorin for 2-6 cycles followed by fluoropyrimidine (CI 5-FU or capecitabine) based chemoradiation. Radiotherapy of 45-46 Gy in 1.8-2 Gy fractions applied at the regions of tumor resection and anastomosis
4. For patients who relapsed after the previous adjuvant treatments FOLFIRINOX or gemcitabine plus albumin-bound paclitaxel might be the option

In case of borderline resectable tumor, the opinions vary a lot because there is limited evidence of benefits from the adjuvant treatment. The chemotherapy regiment that is accepted for this type of tumor is made of FOLFIRINOX or gemcitabine for 2 to 6 cycles plus albumin-bound paclitaxel; in regard with the additional radiotherapy there is no consensus.If chemoradiation is used, the regiment should be one off:

1. Fluoropyrimidine (CI 5-FU or capecitabine) based chemoradiation
2. Gemcitabine based chemoradiation

If chemoradiation was done and the tumor became resectable,the surgical resection will follow after 4 to 8 weeks.

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Unresectable, locally advanced but not metastatic tumors will benefit from the following adjuvant therapeutic options:

A) For patients with good performance status the following chemotherapy agents can be used and afterwards chemoradiation with 5-FU or gemcitabine based will be performed

1. FOLFIRINOX
2. Gemcitabine plus albumin-bound paclitaxel
3. Gemcitabine plus erlotinib
4. Other possible, less used therapies include:

   a) Gemcitabine plus capecitabine

   b) Gemcitabine plus cisplatin

   c) Fixed dose rate of gemcitabine, docetaxel, capecitabine

   d) Fluoropyrimidine plus oxaliplatin

Depending on the complications, palliative surgery should be taken in account. In this cases we usually talk about by-passing different stenosis with anastomosis and pain management with neurolysis.

B) For patients with poor performance status is preferable to start with chemoradiation 5-FU or gemcitabine based. Other chemotherapeutic agents used are:

1. Gemcitabine at 1000 mg/m^2 over 30 min., weekly for 3 weeks every 28 days
2. Other possible, less used therapies include:

   a) Fixed dose rate of gemcitabine 10mg/m^2/min over 30 min.

   b) Capecitabine or continuous infusion of 5-FU

If we talk about complications,these have to solved in a simpler way, because these patients don't stand for complex surgeries. Taken that in account, for these cases, minimal invasive approach will be the way, laparoscopic, endoscopic or percutaneous drainage.

C) Chemoradiation alone can be used only in selected patients:

1. Fluoropyrimidine (CI 5-FU or capecitabine) based
2. Gemcitabine based

Unresectable, metastatic tumors will benefit from the following adjuvant therapeutic options and the same surgical treatment as the one without metastatic tumors but unresectable.

A) For patients with good performance status, the following chemotherapy agents can be used:

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1. FOLFIRINOX
2. Gemcitabine plus albumin-bound paclitaxel
3. Gemcitabine plus erlotinib
4. Other possible, less used therapies include:

    e) Gemcitabine plus capecitabine

    f) Gemcitabine plus cisplatin

    g) Fixed dose rate of gemcitabine, docetaxel, capecitabine

    h) Fluoropyrimidine plus oxaliplatin

B) For patients with poor performance status,no chemoradiation will be used, only chemotherapy:

1. Gemcitabine at 1000 mg/m^2 over 30 min., weekly for 3 weeks every 28 days
2. Other possible, less used therapies include:

    c) Fixed dose rate of gemcitabine 10mg/m^2/min over 30 min.

    d) Capecitabine or continuous infusion of 5-FU

SURGICAL TREATMENT

Depending on the location of the tumor, we can take in consideration a couple of surgical procedures. No matter about witch one we talk about,lymph node dissection should be carried out.

The main goals of surgical treatment in pancreatic cancer are obtaining an R0 resection margin and a prolonged survival. According to the NCCN guidelines, the recommended surgical approach should be the duodenopancreatectomy (Whipple operation) for cephalic pancreatic cancer. Depending on the local advancement of the tumor, venous resection may be imposed, with end-to end an astomosis or graft interposition, in order to obtain an R0 margin. The outcomes after portal vein and superior mesenteric vein resections have been described in the literature as being comparable to pancreatic surgery with no venous resection.

Yu XZ. Studied through a meta-analysis the aspects of venous resection and concluded that in order to achieve an R0 resection margin, venous resection (portal/superior mesenteric) is acceptable and that being done, the postoperative complications and long term survival are comparable with cases that benefited from standard resection [4]. Through multicenter studies, Murakami Y. and Ravikumar R. demonstrated that portal/superior mesenteric vein resection should be performed in cases without concomitant arterial invasion and the overall survival of patients with true venous invasion after resection might be lower [5,6].

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There are no reports of inferior vena cava resections in pancreatic cancer, such cases being considered unresectable.

Arterial resection in pancreatic cancer is currently debated in the literature. When considering such an operation, the surgeon must take into account the degree of invasion which consequently deems the tumor resectable or not.

It was demonstrated through meta-analysis (Mollberg N.) [7] and by case-control, cohort studies [8-10]that patients with arterial resection have survival rates similar to cases without arterial resection(palliative treatment) or standard surgery. Usually arterial resection gives more postoperative complications [7,9,10], lower long-term survival and usually indicates unresectability [7]; however, if this resection wants to be done, it should be performed in specialized centers [8,9].

The downfall of preoperative imaging is that it cannot indicate hystological invasion of the vascular elements or just inflammatory adhesions. The fact that peritumoral fibrosis may mimic tumor tissue on CT findings is invoked by the teams that support arterial resection (Table 1).

Table 1: Resection indications in pancreatic cancer with arterial invasion.
Comparison between the NCCN guidelines and D.B. Evans et al.'s [3,11]

	NCCN guidelines	Medical College of Wisconsin*
Vascular structure	Invasion	
Superior mesenteric artery	≤180° solid contact	>180° but ≤270°
Celiac artery	>180° solid contact without aortic or gastroduodenal artery involvement	>180° without aortic invasion, and possibility of celiac resection
Hepatic artery	Solid contact without extension to the celiac artery or hepatic bifurcation allowing for safe resection and reconstruction	>180° with invasion of celiac artery but possibility of resection with reconstruction
Superior mesenteric vein/ portal vein	>180° solid contact or ≤180° contact with irregularities, thrombosis and possibility of safe resection and reconstruction	Occlusion without possibility of reconstruction

*May be considered after neoadjuvant therapy.

Postoperative survival is, of course, dependent on the degree of postoperative complications. The immediate postoperative complications such as pancreatic fistulas, hemorrhage and sepsis have a great impact on the mortality rate. Numerous techniques have been developed with regard to the pancreatic anastomosis in order to reduce these negative outcomes. The surgical techniques can be divided in to two groups based on the organ with which the anastomosis is performed: the stomach or the jejunum. Although some observational studies have concluded that the pancreato-gastrostomy may imply lesser risks and complications [12-14],the bulk of the literature (randomized controlled studies and metaanalyses) suggest there is no difference in outcome between the two approaches [13-15]. In the Wellner's meta-analysis of retrospective studies was noticed a higher incidence of delayed gastric emptying and a higher risk of intraluminal bleeding with pancreato-gastrostomy then with pancreato-jejunostomy [14]. Moreover, the independent factors that influence fistula formation, and therefore survival, have been found to be: pancreatic tissue softness, age, extrapancreatic disease, and duration of surgery >6 hours [16,17].

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When talking about long-term postoperative complications, Delayed Gastric Emptying **(DGE)** is the most common. There are numerous factors that seem to play a part in the development of this complication such as: the extent of gastric resection, resection of the pylorus, disruption of the gastric neural plexus, local ischemia, diabetes, intra abdominal complications. In order to reduce the incidence of delayed gastric emptying, surgeons have focused on the degree of gastric resection and the placement of the jejunal loop, retrocolic or antecolic [18-20]. Initially, the Whipple operation was done by resecting the distal part of the stomach which lead to a 20-40% rate of postoperative delayed gastric emptying. A Pylorus Preserving Duodenopancreatectomy **(PPPD)** was developed by Traverso and Longmire in an effort to reduce DGE. However, the preservation of the entire pylorus along with its nervous supply, did not prove its efficacy, therefore the focus was turned on other techniques. A technique that was practiced more frequently in Japan was the Subtotal Stomach-Preserving Duodenopancreatectomy **(SSPPD)**. In this case, the tight resection above the pylorus allows for the preservation of 95% of the stomach along with vascularization and innervation. The better efficacy in diminishing the delayed gastric emptying from the two techniques was long debated. However, recent review articles and meta-analyses have tipped the scale in favor of SSPPD [21-23]. Other complications such as pancreatic fistulae, postoperative bleeding, bile leakage and wound infection were not influenced by the resection type. Huang W. showed in a meta-analysis a shorter hospital stay and earlier possibility to start oral chemotherapy in SSPPD [22]. In comparison with Huang W [22], Hanna M [23] in his review did not find any significant difference in hospital stay but a lower intra operative blood loss in PPPD and a lower postoperative mortality rate after SSPPD.

Another technique used to improve postoperative outcomes in PPPD was the antecolic gastro-jejunostomy [24]. However, some recent meta-analyses have come to the conclusion that there is no superior route of restoring digestive continuity with regard to DGE incidence [25,26].

When talking about pancreatic adenocarcinoma of the body and tail there is a strong inclination towards the laparoscopic approach. Although the laparoscopic technique for pancreatic resection was introduced 20 years ago, the professionals' reluctance to perform this type of surgery was based on questions about access, intra- and postoperative complications, especially ischemia and pancreatic fistula. However, numerous studies, reviews and meta-analyses favor the laparoscopic approach as it has the same rate of postoperative complications but with les blood loss and shorter hospital stay [27-29]. Recently, the potential advantages of robotic surgery have also been studied with results in favor of this technique when compared to classic laparoscopy [29].

The downfall of distal locations of pancreatic cancer is the late onset of symptoms and the impossibility of a curative treatment at the moment of diagnosis. Surgical resection had been out of the question for tumors of the body and tail that invaded the celiac trunk; however the modified Appleby surgery (which entails the celiac trunk resection) seems to have increased the overall survival of such patients [30]. Postoperative complications can include liver, stomach, duodenal and pancreatic head ischemia as well as disruptions of the nervous plexus with diarrhea and

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malabsorption [30]. Even with this being said, the mortality rate is low [30] and the patients have a better quality of life after it [31]. This is why patients who undergo distal pancreatectomy and celiac trunk resection should be selected and operated in highly specialized centers [30,31].

The fate of the pancreatic stump in distal pancreatic resections is a cause of concern for surgeons. Because of the complications such as pancreatic fistulas, hemorrhageand sepsis, a great deal of effort has been put in developing more effective techniques of dealing with the pancreatic stump. The most used and most debated techniques are hand suture versus mechanical stapler [32,33]. Other novel techniques have been proposed, some even in the animal trial phase. Matsumoto developed a transpancreatic mattress suture with vicryl mesh around the stump with good preliminary results in concern with the occurrence of pancreatic fistula [34]. Akita did a case series in 2015 and by the results obtained he recommended that the closure method should be chosen on a case-by-case basis and if the pancreatic stump is thick, soft coagulation and polyglycolic acid felt with fibrin glue should be applied [35]. Another *in vivo* study was done by Burdío, this time radiofrequency-induced heating being tried versus mechanical stapler; the results showed a better outcome when radiofrequency is performed before section and better efficiency of sealing when applying the radiofrequency technique on the stapled stump [36].

However, no technique stands out yet as the better approach to significantly lower the pancreatic fistulae incidence [32,33].

ADJUVANT THERAPY

The strategy in regard with adjuvant therapy is controversial.

Taken in consideration that over 80% of the patients that over went radical surgery will develop metastatic and/or recurrent disease in the near future, the adjuvant therapy was taken in consideration [37].

There are two lines of therapy that at this moment are taken in consideration: chemotherapy and radiotherapy.

At the moment, the literature has an abundance of studies related with drugs used in pancreatic cancer.

Because of the specific cancer features, is well known that it will create its own vascular network (neoformation). In pancreatic cancer, this new network it's not well organized and has a chaotic disposition and the vascular tissue is of poor quantity and quality. However, even if the angiogenesis process is poor, the pancreatic cell adenocarcinoma needs nutrients as well as oxygen in order to grow so, taken that in account the place for anti-angiogenic agents is still valid. One of the drugs used was Bevacizumab, an anti-vascular endothelial growth factor A monoclonal antibody; unfortunately, the results of the studies were not statistically significant [38-46]. In other studies, Axitinib, a small molecule inhibitor of a vascular endothelial growth factor receptor S was used; still no positive results [47,48]. A more complex molecule, Sorafenib, a inhibitor of

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vascular endothelial growth factor receptor -2, platelet-derived growth factor receptor beta and serine/threonine-protein kinase B-raf was tried in different studies but the results were not as expected [49-52]. The only drug of this type that seems to give promising results is Sunitinib, small molecule inhibitor of vascular endothelial growth factor receptor-s, platelet-derived growth factor receptor-s and mast/stem cell growth factor receptor Kit [53,54].

In particular, pancreatic cancer has a very well developed stroma witch will create a barrier in the path of most drugs used,therefor will create pressure on the vessel walls and by that a decrees of the vascular perfusion and throw that a low delivery of drugs. Due to this suppositions, researchers conducted studies in which they developed drugs that are epidermal growth factors and HER2 receptor inhibitors [55-58], insulin-like growth factor receptor inhibitors [59] but, none of this studies came with promising results.

There are some studies that tried to combine the two inhibitors: angiogenic and epidermal growth factor, creating a much friendlier environment for drug delivery. Some of the results are promising, with an increasing objective response rate of one month and a half in regard with an improved overall survival if both therapeutic agents are used, in this case Bevacizumab, Cetuximab and Gemcitabine [40]. Even if these results seemed promising, other studies that used this type of drugs didn't have the same results [60-62].

In Vitro Pancreatic Cancer Treatment Research

Because of the problematic issue of pancreatic cancer treatment and poor results in delivering the chemotherapeutic agents, a lot of new delivery systems are tried. One of the most promising field of research is nano medicine, with nano materials used with success in other cancer therapies for *in vitro* models [63,64], either as delivery systems or as targets for specific therapeutic procedures [65-68].

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