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par **Aurélien LAMBERT**

Sous la direction du Pr Thierry CONROY

Évaluation de la qualité des marges de résection chirurgicales comme facteur pronostique de récidive et de survie des cancers du pancréas opérés puis traités par chimiothérapie adjuvante

le 5 décembre 2022

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Abréviations

CRF : Case report form
DFS : Disease free survival
DMFS : Distant metastasis free survival
IPMN : Intraductal papillary mucinous neoplasm
MCN : Mucinous cystic neoplasm
MSI : Micro satellite instability
OS : Overall survival
PanIN : Pancreatic intraepithelial neoplasia
PFS : Progression free survival

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Introduction

Le cancer du pancréas

L'adénocarcinome pancréatique est l'un des cancers ayant la plus grande mortalité. Sa prise en charge médicale reste un des plus grand challenges en cancérologie. La survie à 5 ans des patients atteints avoisine les 9% seulement (1). Les estimations GLOBOCAN en 2018 rapportent 432 000 décès imputables à ce cancer dans le monde (2). Les prédictions en font une des causes majeures de décès par cancer dans la décennie à venir (3).
Plus de 80% des cancers du pancréas sont diagnostiqués à un stade avancé, ne laissant de place que pour une prise en charge palliative bien souvent. La survie à 5 ans des patients porteurs d'un adénocarcinome pancréatique n'est que de 2,9% (1,4), et l'on compte peu d'innovations majeures dans son traitement depuis une trentaine d'années. Le cancer du pancréas n'a pas encore connu la révolution qu'ont pu rencontrer d'autres pathologies cancéreuses.

On distingue trois groupes d'évènements oncogéniques différents dans cette pathologie :

- Mutation somatique *KRAS* (90% des cas).
- Mutations de gènes suppresseurs de tumeurs tels que *TP53* (50-70% des cas), *CDKN2A* ou encore *SMAD4*.
- Mutations germinales des gènes de réparation de l'ADN tels que *BRCA1/2* (4 à 7% des cas) ou plus rarement *PALB2* ou *ATM* (<1% des cas).

Les patients présentant une instabilité micro-satellitaire (MSI) sont négligeables dans la population des patients opérés (0,3% des cas).

Le seul traitement potentiellement curatif reste la chirurgie, même si seulement 10 à 20% des patients sont réellement opérables d'emblée si l'on réalise une stadification soigneuse (5). Selon le National Comprehensive Cancer Network (NCCN), un patient opérable d'emblée est défini par l'absence de métastases ganglionnaires ou viscérales à distance ; l'absence d'envahissement vasculaire des veines porte et mésentérique supérieure ; de thrombus veineux ou d'engainement veineux de > 180° et de l'absence d'envahissement artériel du tronc cœliaque , de l'artère hépatique et de l'artère mésentérique supérieure (6).

Malgré tout, les résultats d'une chirurgie seule sont décevants, avec une survie globale médiane de 15 à 20 mois et une survie à 5 ans de 8 à 15% (7–9). La démarche chirurgicale doit s'inscrire dans une stratégie combinée avec les traitements systémiques du cancer, la chimiothérapie adjuvante étant à ce jour le standard. Celle-ci a permis des progrès importants sur la survie depuis plusieurs années, en témoignent les essais adjuvants récents (10–12).

Pour progresser encore dans notre démarche, il est important de tirer les leçons des essais cliniques publiés, qu'ils soient positifs ou non, afin de mieux caractériser les patients et de savoir identifier les facteurs pronostiques indépendants majeurs.

Rationnel

Des marges de résection envahies lors de la chirurgie d'un cancer du pancréas évoquent une résection incomplète et exposent à un risque de récidive locale. Pour mieux évaluer le statut des marges de résection, le Collège Royal des pathologistes en Grande-Bretagne et le manuel de l'AJCC recommandent l'encrage des marges antérieure, médiale (anciennement appelée rétropéritonéale postérieure, mésentérique ou uncinée) et rétropéritonéale des pièces opératoires. R1 est aujourd'hui défini comme une marge inférieure ou égale à 1 mm (www.rcpath.org) avec l'exception de la surface antérieure du pancréas qui n'est pas considérée comme une véritable marge. La valeur pronostique défavorable d'une résection R1 avec un cut-off à 1 mm a également été suggérée dans une méta-analyse, mais seulement pour les tumeurs de la tête du pancréas (13). Un cut-off à 1 mm pour les marges de résections a ensuite été validé pour les cancers du corps et de la queue du pancréas (14).

La mise en place d'un protocole d'examen anatomopathologique standardisé augmente considérablement le pourcentage de limites de résections positives (15,16) et donc de chirurgie R1.

Valeur pronostique controversée

Les marges de résection d'une tumeur du pancréas sont généralement reconnues comme un facteur pronostique indépendant de survie après chirurgie « curative » (17–21).

Dans l'étude de chimiothérapie adjuvante CONKO 001(9) comme dans l'étude PRODIGE 24/ CCTG PA6 (12), le bénéfice du traitement adjuvant est observé quel que soit le statut des marges ou la qualité de l'exérèse. Dans l'essai PRODIGE 24/ CCTG PA6, en analyse uni-

factorielle une résection R1 était un facteur pronostique défavorable pour la survie sans rechute, les patients R1 ayant 1,45 fois plus de risques de rechute (CI 1,16-1,81; p=0,01). Cependant, en analyse multivariée, le caractère R0 ou R1 n'est pas un facteur pronostique, les facteurs pronostiques indépendants étant le grade tumoral et la nécessité ou non d'une résection de la veine porte. Les résultats de survie après résection R0 ou R1 n'ont pas été analysés initialement et ont fait l'objet d'une analyse complémentaire avec les données de survies à 5 ans. La valeur pronostique défavorable est également confirmée dans l'étude ESPAC-3 (22).

Dans une autre étude de chimiothérapie adjuvante, le caractère R1 d'une chirurgie pour cancer du pancréas a été un facteur pronostique indépendant (23). Mais aussi, dans la méta-analyse des essais ESPAC (24), l'envahissement des limites de résection n'a pas constitué un facteur pronostique significatif.

Un contrôle qualité exhaustif a été réalisée dans l'étude PRODIGE 24/ CCTG PA6 à partir de l'ensemble des comptes-rendus anatomopathologiques et des comptes-rendus opératoires. Un encrage des marges a été réalisé dans 51,5% des cas. Les erreurs de classement portant sur le caractère R0 ou R1 de la chirurgie concernait 24,1% des CRF.

Le nombre de patients où la totalité des 7 marges ont été examinées n'était pas connu. On peut émettre l'hypothèse que lorsque des marges n'ont pas été examinées (tout particulièrement la marge médiale et la marge pancréatique postérieure), le caractère R0 de la résection a pu être surestimé et qu'il y a probablement plus de marges qui auraient dû être positives dans l'étude PRODIGE 24/ CCTG PA6. Le faible nombre de résections R1 de l'étude PRODIGE 24/ CCTG PA6 (43%) par rapport à la littérature et à ESPAC-4 (11) est en faveur de cette hypothèse. L'incorporation à tort de gestes chirurgicaux possiblement R1 dans le sous-groupe R0 aurait pu conduire l'aggravation du pronostic du groupe classé R0, ce qui pourrait être une explication à l'absence de valeur pronostique indépendante d'une chirurgie R1 vs. R0.

Objectifs

Suite à l'essai PRODIGE 24/ CCTG PA6, il restait à savoir si ce surcroit de travail demandé au chirurgien et à l'anatomopathologiste pour l'étude des marges était utile et si cela pourrait préciser d'éventuelles indications à une radiochimiothérapie complémentaire après chimiothérapie adjuvante.

Cette étude rétrospective basée sur l'essai PRODIGE 24/ CCTG PA6 (493 patients), visait à déterminer quelles sont les marges qui ont valeur pronostique indépendante et si l'examen de celle-ci est facilité par un encrage de la pièce opératoire.
Ont été considérées les 7 marges recommandées et enregistrées dans les CRF de PRODIGE24 : la transsection pancréatique, la marge sur la voie biliaire, la marge sur le duodénum proximal, le duodénum distal, le lit de la veine mésentérique supérieure, la marge médiale (artère mésentérique supérieure) et la marge postérieure pancréatique.

Plusieurs questions sont posées :

- Le caractère R0/R1 d'une chirurgie est-il un facteur pronostique indépendant dans le contexte d'une chimiothérapie adjuvante lorsque toutes les marges de résection sont examinées ?
- L'absence ou le faible nombre de marges examinées est-il un équivalent pronostique à une résection classée R1 ?
- Le caractère R1 est-il associé à d'autres facteurs cliniques, histologiques ou biologiques ?
- Une marge de résection envahie est-elle associée à une incidence accrue de récidive locale ?
- Quelles sont les marges chirurgicales envahies qui ont la valeur péjorative la plus forte ?

Question de recherche

L'objectif de cette étude était donc d'étudier le pronostique de l'envahissement des marges de résection chirurgicale en termes de survie sans rechute et de récidive de la maladie chez des patients porteurs d'un adénocarcinome pancréatique après une chirurgie de type duodénopancréatectomie céphalique (avec ou sans préservation du pylore) suivie d'une chimiothérapie adjuvante en se basant sur les données de l'essai randomisé PRODIGE 24/ CCTG PA6.

Liens entre les publications

Publication 1 – État de l'art de la prise en charge des cancers du pancréas réalisé après avoir effectué un contrôle de qualité de la base de données de l'essai PRODIGE 24/ CCTG PA-6 (avant publication), qui a permis de définir la question principale de ce travail de thèse. C'est une revue générale du cancer du pancréas.

Publication 2 – Focus sur la stratégique chirurgicale avec les traitements associés et la place de la chimiothérapie, permettant une meilleure appréhension de l'essai clinique PRODIGE 24/ CCTG PA-6 ensuite. La focalisation sur la question de la chirurgie et de la place de la chimiothérapie possiblement première nous a permis de mieux déterminer les facteurs de risques importants dans les stratégiques multimodales.

Publication 3 – Essai clinique PRODIGE 24/ CCTG PA-6, publication des résultats mis à jour avec les données de survie à 5 ans. Base de données issue directement de cet essai.

Publication 4 – Étude du caractère pronostique de la présence de lésion pré-cancéreuses sur les pièces opératoires afin d'évaluer si celles-ci sont un facteur de risque indépendant sur la survie sans rechute de la maladie. Ceci était une étape préalable à l'étude des marges de résection afin de distinguer deux éventuels facteurs de risques locaux confondants. Ceci d'autant plus que les lésions dysplasiques sont fréquentes chez ces patients.

Publication 5 – Étude de l'impact de l'envahissement des marges de résection chirurgicales sur la récidive et la survie des patients traités dans l'essai randomisé PRODIGE 24/ CCTG PA-6 et ayant bénéficié d'une chimiothérapie adjuvant après chirurgie.

Publication 1 – An update on treatment options for pancreatic adenocarcinoma

Revue de la littérature (publiée)

***Lambert A**, Schwarz L, Borbath I, et al. An update on treatment options for pancreatic adenocarcinoma. **Therapeutic Advances in Medical Oncology. 2019**;11. doi:10.1177/1758835919875568*

Cette revue de la littérature reflète la genèse du projet d'étude des facteurs pronostiques de récidive et de survie des cancers du pancréas opérés et traités par chimiothérapie adjuvante. En amont de la rédaction de cet article, nous avions réalisé un contrôle qualité exhaustif de la base de données de l'essai PRODIGE 24/CCTG PA6 avant publication et trouvé un sujet d'intérêt concernant l'étude des marges de résections chirurgicales de ces patients. Pour le mener à terme, une revue exhaustive de la littérature était nécessaire, notamment concernant les traitements d'avenir et les facteurs de risques connus.

Ce recueil nous a permis de faire un état de l'art de la prise en charge des patients suivis pour un cancer du pancréas, quel qu'en soit le stade, en collaboration avec de nombreux experts dans le domaine. La direction d'une telle revue a été l'occasion de d'appréhender de nouvelles approches thérapeutiques qui sont parfois plus éloignées de l'oncologie médicale et des traitements systémiques du cancer.

Le cancer du pancréas étant une maladie longtemps silencieuse, avec peu de symptômes avant-coureurs évidents, et une évolution rapidement métastatique, il était important de distinguer les avantages et les limites des différents traitements, ainsi que de relever les facteurs pronostiques qui aident à la décision thérapeutique.

Il était important de documenter l'ensemble des stratégies thérapeutiques et les pistes d'avenir pour réaliser un travail d'ampleur. L'analyse des essais thérapeutiques en cours à ce moment nous a permis également de suivre l'évolution de ces stratégies dans le temps.

Cette revue appréhende tous les aspects de cette maladie, notamment le versant curatif (adjuvant et néoadjuvant), sujet clé de la suite de nos travaux.

Si cet article met en avant les traitements prometteurs, il s'attache surtout à pointer les questions d'impact majeur et dont la résolution sera plus probablement suivie de nouvelles

combinaisons stratégiques, notamment en ce qui concerne la pertinence des traitements d'induction et l'apport éventuel de la radiothérapie combinée à la chimiothérapie.

Check for updates

Therapeutic Advances in Medical Oncology

Review Article

An update on treatment options for pancreatic adenocarcinoma

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Aurélien Lambert, Lilian Schwarz, Ivan Borbath, Aline Henry, Jean-Luc Van Laethem, David Malka, Michel Ducreux and Thierry Conroy

***Abstract*:** Pancreatic cancer is one of the most lethal solid organ tumors. Due to the rising incidence, late diagnosis, and limited treatment options, it is expected to be the second leading cause of cancer deaths in high income countries in the next decade. The multidisciplinary treatment of this disease depends on the stage of cancer at diagnosis (resectable, borderline, locally advanced, and metastatic disease), and combines surgery, chemotherapy, chemoradiotherapy, and supportive care. The landscape of multidisciplinary pancreatic cancer treatment is changing rapidly, especially in locally advanced disease, and the number of treatment options in metastatic disease, including personalized medicine, innovative targets, immunotherapy, therapeutic vaccines, adoptive T-cell transfer, or stemness inhibitors, will probably expand in the near future. This review summarizes the current literature and provides an overview of how new therapies or new therapeutic strategies (neoadjuvant therapies, conversion surgery) will guide multidisciplinary disease management, future clinical trials, and, hopefully, will increase overall survival.

Keywords: adjuvant chemotherapy, borderline pancreatic cancer, FOLFIRINOX, guidelines, pancreatic cancer, supportive care, surgery

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Introduction

Pancreatic cancer remains one of the greatest challenges in oncology, and is presently the fourth leading cause of cancer deaths in the United States. This review will cover different ways to increase survival or to manage this aggressive disease. We will review the criteria of surgical quality, new data on surgical care, progresses in adjuvant therapy, and the optimal timing of adjuvant chemotherapy. We will also provide an update on systemic therapies for advanced pancreatic cancer, and a comprehensive analysis of published clinical trials in second-line therapy, updates on new options in personalized medicine, management of borderline resectable pancreatic cancer, available data on the effectiveness of neoadjuvant therapies, new data on locally advanced pancreatic cancer, especially the role of conversion surgery, and, finally, supportive and palliative care.

Pancreatic cancer is expected to be the second or the third leading cause of cancer deaths in high-income countries in the next decade.[1,2] Pancreatic ductal adenocarcinoma (PDAC) and its variants are the most frequent type, representing 85–90% of all pancreatic neoplasms. Median age at diagnosis is 70–71 years.[3,4]

The incidence of pancreatic cancer is increasing rapidly, particularly in Europe, North America, Australia, and New Zealand.[5–7] This higher incidence is associated with socioeconomic development, and is due partly to increased life expectancy, as well as to the overweight/obesity epidemic. Despite recent advances in the management of PDAC, poor survival rates continue, with 8–11% of patients in Europe and United States alive at 5 years after diagnosis.[6–8] Owing to the lack of early symptoms, and to the metastatic potential of PDAC cells, up to 80% of patients

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receive a diagnosis at an advanced stage, by which time the tumor is unresectable.[9]

Advances in surgical management of pancreatic cancer

Surgery is the only potentially curative treatment for pancreatic adenocarcinoma, although only 10–20% of patients have clearly resectable disease after careful pretherapeutic staging.[9]

Resectable adenocarcinoma [according to National Comprehensive Cancer Network (NCCN) classification 2019][10] is defined by the absence of distant organ or distal lymph node metastases; the absence of evidence of superior mesenteric vein and portal vein distortion; tumor thrombus, or venous encasement $> 180°$; and the existence of clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA).

However, even after curative surgery, the oncological results of surgery alone are disappointing, with a median survival of 15–20 months and a 5-year survival of 8–15%, owing to the high frequency of local and distant relapses.[9,11–13] Therefore, surgery must be integrated into a complete treatment sequence, also known as multimodal treatment.[14] With surgery and adjuvant chemotherapy, notable progress has been observed over the past 5 years, with a large increase in median overall survival in the most recent adjuvant trials.[15–17] Complications after pancreatic resections are also reduced by progress made in perioperative and critical care, and in the standardization of surgical techniques.

Criteria of surgical quality are now internationally accepted and should be respected. However, the main progress that must be made is improvement in the selection of operable patients and a reduction of postoperative complications.

Criteria of surgical quality

Pancreaticoduodenectomy. In patients with adenocarcinoma located in the head of the pancreas, pancreaticoduodenectomy (PD) is the recommended surgical technique, and skeletalization of the SMA down to adventitia on anterior, lateral, and posterior borders is the standard of care.[18,19] The SMA first approach facilitates lymphadenectomy, and optimizes oncological control of the retroperitoneal margin. In a recent meta-analysis, intraoperative blood loss, pancreatic fistula, delayed gastric emptying, and local recurrence were significantly lower with the SMA first approach than with standard PD.[20]

Dissection of more than 15 lymph nodes is recommended,[21,22] and standard lymphadenectomy must include lymph nodes of the following stations of the Japan Pancreas Society nomenclature[23]: suprapyloric (5), infrapyloric (6), along the common hepatic artery (8a), along the bile and cystic ducts (12b and 12c), on the posterior surface of the pancreatic head (13a, 13b), at the origin of the superior mesenteric artery (SMA) (14a), on the right side of the SMA (14b), and on the anterior surface of the pancreatic head (17a and 17b).[22] More aggressive surgery (i.e. extensive lymphadenectomy) does not improve long-term survival and is not recommended.[24] Para aortic lymph node sampling with frozen section examination is an option, and some authors recommend performing such sampling in all cases of PD due to the negative impact on survival of these metastases.[25–27]

Distal pancreatectomy. In patients with adenocarcinoma located in the left pancreas (body or tail), distal pancreatectomy with splenectomy is recommended. To obtain a histologically complete resection (R0 surgical margin status), Strasberg and colleagues described a modification of the standard technique based on an anterograde approach, complete dissection of N1 lymph node stations and enlargement to the left prerenal fascia of the posterior dissection plane (radical anterograde modular pancreatosplenectomy), which improves the retroperitoneal resection margin.[28,29] However, the potential survival benefit of this procedure should be evaluated in a prospective study.

Regional lymphadenectomy carries the gastrosplenic lymph nodes and those from the left edge of the celiac trunk to that of the superior mesenteric artery. Lymphadenectomy must include lymph node levels 9, 10, 11, and 18.[21,22,24–33] Dissection of $\geqslant$15–20 lymph nodes and skeletalization of the SMA down to adventitia on anterior, left lateral, and posterior borders is recommended.[30]

Surgical resection margin status. The main resection margins (at minimum, superior mesenteric vein, posterior pancreatic surface and the medial margin) of surgical specimens should be inked, examined, and reported using a standardized pathological protocol in agreement with guidelines of

the College of American Pathologists, American Joint Committee on Cancer (AJCC), or the Royal College of Pathologists, to better assess the margin status.[34,35] Tumor clearance is defined by the precise distance between the margin and the tumor cells.[31]

The aim of surgery is to achieve complete resection of the tumor with microscopically negative margins (R0). According to the most recent publications, following PD, R0 resection should be defined as clearance (margin of healthy tissue around the removed tumor) of >1 mm.[31–33] In cases with R1 margin status, additional information should be reported to distinguish cases with a tumor-free margin <1 mm [R1 (<1 mm)] and cases with tumor cells directly at the margin [R1 (direct)], direct invasion having a poorer prognosis.[32] This cut-off was recently validated as an independent determinant of survival after resection for pancreatic adenocarcinoma of the body and tail.[36]

Laparoscopic approach for pancreatic cancer

Laparoscopic PD. According to data from the US National Cancer Database, higher mortality is associated with laparoscopic PD in low volume centers, as defined by thresholds of 10–25 procedures per year, depending on the study.[37–40] In the most complete report, including only pancreatic cancers operated from 2010 to 2012,[40] there was no difference in terms of the rate of positive surgical margins (20.4% *versus* 22.1%, $p = 0.15$), a higher number of lymph nodes was removed in minimally invasive surgery in centers with low activity volume (17.4 *versus* 16.5, $p < 0.01$), and there were no differences in 30-day readmission rate (8.7% *versus* 9.5%, $p = 0.42$), 30-day mortality (2.7% *versus* 2.5%, $p = 0.35$) or 90-day mortality (5.1% *versus* 4.7%, $p = 0.22$). However, in multivariate analysis, minimally invasive surgery was associated with a significantly higher risk of short-term mortality [hazard ratio (HR), 1.95; $p < 0.01$]. There was no impact on the use of adjuvant chemotherapy. Equivalent results for long-term survival have not been demonstrated.

Despite growing interest in the minimally invasive approach for PD, the data in the literature are limited to comparative single-center studies, with few cases of pancreatic adenocarcinoma; hence, laparoscopic PD is not standard.

Laparoscopic distal pancreatectomy. A recent meta-analysis reported a significantly shorter hospital stay for patients who underwent laparoscopic *versus* open distal pancreatectomy.[41] However, there were no differences in mortality, severe morbidity at 3 months, overall morbidity, clinically significant pancreatic fistulas, and R1 resections. In a multicenter European case-control study, intraoperative blood loss (200 *versus* 300 ml, $p = 0.001$) and length of hospital stay (8 *versus* 9 days, $p < 0.001$) were significantly lower with minimally invasive *versus* open resection. No differences were observed in major morbidity and 90-day mortality. The R0 resection rate was significantly higher (67% *versus* 58%, $p = 0.019$), but the prerenal fascia resection rate (31% *versus* 60%, $p < 0.001$) and the number of lymph nodes removed (14 *versus* 22, $p < 0.001$) were lower in the minimally invasive group. Median overall survival was comparable between the two surgical approaches.[42]

With regard to oncological results, the laparoscopic approach is now considered as an option for small pancreatic cancers of the left pancreas in high-volume centers.

Control of postoperative complications and access to adjuvant treatment

Despite improvements in mortality rates associated with pancreatectomy during the past decade, postoperative morbidity rates remain high.[43–45] Given that postoperative complications may have a profound effect on quality of life,[46] access to adjuvant therapy,[47] and, ultimately, patient outcome,[48] reducing morbidity following surgery for pancreatic cancer should be a priority for surgeons.

Reduction of postoperative complications. Several surgical risk scales have been proposed to best select candidates for surgery and to screen patients at high risk of complications.

Some classifications, such as that published by Braga and colleagues,[49] as well as preoperative pancreatic resection (PREPARE) and SOAR (surgical results analysis and search) scoring systems,[50,51] are based on the integration of multiple parameters and appear to be more precise than other methods.

For cancers with a particularly poor prognosis such as pancreatic cancer, the risks and benefits

of surgical resection must be critically evaluated. Given that postoperative complications are associated with a reduction in patients' access to adjuvant therapy and survival, immediate pancreatectomy should be discouraged for particularly high-risk surgical patients, that is, patients with altered performance status, severe pre-existing comorbidities, or advanced age. These patients should be managed actively by a multidisciplinary group of expert physicians, including a specialist dietitian following a pancreas-tailored treatment program, physical therapist, and other specialists as required.

Assessment of nutritional status. Before surgical resection, it is essential to achieve adequate nutritional status, and nutritional supplements, or even parenteral nutrition, should be considered for at least 1–2 weeks before surgery in patients who are malnourished.

Weight loss, low body mass index, and loss of muscle mass have been shown to correlate with poor surgical and oncological outcomes after operations for pancreatic cancer.[52,53] Patients undergoing pancreatic surgery should receive a meticulous evaluation of their nutritional status and risk of developing malnutrition postoperatively.[54] In case of severe metabolic risk, 10–14 days of nutritional therapy are beneficial.[55]

Enhanced recovery after surgery. Enhanced recovery programs (ERPs) are an amalgamation of pre-, intra-, and postoperative measures intended to improve the postoperative course of patients. ERPs originated in Northern Europe and represent a revolution in surgical care.[56] They bring together a technical component (a care protocol including multimodal analgesia, minimally invasive surgery, optimization of perioperative fluid loading, limited use of tubes and drains, reduction of insulin resistance) and an organizational component (team mindset, preoperative conditioning, early mobilization and refeeding, keeping the patient up to date with the anticipated discharge schedule, active patient participation in the healthcare process, and risk management after discharge).[57] Several studies have demonstrated multiple advantages of ERPs, including decreased overall morbidity, quicker return to normal activities, and decreased duration of hospital stay.[58] In addition, some studies suggest that ERPs could improve the prognosis of patients treated for digestive cancer through better nutritional management, a reduction in postoperative complications, possible earlier use of adjuvant treatment, and an improvement in perioperative immune status.[59]

Although few data are available on the surgical management of pancreatic cancer, ERP has emerged as standard care, particularly in pancreatic surgery. Oncology benefit data should be available from current prospective registries.

Biliary drainage. Systematic biliary stenting has been proposed in patients with serum bilirubin levels of $>300\,\mu mol/l$, but preoperative biliary drainage has since been shown to significantly increase the morbidity rate compared with patients undergoing surgery first.[60–62] However, this higher morbidity rate does not appear to affect long-term survival.[63] Patients with severe jaundice may have jaundice-related medical conditions, such as renal failure or malnutrition that may require preoperative biliary drainage before surgery. Thus, preoperative biliary drainage should be considered only when necessary in symptomatic patients or if surgery must be postponed because of any medical condition. Self-expandable metallic stents are currently considered the standard of care in line with published data on biliary stent patency.[64]

Centralization of pancreatic surgery. Several nationwide studies have reported a hospital volume–outcome relationship after pancreatectomy, with significantly lower postoperative mortality in high-volume compared with low-volume centers.[65–67] Recent reports indicate that postoperative mortality after pancreatic resection is mostly attributable to 'failure to rescue' patients with major complication(s), rather than to hospital volume by itself. Failure to rescue is defined as mortality among patients with one or more major complications within 90 days of surgery, and corresponds to ineffective management of postoperative complications.[68] El Amrani and colleagues demonstrated that higher failure-to-rescue rates are associated with lower hospital volume, highlighting variability in the management of postoperative complications.[69] The failure-to-rescue approach suggests that, in addition to a high-volume center and high-volume surgeons, a multidisciplinary team, an intensive care unit, and a surgical service that is available at all times, are key to good functioning of the infrastructure. Consequently, many

authors and national healthcare societies have promoted the centralization of pancreatic surgery to high-volume centers to improve outcomes.[69–71] National assessments are needed to clarify the impact and feasibility of centralizing pancreatic surgery, particularly for pancreatic cancer.

Progresses in adjuvant therapy

Patients undergoing curative resection for pancreatic cancer mostly develop recurrent tumor disease; 69–75% of patients relapse within 2 years and 80–90% relapse within 5 years. The main randomized phase III studies are shown in Table 1.

Table 1. Major randomized phase III trials of adjuvant treatments for pancreatic cancer.

Study	No. of patients	Treatment arms	Outcome				Completion of full treatment[$]	What this trial contributed
			Median DFS (months)	*p* value	Median OS (months)	*p* value		
GITSG 1985[72,73]	43	Observation	NR	NR	20.0	0.035	-	First hope of efficacy of adjuvant treatment
		Split-course radiotherapy plus 5-FU and adjuvant 5-FU			10.9		62%	
ESPAC-1 2004[74,75]	289	Observation	NR	NR	15.5	0.009*	-	First demonstration of efficacy of adjuvant chemotherapy
		Chemoradiotherapy	NR		13.9		70%	
		5-FU/folinic acid	NR		20.1		50%	
		Chemoradiotherapy plus 5-FU/folinic acid	NR		19.9		NR	
CONKO-001 2007[76]	354	Observation	6.7	<0.001	20.2	0.01	-	Change in practice for gemcitabine chemotherapy
		Gemcitabine	13.4		22.8		62%	
ESPAC-3 2010[77]	1088	5-FU/folinic acid	14.1	0.53	23.0	0.39	55%	Confirmation of gemcitabine as standard chemotherapy
		Gemcitabine	14.3		23.6		60%	
JASPAC-01 2016[78]	378	Gemcitabine	11.3	0.0001	25.5	<0.0001	58%	S-1 is standard adjuvant chemotherapy in Japan
		S-1	22.9		46.5		72%	
ESPAC-4 2017[16]	730	Gemcitabine	13.1	0.082	25.5	0.032	65%	Trend in favor of gemcitabine plus capecitabine
		Gemcitabine plus capecitabine	13.9		28.0		54%	
PRODIGE 24-PA6 2018[17]	493	Gemcitabine	12.8	<0.0001	35.0	0.003	79%	Change in practice for mFOLFIRINOX in fit patients
		FOLFIRINOX	21.6		54.4		66,4%	
APACT 2019[79]	866	Gemcitabine	18.8	0.18	36.2	0.045	71%	Encouraging survival in both arms. Large tumor and blood collection for translational studies
		Gemcitabine plus nab-paclitaxel	19.4		40.5		66%	

(Continued)

Table 1. (Continued)

Study	No. of patients	Treatment arms	Outcome				Completion of full treatment[$]	What this trial contributed
			Median DFS (months)	*p* value	Median OS (months)	*p* value		
CONKO-005 2017	436	Gemcitabine	11.4	0.26	26.5	0.61	74%	First trial in R0 population. Confirmation of worse prognostic in patients with increased postoperative CA 19-9 levels.
		Gemcitabine plus erlotinib	11.4		24.6		66%	

[*]*p* value between chemotherapy and no chemotherapy; chemoradiotherapy had a deleterious effect ($p = 0.05$).
[$]Percentage of patients receiving full number of planned cycles.
5-FU, fluorouracil; CONKO, Charité Onkologie; DFS, Disease-Free Survival; GITSG, GastroIntestinal Tumor Study Group; ESPAC, European Group for Pancreatic Cancer; JASPAC, Japan Adjuvant Study of Pancreatic Cancer; NR, not reported; PRODIGE, Partenariat de Recherche en Oncologie DIGEstive; OS, overall survival.

Where are we on adjuvant chemoradiotherapy?

Locoregional tumor recurrence is considered a main cause of relapse, with up to 80% of curatively resected patients undergoing an R1 resection. The potential of adjuvant radiotherapy to reduce locoregional recurrence was first tested in a gastrointestinal tumor study group (GITSG) randomized study using fluorouracil as a radiosensitizer in patients with negative resection margins. The GITSG GI 9173 trial compared observation with split-course radiotherapy of 40 Gy delivered over 6 weeks.[72] Bolus fluorouracil was administered on each of the first 3 days of the two sequences of radiotherapy and weekly for 2 years or until recurrence thereafter. The study ended prematurely after the inclusion of 43 patients because the interim analysis showed a statistically significant survival difference ($p = 0.035$) in favor of the chemoradiation and adjuvant chemotherapy arm. Similar results were achieved in a second nonrandomized cohort of 30 patients.[73]

A European Organisation for Research and Treatment of Cancer (EORTC) trial also addressed the question of whether adjuvant chemoradiotherapy provided benefits following surgical resection in 114 patients with R0 or R1 resection. Patients in the chemoradiation arm received 40 Gy plus continuous fluorouracil infusion. Treatment was well tolerated, but no significant overall survival benefit was observed, either for patients who had adenocarcinoma located in the head of the pancreas or for the treatment group as a whole. However, the study lacked sufficient statistical power to reach definitive results.[80]

The European Study Group for Pancreatic Cancer 1 (ESPAC-1) trial compared, with a two-by-two factorial design, three adjuvant strategies with observation: chemoradiotherapy, chemotherapy alone, and chemoradiotherapy followed by adjuvant chemotherapy. To encourage participation, patients could receive prior treatments before randomization ('background' therapy), and the trial was expanded to include two other randomization options of chemoradiotherapy *versus* observation, and chemotherapy *versus* observation. Chemoradiotherapy consisted of split-course external-beam radiotherapy of 2×20 Gy dose with bolus fluorouracil on the first 3 days of radiotherapy.[74,75,80] A total of 353 patients were included in the chemoradiotherapy analysis. Background therapy was used in 41.9% of the patients. Unfortunately, after a median follow-up of 47 months, adjuvant chemoradiotherapy had a significant deleterious effect on survival [HR, 1.28; 95% confidence interval (CI), 0.99–1.66; $p = 0.05$].[74,75] The main critiques of this trial were the absence of radiation quality control and the heterogeneous treatments fields.

The RTOG 9704 trial was designed to determine whether the addition of gemcitabine to postoperative radiation with fluorouracil improved survival compared with adjuvant fluorouracil. A total of 451 patients received 50.4 Gy radiation with

concurrent continuous fluorouracil infusion after R0 or R1 resection, and were randomly assigned either fluorouracil or gemcitabine for 3 weeks before chemoradiation, then for 12 weeks after chemoradiation.[81] There was no difference in overall disease-free survival between treatment groups. In the subgroup with tumors located in the head of the pancreas ($n = 388$), a survival benefit trend ($p = 0.08$) was observed for the gemcitabine group. Patients with a postoperative carbohydrate antigen (CA) 19-9 serum level of ≥ 180 U/ml had significantly worse survival than those with a CA 19-9 of < 180 U/ml.[82]

Adjuvant chemoradiotherapy with concurrent weekly gemcitabine was also tested in an European randomized phase II study, comparing two cycles of adjuvant gemcitabine followed by chemoradiation to four cycles of adjuvant gemcitabine.[83] This trial showed that adjuvant gemcitabine followed by gemcitabine-based chemoradiotherapy is feasible and well tolerated. Local recurrence as first cause of relapse was less frequent in the chemoradiation arm (11% *versus* 24%). This schedule is under investigation by the RTOG/EORTC 0848 trial, which is evaluating both erlotinib and chemoradiation as adjuvant treatments for patients with resected adenocarcinoma in the head of the pancreas. No benefit was observed for erlotinib after the inclusion of 336 patients, and further patients are being recruited to answer the chemoradiation question.[84]

A retrospective analysis of the US National Cancer Database suggested that addition of radiotherapy to adjuvant chemotherapy is associated with improved overall survival.[85] Patients with resected pancreatic adenocarcinoma from 1998 to 2009, and with at least 3 months of follow up, were included; 2334 patients received chemotherapy alone, and 3831 received chemotherapy and radiation. The median overall survival was 22.3 months with chemotherapy and radiation *versus* 20.0 months with adjuvant chemotherapy alone ($p = 0.001$). The benefit of radiotherapy was greater for patients with R1 margins, or pT3 or pN1 tumors. Radiotherapy was associated with an overall survival benefit when radiotherapy began 1–3 months after the beginning of chemotherapy. Information on the radiotherapy target volume and radiotherapy technique were not available. A probable bias is the absence of data on disease-free survival, so the chemotherapy alone cohort may have included patients with early postoperative progression and palliative chemotherapy.

The above demonstrate the conflicting results that have been reported over the past three decades regarding the combination of chemotherapy and radiation therapy as adjuvant therapy; hence, the impact and the optimal schedule and timing of postoperative chemoradiation remain uncertain. Further trials are required to ascertain the role of chemoradiotherapy after resection of pancreatic cancer.

Progresses on adjuvant chemotherapy

Upfront resection followed by adjuvant chemotherapy is the gold standard for patients with resectable pancreatic cancer. Considerable advances have been made during the past decade and are summarized in Table 1.

Single-agent chemotherapy. The ESPAC-1 trial first demonstrated an overall survival benefit of adjuvant chemotherapy using fluorouracil and folinic acid.[74] A total of 473 patients were included in the chemotherapy analyses (238 were randomly assigned to adjuvant chemotherapy and 235 were randomly assigned to no chemotherapy).[75] Patients who received fluorouracil and folinic acid had significantly improved median overall survival compared with surgery alone (20.1 *versus* 15.5 months, respectively; $p = 0.009$). The 5-year survival rate was 21% among patients who received adjuvant chemotherapy and 8% among patients not receiving chemotherapy ($p = 0.009$).

The German CONKO-001 trial compared adjuvant gemcitabine administered for six cycles, 3 weeks out of 4, with observation alone.[13,76] A total of 368 patients with completely resected pancreatic cancer were included. Patients with a CA 19-9 serum level greater than 2.5 times the upper limit of normal value were not eligible for this trial. Patients receiving gemcitabine had significantly increased median disease-free survival (13.4 *versus* 6.9 months; $p < 0.001$). Overall survival was significantly improved, with a 5-year overall survival rate of 20.7% *versus* 10.4%, and 10-year overall survival rate of 12.2% *versus* 7.7%. These data were subsequently confirmed by a smaller study in Japan, JSAP-2.[86]

The ESPAC-3 study randomly assigned 1888 patients to a 6-month course of fluorouracil and folinic acid, or gemcitabine. Results showed no differences in disease-free survival and overall survival between the two chemotherapy regimens.[77]

Patients receiving fluorouracil plus folinic acid had significantly more serious adverse events than patients receiving gemcitabine (14% *versus* 7.5%), with significantly higher incidence of stomatitis and diarrhea ($p < 0.001$), whereas gemcitabine was associated with lower leukocyte counts and higher incidence of thrombocytopenia. No significant differences in global quality-of-life scores were observed. In 2010, these results established gemcitabine as the standard of care.

The Japan Adjuvant Study Group of Pancreatic Cancer performed the randomized non-inferiority phase III trial JASPAC-1 comparing adjuvant S-1, an oral tegafur-based fluoropyrimidine, with gemcitabine in patients with resected pancreatic cancer.[78] A total of 385 patients were included. Of these patients, 91.5% had stage II disease. S-1 was well tolerated and fewer patients in the S-1 group (28%) discontinued treatment before completion than in the gemcitabine group (42%; $p = 0.005$). With a median follow-up of 82.3 months, the overall survival rate at 5 years was 24.4% in the gemcitabine group *versus* 44.1% in the S-1 group. The HR for overall survival of S-1 compared with gemcitabine was 0.57 (95% CI, 0.44–0.72; $p < 0.0001$ for non-inferiority, $p < 0.0001$ for superiority). The median relapse-free survival was also doubled in the S-1 group (22.9 months *versus* 11.3 months; HR, 0.60; $p < 0.0001$). A major limitation is that all of the patients enrolled were Japanese. Given the different pharmacokinetics and pharmacodynamics of S-1 between Western cancer patients and those from Asia, concerns have been raised on potential excess of gastrointestinal toxicities with S-1 in the Western population. The applicability of these results to a non-Japanese population is unknown.[87]

Combination systemic therapy. Different approaches to improve outcomes with adjuvant combination therapy in patients with operable pancreatic cancer have been tested in phase III trials, but few have been successful. The addition of targeted agents (erlotinib or sorafenib) or immunotherapy (algenpantucel-L) to gemcitabine did not improve overall survival compared with gemcitabine alone.[88,89,90]

A randomized phase II study evaluated the efficacy of uracil/tegafur (UFT) in addition to gemcitabine, compared with gemcitabine alone. A total of 100 patients were included. With a 21-month follow up, no differences were seen in disease-free survival and overall survival between the two treatments.[91] The ESPAC-4 compared gemcitabine and capecitabine with gemcitabine alone, irrespective of CA 19-9 levels.[16] A total of 730 patients were included, of whom 91.5% had stage III disease. The authors reported a slight increase in toxicities and a significant overall survival benefit with adjuvant gemcitabine plus capecitabine compared with gemcitabine alone (HR, 0.82; 95% CI, 0.68–0.98; $p = 0.032$). However, overall survival curves began to separate after 2 years, and no significant benefit in recurrence-free survival was seen. Recurrence-free survival were not significantly different between arms (HR, 0.86; 95% CI, 0.73–1.02; $p = 0.082$), suggesting differences in postrecurrence survival between the two groups. Imbalance in venous resection [39 patients in the combination group (11%), 63 patients in the control group (17%); $p = 0.019$], a strong prognostic factor, and the inclusion of patients with poor prognosis may have favored the combination group. In fact, high postoperative CA19-9 levels > 92.5 KU/l (up to 8,112 KU/l), a powerful independent prognostic factor in the study (HR, 0.62; 95% CI, 0.68–0.98; $p = 0.007$), were seen in 17% of patients, for whom median overall survival was only 13.1 months. Indeed, CA19-9 levels greater than 92.5 KU/l were associated with a significant overall survival benefit for the gemcitabine and capecitabine group. This point and the fact that a computed tomography (CT) scan was required within 3 months before randomization, but was not mandatory postoperatively, suggest that patients with early metastatic disease may have been enrolled.

Combination chemotherapy with fluorouracil, folinic acid, irinotecan, and oxaliplatin (mFOLFIRINOX, with no bolus fluorouracil and 150–180mg/m^2 dose of irinotecan) was compared with gemcitabine in the PRODIGE24-CCTG PA6 trial.[17] Patients aged 18–79 years with ductal adenocarcinoma (R0 or R1 resection) resected within 12 weeks of randomization, and with no evidence of contraindication to the used drugs, no metastatic disease, no severe diarrhea, and postoperative serum CA 19-9 levels $\leqslant 180$ U/ml, were eligible for inclusion. Postoperative CT scans were mandatory before inclusion to exclude any tumor relapse. The primary endpoint was disease-free survival. A total of 493 patients were included in French and Canadian centers. After a median follow up of 33.6 months, median disease-free survival was 21.6 months in the mFOLFIRINOX

group and 12.8 months in the gemcitabine group (stratified HR, 0.58; 95% CI, 0.46–0.73; $p < 0.0001$). The median disease-free survival for patients who received single-agent gemcitabine was in the range reported by previous adjuvant studies (11.3–15.3 months). There was no heterogeneity in the mFOLFIRINOX regimen effect in patient subgroups. Median overall survival was 54.4 months in the mFOLFIRINOX group and 35.0 months in the gemcitabine group (HR, 0.64; 95% CI, 0.48–0.86; $p = 0.003$). These results are the best disease-free survival and overall survival data reported so far for an adjuvant treatment of resectable pancreatic cancer. Grade 3–4 adverse events occurred in 75.9% of patients in the mFOLFIRINOX group and 52.9% of patients in the gemcitabine group but the toxicities were manageable, and the rate of grade 4 toxicities was the same for the two groups (12%). The predominant toxicity of mFOLFIRINOX was grade 3–4 diarrhea, in 19% of the patients, mainly after the first two cycles of treatment. These results suggest that combination chemotherapy, especially using mFOLFIRINOX regimen should now be the standard of care in fit patients [Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no contraindication to fluoropyrimidines, and no severe postsurgical diarrhea]. In frail patients not candidates for mFOLFIRINOX (for example, performance status score of 2, prior peripheral neuropathy) but with no contraindications to fluoropyrimidines, the combination of gemcitabine and capecitabine is a treatment option. mFOLFIRINOX is now the preferred adjuvant regimen in fit patients for ESMO,[9,92] NCCN,[93] and ASCO.[94]

The APACT trial (NCT01964430) has explored nanoparticle albumin-bound nab-paclitaxel and gemcitabine in the adjuvant setting compared with gemcitabine alone.[95] Patients over 18 years with ductal adenocarcinoma (R0 or R1 resection), performance status 0–1, and with no prior therapy, normal postoperative CT scan, and postoperative serum CA 19-9 levels $\leqslant 100$ U/ml, were eligible for inclusion; 866 patients were randomized. Primary endpoint, as assessed by an independent reviewer, was disease-free survival. Unfortunately, median DFS was not different between arms, 19.4 months (nab-paclitaxel/gemcitabine) and 18.8 months (gemcitabine); HR, 0.88; 95% CI, 0.729–1.063; $p = 0.1824$). A modest but significant increase in overall survival was seen at interim analysis in favor of the combination arm (HR, 0.82; 95% CI, 0.68–0.996; $p = 0.045$). Consistently with the PRODIGE24 trial, the survival in the gemcitabine arm was markedly improved (median 36.2 months), probably due to patient selection, optimal follow up, and benefit from contemporary treatments at relapse.

Optimal follow-up schedule for potentially curable pancreatic cancer has not been defined, and varied significantly between trials.[88] Looking at the more recent trials, APACT and CONKO-005 used visits and CT scans at 3-month intervals, PRODIGE24 and JASPAC 01 planned the same follow-up plus CA19-9, while each site determined its own follow-up in the ESPAC-4 trial.

What is the optimal timing for adjuvant chemotherapy?. A further analysis of the ESPAC-3 study was performed to investigate the optimal timing between surgery and the start of chemotherapy, and the optimal duration of chemotherapy.[96] No difference in survival was seen between patients commencing chemotherapy within 8 weeks of surgery and those commencing chemotherapy later than 8 weeks after surgery. Patients who completed all six planned cycles of treatment had better survival than those who received between one and five cycles only (HR, 0.516; 95% CI, 0.443–0.601; $p < 0.001$). Completion of therapy was also an independent factor associated with survival. Thus, an important conclusion of this study is that it is possible to delay the start of adjuvant chemotherapy until full recovery from surgery, and that it is necessary to complete the six cycles of adjuvant chemotherapy. In another retrospective series, including 488 patients from five institutions, delayed initiation of adjuvant chemotherapy >12 weeks after surgery is associated with the same survival benefit than the timely initiation group as compared with no adjuvant chemotherapy.[97]

Data from the SEER-Medicare database suggested the benefit of adjuvant chemotherapy in elderly people (66 years of age and above).[98] Among 4105 patients who underwent a pancreatectomy, early adjuvant therapy (commencing within 12 weeks after surgery) significantly reduced 6-month and 1-year mortality, compared with patients who underwent surgery alone (odds ratio = 0.71; $p = 0.000$). Late initiation of adjuvant therapy was also associated with better outcomes (odds ratio = 0.51; $p = 0.000$) compared with surgery alone.

Significant delays in initiating adjuvant therapy are not uncommon, and at least 20% of patients

are unable to recover sufficiently following surgery to receive any adjuvant therapy. Moreover, population data suggest that many patients do not receive chemotherapy: In a nationwide population-based analysis, 46% of the patients between 2008 and 2013 did not received adjuvant chemotherapy after complete resection, with large differences between centers (26–74%). Patients with stage II–III, age <60 years, and those treated after 2011 were more likely to receive adjuvant chemotherapy.[99] In the Medicare beneficiaries in the US, adjuvant treatment was delivered to 51% in patients aged 64 years or older, with some increase over time, from 50.5% (1991–1996) to 56.1% (2003–2005).[100] In another cohort of patients over 66 years, adjuvant therapy was applied in 51.7% of patients, and was associated with a significant increase in survival.[98] Chemotherapy omission is linked to severe operative morbidity in the American College of Surgeons experience.[101]

Neoadjuvant treatment for resectable pancreatic cancer

The standard treatment for patients with resectable pancreatic cancer is surgical resection followed by adjuvant chemotherapy.[16,17,102] Theoretical advantages of neoadjuvant *versus* adjuvant therapy are testing of chemosensitivity, control of tumor disease (treatment of circulating tumor cells and micrometastases prior to surgery), higher rate of completion of systemic therapy, higher R0 resection rate (downsizing), reduced pancreatic leakage, and better selection of patients (avoidance of surgery in case of disease progression under neoadjuvant therapy). In contrast, a toxic neoadjuvant regimen may be deleterious as it may limit the possibility of surgical resection. The neoadjuvant approach has become the standard of care for most gastrointestinal cancers. Contrary to general concerns, neoadjuvant therapy has been shown previously to be better tolerated than adjuvant therapy, and the rate of access to a complete therapeutic sequence is greater if oncological treatment is started preoperatively. The introduction of neoadjuvant treatment for resectable pancreatic cancer more than 20 years ago seemed an interesting alternative,[103] but data from comparative randomized controlled trials are still lacking, partly because of difficulties in recruiting patients. The main ongoing studies that are attempting to provide evidence for this approach are listed in Tables 2 and 3.

Table 2. Results of randomized trials of neoadjuvant treatments for resectable and borderline pancreatic cancer.

Study	No. of patients eligible	Treatment Arms	Resection rate	R0	Outcome	
					Median DFS (months)	Median OS (months)
PREOPANC-1[104]	248 resectable + BRPC	• 36 Gy/15fr +gemcitabine	60%	63%*	9.9†	17.1
		• Surgery	72%	31%	7.9	13.7
Seoul National University Hospital[105]	58 BRPC	• 54Gy/30 fr + gemcitabine preoperatively	63%	52%‡	_	21§
		• 54Gy/30 fr + gemcitabine postoperatively	78%	26%	_	12
PACT-15[106]	93 resectable	• surgery + gemcitabine	85%	27%	4.7	20.4
		• surgery + 6 PEXG	90%	37%	12.4	26.4
		• 3 PEXG +surgery + 3 PEXG	84%	63%	16.9	38.2

p values: * < 0.001; † = 0.023; ‡ = 0.01; § = 0.028
BRPC, borderline resectable pancreatic cancer; DFS, disease-free survival; OS, overall survival; PEXG, cisplatin, epirubicin, gemcitabine, and capecitabine.

Table 3. Main ongoing randomized phase III trials of neoadjuvant treatments for pancreatic cancer.

Study	Planned enrollment	Treatment arms	Primary objective
PANACHE-01 NCT02959879[107]	160 (France)	4 cycles of FOLFOX 4 cycles of FOLFIRINOX Surgery	Chemotherapy completion rate
NEPAFOX NCT02172976	310 (Germany)	6 cycles of FOLFIRINOX Surgery	Overall survival
NEOPA NCT01900327	410 (Germany)	Gemcitabine 6 weeks + 50.4 Gy Surgery	+ 30% in 3-year overall survival
NEOPAC NCT01314027	310 (Switzerland)	Gemcitabine and Oxaliplatin 4 cycles Surgery	Increase in PFS of 15% at one year
NorPACT-1 NCT02919787[108]	90 (Norway)	4 cycles of FOLFIRINOX Surgery	Reduction in 1-year mortality from 25% to 5%
NEONAX NCT02047513	166 (Germany)	Nab-paclitaxel–gemcitabine As perioperative regimen As adjuvant regimen	DFS > 55% at 18 months
SWOG S1505 NCT02562716	150 (USA)	FOLFIRINOX Nab-paclitaxel–gemcitabine	2-year overall survival

FOLFIRINOX, Oxaliplatin, irinotecan, folinic acid and fluorouracil; FOLFOX, Oxaliplatin, folinic acid and fluorouracil.

Impact of postoperative complications on systemic therapy

The main pitfalls related to the surgical management of pancreatic cancer are the risks of early recurrence, performance status deterioration, and postoperative complications that could prevent the completion of adjuvant therapy. Approximately 50% of patients could not receive adjuvant treatment following pancreatic cancer surgery.[47] In a mono-institutional retrospective study, Tzeng and colleagues found that, in the setting of neoadjuvant therapy, 83% of patients received the complete oncological sequence compared with 58% in the surgery first group.[14] In the surgery first group, the reasons for failure of the complete sequence were: early progression of the disease ($n=13$, 26%), (major complications ($n=5$, 10%), and deterioration of performance status ($n=3$, 6%). The median overall survival of patients who received the complete oncological treatment sequence was significantly longer than those with incomplete treatment (36.0 *versus* 11.0 months, $p<0.001$).

Impact of neoadjuvant therapy on postoperative course after pancreatic excision surgery

Neoadjuvant treatment is generally well tolerated, with no impact on the postoperative course. In noncomparative phase II trials assessing neoadjuvant chemotherapy, no patient was excluded from the surgical project because of toxicity of neoadjuvant therapy.[109,110]

A recent systematic review evaluated the rates of complications after neoadjuvant chemotherapy or chemoradiotherapy and PD for pancreatic cancer.[111] Neoadjuvant therapy was associated with comparable fistula (3–11%) and infection rates (3–7%) and equivalent mortality (0–4%) compared with surgery first. Other studies showed specific complication rates (pancreatic fistula, haemorrhage) outside gastroparesis significantly reduced after neoadjuvant chemoradiotherapy or FOLFIRINOX.[112,113] The most plausible explanation for these findings is that neoadjuvant therapy, in particular chemoradiotherapy, may induce pancreatic fibrosis, which would result in a lower incidence of pancreatic fistula, and, thus, reduce the risk of associated complications.

Downsizing and downstaging effect of neoadjuvant therapy

A recent meta-analysis assessed the impact of neoadjuvant therapy on pathological response.[114] This study confirms the tumor downsizing and downstaging effects of neoadjuvant therapy, with lower T and N stages, lower rates of

perineural and lymphovascular infiltration, and higher R0 resection rates. The rate of tumors classified as T3/T4 was 75% and 88% in the neoadjuvant and surgery first groups, respectively, with a relative risk of 0.78 (95% CI, 0.69–0.89; $p = 0.0002$). N0 status was significantly more frequent following neoadjuvant therapy (58% *versus* 35%; relative risk, 2.14; 95% CI, 1.85–2.46; $p < 0.00001$). In the neoadjuvant therapy group, 83% of patients were classified as R0 *versus* 73% after surgery first (relative risk, 1.13; 95% CI, 1.08–1.18; $p < 0.0001$).

On the basis of these data, but also with regard to the impact of the aforementioned histoprognostic factors (tumor size, lymph node status and resection margin status) on the risk of recurrence and survival, indications of neoadjuvant therapy are regularly discussed.[32,33,115–117] In addition, with regard to the recent ASCO guidelines, surgery first should be proposed only in the following situations[88,118]:

(1) No clinical evidence of metastatic disease;
(2) A performance status and comorbidity profile appropriate for a major abdominal operation;
(3) No radiographic interface between primary tumor and mesenteric vasculature on high-definition cross-sectional imaging;
(4) A CA 19-9 level (in the absence of jaundice) suggestive of localized disease.

Selection of good candidates for neoadjuvant therapy

Risk of tumor progression and testing of the tumor biology. The risk of disease progression during neoadjuvant therapy should be analyzed as part of the optimal selection of good candidates for surgery. Indeed, disease progression during neoadjuvant therapy might be considered equivalent to an early recurrence (within 6 months) after surgical resection. The true rate of resectability, based on surgical exploration after neoadjuvant treatment for resectable pancreatic adenocarcinoma (excluding borderline and locally advanced lesions), is estimated to be between 66% and 88%, in the four available meta-analyses.[103,119–121]

Should priority go to surgery or to comprehensive pretherapeutic assessment?. The waiting time before surgery is often considered a measure of quality of care. However, even if the waiting time before surgery is due to overloaded operating rooms, it has been shown that this time may allow selection of the best patients for surgery, and preparation of the patients for surgery (for example, prerehabilitation, preoperative nutrition). Two retrospective cohort studies from the US national cancer database[122,123] evaluated the impact of waiting time before surgery. Mirkin and colleagues suggested that long-term survival was not affected by the waiting time.[123] In the study published by Swords and colleagues, the delay in access to surgery was short (1–14 days) for 34.4% of patients, average (15–42 days) for 51.6% of patients, and long (43–120 days) for 14.0% of patients.[122] Mortality rates were lower for patients with average (risk ratio 0.94; 95% CI, 0.90–0.97) and long (risk ratio 0.91; 95% CI, 0.86–0.96) waiting times for surgery. There were no differences in lymph node involvement, locoregional, or metastatic unresectability at exploration, or positive margins. The 90-day mortality was lower in the average waiting time group (odds ratio 0.75; 95% CI, 0.65–0.85) and in the long waiting time group (odds ratio 0.72; 95% CI, 0.60–0.88).

Survival after neoadjuvant therapy

Owing to the lack of fully published randomized trials, current evidence of an effect of neoadjuvant therapy on long-term outcomes comes mainly from phase II trials and retrospective analyses. According to the systematic review by Gillen and colleagues,[103] performed before the advent of efficient combination chemotherapy regimens, the overall survival of patients receiving neoadjuvant treatment was slightly better than the survival of those having surgery first. According to this meta-analysis, the median overall survival of patients after surgery alone and after surgery first followed by adjuvant treatment was 16.9–20.2 months and 20.1–23.6 months, respectively, whereas, following neoadjuvant therapy, the median intention-to-treat survival was 23.3 months.

Neoadjuvant chemotherapy for resectable pancreatic adenocarcinoma [specifically excluding borderline resectable pancreatic cancer (BRPC)] has been reported in only two phase II studies.[109,110] These phase II trials showed a median overall survival of 26.5 months and 27.2 months after 2 months of neoadjuvant chemotherapy with or without adjuvant therapy. Again, it is important to note that the intention-to-treat approach was used to analyze these results. Indeed, all patients, regardless of surgical complications,

were included in these trials, in contrast to randomized trials on adjuvant chemotherapy, in which only 40–50% of patients are included.[47]

Recent large cohort studies also suggest a survival benefit for patients who receive neoadjuvant treatment for resectable pancreatic cancer.[11,124] In two separate analyses of the US National Cancer Database, perioperative chemotherapy was associated with survival benefit in patients with early stage pancreatic cancer compared with surgery first. In a study by Lutfi and colleagues,[11] completion of postoperative chemotherapy complementary to preoperative chemotherapy had a significant overall survival advantage over adjuvant chemotherapy alone (HR 0.75; 95% CI, 0.65–0.85). Achieving neoadjuvant chemotherapy alone showed a marginal overall survival benefit compared with adjuvant chemotherapy (HR 0.89; 95% CI, 0.81–0.98). In a study by Mokdad and colleagues,[124] median overall survival was significantly longer in the neoadjuvant group than in the surgery first group (26 *versus* 23 months; $p = 0.01$). Using multivariate analysis, the authors demonstrated a significant survival benefit for patients in the neoadjuvant group compared with the surgery first group following adjuvant chemotherapy (HR 0.83; 95% CI, 0.73–0.89). The main biases of these cohort studies result from the absence of intention-to-treat analysis, and the lack of standardization of criteria for resectability and indications of treatment (for example, chemotherapy *versus* chemoradiotherapy, duration, doses) depending on the stage.

The Milan group reported a randomized three-arm phase II trial, in which patients were randomly assigned to receive surgery followed by adjuvant gemcitabine, surgery followed by six cycles of adjuvant PEXG (cisplatin, epirubicin, gemcitabine, and capecitabine), or three cycles of neoadjuvant PEXG and three further cycles postoperatively (perioperative group).[106] A total of 93 patients were included but five patients from the same institution were excluded because of noncompliance with the protocol. Progressive disease was seen in 1 out of 26 patients during neoadjuvant treatment. No toxic death was observed in any arm. Evidence of the efficacy of neoadjuvant chemotherapy was reported with increase in R0 surgery, median DFS and median overall survival. Intention-to-treat estimates of 5-year overall survival were 13% in the surgery plus gemcitabine group, 24% in the surgery plus adjuvant PEXG group, and 49% in the perioperative PEXG strategy. Despite these promising results, this trial will not continue to phase III, due to different new active regimens available for the metastatic setting.

Randomized phase III studies comparing neoadjuvant treatment with upfront surgery are warranted. These studies are difficult to design and to conduct. Pretherapeutic pathological proof is mandatory, and biliary stenting is often necessary before neoadjuvant treatment. The calculation of the number of patients should take into account the risks of dropout during neoadjuvant treatment, complications related to drainage or chemo(radio)therapy, early progressive disease, risk of surgery refusal, and the risk of unexpected metastases or tumor nonresectability during surgical exploration. For these reasons, the survival results of neoadjuvant trials cannot be compared with adjuvant trial results that include selected populations with no metastases and adequate recovery after surgery. This may explain why the median survivals were disappointing in both arms (17.1 months after preoperative chemoradiotherapy compared with 13.7 months with upfront surgery) in the phase III PREOPANC trial shown in Table 2.[104] However, this first randomized clinical trial demonstrates that preoperative treatment improves outcomes for patients with borderline or resectable pancreatic cancer and is described in the BRPC section.

Discussions of future projects will be based on the use of intensified chemotherapy regimens (with or without stereotactic radiotherapy), which seem promising.

Management of BRPC

There are no universally accepted criteria for defining BRPC. However, the anatomic definitions of BRPC according to European and American guidelines are similar and cover the same standard radiological criteria: arterial contact of $<180°$ (celiac trunk, SMA, common hepatic artery), and venous contact of $\geqslant 180°$ without vein contour irregularity (superior mesenteric vein or portal vein) or $<180°$ amenable to vein reconstruction.[9,18] The MD Anderson classification of BRPC identifies a patient's subgroup (type C) with a marginal performance status or a severe pre-existing comorbidity profile (including

advanced age) that puts them at high risk for a major surgical procedure.[125]

The management of BRPC has been subject to debate, mainly as to whether neoadjuvant treatment is required. Although many concepts support the neoadjuvant approach (including the selection of patients with 'good' tumor biology), there is lack of evidence for its efficacy. A meta-analysis published recently by the Dutch Pancreatic Cancer group[126] compared upfront surgery with neoadjuvant treatment in resectable pancreatic cancer and in BRPC. The authors analyzed 38 studies involving 3884 patients. In the BRPC subgroup, upfront surgery assessed in 4 retrospective studies ($n = 1051$ patients) was compared with neoadjuvant strategies assessed in 21 studies ($n = 976$ patients). Median overall survival was 12.8 months in the upfront surgery group *versus* 19.2 months in the neoadjuvant group. With regard to the type of neoadjuvant therapy, various drugs and designs were used for chemotherapy and chemoradiotherapy, and this heterogeneity made the analysis of subgroups impossible. A patient-level meta-analysis on neoadjuvant FOLFIRINOX in patients with BRPC was recently performed and included 24 studies (8 prospective, 16 retrospective), comprising 313 BRPC patients treated with FOLFIRINOX.[127] The resection rate was 67.8% and the R0-resection rate was 83.9% (95% CI: 76.8–89.1). Patient-level median OS was 22.2 months, with a median progression-free survival of 18.0 months. The authors concluded that BRPC patients treated with neoadjuvant FOLFIRINOX had favorable outcomes, and these results need to be assessed in a randomized trial.

In 2018, two prospective randomized clinical trials specifically assessed the value of neoadjuvant treatment in BRPC (summarized in Table 2).[104,105] In a Korean trial, the authors addressed the role of chemoradiotherapy in the preoperative *versus* postoperative setting.[105] Chemoradiotherapy consisted of 54 Gy in 30 fractions with weekly gemcitabine, then adjuvant gemcitabine for 4-monthly cycles. The primary outcome was the 2-year overall survival rate. The trial closed early after the first interim analysis, and only 58 patients were enrolled; 8 patients were excluded from the analysis because they withdrew consent. Authors showed that the preoperative strategy had a significant advantage: the neoadjuvant group showed a higher resection rate (51.8% *versus* 26.1%) and higher 2-year survival (40.7% *versus* 26.1%; HR, 1.495; 95% CI, 0.66–3.36; $p = 0.028$). Few patients who underwent tumor resection completed maintenance chemotherapy: eight in the neoadjuvant group and six in the upfront surgery group. The recurrence rate was high: 88.2% in the neoadjuvant treatment group and 88.9% in the upfront surgery group. Median overall survival was 21 months *versus* 12 months for neoadjuvant chemoradiotherapy *versus* adjuvant chemoradiotherapy, respectively.

Preliminary results of the PREOPANC-1 trial were communicated in 2018.[104] A total of 248 patients with resectable pancreatic cancer (51%) or BRPC (49%) were randomly assigned to preoperative gemcitabine-based chemoradiotherapy or immediate surgery. In an intent-to-treat analysis, the resection rate was slightly lower with neoadjuvant chemoradiotherapy than with upfront surgery (60% *versus* 72%; $p = 0.065$) but the R0 resection rate was significantly increased (61% *versus* 31%; $p < 0.001$). Moreover, the median time until recurrence was significantly longer after preoperative treatment (9.9 *versus* 7.9 months; $p = 0.023$). Analysis was performed after the occurrence of 149 out of the 176 required events for the primary outcome: overall survival. The median overall survival was 17.1 months after preoperative chemoradiotherapy compared with 13.7 months after upfront surgery followed by adjuvant chemotherapy, but the difference was not statistically significant ($p = 0.074$). Longer follow up and final survival results are needed before any definitive conclusion, although Dutch guidelines have already endorsed the preoperative chemoradiotherapy strategy. The FOLFIRINOX regimen has been evaluated as an neoadjuvant therapy in BRPC in small and mainly retrospective studies, and reviewed in a very recent meta-analysis.[128] Based on data from 288 patients in an intention-to-treat analysis, authors calculated a median overall survival of 22.2 months (95% CI, 18.9–25.6 months), comparable with results obtained for patients with resectable pancreatic cancer operated upfront. The main ongoing randomized studies are presented in Table 4. These trials will hopefully answer two important questions: is induction therapy improving overall survival in patients with BRPC? And should we use chemotherapy or chemoradiotherapy to achieve this goal?

Table 4. Main ongoing randomized trials of induction treatments for borderline pancreatic cancer.

Study	Recruitment status	Planned enrolment	Induction Treatment Arms	Primary objective
PREOPANC NTR3709[104]	Closed	246	36 Gy/15 fr + Gemcitabine Surgery	Increase in median overall of 6 months
ALLIANCE NCT 02839343[129]	Suspended (interim analysis)	112	8 cycles of FOLFIRINOX 7 cycles of FOLFIRINOX then hypofractionated radiation	18-month overall survival
PANDAS-PRODIGE 44 NCT 02676349	Recruiting	92	6 cycles of mFOLFIRINOX 6 cycles of mFOLFIRINOX then chemoradiation 50.4 Gy + capecitabine	R0 resection rate > 50%
Wisconsin medical college NCT 03704662	Not yet recruiting	102	Stereotactic body radiation therapy Preoperative chemoradiotherapy	Percentage of patients with ypN+ disease
PREOPANC-2 NTR 7292[130]	Recruiting	368	4–8 cycles of FOLFIRINOX Chemoradiotherapy 36 Gy/15 fr + Gemcitabine	Overall survival
ESPAC-5F EUDRACT 2013-003932-56	Recruiting	100	Surgery Gemcitabine + capecitabine 2 cycles 4 cycles of FOLFIRINOX Chemoradiotherapy 50.4 Gy + capecitabine	Recruitment rate and overall resection rate

FOLFIRINOX, Oxaliplatin, irinotecan, folinic acid and fluorouracil; Gy, Gray.

Locally advanced pancreatic cancer

What is the standard of care?

Patients with LAPC represent approximately 20–30% of all patients with pancreatic cancer at diagnosis. Median overall survival ranges from 10 to 30 months, depending on the reported series (these differ widely in terms of definitions and treatments). By definition, locally advanced tumors are those that are not metastatic and not potentially resectable owing to 'irreversible' vascular invasion. However, this definition varies and is also evolving over time and with therapeutic strategies.[131,132] Practically, unresectable tumors are those that encase the aorta, obliterate the portal vein or the superior mesenteric vein (confluence), or involve more than 180° of the SMA or celiac trunk, precluding achievement of negative margins at surgical resection.[133] Owing to the difficulty of relying on strict criteria for unresectability, it should now be recommended that all cases with nonmetastatic tumors are discussed by a multidisciplinary board in high-volume centers, and that these evaluations are repeated after treatment induction to confirm definitive unresectability.

Standard management is based on chemotherapy administration as historically generated by the results obtained in randomized trials performed in metastatic disease. Today, the reference treatment remains gemcitabine (grade A recommendation) while active regimens in metastatic pancreatic cancer can be considered good options in patients with performance status scores of 0–1 (FOLFIRINOX, grade B) or 0–2 (nab-paclitaxel–gemcitabine, expert recommendation).[133] There is not yet prospective validation of superior efficacy of these regimens over gemcitabine alone, and the recent reports are mainly observational studies, small phase II or pooled analyses of mixed approaches combining induction chemotherapy with FOLFIRINOX or nab-paclitaxel–gemcitabine with additional chemoradiation in nearly half of the patients. In this setting, a recent pooled analysis of 355 patients from 13 studies reported a median survival of 24.2 months and a median progression-free survival of 15 months with FOLFIRINOX induction therapy that favourably compares to gemcitabine alone (median overall survival of 6–13 months).[134] Similar data were also reported for the nab-paclitaxel–gemcitabine combination, with a median

overall survival of 18 months (and not yet reached for resected patients).[135] From these reports, it is important to note that 26% of these patients had secondary resection (conversion surgery). However, it is to be acknowledged that nearly half of the patients had received complementary chemoradiation, the relative contribution of each modality being therefore highly difficult to distinguish, and even more so in populations that mixed BRPC and LAPC.

Adjunction of radiation therapy in the setting of LAPC has not proven to be of benefit, either upfront or after gemcitabine induction for 4 months; after conflicting data derived from small trials, the LAP07 phase III trial clearly showed no benefit of adding chemoradiation (grade A recommendation).[133,136] Chemoradiation was only shown to improve local control in a subgroup of patients and, consequently, can be proposed as an individual option in selected patients using capecitabine as a radiosensitizer partner (it is suggested to be a better radiosensitizer partner than gemcitabine according to a randomized phase II study).[137] Recently, a meta-analysis of data from 593 pooled patients confirmed that chemoradiation is not superior to chemotherapy alone, with similar overall survival and higher rates of grade 3–4 adverse events.[138] Conversion surgery should be discussed and proposed in all operable cases with good response or local tumor control after induction chemotherapy with or without chemoradiation.

Perspectives and challenges to improve the management of locally advanced pancreatic cancer

New approaches. Practically, LAPC should deserve specific trials in fit patients to evaluate new treatment options, sequences, and strategies based on new drugs and new loco-regional ablative therapies such as stereotactic body radiotherapy (SBRT), proton beam radiation therapy, irreversible electroporation, endoscopic ultrasonography-guided radiofrequency ablation, or intratumoral delivery of innovative agents such as radioactive ^{32}P phosphorus. Multidisciplinary tumor boards make sense for these complex situations and should encourage case-by-case discussions with several represented specialties (i.e. surgeon, radiation oncologist, medical oncologist, pathologist, and radiologist).

Several randomized phase II and III trials are ongoing to evaluate the impact of FOLFIRINOX *versus* gemcitabine alone (NEOPAN; NCT02 539537) and nab-paclitaxel–gemcitabine as an induction therapy followed by intensified radiation therapy *versus* continuous chemotherapy, using DPC4 gene activation as a stratification factor (RTOG 1201; NCT01921751). These studies will provide important information about the best backbone regimen that can be used to add new agents, such as antistromal, immunotherapeutic, or antimetabolic agents.

Beyond the LAP 07 study, there is now room to investigate more active chemotherapy regimens as induction therapies followed by new radiation therapy techniques, such as intensity-modulated radiation therapy or SBRT. In addition to the classical therapeutic tools, emerging local ablative or intratumoral delivery therapies should be also evaluated prospectively.

Finally, the setting of LAPC deserves new strategies to treat these patients by assessing maintenance therapy or therapy-free period in well-controlled tumors; trials combining immunotherapy with chemotherapy, with monitoring by functional imaging and liquid biopsies, are underway.

Role of conversion surgery. The possible role for surgery has been extended recently to LAPC. Induction combination chemotherapy, often followed by chemoradiation, may lead to reconsideration of surgery in patients with initially unresectable disease and responding disease. This prompted colleagues from the Medical College of Wisconsin to propose a new classification for LAPC. This classification may help multidisciplinary boards to define the optimal strategy and the goal of care, potentially curative or palliative intent[131]:

(1) Type A are tumors that may be considered for conversion resection after induction therapy.
(2) Type B are definitively unresectable tumors. Type B tumors are defined as LAPC with >270° SMA encasement, celiac artery with >180° encasement, abutment or encasement of the aorta, and >180° encasement of the hepatic artery with extension beyond bifurcation of the proper hepatic artery into right and left hepatic arteries.

All other patients fit for surgery and chemotherapy may receive induction chemotherapy. In LAPC patient cohorts receiving gemcitabine-based chemotherapy plus chemoradiation, conversion surgery has been infrequent (1–8%).[136,139,140] Median survival after resection has not been reported. In a large retrospective study of patients scheduled for resection after restaging, 322 patients received induction chemoradiation with gemcitabine, and 46% of patients had conversion surgery, of which 31.3% were R0 resections.[141]

The role of more intensive chemotherapy regimens has been explored. Unfortunately, only one phase II randomized study from the Milan group is available, and included only 54 patients with BRPC or LAPC. Induction regimens were nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin (PAXG). The response rates and conversion surgery rates are comparable, with a higher rate of R0 resection (67.5% *versus* 44%) under the PAXG regimen.[142]

Numerous studies have used induction FOLFIRINOX followed, or not, by chemoradiation, and reported promising results. In a recent meta-analysis including data from 365 patients, the response rate after induction FOLFIRINOX was 29%, with a conversion surgery rate of 28%. The R0 resection rate was high, at 77%.[143] In other, smaller, cohorts, median survival for all patients was between 22 months and 35.4 months.[144–146] In two large retrospective studies of patients scheduled for resection post restaging after FOLFIRINOX, the conversion surgery rates were 60.8% and 78.0%, with R0 resection rates from 40.8% to 80.6%.[141,147] The University Hospital of Colorado retrospectively analyzed data from 120 patients with BRPC or LAPC receiving induction chemotherapy with either gemcitabine and nab-paclitaxel or FOLFIRINOX. The tumor progression rate was significantly lower with FOLFIRINOX (13.3% *versus* 40.5%; $p = 0.001$). The R0 resection rate was higher with FOLFIRINOX (66.3% *versus* 32.4%; $p = 0.002$). The perioperative complication rate was also lower (52.7% *versus* 83.3%; $p = 0.051$), and progression-free survival was significantly increased with FOLFIRINOX (15.3 *versus* 8.2 months; $p = 0.003$). No significant increase in median overall survival was observed.[148]

A recent United States National Cancer Database (NCDB) analysis of 8689 patients with LAPC showed that the best chance for survival of LAPC was the ability to undergo pancreatectomy, compared with either no surgery or a more local procedure (HR, 0.39; 95% CI, 0.34–0.46; $p < 0.001$).[149] Patients with LAPC who underwent pancreatectomy had significantly improved survival compared with those who did not (22 *versus* 10.6 months). Multi-agent induction chemotherapy followed by chemoradiotherapy improved the resection rate (9.8%) compared with concurrent chemoradiotherapy (5%) or multi-agent chemotherapy alone (3.3%).

In retrospective studies, SBRT has been suggested to be beneficial. In a retrospective study carried out by the Johns Hopkins University, the addition of SBRT to induction FOLFIRINOX has been shown to correlate with increased probability of conversion surgery.[150]

Specific recommendations for surgical management following induction therapy. After induction therapy for LAPC type A, surgical exploration should be attempted in patients with stable disease or remission to rule out or confirm true vascular infiltration. Induction therapy significantly decreases the accuracy of CT scan in determining operability, T-staging, and R0 resectability of pancreatic head carcinoma.[151,152] Overestimation of tumor size and vascular invasion significantly reduces CT scan specificity after preoperative treatment.

In the setting of LAPC, with superior mesenteric artery or celiac trunk involvement, a surgical exploration with dissection and biopsy of the peri-adventitial tissues (arterial sheaths) is recommended. In case of positive extemporaneous examination, a PD with arterial resection may be attempted with high immediate risk[153,154] and must be weighed against a palliative procedure without resection. Hackert and colleagues recommended biopsy of arterial sheaths, and in case of positivity, nonresection, and palliative treatment.[155] In case of absent viable tumor, the described technique allows to perform radical surgery without arterial resection in this subgroup of patients.[155]

Current guidelines recommend that resected patients who received preoperative therapy be considered for additional postoperative chemotherapy.[118] Carefully selected patients with LAPC (20–30%) who had responded to induction therapy can benefit from conversion surgery.

Update in therapy for advanced pancreatic cancer

Which strategy for first-line chemotherapy?

There are few validated regimens for the treatment of advanced pancreatic cancer in first-line treatment. There has been little novelty regarding the first-line treatment in this setting and several chemotherapy regimens, alone or in combination, have shown an improvement in progression-free survival, most often without overall survival improvement,[156] so we summarized below main trials and current recommendations.

Until the approval of gemcitabine in 1997, fluorouracil was the gold standard chemotherapy agent in advanced pancreatic cancer.[157] Gemcitabine significantly increased the 'clinical benefit response', median progression-free survival and overall survival (from 4.4 months to 5.7 months; $p = 0.0025$) with an acceptable tolerance compared with bolus fluorouracil in a randomized phase II study.[157] Table 5 shows the main randomized trials for first-line regimens in advanced pancreatic cancer.

More than 20 randomized trials addressed the comparison of gemcitabine to gemcitabine with addition of a second cytotoxic agent or targeted therapy. All failed to show any survival improvement,[156] except erlotinib, which provided a statistically significant, albeit modest median overall survival benefit of 6.24 months *versus* 5.91 months ($p = 0.038$) and a 1-year survival of 23% *versus* 17% ($p = 0.023$) in a NCIC phase III trial that included 569 patients with both metastatic and locally advanced pancreatic cancer (LAPC).[158] This improvement in median overall survival of 10 days, although significant, is not relevant in clinical practice. There were no significant differences between the gemcitabine and gemcitabine–erlotinib arms in response rate or quality of life, with worse diarrhea change scores in the erlotinib plus gemcitabine arm ($p = 0.001$). Toxic effects were significantly increased in this combination arm; mainly rash, diarrhea, and stomatitis. Furthermore, there were six protocol-related deaths and seven patients with interstitial pneumonitis in the combination arm. Survival benefit was not confirmed by the later LAP07 trial; this trial included 449 patients with LAPC for whom no benefit from use of erlotinib was found.[136]

Table 5. Main randomized trials performed in first-line therapy for advanced pancreatic cancer.

Trial	Number of patients	Median OS (months)	HR	Response rate	What this trial contributed	Quality of life
Gemcitabine *versus* bolus fluorouracil[157]	126	5.65 *versus* 4.41	N/A	5.4% *versus* 1%	Gemcitabine has become the standard in first-line setting	'Clinical benefit' 23.8% *versus* 4.8%
Gemcitabine plus erlotinib *versus* gemcitabine[158]	569	6.24 *versus* 5.91	0.82	8.6% *versus* 8%	No change in standards	No difference but more diarrhea with erlotinib (EORTC QLQ-C30)
FOLFIRINOX *versus* gemcitabine[159]	342	11.1 *versus* 6.8	0.57	31.6% *versus* 9.4%	FOLFIRINOX has become the standard in the first-line for patients with good performance status	Significantly reduces QoL impairment (EORTC QLQ-C30)
FOLFIRINOX *versus* gemcitabine[160]	310	10.8 *versus* 7.4	0.48	29.6% *versus* 8.3%	When fully published, will confirm FOLFIRINOX as first-line standard therapy in fit patients	Significantly reduces QoL impairment (EORTC QLQ-C30)
Nab-paclitaxel–gemcitabine *versus* gemcitabine[161]	861	8.5 *versus* 6.7	0.72	23% *versus* 7%	Nab-paclitaxel–gemcitabine has become an option as first-line therapy for patients PS 0-2, 17%	N/A

FOLFIRINOX, Oxaliplatin, irinotecan, folinic acid and fluorouracil; HR, hazard ratio; N/A, Not available; OS, overall survival; QoL, quality of life.

In 2005, Reni and colleagues first tested an aggressive polychemotherapy regimen with cisplatin, epirubicin, fluorouracil, and gemcitabine (PEFG) *versus* gemcitabine alone. A total of 99 patients were included, and the response rate was 38.5% in the PEFG group *versus* 8.5% with gemcitabine. The primary endpoint (4-month progression-free survival) was significantly increased in the PEFG arm (60% *versus* 28%; HR, 0.46, $p = 0.001$), but there was no significant difference in overall survival.[162]

The pivotal PRODIGE 4-ACCORD11 trial compared FOLFIRINOX, a combination of oxaliplatin, irinotecan, folinic acid, and fluorouracil to gemcitabine in patients below 75 years of age with metastatic pancreatic cancer.[159] Overall survival was significantly increased, with median survival of 11.1 months for FOLFIRINOX and 6.8 months for the gemcitabine regimen (HR 0.57; 95% CI, 0.45–0.73; $p < 0.001$).[159] Moreover, FOLFIRINOX significantly delayed quality of life deterioration compared with gemcitabine.[163] These results were confirmed by another, still unpublished, phase III study, in which the median overall survival was 10.8 months in the FOLFIRINOX group and 7.4 months in the gemcitabine group (HR, 0.48; 95% CI, 0.41–0.68; $p < 0.001$).[160] Since then, FOLFIRINOX has become the standard regimen for fit patients with metastatic disease, ECOG performance status score of 0 or 1, no significant cardiac comorbidity, and no increase in bilirubin level.

With the MPACT trial in 2013, Von Hoff and colleagues reported that a combination of gemcitabine with nab-paclitaxel was superior to gemcitabine alone as a first-line regimen for the treatment of patients with metastatic pancreatic cancer.[161] This study involved 861 patients with an ECOG performance status score of 0–2. The median overall survival was 8.5 months in the nab-paclitaxel arm and 6.7 months in the gemcitabine arm (HR 0.72; 95% CI, 0.62–0.83; $p < 0.001$).

To date, no prospective trial has compared directly FOLFIRINOX to nab-paclitaxel plus gemcitabine. Retrospective studies comparing both regimens suggest greater activity of FOLFIRINOX, but caution should be taken outside randomized studies. A phase II trial is currently underway in the Japanese population to compare the 1-year overall survival rate of both regimens (UMIN Clinical Trials Registry: UMIN000023143). To the best of the authors' knowledge, no other trial is running or even scheduled. Recently, Kim and colleagues compared FOLFIRINOX and nab-paclitaxel–gemcitabine in a real-world retrospective review that showed similar trends for both regimens in terms of overall survival.[164]

In routine practice, the FOLFIRINOX regimen is recommended as standard for metastatic pancreatic cancer by the NCCN, the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO) for patients with an ECOG performance status score of 0 or 1 and a favorable comorbidity profile.[9,18,88,165,166]

This regimen should be considered with caution for fragile or elderly people. Between 2008 and 2015, Baldini and colleagues enrolled 42 patients retrospectively with a median age of 73 (range 70–79), an ECOG performance status score of 0 or 1 for the large majority (93%), and few comorbidities (median Charlson index = 10).[167] This study found that patients with metastatic disease ($n = 37$ out of 42; 88%) benefited from a dose reduction of FOLFIRINOX from the first cycle (57%), and reported similar trends as the pivotal PRODIGE 4-ACCORD11 trial in terms of overall survival (12.6 months). Moreover, dose reduction did not appear to have an effect on overall survival (median, 11.7 *versus* 16.6 months, $p = 0.69$). Yet, toxicity was easier to manage. It was recently suggested by a retrospective analysis conducted by Kang and colleagues that modified FOLFIRINOX (mFOLFIRINOX) has comparable efficacy to FOLFIRINOX, and better tolerance than standard FOLFIRINOX.[168] mFOLFIRINOX typically consists of a fluorouracil bolus suppression or a dose reduction of irinotecan (or both). To date, no well-conducted trial has formally demonstrated the equivalence of FOLFIRINOX and mFOLFIRINOX in metastatic pancreatic cancer. A proposed algorithm for choosing first-line therapy is shown in Figure 1.

Facing these alternatives, prognostic factors are to be considered to help decision making between treatments. The ECOG performance status score,

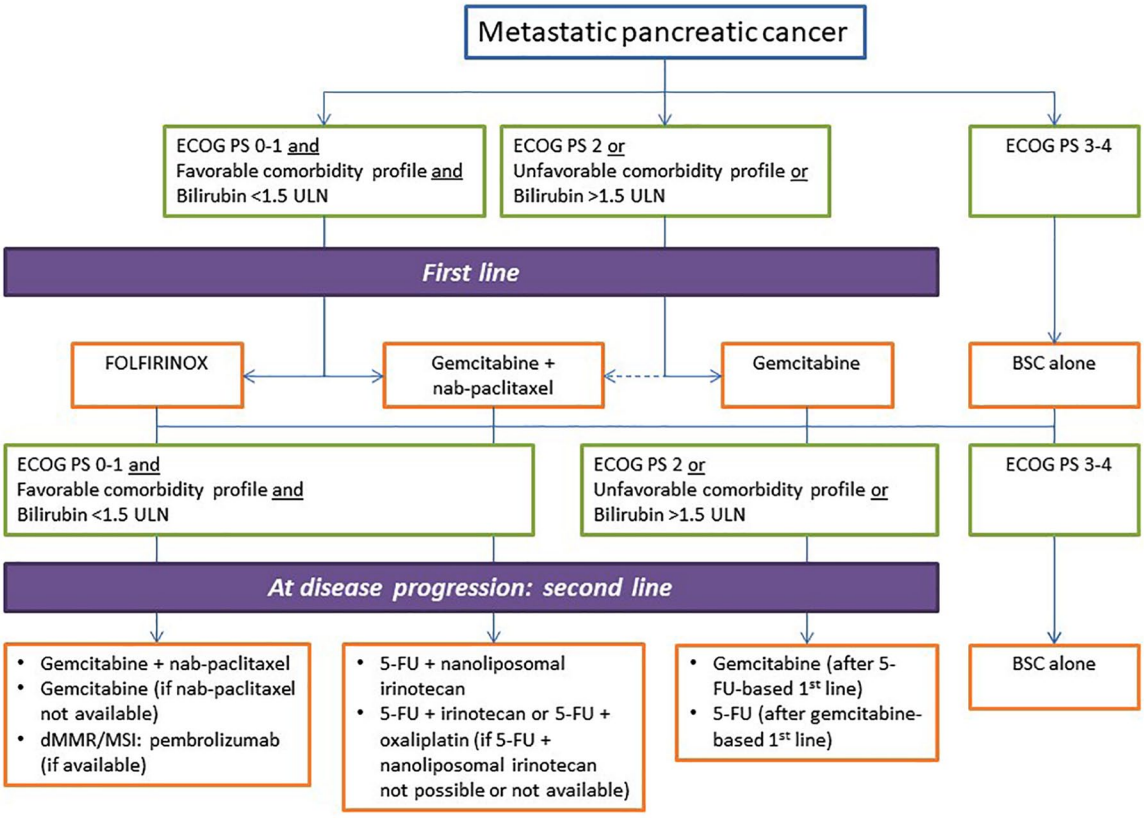

Figure 1. Proposed algorithm for choice of first- and second-line chemotherapy in metastatic pancreatic cancer.
5-FU, 5-fluorouracil; BSC, best supportive care; dMMR, deficient mismatch repair; MSI, microsatellite instability; PS, performance status; ULN, upper limit of normal range.

or Karnofsky index, are historically the strongest predictors of survival, but an analysis of the phase III MPACT study showed that liver metastases, age, and number of metastatic sites were also good prognostic factors for survival, and should be considered for treatment decisions.[169] Sarcopenia at diagnosis and depletion of skeletal muscle during chemotherapy are also prognostic factors for survival,[170] as is nutritional index,[171] and might also be considered. High carcinoembryonic antigen serum level, synchronous metastatic disease (stage IV disease), sarcopenia, neutrophilia, and high lactate dehydrogenase serum level have been confirmed as independent prognostic factors for overall survival in a retrospective chart review.[172]

Undoubtedly, performance status is the primary factor when it comes to choose a FOLFIRINOX regimen. However, Sehdev and colleagues showed a promising way to help decision making, in a single-institution, retrospective study concluding that the presence of DNA damage response (*DDR*) gene mutations are associated with improved overall survival in patients with pancreatic cancer treated with FOLFIRINOX.[173] BRCA tumor suppressor gene mutations are also correlated with better survival under exposure to platinum chemotherapy.[174]

What options for second-line chemotherapy?

After progression under first-line chemotherapy, approximately 40–50% of patients with advanced pancreatic cancer are able to receive second-line chemotherapy or subsequent lines.[175] In a retrospective series of patients with metastatic pancreatic cancer, 45% and 21% of patients received two or more lines of treatment after failure of gemcitabine, respectively.[176] In a systematic review of 24 first-line studies (52 treatment arms) conducted between 1998 and 2012, the pooled

mean rate of second-line therapy (noted in 17% of all studies) was 43% (range, 16–68%).[177] This rate increased significantly from 35% for studies published before 2007 and 48% for those published after 2007. Of note, all of these studies were conducted in the pre-FOLFIRINOX and nab-paclitaxel–gemcitabine era, and thus mostly included patients who received a gemcitabine-based first-line regimen. In the combination chemotherapy arms of PRODIGE 4-ACCORD 11[159] and of MPACT[161] trials, 47% and 38% of patients received subsequent anticancer therapy, respectively.

The higher efficacy of upfront combination regimens is likely to result in improved patient outcomes, increasing the proportion of patients fit for second-line therapy. According to guidelines recommending the avoidance of cancer-directed therapies for patients with solid tumors and altered general condition,[178] most clinical trials included patients with ECOG performance status scores of 0 or 1. In the real-world setting, the majority of patients are ineligible for such clinical trials and have a poor prognosis (median overall survival with best supportive care alone of approximately 2 months, compared with 5–6 months in treated patients).[179]

There is no definite standard of care after disease progression under upfront chemotherapy. In a systematic review of second-line therapy, combination therapies resulted in improved progression-free survival (2.5 *versus* 1.9 months; $p = 0.018$) but not overall survival (5.1 *versus* 4.3 months; $p = 0.169$) compared with single-agent therapies.[177] Gemcitabine–platinum and fluoropyrimidine–platinum combination regimens seem to provide similar survival results in meta-analyses of second-line studies.[177,180,181]

Three randomized phase III trials have explored the role of oxaliplatin-based chemotherapy after failure of first-line, single-agent gemcitabine therapy (Table 6). The German CONKO group conducted a phase III trial in which patients were randomly assigned to a combination of oxaliplatin, folinic acid, and 5-FU (OFF regimen), or to best supportive care alone.[182] This trial was terminated early after only 46 patients were enrolled because of slow accrual. Nevertheless, there was a significant overall survival benefit in the OFF group (4.8 *versus* 2.3 months; $p = 0.008$). As expected, there was a higher incidence of grade 1–2 hematological, gastrointestinal, and sensory neurotoxicity in the OFF group, but no significant increase in grade 3–4 toxicity. In the subsequent CONKO-003 trial, the OFF regimen provided a significant overall survival benefit over 5-FU–folinic acid (FF regimen; median, 5.9 *versus* 3.3 months; HR, 0.66; $p = 0.01$).[183] By contrast, no benefit in progression-free survival (the primary endpoint), objective response rate, or time to deterioration was seen with the modified FOLFOX6 regimen (mFOLFOX6) compared with 5-FU–folinic acid in the PANCREOX trial[184]; indeed, patients in the 5-FU–folinic acid arm had longer overall survival (median, 9.9 months *versus* 6.1 months; $p = 0.02$). This somewhat surprising result was thought to be caused by an imbalance in use of postprogression therapies (7% *versus* 23%; $p = 0.015$), and by an increased toxicity in the mFOLFOX6 arm (grade 3–4 adverse events, 63% *versus* 11%) with a higher number of patients withdrawing from the study owing to adverse events (20% *versus* 2%). Of note, because these randomized trials were conducted during a period in which single-agent gemcitabine was the only standard of care in the first-line setting, their results cannot be extrapolated to the vast majority of patients treated with upfront FOLFIRINOX or nab-paclitaxel–gemcitabine (furthermore, both being neurotoxic). In fact, at the present time they may only be relevant to the small subset of patients who are deemed unfit for upfront combination chemotherapy and are treated with single-agent gemcitabine, and who are fit enough for oxaliplatin-based combination chemotherapy in the second-line setting, with the controversial results of the randomized trials summarized above.

Nanoliposomal irinotecan (MM-398), a novel formulation of irinotecan encapsulated in polyethylene glycolated nanoliposomes, has been developed to improve the therapeutic index of irinotecan by increasing the exposure of tumor tissue to this drug, irinotecan nanoliposomes accumulate in tumor-associated macrophages, and reducing exposure of normal tissues

Table 6. Randomized trials in advanced pancreatic cancer after first-line gemcitabine progression.

Trial	Treatment arms	Phase	Patients	Primary endpoint	ORR (%)	PFS (months)	HR (95% CI)	*p* value	OS (months)	HR (95% CI)	*p* value
CONKO-003[182]	OFF	III	23	OS	NR	NR	NR	NR	4.8	0.45 (0.24–0.83)	0.008
	BSC		23		NR	NR			2.3		
CONKO-003[183]	OFF	III	76	OS	NR	2.9*	0.68 (0.50–0.94)	0.019	5.9	0.66 (0.48–0.91)	0.01
	FF		84		NR	2.0*			3.3		
PANCREOX[184]	mFOLFOX	III	54	PFS	13	3.1	1.00 (0.66–1.53)	0.99	6.1	1.78 (1.08–2.93)	0.02
	5-FU/FA		54		9	2.9			9.9		
NCT01074996[185]	S-1 + oral FA	IIR	45	6-month OS	8	3.0	0.86 (0.66–1.63)	0.86	6.3	0.83 (0.66–1.67)	0.83
	S-1		47		5	1.9			5.5		
Japic CTI-111554[186]	S-1 + oral FA	IIR	69	PFS	28	3.8	0.56 (0.37–0.85)	0.003	6.3	0.82 (0.54–1.22)	0.46
	S-1		71		20	2.7			6.1		
Japic CTI-090685[187]	SOX	IIR	134	PFS	21	3.0	0.84 (0.65–1.08)	0.18	7.4	1.03 (0.79–1.34)	0.82
	S-1		130		12	2.8			6.9		
SWOG S1115[188]	Selumetinib + MK-2206	IIR	58	OS	2	1.9	1.61 (1.07–2.43)	0.02	3.9	1.37 (0.90–2.08)	0.15
	mFOLFOX		62		8	2.0			6.7		
NCT00786006[189]	mFOLFIRI.3	IIR	31	6-month OS	0	1.9	NR	NR	3.8	NR	NR
	mFOLFOX		30		7	1.4			3.4		
RECAP[190]	Capecitabine + ruxolitinib	IIR	64	OS	8	2.7	0.47 (0.26–0.85)	0.011	4.5	0.79 (0.53–1.18)	0.25
	Capecitabine + placebo		63		0	1.8			4.3		

(Continued)

Table 6. (Continued)

Trial	Treatment arms	Phase	Patients	Primary endpoint	ORR (%)	PFS (months)	HR (95% CI)	*p* value	OS (months)	HR (95% CI)	*p* value
JANUS 1[191]	Capecitabine + ruxolitinib	III	161	OS	4	1.4	1.06 (0.83–1.35)	0.67	2.9	0.97 (0.75–1.26)	0.41
	Capecitabine + placebo		160		2	1.4			3.1		
JANUS 2[191]	Capecitabine + ruxolitinib	III	43	OS	5	1.6	1.17 (0.69–1.98)	0.72	3.5	1.58 (0.89–2.83)	0.94
	Capecitabine + placebo		43		2	2.0			4.9		
Raltitrexed +/- irinotecan[192]	Raltitrexed + irinotecan	IIR	19	ORR	16	4.0	NR	NR	6.5	NR	NR
	Raltitrexed		19		0	2.5			4.3		
S-1 +/- irinotecan[193]	IRIS	IIR	60	PFS	18	3.5	0.77 (0.53–1.11)	0.18	6.8	0.75 (0.51–1.09)	0.13
	S-1		67		6	1.9			5.8		
NAPOLI-1[194]	Nal-Iri + 5-FU/FA	III	117	OS	16	3.1	0.56 (0.41–0.75)	0.001	6.1	0.67 (0.49–0.92)	0.01
	5-FU/FA[$]		119		1	1.5			4.2		
	Nal-Iri		151		6	2.7	0.81 (0.63–1.04)	0.10	4.9	0.99 (0.77–1.28)	0.94
	5-FU/FA[‡]		149		1	1.6			4.2		

*Time to disease progression.
[$]Combination therapy control.
[‡]Monotherapy control.
5-FU, fluorouracil; BSC, best supportive care; CI, confidence interval; CONKO, Charité Onkologie; FA, folinic acid; FOLFIRI, fluorouracil, folinic acid, and irinotecan; FOLFOX, modified FOLFOX (oxaliplatin day 1, LV day 1, FU days 1 and 2, every 2 weeks); HR, hazard ratio; Nal-Iri, nanoliposomal irinotecan; IRIS, irinotecan plus S-1; LV, leucovorin; mFOLFIRI.3, modified FOLFIRI.3 (irinotecan days 1 and 3, FA day 1, and FU days 1 and 2, every 2 weeks); MK-2206, AKT inhibitor; Nal-Iri, nanoliposomal irinotecan; NR, not reported; OFF, oxaliplatin, FA and 5-FU; OFF, oxaliplatin, folinic acid and 5-fluorouracil; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomized; Selumetinib, MEK inhibitor; SOX, S-1 plus oxaliplatin.

as potential sites of toxicity.[195,196] In pancreatic cancer, after a single-arm phase II study in 40 patients with metastatic disease after progression on first-line gemcitabine-containing regimens met its primary endpoint, with 75% of patients surviving at least 3 months,[197] the NAPOLI-1 phase III trial randomly assigned 417 patients with metastatic pancreatic cancer previously treated with gemcitabine-containing regimens to nanoliposomal irinotecan monotherapy (120 mg/m^2 every 3 weeks), 5-FU-folinic acid (every 2 weeks) or, after a protocol amendment, nanoliposomal irinotecan (80 mg/m^2), 5-FU, and folinic acid (every 2 weeks).[194] Approximately one-third of the patients received two or more previous lines of chemotherapy for metastatic disease. Patients assigned to nanoliposomal irinotecan plus 5-FU and folinic acid had a longer overall survival than patients treated with 5-FU and folinic acid (median, 6.1 months *versus* 4.2 months; HR, 0.75; $p = 0.012$). Other efficacy endpoints (progression-free survival, objective response rate, time to treatment failure, and CA19-9 responses) were also significantly superior in patients assigned to the experimental arm compared with those in patients receiving 5-FU and folinic acid. In contrast, there was no overall survival benefit of nanoliposomal irinotecan monotherapy over 5-FU-folinic acid. The most common grade 3–4 toxicities in the nanoliposomal irinotecan plus 5-FU and folinic group were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[198] Nevertheless, patients' quality of life was maintained during treatment, and there were no significant differences in quality of life compared with patients treated with 5-FU-folinic acid.[199] These results led to the approval of nanoliposomal irinotecan in combination with 5-FU and folinic acid in this setting. It may be more suitable after first-line nab-paclitaxel-gemcitabine, a regimen associated with substantial neurotoxicity, than would be the neurotoxic oxaliplatin-based regimens (which could then be administered as a third line).[200] Whether nanoliposomal irinotecan may have significant clinical activity in irinotecan-pretreated patients (notably with upfront FOLFIRINOX) deserves further analysis before clinical application.

Data on second-line treatments in patients with metastatic pancreatic cancer progressing on gemcitabine plus nab-paclitaxel or FOLFIRINOX are limited to retrospective studies.[201–204] In one of these studies, the progression-free and overall survival medians with gemcitabine and nab-paclitaxel after failure of upfront FOLFIRINOX were 5.1 months and 8.8 months, respectively, with no influence of response to first-line FOLFIRINOX on response to nab-paclitaxel–gemcitabine.[203] In a *post hoc* analysis of the phase III MPACT trial, approximately 40% of patients received a second-line therapy.[204] Patients ($n = 18$) who received FOLFIRINOX as second-line therapy after nab-paclitaxel–gemcitabine failure had a median overall survival of 15.7 months.

To date, other cytotoxic agents or targeted agents evaluated in the second-line setting (and beyond) for patients with advanced pancreatic cancer have shown no benefit in randomized studies (for example, glufosfamide,[205] or the Jak1 and Jak2 tyrosine kinase inhibitor ruxolitinib[190,191]) or were tested only in small, single-arm phase II studies.

One notable exception relates to patients who tested positive for deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) by immunohistochemistry (IHC), polymerase chain reaction (PCR) or next-generation sequencing (NGS). In a study of 86 patients with 12 different cancer types testing positive for dMMR, and who had received at least one prior therapy and had evidence of progressive disease, there was a complete radiographic response to the PD-1 immune checkpoint inhibitor pembrolizumab in 21% of cases, an objective response rate of 53%, and a disease control rate of 77%.[206] Among the eight patients with pancreatic cancer included in this study, two experienced complete radiographic response, and disease control was obtained in six patients. In 2017, the US Food and Drug Administration approved pembrolizumab for dMMR/MSI-H tumors, regardless of disease site. Thus, although approximately 1% of pancreatic cancers are expected to have tumors with this characteristic,[207] the potential for effective treatment is high. Tumor mutation burden, as measured by NGS, is thought to indicate potential for response to immunotherapy because it may be associated with a greater number of neoantigens. These, in turn, can be recognized by the immune system in response to immune checkpoint blockade. Tumor mutation burden may be predictive of greater and more durable responses to immunotherapy in a variety of solid tumors.[208] Whether a high tumor mutation burden may also be a predictor of response to immunotherapy in metastatic pancreatic cancer is still unknown, thus recommendation of the use of

immunotherapy for such tumors is premature. Clear definitions of high tumor mutation burdens and reduced variability among commercially available assays are also necessary for appropriate clinical implementation of this potential biomarker.

Looking at another process of DNA instability, the rate of positive tests for BRCA mutation is approximately 5% in the population with advanced pancreatic cancer,[209] and poly ADP-ribose polymerase (PARP) inhibitors are promising as a targeted therapy, and are, therefore, being studied in patients with advanced pancreatic cancer and a known BRCA mutation.[210,211]

American and European guidelines suggest that the choice of second-line therapy should depend on performance status, comorbidities, organ function, residual toxicities from first-line therapy, and a support system for aggressive medical therapy (Figure 1)[9,165]:

(1) In patients with an ECOG score of 0–1 and a favorable comorbidity profile:
   (a) After first-line treatment with gemcitabine plus nab-paclitaxel, 5-FU plus nanoliposomal irinotecan is the preferred option. 5-FU plus irinotecan or 5-FU plus oxaliplatin can be offered when there is a lack of availability of nanoliposomal irinotecan or when residual toxicity from first-line therapy or comorbidity profile precludes the use of 5-FU plus nanoliposomal irinotecan. The choice between 5-FU plus irinotecan or 5-FU plus oxaliplatin depends on, for example, the existence of limiting neuropathy after upfront nab-paclitaxel. These recommendations (5-FU plus nanoliposomal irinotecan, irinotecan, or oxaliplatin) may also apply to the small subset of patients fit for second-line therapy after first-line gemcitabine monotherapy.
   (b) After first-line treatment with FOLFIRINOX, gemcitabine plus nab-paclitaxel is preferred (off-label use in the EU); gemcitabine alone should be offered when there is a lack of availability of nab-paclitaxel.
(2) In patients with either an ECOG score of 2 or a comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy, gemcitabine or 5-FU is recommended.
(3) In patients with an ECOG score of >2, best supportive care alone is recommended.
(4) For patients who are considered to be candidates for checkpoint inhibitor therapy (when available), routine testing for dMMR or MSI using IHC, PCR, or NGS is recommended, and pembrolizumab (when available) is recommended as second-line therapy for patients with dMMR or MSI tumors.
(5) No data are available to recommend third-line (or above) therapy with a cytotoxic agent. Inclusion in a clinical trial is encouraged.

Update on personalized medicine

Personalized medicine has improved the prognosis of very aggressive cancers such as lung cancers. It is easy to imagine that personalized medicine could help to solve the major therapeutic problem that is pancreatic cancer. Furthermore, it has long been known that the tyrosine kinase signaling pathways that encompass the RAS–MAPK but also the PI3K–AKT cascades have a major role in the carcinogenesis and proliferation of pancreatic cancer.[212] Unfortunately, attempts to target this pathway (e.g. tipifarnib, lonafarnib) have yielded very disappointing results.[213] The personalized medicine approach still needs to remove some barriers to be effective in routine, as shown by the results of the IMPaCT study where 93 patients were included and only 73 were screened.[214] To date, 22 candidate cases have been identified: 14 KRAS wild type, 5 cases of HER2 amplification, 2 mutations in BRCA2, and one ATM mutation, but no patient has been successfully treated on the IMPaCT study. Main reasons were worsening of their general condition, biological status, or death; the occurrence of an intercurrent pathology; final other cancer diagnosis; refusal to participate after screening; or even start of chemotherapy before molecular results.

However, a small subgroup of patients (~2%) with BRCA1 or BRCA2 mutations could be candidates for treatment with PARP inhibitors such as olaparib or veliparib.[215] The POLO (Pancreas Cancer Olaparib Ongoing) trial evaluated the efficacy of maintenance therapy with olaparib in patients with a germline *BRCA* mutation and metastatic pancreatic adenocarcinoma that had

not progressed during first-line platinum-based chemotherapy.[216] A total of 154 patients were randomized between olaparib and placebo. The median progression-free survival was significantly longer with maintenance olaparib than with placebo (7.4 months *versus*. 3.8 months; HR 0.53; 95% CI, 0.35–0.82; $p = 0.004$). Overall survival and health-related quality of life were not significantly different and toxicity was mild.

These modest results could be the consequence of the complexity of the carcinogenesis of pancreatic cancer, involving multiple pathways. New personalized medicine programs will need to take into account recent molecular genomic approaches. A comprehensive integrated genomic analysis of 456 pancreatic cancer samples and their histopathological variants identified 32 recurrently mutated genes that aggregate into 10 pathways: *KRAS*, *TGF*-β, *WNT*, *NOTCH*, *ROBO*/*SLIT* signaling, *G1*/*S* transition, *SWI*/*SNF*, chromatin modification, DNA repair, and RNA processing. Expression analysis defined four subtypes that correlate with histopathological characteristics: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine.[217] The Cancer Genome Atlas work confirmed the complex molecular landscape of pancreatic cancer and provides a roadmap for precision medicine in pancreatic cancer.[218] For example, COMPASS is the first prospective translational study to establish the feasibility of comprehensive real-time genomic analysis of advanced pancreatic cancer using whole-genome and RNA sequencing with the possibility of clinically meaningful routine use.[219] Early results from COMPASS demonstrate that there are unique advanced pancreatic cancer genomic and transcriptomic subtypes with molecular heterogeneity between individual cases, and with differing responses to chemotherapy. This is the first prospective evidence that molecular profiling that defines classical *versus* basal-like subtypes may predict differential responses to chemotherapy among patients with advanced pancreatic cancer with different RNA subtypes.[219]

Targeting the stromal desmoplastic reaction. PEGPH20, a recombinant pegylated hyaluronidase enzyme, was developed to specifically target hyaluronan in the tumor stroma. A large randomized phase II study reported promising results with this drug combined with nab-paclitaxel–gemcitabine.[220] In patients with tumor hyaluronic acid overexpression (IHC; 47/136 patients), the addition of PEGPH20 to nab-paclitaxel–gemcitabine significantly increased median progression-free survival from 5.2 to 9.2 months (HR: 0.51, $p = 0.048$). A large phase III trial (420 patients) that includes the specific subpopulation of patients with positive hyaluronidase IHC is evaluating PEGPH20 in combination with nab-paclitaxel–gemcitabine.[221] However, these results should be weighted with the recent publication of the randomized phase IB/II trial SWOG S1313, which found a deleterious effect of PEGPH20 in patients unselected for tumor hyaluronan status when combined with an mFOLFIRINOX protocol.[222]

Another potential way to decrease the putative protective effect of the stroma is to block the Hedgehog signaling pathway.[223] After disappointing results of the agents of this therapeutic class in phase I/II studies,[224,225] a phase III evaluating vismodegib is ongoing.

Immunotherapy

Immune checkpoint inhibitors. The first experimental attempt to use a CD40 agonist in combination with gemcitabine was relatively successful.[226] However, subsequent studies evaluating either anti-CTL4 or anti-PD1/PDL1 agents were disappointing. For example, in the case of anti-CTL4 agents, phase II studies of ipilimumab[227] and tremelimumab[228] reported no clinically significant effects. In a randomized phase II trial evaluating durvalumab in one arm and durvalumab plus tremelimumab in the other arm as a second-line treatment for pancreatic cancer, the disease control rate was less than 10% in both arms.[229] The development of this combination as a second-line treatment for pancreatic cancer has been cancelled. However, in the safety run of a randomized phase II study assessing the efficacy and safety of nab-paclitaxel–gemcitabine *versus* nab-paclitaxel–gemcitabine, durvalumab, and tremelimumab in 10 patients with untreated pancreatic cancer, the disease control rate was 100%, and median progression-free survival was 7.9 months.[230] Results of other studies evaluating the combination of ipilimumab and nivolumab plus chemotherapy (NCT022688825, NCT02558894) are pending.

Despite lack of hope that immune checkpoint inhibitors will show major efficacy in this disease, for the very few patients with a pathologically proven pancreatic cancer harboring a dMMR phenotype, a very high response rate has been observed with PD1/PD-L1 inhibitors in such

dMMR/MSI tumors,[231] including in patients with pancreatic cancer. However, this eventuality is exceptional among cases of pancreatic cancer.[232]

Vaccines. Cellular-based vaccines have given encouraging results but there is currently no clear proof that they will be used in clinical practice in the near future.

Peptide-based cancer vaccines. After a promising phase I/II study, a phase III trial evaluating a combination of chemotherapy with a telomerase vaccination (GV1001) failed to show a benefit.[233] Personalized peptides that aim to prevent progressive tolerance to cancer-related antigens have been developed and tested in combination with gemcitabine, with promising results.[234] G17DT, an immunogen producing neutralizing antibodies against the tumor growth factors amidated and glycine-extended forms of gastrin-17 was tested in an international multicenter randomized controlled trial.[235] Patients developing anti-G17DT responses (73.8%) survived longer than nonresponders or those on placebo (median survival, 176 *versus* 63 *versus* 83; log-rank test, $p = 0.003$).

Further clinical investigation is warranted to determine the effectiveness of such new combination therapies.

Whole-cell cancer vaccines. The concept of GVAX is based on the development of genetically engineered tumor cells that secrete granulocyte-macrophage colony-stimulating factor. GVAX has been combined with different substances, and, especially, with a Listeria vaccine expressing mesothelin. However, results remain disappointing at this time. Algenpantucel-L, composed of irradiated cancer cells expressing alpha-1,3-galactosyltransferase, gave promising results in a phase II study combining this whole-cancer vaccine with radiochemotherapy in an adjuvant setting (60 patients, median disease-free survival of 17.3 months).[236] However, a phase III trial (IMPRESS) did not meet its primary endpoint and the development of this compound has been stopped.[90]

Combination of vaccines and immune checkpoint inhibitors. Ipilimumab combined with GVAX gave favorable survival results compared with ipilimumab alone in a small phase Ib randomized study (5.7 months *versus* 3.6 months).[237] Larger randomized trials evaluating the efficacy of this approach are ongoing (NCT01896869, NCT02548169). Depletion of tumor-associated fibroblasts by targeting the CXC112–CXCR4 axis may enhance T-cell infiltration and could be combined specifically with immune checkpoint inhibitors. An ongoing phase II trial is evaluating the efficacy of the combination of an anti-CXCR4 antibody (ulocuplumab) and nivolumab in pancreatic cancer and other solid tumors (NCT02472977).

Adoptive T-cell transfer. This kind of treatment requires collection of the patient's T cells, followed by expansion and activation of the cells before they are reinfused. Three different types of T cells can be produced according to the method used for activation: tumor infiltrating lymphocytes (TILs), engineered T cells expressing a specific cancer T-cell receptor (TCR), and T cells that express a chimeric antigen receptor (CAR). The CAR-T cell method appears to be the most effective of these techniques. Preliminary data on the use of antimesothelin CAR-T cells suggest some activity in pancreatic cancer.[238] The carcinoembryonic antigen can also be targeted in pancreatic cancer, and there are trials ongoing to evaluate the role of CAR-T cells activated with carcinoembryonic antigen in pancreatic cancer.[239] The efficacy of CAR-T cells may even be increased in combination with immune modulators such as cyclophosphamide, or anti-CTLA4 and anti-PD1 agents, and several randomized trials are ongoing.

Cancer stemness inhibitors. A phase Ib/II trial testing a cancer stemness inhibitor, napabucasin (BBI-608), in combination with nab-paclitaxel–gemcitabine in metastatic pancreatic adenocarcinoma showed favorable trends in terms of response rate and survival.[240] Among 71 intent-to-treat patients, disease control was observed in 55 (77%), with 1 complete response (1.4%) and 26 partial responses (37%). A phase III trial is currently underway to confirm these data (NCT02231723).

Which treatments for elderly patients?

Patients over 65 years are unrepresented in clinical trials, and no randomized study is available in any setting. Concerning resectable patients, a large ($n = 9533$) retrospective study evaluated trends in resection rates and operative mortality in adults aged ⩾66 with locoregional pancreatic cancer and showed that the resection rate decreased with increasing age.[241] Increasing age

also decreased the likelihood of evaluation by a surgeon (81% of those <70 *versus* 45% ⩾85 years). Surgical evaluation and resection rates decreased with age regardless of comorbidity status.

But, more generally, age is not correlated with an increased risk of death.[242] Given a significant increased rate of complications, surgical candidates need to be carefully selected, but PD is not excluded in elderly patients.[243] Some adjuvant trials with chemotherapy reported survival outcomes in patients ⩾65 years. In ESPAC-1,[74] ESPAC-3,[77] and JASPAC-1,[78] age was not found to be a prognostic factor for survival. In PRODIGE 24, no difference of efficacy was seen in patients ⩾65 compared with those ⩽ 65, demonstrated a preserved benefit in the older group.[17] However, the benefit for FOLFIRINOX in patients ⩾70 years was not significant.

Looking at palliative chemotherapy, older patients are less likely to received chemotherapy. Aldoss and colleagues reviewed cases of 440 metastatic patients aged ⩾80 years in the Veterans Affairs Central Cancer Registry from 1995 to 2007 and analyzed their median overall survival as their baseline comorbid conditions.[244] The multivariate analysis demonstrated that chemotherapy was associated with significant superior median overall survival (4.9 months, 95% CI 3.57–5.77) compared with no therapy (1.7 months, 95% CI 0.9–1.3) (HR = 0.41, $p < 0.0001$). A recent literature review found a number of studies showing that aging did not exclude the use of chemotherapy, since older patients appeared to have similar benefits to younger patients, although reduced-dose chemotherapy and enhanced supportive care were often required to ensure good safety.[245]Similar data were found in patients ⩾70 or 75 years receiving gemcitabine.[246,247]

Regarding gemcitabine + nab-paclitaxel and FOLFIRINOX pivotal trials, no difference of efficacy was seen between older and younger patients.[159,161] Another small series confirmed the PRODIGE4 Accord 11 data using modified FOLFIRINOX.[248] A retrospective analysis of systemic therapy use of 237 patients ⩾75 years with metastatic disease, conducted between 2005 and 2013, found that systemic therapy was associated with longer survival in elderly patients. No significant difference was detected in survival between age groups 75–79, 80–84, and ⩾85 years of age among those who received systemic therapy.[249] Specific screening tools, such as Comprehensive Geriatric Assessment, may help to identify frail patients and better guide treatment decision in this population.[242]

Supportive care and palliative care

In patients with locally advanced or metastatic pancreatic cancer, the objectives of palliative care are as follows.

(1) To promote the integration of a palliative care specialist as early as possible. Indeed, to be most effective, the concept of palliative care should be introduced early in the course of an illness, in conjunction with active disease treatment,[250] and, according to ASCO, preferably at the first visit.[166]
(2) To encourage the palliative care specialist to view the patient's care as his or her sole focus. This implies clear and accurate information regarding the disease diagnosis, including the communication of incurability, in order to choose 'the right treatment, for the right patient, in the right setting'.[250] Therefore, multidisciplinary management (involving an oncologist, surgeon, radiotherapist, and palliative care physician) and shared decision making are needed at every stage of disease.
(3) To pay close attention to the physical comfort, psychosocial concerns, and spiritual well-being of the patient throughout the trajectory of illness.[166]
(4) To take charge of the main physical symptoms related to the disease and their evolution (for example, pain, anorexia, weight loss, depression and anxiety, jaundice, gastric or duodenal obstruction, ascites, venous thromboembolism, asthenia). The aim is to maintain or improve quality of life.
(5) To address the issues of the end of life, and to encourage the writing of advance directives.
(6) To accompany and support the family, the entourage, and the caregivers.

Pain management

The ASCO recommends aggressive treatment of pain for patients with advanced pancreatic cancer.[166] Of these patients, 75% present with abdominal or back pain, and 80% of patients with advanced pancreatic cancer experience severe pain prior to death, commonly associated with malignant invasion of the celiac plexus.[250]

Pain in pancreatic cancer has a complex physiopathology. It implies neural invasion and neurogenic inflammation. Therefore, the pain is nociceptive and neuropathic.[251] Pain management is based on several modalities: medical approach, chemotherapy and radiation therapy, interventional therapies, intrathecal therapy, and alternative medicine.

Medical approach. Opioids are considered to be the first-line medical therapy for visceral cancer pain, including pain from cancer of the pancreas (tramadol, morphine, oxycodone, or fentanyl).[166] Antiepileptics such as gabapentin and pregabalin are used as first-line treatment for neuropathic pain. Their effectiveness is also demonstrated in cancer-related neuropathic pain.[251] Nortriptyline and duloxetine also have analgesic efficacy.[166] Methadone can also be used in refractory neuropathic pain. However, its use must be managed by expert teams because of its long half-life and multiple drug–drug interactions.[252] Corticosteroids have proved particularly useful as adjuvant therapy for visceral pain.[251]

Chemotherapy and radiation therapy. Pain control is largely implemented as a secondary end point in trials evaluating chemotherapy regimens in pancreatic cancer. For instance, FOLFIRINOX has been shown to be associated with better quality of life and pain control than gemcitabine in the management of metastatic pancreatic cancer.[163] Radiation therapy is particularly effective in controlling and relieving pain caused by large tumors compressing other organs or structures, such as nerves or the spine. The radiation therapy can shrink the tumor, which may help in relieving the pain.[251]

Interventional therapies. For patients whose pain is refractory to opioids or who develop dose-limiting side effects from opioids, a block of the celiac plexus with local anesthetic is often employed.[251] The major component of pancreatic cancer pain is mediated by sympathetic fibers from the pancreas, and is relayed through the celiac plexus to the splanchnic nerves. A local anesthetic, usually bupivacaine, can be used in combination with steroids to temporarily inhibit the celiac plexus. Celiac plexus neurolysis represents the prolonged interruption of the plexus by the injection of alcohol or phenol. This technique is performed by anesthetists, radiologists, or endoscopists (using endoscopic ultrasonography).[252] In a double-blind, randomized clinical trial by the Mayo Clinic, early execution of neurolytic celiac plexus block was found to deliver a larger initial decrease in pain, and the improvement lasted longer than systemic analgesic therapy.[253] A meta-analysis of eight randomized studies reported that pancreatic cancer patients treated with celiac plexus block experienced lower levels of pain at 4 weeks and required less opioid medication than those on standard analgesics, but the difference in pain score did not maintain significance at 8 weeks.[254]

Intrathecal therapy. Intrathecal therapy can be proposed for end-of-life stages or for refractory pain. Various molecules can be used, including morphine, fentanyl, local anesthetics, baclofen, or clonidine.[255,256]

Alternative medicine. Acupuncture[257] and hypnosis[258,259] are increasingly common approaches to control pain in patients with cancer. They are an effective adjunctive method to manage cancer pain, and pain relief is improved compared with drug therapy alone.

Anorexia and weight loss

Patients with pancreatic cancer experience cachexia owing to appetite loss, malnutrition, and hypercatabolism.[250] The weight loss leads to weakness, fatigue, and a poor quality of life. Nutritional management must be carried out by a nutritionist or dietitian.[166] Patients on pancreatic enzymes along with dietary counseling gain body weight.[260] Appetite stimulant medications such as anamorelin may be considered in severe cases,[166] and achieved significant increases in hunger and caloric intake in a recent phase I study.[261]

Depression and anxiety

The severity of the prognosis of pancreatic cancer can lead to depression and anxiety, even early in the course of disease. From 33% to 50% of patients with pancreatic cancer have depressive symptoms. Symptoms of clinical depression may include anorexia and weight loss, negative thoughts and behavior, sleep disturbance, anhedonia, fatigue, and feelings of hopelessness.[262,263] Psychosocial factors (financial concerns or emotional support), medical factors (prognosis or metabolic derangements), and psychological factors (coping ability or perceptions of illness) can cause depression. Most experts recommend an approach that combines supportive psychotherapy, patient and family education, and stimulants or antidepressants/anxiolytics, or both.[254]

Methylphenidate can be used by patients with limited life expectancy. It can improve energy, alertness, and weakness.[264] When the life expectancy of the patient is longer, selective serotonin reuptake inhibitors are used first.[252]

Jaundice

During the course of disease, 70% to 80% of patients with tumors located in the head of the pancreas develop obstructive jaundice through blockage of the biliary tree.[265] The preferred treatment is endoscopic placement of a self-expanding stent in the bile duct to re-establish drainage to achieve relief of jaundice and pruritus.[166]

Gastric or duodenal obstruction

Nearly 10% of patients will have gastric or duodenal obstruction.[265] Symptoms include early satiety, nausea, postprandial vomiting, and weight loss. Endoscopic duodenal stenting is usually successful.

Ascites

Ascites cause abdominal discomfort, nausea, and vomiting, and dyspnea from pressure of the fluid against the diaphragm. Their management is based on intermittent paracentesis, the use of diuretics such as spironolactone, or placement of a long-term drainage catheter.[166]

Venous thromboembolism

Patients with pancreatic cancer have one of the highest risk of deep vein thrombosis or pulmonary embolism, with incidences ranging from 17% to 57% with a relative risk of venous thrombosis of 8.8.[266] The ASCO guidelines recommend primary prevention of venous thromboembolism with the use of low-molecular-weight heparins in all patients with potentially curable pancreatic cancer after resection, and in a case-by-case selection of high-risk patients undergoing systemic therapy.[166]

Asthenia

Asthenia is one of the commonest symptoms of pancreatic cancer. Exercise during oncological treatment reduces fatigue and improves quality of life.[267] Studies dedicated to pancreatic cancer are ongoing. An adapted physical activity program should be proposed to limit this symptom. Medications such as corticosteroids, megestrol acetate, and stimulants (adrafanil, methylphenidate) can be used but they have limited effectiveness over time, and are a source of side effects such as the increase of thromboembolic risk with megestrol acetate.[268]

To conclude, controlling physical symptoms, providing emotional support, preserving dignity, exploring realistic goals, and discussing day-to-day living are important to maintain hope in patients who are terminally ill with cancer, and in their families.[269] This is only possible with close collaboration between oncology teams and teams providing support and palliative care.

Conclusions

Pancreatic cancer is extremely difficult to treat. The goals of care and patient preferences should be discussed and precised with every patient diagnosed with pancreatic cancer. The absence of early warning symptoms, rapid metastatic dissemination, frequent sudden adverse events, and degradation of performance status score makes many patients unfit for chemotherapy. Palliative care will help to relieve main physical symptoms and to postpone degradation of quality of life. More efficient first-line regimens, such as FOLFIRINOX and gemcitabine with nab-paclitaxel, have improved overall survival in fit patients with metastatic disease, and may lead to conversion surgery in some patients with LAPC. Second-line chemotherapy regimens have been validated, mainly after gemcitabine as first-line therapy. Personalized medicine and immunotherapy had so far failed to improve the prognosis of these patients, yet a small subgroup of patients with BRCA mutations appear to be good candidates for treatment with PARP inhibitors.

Surgery combined with chemotherapy is still the only potentially curative treatment, but must be integrated into a complete multidisciplinary treatment sequence to optimize its effectiveness. Surgical progress has been made, improving overall survival, with perioperative and critical care and standardization of the surgical technique. In the borderline setting, the American and European definition criteria are similar, and allow a staging of the disease that must be used in routine practice. The two main remaining questions are: does induction therapy improve overall survival? And should we use chemotherapy or chemoradiotherapy to achieve this goal? Current trials underway should provide us with answers.

After resection, in the adjuvant setting, the mFOLFIRINOX regimen has recently shown superiority over gemcitabine alone and is a new standard of care in fit patients. The impact of chemoradiation remains uncertain both as adjuvant treatment and in locally advanced disease. The future major issue will be to test and to validate neoadjuvant or perioperative regimens using combination chemotherapy regimens.

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Publication 2 – Neoadjuvant Treatment Strategies in Resectable Pancreatic Cancer

Revue de la littérature (publiée)

***Lambert, A.**; Schwarz, L.; Ducreux, M.; Conroy, T. Neoadjuvant Treatment Strategies in Resectable Pancreatic Cancer. **Cancers 2021**, 13, 4724. https://doi.org/10.3390/cancers13184724*

Une fois le travail de revue effectué concernant l'ensemble des stratégies thérapeutiques, il nous est apparu pertinent de faire un focus plus particulier sur la question des traitements néoadjuvants. En effet, cette question porte sur une comparaison des stratégies actuelles (chirurgie puis chimiothérapie adjuvante pour les patients résécables d'emblés) avec les approches de chimiothérapie d'induction ou néoadjuvantes (qui restent à valider).
Cette approche est d'autant plus utile pour le sujet qui nous intéresse que l'intégration des questions concernant les patients borderlines et localement avancés porte nécessairement sur l'intérêt de l'évaluation de facteurs pronostiques locaux telles que la présence de lésions dysplasiques ou encore de la qualité de résection des marges chirurgicales.

Les stratégies de chimiothérapie première ne sont pour le moment pas entrées dans les recommandations à la suite d'essais contrôlés et randomisés mais cet article fait la lumière sur l'état de la science à ce titre et propose des hypothèses plausibles sur l'évolution des pratiques.
Il pose également la question des complications et comorbidités qui pourraient être moins fréquentes chez les patients ayant reçu un traitement systémique avant chirurgie. Il n'est également pas assuré qu'un bénéfice persiste à une chimiothérapie adjuvante si celle-ci est administrée après chimiothérapie première puis chirurgie.
Cette publication recense les questions qu'il serait utile de considérer lors du développement de futurs essais thérapeutiques.

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Review

Neoadjuvant Treatment Strategies in Resectable Pancreatic Cancer

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Simple Summary: Only 10–20% of patients with newly diagnosed resectable pancreatic adenocarcinoma have potentially resectable disease. Upfront surgery is the gold standard, but it is rarely curative. After surgical extirpation of tumors, up to 80% of patients will develop cancer recurrence, and the initial relapse is metastatic in 50–70% of these patients. Adjuvant chemotherapy offers the best strategy to date to improve overall survival but faces real challenges; some patients will experience rapid disease progression within 3 months of surgery and patients who do not receive all planned cycles of chemotherapy have unfavourable oncological outcomes. The neoadjuvant approach is therefore logical but requires further investigation. This approach shows favourable trends regarding disease-free survival and overall survival but, in the absence of rigorous published phase III trials, is not validated to date. Here, we intend to provide a comprehensive analysis of the literature to provide direction for future studies.

Abstract: Complete surgical resection is the cornerstone of curative therapy for resectable pancreatic adenocarcinoma. Upfront surgery is the gold standard, but it is rarely curative. Neoadjuvant treatment is a logical option, as it may overcome some of the limitations of adjuvant therapy and has already shown some encouraging results. The main concern regarding neoadjuvant therapy is the risk of disease progression during chemotherapy, meaning the opportunity to undergo the intended curative surgery is missed. We reviewed all recent literature in the following areas: major surveys, retrospective studies, meta-analyses, and randomized trials. We then selected the ongoing trials that we believe are of interest in this field and report here the results of a comprehensive review of the literature. Meta-analyses and randomized trials suggest that neoadjuvant treatment has a positive effect. However, no study to date can be considered practice changing. We considered design, endpoints, inclusion criteria and results of available randomized trials. Neoadjuvant treatment appears to be at least a feasible strategy for patients with resectable pancreatic cancer.

Keywords: chemoradiotherapy; neoadjuvant chemotherapy; FOLFIRINOX; gemcitabine; nab-paclitaxel; pancreatic cancer; surgery

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1. Introduction

Pancreatic cancer accounted for almost as many deaths (466,000) as new cases (496,000) worldwide in 2020 and is the seventh leading cause of cancer death in both sexes [1]. The prognosis of patients with pancreatic cancer has changed little over the past two decades: the overall 5 year survival rates in Europe and the USA remain dismal at 8–10% [2,3]. Pancreatic cancer is now classified into four categories: resectable tumors that have a

high likelihood of achieving an R0 resection, borderline resectable tumors (BRPC) that are potentially resectable but have a high risk of an R1 resection with upfront resection, locally advanced unresectable pancreatic cancer (LAPC), and metastatic disease. This review on neoadjuvant strategies will concentrate on upfront resectable tumors.

Complete surgical resection is the cornerstone of curative therapy for resectable pancreatic adenocarcinoma; unfortunately, only 10–20% of newly diagnosed patients have potentially resectable disease. Upfront surgery is the gold standard, but it is rarely curative. Adjuvant chemotherapy has been shown to improve survival, and upfront surgery with subsequent adjuvant therapy is still the standard of care for all patients with resectable pancreatic cancer (RPC). However, about 10% of patients with RPC according to initial workup do not undergo resection because of occult metastatic disease found during surgical exploration [4]. Median survival with this multimodal therapy in patients with RPC was 17.7 months in a recent meta-analysis [5], and long-term survival remains limited, at approximately 10% with surgery and gemcitabine [6]. Recent randomized trials have reported an improved median disease-free survival (DFS) of 21.6–22.9 months with adjuvant mFOLFIRINOX (leucovorin, oxaliplatin, irinotecan, fluorouracil) or S-1 [7,8]. However, neither of these trials report how many patients were excluded from randomization due to chemotherapy contraindication or to poor performance status. After surgical extirpation of tumors, up to 80% of patients will develop cancer recurrence, and the initial relapse is metastatic in 50–70% of these patients. As a result of this, pancreatic cancer is often regarded as a systemic disease "ab initio" despite surgery [9,10], and there is growing interest in earlier use of systemic therapy.

2. Main Pitfalls of Adjuvant Therapy

Adjuvant treatment after macroscopically curative resection for pancreatic cancer is underutilized. Large retrospective series showed that 33–49% of patients who undergo curative resection do not receive adjuvant chemotherapy, mainly due to postoperative morbidity, comorbidity, prolonged recovery, patient refusal, and early disease recurrence [11–14]. In a US Surveillance Epidemiology and End Results series of 2440 patients from 2004 to 2013, only 7% of patients who underwent resection for pancreatic cancer completed their planned chemotherapy regimens, whereas 28% did not complete their courses and 65% received no adjuvant chemotherapy [15]. A similarly limited use of adjuvant chemotherapy has been reported in a recent population-based Dutch series. From 2008 to 2013, 46% of patients did not receive adjuvant chemotherapy following pancreatic resection. In the subgroup of patients >75 years, only 16% underwent adjuvant chemotherapy [16]. In the US National Cancer Database study from 2010 to 2014 of 18,470 patients with stage I or II resected pancreatic cancer, 27.5% did not receive any systemic therapy [17]. In another Dutch nationwide study, predictive factors for not receiving adjuvant chemotherapy were older age, worse performance status, postoperative complications, especially pancreatic fistula and postpancreatectomy hemorrhage, and lower annual surgical volume [18].

To our knowledge, incidence of early tumor recurrence before adjuvant chemotherapy has not been evaluated to date, but local recurrence may be detected at the first postoperative computed tomography (CT) scan or by elevated levels of the tumor marker CA 19-9 [19]. Postoperative CT or magnetic resonance imaging (MRI) scans and measurement of serum CA 19-9 levels may be useful for detecting early metastatic disease [7,20]. One retrospective study revealed that from a total of 957 patients with primary resection, 85 (8.9%) developed rapid disease progression within 3 months of surgery [14], suggesting that resection was not beneficial for these patients. Poor rates of completion of adjuvant chemotherapy is also a major problem, as many patients are unable to finish the planned cycles. The proportion of patients completing the full number of cycles has been shown to be 58–65% with gemcitabine [8,21–23] in all studies except PRODIGE 24 (in which it was 79%), 55% in the fluorouracil plus folinic acid group of ESPAC-3, 54% in the gemcitabine plus capecitabine group of ESPAC-4, 62% with S-1 (JASPAC-1), and 66% with mFOLFIRINOX [7,8,21–23]. This poor feasibility of completing adjuvant chemotherapy may be

deleterious; completion of all cycles of planned adjuvant chemotherapy was identified as an independent prognostic factor in the ESPAC-3 trial [24].

3. Rationale for Neoadjuvant Therapy

Preoperative (neoadjuvant) treatment of localized pancreatic cancer is a logical strategy for a disease that is systemic at diagnosis in most patients. This multimodality approach may also overcome some of the limitations of adjuvant therapy. The improved response rates observed with FOLFIRINOX or gemcitabine with nab-paclitaxel and the recent positive results observed with neoadjuvant chemoradiotherapy (CRT) in BRPC [25,26] have encouraged their use in neoadjuvant settings. Neoadjuvant chemotherapy and/or CRT have theoretical and empirical advantages [27,28] and are given to patients with the following aims:

- To eliminate presumed occult metastatic disease earlier after diagnosis and reduce distant relapse rates.
- To give some patients time to allow for preoperative conditioning (nutrition, physical training, treatment of comorbidities and symptoms, etc.).
- To increase complete resection (R0) rates.
- To evaluate the histological response to therapy.
- To shrink tumors to smaller sizes and reduce involvement of vascular structures, and to facilitate R0 resection, which is associated with improved survival.
- To downstage the tumor and reduce regional nodal disease and histological poor prognostic factors.
- To reduce surgical complexity and postoperative complications.
- To maximize the number of patients completing all cycles of chemotherapy and/or full doses of CRT.
- To improve tolerance, resulting in a higher rate of treatment compliance and improved dose intensity.
- To identify patients with rapidly progressive disease who are unlikely to benefit from resection and spare them from nonbeneficial surgery.
- To test in vivo chemosensitivity and investigate novel sequential treatments and drug combinations.
- Finally, to increase overall survival (OS) and quality of life of patients with RPC.

4. Main Concerns about Neoadjuvant Therapy

A surgery-first approach with adjuvant therapy may have benefits over neoadjuvant therapy. The main potential risk of neoadjuvant therapy is locoregional tumor growth or metastatic spreading of disease, and some patients may miss their "window" for curative-intent surgery. In metastatic disease settings, even with combination chemotherapy regimens, the risk of tumor progression is significant. Toxicities of neoadjuvant treatments may also result in decreased performance status, precluding surgery. Pancreatitis (e.g., after biliary stent placement) might be mistaken for tumor progression or unresectable disease. Some patients with inaccurate pretreatment staging, particularly those with missed peritoneal metastatic disease, may have inappropriate therapeutic sequences, especially those patients receiving neoadjuvant CRT. Increased postoperative complications and mortality rates may also be a significant risk. Potential overtreatment does not seem to be a significant problem, due to the small proportion of patients who are cured with standard treatments. So, the major point is: do we have level 1A evidence of evidence of the efficacy of neoadjuvant therapy through available literature and randomized trials?

Three main approaches have been developed:

- Neoadjuvant chemotherapy, of which the main potential advantage is the earlier eradication of distant metastases that are already present at the time of the initial diagnosis. Reducing the delay between diagnosis and start of chemotherapy may reduce the metastatic rate and may improve the prognosis of patients.

- Neoadjuvant CRT may also downstage the tumor, increase the R0 resection rate, and reduce the risk of local recurrences.
- Combined neoadjuvant chemotherapy and preoperative CRT has also been tested, mainly in expert centers.

5. Meta-Analysis of Neoadjuvant Therapy

Numerous meta-analyses, a Markov decision analysis, and Bayesian network meta-analyses of nonrandomized prospective and retrospective studies have been performed. Most have mixed RPC, BRPC, and LAPC and have reported improved R0 rates, decreased incidence of lymph nodes metastases, and significant OS benefit with neoadjuvant therapy. However, their impact is limited due to their inherent selection biases, as nonrandomized studies report survival data of the subgroup of patients who underwent pancreatic resection and patients with disease progression are often excluded [29–31]. Moreover, retrospective studies are known to underreport toxicity outcomes. In a systematic review that only included studies of RPC, Bradley and Van der Meer reported six phase II studies on neoadjuvant therapy, pooling 371 patients [32]. The proportion of patients who had surgery was 76.08% (95% CI: 60.8–88.5). Overall, the analysis, based on eight other studies and 9197 participants, marginally favors neoadjuvant therapy across outcomes of R0 resection rates and 5-year survival rates. All available meta-analyses are literature-based and did not use individual patient-level data.

Two recent meta-analyses compared neoadjuvant treatment to upfront surgery followed by adjuvant chemotherapy. A meta-analysis from the Amsterdam Cancer Center [5] selected 38 studies (three randomized trials, nine phase I or II trials, 12 prospective cohort studies, and 14 retrospective cohort studies) including 3484 patients treated with radiation (29 studies) and/or chemotherapy, mainly with gemcitabine (26 studies), for BRPC or RPC. The overall resection rate was lower in patients who had neoadjuvant treatment than in those who had upfront surgery (66.0% vs. 81.3%; $p < 0.001$). It is important to note that 17.8% of patients who received neoadjuvant treatment did not subsequently undergo exploratory surgery; disease progression was the reason for not undertaking surgery in 64.4% of these patients. When reported by intention to treat, the R0 resection rate was not significantly higher with neoadjuvant treatment (58.0% vs. 54.9%; $p = 0.088$). For the 18 studies that reported the median OS of 857 patients with RPC, the median OS was 17.7 months with upfront surgery compared to 18.2 months with neoadjuvant treatment. In an intention-to-treat analysis on the whole population of patients with RPC and BRPC, the median OS was 18.8 months after neoadjuvant treatment versus 14.8 months after upfront surgery (significance level not reported). However, the authors discussed the possible limitations introduced by the inclusion of retrospective studies that may have included bias.

One important meta-analysis from the Ohio State Wexner Medical Center [33] selected only prospective randomized controlled trials; six trials including 850 patients were relevant. Of the six trials, four included patients with RPC, one included patients with BRPC, and one included patients with either RPC or BRPC. Two trials used gemcitabine-based neoadjuvant chemotherapy, while four used neoadjuvant CRT. There was no significant difference in overall resection rates among the two groups, but there was an increased R0 resection rate (risk ratio [RR] 1.51, 95% CI 1.18–1.93) and an increased pN0 rate (RR 2.07, 95% CI 1.47–2.91) in the neoadjuvant group. Moreover, a significant overall benefit was reported (pooled hazard ratio [HR] 0.73, 95% CI 0.61–0.86). In subset analyses, the pooled HR remained significant both in RPC (HR 0.73, 95% CI 0.59–0.91) and in BRPC settings (HR 0.51, 95% CI 0.28–0.93).

6. Conditioning and Monitoring of the Patient during Neoadjuvant Treatment

Neoadjuvant therapy first requires a histological or cytological diagnosis of pancreatic cancer, either via endoscopic ultrasonography guided fine needle aspiration/biopsy or by endoscopic retrograde cholangiopancreatography with intraductal biopsy/brush, and

biliary stenting for obstructive jaundice. For pancreatic head cancer, biliary drainage should be reserved for patients with jaundice [34]. Before starting neoadjuvant therapy, plastic stents should be replaced by fully covered self-expandable metallic stents, since they can be exchanged or removed [35].

Careful preoperative nutritional evaluation and nutritional support are important to reduce chemotherapy-related toxicities and improve tolerance to chemotherapy. A retrospective study on 62 patients, mostly treated with neoadjuvant CRT, suggested that neoadjuvant therapy could aggravate nutritional status and hamper postoperative recovery [36]. Conversely, in another retrospective series of 199 patients with BRPC and mainly treated with neoadjuvant chemotherapy, preoperative high prognostic nutritional index was an independent prognostic factor for survival [37]. Therefore, maintaining good nutritional status during preoperative treatment is important to prevent patient weight loss and reduce malnutrition, which are associated with increased morbidity and mortality and reduced QoL [38].

Prior to neoadjuvant treatment, MRI with diffusion-weighted imaging and/or laparoscopy allows the detection and biopsy of small peritoneal and/or liver metastases [4,39] and may help to avoid unnecessary morbidity from a nontherapeutic laparotomy, especially in patients at increased risk of metastatic disease: those with body or tail tumors, markedly elevated CA 19-9 levels, large primary tumors, or large regional lymph nodes [35,40]. Tumor board meetings and visits with the surgeon and the anesthetist should be organized before neoadjuvant treatment, as they play an important role in multidisciplinary team cancer care of surgical patients.

Patients are usually required to have a performance status of ECOG of 0 or 1 to receive chemotherapy. Placement of a central venous access or peripherally inserted central catheter line is required, and where the FOLFIRINOX regimen is used, screening for dihydropyrimidine dehydrogenase deficiency, blood tests for measurement of total bilirubin and unconjugated bilirubin (or for UGT1A1 genotyping) and serum CA 19-9 levels, cardiology visits, and electrocardiograms are typical. The optimal combination of prophylactic antiemetics should also be delivered to optimize compliance with treatment.

Restaging of pancreatic cancer, including chest and abdominopelvic CT scans, should be repeated every two months and following neoadjuvant therapy to evaluate the response to treatment and to rule out both unresectability or distant metastatic disease. A RECIST partial response and a reduction in tumor volume are favorable prognostic factors [41]. However, all patients with stable disease and no extrahepatic progression should undergo surgical exploration. CA 19-9 levels should be evaluated every two months and compared with baseline levels, as a low posttreatment CA 19-9 level [41,42] is of prognostic value.

Treatment in a high-volume center ($\geq$40 procedures annually) should be preferred, as compliance to international recommendations is better, operative mortality is lower, and OS is increased [18,43].

7. Major Surveys and Retrospective Studies

Among the large retrospective studies available, some are of particular interest. A recent analysis included 11,699 patients with stage II pancreatic cancer from the National Cancer Database between 2010 and 2017 who had undergone R1/R2 surgery [44]. This study shows a strong signal in favor of surgery, even for patients with an R1 status, compared with patients who received chemotherapy alone, particularly in the setting of neoadjuvant chemotherapy. However, those results should be considered in light of various factors, such as the imbalance between the treatment groups, the assessment of resectability, the criteria for which may vary from one center to another, and the simple fact that patients who receive chemotherapy alone generally have a poorer prognosis.

The R1 status of more than 1 mm, as defined by the Royal College of Pathologists [45] is still under discussion regarding its prognostic role, even in randomized controlled trials such as CONKO 001 [21], PRODIGE24 [7], or ESPAC-3 [46].

In another database analysis, 16,666 patients (14,012 upfront resection; 2654 neoadjuvant therapy) were retrieved (National Cancer Database from 2007 to 2015) [47]. It showed that patients with neoadjuvant therapy had a significantly (log-rank, $p < 0.001$) better median OS (27.9 months, 95% CI 26.2–29.1) and 5-year OS (24.1%, 95% CI 21.9–26.3%) than the upfront surgery group (median OS 21.2 months, 95% CI 20.7–21.6; 5-year survival 20.9%, 95% CI 20.1–21.7%). A similar retrospective cohort study of 19,031 patients from the US National Cancer Database compared neoadjuvant therapy to upfront surgery. Preoperative therapy was used in 1772 patients and downstaged 38% of cN1 patients to ypN0. It was also shown that half of the patients treated with upfront surgery initially considered node free at clinical staging (cN0) had node-positive tumors (pN1) on the final pathology report [48]. This indicates that downstaging with neoadjuvant therapy is undervalued. This also shows the need to question the preparation of resection specimens, especially examining resection margins by comparing R0 and R1 status in future trials, as this emerges as a likely discriminating factor in large retrospective studies [13,47]. The margins of the pancreas should be painted with a color code before blocks are taken. However, there is currently no standardization of the histopathological examination technique, thus inducing a bias. R0/R1 margins and lymph node status should be more carefully evaluated in future trials, using standardized methods.

Nevertheless, a study of 458 patients identified by the California Cancer Surveillance Program reported that neoadjuvant therapy is associated with a lower rate of lymph node positivity (45% vs. 65%; $p = 0.011$) and an improved OS (31 vs. 19 months; $p = 0.018$) [49]. A potential bias of this retrospective cohort is the absence of data on resectability rates and on dropout for patients considered for neoadjuvant therapy. Such results have also been confirmed by another study in a matched cohort of 191 patients, with a significantly longer median OS (23.1 months vs. 18.5 months, $p = 0.043$), a lower incidence of positive surgical margins (8% vs. 30%, $p < 0.002$), and less lymph node metastasis (45% vs. 78%, $p < 0.001$) found in patients receiving neoadjuvant therapy versus those undergoing upfront surgery [50].

Focusing on older adult patients, neoadjuvant therapy still has serious arguments in its favor, as reported by Rieser et al. [51]. In their single institution retrospective study, they showed a favorable trend for neoadjuvant chemotherapy (versus a surgery-first approach) among patients of 75 years old and over. Median OS was higher in patients treated with neoadjuvant chemotherapy than in those who received upfront surgery (24.6 vs. 17.6 months; $p = 0.01$). Moreover, patients with upfront surgery had a trend toward higher rates of major complications (38% vs. 24%; $p = 0.06$) compared with patients who received neoadjuvant therapy.

Other factors, such as the proportion of patients receiving postoperative chemotherapy ratio, rapid progressive disease, and tumor side, are also to be considered. As an example, a study of 15,237 patients showed that 33% of patients who underwent upfront resection did not receive postoperative systemic chemotherapy [13].

Focusing on the tumor location, Ocuin et al. reported from the US National Cancer Database that in 6523 patients undergoing distal pancreatectomy, those who received neoadjuvant chemotherapy had a longer median OS (28.8 vs. 22.0 months; $p < 0.001$). However, multiagent neoadjuvant chemotherapy regimens were associated with improved OS compared with multiagent adjuvant regimens (30.2 vs. 23.1 months; $p < 0.001$), whereas single-agent regimens were not associated with a survival benefit [52]. To date, there are no data suggesting that pancreatic tumor location should be a consideration in the decision of whether to give neoadjuvant chemotherapy.

The question of the postoperative complications rate has not yet been resolved. There are still contradictory trends, as presented in Table 1. A dedicated focus should be placed on this in future trials.

Table 1. Early postoperative complications: neoadjuvant therapy versus upfront surgery.

Study	Difference in Postoperative Morbidity and Mortality	Result	Number of Patients	Trend
Mokdad et al. [13]	No	N/A	15,237	None
Ocuin et al. [52]	Yes	NAT patients: - Shorter length of stay (7.4 vs. 7.9 days; $p = 0.011$) - Lower rate of 30-day readmission (7.7% vs. 10.4%; $p = 0.013$) - Lower rate of 90-day postoperative mortality (3.0% vs. 5.6%; $p = 0.005$)	6523	Favors NAT
Rieser et al. [51]	Yes	US patients: - Higher rates of major postoperative complications (38% vs. 24%; $p = 0.06$) - Higher Comprehensive Complication Index totals (20.9 vs. 20; $p = 0.03$)	158	Favors NAT
Arrington et al. [44]	No	Patients who died within 2 months of diagnosis in the chemotherapy alone group or within 2 months of surgery in the surgical groups were excluded from the survival analyses	11,699	None
Cooper et al. [53]	Yes	NAT patients: - No significant difference in complications Neoadjuvant radiation associated with lower pancreatic fistula rates	1562	Favors NAT
Dhir et al. [54]	Yes	NAT patients: - Lower rate of 30-day readmission (univariable 5.5% vs. 7.4%, $p = 0.006$; multivariable OR 0.74, 95% CI 0.6–0.92, $p = 0.006$) - No significant difference in the length of stay and 30- or 90-day mortality - Higher rates of margin-negative resection (83% vs. 80%, $p = 0.004$) - No difference in OS (NAT vs. US: median 27 vs. 26 months, $p = 0.02$)	73,313	Favors NAT
Marchegiani et al. [55]	Yes	NAT patients: - Reduced incidence of pancreatic fistula and postpancreatectomy hemorrhage - Increased incidence of delayed gastric emptying and clinical burden	445	None

Abbreviations: N/A: not available; NAT: neoadjuvant therapy; OR: odds ratio; OS: overall survival; US: upfront surgery.

8. Randomized Trials of Chemoradiotherapy and Neoadjuvant Chemotherapy

After meta-analyses suggested that neoadjuvant treatment had an effect [33,56], a number of randomized trials were set up and have been completed and published at this time. The first was a small German trial comparing CRT using gemcitabine and cisplatin before surgery with upfront surgery in RPC [57]. The trial was stopped after inclusion of 73 patients; 66 patients were eligible for analysis. Radiotherapy was completed in all patients. Chemotherapy was changed in three patients due to toxicity. Tumor resection was performed in 23 patients in the surgery group and in 19 patients in the neoadjuvant group. The R0 resection rate was 48% in the surgery group and 52% in the neoadjuvant group ($p = 0.81$), and (y)pN0 was 30% versus 39% ($p = 0.44$), respectively. Postoperative complications were comparable between the groups. Median OS was 14.4 months in the surgery group versus 17.4 months in the neoadjuvant group (intention-to-treat analysis; $p = 0.96$). After tumor resection, median OS was 18.9 in the surgery group versus 25.0 months in the neoadjuvant group ($p = 0.79$). This worldwide first randomized trial for neoadjuvant CRT in pancreatic cancer showed that neoadjuvant CRT is safe with respect to toxicity, perioperative morbidity, and mortality. Nevertheless, the trial was terminated early due

to slow recruiting, and the results were not significant. The second was an Italian trial, in which 93 patients were randomly allocated to treatment between 5 October 2010 and 30 May 2015 [58]. One center was found to be noncompliant with the protocol, and all five patients at this center were excluded from the study. Thus, 88 patients were included in the final study population: 26 in Group A, to receive surgery followed by adjuvant gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks for six cycles; 30 in Group B, to receive surgery followed by six cycles of adjuvant PEXG (cisplatin 30 mg/m^2, epirubicin 30 mg/m^2, and gemcitabine 800 mg/m^2 on days 1 and 15 every 4 weeks and capecitabine 1250 mg/m^2 on days 1–28); and 32 in Group C, to receive three cycles of PEXG before and three cycles after surgery. In the per-protocol population, six (23%, 95% CI 7–39) of 30 patients in Group A were event-free at 1 year, as were 15 (50%, 95% CI 32–68) of 30 in Group B, and 19 (66%, 95% CI 49–83) of 29 in Group C. The main grade 4 toxicity reported was neutropenia (two [11%] in Group A, four [19%] in Group B, none in Group C). Febrile neutropenia was observed in one patient (3%) before surgery in Group C. No treatment-related deaths were observed. Median OS was 20.4 months (95% CI 15.6–25.8) for patients in Group A, 26.4 months (95% CI 15.8–26.7) for patients in Group B, and 38.2 months (95% CI 27.3–49.1) for patients in Group C. In the per-protocol population of Group C, median OS was 39.8 months (95% CI 28.8–50.8). The trial was stopped at its phase II level because the standard of care in terms of multiagent chemotherapy changed during the inclusion period.

The third trial, PREOPANC-1, recently published by the Dutch Pancreatic Cancer Group, is much more solid in terms of evidence-based medicine [26]. Patients were treated either with surgery followed by six cycles of gemcitabine in the control group (127 patients) or with one cycle of gemcitabine, followed by CRT (radiotherapy: 36 Gy in 15 fractions + gemcitabine), followed by one cycle of gemcitabine and then surgery, followed by the last four cycles of gemcitabine (119 patients). Unfortunately, inclusion was not restricted to RPC but also included BRPC. Between April 2013 and July 2017, 246 eligible patients were randomly assigned; 119 were assigned to neoadjuvant CRT and 127 to upfront surgery. Median OS by intention to treat was 16.0 months with neoadjuvant CRT and 14.3 months with immediate surgery (HR 0.78; 95% CI, 0.58–1.05; $p = 0.096$), and the resection rate was 61% and 72% ($p = 0.058$), respectively. The R0 resection rate was 71% (51 of 72) in patients who received neoadjuvant CRT and 40% (37 of 92) in patients assigned to immediate surgery ($p < 0.001$). Neoadjuvant CRT was associated with significantly better DFS and locoregional failure-free interval as well as with significantly lower rates of pathologic lymph nodes, perineural invasion, and venous invasion. Survival analysis of the patients who underwent tumor resection and started adjuvant chemotherapy showed improved survival with neoadjuvant CRT (35.2 vs. 19.8 months; $p = 0.029$). The proportion of patients who suffered serious adverse events was 52% with neoadjuvant CRT versus 41% with immediate surgery ($p = 0.096$). Although the results of this large trial favor neoadjuvant treatment, the study was not considered to be practice changing outside of the Netherlands. The main reasons were the mixed population of resectable and borderline resectable patients, the use of gemcitabine monotherapy as an adjuvant chemotherapy, and lower OS rates than expected.

A Japanese trial evaluated the role of a combination regimen used only in Japan: gemcitabine and S-1 for two cycles followed by surgery. In both arms, patients received four cycles of adjuvant S-1 for 6 months after curative surgery, which is considered to be the standard of care after surgery for pancreatic cancer in Japan [59]. From January 2013 to January 2016, 364 patients were enrolled in 57 centers (182 to neoadjuvant treatment and 182 to upfront surgery). Of these, two were excluded because of ineligibility, therefore 182 patients in the neoadjuvant treatment group and 180 in the upfront surgery group constituted the intention-to-treat analysis set. The median OS was 36.7 months in the neoadjuvant treatment group and 26.6 months in the upfront surgery group; HR 0.72 (95% CI 0.55–0.94; $p = 0.015$). Grade 3 or 4 adverse events frequently (72.8%) observed in the neoadjuvant group were leukopenia or neutropenia. However, the resection rate, R0

resection rate, and operative morbidity were equivalent in the two groups. There was no perioperative mortality in either group. The authors concluded that this phase III study demonstrated significant survival benefits of neoadjuvant treatment in RPC. They added that the results indicated that neoadjuvant chemotherapy could be a standard of care for these patients [60]. However, the oral fluoropyrimidine S-1 is not available in Europe and the US. It is also difficult to understand why the patients in the neoadjuvant arm received two more cycles than the patients treated in the upfront surgery group. Finally, full publication of the data from this trial, currently available as an abstract from 2019 conference proceedings, is still awaited.

The most recent trial is a randomized trial that did not really evaluate the role of neoadjuvant treatment in pancreatic cancer, since it randomized 102 patients with RPC to different schedules of chemotherapy before surgery (the SWOG s1505 trial) [61]. Patients received one of the two active combination regimens used in the treatment of metastatic pancreatic cancer: modified FOLFIRINOX or gemcitabine/nab-paclitaxel. The primary outcome measure was 2-year OS, using a "pick the winner" design; for 100 eligible patients, accrual up to 150 patients was planned to account for cases deemed ineligible at central radiology review. From 2015 to 2018, 147 patients were enrolled and 102 were eligible; 55 in the FOLFIRINOX group (arm 1), 47 in the gemcitabine/nab-paclitaxel group (arm 2). For the FOLFIRINOX and gemcitabine/nab-paclitaxel groups, respectively, the 2-year OS was 41.6% and 48.8 and median OS was 22.4 months and 23.6 months. Neither arm's 2-year OS estimate was statistically significantly higher than the a priori threshold of 40% ($p = 0.42$ in Arm 1 and $p = 0.12$ in Arm 2). Median DFS after resection was 10.9 months in Arm 1 and 14.2 months in Arm 2 ($p = 0.87$). The conclusion made by the authors is that it seems feasible and possible to obtain adequate safety and high resectability rates with neoadjuvant chemotherapy but that this trial brought little evidence that either regimen improves OS compared with the historical standard. In addition, the number of patients in this trial was limited and the trial used a randomized phase II design that is not completely adequate to evaluate the role of neoadjuvant treatment.

These results from randomized clinical trials (summarized in Table 2) suggest that although there is no definitive evidence for the efficacy of neoadjuvant therapy in RPC, this strategy should be evaluated in future trials.

Table 2. Randomized trials of chemoradiotherapy and neoadjuvant chemotherapy.

Trial	Inclusion Criteria	Design of the Trial	Number of Patients	Primary Endpoint	Secondary Endpoints
Golcher et al. [57]	Resectable	Surgery (arm A) or CRT with gemcitabine + cisplatin followed by surgery (arm B)	33 33	Median OS: 14.4 17.4 ($p = 0.96$)	Time to progression: 8.7 (A) vs. 8.4 (B); $p = 0.95$ Tumor resection: 48% (A) vs. 52% (B); $p = 0.81$ (y)pN0: 30% (A) vs. 39% (B); $p = 0.44$
PACT-15 Reni et al. [58]	Resectable	Surgery followed by gemcitabine (arm A) or Surgery followed by 6 cycles of PEXG (arm B) or 3 cycles of PEXG before and after surgery (arm C)	26 30 32	Event free at 1 year: 6 (23%) 15 (50%) 19 (66%)	Median OS: 20.4 (A) (95% CI 14·6–25·8) vs. 26.4 (B) (15·8–26·7) vs. 38.2 (C) (27·3–49·1) (NS) 3-year OS: 35% (A) vs. 43% (B) vs. 55% (C) 5-year OS: 13% (A) vs. 24% (B) vs. 49% (C)

Table 2. *Cont.*

Trial	Inclusion Criteria	Design of the Trial	Number of Patients	Primary Endpoint	Secondary Endpoints
PREOPANC Versteijine et al. [26]	Resectable: Borderline resectable:	Surgery followed by 6 courses of gemcitabine (arm A) or 3 courses of gemcitabine, the second combined with 15 × 2.4 Gy radiotherapy, followed by surgery and 4 courses of adjuvant gemcitabine (arm B)	127 119	Median OS: 19.8 35.2 (p = 0.029)	R0 resection rate: 40% (A) vs. 71% (B); $p < 0.001$ Serious adverse events: 41% (A) vs. 52% (B); p = 0.096
PREOP-02/JSP05 trial Unno et al. [60]	Resectable	Surgery followed by 6 months of S-1 (arm A) or 2 cycles of gemcitabine + S-1 followed by surgery and 6 months of S-1 (arm B)	182 182	Median OS: 26.6 36.7 (p = 0.01)	Grade 3 or 4 adverse events (leukopenia, neutropenia): 72.8% (B) Resection rate, R0 rat and morbidity were similar in both arms
SWOG S1505 Sohal et al. [61]	Resectable	12 weeks of mFOLFIRINOX before and after surgery (arm A) Or 12 weeks of gemcitabine + nap-paclitaxel before and after surgery (arm B)	55 47	2-year OS: 41.6% 48.8%	Median OS: 22.4 (A) vs. 23.6 (B) Median DFS: 10.9 (A) vs. 14.2 (B); p = 0.87

Abbreviations: NS: not statistically significant; PEXG: PEXG (cisplatin, epirubicin, gemcitabine, capecitabine); Gem/gemcitabine; CRT: chemoradiotherapy; mFOLFIRINOX: leucovorin, oxaliplatin, irinotecan, fluorouracil; Median OS and DFS and Time to progression in months.

9. Ongoing Randomized Trials

A number of phase II–III randomized trials are ongoing and are presented in Table 3. Some randomized trials using neoadjuvant regimens have been terminated early due to slow accrual. The NEOPAC phase III trial, comparing neoadjuvant gemcitabine and oxaliplatin to adjuvant gemcitabine, enrolled only two patients out of the 310 planned. The NEOPA trial had included 32 patients with BRPC or RPC in 4 years instead of the 410 patients initially planned [62]. The NEPAFOX study was closed early after enrollment of 40/126 patients [63]. Most of the ongoing studies use neoadjuvant gemcitabine-based CRT or FOLFIRINOX as neoadjuvant regimens versus upfront surgery, with OS as the primary endpoint. The timing of surgery after neoadjuvant chemotherapy—for example, whether to perform surgery after 4 or 8 cycles—still needs to be further investigated. If it is logical to think that if there is a benefit to neoadjuvant chemotherapy for tumors that can be operated on right away, this benefit should be possible for borderline tumors. To obtain reliable answers, it will be interesting to wait for the results of the PRODIGE 44/PANDAS study (NCT02676349) which seeks to evaluate the addition of radiochemotherapy after neoadjuvant treatment with mFOLFIRINOX in borderline pancreatic tumors.

Table 3. Ongoing randomized clinical trials.

Trial	Inclusion	Modality and Regimens of Neoadjuvant Therapy	Planned Number of Patients	Primary Endpoint(s)	Secondary Endpoints
NEOPAC NCT01521702 [64]	R	Gemcitabine + oxaliplatin, 4 cycles or Upfront surgery	155 155	+15% in 1-year PFS	PFS; Histological response; OS; Complication rates after surgery; feasibility of adjuvant chemotherapy

Table 3. *Cont.*

Trial	Inclusion	Modality and Regimens of Neoadjuvant Therapy	Planned Number of Patients	Primary Endpoint(s)	Secondary Endpoints
NEOPA NCT01900327	R and BRPC	Gemcitabine + radiotherapy 50.4 Gy or Upfront surgery + adjuvant gemcitabine	205 205	+30% in 3-year OS	R0 resection rate; Frequency of toxicity events; Resectability rate; Rate of intraoperative irregularities; Postoperative complications; Disease progression during adjuvant therapy; DFS, QoL; First site of tumor recurrence
NorPACT-1 NCT02919787 [65]	R pancreatic head cancer	FOLFIRINOX, 4 cycles (+ 8 cycles of adjuvant chemotherapy) or Upfront surgery + mFOLFIRINOX (12)	54 36	Reduction in 1-year mortality from 25 to 5%	Overall mortality at one year; DFS; Histopathological response; Complication rate after surgery; Feasibility of chemotherapy; QoL; Health economics
PANACHE 01-PRODIGE 48 NCT02959879 [66]	R	FOLFIRINOX, 4 cycles (+ 8 cycles of adjuvant chemotherapy) or FOLFOX, 4 cycles (+ 8 cycles of adjuvant chemotherapy) or Upfront surgery (+ 12 cycles of adjuvant chemotherapy)	64 64 32	1-year survival Chemotherapy completion rate	Adverse events; Post-operative complications; Patients alive and without recurrence; R0 resection rate; QoL
PREOPANC-2 NL7094 [67]	R and BRPC	Chemoradiation 36 Gy/15 fractions with 3 cycles of gemcitabine, and adjuvant gemcitabine, 4 cycles or FOLFIRINOX, 4 to 8 cycles, and no adjuvant chemotherapy	184 184	OS	PFS; Locoregional progression-free interval; Distant metastases-free interval; Resection rate; R0 resection rate; Chemotherapy start rate; Chemotherapy completion rate; Toxicity; Post-operative complications; Radiologic response; Tumor marker response (CA 19–9 CEA); Pathologic response; QoL
PREOPANC-3 NCT04927780	R	FOLFIRINOX 8 cycles (+4 cycles in adjuvant setting) or Upfront surgery + FOLFIRINOX 12 cycles	189 189	OS	PFS; Distant metastases free survival; Locoregional PFS; Chemotherapy start date, Number of chemotherapy cycles and completion rate; Resection rate, R0 resection rate; N0 resection rate; pathological response; adverse events; CA 19-9 and CEA response: RECIST response; QoL
NEONAX NCT02047513 [68]	R	Nab-paclitaxel + gemcitabine 2 cycles (+ 4 cycles in adjuvant setting) or Upfront surgery + 6 cycles nab-paclitaxel + gemcitabine	83 83	DFS of $\geq$55% at 18 months in at least one arm	Safety; Morbidity and mortality; Toxicity; Resection rate; Tumor response; R0 resection rate, OS; Tumor recurrence; QoL

Table 3. *Cont.*

Trial	Inclusion	Modality and Regimens of Neoadjuvant Therapy	Planned Number of Patients	Primary Endpoint(s)	Secondary Endpoints
Alliance A021806 NCT04340141	R	mFOLFIRINOX 8 cycles, (+ 4 cycles in adjuvant setting) or Upfront surgery + mFOLFIRINOX (12 cycles)	176 176	OS	DFS; Time to locoregional or distant recurrence; R0 resection rate: pathological response; adverse events; QoL; Nutritional evaluation; Radiomics
PANDAS PRODIGE 44 NCT02676349	BRPC	Neoadjuvant mFOLFIRINOX regimen, with or without preoperative concomitant chemoradiotherapy (50.4 Gy + capecitabine)	45 45	histological R0 resection margin rate	Toxicites, proportions of resected patients, response rates to treatments, perioperative mortality and morbidity rates, OS, QoL, PFS

Abbreviations: BRPC: borderline resectable pancreatic cancer; DFS: disease-free survival; PFS: progression-free survival; R: resectable; mFOLFIRINOX: leucovorin, oxaliplatin, irinotecan, fluorouracil; QoL: Quality of Life.

10. Surgical Considerations Following Neoadjuvant Therapy for RPC

In the setting of neoadjuvant treatment, various points must be taken into consideration for surgical management: the rationale for staging laparoscopy and paraaortic lymph node sampling, the surgical approach and technique, and the importance of surgical margins, but also the possible impact of neoadjuvant therapy on the postoperative disease course. It should never be forgotten that reporting on neoadjuvant treatment studies is often done on intention-to-treat populations, whereas this is not always the case for adjuvant studies.

10.1. Staging Laparoscopy

The role of surgery in the management of RPC is not limited to surgical resection of the primary tumor. Indeed, different authors have shown the advantages of surgical exploration by laparoscopy. The main objective of preoperative workup is to track down occult metastases, to avoid futile resection and late introduction of systemic chemotherapy.

Despite remarkable technological advances in medical imaging modalities, approximately 20–50% of patients are found to have metastases at the time of surgery [69,70]. A new definition of radiologically occult pancreatic cancer metastases (ROMPC) has recently been proposed and corresponds to pancreatic cancer with metastases identified during surgery or within 6 months of resection [71]. Indeed, a nonnegligible rate of patients progress during neoadjuvant therapy or are unresectable during surgery for unknown metastasis, corresponding to the ROMPC situation. In the Dutch PREOPANC-1 trial [26], approximately 20% of patients were deemed ineligible based solely upon staging laparoscopy. Similar results were observed in two other recently published clinical trials (PREP-2/JSAP-05 trial, 28% [60]; Korean Phase III trial, 22% [25]). Based on these observations, some authors recommend the strategy of routinely incorporating baseline staging laparoscopy before neoadjuvant therapy for patients with PDAC [72]. The criteria usually used to indicate exploratory laparoscopy are tumor size >3 cm, body and tail tumor location, and CA 19-9 levels of >200 UI [73]. In the SLING Trial, Oba et al. demonstrated that staging laparoscopy with contrast-enhanced intraoperative ultrasound and indocyanine green fluorescence imaging was effective in such subgroups of patients, with the technique detecting ROMPC in 12 out of the 31 patients enrolled [74]. To help appropriate selection of patients for chemotherapy or surgery but also to decrease the perioperative morbidity of futile laparotomy, the routine use of staging laparoscopy needs to be discussed, even though it is considered still as an option by the National Comprehensive Cancer Network (NCCN) Guidelines [35].

10.2. Paraaortic Lymph Node Sampling—Is It Useful or Recommended Following Neoadjuvant Therapy?

The dismal prognosis of RPC following upfront surgery is, in part, related to the high frequency of distant lymph node metastasis, undiagnosed preoperatively. Lymph node metastasis of PDAC primarily involves peripancreatic nodes and eventually spreads to distant lymph nodes, including the paraaortic lymph nodes (PALN group 16b of the Japanese Pancreas Society Classification of Pancreatic Cancer) [75,76]. Although cross-sectional imaging has improved considerably during the last decade, the preoperative diagnosis of lymph node involvement in pancreatic cancer is still challenging and lymph node size remains the most frequently used criterion, although it has been shown to be not particularly sensitive for the detection of lymph node involvement [77]. To date, few data are available on neoadjuvant treatment and its impact on distant lymph node involvement or on oncological outcome. In the review by van Rijssen et al. [78], the number of patients with or without lymph node metastasis specifically receiving neoadjuvant therapy was not described. It was therefore not possible to analyze the impact of neoadjuvant treatment on outcomes in patients with distant lymph node metastasis. It could be hypothesized that neoadjuvant treatment may reduce the incidence of distant lymph node metastasis, especially paraaortic lymph node metastasis, but data are currently lacking.

10.3. Surgical Management

Usually, surgical resection is planned 4 to 8 weeks after the end of neoadjuvant treatment. Regarding surgical techniques, the main criteria for surgical quality are internationally accepted and should be respected, whether or not neoadjuvant treatment has been offered. In patients with adenocarcinoma located in the head of the pancreas, pancreaticoduodenectomy is the recommended surgical technique, and skeletonization of the superior mesenteric artery down to the adventitia on the anterior, lateral, and posterior borders is the standard of care [35,79]. The superior mesenteric artery–first approach seems to facilitate lymphadenectomy and optimize oncologic control of the retroperitoneal margin. The MAPLE-PD randomized trial (NCT03317886) aims to corroborate these results. In terms of lymph node dissection, it is well demonstrated that extensive lymphadenectomy does not improve long-term survival [80]. In patients with adenocarcinoma located in the left pancreas (body and/or tail), left splenopancreatectomy is recommended. Two techniques can be used, the so-called "standard" technique or a modified technique based on an antegrade approach (RAMPS: Radical antegrade modular pancreatosplenectomy), which aims to improve the retroperitoneal resection margin and lymphadenectomy [81]. The prospective randomized multicenter REMIND study aims to confirm these results (NCT03679169).

Regarding vascular contact/involvement, venous resection does not affect postoperative mortality although if it may slightly increase morbidity [82]. To optimize the chance of achieving an R0 resection, some surgical teams may even justify extreme positions such as performing routine venous resection during pancreatectomies, based on the results reported by Turrini et al. [83]. Indeed, in that study, patients who underwent portal vein or superior mesenteric venous venous resection but whose tumors did not infiltrate the vessel at final histology had significantly longer survival than patients in a matched control group who had pancreaticoduodenectomy without venous resection (42 months vs. 24 respectively, $p = 0.02$). Therefore, venous resection should not prevent surgeons from performing a pancreatectomy with curative intent, and patients with RPC should be managed by surgeons competent in vascular surgery, especially following neoadjuvant therapy.

10.4. Resectability and Resection Margins

The most recent analysis revealed that surgical exploration after neoadjuvant therapy was attempted in about 75% of patients but that among those patients only 72% were successfully resected (corresponding to 54% of all patients who received neoadjuvant therapy in intention-to-treat analysis) [84,85]. The goal of multimodal treatment is to achieve margin-free surgery. In surgical specimens, the most frequently involved margins

are the posterior margin (retroperitoneal) (37%) and the portal vein–superior mesenteric vein margin (41%) [79]. The rationale for venous resection previously discussed is based on these observations. A meta-analysis by Schorn et al. showed that there is a lower risk of margins being classified as R1 after neoadjuvant therapy than after upfront surgery (RR 0.66, 95% CI 0.58–0.76, $p < 0.00001$) [86]. After neoadjuvant therapy for resectable PDAC, in resected patients the R0 rate was estimated to be around 70% [84] using the consensual guidelines of the College of American Pathologists [87]. As Verbeke et al. reported recently, pathologists should be aware that response after neoadjuvant treatment is frequently heterogeneous [88]. Indeed, the response to therapy within the tumor often results in multiple small foci of residual tumor cells in a background of mass-forming fibrosis and/or chronic pancreatitis, creating difficulties and inconsistencies in determining the appropriate tumor size or tumor-free margin measurement.

10.5. Postoperative Complications after Pancreatectomy Following Neoadjuvant Therapy

A retrospective study using ACS-NSQIP Targeted Pancreatectomy data identified 3748 operated patients, including 926 (25%) who had received neoadjuvant therapy (54.6% chemotherapy alone). The authors reported similar rates of postoperative mortality and overall complications between the two subgroups (neoadjuvant therapy versus upfront surgery), with a multivariable analysis revealing a reduced incidence of pancreatic fistula in those who had received neoadjuvant therapy (OR, 0.67; $p < 0.001$). The proposed mechanism for this effect of neoadjuvant therapy is through impairment of pancreatic function and induction of pancreatic fibrosis, thus making the pancreas more favorable for pancreatic ductal anastomosis [89]. The experience of the Verona group is consistent with the previous study, with patients receiving neoadjuvant therapy exhibiting a reduced incidence of postoperative fistula and hemorrhage versus patients who underwent upfront surgery. However, in the setting of the occurrence of such complications, the clinical burden was increased in patients who received neoadjuvant therapy [55]. There are currently no available prospective data about postoperative complications following neoadjuvant therapy with FOLFIRINOX, other than from the SWOG S1505 trial, in which no difference was observed between patients receiving FOLFIRINOX and those receiving gemcitabine/nab-paclitaxel, with no postoperative mortality observed in either group [84]. This reassuring approach is also confirmed in the study by van Dongen et al. where preoperative chemoradiotherapy did not increase the incidence of surgical complications or mortality [90].

10.6. Biological Borderline Pancreatic Cancer

According to the international consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma, we should embrace the yet unproven definition of a biological borderline pancreatic cancer with a CA 19-9 threshold of 500 units/mL or regional lymph nodes metastasis diagnosed by biopsy or PET-CT, which reflects the suspected distant metastasis [91]. The approach of Isaji et al. is a way to estimate distant locations not detected by the usual methods. Anticipating the presence of an advanced situation could allow us to better select patients and thus propose the best strategy. Perhaps neoadjuvant chemotherapy should be favored in patients with "biologically" advanced disease.

11. Conclusions

Resectable pancreatic cancer is a systemic disease and neoadjuvant chemotherapy is a logical approach with acceptable morbidity and no increased postoperative mortality. Numerous meta-analyses and large prospective and retrospective studies comparing neoadjuvant therapy with upfront surgery have reported tumor shrinkage, decreased node-positive disease, reduced rates of pancreatic fistula, and significantly improved overall survival rates in neoadjuvant therapy groups. However, the survival benefit with neoadjuvant therapy still needs to be investigated through high-quality published randomized studies. Moreover, benefit of adjuvant chemotherapy following neoadjuvant therapy and

pancreatectomy is not well established and randomized data to answer this question are still lacking. All authors have read and agreed to the published version of the manuscript.

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Publication 3 – Five-Year Outcomes of FOLFIRINOX vs Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. A Randomized Clinical Trial

Article original (publié)

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L'actualisation de l'essai PRODIGE 24/ CCTG PA6 avec les données de survie à 5 ans est une étape importante concernant la question scientifique des facteurs de risque locaux concernant la récidive et la survie des patients opérés pour un adénocarcinome du pancréas.

Tout d'abord, cette analyse de survie à 5 ans confirme les bons résultats de la publication initiale de 2018 (12) (sur laquelle nous avions réalisé le contrôle qualité complet et qui a motivé ce travail) et renforce choix de cette stratégie d'utiliser la chimiothérapie par mFOLFIRINOX en adjuvant comme nouveau standard des cancers du pancréas opérés.

La médiane de survie sans progression était de 21,4 mois (95% CI, 17.5-26.7) contre 12,8 mois (95% CI, 11.6-15.2) (hazard ratio [HR], 0.66; 95% CI, 0.54-0.82; $P < .001$) et la médiane de survie globale était de 53,5 mois (95% CI, 43.5-58.4) contre 35,5 mois (95% CI, 30.1-40.3) (HR, 0.68; 95% CI, 0.54-0.85; $P = .001$) dans les bras mFOLFIRINOX et gemcitabine respectivement. La survie sans maladie à 5 ans était de 26,1% contre 19% et la survie globale à 5 ans de 43,2% contre 31,4% dans les bras mFOLFIRINOX et gemcitabine respectivement.

Dans cette étude, les facteurs de bon pronostique étaient la chimiothérapie par mFOLFIRINOX, l'âge, le grade de la tumeur, le stade de la tumeur et les centres de plus grand

volume concernant la survie globale. Un délai de rechute court était un facteur de mauvais pronostique.

Le statut de résection R0/R1 ne ressortait pas comme un facteur pronostique de la survie. Il était donc intéressant d'explorer plus attentivement les raisons de cette absence d'impact.

JAMA Oncology | Original Investigation

Five-Year Outcomes of FOLFIRINOX vs Gemcitabine as Adjuvant Therapy for Pancreatic Cancer
A Randomized Clinical Trial

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IMPORTANCE Early results at 3 years from the PRODIGE 24/Canadian Cancer Trials Group PA6 randomized clinical trial showed survival benefits with adjuvant treatment with modified FOLFIRINOX vs gemcitabine in patients with resected pancreatic ductal adenocarcinoma; mature data are now available.

OBJECTIVE To report 5-year outcomes and explore prognostic factors for overall survival.

DESIGN, SETTING, AND PARTICIPANTS This open-label, phase 3 randomized clinical trial was conducted at 77 hospitals in France and Canada and included patients aged 18 to 79 years with histologically confirmed pancreatic ductal adenocarcinoma who had undergone complete macroscopic (R0/R1) resection within 3 to 12 weeks before randomization. Patients were included from April 16, 2012, through October 3, 2016. The cutoff date for this analysis was June 28, 2021.

INTERVENTIONS A total of 493 patients were randomized (1:1) to receive treatment with modified FOLFIRINOX (oxaliplatin, 85 mg/m^2 of body surface area; irinotecan, 150-180 mg/m^2; leucovorin, 400 mg/m^2; and fluorouracil, 2400 mg/m^2, every 2 weeks) or gemcitabine (1000 mg/m^2, days 1, 8, and 15, every 4 weeks) as adjuvant therapy for 24 weeks.

MAIN OUTCOMES AND MEASURES Primary end point was disease-free survival. Secondary end points included overall survival, metastasis-free survival, and cancer-specific survival. Prognostic factors for overall survival were determined.

RESULTS Of the 493 patients, 216 (43.8%) were women, and the mean (SD) age was 62.0 (8.9) years. At a median of 69.7 months' follow-up, 367 disease-free survival events were observed. In patients receiving chemotherapy with modified FOLFIRINOX vs gemcitabine, median disease-free survival was 21.4 months (95% CI, 17.5-26.7) vs 12.8 months (95% CI, 11.6-15.2) (hazard ratio [HR], 0.66; 95% CI, 0.54-0.82; $P < .001$) and 5-year disease-free survival was 26.1% vs 19.0%; median overall survival was 53.5 months (95% CI, 43.5-58.4) vs 35.5 months (95% CI, 30.1-40.3) (HR, 0.68; 95% CI, 0.54-0.85; $P = .001$), and 5-year overall survival was 43.2% vs 31.4%; median metastasis-free survival was 29.4 months (95% CI, 21.4-40.1) vs 17.7 months (95% CI, 14.0-21.2) (HR, 0.64; 95% CI, 0.52-0.80; $P < .001$); and median cancer-specific survival was 54.7 months (95% CI, 45.8-68.4) vs 36.3 months (95% CI, 30.5–43.9) (HR, 0.65; 95% CI, 0.51-0.82; $P < .001$). Multivariable analysis identified modified FOLFIRINOX, age, tumor grade, tumor staging, and larger-volume center as significant favorable prognostic factors for overall survival. Shorter relapse delay was an adverse prognostic factor.

CONCLUSIONS AND RELEVANCE The final 5-year results from the PRODIGE 24/Canadian Cancer Trials Group PA6 randomized clinical trial indicate that adjuvant treatment with modified FOLFIRINOX yields significantly longer survival than gemcitabine in patients with resected pancreatic ductal adenocarcinoma.

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Visual Abstract

Supplemental content

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Group Information: The members of the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group who participated in this study appear in Supplement 3.

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Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related death worldwide.[1-5] In Europe, mortality of PDAC is projected to rise by 42% by 2039.[6-8] While surgical excision is potentially curative, only 15% to 20% of patients are eligible for up-front surgery,[8] and resection alone is associated with a 5-year overall survival (OS) rate of approximately 10%.[9,10]

Adjuvant chemotherapy improves survival outcomes in patients with resected PDAC.[9-13] In the phase 3 CONKO-001 randomized clinical trial, use of adjuvant gemcitabine for 6 months after PDAC resection significantly improved disease-free survival (13.4 vs 6.9 months; $P < .001$) and OS (22.8 vs 20.2 months; $P = .01$) compared with observation alone.[10] The ESPAC-4 trial subsequently demonstrated that adjuvant combination of gemcitabine plus capecitabine was superior to gemcitabine alone in prolonging median overall survival (28.0 vs 25.5 months; $P = .03$).[11] The multicenter, randomized, phase 3 PRODIGE 24/CCTG PA6 clinical trial evaluated the safety and efficacy of a modified FOLFIRINOX (mFOLFIRINOX) chemotherapy regimen compared with gemcitabine as adjuvant therapy in 493 patients with resected PDAC.[14] At a median follow-up of 33.6 (IQR, 22.1-46.0) months, the primary end point of disease-free survival was significantly longer with treatment with mFOLFIRINOX compared with gemcitabine (median 21.6 [IQR, 9.9-nonestimable (NE)] vs 12.8 [IQR, 8.0-28.9] months; stratified hazard ratio [HR] of 0.58; 95% CI, 0.46-0.73; $P < .001$), as well as OS (median, 54.4 [IQR, 23.0-NE] vs 35.0 [IQR, 20.3-63.6] months; 3-year OS, 63.4% vs 48.6%). Treatment with mFOLFIRINOX is now a standard of adjuvant chemotherapy after resection of PDAC in eligible patients.[15,16]

The 3-year outcomes of PRODIGE 24/CCTG PA6 were based on a premature database lock following a recommendation in February 2018 by the independent data and safety monitoring committee to analyze and publish the data early in view of a large difference in efficacy between the treatment groups. The database was locked on April 13, 2018, at which time 91.8% of the expected events regarding disease-free survival had occurred. In this article, we report the updated 5-year survival outcomes from the final analysis of PRODIGE 24/CCTG PA6, with new results on prognostic factors for OS.

Key Points

Question Do the 5-year outcomes of the PRODIGE 24/Canadian Cancer Trials Group PA6 trial confirm the survival benefits of treatment with adjuvant modified FOLFIRINOX vs gemcitabine for resected pancreatic ductal adenocarcinoma (PDAC), and which factors predict better survival?

Findings The final results of this randomized clinical trial of 493 patients with PDAC confirmed significantly improved overall survival with treatment with modified FOLFIRINOX vs gemcitabine (median survival, 53.5 vs 35.5 months). Receipt of modified FOLFIRINOX, younger age, well-differentiated tumors, lower-stage tumors, larger-volume centers, and completing treatment predicted better survival; early disease relapse was an adverse prognostic factor for overall survival from relapse.

Meaning The results of this randomized clinical trial found modified FOLFIRINOX to be a recommended adjuvant regimen following PDAC resection.

Methods

Trial Overview

Full details of the PRODIGE 24/CCTG PA6 trial design have been published previously (Supplement 1).[14] This randomized, open-label, phase 3 clinical trial was conducted at 77 hospitals in France and Canada. Main inclusion criteria were age 18 to 79 years, histologically confirmed PDAC, complete macroscopic R0 or R1 resection within 12 weeks before randomization, no metastatic disease, World Health Organization performance status score of 0 or 1, and adequate hematologic, liver, and kidney functions. Patients were excluded in case of a serum cancer antigen (CA) 19-9 level of more than 180 U/mL (to convert to kU/L, multiply by 1) within 21 days before randomization, prior chemotherapy or radiotherapy, or coronary heart disease. Patients provided written informed consent before enrollment. The study protocol was approved by an independent ethics committee in France (Comité de Protection des Personnes Est III) and by ethics committees at participating centers in Canada.

Eligible patients were randomly assigned (1:1) to receive adjuvant mFOLFIRINOX (oxaliplatin, 85 mg/m^2; leucovorin, 400 mg/m^2; irinotecan, 150-180 mg/m^2 [the dose was reduced from 180 mg/m^2 to 150 mg/m^2 after the enrollment of 162 patients, in accordance with a protocol-specified safety analysis]; and fluorouracil, 2400 mg/m^2), every 14 days for 24 weeks (12 cycles), or adjuvant gemcitabine, 1000 mg/m^2, on days 1, 8, and 15, every 28 days for 24 weeks (6 cycles).

The primary end point was disease-free survival, which was calculated from the date of randomization until date of first cancer-related event, second cancer, or death of any cause. Secondary end points included OS, metastasis-free survival, cancer-specific survival, and safety. Follow-up included clinical examination, CA 19-9 levels, and a computed tomography scan every 3 months for the first 2 years, and every 6 months thereafter. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Statistical Analyses

Overall, 490 patients had to be included in the trial to observe 342 events and demonstrate a gain in 3-year disease-free survival of 10% (from 17% to 27%) and HR of 0.74, with a 80% power and 2-sided significance level of 5%.[12] All efficacy analyses were performed in the intention-to-treat (ITT) population. Survival rate estimates were calculated using the Kaplan-Meier method, with comparison using a stratified log-rank test. A Cox proportional hazards model (stratified according to the stratification factors, except for trial center) was used to estimate HRs with 95% CIs.

In post hoc analyses, a Cox proportional hazards model was used to evaluate the effects of prognostic factors on OS in univariate and multivariable analyses. Prognostic factors

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explored included age; sex; World Health Organization performance status; excision procedure; tumor location, stage, and histological grade; lymph node ratio[17]; lymph nodes dissection (≤12 vs >12 nodes); lymphovascular invasion; perineural invasion; resection status (R0 vs R1); venous resection; and time between surgery and the start of chemotherapy. Clinically relevant factors or variables with *P* values of less than .20 were explored further in a multivariable analysis with the use of ascending or descending selection techniques. Hazard ratios and 95% CIs were calculated.

The effect on overall survival of factors collected at the end of adjuvant therapy was also explored using a landmark method.[18] These included a dose intensity of 0.80 or greater for all drugs; duration of treatment (<6 vs ≥6 months), and completion of all treatment cycles. An 8-month landmark point was selected based on the ESPAC-3 trial.[19] Patients lost to follow-up or who died within 8 months of randomization were not selected to avoid the potential immortal time bias. Sensitivity analyses using landmark of 9 to 12 months were performed. The median times to recurrence according to the type of recurrence were compared with a Kruskal-Wallis test.

A Cox proportional hazards model was used to explore the effect on OS of time between first relapse and relapse treatment according to center size (inclusion volume <10 vs ≥10 patients), as well as time between end of adjuvant chemotherapy and relapse (<6 vs >6 months, and <12 vs >12 months). The latter analysis included treated patients who had local or metastatic relapse after the treatment and excluded all patients who progressed during treatment, had a second cancer, or died as a first event. Hazard ratios and 95% CIs were calculated.

Results

Patients and Treatment

A total of 493 patients (mFOLFIRINOX: 247 [50.1%]; gemcitabine: 246 [49.9%]) were enrolled between April 16, 2012, and October 3, 2016, and formed the ITT population (eFigure 1 in Supplement 2). Patient baseline demographic characteristics were similar between treatment groups[14]; this remained the case following centralized review, with the only significant difference being a greater rate of lymphovascular invasion in the mFOLFIRINOX group (73.7% vs 63.1%; *P* = .02; eTable 1 in Supplement 2).

At this final analysis (cutoff date: June 28, 2021), the median follow-up was 69.7 months (95% CI, 67.1-73.9). The median duration of treatment was 24.6 weeks (range, 2.0-36.6) and 24.0 weeks (range, 3.0-36.0) in the mFOLFIRINOX and gemcitabine groups, respectively; 160 patients (67.2%) and 192 patients (79.0%), respectively, received all planned cycles of chemotherapy. The relative dose intensity was 0.80 or greater in 80 patients (33.6%) receiving mFOLFIRINOX and 192 patients (79.0%) receiving gemcitabine (*P* < .001). The relative dose intensity was 0.80 or greater during the first 3 months of treatment for 139 patients (58.4%) in the mFOLFIRINOX group vs 207 (85.2%) in the gemcitabine group. This was because of several factors, including delays in treatments administration, dose reductions, and early discontinuation of treatment with oxaliplatin. At least 1 delay in treatment administration occurred in 157 patients (66%) receiving mFOLFIRINOX vs 95 patients (39.1%) receiving gemcitabine. At least 1 dose reduction was reported for 82 patients (33.7%) receiving gemcitabine, and in 149 (62.6%), 132 (55.5%), and 81 (34.0%) patients receiving treatment with oxaliplatin, irinotecan, and fluorouracil, respectively. The relative dose intensity was 0.80 or greater in 100 patients (42%) for oxaliplatin, 141 (59%) for irinotecan, and 167 (70%) for fluorouracil. The median number of oxaliplatin cycles was 9 (range, 1-12), and 131 patients (55.0%) discontinued treatment with oxaliplatin at least once.

Survival Analyses

After a median follow-up of 69.7 (IQR, 59.4-84.1) months, 367 events had occurred in the ITT population (mFOLFIRINOX, 173 events [47.1%]; gemcitabine, 194 events [52.9%]). The median disease-free survival was 21.4 (IQR, 9.9-70.0) months in the mFOLFIRINOX group vs 12.8 (IQR, 7.9-29.8) months in the gemcitabine group (stratified HR for cancer-related event, second cancer, or death: 0.66; 95% CI, 0.54-0.82; *P* < .001; **Figure 1**A). The 5-year disease-free survival rate was 26.1% (95% CI, 20.5%-32.1%) with chemotherapy with mFOLFIRINOX compared with 19.0% (95% CI, 14.3%-24.3%) with gemcitabine. A total of 304 patients died (mFOLFIRINOX, 136 [44.7%]; gemcitabine, 168 [55.3%]). The median overall survival was 53.5 (IQR, 22.4-NE) months in the mFOLFIRINOX group compared with 35.5 (IQR, 20.3-80.8) months in the gemcitabine group (stratified HR for death, 0.68; 95% CI, 0.54-0.85; *P* = .001; Figure 1B). The 5-year overall survival rate was 43.2% (95% CI, 36.5%-49.7%) with chemotherapy with mFOLFIRINOX and 31.4% (95% CI, 25.5%-37.5%) with gemcitabine. A subgroup analysis showed no evidence of heterogeneity of the effect size of treatment on OS (**Figure 2**). Patients in the mFOLFIRINOX group vs gemcitabine group also had improved metastasis-free survival (median 29.4 months [IQR, 12.1-95.3] vs 17.7 months [IQR, 8.8-43.9]; stratified HR, 0.64; 95% CI, 0.52-0.80; *P* < .001; Figure 1C) and cancer-specific survival (54.7 months vs 36.6 months; stratified HR, 0.65; 95% CI, 0.51-0.82; *P* < .001; Figure 1D).

Patterns of Recurrence

The pattern of disease recurrence was similar between the treatment groups (eTable 2 in Supplement 2). Local recurrence as first event occurred at a median of 12.4 months (95% CI, 9.5-15.2 months), with no significant difference (*P* = .74) with the median times compared with metastatic recurrence (12.0 months; 95% CI, 10.4-14.2) or local and distant recurrences (10.2 months; 95% CI, 9.3-13.7). Median OS from relapse was 18.5 months in patients with only local recurrence (95% CI, 13.4-22.4), 14.0 months with only metastatic recurrence (95% CI, 11.6-18.0), and 11.4 months with local and metastatic recurrences (95% CI, 10.0-15.0), with no significant difference.

The most common first relapse event in both groups was the occurrence of metastases (mFOLFIRINOX, 54.3%;

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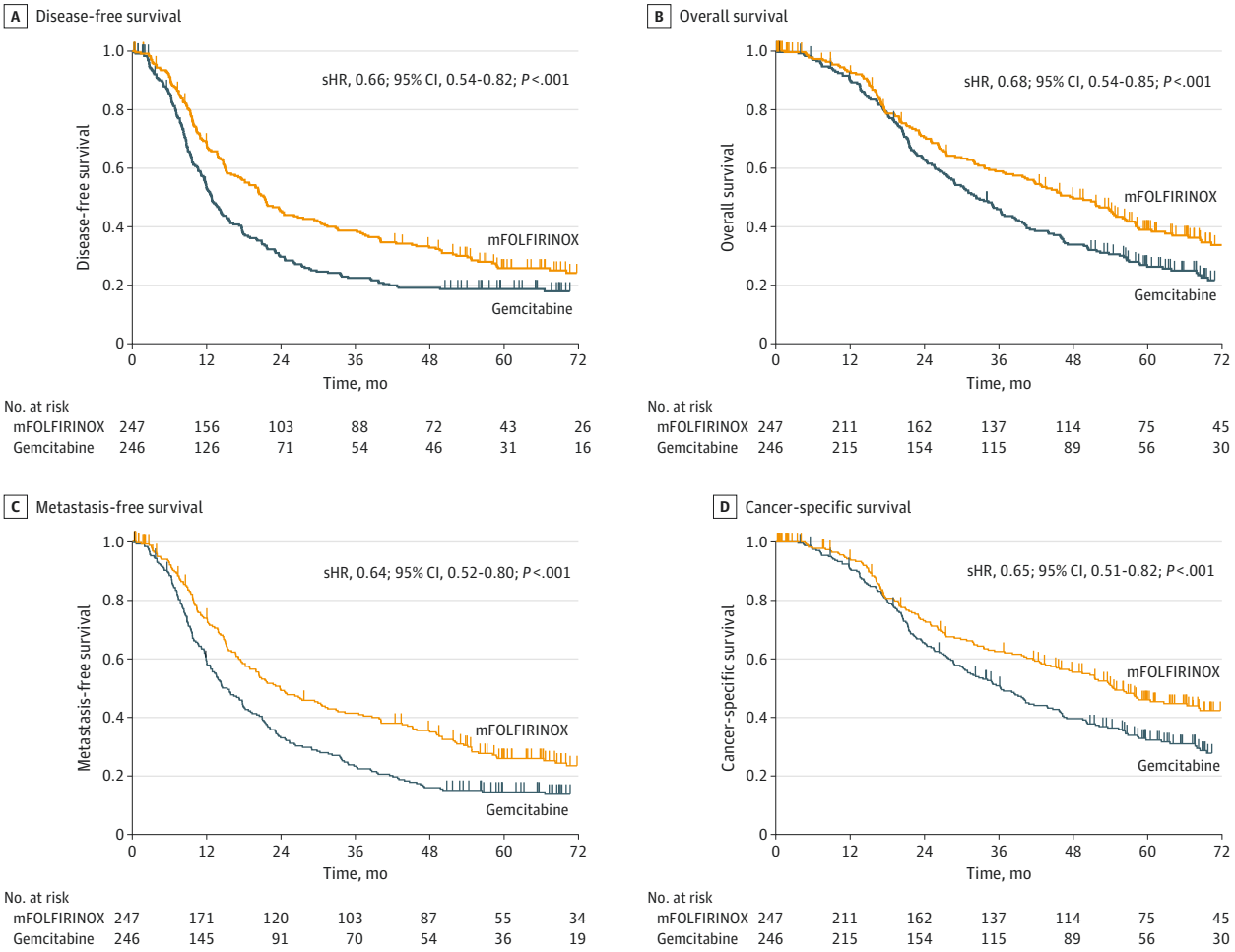
Figure 1. Kaplan-Meier Analysis of Survival in the Intention-to-Treat Population



P values based on log rank test stratified by lymph node status, resection margins, and postoperative CA 19-9. mFOLFIRINOX indicates modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; sHR, stratified hazard ratio.

gemcitabine, 46.9%) with significantly more patients with single-site lung metastases (39.4% vs 24.6%) and fewer liver and peritoneal metastases as a single site in the mFOLFIRINOX group (P = .03). Polymetastatic, liver-only, and peritoneal-only metastatic disease occurred soonest, with a median of 9.2 months (95% CI, 7.9-14.2 months), 9.7 months (95% CI, 8.5-11.9 months), and 9.8 months (95% CI, 7.7-14.2 months), respectively, compared with lung metastases, which occurred after 18.7 months (95% CI, 13.8-21.4 months). In patients who had metastatic disease as a first event (eTable 3 in Supplement 2), the median overall survival from relapse was significantly longer in cases of lung-only metastases (26.0 months; 95% CI, 16.8-30.3) compared with multiple metastatic or other sites (11.5 months; 95% CI, 10.2-13.9) (HR, 0.50; 95% CI, 0.36-0.70; P < .001).

Relapse Treatment

Chemotherapy was administered at relapse in 107 of 160 patients (66.9%) in the mFOLFIRINOX group (of whom 72 [67.3%] received a gemcitabine-based regimen) and in 151 of 182 patients (83.0%) in the gemcitabine group (of whom 112 [74.2%] received FOLFIRINOX) (eTable 4 in Supplement 2). The time between first relapse and reintroduction of chemotherapy was 0.77 months (range, 0-14.0) and 0.80 months (range, 0.03-7.75), respectively (P = .57), with no difference according to center inclusion volume. The median postrelapse survival was 13.1 (95% CI, 10.43-18.3) and 15.0 (95% CI, 12.3-18.4) months in the mFOLFIRINOX and gemcitabine groups, respectively. Patients in the mFOLFIRINOX group received more frequent radiation therapy and/or surgery as part of treatment for relapse (27.2% vs 16.5%; P = .02). Three patients in the gemcitabine group had surgery for pulmonary metastases vs 8 patients in the mFOLFIRINOX group; 1 patient in each group was disease free.

Prognostic Factors for OS

In univariate analysis, prognostic factors present at the study baseline that were significantly associated with an improved survival included mFOLFIRINOX group, body/tail tumor location, well-differentiated tumor grade, pT1 to 2

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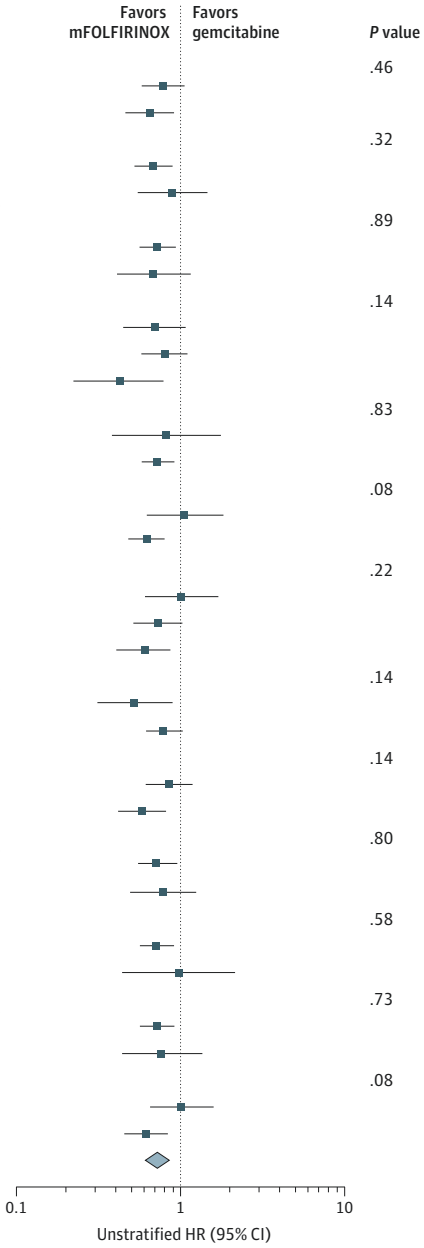
Figure 2. Treatment Effect on Overall Survival in Subgroup Analyses

Subgroup	mFOLFIRINOX (event/n)	Gemcitabine (event/n)	Unstratified HR (95% CI)	*P* value
Sex				.46
Male	80/142	91/135	0.79 (0.58-1.06)	
Female	56/105	77/111	0.66 (0.47-0.93)	
Age				.32
<70 y	104/200	132/192	0.69 (0.53-0.90)	
≥70 y	32/47	36/54	0.90 (0.56-1.46)	
Tumor location				.89
Head	112/197	130/183	0.73 (0.57-0.94)	
Other	24/50	38/63	0.69 (0.42-1.16)	
Tumor grading				.14
Well differentiated	35/70	53/79	0.71 (0.46-1.08)	
Moderately differentiated	75/124	87/125	0.80 (0.59-1.10)	
Poorly differentiated or undifferentiated	19/35	23/29	0.44 (0.23-0.81)	
Primary tumor status				.83
pT1 or pT2	15/31	13/25	0.82 (0.39-1.73)	
pT3 or pT4	121/216	155/221	0.73 (0.58-0.93)	
Nodal status				.08
pN0	26/55	30/61	1.07 (0.63-1.81)	
pN1	110/192	138/185	0.63 (0.49-0.81)	
Lymph nodes ratio				.22
0	27/57	31/61	1.02 (0.61-1.71)	
0-0.20	64/118	66/102	0.73 (0.52-1.03)	
>0.20	45/72	70/82	0.61 (0.42-0.89)	
Regional lymph nodes retrieved, No.				.14
<12	22/46	40/54	0.53 (0.32-0.90)	
≥12	114/201	127/191	0.80 (0.62-1.03)	
Status of surgical margins				.14
R0	72/148	78/134	0.86 (0.63-1.19)	
R1	64/99	90/112	0.60 (0.43-0.83)	
Venous resection				.80
No	104/192	118/176	0.73 (0.56-0.96)	
Yes	31/53	49/69	0.79 (0.50-1.23)	
Superior-mesenteric-vein resection				.58
No	126/228	150/221	0.72 (0.57-0.92)	
Yes	10/19	18/25	0.98 (0.45-2.14)	
Portal-vein resection				.73
No	115/215	136/204	0.73 (0.57-0.93)	
Yes	21/32	32/42	0.78 (0.45-1.36)	
Lymphovascular invasion				.08
No	32/55	45/79	1.02 (0.65-1.60)	
Yes	86/154	100/135	0.63 (0.47-0.84)	
Overall	136/247	168/246	0.73 (0.58-0.92)	



HR indicates hazard ratio; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin.

stage, pN0 status, lower tumor stage (I, IIA, and IIB vs III/IV), lower lymph node ratio (0, 0-0.20, and 0.20-0.40 vs >0.40), R0 resection status, and no venous resection (eTable 5 in Supplement 2). In multivariable analysis, significant favorable baseline prognostic factors for OS were mFOLFIRINOX, being younger than 70 years, well-differentiated tumor grade, lower tumor stage, and larger-volume center (**Table 1**).

To complete all treatment cycles was a significant positive predictor for OS for each regimen (data not shown) and for all patients (HR, 0.64; 95% CI, 0.49-0.84; *P* = .002; **Table 2**; eFigure 2 in the Supplement). A shorter time from end of adjuvant therapy to disease relapse was identified as an adverse prognostic factor for OS from relapse (HR, 1.03; 95% CI, 1.01-1.04; *P* < .001). A cutoff at 12 months was found optimal to dichotomize the time from end of adjuvant therapy to disease relapse (HR, 1.95; 95% CI, 1.49-2.54; *P* < .001; eFigure 3 in Supplement 2).

Safety

Safety data have been published in detail previously.[14] The safety profile of the mFOLFIRINOX regimen was less favorable than that of gemcitabine but manageable.[14] No new safety signals were identified with longer follow-up.

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Table 1. Multivariable Analysis of Prognostic Factors for Overall Survival Present at Study Inclusion

Factor	HR (95% CI)[a]	*P* value[b]
Adjuvant chemotherapy		
Gemcitabine	1 [Reference]	<.001
mFOLFIRINOX	0.65 (0.51-0.82)	
Center volume		
Inclusion of ≥10 patients	0.77 (0.61-0.98)	.03
Inclusion of <10 patients	1 [Reference]	
Age, y		
<70	0.70 (0.52-0.93)	.02
≥70	1 [Reference]	
Tumor grading		
Well differentiated	0.69 (0.53-0.90)	.01
Moderately/poorly/undifferentiated	1 [Reference]	
Tumor staging		
IA/IB	0.10 (0.03-0.33)	.002
IIA	0.24 (0.09-0.60)	
IIB	0.35 (0.17-0.72)	
III/IV	1 [Reference]	

Abbreviations: HR, hazard ratio; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin.

[a] Stratified Cox model and log-rank test on lymph node status, resection margins, and postoperative CA 19-9.

[b] Likelihood ratio test.

Table 2. Univariate Analysis of Prognostic Factors Collected at the End of Treatment for OS

Factor	No. event/ No. total	5-y OS, %	HR (95% CI)	*P* value
Dose intensity ≥0.80[a]				
No	126/200	39.2	1 [Reference]	.93
Yes	159/249	38.2	1.01 (0.80-1.28)	
Duration of treatment, mo				
<6	260/407	38.0	1 [Reference]	.44
≥6	25/42	46.1	0.85 (0.57-1.29)	
All treatment cycles completed[b]				
No	72/103	27.4	1 [Reference]	.002
Yes	213/346	41.9	0.64 (0.49-0.84)	

Abbreviations: HR, hazard ratio; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; OS, overall survival.

[a] Relative dose intensity of 0.80 or greater for all drugs.

[b] Equates to 12 treatment cycles of mFOLFIRINOX (at least for fluorouracil) and 6 cycles of gemcitabine.

Discussion

This final 5-year analysis with mature data from the PRODIGE 24 randomized clinical trial indicates that adjuvant chemotherapy with a mFOLFIRINOX regimen significantly prolonged disease-free survival, OS, metastasis-free survival, and cancer-specific survival compared with treatment with gemcitabine. The OS benefit with mFOLFIRINOX was significant in most subgroups, including those with adverse prognostic factors (ie, poorly differentiated tumor, pT3-T4 tumor, positive lymph nodes, lymph node ratio >0.20, or R1 resection).

The median disease-free survival of 21.4 months with mFOLFIRINOX is to our knowledge one of the longest reported in randomized clinical trials of adjuvant therapy in resected PDAC (**Table 3**[9-13,20,21]) and was 8.6 months longer than in gemcitabine group. It seems unlikely that the difference between treatment groups was because of a patient selection bias, as the median disease-free survival of 12.8 months in the gemcitabine group aligns with other trials (Table 3). Patient selection criteria were comparable with those in other trials,[10-13,20,22] despite that the threshold value for CA 19-9 in PRODIGE 24 (180 U/mL) was higher than in CONKO-001 (100 U/mL) for patient inclusion.[10]

Noticeably, the gain in disease-free survival with treatment with mFOLFIRINOX translates into an OS benefit, with a 32% reduction in risk of death compared with the gemcitabine group. The median overall survival in PRODIGE 24 was 18 months longer with mFOLFIRINOX than with gemcitabine, with a 5-year overall survival rate of 43.2% compared with 31.4%. The median survival with treatment with gemcitabine (35.5 months) in the present trial was longer than in most other trials (22.3-26.0 months; Table 3). Also, the overall survival outcomes with gemcitabine in PRODIGE 24 were similar to those reported in the recent APACT trial after a similar length of follow-up (Table 3).[21]

Postrecurrence median survival rates (18.5 months with local recurrence and 14.0 months with metastatic recurrence) were relatively long compared with the ESPAC-4 data (9.4 and 8.9 months for local and distant recurrence, respectively).[11] This may be because of an earlier diagnosis of recurrence using CA 19-9 levels and a computed tomography scan and the administration of subsequent treatments after tumor relapse. In the ESPAC-4 trial, only 35.7% of patients received treatment for relapse, vs 93.4% in PRODIGE 24. The use of mFOLFIRINOX at recurrence in 74.2% of patients of the gemcitabine group may explain their survival improvement. Fewer single-site liver and peritoneal metastases and more single-site lung metastases occurred in the mFOLFIRINOX group. As a short time to relapse following the end of adjuvant therapy constituted a significant adverse prognostic factor for OS, it is important to early detect and to treat promptly the relapse. In a nationwide Dutch cohort study, patients with asymptomatic recurrence detected by follow-up imaging after PDAC resection had a higher probability to receive recurrence treatment, which was significantly associated with improved survival.[23]

Defining prognostic factors may help to predict recurrence and poor survival outcomes. Completion of all cycles of adjuvant chemotherapy in the present study was associated with improved OS in both treatment groups, as previously reported.[12,24] Other prognostic factors were mFOLFIRINOX treatment, tumor location, stage, grade, and being younger than 70 years. To our knowledge, this is the first demonstration of the effect of larger-volume centers (≥10 patients included) on survival after recurrence. Translational studies may help to identify tumor molecular signatures to better select chemotherapy regimens.

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Table 3. Five-Year Outcomes From Randomized Clinical Trials of Adjuvant Chemotherapy in Patients With Resected PDAC

				DFS		OS	
Source	Patients, No.	Adjuvant therapy	Median follow-up, mo (IQR)	Median, mo (95% CI)	5-y, %	Median, mo (95% CI)	5-y, %
ESPAC-1[9]	147	FU + leucovorin	47.0 (33-62)	15.3 (10.5-19.2)	NA	20.1 (16.5-22.7)	21.1[a]
	142	Observation	47.0 (33-62)	9.4 (8.4-15.2)	NA	15.5 (13.0-17.7)	8.0[a]
CONKO-001[10]	179	Gemcitabine	136 (104-144)	13.4 (11.6-15.3)	16.6	22.8 (NA)	20.7
	175	Observation	136 (104-144)	6.7 (6.0-7.5)	7.0	20.2 (NA)	10.4
JSAP-02[13]	58	Gemcitabine	60.4 (40.6-77.1)	11.4 (8.0-14.5)	NA	22.3 (16.1-30.7)	23.9
	60	Observation	60.4 (40.6-77.1)	5.0 (3.7-8.9)	NA	18.4 (15.1-25.3)	10.6
ESPAC-3[12]	537	Gemcitabine	34.2 (27.1-43.4)	14.3 (13.5-15.6)[b]	NA	23.6 (21.4-26.4)	17.5[a]
	551	FU + leucovorin	34.2 (27.1-43.4)	14.1 (12.5-15.3)[b]	NA	23.0 (21.1-25.0)	15.9[a]
JASPAC-01[20]	187	S-1	79.3 (72.0-89.0)	22.9 (NA)[c]	33.3	46.5 (37.8-63.7)	44.1[a]
	190	Gemcitabine	83.2 (71.8-88.5)	11.3 (9.7-13.6)[c]	16.8	25.5 (22.5-29.6)	24.4[a]
ESPAC-4[11]	364	Gemcitabine + capecitabine	43.2 (39.7-45.5)	13.9 (12.1-16.6)	18.6	28.0 (23.5-31.5)	28.8[a]
	366	Gemcitabine	43.2 (39.7-45.5)	13.1 (11.6-15.3)[c]	11.9	25.5 (22.7-27.9)	16.3[a]
APACT[21]	432	Gemcitabine + nab-paclitaxel	63.2 (NA)[c]	16.6 (NA)	NA	41.8 (NA)[d]	38[d]
	434	Gemcitabine	63.2 (NA)[c]	13.7 (NA)	NA	37.7 (NA)[d]	31[d]
PRODIGE 24	247	mFOLFIRINOX	69.7 (59.4-84.1)	21.4 (17.5-26.7)	26.1	53.5 (22.4-NE)	43.2
	246	Gemcitabine	69.7 (59.4-84.1)	12.8 (11.6-15.2)	19.0	35.5 (20.3-80.8)	31.4

Abbreviations: DFS, disease-free survival; FU, fluorouracil; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; NA, not available; NE, nonestimable; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

[a] Estimated 5-year survival.

[b] Progression-free survival.

[c] Recurrence-free survival.

[d] Post hoc analysis; data cutoff date of April 9, 2021 (88% mature).

Limitations

This study has several limitations: quality of life was not planned as a secondary objective. Despite the fact that the upper age limit for inclusion in the trial was 80 years, only 20.5% of the patients were 70 years or older. More elderly patients are receiving diagnoses of pancreatic cancer and are now being considered for resection and adjuvant chemotherapy. Another limitation comes from inclusion criteria: selected patients had no cardiac ischemia and good performance status (World Health Organization 0 or 1). In routine practice, up to 30% of patients do not receive adjuvant chemotherapy because of the morbidity of pancreatectomy, slow recovery from surgery, comorbidities, development of early recurrence, or reduced performance status.[24] This trial authorized inclusion until 12 weeks after resection to ensure adequate postoperative recovery and maximize the chance of receiving chemotherapy. Perioperative chemotherapy will deliver systemic chemotherapy earlier and may increase the completion rate of multimodal treatment. Ongoing randomized clinical trials will help define the role of preoperative chemotherapy, particularly mFOLFIRINOX, in the resectable setting.

Conclusions

With mature data and longer follow-up, the final results analysis of the PRODIGE 24/CCTG PA6 randomized clinical trial demonstrates that mFOLFIRINOX adjuvant chemotherapy significantly improves OS after complete resection of PDAC compared with single-agent adjuvant gemcitabine. The benefits were seen across all survival end points in all predefined subgroups. These findings confirm treatment with mFOLFIRINOX as the recommended adjuvant regimen in eligible patients.

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Publication 4 – Preneoplastic Lesions in Surgical Specimens Do Not Worsen the Prognosis of Patients Who Underwent Surgery for Pancreatic Adenocarcinoma: Post-Hoc Analysis of the PRODIGE 24-CCTG PA 6 Trial

Article original (publié)

Legrand, T.; Salleron, J.; Conroy, T.; Marchal, F.; Thomas, J.; Monard, L.; Biagi, J.J.; ***Lambert, A****. Preneoplastic Lesions in Surgical Specimens Do Not Worsen the Prognosis of Patients Who Underwent Surgery for Pancreatic Adenocarcinoma: Post-Hoc Analysis of the PRODIGE 24-CCTG PA 6 Trial.* ***Cancers 2022****, 14, 3945. https://doi.org/10.3390/cancers14163945*

Avant de pouvoir étudier le rôle des marges de résection comme facteur pronostic de récidive des patients opérés d'un cancer du pancréas, nous nous sommes intéressés à un autre facteur de risque potentiel, la présence de lésions pré-cancéreuses sur les pièces opératoires.
L'objectif de cette étude était d'évaluer si la présence d'une lésion dysplasique (PanIN, MCN, IPMN) était un facteur de mauvais pronostique sur la survie sans rechute des patients opérés pour un adénocarcinome pancréatique et ayant bénéficié d'une chimiothérapie adjuvante par gemcitabine ou mFOLFIRINOX dans le cadre de l'étude PRODIGE 24/ CCTG PA6.

Parmi les 493 patients de l'étude, 226 (45,9%) présentaient des lésions dysplasiques, ce qui en fait un évènement fréquent dans cette cohorte. C'étaient en majorité des PanIN (193 patients dont 100 étaient de haut grade).

En analyse multivariée, ces lésions dysplasiques n'étaient pas un facteur pronostic indépendant de façon significative. Contre-intuitivement peut être, la présence de lésion pré-cancéreuse n'altèrait par la survie sans rechute des patients dans cette étude. La présence de lésions dysplasiques n'est donc pas synonyme de récidive locale plus fréquente et incite à poursuivre l'intention curative chez ces patients.

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Preneoplastic Lesions in Surgical Specimens Do Not Worsen the Prognosis of Patients Who Underwent Surgery for Pancreatic Adenocarcinoma: Post-Hoc Analysis of the PRODIGE 24-CCTG PA 6 Trial

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Simple Summary: Pancreatic cancer patients who undergo curative surgery are still likely to recur. We therefore analyzed the data of the 493 patients from the PRODIGE 24-CCTG PA 6 trial, which validated the benefit of adjuvant mFOLFIRINOX regimen over gemcitabine after pancreatic adenocarcinoma resection. We investigated whether the presence of dysplasia (noninvasive intraductal papillary mucinous neoplasm, mucinous cystic neoplasm or pancreatic intraepithelial neoplasia) might decrease in disease-free survival. A preneoplastic lesion was identified in 226 patients (45.8%). In a multivariate analysis, the presence of dysplasia is not an independent predictor of diminished disease-free survival. This finding should be useful for future prospective trials and for surgeons' decision making, as the pre-existence of a preneoplastic lesion should not preclude a plan for curative surgery.

Abstract: Objective: The prognosis of pancreatic cancer after curative surgery is burdened by frequent recurrence. The aim of this study was to evaluate the impact of dysplasia in the surgical specimen on disease-free survival (DFS). Methods: A post-hoc analysis of the phase III PRODIGE 24-CCTG PA 6 trial was performed. From April 2012 to October 2016, 493 patients were included in the primary study. Assessment for dysplasia in the surgical specimens was secondarily performed. Dysplasia was defined based on presence and grade of three most common pre-malignant lesions (intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN) and pancreatic intraepithelial neoplasia (PanIN). The primary endpoint was DFS validated through multivariate analysis. Results: Two hundred twenty-six patients (45.9%) had a preneoplastic lesion. PanIN lesions were found in 193 patients (39.2%), including 100 high-grade lesions (20.6%); 43 patients had IPMN lesions (8.7%), including high-grade lesions in 32 (6.5%). Three MCN were described (0.6%). In bivariate analysis, the presence of dysplasia was not associated with poorer DFS (HR = 0.82, 95% CI [0.66; 1.03]). In multivariate analysis, risk factors for poorer DFS were poorly differentiated/undifferentiated tumor, N1 status, R1 surgical margins and perineural invasion. Conclusions: The presence of dysplasia in the surgical specimen after pancreatic cancer surgery does not worsen DFS.

Keywords: pancreatic cancer; dysplasia; PanIN; IPMN; MCN; surgery

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1. Introduction

Pancreatic cancer has become the third leading cause of death by cancer in men and women combined and is expected to be the second leading cause by 2040 [1]. Its mor-

tality has increased slightly in men and remained relatively stable in women for the last 20 years [2]. The 5-year overall survival (OS) after curative pancreatic surgery remains low and leaves room for improvements. The PRODIGE 24-CCTG PA 6 clinical trial was designed to compare the efficacy and safety of mFOLFIRINOX (modified FOLFIRINOX) to gemcitabine as adjuvant treatment in patients with resected pancreatic ductal adenocarcinoma. This study demonstrated improved OS and disease-free survival (DFS) with mFOLFIRINOX at the cost of increased but manageable toxicity [3].

The three most common preneoplastic lesions (dysplasia) of the pancreas are: intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasms (MCN), and pancreatic intraepithelial neoplasia (PanIN) [4]. IPMNs are tumors that grow within the pancreatic ducts and produce mucin. IPMNs are fairly common and frequently present as incidental pancreatic cyst. The prevalence increase with age until it reaches in up to 10% of persons aged 70 years or older. Depending on their location in the ductal system, some of them progress to invasive cancer if they are left untreated [5,6]. PanIN are an important and well-known asymptomatic precursor of ductal pancreatic adenocarcinoma [7]. High-grade pancreatic intraepithelial neoplasia (previously named PanIN-3) are nearly exclusively adjacent to pancreatic adenocarcinoma or detected in patients with a family history of pancreatic cancer or a predisposing germline mutation [5,8]. MCNs are seen nearly exclusively in women and are usually (95% of cases) located in the body or tail of the pancreas [6].

Dysplasia within the resection specimen after a pancreatectomy for non-invasive IPMN is associated with 21% recurrence as new cyst, IPMN or pancreatic carcinoma [9]. Moreover, dysplasia at a resection margin was associated with a three-fold increased risk of recurrence ($p = 0.02$) after resection of non-invasive IPMN, even if no relationship between dysplasia and cancer was found [9]. These findings warrant further investigation as the recurrence rate differs depending on the status of the resected margin after surgery of invasive or non-invasive IPMN [10].

The presence of a preneoplastic lesion either on the tumor margin or within the parenchyma, following pancreatic cancer surgery, has never been explored and its impact on possible recurrence is unknown. The objective of this study was to evaluate whether the presence of dysplasia in resected specimens is a poor prognostic factor for DFS.

2. Materials and Methods

A post-hoc analysis based on data from the prospective phase III PRODIGE 24 CCTG PA 6 trial was performed. Inclusion criteria were: age from 18 to 79 years, histologically confirmed pancreatic ductal adenocarcinoma, complete macroscopic R0 [no cancer cells within 1 mm of all resection margins] or R1 [cancer cells present within 1 mm of one or more resection margins] resection within 3 to 12 weeks before randomization, no evidence of metastatic disease, malignant ascites, or pleural effusion. Other inclusion criteria were: full recovery from surgery, a World Health Organization (WHO) performance status score of 0 or 1, and adequate hematologic, liver, and renal function. Patients with non-ductal pancreatic tumors, incomplete (R2) resection, a serum CA 19-9 level of more than 180 kU/L within 21 days before randomization, previous chemotherapy or radiotherapy, or symptomatic heart failure or coronary heart disease were ineligible.

From April 2012 to October 2016, a total of 493 patients from 58 centers in France and 19 centers in Canada were randomly assigned to receive a planned 6-month course of either mFOLFIRINOX (247 patients) or gemcitabine (246 patients). Recommendations were made for surgeons and pathologists to orient the tumor specimen to accurately identify the resection limits. During surgery, pancreatic neck margin was checked by intraoperative frozen section. In case of positivity, an additional resection was advised until a negative margin was obtained. Patients had regular standardized surveillance, which included thoraco-abdominopelvic computed tomography scans or MRI, serum CA 19-9 levels, and clinical examinations repeated every 3 months for 2 years and then every 6 months for 3 years. Full treatment details have been published previously [3]. The database was locked

on 13 April 2018, at which time 314 cancer-related events, second cancers, or deaths from any cause (91.8% of the expected DFS events) had occurred.

Our current study was based on 3-year data from the PRODIGE 24-CCTG PA 6 clinical trial, and all patients were analyzed.

Pathology reports of each patient were reviewed to determine the presence of a preneoplastic lesion (IPMN, MCN, PanIN or mixed), associated with the primary invasive tumor and its location, i.e., on the tumor resection margin, within the pancreatic parenchyma or both. The location of the lesions on the tumor resection margin was specified, i.e., on the main pancreatic duct or on the branch ducts. Grade of the dysplasia was classified as low/intermediate grade, high-grade or invasive according to the Baltimore consensus [11]. For parenchymal dysplastic lesions, the type of lesion and its grade were also classified according to the Baltimore consensus. When dysplasia was present at multiple locations within the pancreas with different grades, we classified considering the highest grade.

This study was declared to the French National Commission on Informatics and Liberties (CNIL) and received prior authorization from the study sponsor, Unicancer.

The primary endpoint was DFS based on the presence or absence of a preneoplastic lesion in the surgical sample. DFS was calculated from the date of randomization to the date of the first cancer-related event, second cancer or death from any cause. Patients without events at the time of analysis had their data censored on the date of last informative follow-up.

Statistical Analysis

All statistical analyses were performed using SAS software, v9.4 (SAS Institute Inc., Cary, NC 25513, USA). Two-sided p-values < 0.05 were considered statistically significant. Qualitative parameters were described by frequency and percentage.

Predictive factors for DFS were assessed using bivariate Cox proportional hazards models adjusted by treatment arm [12]. The results were expressed as adjusted hazard ratio (HR) and 95% confidence interval. The validity of the proportional hazard assumption was checked using the Scaled Schoenfeld Residuals. Parameters with a p-value less than 0.2 were introduced in a full multivariate model. In line with the parsimony principle, this full model was then simplified with a backward selection.

Due to missing values on demographic and disease characteristics at inclusion, multiple imputations (MI) were performed according to FDA-approved methods, and we assumed that the described observations were missing at random [13]. Multiple pilot runs of various numbers of imputations were performed to assess the number of imputations and the stability of the parameter estimates for a given number of imputations. The number of 5 imputations was defined according to the fraction of missing information and the relative efficiency. The following method was applied: (a) multiple imputation using fully conditional specification was performed on 5 datasets using the proc mi in SAS; the MI model was performed on all demographic and disease characteristics. The DFS and time to events were also included. (b) For each imputed dataset, the effect of each predictive factors was assessed using bivariate Cox proportional hazards model adjusted on treatment arm. (c) The 5 estimates were then combined across imputed datasets with the proc mianalyze. As for complete case analysis, parameters with a p-value less than 0.2 were selected for the full multivariate analysis. For each imputed data set, we constructed 200 bootstrap data sets by randomly drawing with replacement. The total number of data sets was thus equal to 1000 data sets (5 (number of imputations) times 200 (number of bootstrap samples)). We then applied a backward selection on them and calculated the proportion of times that a variable appears in the final model namely the inclusion frequency. Parameters with an inclusion frequency greater than 0.7 were selected for the final multivariate model. The adjusted effect of each selected predictive factors was computed by combining the 5 estimates across imputed datasets with the proc mianalyze.

3. Results

Table 1 presents the demographic and disease characteristics of the 493 patients at baseline for the whole population. The majority were male (56.2%), younger than 65 years (59.1%) and of WHO performance status 0 (51.1%). Regarding comorbidities, 25.9% had diabetes mellitus and 46% were smokers.

Concerning histopathologic features, 98.8% of the patients had a ductal adenocarcinoma (98.8%), moderately (53.9%) or well (32.3%) differentiated, and location as head of the pancreas for 75.4%. Also, 88.6% of the tumors were classified as pT3 or pT4 and 76.5% as pN1, i.e., stage IIa or IIb in 91.7% of patients. The surgical margins were classified as R0 in 57.2% of patients. Lympho-vascular invasion was observed in 68.3% of cases and peri-neural invasion in 91.2%.

The rates of preneoplastic lesions are detailed in Table 2. Complete final pathology reports were available for 492 patients (99.8%). A preneoplastic lesion was found in 226 (45.9%) of resected tumors. In twenty cases (4.1%), a lesion was observed on the tumor margin only, in 161 (32.7%) in the pancreatic parenchyma only and in 45 (9.2%) the location was mixed, both on the surgical margin and the resected specimen. PanIN lesions were found in 193 patients (39.2%): 86 had low or intermediate grade lesions (17.7%), 100 had high-grade lesions (20.6%). A total of 7 additional patients with PanIN described were unspecified regarding the grade of differentiation.

IPMN lesions were present in 43 patients (8.7%), with low or intermediate grade for 10 (2%) and high-grade in 32 (6.5%). Three MCN were described (0.6%), one of which was intermediate grade and two were high-grade.

The median follow-up duration was 33.6 months, 95% CI [30.3; 36.0] and DFS at 3 years was 39.7%, 95% CI [32.8; 46.6] in the mFOLFIRINOX group (134 recurrences), as compared with 21.4% 95% CI [15.8; 27.5] in the gemcitabine group (180 recurrences, $p < 0.001$).

Pooling the 2 treatment arms, results of bivariate analyses adjusted on arm and after multiple imputations are presented Table 3. The presence of a preneoplastic lesion is not associated with a significant reduced DFS with a hazard ratio of 0.82, [95% CI 0.66; 1.03] ($p = 0.088$) (Figure 1). Regarding the location of these preneoplastic lesions, lesions on both tumor margin and parenchyma were associated with a better DFS (HR 0.58, [95% CI 0.37; 0.90], $p = 0.015$). IPMN lesions were also associated with a better DFS (HR 0.63, [95% CI 0.41; 0.97], $p = 0.038$), but no significant association was found for low/intermediate grade and high-grade separately. The DFS was not different according to the presence of PanIN lesions (HR 0.97, [95% CI 0.78; 1.22], $p = 0.8$).

An analysis was performed to determine whether the presence of precancerous lesions increased the risk of locoregional relapse. No association was found between the presence of preneoplastic lesions and locoregional relapse after adjustment for treatment arm (HR 0.82 [95% CI 0.59; 1.15], $p = 0.252$).

When analyzing other potential prognostic factors, higher tumor grade is associated with poorer DFS. DFS was also significantly associated with pN1 status (HR 1.76, [95% CI 1.32; 2.35]), stage IIa/IIb or III/IV (HR 2.09 [1.14; 3.81] and HR 6.62 [2.72; 16.14] respectively), surgical margins R1 (HR 1.47 [1.18; 1.84]) as well as venous resection (HR 1.41 [1.10; 1.80]), and in particular portal vein resection (HR 1.41 [1.06; 1.88]). The presence of lymphovascular invasion was also a poor predictive factor with a hazard ratio of 1.40 [1.09; 1.80] as well as perineural invasion (2.52 [1.57; 4.05]).

Including all predictive factors in a multivariate model (Table 4), with adjustment for treatment arm, the independent risk factors for DFS were poorly differentiated/undifferentiated tumor, pN1 nodal status, R1 surgical margins and perineural invasion. Location of preneoplastic lesions and the presence of IPMN lesions did not remain associated with DFS in the multivariate analysis. It should be noted that the presence or not of a dysplasia on the tumor margin was included as a risk factor in the analysis, but this had no impact on the DFS in multivariate analysis.

Table 1. Demographic and clinical characteristics of the patients at baseline.

Characteristics	No. (%)
Study arm	
Gemcitabine	246/493 (49.9)
mFOLFIRINOX	247/493 (50.1)
Age (years) $\geq$ 65	201/493 (40.8)
Male sex	277/493 (56.2)
WHO performance-status score	
0	249/487 (51.1)
1	238/487 (48.9)
Diabetes mellitus	126/487 (25.9)
Location of the tumor	
Head of the pancreas	372/492 (75.6)
Other	120/492 (24.4)
Tumor histologic findings	
Ductal adenocarcinoma	486/492 (98.8)
Nonductal adenocarcinoma	6/492 (1.2)
Tumor grade	
Well differentiated	149/462 (32.2)
Moderately differentiated	249/462 (54.0)
Poorly differentiated or undifferentiated	64/462 (13.8)
Primary tumor status	
pT1 or pT2	56/493 (11.4)
pT3 or pT4	437/493 (88.6)
Lymph node status	
pN0	116/493 (23.5)
pN1	377/493 (76.5)
Tumor stage	
IA or IB	26/493 (5.3)
IIA or IIB	452/493 (91.7)
III or IV	15/493 (3.0)
Surgical margins	
R0	282/493 (57.2)
R1	211/493 (42.8)
Lymphovascular invasion	289/423 (68.3)
Perineural invasion	412/452 (91.2)
Capsular rupture	75/432 (17.4)
Vascular resection	
Venous resection	122/490 (24.9)
Portal vein resection	74/493 (15.0)
Superior mesenteric vein resection	44/493 (8.9)
Arterial resection	15/492 (3.1)
Postoperative CA 19-9 level	
$\leq$90 U/mL	457/493 (92.7)
>90 U/mL	36/493 (7.3)
Results presented as no./total no. (%)	

Table 2. Description of dysplastic lesions.

	All N = 493	**Gemcitabine Arm N = 246**	**mFOLFIRINOX Arm N = 247**
Preneoplastic lesion (n^0, %)	226/492 $^{\alpha}$ (45.9)	118/246 (48)	108/246 $^{\alpha}$ (43.9)
Location of preneoplastic lesions			
Tumor margin	20/492 (4.1)	12/246 (4,9)	8/246 (3.3)
Parenchyma	161/492 (32.7)	82/246 (33,3)	79/246 (32.1)
Tumor margin and parenchyma	45/492 (9.2)	24/246 (9.8)	21/246 (8.5)
IPMN lesions	43/492 (8.7)	27/246 (11.0)	16/246 (6.5)
Grading IPMN			
Low- or intermediate-grade	10/491 (2)	7/245 (2.9)	3/246 (1.2)
High-grade	32/491 (6.5)	19/245 (7.8)	13/246 (5.3)
PanIN lesions	193/492 (39.2)	97/246 (39.4)	96/246 (39.0)
Grading PanIN			
Low- or intermediate-grade	86/485 (17.7)	41/242 (16.9)	45/243 (18.5)
High-grade	100/485 (20.6)	52/242 (21.5)	48/243 (19.8)
MCN lesions	3/492(0.6)	1/246 (0.4)	2/246 (0.8)
Grading MCN			
Low- or intermediate-grade	1/492 (0.2)	1/246 (0.4)	0
High-grade	2/492 (0.4)	0	2/246 (0.8)

Results presented as no./total no. (%). $^{\alpha}$ Missing data for one patient regarding the preneoplastic lesions. Abbreviations: IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasms; PanIN: pancreatic intraepithelial neoplasia.

Table 3. Bivariate analyses adjusted on treatment arm (mFOLFIRINOX regimen or gemcitabine) after multiple imputations.

Characteristics		**HR and 95% CI**	***p*-Value**
Age	≥65 vs. <65	1 [0.8; 1.25]	1
Gender	Male vs. Female	1 [0.80; 1.25]	1
WHO performance status score	1 vs. 0	1.09 [0.88; 1.37]	0.4
Diabetes mellitus	Yes vs. No	1.11 [0.86; 1.42]	0.4
Tumor location	Head vs. Other	1.13 [0.87; 1.47]	0.3
Tumor histologic findings	Ductal adenocarcinoma	1	
	Nonductal carcinoma	0.94 [0.35; 2.54]	0.9
Tumor grade	Well differentiated	1	
	Moderately differentiated	1.3 [1.01; 1.68]	0.043
	Poorly differentiated or undifferentiated	1.79 [1.26; 2.55]	0.001
Primary tumor pT stage	pT3 or pT4 vs. pT1 or pT2	1.28 [0.89; 1.84]	0.18
Nodal status	pN1 vs. pN0	1.76 [1.32; 2.35]	<0.001
Tumor stage	IA or IB	1	
	IIA or IIB	2.09 [1.14; 3.81]	0.017
	III or IV	6.62 [2.72; 16.14]	<0.001
Status of surgical margins	R1 vs. R0	1.47 [1.18; 1.84]	<0.001
Lymphovascular invasion	Yes vs. No	1.40 [1.09; 1.80]	0.009
Perineural invasion	Yes vs. No	2.52 [1.57; 4.05]	<0.001

Table 3. *Cont.*

Characteristics		HR and 95% CI	*p*-Value
Capsular rupture	Yes vs. No	1.47 [1.10; 1.95]	0.008
Venous resection	Yes vs. No	1.41 [1.10; 1.80]	0.007
Portal-vein resection	Yes vs. No	1.41 [1.06; 1.88]	0.020
Superior-mesenteric vein resection	Yes vs. No	1.44 [0.99; 2.10]	0.053
Arterial resection	Yes vs. No	0.78 [0.40; 1.52]	0.5
Postoperative CA 19-9 level	>90 U/mL vs. ≤90 U/mL	1.39 [0.93; 2.1]	0.11
Preneoplastic lesion	Yes vs. No	0.82 [0.66; 1.03]	0.088
Location of preneoplastic lesions	Tumor margin	1.02 [0.58; 1.80]	0.9
	Parenchyma	0.88 [0.69; 1.12]	0.3
	Tumor margin and parenchyma	0.58 [0.37; 0.90]	0.015
IPMN lesions	Yes vs. No	0.63 [0.41; 0.97]	0.038
Grading IPMN	Low or intermediate grade	0.64 [0.26; 1.58]	0.4
	High-grade—Invasive	0.63 [0.38; 1.03]	0.064
PanIn lesions	Yes vs. No	0.97 [0.78; 1.22]	0.8
Grading PanIn	Low or intermediate grade	1.00 [0.74; 1.36]	1
	High-grade	1.04 [0.72; 1.26]	0.7

Abbreviations: IPMN: intraductal papillary mucinous neoplasm; PanIN: pancreatic intraepithelial neoplasia; HR hazard ratio; 95% CI: 95% confidence interval.

Table 4. Multivariate analyses after multiple imputations.

	Full Multivariate Model		Final Multivariate Model *	
	HR and 95% CI	*p*-Value	HR and 95% CI	*p*-Value
Arm				
Gemcitabine	1		1	
mFOLFIRINOX	0.54 [0.43; 0.69]	<0.001	0.56 [0.45; 0.71]	<0.001
Tumor grade				
Well differentiated	1		1	
Moderately differentiated	1.2 [0.93; 1.55]	0.164	1.22 [0.94; 1.57]	0.131
Poorly differentiated or undifferentiated	1.86 [1.28; 2.71]	0.001	1.8 [1.26; 2.57]	0.001
Nodal status				
pN0	1		1	
pN1	1.38 [1.01; 1.89]	0.042	1.46 [1.08; 1.97]	0.014
Status of surgical margins				
R0	1		1	
R1	1.31 [1.04; 1.65]	0.021	1.33 [1.06; 1.67]	0.013
Lymphovascular invasion				
No	1			
Yes	1.1 [0.84; 1.45]	0.468	-	
Perineural invasion				
No	1			
Yes	1.9 [1.16; 3.12]	0.011	1.98 [1.21; 3.23]	0.006
Location of preneoplastic lesions				
Tumor margin	0.91 [0.5; 1.66]	0.757	-	
Parenchyma	0.86 [0.66; 1.11]	0.247	-	
Tumor margin and parenchyma	0.61 [0.38; 0.98]	0.041	-	
IPMN lesions				
No	1			
Yes	0.95 [0.59; 1.53]	0.838	-	

* After backward selection with bootstrap resampling method on each imputed data set. Abbreviations: IPMN intraductal papillary mucinous neoplasm; P; HR hazard ratio; 95% CI: 95% confidence interval.

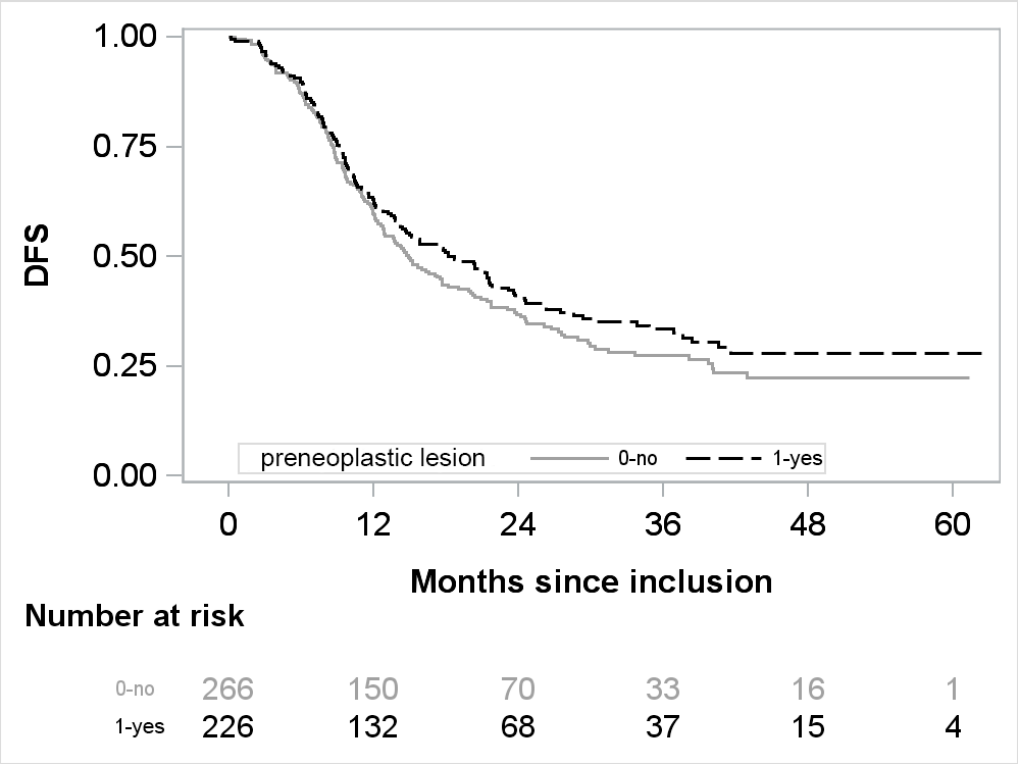

Figure 1. DFS over time regarding the presence or absence of preneoplastic lesion.

4. Discussion

We aimed to identify if the presence of preneoplastic lesions in resected pancreatic cancer specimens affect DFS of the patients included in the international PRODIGE 24-CCTG PA 6 study. In this population, we did not find a significant correlation between DFS and dysplasia at tumor margin or within the pancreatic specimen, neither on a preneoplastic lesion in the resected parenchyma, nor specifically according to the presence of an IPMN or a PanIN. It is worth noting the low number of MCN present, namely none on tumor margin and 0.6% on the rest of the pancreatic tissue.

Based on a large population and robust statistical analysis (multiple imputations combined with bootstrap resampling method), our study confirmed the main prognostic factors already known [3,14–21]. The most important pejorative factors seem to be on the one hand the histological characteristics of the primary tumor, in particular poorly differentiated or undifferentiated grade, pN1 status, presence of capsular rupture, perineural invasion and stage II-III-IV and, on the other hand, surgical factors, including invasive carcinoma on a surgical margin (R1 status) and the need for venous resection.

The rate of IPMN found in our study (8.7% of patients) is consistent with the data in the literature [22–24]. Counterintuitively, the presence of IPMNs associated with carcinoma rather shows a protective effect on DFS. One explanation for this significance in bivariate analysis is the fact that there is more pN0 status and overall, less risk factors in patients with IPMN than without (data not shown). This would come from the fact that a proportion of these patients may have been monitored in a context of known cyst lesion and had surgery for malignant IPMN. Other series also suggest that pancreatic ductal adenocarcinomas derived from IPMN and those concomitant with IPMN are significantly smaller, less invasive, and less extensive than ordinary pancreatic ductal adenocarcinoma [25,26]. Two series undergoing resection for IPMN-associated carcinoma indicated that prognosis of IPMN-associated carcinoma depends on histologic tumor subtype and grading [27,28]. A series of 35 patients having pancreatic resection for cancer aimed to assess the impact of the preneoplastic lesion pattern on survival. The authors reported that PanIN-related carcinomas displayed more aggressive features than IPMN-related carcinomas. Survival

was significantly lower in cancers arising from PanIN preneoplastic lesions [27]. In a large series of 424 patients of IPMN-associated carcinomas, IPMN-ductal adenocarcinomas were diagnosed at more advanced tumor stages, more frequently involved lymph nodes, poorer differentiation and positive-margin resection and were associated with shorter median overall survival than IPMN-colloid carcinoma (26.7 months vs. 91.3 months) [28].

In the extensive review of the expert working group of the International Association of Pancreatology, the mean frequency of invasive IPMNs is 18.5% (6.1–37.7%) in branch duct IPMNs versus 43.1% (11–81%) in main duct IPMNs [29]. So, surgical treatment is recommended in all cases of IPMN with involvement of the main pancreatic duct and if there are high risk factors for malignancy [29–31] or worrisome features with involvement of the branch ducts [32]. Similarly, despite a lower risk of invasive carcinoma (about 13%), surgery is indicated for MCN $\geq$ 40 mm and patients who are symptomatic or have risk factors, such as mural nodule [7,31]

To our knowledge, few studies examined the prognostic impact of dysplasia on resected invasive pancreatic cancer. Frankel et al. addressed this question after pancreatic surgery in a series of 192 patients with non-invasive IPMN [9]. The presence of PanIN on the surgical margin was associated with a nearly doubled rate of recurrence at the remnant pancreas (p = 0.02). When any dysplasia (IPMN or PanIN) was present, the recurrence rate was 31% compared with 12% when the margin was not involved (p = 0.002). This was associated with a significantly decreased DFS (p = 0.001) without significant impact on OS. The meta-analysis by Leng et al. examined the impact of marginal status and lymph node involvement after surgery for invasive and non-invasive IPMN [10]. Out of 11 studies including 339 patients with invasive IPMNs, the incidence of recurrence with invasive IPMNs was 33.9% when margins were negative and 53.7% with positive margins (OR = 0.47; 95% CI: 0.25–0.88, p = 0.02). This significant unfavorable impact on recurrence when the margins were positive was also detected for non-invasive IPMNs: in 701 patients from 12 studies, the recurrence rate in patients with noninvasive IPMNs was 3.7% when margins were negative and 9.6% when margins were positive, a significant difference (OR = 0.37, 95% CI: 0.17–0.78, p = 0.01). Therefore, they recommended that the R0 surgery designation include margin dysplasia. In our study, we did not find any impact on locoregional relapse, but it should be noted that our patients had resection for pancreatic adenocarcinoma and received adjuvant chemotherapy. In the PRODIGE 24 trial, the median DFS in all patients was 15.8 months [14.2–18.9] [3]. Locoregional recurrence was the first event in 22.6% of the patients, locoregional plus distant recurrence occurred in 21% and distant recurrence occurred in 48.4%. This indicates that pancreatic cancer can be regarded as a systemic disease despite resection and adjuvant chemotherapy. This may explain our results: the poor prognosis of the pancreatic cancer largely outweighs the risk of local relapse linked to a preneoplastic lesion. Complementary work on the invasion of the margins by an invasive tumor is in progress to clarify the impact of each positive margin on the risk of local recurrence, in particular after Whipple resection.

One limitation of our trial is the short follow-up of 33.6 months. However, in the PRODIGE 24 updated 5-year analysis [33], local recurrence as first event occurred early at a median of 12.4 months (95% CI, 9.5–15.2 months), with no difference between local and metastatic relapse (10.2 months; 95% CI, 9.3–13.7), and we do not think that a longer follow-up should change these data.

The strength of our results lies in the large cohort of patients from a prospective, multicenter and international trial [3]. One limitation is that our conclusions are not based on OS but only on DFS. Even if it is not a validated surrogate endpoint for OS, it provides an earlier and robust outcome, especially for pancreatic cancers where death is both early and frequent.

5. Conclusions

In this post-hoc analysis of the PRODIGE 24 CCTG PA 6 trial, the presence of dysplasia (TIPMP, MCN or PanIN) in the surgical specimen, regardless of its grade of differentiation

and location, has no deleterious effect on DFS in patients operated for pancreatic cancer and receiving adjuvant chemotherapy.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Institut de Cancérologie de Lorraine. This study was declared to the French National Commission on Informatics and Liberties (CNIL) and received prior authorization from the sponsor of the trial Unicancer.

Informed Consent Statement: Written patient consent was waived for this study because they have already signed consent in the pivotal study PRODIGE 24-CCTG PA 6 and for subsequent analyses.

Data Availability Statement: The data can be shared up on request.

Conflicts of Interest: The authors declare no conflict of interest.

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Publication 5 – Impact of positive resection margins on recurrence and survival following resection and adjuvant chemotherapy in pancreatic cancer: results of the PRODIGE 24-CCTG PA-6 trial

Article original

***Aurélien Lambert**, Julia Salleron, Alexandre Harlé, James J. Biagi, Agnès Leroux, Jacques Thomas, Laure Monard, Jérôme Cros, Frédéric Marchal, Ahmet Ayav, Thierry Conroy. Impact of positive resection margins on recurrence and survival following resection and adjuvant chemotherapy in pancreatic cancer: results of the PRODIGE 24-CCTG PA-6 trial. Annals of Surgery (submission 2022).*

Cette analyse traite du cœur de ce sujet concernant l'impact des marges de résection chirurgicale chez les patients opérés d'un adénocarcinome pancréatique dans le cadre de l'essai randomisé PRODIGE 24/ CCTG PA6.

La question était de savoir si l'envahissement d'une marge chirurgicale avait un impact sur la survie sans rechute ou la récidive locale et si la qualité et l'exhaustivité des marges était importante.

Nous avons pour cela analysé l'ensemble des dossiers (comptes-rendus anatomopathologiques et opératoires) ainsi que les données de l'étude issues des CRF pour évaluer ce facteur pronostique.

Pour répondre à la question de façon précise, nous avons fait le choix d'exclure les patients qui n'avaient pas bénéficié d'une duodénopancréatectomie céphalique (ou geste apparenté) étant donné le peu de pertinence de certaines marges lors des autres gestes (par exemple les marges duodénales ou vésiculaires ont peu d'importance en cas de splénopancréatectomie gauche).

Ceci nous laissait exactement 400 dossiers (sur 493) d'intérêt pour analyse.

Il nous est apparu lors de ce travail que 3 marges d'intérêt étaient de meilleur pronostique que les autres (la marge médiale, le lit de la veine mésentérique supérieure et la marge postérieure).

Nous avons également démontré que l'analyse de ces 3 marges d'intérêt était comparable à un recueil exhaustif des 7 marges recommandées par les référentiels.

Enfin nous avons pu trouver une hypothèse sérieuse expliquant la différence en termes de survie sans rechute et survie globale dans les deux bras de l'étude. Le mFOLFIRINOX rattrapant probablement l'impact des marges envahies localement et gommant ainsi l'effet des résections R1 comparé au bras gemcitabine qui lui restait significatif sur de facteur pronostique.

Impact of positive resection margins on recurrence and survival following resection and adjuvant chemotherapy in pancreatic cancer: results of the PRODIGE 24-CCTG PA-6 trial.

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Keyword

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, and the only potentially curative therapy is surgical resection; however, only 10-15% of patients present with upfront resectable tumors. Even after resection, most of the patients develop recurrence and median survival after surgery and adjuvant chemotherapy was 18.8 months in a recent meta-analysis[1]. Positive resection margins are generally accepted as a risk factor for tumor recurrence and as a poor prognostic factor for survival[2–6]. However, data are incongruent and when using for R1 definition the presence of microscopic residual tumor on the surgical edges of the specimens, resection margin direct invasion is not constantly a significant prognostic factor[7].

Adoption of a rigorous standardized pathological assessment with a minimum tumor clearance of 1 mm from tumor cells to the margin significantly increased the R1 rate for PDAC and help to better evaluate this key prognostic factor[8–11]. The International Study Group of Pancreatic Surgery also recommended to use this cut-off margin of 1 mm or less for the R1 definition[12], and more recently the International Collaboration on Cancer Reporting also endorsed the 1mm rule[13]. To better assess the status of resection margins, both the UK Royal College of Pathologists and the American Joint Committee on Cancer manual recommend inking the anterior, medial, and retroperitoneal margins of surgical specimens[10,14]. They recommend surgeons and pathologists to identify seven margins for pancreaticoduodenectomy resection: bile duct, pancreatic neck, proximal duodenum (enteric), distal duodenum, superior mesenteric vein (SMV) groove (retroportal), superior mesenteric artery (SMA)/uncinate or medial and posterior pancreas (retroperitoneal). For distal pancreatectomy, margins to examine are transection pancreatic margin, transection splenic vessels, anterior pancreatic surface and posterior margin[15]. Tumor clearance should be provided for all these margins.

Therefore, within standardized pathology protocols, the independent prognostic relevance for overall survival of R0 versus R1 resection was confirmed retrospectively first for pancreatic head cancers[16], then for cancers of the body and tail[17]. The presence of multiple positive margins is a risk factor for PDAC recurrence and for poor survival and the different surgical margins may have different prognostic roles[18]. However, information on all resection margins is difficult to obtain because of anatomical complexity and disparities in local handling of the specimens. This may have potentially important consequences for subsequent treatments and for groups' comparability of randomized controlled trials on resected PDAC as controlled trials generally stratify on resection margin status.

The PRODIGE [Partenariat de Recherche en Oncologie Digestive] 24-CCTG PA [Canadian Cancer Trials Group Pancreatic Adenocarcinoma]-6 trial is a randomized multicentric controlled Phase 3 study comparing modified FOLFIRINOX (mFOLFIRINOX) regimen versus gemcitabine as adjuvant chemotherapy in patients after complete resection of a PDAC. With a median follow-up of 69.7 months, disease-free survival (DFS), the primary objective, was 21.4 months in the mFOLFIRINOX group versus 12.8 months in the gemcitabine group (stratified hazard ratio for cancer-related event, second cancer, or death, 0.66; 95% confidence interval [CI], 0.54 to 0.82; P<0.001)[19].

The primary objective of this study was to analyze the prognostic value of margins involvement on disease recurrence and disease-free survival in PDAC patients who have benefited from a pancreaticoduodenectomy or total pancreatectomy for a tumor of the head and/or body of the pancreas. Secondary objectives were to investigate whether the absence of reporting the status of some margins has a similar prognosis than a R1 resection, and to evaluate whether positive resection margins are related to other clinical or pathological prognostic factors.

To answer these questions, we identified three subpopulations:
(1) The “accurate $R0_7$” subgroup that contains patients with all 7 margins examined and no positive margins, so the R0 classification is accurate.
(2) The “accurate $R1_7$” subgroup that contains patients with at least one involved margin, so the R1 classification is accurate.
(3) The “presumed $R0_7$” subgroup that contains tumors with less than 7 margins documented and none of them involved, therefore the R0 classification is "presumed".

Patients and Methods

In PRODIGE 24-CCTG PA-6 trial, patients had to have histologically proven PDAC that had been macroscopically resected. Patients were randomly assigned to each treatment arm on a 1:1 basis with the use of a centrally independent Web-based system, using a computer-generated variable-size blocked randomization method with stratification according to center, lymph-node status, resection status (R0 versus R1), and postoperative CA 19-9 level. The primary outcome measure was DFS and the secondary endpoints were overall survival (OS),

metastasis-free survival, cancer-specific survival, and safety. Histopathological data and R status was collected prospectively before registration into the trial as the resection status was a stratification factor. Recommendations were made for surgeons and pathologists to orient tumor specimen so the resection limits could be clearly identified. During Whipple procedure pancreatic neck margin was checked by frozen section. In case of positivity, an additional resection was advised until a negative margin was obtained. The final pancreatic neck margin (also called transection margin) was identified with strings. Protocol recommended that the surgeon prepared the tumor specimen by inking the resection margins, especially SMV groove, SMA, and posterior pancreas using different tissue-marking dyes. If the surgeon has not already done so, the pathologist inked these margins. Each participating center defined local organization for preparation and inking the tumor specimens. Axial slicing of the surgical specimen perpendicular to the long axis of the duodenum was performed[8].

Tumor stage was assessed according to the 2009 TNM classification, 7th edition[20]. R1 was defined as direct infiltration of tumor margin or any cancer cell present within 1 mm of one or more resection margins. Margins to examine included the transection margins of pancreas, bile duct, proximal gastric or duodenum, distal duodenum or jejunum, the SMV groove, the medial margin (SMA) and the posterior pancreatic margin. Each margin was classified as >1 mm or ≤ 1 mm. The anterior surface of the pancreas was not considered as a surgical margin but extension beyond this surface was classified as pT3. All patient imaging, surgical reports, and histology reports were centrally reassessed by an external review committee including pathologists, surgeons, radiologists and medical oncologists to check the major prognostic factors. Centralized review of pathology reports included inking of retroperitoneal margins, maximum size of the primary tumor, histotype, tumor grading, presence of vascular or perineural invasion, number of regional lymph nodes invaded/retrieved, paraaortic lymph nodes invasion, pTNM classification, resection margins (bile duct, pancreatic neck transection, proximal gastric, distal duodenal, SMV groove, medial and posterior/retroperitoneal), and completeness of excision. Two authors checked separately each pathology report using a standardized data pathology form. Disagreement between data extractors was resolved by multidisciplinary discussion between expert reviewers.

All patients received adjuvant chemotherapy, either gemcitabine or mFOLFIRINOX for 6 months after resection of pancreatic ductal adenocarcinoma.

Statistical analysis

Qualitative parameters were described as frequencies and percentages. DFS was defined as time interval between the date of randomization and the date of locoregional relapse/recurrence or occurrence of distant metastases (liver or non-liver) or appearance of second pancreatic cancer or death (all causes), whichever occurs first[21]. The agreement between R_3 and R_7 was assessed by the Cohen's kappa coefficient. A kappa value greater than 0.8 was considered as as almost perfect agreement[22]. DFS was described by the Kaplan-Meier method. Prognostic factors and some interactions were tested using the Cox proportional hazard model (CPHM) in bivariate analyses adjusted on treatment arm. All parameters with a p-value less than 0.1 were included in multivariate CPHM. Due to missing values, multiple imputations (MI) on patient and tumor characteristics were performed[23]. Multiple pilot runs of various numbers of imputations were performed to assess the number of imputations and the stability of the parameter estimates for a given number of imputations. The number of 6 imputations was defined according to the fraction of missing information and the relative efficiency[24]. The following method was applied: (a) multiple imputation using fully conditional specification was performed on 6 datasets using the proc mi in SAS, version 9.4; the multiple imputation model was performed on all described patient and tumor characteristics. The DFS time were also included; (b) The 6 hazard ratios were then combined across imputed datasets with the proc mi analyze. A confirmatory analysis was performed on completed cases without MI.

A sensitivity analysis was performed in each treatment arm: the same parameters identified in bivariate analyses in the whole population were used in the multivariate analyses.

As exploratory analyses, the Time to local recurrence (TLR) and the Distant Metastasis Free Survival (DMFS) were described in each treatment arm and compared according to R_3 status. TLR was defined as the time interval between the date of randomization and the date of locoregional relapse/recurrence whichever occurs first[21]. TLR was described with cumulative incidence methods while considering distance metastases or second cancer or death as competing risks. The impact of patient and tumor characteristics on TLR was evaluated using the Fine and Gray test[25]. DMFS was defined as the time interval between the date of randomization and the date of the occurrence of distant metastases (including liver and non-liver metastases) or death (all causes), whichever occurs first[21]. DMFS was analyzed with Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using SAS software v9.4 (Institute Inc., Cary, NC 25513). P-values <0.05 were considered statistically significant.

Results

From April 2012 through October 2016, a total of 493 patients at 77 centers in France and Canada from university hospitals, comprehensive cancer centers, general public hospitals, and private hospitals were randomized to receive the mFOLFIRINOX regimen or gemcitabine. Median follow-up was 33.6 months. A copy of the original surgery and pathology reports was available for central review in 492 patients (99.8%). One pathological report is lacking. Margin inking was performed in 64.9% of cases. Misclassification of the R1 status concerned 24.1% of the files, mainly due to inadequate R0 classification when microscopic residual tumor was very close to the resection margin with 1 mm or less than 1 mm tumor distance.

Of the 493 patients in the PRODIGE 24-CCTG PA-6 trial, 93 were excluded (84 had a distal pancreatectomy; 7 had a distal pancreatectomy; 1 had a central pancreatectomy; 1 had a central and distal pancreatectomy). 197 patients were in the gemcitabine arm and 203 in the mFolfirinox arm. Among these 400 patients included in the study, the median number of margins documented was 6, IQR (inter-quartile range 5-7). 214 patients (53.5%) had less than 7 margins reported. Median follow-up of these 400 patients was 23 months, IQR (16-35). Characteristics of the population are presented in Table 1.

Classification according to R_7 status was as follow:

(1) The "accurate $R0_7$" subgroup contained 92 patients.

(2) The "accurate $R1_7$" subgroup contained 190 patients (94/190 (49.5%) with 7 margins examined and 96/190 (50.5%) with less than 7 margins reported).

(3) The "presumed $R0_7$" subgroup contained 118 patients. The median number of margins documented was 5, IQR (4-5).

The resection margins were not documented on the bile duct in 5% of cases, on the pancreatic neck transection in 3.3% of the cases, 13% on the proximal duodenum, 10.8% on the distal duodenum, 22.5% on the SMV groove, 38.8% on the SMA and 28% on the posterior margin respectively; excluding these patients with not documented data, the most frequent margin involvement was on the SMV groove (28.3%), on the posterior margin (21%), on the SMA (14.5%) and on pancreatic neck transection (5.3%). Involvement of the bile duct margin, proximal duodenum and distal duodenum was rare, 1.5%, 0% and 0.25% of the tumors respectively (Table 2).

DFS at 5 years was 34.1%; 95% CI [26.1; 42.2] in the mFOLFIRINOX arm and 16.1%; 95% CI [9.9; 23.6] in the gemcitabine arm (p<.001) with a median follow-up time of 23 months, IQR (16-35).

The impact of each margin on DFS after adjustment on treatment arm is presented in Table 2. Only three margins, the SMV groove, the medial and the posterior pancreas, had a significant prognostic impact on DFS. Considering only those 3 margins, 209/400 patients (52.2%) had these 3 margins reported and classification according to R_3 status was as follow:

(1) The "accurate $R0_3$" subgroup contained 110 patients.

(2) The "accurate $R1_3$" subgroup contained 180 patients (99/180 (55%) with the 3 major margins reported and 81/180 (45%) with less than 3 margins reported.

(3) The "presumed $R0_3$" subgroup contained 110 patients (strictly less than 3 margins reported).

The R0/R1 status would be modified for 25 patients (6.3%) between R_3 (resection with the 3 prognostic margins examined) and R_7 (resection with all 7 margins examined) classifications. The Kappa between the R_3 and R_7 classification is excellent: 0.90, 95% CI [0.87; 0.94] (Table 3). Of the 190 accurate $R1_7$ patients, 180 patients were also classified as $R1_3$ and 10 patients would be classified as presumed $R0_3$. Of the 118 presumed $R0_7$ patients, 15 would be considered as accurate $R0_3$ and 103 would be considered presumed $R0_3$ (Table 3).

Prognostic factors for DFS in bivariate analysis for the 400 patients adjusted on the study arm (mFOLFIRINOX or gemcitabine) and resection quality with 3 or 7 margins are presented in Table 4. The Uno's Concordance Statistic for arm only was 0.56, 95% CI [0.53; 0.59]. It was significantly higher by adding R_3 (0.59, 95% CI [0.551; 0.62], p=.020) or R_7 (0.59, 95% CI [0.56; 0.63], p=.016) in the model without significant difference between R_3 and R_7 (p=.757).

Multivariate analyses to predict DFS are presented in Table 5. In multivariate analysis for R_3, and comparatively to accurate $R0_3$, $R1_3$ was significantly associated with a poorer DFS (HR=1.66 [1.2; 2.3]; p=.002) and presumed $R0_3$ was not (HR=1.39 [0.96; 2]; p=.078). DFS according to R3 status is presented Figure 1. Consistent results were found for R_7 (HR=1.41 [0.96; 2.06]; p=.08 for $R1_7$ and 1.41 [0.96; 2.06]; p=.08 for presumed $R0_7$ respectively). Multivariate analyses without imputation on the 282 complete cases are presented in supplementary appendix.

The interaction between arm and R_3 was not significant (p=.440). In multivariate analyses, DFS was significantly different according to the R_3 classification in the gemcitabine arm but not in the mFOLFIRINOX arm (Table 6, Figures 2a-2b)**.** Consistent results according to R_7 are presented in supplementary table.

In the gemcitabine arm, the cumulative incidence of LR at 5 years was 40.0%, 95% CI [22.7; 57.0] for accurate $R0_3$ patients and 54.1%, 95% CI [40.8; 65.6%) for $R1_3$ patients (p<.001). In the mFolfirinox arm, it was 21.2%, 95% CI [11.2; 33.3] for accurate $R0_3$ patients and 40.0%, 95% CI [27.7; 52.1%) for $R1_3$ patients (p=.063).

The impact of R_3 on DMFS was significant in the gemcitabine arm (p=.012) and not in the mFOLFIRINOX arm (p=.460, Figures 2c-2d). In the gemcitabine arm, the DMFS at 5 years was 18.5%, 95% CI [4.5; 39.8] for accurate $R0_3$ patients and 7.7%, 95% CI [1.9; 19.2] for accurate $R1_3$ patients. In the mFOLFIRINOX arm, it was 53.8%, 95% CI [39.2; 64.4] at 5 years for accurate $R0_3$ patients and 43.6 %, 95% CI [32.0; 54.6] for accurate $R1_3$ patients.

Discussion

To better assess the major prognostic factors, an independent quality control of all the pathological reports was carried out before the first analysis of the PRODIGE 24-CCTG PA6 study results[26], making it possible to standardize the classification in R0 or R1 considering the invasion or not of each surgical margin using the minimum 1-mm margin definition. We present here the results of the 400 pancreaticoduodenectomy resection specimens. The trial protocol planned the examination of 7 margins on pancreaticoduodenectomy specimens. Among the 77 French and Canadian hospitals with different status and experience participating in the study, compliance with pathology requirements was good, with a median number of six margins status documented (inter-quartile range 5-7). Inking of margins was also performed as requested in 64.9% of the cases.

In our study, the overall rate of margin involvement was 47.5% (190 R1 cases out of 400), with the most commonly involved margin being the SMV groove margin (113 cases; 36.5%), the posterior margin (84 cases; 29.2%) followed by the medial margin (58 cases; 23.7 %). Pancreatic neck transection margin was involved in only 5.3% of the cases. However, this low rate of involvement probably reflects the use of intraoperative frozen-section examination of that margin. This is also in line with the 9% rate observed in the ESPAC-3 study[27]. Bile duct margin or proximal and distal duodenum margins were very rarely involved, in 1.5%, 0% and

0.25% of the tumors respectively. The examination of the distal transection margin was previously reported as virtually always irrelevant[28].
When positive, only three margins (SMV groove, medial and posterior) were significant factors for prognosis in unifactorial analysis (all $p<0.01$). When combined, one positive margin among these three margins (R1 status) has an independent prognostic value in multivariable analysis. Gemcitabine group, poor tumor differentiation, positive lymph node status, capsular rupture, perineural invasion, postoperative CA 19-9 level >90 U/ml and accurate R1 status were all independently significantly associated with reduced DFS.

The prognostic impact of an involved margin out of the examined 7 margins is also major in the gemcitabine group, with a hazard ratio of 2.09 [1.26; 3.46; $p=0.004$] and hazard ratio remains comparable when only the 3 prognostic margins (SMV groove, medial and posterior) are considered, 1.97 [1.23; 3.16]. However, all identified potential prognostic factors, including R1 resection, had no prognostic value in the mFOLFIRINOX group. In the PRODIGE 24/ CCTG PA6 trial, R1 status was not a prognostic factor in multifactorial analysis, either for DFS or for OS[19,26]. However, as all the seven recommended margins were not reported for all patients, the R1 status may have been underestimated. The low number of R1 resections in the PRODIGE 24/ CCTG PA6 trial (42.8%) and in this pancreaticoduodenectomy subgroup (47.5%) compared with the recent literature supports this hypothesis[27,29].

Few studies have examined the prognostic implications of each cut surface. In a Dutch study with a total of 322 patients undergoing pancreatectomy, prognostic factors for OS were involved lymph nodes, adjuvant chemotherapy, perineural invasion and R1 resection margin. However, the location of the R1 margin had no statistically significant association with OS and locoregional recurrence[30]. Delpero *et al.* [31] also found that a positive posterior margin had no impact on progression-free survival in patients after pancreaticoduodenectomy. Conversely, data from 1151 patients from the ESPAC-3 trial[27] having pancreatic resection with any procedure (pancreaticoduodenectomy, distal pancreatic resection or total pancreatectomy) showed that R1-direct involvement of posterior margin was associated with shorter OS in multivariable analyses; involvement of proximal gastric, posterior resection, medial, or pancreatic transection margins were associated with shorter recurrence-free survival, but not with reduced OS. Tumor involvement of the anterior surface had no prognostic value for either recurrence-free survival or OS. Analyses from ESPAC-3 also showed that patients with

involved lymph nodes were more likely to have positive R1 resection margins (either an R1-direct or an R1<1mm margin). R1-direct invasion of the medial margin was associated with local recurrence, but not R1 using the <1 mm definition[27]. Delpero *et al.*[32] showed in subgroups analysis that clearance of 1.0 mm or less and 1.5 mm or less for at least one positive margin was an independent determinant of decreased survival after pancreaticoduodenectomy in patients who did not receive neoadjuvant therapy; however, the R1 status of medial margin was not a significant predictor of survival. In a prospective institutional cohort of 174 pancreaticoduodenectomies, medial margin involvement was associated with a better median survival when compared with posterior margin involvement (31.0 months versus 14.8 months)[16]. The infiltration at the anterior surface had no negative impact on overall survival.
Another multicenter study assessed margin clearance prognosis on 531 pancreaticoduodenectomies[33]. Patients with a margin clearance of 1 mm or more demonstrated a significant survival advantage versus direct microscopic involvement (0 mm margin). Patients with any positive margin, positive SMA/uncinated margin, or positive posterior retroperitoneal margin had a poorer prognostic as compared to those with R0 resection. Patients with a positive SMA margin had a trend towards worse survival.
One important point of our study is the description of an independent prognostic value of the SMV groove margin which has not been previously described to our knowledge.

A recent metanalysis[34] also confirmed the prognostic significance of the new definition of R0 resection, from 8 studies using multivariate analysis and having included a total of 3568 patients. R0 resection was significantly associated with an improved median OS (HR 1.36, 95% CI 1.23-1.51). Among these, only three studies used exclusively pancreaticoduodenectomies to analyze the association of OS and margin status[30,32,33].
The strengths of this study should be highlighted: data are coming from an international trial with extensive quality review of the surgical and pathologic data; all surgical procedures included pancreaticoduodenectomy, permitting assessment of prognostic value of identical margins; all patients received adjuvant chemotherapy.

The limitations of our study are as follows: first, no pathological central review was planned according to trial protocol. However, pathological reports were centrally reviewed by an external committee including pathologists and surgeons to standardize the results. Second, no data are available on anterior surface which was not identified as a margin according to the protocol. Finally, R1 status was probably underestimated, and patients with presumed R0 with

some margins not examined had an intermediate prognostic between R0 with accurate assessment of all margins and R1.

Conclusion

In light of this work, we consider that every effort should be made to evaluate the 3 margins of highest prognosis (SMV groove, medial and posterior pancreas), the others being secondary. The prognostic value of one of these 3 margins is important, however, if any of them is missing, it will affect the possibility of prediction.

A finding of this work is the likely effect of mFOLFIRINOX on local invasion in operated patients. Indeed, it seems that this chemotherapy regimen (unlike gemcitabine) corrects the impairment related to margin involvement, probably explaining all or part of the improvement of DFS[26] and OS[19]. Thus, the value of additional therapies, such as cloture radiotherapy in patients with unknown marginal status or in those who did not benefit from chemotherapy with mFOLFIRINOX, can still be evaluated. A patient who has received mFOLFIRINOX as adjuvant treatment for pancreatic cancer after surgery and whose margins are not involved is less likely to benefit from cloture therapy and more likely to recur with a distant metastasis.

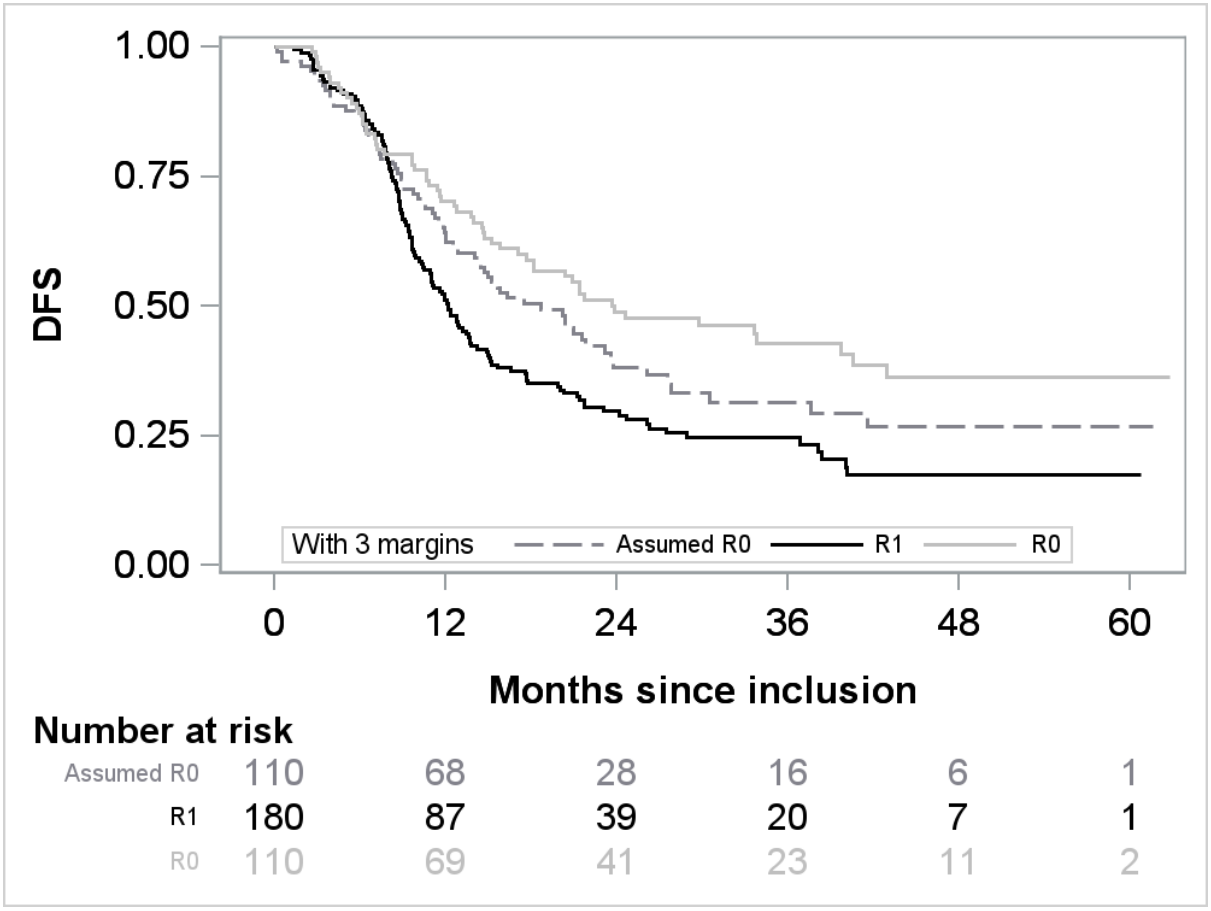

Figure 1. DFS according to the 3 margins status.
DFS: Disease free survival

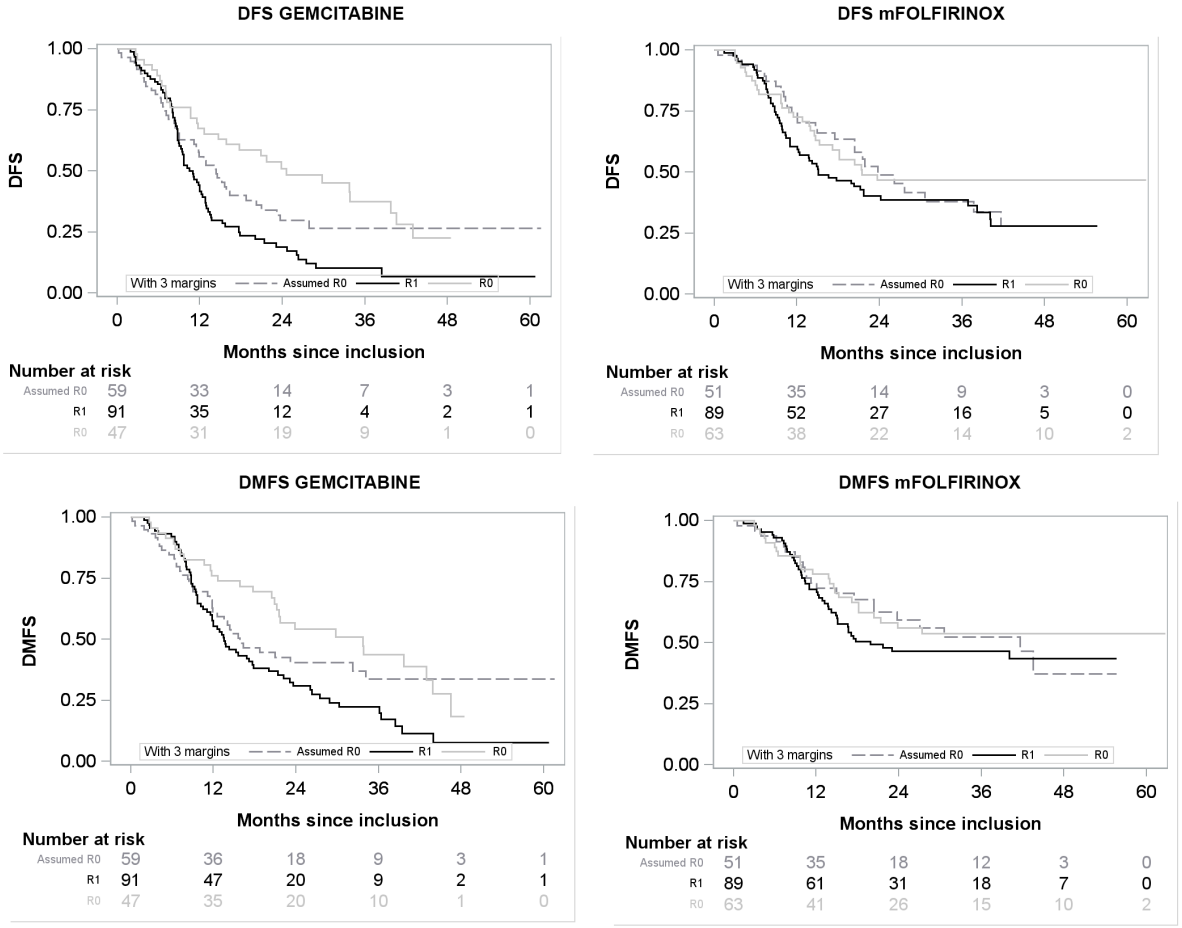

Figure 2. a) DFS in the gemcitabine arm; b) DFS in the mFOLFIRINOX arm; c) DMFS in the gemcitabine arm; d) DMFS in the mFOLFIRINOX arm.
DFS: Disease free survival; DMFS: Distant metastasis free survival

Table 1: Characteristics of the 400 patients who underwent Whipple resection.

Arm	
Gemcitabine	197/400 (49.2%)
mFolfirinox	203/400 (50.8%)
Age ≥65	163/400 (40.7%)
Male sex	235/400 (58.7%)
WHO performance status score	
0	193/400 (49.0%)
1	201/400 (51.0%)
Diabetes mellitus	96/395 (24.3%)
Tumor location	
Head	367/396 (92.7%)
Other	29/396 (7.3%)
Tumor histologic findings	
Ductal adenocarcinoma	396/400 (99.0%)
Nonductal carcinoma	4/400 (1.0%)
Tumor grade	
Well differentiated	123/382 (32.2%)
Moderately differentiated	209/382 (54.7%)
Poorly differentiated or undifferentiated	50/382 (13.1%)
Primary tumor status	
pT1 or pT2	41/400 (10.2%)
pT3 or pT4	359/400 (89.8%)
Nodal status	
pN0	78/400 (19.5%)
pN1	322/400 (80.5%)
Tumor stage	
IA or IB	15/400 (3.8%)
IIA or IIB	373/400 (93.2%)
III or IV	12/400 (3.0%)
Lymphovascular invasion	255/350 (72.9%)
Perineural invasion	343/372 (92.2%)
Capsular rupture	62/351 (17.7%)
Surgery	
Venous resection	104/398 (26.1%)
Portal-vein resection	68/400 (17.0%)
Superior-mesenteric vein resection	42/400 (10.5%)
Arterial resection	8/400 (2.00%)
Status of surgical margins	
R0	210/400 (52.5%)
R1	190/400 (47.5%)
Postoperative CA 19-9 level	
≤90 U/ml	368/400 (92.0%)
>90 U/ml	32/400 (8.0%)

Table 2. Description and impact of each margin on disease-free survival, bivariate analysis adjusted for treatment arm among the 400 patients.

	N (%)	HR and 95% CI	p-value
Bile duct			
Healthy	374 (93.5%)	1	
Involved	6 (1.5%)	1.37 [0.56;3.35]	.486
Unknown	20 (5%)	1.27 [0.73;2.24]	.398
Pancreatic neck transection			
Healthy	366 (91.5%)	1	
Involved	21 (5.25%)	0.95 [0.53;1.7]	.865
Unknown	13 (3.25%)	1.16 [0.62;2.19]	.646
Proximal duodenum (enteric)			
Healthy	348 (87%)	1	
Involved	0	-	
Unknown	52 (13%)	0.93 [0.63;1.37]	.703
Distal duodenum			
Healthy	356 (89%)	1	
Involved	1 (0.25%)	1.42 [0.2;10.21]	.725
Unknown	43 (10.75%)	1.02 [0.68;1.55]	.916
SMV groove (retroportal)			
Healthy	197 (49.25%)	1	
Involved	113 (28.25%)	1.48 [1.11;1.96]	.007
Unknown	90 (22.5%)	1.22 [0.89;1.68]	.208
SMA (medial)			
Healthy	187 (46.75%)	1	
Involved	58 (14.5%)	1.92 [1.36;2.73]	<.001
Unknown	155 (38.75%)	1.25 [0.96;1.64]	.102
Posterior (retroperitoneal)			
Healthy	204 (51%)	1	
Involved	84 (21%)	1.65 [1.21;2.24]	.002
Unknown	112 (28%)	1.22 [0.91;1.63]	.187

Table 3: Comparison between the analysis with 3 margins and 7 margins.

	Accurate $R0_7$	Accurate $R1_7$	Presumed $R0_7$	Total
Accurate $R0_3$	92 (23.0%)	3 (1.6%)	15 (3.8%)	110
Accurate $R1_3$	0	180 (45.0%)	0	180
Presumed $R0_3$	0	7 (1.8%)	103 (25.8%)	110
Total	92	190	118	400

Table 4. Prognostic factors for DFS in bivariate analysis for the 400 patients adjusted on the study arm (mFOLFIRINOX).

	HR and 95% CI	p-value
Age ≥65	1.02 [0.79;1.3]	.901
Male sex	0.95 [0.74;1.21]	.668
WHO performance status score		
0	1	
1	1.11 [0.87;1.42]	.408
Diabetes mellitus	0.98 [0.74;1.31]	.899
Tumor location		
Head	1.1 [0.69;1.76]	.701
Other	1	
Tumor histologic findings		
Ductal adenocarcinoma	0.77 [0.29;2.07]	.603
Nonductal carcinoma	1	
Tumor grade		
Well differentiated	1	
Moderately differentiated	1.19 [0.9;1.58]	.218
Poorly differentiated or undifferentiated	1.6 [1.07;2.4]	.022
Primary tumor status		
pT1 or pT2	1	
pT3 or pT4	1.2 [0.79;1.81]	.391
Nodal status		
pN0	1	
pN1	2.13 [1.49;3.05]	<.001
Tumor stage		
IA or IB	1	
IIA or IIB	1.89 [0.89;4]	.098
III or IV	7.96 [2.93;21.59]	<.001
Lymphovascular invasion	1.46 [1.08;1.99]	.015
Perineural invasion	2.93 [1.59;5.38]	.001
Capsular rupture	1.64 [1.19;2.26]	.003
Postoperative CA 19-9 level		
≤90 U/ml	1	
>90 U/ml	1.7 [1.11;2.58]	.014
Status of surgical margins		
R0	1	
R1	1.53 [1.2;1.96]	.001
Actual quality of resection with 7 margins		
Accurate $R0_7$	1	
Presumed $R0_7$	1.33 [0.92;1.92]	.130
$R1_7$	1.8 [1.29;2.52]	.001
Actual quality of resection with 3 margins		
Accurate $R0_3$	1	
Presumed $R0_3$	1.29 [0.91;1.84]	.153
$R1_3$	1.81 [1.32;2.48]	<.001

Table 5. Multivariate analyses after multiple imputation.

	7 margins		3 margins	
	HR and 95% CI	p-value	HR and 95% CI	p-value
Arm				
Gemcitabine	1		1	
mFOLFIRINOX	0.55 [0.43; 0.71]	<.001	0.56 [0.43; 0.72]	<.001
Tumor grade				
Well differentiated	1		1	
Moderately differentiated	1.21 [0.91; 1.61]	0.181	1.22 [0.92; 1.63]	0.162
Poorly differentiated or undifferentiated	1.66 [1.11; 2.49]	0.013	1.68 [1.13; 2.52]	0.011
Nodal status				
pN0	1		1	
pN1	1.61 [1.1;2.36]	0.015	1.58 [1.08;2.32]	0.02
Lymphovascular invasion	1.10 [0.79;1.54]	0.556	1.09 [0.78;1.52]	0.612
Perineural invasion	1.86 [1;3.45]	0.049	1.91 [1.03;3.54]	0.04
Capsular rupture	1.48 [1.06;2.06]	0.022	1.48 [1.06;2.06]	0.023
Postoperative CA 19-9 level				
≤90 U/ml	1		1	
>90 U/ml	1.83 [1.16;2.87]	0.009	1.81 [1.15;2.84]	0.01
Actual resection margin status				
Accurate R0	1		1	
Presumed R0	1.41 [0.96;2.06]	0.08	1.39 [0.96;2]	0.078
Accurate R1	1.66 [1.18;2.34]	0.004	1.66 [1.2;2.3]	0.002

Table 6. Multivariate analyses for DFS stratified on treatment arm with R_3 status adjusted on prognostic factors after multiple imputation.

	Gemcitabine arm (n=197)		**mFOLFIRINOX arm (n=203)**	
	HR and 95% CI	p-value	**HR and 95% CI**	p-value
Tumor grade				
Well differentiated	1		1	
Moderately differentiated	1.05 [0.71;1.56]	0.805	1.36 [0.88;2.11]	0.17
Poorly differentiated or undifferentiated	1.69 [0.98;2.93]	0.061	1.74 [0.93;3.24]	0.082
Nodal status				
pN0	1		1	
pN1	1.68 [0.98;2.86]	0.058	1.36 [0.77;2.4]	0.292
Lymphovascular invasion	1.24 [0.8;1.93]	<.001	0.94 [0.58;1.54]	0.817
Perineural invasion	2.92 [1.16;7.37]	0.024	1.06 [0.45;2.47]	0.895
Capsular rupture	1.53 [0.93;2.49]	0.091	1.37 [0.75;2.5]	0.301
Postoperative CA 19-9 level				
≤90 U/ml	1		1	
>90 U/ml	2.02 [1.06;3.85]	0.033	1.71 [0.89;3.3]	0.11
R_3 status				
Accurate $R0_3$	1		1	
Presumed $R0_3$	1.75 [1.05;2.93]	0.033	1.19 [0.68;2.07]	0.54
Accurate $R1_3$	1.97 [1.23;3.16]	0.005	1.46 [0.91;2.35]	0.114

Supplementary Table: Multivariate analyses without multiple imputation on the 282 complete cases

	7 margins		3 margins	
	HR and 95% CI	p-value	HR and 95% CI	p-value
Arm				
Gemcitabine	1		1	
mFOLFIRINOX	0.5 0[0.37;0.67]	<0.001	0.51 [0.37;0.69]	<0.001
Tumor grade				
Well differentiated	1		1	
Moderately differentiated	1.25 [0.89;1.76]	0.199	1.25 [0.89;1.76]	0.191
Poorly differentiated or undifferentiated	1.99 [1.22;3.26]	0.006	2.07 [1.27;3.38]	0.004
Nodal status				
pN0	1		1	
pN1	1.68 [1.07;2.64]	0.025	1.61 [1.02;2.53]	0.039
Lymphovascular invasion	1.28 [0.89;1.84]	0.177	1.26 [0.88;1.82]	0.207
Perineural invasion	1.57 [0.76;3.27]	0.225	1.63 [0.79;3.39]	0.187
Capsular rupture	1.61 [1.11;2.34]	0.012	1.63 [1.12;2.36]	0.011
Postoperative CA 19-9 level				
≤90 U/ml	1		1	
>90 U/ml	1.83 [1.02;3.29]	0.044	1.82 [1.01;3.28]	0.046
Actual resection margin status				
Accurate R0	1		1	
Presumed R0	1.59 [1.02;2.5]	0.043	1.56 [1.01;2.41]	0.043
Accurate R1	1.76 [1.19;2.61]	0.005	1.78 [1.23;2.58]	0.002

Supplementary Table: Multivariate analyses for DFS stratified on treatment arm with R_7 status adjusted on prognostic factors after multiple imputation The interaction between arm and R_7 was not significant (p=.430).

	Gemcitabine arm (n=197)		**mFOLFIRINOX arm (n=203)**	
	HR and 95% CI	p-value	**HR and 95% CI**	p-value
Tumor grade				
Well differentiated	1		1	
Moderately differentiated	1.02 [0.69;1.52]	0.914	1.35 [0.87;2.09]	0.188
Poorly differentiated or undifferentiated	1.71 [0.99;2.96]	0.056	1.7 [0.92;3.17]	0.092
Nodal status				
pN0	1		1	
pN1	1.74 [1.02;2.97]	0.042	1.37 [0.78;2.43]	0.275
Lymphovascular invasion	1.26 [0.82;1.95]	<.001	0.95 [0.58;1.56]	0.85
Perineural invasion	2.81 [1.11;7.12]	0.029	1.04 [0.45;2.43]	0.926
Capsular rupture	1.49 [0.92;2.42]	0.103	1.39 [0.76;2.53]	0.275
Postoperative CA 19-9 level				
≤90 U/ml	1		1	
>90 U/ml	2.01 [1.06;3.8]	0.033	1.74 [0.9;3.38]	0.099
R_7 status				
Accurate $R0_7$	1		1	
Presumed $R0_7$	1.86 [1.08;3.2]	0.024	1.16 [0.65;2.05]	0.618
Accurate $R1_7$	2.09 [1.26;3.46]	0.004	1.39 [0.84;2.3]	0.202

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Discussion

Le contrôle de qualité indépendant de tous les rapports anatomopathologiques et opératoires a été réalisé avant la première analyse des résultats de l'étude PRODIGE 24/ CCTG PA6 (12) et nous a permis de standardiser la classification en R0 ou R1 en considérant l'invasion ou non de chaque marge chirurgicale en utilisant la définition de la marge minimale de 1 mm comme recommandé par le Royal College of Pathologists et l'American Joint Committee on Cancer. Nous avons présenté ici les résultats des 400 pièces de résection de duodénopancréatectomie (ou apparenté). Le protocole de l'essai prévoyait l'examen de 7 marges sur des pièces opératoires. Parmi les 77 hôpitaux français et canadiens de statut et d'expérience différents participant à l'étude, la conformité aux exigences était bonne, avec un nombre médian de six marges documentées (intervalle interquartile 5-7). L'encrage des marges a également été effectué comme demandé dans 64,9 % des cas. Dans notre étude, le taux global d'atteinte des marges était de 47,5 % (190 cas de R1 sur 400), la marge la plus fréquemment atteinte étant celle du lit de la veine mésentérique supérieure (113 cas ; 36,5 %), la marge postérieure (84 cas ; 29,2 %) suivie de la marge médiale (58 cas ; 23,7 %). La marge de transection du pancréas n'a été retrouvée que dans 5,3 % des cas. Cependant, ce faible taux reflète probablement l'utilisation de l'analyse extemporanée per opératoire. Ce taux est également conforme à celui de 9 % observé dans l'étude ESPAC-3. La marge du canal de la vésicule biliaire ou les marges proximale et distale du duodénum ont été très rarement impliquées, dans 1,5%, 0% et 0,25 % des tumeurs respectivement. Lorsqu'elles étaient positives, seules trois marges (lit de la veine mésentérique supérieure, médiale et postérieure) étaient des facteurs significatifs de pronostic dans l'analyse unifactorielle (toutes $p<0,01$). Lorsqu'elles sont combinées, une marge positive parmi ces trois marges (statut R1) a une valeur pronostique indépendante en analyse multivariée. Le bras gemcitabine, la faible différenciation tumorale, le statut ganglionnaire positif, la rupture capsulaire, l'invasion périnerveuse, le niveau postopératoire de CA 19-9 >90 U/ml et le statut R1 étaient tous associés de manière indépendante et significative à une survie sans rechute réduite.

Il est intéressant de constater que l'atteinte d'une marge de résection reste un facteur pronostique significatif dans le bras gemcitabine mais plus dans le bras mFOLFIRINOX, que ce soit en analysant la totalité des 7 marges recommandées ou bien seulement les 3 marges de plus grand pronostique.

Chez les patients en rechute dans le bras mFOLFIRINOX, on constatait 80% de métastases à distance contre seulement 20% de récidives locales. Ceci permet de penser que le mFOLFIRINOX gomme le surrisque lié à l'atteinte d'une marge, là ou la gemcitabine n'y parvient pas.
Ceci pourrait également expliquer les disparités de pronostique du statut R0/R1 dans les différents essais en adjuvant (facteur de risque confirmé dans l'essai ESPAC-3 (22) mais pas dans la méta-analyse des essais ESPAC (24)).
C'est possiblement le témoin de l'efficacité de certaines molécules sur l'envahissement local. Il serait intéressant de regarder selon chaque type de chimiothérapie adjuvante testée s'il y a un bénéfice local mais à date seule la gemcitabine et le mFOLFIRINOX sont recommandés, le nab-paclitaxel en association avec la gemcitabine ayant échoué à améliorer la survie des patients en adjuvant de manière significative.

La force de ce travail est d'avoir montré, d'après les données solides d'un essai prospectif et randomisé international que l'analyse de 3 marges seulement pouvaient suffire pour prédire la survie sans rechute plutôt que la totalité des 7 marges habituelles et que l'atteinte de l'une seule d'entre elle suffisait déjà à grever ce pronostique.
Tous les efforts dans les futurs essais cliniques doivent être faits pour renseigner de manière systématique ces 3 marges au minimum.

Enfin l'analyse de cette étude a permis de proposer une explication plausible sur le bénéfice local d'une chimiothérapie adjuvante par mFOLFIRINOX comparé à la gemcitabine chez les patients opérés d'un cancer du pancréas.

Conclusion et perspectives

Nous avons le sentiment qu'une nouvelle population de patients émerge de cette étude, les patients qui sont rattrapés sur le plan local après chirurgie par une chimiothérapie de type mFOLFIRINOX et pour ceux parmi eux qui vont récidiver, le faire majoritairement sous forme de métastases à distance et préférentiellement pulmonaires, avec une survie médiane de 28 mois (25).

Nous envisageons de combiner nos résultats à une analyse translationnelle prélèvements des patients qui sera utile pour mieux les caractériser et réaliser une signature moléculaire afin de distinguer les sous-groupes pronostiques pertinents (financement obtenu dans cadre du PRTK MOSAPAC, données disponibles pour 374 patients sur 493).
L'analyse de l'ADN tumoral circulant sera également un facteur pronostique à prendre en compte dans de futurs essais.

Les essais cliniques comportant de la radiothérapie sont pour le moment décevants en ce qui concerne la survie globale. En situation adjuvante les essais sont régulièrement négatifs, et en situation néoadjuvante, le bénéfice reste encore à prouver, nous attendons pour cela les résultats de l'étude PANDAS-PRODIGE 44 (NCT02676349) dont les inclusions viennent de se terminer et qui évaluait la stratégie de chimiothérapie néoadjuvante par mFOLFIRINOX +/- radiochimiothérapie avant chirurgie.
Il est fort possible qu'avec une meilleure caractérisation des populations il soit possible de mieux sélectionner les patients pouvant bénéficier d'un traitement complémentaire par radiothérapie.
Dans notre cas il serait intéressant de savoir si les patients qui n'ont pas bénéficié de mFOLFIRINOX ou bien ceux dont le traitement n'a pas pu être conduit complétement ou encore ceux dont une des 3 marges est atteinte pourraient profiter d'une radiothérapie de clôture.
Il est probable que les patients ayant pu recevoir toute la séquence et dont les marges ne sont pas envahies ne tirent pas profit d'une irradiation locale, la chimiothérapie ayant déjà apporté le bénéfice (ce sont ces patients qui récidivent majoritairement sous forme de métastases à distance).

Enfin nous envisageons de travailler avec la base européenne de l'essai ESPAC-4 (730 patients) (11), mais il n'y a pas eu de contrôle qualité sur les marges chirurgicales, et le taux de chirurgie classée R1 (60%) est supérieur à celui de l'étude PRODIGE 24/ CCTG PA6 (42,8%).

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Title: Impact of positive resection margins on recurrence and survival following resection and adjuvant chemotherapy in pancreatic cancer

Abstract:
Pancreatic cancer is a disease with a poor prognosis, with a limited rate of operable (i.e. curable) patients, the majority of whom will recur locally or as distant metastases. Invaded resection margins during pancreatic cancer surgery suggest incomplete resection and put the patient at risk of local recurrence. The Royal College of Pathologists in Great Britain and the AJCC (American Joint Commission on Cancer) manual recommend inking the anterior, medial and retroperitoneal margins of surgical specimens. An R1 status is now defined as a margin less than or equal to 1 mm. The implementation of a standardized anatomopathological examination protocol considerably increases the percentage of positive resection limits and therefore of surgery classified as R1.
An exhaustive quality control was performed in the PRODIGE 24/ CCTG PA6 study (Multicenter randomized phase III trial comparing 6-month adjuvant chemotherapy with gemcitabine versus mFOLFIRINOX in patients operated on for pancreatic adenocarcinoma) using all pathology and operative reports. The misclassification of R0 or R1 surgery concerned 24.1% of the reports. Following the analysis of the PRODIGE 24/ CCTG PA6 study, we were able to show that 3 resection margins had a much better prognosis than the others (the medial margin, the posterior margin and the groove of the superior mesenteric vein). The analysis of this database also allowed us to demonstrate a corrective effect of mFOLFIRINOX compared to gemcitabine, thus explaining part of the improvement in progression-free survival and overall survival of the included patients.

Keywords: pancreatic cancer; adenocarcinoma; surgery; prognosis; resection margin

Titre : Évaluation de la qualité des marges de résection chirurgicales comme facteur pronostique de récidive et de survie des cancers du pancréas opérés puis traités par chimiothérapie adjuvante.

Résumé :
Le cancer du pancréas est une maladie au pronostic défavorable, avec un taux de patients opérables (donc curatifs) limité, dont une majorité récidivera localement ou sous forme de métastases à distance. Des marges de résection envahies lors de la chirurgie d'un cancer du pancréas évoquent une résection incomplète et exposent à un risque de récidive locale.
Le Collège Royal des pathologistes en Grande-Bretagne et le manuel de l'AJCC (American Joint Commission on Cancer) recommandent l'encrage des marges antérieure, médiale et rétropéritonéale des pièces opératoires. Un statut R1 est aujourd'hui défini comme une marge inférieure ou égale à 1 mm. La mise en place d'un protocole d'examen anatomopathologique standardisé augmente considérablement le pourcentage de limites de résections positives et donc de chirurgie classée R1.
Un contrôle qualité exhaustif a été réalisée dans l'étude PRODIGE 24/ CCTG PA6 (Essai de phase III randomisé multicentrique comparant une chimiothérapie adjuvante de 6 mois par gemcitabine versus mFOLFIRINOX chez des patients opérés d'un adenocarcinome pancréatique) à partir de l'ensemble des comptes-rendus anatomopathologiques et des comptes-rendus opératoires. Les erreurs de classement portant sur le caractère R0 ou R1 de la chirurgie concernait 24,1% des comptes-rendus.
Suite à l'analyse de l'étude PRODIGE 24/ CCTG PA6, nous avons pu montrer que 3 marges de résection avaient un pronostic bien supérieur aux autres (la marge médiale, la marge postérieure et le lit de la veine mésentérique supérieure). L'analyse de cette base de données nous a également permis de mettre en évidence un effet correcteur du mFOLFIRINOX par rapport à la gemcitabine, expliquant ainsi une partie de l'amélioration de la survie sans progression et de la survie globale des patients inclus.

Mots clés : cancer du pancréas ; adénocarcinome ; chirurgie ; pronostique ; marges de résection

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