Mise au point d'un protocole de chimiothérapie néo-adjuvante pour les adénocarcinomes du pancréas

Mbaidjol Kabra, Zacharia

Section de médecine Clinique
Département de Chirurgie

Service de chirurgie viscérale

Thèse préparée sous la direction du Professeur Léo BÜHLER

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Zacharia MBAIDJOL KABRA

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Zacharia MBAIDJOL KABRA
originaire de Genève, Suisse

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"No challenges are too great to overcome. The question is what are you willing to do to achieve your goals".

Zacharia Mbaidjol

Implementation of Neo-adjuvant chemotherapy guidelines for Pancreatic Adenocarcinoma at the Geneva University Hospital (HUG)

Travail par Zacharia MBAIDJOL KABRA
Sous la direction du Professeur Léo BÜHLER

Faculté de Médecine de l'Université de Genève

Résumé

Le cancer du pancréas est la 10ème causes de décès au monde. C'est une tumeur agressive avec un taux de survie global à 5 ans inferieur à 5% pour les adénocarcinomes canalaires confirmés. Il n'existe pas de consensus aux Hôpitaux universitaires de Genève pour la prise en charge de ces tumeurs. Après une revue de la littérature des essais cliniques prospectifs ayant été effectués entre janvier 2000 et janvier 2015, utilisant de la chimiothérapie néo-adjuvante, nous avons comparé les réponses thérapeutiques de la combinaison chimiothérapeutique FOLFIRNOX à la combinaison Gemcitabine-nab-Paclitaxel. Sur la base de cette revue, nous proposons d'adopter la classification du Centre MD Anderson pour les adénocarcinomes du pancréas. Les tumeurs d'emblée résecables et borderlines peuvent bénéficier d'une prise en charge chirurgicale primaire et de chimiothérapie adjuvante. Pour les tumeurs non-résecables, une chimiothérapie néo-adjuvante avec un protocole à base de FOLFIRINOX sera proposée et la progression/régression de la tumeur sera réévaluée.

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1a- Abstract

Le cancer du pancréas est la 10ème causes de décès au monde. C'est une tumeur très mortelle et agressive avec un taux de survie global à 5 ans en dessous de 5% pour les adénocarcinomes canalaires confirmés. Bien que plusieurs gènes aient pu être identifiés comme d'éventuels cibles de traitements à un stage précoce, la chirurgie reste l'unique traitement curatif pour cette maladie. L'incidence des nouveaux cas ne fléchit pas. Le cancer du pancréas est actuellement la 4ème cause de décès la plus fréquente, causé par un cancer et pourrait d'ici quelques années devenir la 2ème cause la plus fréquente. 80 % des patients atteints d'un cancer du pancréas ont un stade avancé au moment du diagnostic. De plus, pour 1/3 des tumeurs initialement considérées comme résecables durant le staging, une résection en marge saine n'est pas possible.

Plusieurs études rétrospectives ont montré que les traitements néo-adjuvants de chimiothérapie ont un effet bénéfique sur les cancers du pancréas et ont le potentiel d'augmenter le taux de survie après chirurgie pour les tumeurs résecables, d'augmenter le nombre de résection en zone saine pour les tumeurs borderline et d'éventuellement rendre résecable les tumeurs non-résecable. Il n'existe pas de consensus actuellement en place aux Hôpitaux Universitaires de Genève pour la prise en charge de ces tumeurs dites « borderlines ». Nous avons effectué une revue de la littérature de tous les essais cliniques prospectifs ayant été effectués entre janvier 2000 et janvier 2015, utilisant exclusivement que de la chimiothérapie néo-adjuvante. Par la suite, nous avons comparé les réponses thérapeutiques de la combinaison chimiothérapeutique Oxaliplatin, Irinotecan, Fluorouracil et Leucovorin (FOLFIRNOX) à la combinaison Gemcitabine-nab-Paclitaxel. 5 études ont été effectuées, démontrant toutes un bénéfice à utiliser de la chimiothérapie néo-adjuvante. De plus, le FOLFIRINOX est le régime montrant le plus haut taux de réponse à 31.6%. Sur la base de cette revue, nous proposons d'adopter la

classification du Centre MD Anderson pour les adénocarcinomes du pancréas. Les tumeurs d'emblée résecables et borderlines peuvent bénéficier d'une prise en charge chirurgicale primaire et de chimiothérapie adjuvante avec un protocole à base de FOLFIRINOX. Pour les tumeurs non-résecables, une chimiothérapie adjuvante sera proposé et la progression/régression de la tumeur sera par la suite réévaluée. Deux options chimiothérapeutiques ont montré les plus haut taux de survie moyen: le régiment FOLFIRINOX et la combinaison Nab-Paclitaxel-Gemcitabine.

1b- Abstract

Pancreatic cancer is the 10th leading cause of death worldwide. It is a very lethal and aggressive tumor, with a 5-year overall survival rate under 5% for confirmed ductal adenocarcinoma. Even though many genes have been identified as possible targets to detect and treat pancreatic cancer at an early stage, surgery remains to date the only curative treatment. The incidence of new cases is not declining and pancreatic cancer could soon become the 4th cancer leading cause of death. 80% of pancreatic cancer patients are at an advance stage when the diagnostic is made. Furthermore, 1/3 of tumors thought to be resectable during staging turn out to be non-resectable during surgery. Many retrospective studies have shown that neo-adjuvant chemotherapy had a positive effect on pancreatic cancer and could turn borderline non-resectable tumors into resectable ones. No guidelines are currently in place at the Geneva University Hospital to classify the different type of tumors and what neo-adjuvant regimen to use. We performed an extensive review of the literature of all prospective trials performed between January 2000 and January 2015 that used exclusively chemotherapy for neo-adjuvant therapy in pancreatic cancer. Furthermore we compared the response rate of the chemotherapeutic regimen Oxaliplatin, Irinotecan, Fluorouracil and Leucovorin (FOLFIRINOX) to the combination Gemcitabine- nab-Paclitaxel.

We found 5 trials that all indicate that neo-adjuvant chemotherapy seems to increase the R0 resection rate for tumors classified as resectable or borderline resectable according to the MD Anderson staging system. Furthermore, FOLFIRINOX appear to be the chemotherapeutic regimen of choice with a response rate of 31.6%.
Based on this review and after a multi-disciplinary evaluation, we suggest adopting the classification of the MD Anderson Cancer Center for pancreas adenocarcinoma. Tumors that are resectable or borderline resectable should be operated and patients should then

receive adjuvant therapy. For patients with non-resectable tumors, according to the MD Anderson staging system, chemotherapy will be proposed and the progression/regression of the tumor will then be reevaluated. Two chemotherapeutic options have shown the highest median survival rate: the FOLFIRINOX regimen and the combination Nab-Paclitaxel plus Gemcitabine.

2a- Introduction

Le cancer du pancréas est depuis bien longtemps étudié. Bien que nous ayons énormément appris sur cette glande au cours des siècles passés, le taux de mortalité reste très élevé et il en revient à la médecine moderne de trouver un moyen de le réduire. L'étude du pancréas possède une très vieille histoire, datant de la Grèce ancienne, environ 300 -JC. Le pancréas fut alors pour la première fois décrit comme organe[1]. La description ne fut pas aisée du fait de sa position retro-péritonéale. L'impression générale des anatomistes de l'époque était qu'il s'agissait d'un organe entièrement constitué de chaire. Rufus d'Ephese fut le premier à en faire la description et à la nommer : *Pan-Kreas (tout-chaire).*

Des études plus approfondies ont permis une meilleure compréhension de sa composition glandulaire et acinaire, notamment par d'éminent anatomiste et physiologiste tel que Wirsung, Bruner et Langerhans. La double fonction exocrine et endocrine du pancréas fut également découverte ainsi que son rôle dans la digestion avec la composition du jus pancréatique. C'est seulement en 1889 par l'expérimentation animale qu'un lien fut clairement établi entre le pancréas et le diabète. Cette même année, Réginald Fitz, un pathologiste, établit les signes et critères pour le diagnostic de la pancréatite. Au moment où le cancer du pancréas devint une entité clairement connue du monde scientifique, la difficulté pour le traiter devint également un fait réel.

Malgré des connaissances plus approfondies, de meilleures techniques chirurgicales et de nouveaux traitements médicamenteux, le taux de survie reste loin d'être acceptable. Ceci est en partie dû au diagnostic de la maladie qui est souvent retardé, permettant à la tumeur d'avoir souvent atteint les structures avoisinantes ou fait des métastases. Les facteurs de risque ont également pu être mis en évidence avec

le tabac comme cause principal exogène du cancer ; on observe une incidence 2 fois plus haute chez les fumeurs.

Historiquement, différentes techniques opératoires furent mise en place pour la prise en charge chirurgicale des tumeurs de la tête du pancréas. La 1ère pancreatico-duodenectomie partielle fut effectuée en 1912 par Walter Kausch en Allemagne et Alessandro Codvilla en Italie. Cette procédure fut cependant popularisée par le Dr. Allen Oldfather Whipple aux Etats-Unis en 1935. Initialement effectué en 2 temps, elle fut convertie en 1 temps par la suite et reste jusqu'à présent la référence pour les adénocarcinomes de la tête du pancréas. L'opération dite de Whipple, consiste à effectuer une résection de la tête du pancréas avec une gastrectomie, une duodenectomie, une résection jéjunale proximale ainsi qu'une résection de la voie biliaire principale et de la vésicule biliaire. Une variante de cette opération permet de préserver le pylore gastrique (pylorus- preserving pancreaticoduodenectomy). C'est une procédure complexe avec un taux de mortalité entre 2-5% et une morbidité entre 30-55% dans les centres spécialisés.

Les avancées chirurgicales modernes permettent également une approche laparoscopique et robotique. Pour les tumeurs localisées dans le corps ou la queue du pancréas, une pancreatico-duodenectomie distale subtotale « gauche » est pratiquée pour extirper le corps et la queue du pancréas. Une splénectomie est parfois également nécessaire pour obtenir une résection en zone saine. Une résection « en bloc » de la tumeur et des structures avoisinantes avec résection de la veine porte fut un temps systématiquement pratiqué afin d'améliorer les chances de guérisons. Un consensus a été décidé[2] basé sur les données de 4 grandes études prospectives randomisées comparant les pancreatico-duodenectomie pour les adénocarcinomes de la tête du pancréas avec lymphadenectomie standard versus lymphadenectomie étendue. La

conclusion fut que la lymphadenectomie standard devrait être l'opération de choix pour les patients avec des adénocarcinomes canalaire de la tête du pancréas car les lymphadenectomies étendues ajoutaient du temps à l'opération, compromettait la qualité de vie des patients sans pour autant apporté un bénéfice à la survie. Le consensus actuel est qu'un minimum de 15 ganglions lymphatiques est nécessaire pour l'analyse pathologique.

Il est également reconnu que le pronostic de guérison est péjoré après résection avec reconstruction veineuse en raison de la difficulté de cette procédure[3]. Ce consensus a cependant établi que les pancreatico-duodenectomie avec résection veineuse et reconstruction pouvaient être effectuées lors d'invasion tumorale de la veine porte et de la veine mésentérique supérieure à condition qu'un flux veineux adéquat puisse être conservé et que l'invasion tumorale ne concerne pas l'artère mésentérique supérieure ou les artères hépatiques et que une résection R0/R1 est raisonnablement attendue[26].

La chirurgie reste le seul moyen actuel de traiter de manière curative le cancer du pancréas. Une étude effectuée par Bockhorn et al [4] a montré que le taux de survie après résection pancréatique avec ou sans résection et reconstruction artérielle était significativement plus haut que lorsque les patients recevaient simplement un traitement chirurgical palliatif. Aux Etats-Unis, le taux de survie globale à 5 ans est < 5% [5]et le taux de survie médian après une procédure de Whipple et chimiothérapie adjuvante entre 20 et 24 mois[6]. Environ 70% des patients récidivent sous forme de métastases après résection à but curatif [7, 8] .

L'utilisation de la chimiothérapie et de la radiothérapie a été entreprise de plusieurs manières : adjuvante, locale, systémique et intra-opérative. Les bénéfices de la thérapie adjuvante ont depuis longtemps été établis avec l'étude du **Gastrointestinal**

Tumor Study Group (GITSG) en 1985 qui a pu montrer que les patient ayant un adénocarcinomes du pancréas qui avaient pu bénéficier d'une chirurgie à bu curatif, avait un taux de survie plus élevé lorsqu'un traitement adjuvant était par la suite introduit[9]. Le traitement adjuvant consistait de 5-fluorouracil (5-FU), de mitomycin C (MMC) et de radiothérapie. Bien que la radiothérapie tienne toujours un rôle central dans la thérapie adjuvante, ce n'est pas le cas en Europe.

L'étude randomisée du **European Study Group for Pancreatic Cancer en 2004 (ESPAC-1**) avait comparé la chimio-radiothérapie adjuvante à la chimiothérapie seule utilisée de manière adjuvante pour les adénocarcinomes pancréatique réséqué à but curatif. Cette étude avait montré que les patients recevant de la chimio-radiothérapie avait un taux de survie plus bas et que la chimiothérapie améliorait de manière significative le taux de survie global (P = 0.009) [10]. La radiothérapie ne fait depuis lors plus partie des protocoles standards de thérapie adjuvante en Europe.

L'étude CONKO-001 publié en 2008 fut la seule série prospective randomisée qui établit clairement le rôle de la thérapie adjuvante en randomisant les patients pour recevoir un traitement adjuvant de gemcitabine ou aucun traitement adjuvant. Ceci après une résection complète (R0 ou R1). La conclusion fut que la gemcitabine (ou les autres traitements adjuvants) permettent d'augmenté la survie globale et la durée de rémission [11]. Plusieurs groupes ont depuis essayé d'améliorer le régiment thérapeutique ou l'agent utilisé. La gemcitabine a pendant longtemps été considéré comme l'agent de choix, permettant d'obtenir le plus haut taux de survie. Plus récemment, il a été admis que la combinaison oxaliplatin, irinotecan, fluorouracil et leucovorin (FOLFIRINOX) permettait un taux de survie plus haut que la gemcitabine pour les cancers métastatiques du pancréas [12].Il a également été récemment démontré que la combinaison nab-Paclitaxel- Gemcitabine permettait un taux de survie comparable. En

effet, cette dernière combinaison augmenterait de manière significative le taux de survie comparé à la gemcitabine seule (8.5 mois contre 6.7 mois, P<0.0001).

L'approche adjuvante n'est cependant pas la seule approche considérée. D'autres options sont également en cours d'investigations telle que le traitement ciblé [13]visant à cibler des éléments précis qui inhiberaient la croissance tumorale come par exemple des facteurs de croissances ou leurs récepteurs (ex : VEGF, EGF, IGF). Une autre option serait la mise en place de ces traitements en néo-adjuvant. Ce concept n'est pas nouveau en soit ; Cependant l'expérience acquise sur l'utilisation de traitements cytotoxiques en néo-adjuvant est basée sur des études rétrospectives, des méta analyses ou des études de cas. Très peu de grandes études prospectives sont décrites dans la littérature.

Dans cette revue, non-systématique, nous effectuerons tout d'abord le point sur la pathologie qu'est le cancer du pancréas en abordant les facteurs de risques et les méthodes diagnostiques. Nous parlerons ensuite des 2 régiments cytotoxiques actuellement considéré en 1ère ligne de traitement : le régime FOLFIRINOX et la combinaison gemcitabine plus nab-paclitaxel. Nous discuterons ensuite de l'utilité de la mise en place d'un traitement néo-adjuvant. Finalement nous discuterons des études prospectives effectuées depuis Janvier 2000 sur la chimiothérapie néo-adjuvante pour les adénocarcinomes du pancréas. Ceci nous permettra d'établir des recommandations pour la prise en charge des adénocarcinomes du pancréas aux Hôpitaux Universitaires de Genève.

2b- Introduction

Pancreatic cancer has been studied for a very long time. Though we have learned a lot about this gland in the course of the past centuries, it retains a very high mortality rate that modern medicine has yet to reduce. The study of the Pancreas has a very ancient history that dates back to ancient Greece at around 300 BC. The pancreas was then first described as an organ. It was not easily described due to its retroperitoneal position. It was simply admitted that it consisted of solely flesh. Thus the given Greek name *Pan-Kreas (all-flesh)* by the anatomist Rufus of Ephesus.

Further studies allowed a better understanding on its glandular and ductal composition by eminent anatomist and physiologist such as Wirsung, Bruner and Langerhans. The dual exocrine and endocrine function of the pancreas was also uncovered with also its role in digestion and the composition of the pancreatic juice. But it was only in 1889 that animal's experiments allowed to clearly establish the link between the pancreas and diabetes. The same year, Reginald Fitz, a pathologist, listed the signs and symptoms of pancreatitis. When pancreatic cancer became well known as an entity, so became the difficulty in treating it. Despite a better understanding of the pancreas, improved surgical techniques and better medical treatments, the survival rate remains far from acceptable. This is partially due to the late detection of the disease, which has often reach surrounding structures or metastasized at the time of diagnostic. Risk factors have also been identified with Tobacco as the main one, increasing the risk of pancreatic cancer by 2 folds. Various techniques have been elaborated to resect tumors from the head of the pancreas.

The first partial pancreaticoduodenectomy was performed in 1912 by Walter Kausch in Germany and by Alessandro Codvilla in Italy. Nevertheless, Dr. Allen Oldfather Whipple in the United States popularized this procedure in 1935. Initially performed in 2

stages, it was then improved as a one stage procedure, which is the current gold standard for pancreatic cancer of the head of the pancreas. The so called "Whipple procedure" consists of a pancreatic head resection with a gastrectomy, a duodectomy, a proximal jejunal resection as well as a gallbladder and common bile duct resection. Variant of this operation allows sparing of the gastric pylorus (pylorus- preserving pancreticoduodenectomy. It is a complex procedure with a morbidity ranging from 30-55% and a mortality rate from 2-5% in specialized centers.

Modern surgical advances have allowed laparoscopic and a robotic approaches. For tumors of the body and tail, rather than a Whipple procedure, a distal pancreatectomy is performed to remove the body and tail of the pancreas. A splenectomy is sometimes also necessary to achieve a R0 resection. There is an ongoing debate regarding the need for a bloc resection of the tumor and surrounding structures, to remove more lymph nodes, tissue and vascular structures, to better achieve a R0 resection. A consensus statement was decided[2] based on data from four major randomized prospective trials comparing standard versus extended lymphadenectomy for adenocarcinoma of the head of the pancreas. It concluded that **standard lymphadenectomy should be the operation of choice for patients with ductal adenocarcinoma of the head of the pancreas** because extended lymphadenectomy added time to the procedure, compromised the quality of life and had no survival benefit.

It is also recognize that the survival rate of patients undergoing a venous resection and reconstruction might be inferior[3]. This due to the aggressive nature of the tumor and the complexity of this procedure. The consensus statement also stated that pancreatico-duodenectomy with vein resection and reconstruction is the standard for pancreatic adenocarcinomas, locally involving the portal vein and superior mesenteric

vein, providing that adequate inflow and outflow veins are present, the tumor does not involve the superior mesenteric artery or hepatic artery and a R0/R1 resection is reasonably expected[2].

Surgery remains the only curative way to treat pancreatic cancer. A study by Bockhorn et al[4]. showed that the survival rate following pancreatic resection with or without arterial resection and reconstruction was significantly higher compare to when a palliative surgery was performed. Despite an appropriate pre-operative staging, and adjuvant therapy, the overall 5 year survival rate after a Whipple procedure is < 5% in the US[5] and the mean survival rate is between 25 and 35% and between 20 and 24 months[6]. Local recurrences occur in 70% of patients after surgical resection with curative intent followed by adjuvant radio-chemotherapy[7, 8]. The use of chemotherapy and radiotherapy has been investigated in multiple settings: adjuvant, local, systemic and intra-operative.

The benefits of adjuvant therapy have long been established with **The Gastrointestinal Tumor Study Group (GITSG)** that demonstrated in 1985 that pancreatic cancer patient's survival increased with surgery followed by radiotherapy combined with chemotherapy[9]. Though radiotherapy is part of the standard adjuvant therapy treatment in the United States, its role in patient's survival has been put into question with the **European Study Group for Pancreatic Cancer in 2004 (ESPAC-1**), which in a randomized trial compared adjuvant chemoradiotherapy and chemotherapy and showed that patients receiving chemoradiotherapy had a lower survival rate and that chemotherapy caused improvement in overall survival (P = 0.009) [10]. Radiotherapy is therefore not part of standard treatment protocols in Europe.

Many randomized study groups have since been trying to improve the therapy regimen or the agent used. Despite an appropriate pre-operative staging, and adjuvant

chemoradiotherapy, the recurrence rate and the mortality rate remain very high. The array of cytotoxic agent has also evolved from 5-fluorouracil (5-FU) and mitomycin C (MMC) to r Gemcitabine based regimens and recently to the FOLFIRNOX regimen. It is a combination of oxaliplatin, irinotecan, fluorouracil and leucovorin. It has been showed that this regimen allows a higher survival rate for metastatic pancreatic adenocarinoma. It has also been showed that the combination nab-Paclitaxel with gemcitabine allowed a comparable survival rate. Indeed, this last combination could significantly increase the survival rate compared to Gemcitabine alone (8.5 months versus 6.7 months, $P<0.0001$).

Though the disease free interval and the overall survival are prolonged with adjuvant chemotherapy, new methods of treatment are being investigated including targeted therapy and multiple regimen chemotherapy. [13]

Another also very appealing option is to use these molecules in a neo-adjuvant setting. This is an idea that many specialized centers have had for quite some time but only few big prospective studies have yet been published. The experience described with neo-adjuvant treatments is mostly based on retrospective studies and case reports. But they all showed promising results.

In this review, we intend to first describe the understanding of pancreatic cancer we have gained so far, what causes the disease, how it presents itself and how to detect it. We will then discuss the 2 chemotherapeutic treatments currently used as first line treatment: The FOLFIRINOX regimen and the combination nab-Paclitaxel-gemcitabine. We will then consider the rational for applying it in a neo-adjuvant setting. We will finally review articles about the use of neo-adjuvant chemotherapy in a neo-adjuvant setting by doing a review of randomized prospective trials conducted since January 2000. This will

allow us to implement neo-adjuvant chemotherapy guidelines for the treatment of pancreatic adenocarcinoma of the Pancreas at the Geneva University Hospital.

3- Epidemiology:

Pancreatic Cancer (PC) remains a leading cause of death worldwide and is one of the most lethal tumors with an incidence of over 185000 cases worldwide[14]. The highest incidence is in the United States at 12.4/100000[15]. PC has been steadily increasing since the 1980's possibly due to more accurate diagnostic tools. In Switzerland, the incidence average was 504 cases per year for men versus 551 for women (1985-2009 data) [16]. It is the 10th leading cause of cancer for men and the 8th for women, which is comparable to the European population (8th leading cause for men and 9th for women) and the worldwide data (10th for men and women).

The incidence increases with age, with the highest pick in the population over 70 (60% of all the new cases) [16]. It is the 4th leading cause of death amongst men and women behind lung cancer, colon cancer and prostate cancer for men and behind breast cancer and colon cancer for women. Patients diagnosed with an exocrine pancreatic cancer have a short life expectancy due to the aggressive nature of this tumor with early metastasis, the high morbidity and the resistance of the cancer cells[3]. Furthermore, more than 80% of pancreatic cancer patients are already at an advanced stage of the disease when initially diagnosed. The 5-year survival rate approaches 0% for histologically confirmed metastatic ductal carcinoma and the median overall survival rate is 5-6 months[17]. For the 20% of patients with resectable tumors with negative margin accomplished after pancreaticoduodenectomy (R0), the median survival is 12-26 months. Many attempts are made to clearly stage the tumor and classify it as resectable, borderline or non-resectable, to avoid the burden of an invasive surgery and neo adjuvant chemotherapy for a non-resectable tumor.

4- Etiology and risk factors:

The incidence of pancreatic cancer has been progressively increasing over the years, not significantly but steadily. Many studies have been made and are still ongoing to try to understand the carcinogenesis. It is a multi-factorial disease with demographic, environmental, genetic and medical factors. The most consistent risk factor reported is old age and cigarette smoking [18]. Cigarette smoking is estimated to account for 25% to 29% of pancreatic cancer incidence. Lower incidence is observed 10 years after cessation when compared to active smokers [19, 20].

Pancreatic tumors have been linked to other lifestyle factors such as heavy alcohol consumption (>60ml of ethanol solution/day), low dietary intake of fruits and vegetables, high grilled food intake and occupational exposure [15, 19, 21]. The incidence is also ethnicity dependent, being 2 to 3 times more prevalent among the black population. 5-10% of pancreatic cancer patients report a history of pancreatic cancer with a close family member, thus the term "Familial Pancreatic Cancer".

Registries are in place in Europe and in the US with ongoing research to understand the pancreatic cancer biology and identify susceptible genes in order to develop new biomarkers. Recent genetic studies and sequencing of pancreatic tumors has allowed pointing out specific genetic alteration and point mutations. Commonly mutated genes include K-RAS and HER/2-neu, MYB, AKT2, AIB1 oncogenes and tumor suppressing genes such as, BRCA-2, TP53, p16/CDKN2A, SMAD4, MKK4, LKB1/STK11, ALK5 and TGF ßR2[15, 22]. Having a genetic predisposition to pancreatic ductal carcinoma can raise the risk factor by a 132 folds compared to the general population and the risk is also increased two folds if there is a family history of pancreatic carcinoma [23].

The implementation of appropriate screening procedures might allow to detect pancreatic cancer at an earlier stage. Studies have also been able to show a link between pancreatic cancer and familial breast cancer, familial atypical multiple mole melanoma and Peutz-Jegher syndrome amongst others[19](Table 1). It seems there is also a strong association with common medical conditions, particularly diabetic mellitus chronic pancreatitis, and previous gastric surgeries.

Risk factors for pancreatic cancer

Demographic factors
Old age (most reliable and important predictor)
Sex (more common in males than in females)
Ethnic origin (mortality highest in black populations)

Genetic factors and medical conditions
Family history
Hereditary pancreatitis
Hereditary non-polyposis colorectal cancer
Ataxia-telangiectasia
Peutz-Jeghers syndrome
Familial breast cancer
Familial atypical multiple mole melanoma
Chronic pancreatitis
Diabetic mellitus
Gastrectomy
Deficiency in carcinogen metabolism and DNA repair

Environmental and lifestyle factors
Cigarette smoking
Occupational exposures
Low dietary intake of fruits and vegetables
Food preparation and cooking methods (grilling or charring confers the highest risk)

Table 1

Risk factors for pancreatic cancer: From the Lancet, Volume 363, issue 9414, 27: 1049-1057

5- Pancreatic tumors classification

Through its dual function, the pancreas is a nodular gland composed of exocrine (80%) and endocrine cells. The endocrine portion consists of islets of Langerhans cells whereas the exocrine portion is composed of pancreatic ducts and acini, which are the subunits of lobules. 85-90% of pancreatic tumors are of ductal origin, of which 85-90% are invasive adenocarcinoma[15].

5.1- Ductal Adenocarcinoma

60-70% of ductal adenocarcinomas occur in the head of the pancreas, the rest are found in the rest of the gland. Body and tail tumors are usually discovered at an advanced staged due to delayed detection. Histologically, ductal adenocarcinoma is characterized by well-developed glandular structures embedded in a desmoplastic stroma. Metastasis has often occurred at the time of diagnosis, to surrounding structures via direct extension, lymphatic and haematogenous spread (liver, lungs, adrenals, kidneys, bones, brain and skin. Adenosquamous carcinoma (3-4%), undifferentiated (anaplastic) carcinoma (2-7%) mucinous noncystic adenocarcinoma (1-3%) and signet ring carcinoma are considered rare variant of ductal adenocarcinoma. In contrast to ductal adenocarcinoma, these are poorly differentiated and contain nonetheless foci of neoplasic glands. Other extremely rare ductal carcinoma include mixed ductal-endocrine carcinoma is a mixture of ductal and endocrine cells in the primary tumor, clear cell carcinoma and ciliated cell carcinomas.

5.2- Mucinous Cystic Neoplasm (MCN)

As opposed to Serous Cystic neoplasm, mucinous cystic tumors occur almost exclusively in women and in the body-tail part of the pancreas. Their cystic epithelium, which is embedded in an ovarian type stroma, produces mucin and have no communication to the pancreatic ductal system. They are classified according to their degree of differentiation as adenoma, adenoma with moderate dysplasia, non-invasive adenocarcinoma and invasive carcinoma. The prognostic is excellent when RO is achieved.

5.3- Intraductal Papillary-Mucinous Neoplasm (IPMN)

IPMN have been confused with MCN, as they are both mucin-producing tumors. One main difference being that IPMN are in communication with the ductal system while MCN are not. The latter have an ovarian stroma, which is not the case with IPMN. They account for around 1-3% of the exocrine pancreas neoplasm. IPMN are divided as main duct or branch duct depending if they arise respectively from the main pancreatic duct or from a branch duct. They are further divided according to their malignancy potential. The intraductal papillary-mucinous adenoma being benign tumors. Typically, main branch duct tumors have been shown to be more aggressive than the branch duct type and to have a malignancy rate as high as 70%. IPMN are classified as adenoma, borderline and carcinoma. The survival rate depends on the level of dysplasia, the stage of the tumor and the presence or absence of invasion[15, 24]

6- Symptoms of pancreatic carcinoma

There are no pathognomonic signs for pancreatic carcinoma. Symptoms are usually aspecific and related to the compression of surrounding structures: the bile ducts, mesenteric and celiac nerves, the pancreatic ducts and the duodenum. They often induce abdominal pain, nausea, obstructive jaundice, pruritus, weight loss, cachexia and transit disturbance[19]. In cases of small tumors, they often remain asymptomatic for a long period of time and can be incidentally discovered during imaging studies for other unrelated problems. When the tumor becomes symptomatic, it is unfortunately often at an advanced stage.

7- Pre-operative diagnostic modalities

7.1- Multiphasic Helical CT has the highest accuracy (91%) in assessing the extent of pancreatic tumor and predicting resectability and is currently the standard staging method. With a sensitivity of 77% and specificity of 100% for tumors measuring 2cm or smaller[25]. For tumors > 2cm, the sensitivity is as high as 98%[26]. It has furthermore a specificity of 77% and sensitivity of 81% for the diagnosis of vascular invasion. The imaging protocol requires the injection of a nonionic iodinated contrast material. The patient is then scanned twice with thin slices obtained, first for an early arterial phase and then after 20 seconds which allows better visualization of the parenchyma and opacification of the celiac axis, superior mesenteric artery (SMA) and peri-pancreatic arteries[27].

Finally, a last scan is obtained at 70 seconds for a portal venous phase, which allows opacification of the superior mesenteric vein (SMV), splenic vein and portal vein, to enhance the pancreas tissue and to detect the presence of liver metastases. Pancreatic adenocarcinoma appears hypodense, the hyperdense lesions being mostly **neuroendocrine tumors**. The IV contrast medium is coupled with a hypodense oral contrast medium, such as water to distend the stomach and duodenum to better visualize the pancreas. With 3D reconstruction, the negative predictive value is enhanced from 76% to 96%[27].

7.2- Magnetic Resonance Imaging (MRI) has not demonstrated clear advantages over CT scan and has a diagnostic accuracy of 70% for pancreatic carcinoma[26]. While Magnetic Resonance Cholangio- pancreatography (MRCP) gives information regarding the extra hepatic bile duct and pancreatic duct, it has been shown to have a sensitivity of 100% a specificity of 83%, a positive predictive value of 100% (PPV) a negative predictive value of 94% (NPV) and an accuracy ranging between 70

and 94% for determining the resectability of a pancreatic carcinoma[26]. MRCP may complement CT scan for non-contouring lesions, for differentiating malignant from benign tumors and for assessing small pancreatic malignancies or suspected hepatic metastases [28]. Alternative method are also used for the diagnostic and staging of pancreatic tumors.

7.3- Endoscopic ultrasonography (EUS) is highly sensitive for detecting small tumors < 3cm, detecting vascular involvement and predicting resectability and has a sensitivity over 90% in some studies[29]. Furthermore, EUS is very precise for the detection of portal and splenic vein invasion with accuracy ranging from 77% to 85%[29]. It is 75% to 95% accurate in assessing T stage and 74% to 87% accurate in assessing N stage [17, 29]. EUS therefore helps with the loco regional staging and complements Helical CT in the decision-making.

7.4- Fine Needle aspiration (FNA) can be performed under EUS or CT guidance. It allows making the diagnostic with tissue analysis without the risk of tumor seeding [19, 27]. The main issue is the rate of false negative, EUS guided FNA has a sensitivity of 80% and specificity of 100%[29] and was nevertheless found to be superior to Endoscopic Retrograde Pancreatography (ERCP) in terms of complications (2%) and cost effectiveness[27, 29]. **Consequently, it should be performed in all patients with or suspected of having a pancreatic tumor prior to surgery[27]**.

7.5- Positron Emission Tomography (PET) use for the detection of pancreatic tumors remains controversial. It has a sensitivity of 89% and specificity of 88% for the staging of pancreatic cancer[17]. It might have a place for the detection of distant metastasis unnoticed with routine staging investigations, by adding sensitivity when

coupled with CT and by helping to differentiate chronic pancreatic from pancreatic cancer[24]. But its use is still on trial [17, 27].

7.6- Serum Marker Carbohydrate Antigen 19-9 (CA 19-9) is a sialylated Lewis (Le)^a blood group antigen. While patients lacking the Lewis antigen glycosyltransferase are unable to synthesize CA-19.9. It is elevated in 60- 80% of advanced pancreatic cancer patients[30]. Since it has first been described by Kaprowsky et al in 1981[31], CA-19.9 has long been associated with pancreatic cancer. It is often used as a predictive and prognostic marker and some studies have also shown a correlation between lower CA 19.9 values and an improved outcome of pancreatic cancer treatment. There is however no consensus on the timing for the measurement of CA 19.9 and the cutoff value of decline from baseline to use. While other studies have shown that a decrease in CA 19.9 value is not a good indicator for survival [32], it has also been demonstrated that a rise in CA 19.9 during chemotherapy treatment can serve as a negative predictive value [33]. The use of CA 19.9 as a prognostic marker and an indicator of the tumor load remain therefore controversial [21].

7.7- Laparoscopic staging is usually done for patients with ambiguous radiological findings or when an advanced stage of the disease is strongly suspected. It assesses the presence of metastasis that could have been missed during the routine staging and predicts with an even higher accuracy the resectability of the tumor. It consequently avoids the heavy burden of an inoperable tumor if a R0 resection cannot be achieved. **1/3 of patient thought to have resectable tumors after the initial staging are deemed inoperable** after laparoscopic staging[27]. A 2009 expert consensus established that laparoscopy should be reserved for large tumors of the head (> 3cm), tumors of the body and tail, high CA 19-9 levels (>100 U/ml) or doubts

regarding distant metastasis and resectability on routine staging[27]. Staging laparoscopy and laparoscopic ultrasonography was found to have an overall sensitivity and specificity of 64% and 99% respectively and to improve the resection rate from 61% to 80%[26].

8- Pancreatic tumor staging

The extent of the tumor allows a standardized TNM classification. Though the prognosis is mostly based on the staging of the tumor[34](Table 3).

Table 2:
TNM Staging of pancreatic tumors

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of a primary tumor		
Tis	Carcinoma in situ[a]		
T1	Tumor limited to the pancreas, ≤ 2 cm in diameter		
T2	Tumor limited to the pancreas, > 2 cm in diameter		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node(s) metastasis		
N1	Regional lymph node(s) metastasis		
Distant metastasis (M)			
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1–3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

[a] This also includes the "PanINIII" classification

From Edge SP, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

Pancreatic tumors can be classified in three broad categories: resectable, borderline and non-resectable. As previously mentioned, because 80% of pancreatic tumors are at an

advanced stage when initially diagnosed, it is important to differentiate a patient with a borderline tumor who could benefit from a surgery with the goal of an R0 resection from a patient with an inoperative tumor.

There are multiple definitions of Borderline tumors in the literature but all agree that borderline tumors have a greater risk of having metastases not seen on imaging. They therefore carry a higher risk of positive margin resection and a higher risk of recurrence [35]. The Three main used classifications found in the literature are:

1- The National Comprehensive Cancer Network's (NCCN)

2- The American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology guidelines

3- The MD Anderson Varadhachary/ Katz CT staging system for adenocarcinoma of the pancreatic head and uncinate process[27].

Additional classifications have been proposed to include the presence of extra-pancreatic disease, the tumor size and taking the performance status in consideration. Katz and colleagues therefore introduced in 2008 the Katz classification sub-dividing borderline pancreatic tumors into MD Anderson type A, B and C, taking these other factors into account [36].

Group A: patients with tumor abutment of the visceral arteries or short-segment occlusion of the Superior Mesenteric Vein.

Group B: includes patients where there is a doubt on CT findings that the disease has already extra-pancreatic metastasis. Group B also includes patients with known N1 disease from previous exploration.

Group C: patients with marginal performance status

Table 3

MD Anderson staging system for adenocarcinoma of the pancreatic head and uncinate process

Resectable (all four required to be resectable)
Superior Mesenteric Artery (SMA): Normal tissue plane between tumor and vessel
Celiac axis: Normal tissue plane between tumor and vessel
Common Hepatic Artery (CHA): Normal tissue plane between tumor and vessel
Superior Mesenteric Vein (SMV)- Portal Vein (PV): patent (may include tumor abutment or encasement)

Borderline resectable (only one of the four required)
SMA: abutment
Celiac axis: Abutment
CHA: Abutment or short segment encasement
SMV-PV: may have short segment occlusion if reconstruction possible

Locally advanced (only one of the four required)
SMA: Encasement
Celiac axis: Encasement
CHA: Extensive encasement with no technical option for reconstruction
SMV-PV: Occluded with no technical option for reconstruction

Definition: **Abutment**, ≤ 180° or ≤ 50% of the vessel circumference; **Encasement**, > 180° or > 50% of the vessel circumference

Table 4

Consensus Statement of the Hepato-pancreato-Biliary Association (HPBA), Society for Surgery of the Alimentary Tract (SSA), The Society of Surgical Oncology (SSO) [27]

1- Tumors considered **localized and resectable** should demonstrate the following:

a. No distant metastases
b. No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement
c. Clear fat plans around the celiac axis, hepatic artery, and SMA

2- Tumors considered **borderline resectable** include the following:

No distant metastases
Venous involvement of the SMV vein/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the nearby arteries, or short segment venous
occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
Tumor abutment of the SMA not to exceed > 180° of the circumference of the vessel wall.

Table 5
NCCN criteria defining resectability status

Tumors considered localized and **clearly resectable** should demonstrate the following:
No distant metastases
No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion
Clear flat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA)

Tumors considered **borderline resectable** include the following:
No distant metastases
Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement.
Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
Tumor abutment of the SMA not exceeds greater than 180° of circumference of the vessel wall.

Tumors considered to be **unresectable** demonstrate the following:

- HEAD
. Distant metastases

. Greater than 180° SMA encasement, an celiac abutment, IVA
. Unreconstructible SMV/portal occlusion
. Aortic invasion or encasement
- BODY
. Distant metastases
. SMA or celiac encasement greater than 180°
. Unreconstructible SMV/portal occlusion
. Aortic invasion
- TAIL
. Distant metastases
. SMA or celiac encasement greater than 180°
- Nodal Status
. Metastases to lymph nodes beyond the field of resection should be considered unresectable.

For tumors considered resectable, the histological degree of differentiation of the tumor cells allows a grading which helps determine post-operative survival rates. Tumors composed of > 95% of glands are considered well differentiated, 50-95% glandular is moderately differentiated and < 50% glandular defines tumors as poorly differentiated. Undifferentiated tumors are more aggressive and malignant [59]

Table 6
Tumor grading system

Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated
Grade 4	Anaplastic tumors

According to the Survival, epidemiology and end result database (SEER), 16% of grade 1 carcinomas have a median survival of 5.7 months and 6.6% of Grade 4 carcinomas have a survival rate of 2.2 months[37].

9- Rationale for a neo-adjuvant chemotherapy protocol

Radiotherapy and chemotherapy induces apoptotic cell death in malignant tumors[38]. The effects have been clearly demonstrated with gastric, esophageal and rectal cancer. **More than 80% of pancreatic cancer patients are already at an advanced stage** of the disease when initially diagnosed, when an R0 resection in therefore not attainable, mostly due to distant metastasis and vascular involvement. Furthermore, surgery results in a palliative care in 25% of cases. The purpose of neo adjuvant therapy would be first, **to render borderline and non-resectable pancreatic tumors into resectable** ones by inducing shrinkage of the tumor, away from the vasculature.

A comprehensive review performed by Sonja Gillen and al showed that **1/3 of tumor initially classified as non resectable were subsequently downstaged into resectable ones after neo-adjuvant therapy** and the survival rate was thereafter comparable to resectable adenocarcinomas (with or without neo-adjuvant therapy) with 20.5 months and 20.1-23.6 months respectively [39] . Assifi et al. further performed a meta-analysis of all Phase II trials from 1960 to 2010 concerning neo-adjuvant therapy (including chimiotherapy and chimioradiotherapy). They showed with this review that the response of neo-adjuvant chimiotherapy was more pronounced in patients with borderline or unresectable disease. After neoadjuvant therapy followed by surgery, the survival time for borderline and unresectable tumors was increased to to level comparable to resectable tumors.

Also like the Gillen et al. they showed that almost 1/3 of tumors can be converted from borderline or unresectable to resectable with neo-adjuvant therapy. Second, **preoperative therapy could avoid operating unresectable tumors unaffected by**

neo- adjuvant therapy. Patients would then not have to endure the burden of an extensive surgical procedure and the effects of adjuvant therapy. Additionally, neo-adjuvant therapy may provide a treatment for micro-metastases.

Studies have also shown that pancreatic resection expected to be R0 are often R1 with a resection rate ranging from 15-20% [40] [41]. **Patients who are often unable to go on with adjuvant therapy** because of postoperative complications would be able to benefit from a pre-operative treatment. They would be able to receive the fully planed regimen [40]. The difficulty for standardized protocols lies in the heterogeneity of the definition of resectable, unresectable and borderline tumors from one center to another, in the preoperative assessment for the staging of the tumor and the chemotherapeutic agent to use. 2 regimens are currently considered as gold standard for the treatment of PDAC: **FOLFIRINOX** and the combination **nab-Paclitaxel with Gemcitabine**.

9-1- Gemcitabine

Since the late 90s, Gemcitabine has been FDA approved for the treatment of pancreatic cancer in the United States and has been until recently, used as a first line treatment for both unresectable pancreatic cancer and later as adjuvant therapy. A randomized trial showed that Gemcitabine had a higher overall median survival rate when compared to the previous standard treatment, fluorouracil (5-FU) (5.6 vs. 4.4 months). Gemcitabine is a nucleoside analogue that has a cytotoxic effect on tumoral cells by blocking cellular replication cycle in the S phase, therefore inhibiting DNA synthesis. It is so far only intravenously administered and is also used to treat other solid tumors including ovaries, lungs and breast. Gemcitabine toxicity is dose dependant. WHO grade 3 and 4 toxicity have been reported for hemoglobin, neutrophils, thrombocytes, vomiting and diarrhea. But overall gemcitabine seems to be well tolerated

with mild toxicity and only transient myelosuppression, pulmonary toxicity and rarely alopecia [42]

In 2011, the study performed by Conroy et al. showed that the FOLFIRINOX regimen (5FU, Oxaliplatin and Irinotecan) enabled a higher overall rate. Thought it also had a lower safety profile, it became the first line treatment of choice. Nevertheless, the same year, Van Hoff et al. were able to show that when combined with albumin bound paclitaxel particles (Nab-Paclitaxel), the intratumoral concentration of Gemcitabine could be enhanced, incrasing the overall median survival rate when compared to Gemcitabine alone. This led to this new combination to be considered another choice for fist line therapy.

9.2- Nab-Paclitaxel (Abraxane)

As opposed to Gemcitabine, nab-Paclitaxel is a fairly new chemotherapeutic drug, approved by the FDA in the United States since 2004. It acts by preventing cell division and inhibiting mitosis by blocking cells in the G2 and M phases [43]. It is mainly used for the treatment of lung, ovarian and breast cancer. nab-Paclitaxel was developed as an alternative to unsolvable taxanes forms that need the addition of a solvent prior to administration. It is formulated with albumin and is highly soluble. A study evaluating nab- Paclitaxel as a treatment for refractory pancreatic cancer [44] reported neutropenia and dehydration as grade 3 and 4 toxicities.

As previously mentioned, Daniel D. Van Hoff et al in a multicentric randomized phase III trial compared nab-Paclitaxel followed by Gemcitabine and Gemcitabine alone in patients with proven metastatic pancreatic cancer [45]. They showed that in the combination arm, the median survival rate was significantly increased (8.5 versus 6.7 months) (hazard ratio for death, 0.72; 95% CI, 0.62 to 0.83; P<0.001). **The response**

rate in the nab- Paclitaxel plus Gemcitabine group was 29% versus 8% in the Gemcitabine alone group. They reported a higher rate of grade 3-4 toxicity in the nab-Paclitaxel- Gemcitabine group (neutropenia, thrombocytopenia, leucopenia, anemia, neuropathy, fatigue, diarrhea). An experimental model also indicated that nab-Paclitaxel had the potential to increase gemcitabine concentration in tumor and plasma [43] [46].

9.3- FOLFIRINOX

FOLFIRINOX is also a new chemotherapeutic regimen. It combines oxaliplatin, irinotecan, 5-Fluorouracil and leucovorin. Through this multiple therapeutic association, FOLFIRINOX acts at multiple level of the tumor DNA by blocking synthesis, duplication and repair. Its effects were demonstrated in the 2011 Randomized phase III **ACCORD 4/Prodige 11 trial [12]** that compared chemotherapy with Folfirnox versus Gemcitabine for metastatic pancreatic cancer as a first line regimen. From this trial, FOLFIRINOX emerged as the new promising therapeutic regimen. This study showed that patients treated with FOLFIRINOX had a higher tumor response and increased median survival rate compared to those treated with Gemcitabine alone 11.1 months vs. 6.8 months; hazard death ratio 0.57; 95% CI: 0.37-0.59; P<0.0001). They were able to obtain **a response rate of 31.6%** (9.4% for Gemcitabine) after 12 cycles of chemotherapy. The main drawback was the **higher toxicity effect in the FOLFIRINOX group** resulting in grade 3 or 4 febrile neutropenia, diarrhea, thrombocytopenia and sensory neuropathy [47]. Because of this, FOLFIRINOX is used for patients with a **good performance status** (Eastern Cooperative Oncology group performance status of 0 or 1, bilirubin less than 1.5 times the upper limit of normal, adequate bone marrow function, and less than 76 years[62]. Brian A. Boone et al. [48] retrospectively reviewed FOLFIRINOX use as a neoadjuvant adjunct in a study and were able to safely perform surgery after the administration of FOLFIRINOX while managing

the toxicity issue. They also had no delay to perform surgery after the administration of FOLFIRINOX and the postoperative complications were comparable to those treated by Gemcitabine found in the literature. The resection rate for borderline tumors was 43% with 33% R0. They were also able to obtain a 5% complete pathological response with FOLFIRINOX (2.5% with gemcitabine alone). Hosein et al also retrospectively assessed the effect of neoadjuvant FOLFIRINOX on locally advanced pancreatic cancer. They had a 39% rate of conversion from unresectable to resectable with an overall R0 resection rate of 44% [49].

Because of the reported toxicity of the FOLFIRINOX regimen, Blazer et al. [50]reported a modified version (mFOLFIRINOX) which consisted in no bolus of fluorouracil, no leucovorin and decreased irinotecan for patients with advanced non metastatic pancreatic adenocarcinoma. Though their study was retrospective and included a small number of patients, it showed that the mFOLFIRINOX regimen caused less toxicity with an 86.4 % R0 resection. This study outlined that there is still a potential in improving the FOLFIRINOX regimen.

More recently a French prospective observational study looked at the effect of FOLFIRINOX on locally advanced pancreatic adenocarcinoma. They enrolled 77 patients and were able to obtain a disease control rate and an objective response rate of 84% and 28% respectively. The median progression free survival was 13 months and the overall survival 22 months and only 6 % of patients had to discontinue treatment because of toxicity. [51]

There are currently no studies comparing directly FOLFIRINOX and Nab-Paclitaxel with Gemcitabine.

Table 7:

Comparison of most common grade 3 and 4 adverse events occurring in more than 5% of the patients for FOLFIRINOX and Nab-Paclitaxel+Gemcitabine.

	FOLFIRINOX	Nab-Paclitaxel + Gemcitabine
Response rate	34.1%	23%
Median overall Survical	11.1months	8.5 months
Median Progression free survival	6.4 months	5.5 months
Adverse events Neutropenia	45.7%	38%
Febrile Neutropenia	5.4%	3%
Thrombocytopenia	9.1%	13%
Anemia	7.8%	13%
Leukopenia	_	31%
Fatigue	23.6%	17%
Vomiting	14.5%	__
Diarrhea	12.7%	6%
Sensory Neuropathy	9%	__
Peripheral Neuropathy	__	17%
Elevated level of alanine aminotransferase	7.3%	__
Thromboembolism	6.6%	__

10- Literature review of prospective trials of neo-adjuvant chemotherapy between 2000 and 2015

A search was performed on Pubmed, The Google scholar, Scopus and the Web of Science database selecting articles and abstracts related to neo-adjuvant chemotherapy from January 2000 to January 2015 with key words including pancreas cancer, neo-adjuvant therapy and pre-operative treatments.

The purpose was to identify all prospective trials, using exclusively chemotherapy in a pre-operative setting. There were no restrictions to the regimens used. Search criteria were further adjusted to include articles referenced in the reviewed articles. To further insure accuracy, all relevant articles found were correlated between the different databases. Criteria of exclusion were: studies evaluating the combination of chemotherapy with radiotherapy, retrospective trials, case reports, review articles and Meta-analysis.

Table 7:

Search results by key words according to the 4 search engines

	Neoadjuvant Pancreas Cancer	Neoadjuvant Pancreas treatment	Pre-Operative treatment pancreatic cancer
Google Scholar	>20000	>20000	>20000
Scopus	887	1107	200
Web of Science	40	937	538
Pubmed	943	972	222

Only 5 prospective trials were found. These were prospective non-randomized cohort studies (see table 7).

M. Gnant et al. [52] in 2004, through a **phase II study** looked at the effect of neo-adjuvant chemotherapy with **gemcitabine and doxetaxel** for patients with **locally advanced non-metastastatic pancreatic cancer**. They enrolled 61 patients with confirmed pancreatic cancer (T2-4, Nx, M0). They were staged with multi CT or MRI and non-resectability was confirmed. They received chemotherapy with escalation dosage during 8 -12 weeks with gemcitabine and doxetaxel. Patients were then reassessed for resectability. Patients, who had tumors deemed resectable, underwent surgery within 4 weeks after chemotherapy. **79% of patients (48/61) had tumors resected successfully** and all resections had free margin (R0). The 1 and 3 years survival rate were respectively 85 % and 69%. M. Gnant et al. therefore, concluded that neo-adjuvant chemotherapy with Gemcitabine and doxetaxel was able to downstage unresectable tumor into resectable ones in most patients leading to a survival increase

Daniel H. Palmer et al. [40] in 2006 compared neo adjuvant therapy with **gemcitabine versus Gemcitabine + Cisplatin** in a **randomized phase II** study. 50 patients with potentially resectable pancreatic cancer of the head of the pancreas were recruited. Patients with tumor surrounding >180° of the circumference of the portal or superior mesenteric vein, or direct tumor extension to either the superior mesenteric artery or the celiac axis, or with evidence of extra pancreatic disease on CT Scan were considered non resectable and excluded. The protocol was for patients to receive their treatment every 7 days for 43 days. Patients then went on with surgery after completion of the pre-operative therapy with no further adjuvant therapy. Their study was mainly able to demonstrate that neo- adjuvant therapy with a combination of Gemcitabine and Cisplatin was well tolerated by patients in this setting and increased the resection rate from 42%

to 70%. They also had a 75% R0 and 44% node-negative resection rate. Daniel H. Palmer et al. further concluded that this was due to a dowstaging effect of the neo-adjuvant therapy.

The 12 month survival rate was 41.7% for patient treated with Gemcitabine and 61.5% for patient with Gemcitabine + Cisplatin. Both regimens were well tolerated with Grade III/IV hematological toxicity experienced by 41% in the Gemcitabine arm and 41.7% in the Gemcitabine + Cisplatin arm. There was no Grade III/IV non-hematological toxicity in the Gemcitabine arm and was uncommon in the combination arm. No chemotherapy-related biliary stent complications were reported. The conclusion of this trial was that neoadjuvant chemotherapy with Gemcitabine was feasible and higher resection rate were obtain when neo-adjuvant therapy associated Gemcitabine with Cisplatin. Though this study does not enable to draw conclusion regarding the efficacy of neoadjuvant chemotherapy compared to surgery alone, it does give us an indication of resection rate obtained when neoadjuvant chemotherapy is applied.

Stefan Heinrich et al. [53] [54] in Zurich initiated a phase III prospective randomized trial in progress since 2011 (NEOPAC study). In the **phase II trial**, they recruited 28 patients between 2001 and 2007 that had cytologically proven **resesctable head pancreatic adenocarcinoma** to receive neo-adjuvant chemotherapy. Patients with distant metastases, vascular infiltration of the superior or celiac axis were excluded. The selected patients then received **gemcitabine and cisplatin**. After the last cycle, patients were restaged before going onto surgery. They were able to obtain a cytopathic effect and histological response in a majority of patients as reported by results from their phase II trial. The positive response was confirmed by a decrease in the CA-19-9

level in most patients and a decrease in the metabolic activity by the pancreatic tumor using a FDG PET-CT. Furthermore, the median survival rate was 26.5 months.

In Conclusion, like other trials looking into the effect of neoadjuvant chemotherapy, a positive response is obtained on the tumor. The purpose of their ongoing phase III multicenter randomized trial is to assess the effect of neoadjuvant chemotherapy on survival for patients with pancreatic head carcinoma. Patients with proven adenocarcinoma with the same criteria as the phase II trial are enrolled in 2 arms. The experimental arm is treated with 4 bi-weekly cycles of gemcitabine 1000 mg/m2 and oxaliplatin 100 mg/m2 followed by surgery. The control arm is treated with primary surgery. Both arms then receive adjuvant chemotherapy with gemcitabine 1000 mg/m2 for 6 months.

Motoi et al. [55] in a **prospective phase 2 trial** looked at the effect of neoadjuvant chemotherapy with Gemcitabine and S-1. S-1 is an oral fluoropyrimidine derivative associated with an antitumoral activity. The combination of S-1 and Gemcitabine has been shown to be non-inferior and even superior to Gemcitabine alone [6] [55]. Their study included 35 patients with confirmed PDAC. The tumors were all considered resectable or borderline resectable. After neoadjuvant chemotherapy patients with no distant metastases were refered for surgery. They showed that one of advantage of neoadjuvant chemotherapy was that patients that were able to receive the treatment had a high rate of resection, R0 resection (86%) and an increased 2 year survival rate (45-50%). Motoi et al. noted as a disadvantage that neoadjuvant chemotherapy delayed the time to surgery thus potentially allowing tumor progression.

O'Reilly et al. in 2014 [56] also investigated the rationale of neoadjuvant chemotherapy in a single arm non-randomized phase II trial that assessed the effect of

the regimen Gemcitabine with Oxaliplatine. Out of 38 patients with radiologically confirmed resectable PDAC that completed neoadjuvant chemotherapy, 74% underwent a R0 resection and the median overall survival was 27.2 months.

To be mentioned is a multicenter prospective randomized trial performed in 2007 by Brunner et al. [57] comparing primary surgery and neoadjuvant chemoradiotherapy followed by surgery. 73 patients with histologically proven ductal adenocarcinoma of the pancreatic head, <180 contact to peri-pancreatic vessels were recruited.

As oppose to the study performed by Palmer et al [40]., though they use the same chemotherapeutic molecules their **neo-adjuvant protocol included the use of radiotherapy**. Patients enrolled in this study were divided in 2 arms. The experimental arm was composed of patients treated with gemcitabine, cisplatin and fractioned radiotherapy on the tumor site and the regional lymph nodes. The preoperative treatment was well tolerated with a low-grade 4 toxicity rate. **R0 resection was achieved in 67% versus 90% in the neoadjuvant group**. Furthermore, survival was increase from 18 to 25 months in the neo-adjuvant group. As with other trials evaluating neoadjuvant therapy for pancreatic cancer, these results are encouraging but a larger trial is still needed.

Table 8

Summary of non-randomized cohort studies for neoadjuvant chemotherapy trials

Author	Trial year	N patients	Neoadjuant Regimen	Type of study	R0 Resection	Tumor Classification
Gnant et al. [52]	2004	61	Gemcitabine and doxetaxel	phase II	79%	Locally advanced non metastatic
Palmer et al [40].	2006	50	Gemcitabine + Cisplatin	phase II	75%	Resectable
Heinrich et al. [54]	2007	28	Gemcitabine and Cisplatin	phase II	93%	Resectable
Motoi et al [55].	2010	35	Gemcitabine and S-1	phase II	86%	resectable or borderline resectable
O'Reilly et al [56]	2011	38	Gemcitabine and Oxaliplatine	Phase II	74%	Resectable

Andriulli and al. [58] Performed a meta-analysis of all prospective studies (including radiotherapy) from 1996 to 2010. It included 20 studies and 707 participants but no phase III trials. A clear benefit for patient with initially resectable tumors was not demonstrated as they were not able to illustrate that the rate of clear margin resections and the survival rate was increased for patients treated with preoperative therapy followed by surgery compared to primary surgery followed by adjuvant therapy. For patients with tumors classified as unresectable, their review sided with the claim that neo-adjuvant chemoradiotherapy was able to downstage the tumor, though this benefit had to be weighed against the toxicity effect of neo-adjuvant chemoradiotherapy. Andriulli and al. showed that tumors initially classified as unresectable were downstage

in 28% of the 362 cases they reviewed. When patients were surgically reassessed, 72% were able to undergo a successful resection with a survival rate increased from 8.4 months to 16.7 months. (Compared to 30.5 months for patients with initially resectable tumors). On the other hand, the majority of patients with unresectable tumors (70%) did not benefit from preoperative therapy.

11- Conclusion:

The purpose of this work was to define precise guidelines to follow when treating pancreatic cancer patients and to identify the role of neo-adjuvant chemotherapy. Based on the literature review, we were able to find 5 trials assessing the role of neo-adjuvant chemotherapy for the treatment of pancreatic adenocarcinoma. Most of these trials are limited and were non-randomized prospective cohort studies. However they all showed a possible benefit in allowing patients to undergo higher R0 resections, compared to similar patients who did not receive neo-adjuvant chemotherapy. Also, though worldwide the criteria defining the resectability of a tumor vary from one center to another, we can clearly state that there are 3 categories of management for pancreatic adenocarcinoma and patients need to be treated accordingly. Tumors classified as Borderline benefit the most from neoadjuvant chemotherapy. At the Geneva University Hospital, we propose to rely on the MD Anderson staging system for adenocarcinoma of the pancreatic head and uncinate process (see table 8). Therefore, after a multi-disciplinary discussion, we propose the guidelines as follow:
for patients with clearly resectable tumors based on the MD Anderson staging system, surgery will be proposed with the intent to achieve a R0 resection. For patients with borderline resectable tumors, surgery will also be carried out. For both of these categories treated with curative intent, surgery with be followed by adjuvant chemotherapy as studies have shown that this combination increased the overall survival rate and reduced the risk of death when tolerated by the patient.
For patients with non-resectable tumors, according to the MD Anderson staging system, chemotherapy will be proposed and the progression/regression of the tumor will then be reevaluated. Two chemotherapeutic options have shown the highest median survival rate: the FOLFIRINOX regimen and the combination Nab-Paclitaxel plus Gemcitabine.

Treating pancreatic cancer patients will remain a challenge for the years to come and the ongoing prospective randomized trials will allow to improve the treatments.

Table 9

Criteria implemented at the Geneva University Hospital (HUG) for the treatment of Pancreatic Adenocarcinoma according the M.D. Anderson Cancer Center:

Vessel	**Resectable**	**Borderline**	**Locally adanced**
Superior Mesenteric Artery (SMA)	Normal tissue plane between tumor and vessel	Tumor in contact with the artery (less than 180° or 50% of the vessel circumference	Invasion of the artery (more or less than 180° of the vessel circumference
Celiac axis/ Common Hepatic Artery (CHA)	Normal tissue plane between tumor and vessel	Tumor in contact with the artery (less than 180° or less than 50% of the vessel circumference) or invasion of short segment of the CHA (more than 180° or 50% of the vessel circumference allowing safe resection and reconstruction	Invasion with no technical option for reconstruction Due to tumor extension to the Celiac axis/Splenic a./left Gastric a.
Superior Mesenteric Vein (SMV)- Portal Vein (PV)	Patent/Tumor in contact with the vein (more or less than 180° of the vessel circumference	May have short segment occlusion if reconstruction possible (Patent vessels above and under the occlusion).	Occluded with no technical option for reconstruction

Resectable	**Borderline**	**Locally advanced and/or metastatic**
Surgery/ Adjuvant chemotherapy	Surgery/ Adjuvant chemotherapy	Chemotherapy

Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, Lee JE, Pisters PW, Evans DB, Wolff RA. Borderline resectable pancreatic

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