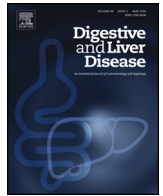




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Review Article

Pancreatic cancer: French clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, AFC)



Download Clinical Guidelines

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ABSTRACT

Background: This document is a summary of the French intergroup guidelines regarding the management of pancreatic adenocarcinoma (PA), updated in July 2018.

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Keywords:
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Design: This collaborative work was produced under the auspices of all French medical and surgical societies involved in the management of PA. It is based on the previous guidelines, recent literature review and expert opinions. Recommendations were graded in three categories, according to the level of evidence.

Results: Over the last seven years, significant changes in PA management have been implemented in clinical practice. **Imaging/staging:** diffusion magnetic resonance imaging is useful before surgery to rule out small liver metastases. **Surgery:** centralization of pancreatic surgery in expert centers is associated with a decreased postoperative mortality. **Adjuvant chemotherapy:** modified FOLFIRINOX in fit patients, or gemcitabine, or 5-FU, or gemcitabine plus capecitabine, to be discussed on a case-by-case basis. **Locally advanced PA:** no survival benefit of chemoradiotherapy. **Metastatic PA:** FOLFIRINOX and gemcitabine plus nab-paclitaxel combination are first-line standards in fit patients; second-line with 5FU/nal-IRI or 5FU/oxaliplatin combination after first-line gemcitabine.

Conclusion: Guidelines for management of PA are continuously evolving and need to be regularly updated. This constant progress is made possible through clinical and translational research. However, as each individual case is particular, they cannot substitute to multidisciplinary tumor board discussion.

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1. Introduction

1.1. Methods

This guideline is a collaborative work under the auspices of all French medical and surgical societies involved in the management of pancreatic cancer. The primary aim was to develop recommendations using only methodologically established evidence-based guidelines or primary evidence, and to achieve an interdisciplinary consensus. A writing multidisciplinary committee (from nine medical societies) gathering experts from different specialties involved in the management of pancreatic cancer (pathologist, surgeons, radiation oncologists, medical oncologists, and gastroenterologists) was designated to review recent literature (PubMed search until December 2017 and international congress abstracts of randomized trials) and to write a first document after interactive discussions. This initial document was reviewed and modified after further evaluation by a review committee and the last version was finally validated by the steering committee of the participating National Societies. The present article is a summary of the French intergroup guidelines published in July 2018 on the web site of the SNFGE society www.tncd.org. Recommendations based on this level of evidence were scored in 3 categories (grade A–C) according to the GRADE system [1,2], with only expert opinion (agreement or not, grade D) when no scientific evidence was validated [Table 1]. All the statements in the present article completely match the original full guidelines, with no additional data or comments.

1.2. Epidemiology

Pancreatic ductal adenocarcinoma (PDAC) accounts for 90% of pancreatic malignant neoplasms and is expected to become the second leading cause of cancer death in Europe in 2030 [3,4]. Its incidence in France increased twofold in men and threefold in women between 1982 and 2012, with a percentage of annual variation of +2.30% and +3.60%, respectively, which is the highest rate in Western countries, without clear explanation [5]. PDAC remains the digestive cancer with the poorest prognosis, with a 5-year overall survival (OS) rate, all stages taken together, of 7%–8% (www.invs.santepubliquefrance.fr) [6].

2. Diagnosis and pre-therapeutic explorations

2.1. Clinical presentation

Clinical presentation depends mainly on the primary tumor location and its stage at diagnosis [7]. PDAC localized in the head of

the pancreas (70%–80%) are more rapidly symptomatic than those developed in the body or tail (20%–30%) [8]. Jaundice can be an early sign caused by a cephalic tumor obstructing the main bile duct [7]. Diabetes mellitus is present in more than 50% of cases [9,10]. An intense abdominal pain (requiring opioid analgesics), with posterior and/or dorsal irradiation, is suggestive of an unresectable tumor due to celiac plexus invasion and associated with a poor prognosis [7,11]. Other clinical presentations are less frequent and not specific.

2.2. Serum tumor markers: CA19-9

2.2.1. Diagnosis

Carbohydrate 19-9 antigen (CA19-9) does not fulfill the performance criteria required to be a reliable diagnostic marker. Its sensitivity and specificity are 80% and 80%–90%, respectively, in symptomatic patients, but its positive predictive value is insufficient for the diagnosis or screening of PDAC [12,13]. Nevertheless, in very selected patients with advanced tumor responsible for altered performance status (Eastern Cooperative Oncology Group [ECOG] PS = 2) requiring urgent chemotherapy, following at least one non-contributory diagnostic biopsy attempt, a body of clinical, biological (i.e., CA19-9 > 10 times the upper limit of normal [ULN] in the absence of cholestasis) and imaging arguments may be sufficient to initiate chemotherapy [14,15]. Such decision must be validated by multidisciplinary tumor board (MTB).

2.2.2. Prognosis

Serum CA19-9 level provides prognostic information in two circumstances: (i) help predict tumor resectability at diagnosis when serum level is <200 U/mL or unresectability and probable metastatic spread when >1000 U/mL; (ii) help in the therapeutic follow-up, as normalization after surgery is associated with good prognosis, while decrease under chemotherapy or radiation therapy suggests tumor control [16,17].

2.2.3. Interpretation of CA19-9

It is necessary to be aware of (i) false negative results of serum CA19-9 in patients with a Lewis negative phenotype (5%–10% of general population); (ii) false positivity in case of cholestasis, diabetes mellitus, chronic pancreatitis, cirrhosis, or other cancers [15,16]. Overall, the CA19-9 should be handled with caution, always coupled with imaging examination, and accompanied by careful explanation to the patient about its limitations.

Table 1
Grade of recommendations according to the GRADE system [1,2].

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on highly robust scientific evidence (e.g. several randomized controlled trials/meta-analysis) Further research is very unlikely to change our confidence in the estimate of effect
B	Moderate	Usually recommended based on scientific presumption (e.g. one randomized controlled trial) Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Low	Option based on weak scientific evidence (e.g. one or several non-randomized trials) Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Very low	Expert opinion (agreement or not) Any estimate of effect is very uncertain

2.2.4. Other markers

Other blood markers are under investigation but still not validated and cannot be recommended to date.

2.3. Imaging

2.3.1. Multi-detector computed tomography (MDCT)

Once the diagnosis of PDAC is clinically suspected or after a pancreatic mass has been detected, thoraco-abdomino-pelvic MDCT with thin sections and intravenous contrast injection is the imaging modality of choice for initial staging, evaluation of tumor resectability, and discussion of patient therapeutic management.

PDAC lesions, both primary and metastases, are classically hypoattenuating at the arterial phase and isoattenuating/poorly enhanced at the portal phase.

The standardized MDCT report must mention: (i) tumor size, (ii) aspect before and after contrast injection, (iii) location, (iv) presence of biliary and/or pancreatic ductal narrowing and/or upstream dilatation, (v) contacts with vessels, and (vi) extra-pancreatic spreading contra-indicating surgery [18,19]. The assessment of tumor resectability requires precise description of arterial and venous involvement by the tumor [18,19]. Imaging must be recent (<4 weeks) since long imaging-to-management interval is associated with a higher risk of unanticipated peroperative discovery of metastases in patients with a presumably resectable tumor [20,21].

2.3.2. Magnetic resonance imaging (MRI)

MRI with diffusion-weighted (DW) and cholangiopancreatography sequences is an alternative imaging modality that is as sensitive and specific as MDCT for the diagnosis and staging of PDAC at the abdominal level, but less frequently used due to its cost and more limited availability [22].

MRI additional value is the characterization of not or poorly visible isoattenuating pancreatic lesions and small or indeterminate liver lesions at MDCT. It is recommended to perform a liver DW-MRI in the preoperative workup of any localized PDAC (resectable, borderline resectable, or locally advanced after successful induction treatment) to exclude infra-centimetric liver metastases. MRI may avoid futile laparotomy in 12% of patients with presumably resectable PDAC [23]. False positive cases are possible but uncommon (3.5%); the decision to contra-indicate surgical resection or to obtain histological evidence should be discussed at MTB meeting. When MRI is performed for abdominal staging, a thoracic MDCT must be added to detect lung metastases [18].

2.3.3. Endoscopic ultrasound (EUS)

The main role of EUS is to allow tumor tissue sampling for cytological or histological analysis. It can also provide valuable information on locoregional tumor extension. Nevertheless, EUS is operator-dependent and not considered as the reference examination for the evaluation of vascular involvement in PDAC.

The four indications of EUS are: (i) strong suspicion of PDAC not visualized by other imaging examinations, especially in case of main pancreatic duct narrowing; (ii) pancreatic mass of uncertain

nature on MDCT and MRI (e.g. differential diagnosis with pseudo-tumoral autoimmune pancreatitis [AIP]); (iii) the need to obtain pathological confirmation of PDAC when there is no other site of easier access; or (iv) when endoscopic retrograde cholangiopancreatography (ERCP) is indicated to perform a biliary drainage procedure [24]. Technical improvements of EUS (sono-elastometry, contrast venous injection, confocal endo-microscopy) have not been sufficiently evaluated to be recommended.

2.3.4. Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP has a therapeutic role to relieve bile duct obstruction. Diagnostic endobiliary brushing can be performed during the procedure, but its sensitivity is lower than that of EUS-guided needle aspiration/biopsy [25]. Outside the emergency setting, a biliary stent should be inserted only after complete cross-sectional imaging study and should ideally be discussed at MTB meeting with endoscopists and specialized surgeons. If there is any doubt about the nature or the resectability of the tumor, a short covered metallic biliary stent should be favoured.

2.3.5. 18-Fluorodeoxyglucose positron emission tomography (18FDG-PET)

18FDG-PET is not included in the systematic pre-therapeutic staging of PDAC. It is inconstantly positive in PDAC, particularly in mucin-producing or low cellularity variants, or in case of unbalanced diabetes mellitus. On the other hand, non-malignant inflammatory diseases, such as AIP, can cause false positives. Overall, the role of 18FDG-PET in the management of PDAC patients remains controversial [23,26–28].

2.3.6. Laparoscopy

Laparoscopy allows the detection and biopsy of small peritoneal and/or liver metastases that would lead to reconsider the therapeutic strategy in a limited number of patients with presumably resectable tumor after a rigorous imaging assessment [29,30].

Laparoscopy may be considered in the following cases: (i) before resection of a bulky tumor in the body or tail, and/or (ii) in case of high CA19-9 serum level (cut off >130 to 400 U/mL), or (iii) when neoadjuvant or induction therapy is considered [29–31].

2.4. Pathological diagnosis

The most accessible tumor site should be biopsied (classically, the pancreas or liver); EUS should be preferred over transperitoneal route (under MDCT control) to biopsy the pancreas in the absence of easily accessible metastasis (e.g. locally advanced tumour or small liver lesions) [32,33]. A tumor biopsy is indicated in three situations: (i) doubtful diagnosis vs. benign lesion or other neoplasm (e.g. neuroendocrine tumor); (ii) unresectable tumor, to ascertain malignancy before starting chemotherapy; (iii) potentially resectable tumor, when neoadjuvant treatment is considered. Size and type of needle and technical modalities may influence the performance of biopsies under EUS.

Table 2
Clinical tumor, node and metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC) and of the Union for International Cancer Control (UICC), 8th edition (2017).

	Definition
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i> (including high grade dysplasia)
T1a	Tumor ≤ 0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤ 4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in ≥ 4 regional lymph nodes
Distant metastasis (M)	
M0	No distant metastases
M1	≥ 1 distant metastasis
Stage grouping	
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T3 N0 M0
Stage IIB	T1–3 N1 M0
Stage III	T1–3 N2 M0
Stage IV	T4 Any N M1

Pre-operative pathological assessment is not systematically required for resectable tumor when upfront radical surgery is planned; biopsy should not delay surgical resection and a negative result would not fully reassure when PDAC is strongly suspected.

2.5. Therapeutic classification

The 2017 American Joint Committee on Cancer (AJCC) TNM classification (8th version) introduced changes in the definitions of T and N categories [Table 2] [34].

The definition of regional lymph nodes for PDAC is not consensual. Classically, regional lymph nodes for tumors developed in the pancreatic head and uncinate process are defined as those along the common bile duct, common hepatic artery, portal vein (PV), pyloric, anterior and posterior to pancreatico-duodenal vessels, and along the superior mesenteric vein (SMV) and the right lateral edge of the superior mesenteric artery (SMA) (AJCC 2017). Likewise, regional lymph nodes may not be the same for tumors of the proximal body and tail. Classically, they are defined as those along the common hepatic artery, celiac axis, splenic artery, and splenic hilum (AJCC 2017).

In practice, the classification of PDAC into resectable, borderline, locally advanced, or metastatic tumors is the framework for treatment strategy [35].

The degree of vascular involvement should be assessed during MTB meeting with expert radiologists, surgeons and oncologists/gastroenterologists. In the case of malignant intraductal papillary mucinous neoplasm (IPMN), vascular involvement might be overestimated.

Not all vascular extensions are synonymous of non-resectability. In particular, invasion of the splenic artery and/or vein is not a contra-indication to surgical resection for tumors of the body or tail of the pancreas. Invasion of peri-pancreatic lymph nodes is an independent negative prognostic factor for survival, but it

does not contra-indicate surgical resection [36]. In contrast, distant lymph node involvement (e.g. root of the small-bowel mesentery, retroperitoneum, or inter-aorto-caval space) is a very poor prognostic factor and should contra-indicate an upfront surgical strategy.

2.6. Prognostic stratification

2.6.1. Resectable tumors

The prognosis is mainly determined by tumor-related factors (diameter, differentiation, lymph node involvement and/or margins), and the administration of adjuvant chemotherapy [8]. Age itself is not a criterion in patient selection for surgery [37]. Severe comorbidities, ECOG PS >2 , or severe malnutrition despite optimal supportive care may preclude an otherwise technically possible resection. North American algorithms may be of interest to evaluate the risk of postoperative morbidity and mortality in this setting (<https://riskcalculator.facs.org/RiskCalculator/>).

2.6.2. Metastatic tumors

Factors related to the patient and tumor burden play a major prognostic role. Altered general condition (ECOG PS ≥ 2), age >65 years, albuminemia <35 g/L, impaired quality of life, presence of synchronous metastases and their location in the liver, number of metastatic sites, elevated serum CA19-9 levels and neutrophil-to-lymphocyte ratio are negatively associated with survival [38–42].

2.7. Recommendations for pre-therapeutic explorations

2.7.1. Recommendations

The diagnostic, staging and resectability evaluation are based on:

- ECOG PS, nutritional status, and comorbidities.
- Thoraco-abdomino-pelvic MDCT (recommendation: grade A).
- Serum CA 19-9: no diagnostic utility, but prognostic value before surgery and for therapeutic follow-up (recommendation: grade B).

Indications of biopsy:

- Operable/resectable tumor: under EUS in case of doubtful diagnosis or if a neoadjuvant treatment is considered (recommendation: grade A).
- Non-operable/non-resectable tumor: biopsy of the most easily accessible site, preferably under EUS control for the pancreas, or by transparietal route (under ultrasound or MDCT guidance) in case of easy accessible liver metastases (recommendation: grade A).

2.7.2. Options

- EUS: its main indication is to guide biopsies of the pancreas (recommendation: grade A). Other indications: strong suspicion of PDAC not visible with other imaging tests, or pancreatic mass of indeterminate nature.
- DW-MRI in addition to the thoraco-abdomino-pelvic MDCT before surgery for any potentially operable tumor (upfront resectable or after induction therapy), to rule out small liver metastases, without delaying the surgical procedure (recommendation: grade B).
- MRI with cholangiopancreatography sequences as an alternative to abdomino-pelvic MDCT, or in the case of pancreatic isoattenuating tumor or indeterminate liver lesion on MDCT (rec-

ommendation: grade B). If chosen, thoracic CT scan should be performed to complete staging.

- Per-ERCP biliary brushing when indication of biliary drainage procedure (recommendation: grade B).
- Laparoscopy before attempting resection or starting neoadjuvant/induction therapy in case of large tumor of the body or tail, and/or serum CA 19-9 level >200 U/mL (expert opinion).

3. Screening and familial PDAC

3.1. Precancerous lesions

They include pancreatic intraepithelial neoplasia (PanIN), IPMN and mucinous cystadenomas [43–45]. Several recommendations have been published to guide the surgical indications for IPMN and mucinous cystadenomas [46,47].

3.2. Genetic forms

Genetic susceptibility accounts for about 5%–10% of PDAC [48]. Familial pancreatic cancers (FPC) are defined by ≥ 2 first-degree relatives with confirmed PDAC, or ≥ 3 cases in the same familial branch regardless of the degree of relationship and age of onset. The theoretical risk of PDAC in relatives increases depending on the number of cases in the family [48–50].

Inherited tumor syndromes associated with increased risk of PDAC are summarized in Table 3 [48,50]. No germline mutation is identified in about 85% of cases of FPC (non-syndromic family aggregation); alternatively, germline mutations (*BRCA1/2*, *ATM*, *PALB2*, *MLH1*, *CDKN2A* and *TP53*) can be found in patients without family history [51].

3.3. Screening

The aim of PDAC screening is to detect precancerous lesions that are amenable to curative surgical treatment and therefore only in individuals who are eligible for surgery. It applies to individuals with a cumulative theoretical risk of PDAC >5% over lifetime or an estimated relative risk [RR] ≥ 5 [48,50,52]: (i) having ≥ 2 relatives with PDAC including ≥ 1 at first degree; (ii) carrying a germline mutation of a predisposing gene and having ≥ 2 relatives with PDAC or ≥ 1 at first degree; (iii) any patient with Peutz–Jeghers syndrome, regardless of family history.

These individuals should be referred to expert centers for onco-genetic consultation and MTB discussion of the benefit/risk ratio and the modalities of possible screening, in accordance with the international CAPS recommendations [50].

In all cases, the management of subjects at risk must include the correction of risk co-factors (smoking, overweight or diabetes), and take into account their life expectancy and operability, as well as the psychological acceptability of screening, once explained its constraints and uncertainties regarding its efficacy.

Recommendations

- Screening should be considered for subjects with a cumulative theoretical risk of PDAC >5% or RR ≥ 5 (having ≥ 2 relatives PDAC including ≥ 1 at first degree, or having a germline mutation of a predisposing gene and ≥ 2 relatives with PDAC or ≥ 1 at first degree, or Peutz–Jeghers syndrome), and eligible for a possible pancreatic resection (theoretical life expectancy, comorbidities), and after discussion of the benefit/risk ratio of such screening (expert agreement).
- Screening modalities should be defined by MTB in an expert center (expert agreement).

Table 3
Major inherited syndromes of predisposition to pancreatic ductal adenocarcinoma (PDAC) and risk of developing PDAC.

Family history and hereditary predisposition syndromes	Gene(s)	Relative risk	Cumulative risk of PDAC by age 70 (%)	% Among familial pancreatic cancers	Other associated cancers
No family history	–	1	0.5–1	–	–
≥ 2 first-degree relatives with confirmed PDAC	Unknown	4–6	5–12	80–85	?
≥ 3 first-degree relatives with confirmed PDAC	Unknown	20–40	40		?
Hereditary breast and ovarian cancers	<i>BRCA1</i> <i>BRCA2</i>	2–4 2–10	3–4 4–5	1–5 –20	Breast, ovary, prostate, \pm colon, melanoma
Hereditary pancreatitis	<i>PALB2</i> , <i>FANCC/G</i>	2–6	4–5	1–3	
Familial atypical multiple mole melanoma (FAMMM) syndrome	<i>PRSS1</i>	50–80	40–55	1–4	Melanoma, kidney, head and neck carcinoma, glioblastoma, pleura
Peutz–Jeghers syndrome	<i>p16/CDKN2A</i>	10–25	5–25	2–3	Colon, stomach, small intestine, breast, cervix, ovary, testicle
Lynch syndrome	<i>LKB1/STK11</i>	100–130	30–40	1–3	Colon, endometrium, small intestine, stomach, urinary tract, ovary, biliary tract
Ataxia-telangiectasia syndrome	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> (MMR genes)	4–8	3–5	1–3	Hematologic malignancies, breast, stomach
Li–Fraumeni syndrome	<i>ATM</i>	?	?	<2	Sarcomas, breast, hematologic malignancies, brain, adrenal gland
McCune–Albright syndrome	<i>TP53</i>	?	?	<2	Thyroid IPMN
	<i>GNAS</i>	?	?	0	

IPMN: intraductal papillary mucinous neoplasm, MMR: mismatch repair, ? : unknown.

- Correction of other risk factors is recommended (expert agreement).

4. Treatments

4.1. Upfront resectable tumors

4.1.1. Surgery

After careful pre-therapeutic evaluation, only 15%–20% of patients are candidates for surgical resection. The major goal of surgery is to achieve R0 resection to be potentially curative [53]. To optimize the chance to achieve this, it must be performed in a high-volume expert center, the exact definition of which remains controversial [54,55], and within 4 weeks following the latest MDCT scan [56].

The initial workup must identify and assess: (i) possible contra-indication(s): distant metastases, technical contra-indications, or severe comorbidities; (ii) the risk of postoperative mortality; (iii) the possibilities of R0 resection (upfront resectable vs. borderline tumor requiring induction therapy); (iv) optimal management of jaundice and nutritional status.

The type of surgical resection procedure is determined by the location and extension of the tumor [57].

For PDAC of the pancreatic head, pancreaticoduodenectomy (PD) is the standard procedure. Dissection of more than 15 lymph nodes [58] and resection of the retroportal lamina exposing the right edge of the SMA is recommended. More aggressive surgery (*i.e.*, extensive lymphadenectomy and/or arterial resection) does not improve long-term survival and is not recommended [58,59]. Pylorus preservation has no negative prognostic influence [60,61]. Inter-aortico-caval picking with frozen section examination is an option [62]. The presence of a right hepatic artery or median arcuate ligament does not definitively contra-indicate a resection attempt but must be detected pre-operatively [63–65].

PDAC of the body or tail of the pancreas are resected by left splenopancreatectomy (LSP), which must be performed from right to left with RAMPS (radical anterograde modular pancreatectomy) approach and with dissection of ≥ 15 –20 lymph nodes [66].

Indications for performing a total pancreatectomy are limited to: (i) degenerated diffuse IPMN, (ii) or second PDAC tumor (or more rarely a single locoregional recurrence) localized to the pancreatic remnant.

The laparoscopic approach is not yet validated. It may be considered for small tumors of the left pancreas in expert high volume centers [67,68].

Extemporaneous examination (frozen section) is systematic to rule out an invasion of the surgical margin and possibly widen the surgical resection.

The definition of an R0 resection, whose rate has been overestimated in the past, requires a careful examination of the three resection margins (SMV/PV, SMA and posterior margin) including the multicolored inking by the surgeon. R0 resection should be defined as clearance (tumor cell-margin distance) > 1 mm [69,70]. The surgical specimen should be classified according to the WHO 2010 and AJCC 2017. Standardization of the report (*e.g.* www.rcpath.org or www.cap.org) is encouraged.

4.1.2. Biliary drainage

Pre-operative ERCP with biliary stenting is not systematic since it increases the rate of infectious complications [71,72]. If performed, the use of a short metallic stent should be preferred to a plastic one [73]. Pre-operative biliary drainage is considered in case of: (i) cholangitis, (ii) bilirubin level > 250 $\mu\text{mol/L}$, (iii) neoadjuvant treatment, or (iv) delayed surgery (> 4 weeks).

4.1.3. Adjuvant treatment

About 80% of patients treated by a curative-intent resection for localized PDAC will develop metastatic (70%) and/or local recurrence (30%) [74]. Adjuvant therapy is indicated in all patients following resection of PDAC, irrespective of the pTNM stage, and should be started within three months of surgery [75].

Adjuvant chemotherapy has been a standard since 2001 [76,77]. Based on the CONKO-001 [78] (gemcitabine superior to observation) and ESPAC-3 [79] (gemcitabine as effective as bolus 5-fluorouracil [5-FU], but less toxic) phase III studies, adjuvant chemotherapy with gemcitabine or 5-FU for six months is recommended. The expression of the hENT-1 transporter has been proposed as a predictive marker of the efficacy of gemcitabine [80], but cannot be recommended due to discordant results and in the absence of validated antibodies for routine assessment [81].

In 2017, the ESPAC-4 phase III study showed an increase in OS from 25.5 to 28 months (HR: 0.82, $p = 0.032$) with the combination of gemcitabine plus capecitabine versus gemcitabine alone [82]. Nevertheless, this study has been the subject of methodological criticism, in particular because of the absence of post-operative MDCT at baseline and the absence of significant disease-free survival (DFS) benefit [83].

S-1, an oral fluoropyrimidine derivative, was non-inferior and even superior to gemcitabine in a randomized phase III trial in a Japanese population (JASPAC-01) but this compound has not been tested in Europe and is not available in France [84].

The PRODIGE 24 phase III study (presented at the ASCO meeting 2018) showed that compared to gemcitabine, modified FOLFIRINOX (5-FU, folinic acid [FA], irinotecan, and oxaliplatin) combination improved median DFS (21.6 vs. 12.8 months, stratified hazard ratio [HR]: 0.58, $p < 0.0001$) and OS (54.4 vs. 35 months, stratified HR: 0.64, $p = 0.003$) in patients with ECOG PS 0–1 without severe diarrhoea nor cardiac contra-indication to 5-FU [85]. Results of the AFACT phase III study (gemcitabine plus *nab*-paclitaxel vs. gemcitabine single agent) are pending.

Whichever chemotherapy regimen is prescribed, it seems that the completion of the six-month chemotherapy plan is more important than the delay in starting it (but within 3 months post-surgery) [75].

The role of radiotherapy in adjuvant setting is not consensual (contradictory but old studies with non-optimal/uncontrolled radiation protocols) [77,86–93]. Even in case of R1 resection, no survival benefit has been prospectively shown using adjuvant chemoradiotherapy; a randomized trial in this indication is underway in the United States (RTOG-0848). Chemoradiotherapy is therefore not recommended on adjuvant setting, even in case of R1 resection.

4.1.4. Neoadjuvant treatment

While this strategy is currently not the reference, several phase II/III trials are ongoing to assess its role. Its rationale is to: (i) provide an observation period (4–6 months) to identify patients who have an aggressive tumor with early metastatic evolution, who are therefore not good candidates for surgery (about 30%); (ii) induce a tumor response and thus increase the probability of R0 resection; (iii) treat early a potential micrometastatic disease; (iv) test the chemosensitivity of the tumor, as well as the patient's tolerance to this treatment, to help guide patient selection for surgery. First results from a randomized phase II study (PACT-15) using the PEXG regimen (cisplatin, epirubicin, gemcitabine and capecitabine combination) before and after surgery in 32 patients were encouraging, showing the feasibility of this strategy [94]. The results of the NEOPAC Phase III study comparing adjuvant gemcitabine to neoadjuvant GEMOX (or FOLFIRINOX following an amendment) plus adjuvant gemcitabine are pending. Questions remain unanswered regarding: (i) the potential role of pre-operative chemoradiother-

apy after chemotherapy and (ii) the type and duration of adjuvant chemotherapy in this situation.

4.2. Borderline tumors

4.2.1. Treatment

The definition of borderline tumors is anatomical and radiological, and refers to resectability based on the extent of vascular involvement (NCCN classification [35]). These tumors display a high risk of positive surgical margins (R1) and recurrence. Beside these technical criteria, the concept of “biological” and “clinical” borderline PDAC, based on tumor pathological or molecular features or patient comorbidities, respectively, has been proposed and warrants further clinical evaluation [95].

Patients with borderline PDAC should whenever possible be referred to an expert center and enrolled in clinical trials.

Because of the high risk of R1 resection and despite the absence of high-level evidence, induction therapy is often favored over upfront surgery. Neoadjuvant chemotherapy seems often feasible and showed promising results [96–99].

In ongoing trials, induction strategy most often relies on FOLFIRINOX or gemcitabine plus *nab*-paclitaxel combinations, followed or not by a course of chemoradiotherapy, which seems to increase the pathologic response rate [99]. There are currently no data about adjuvant chemotherapy in this setting.

4.2.2. Evaluation of tumor response

The assessment of tumor response to induction therapy using current imaging techniques is challenging [100–102]. Perivascular infiltration often persists after chemotherapy and/or radiotherapy, and it is difficult to distinguish fibro-inflammatory changes from residual tumor infiltration [103]. Nonetheless, partial regression of the contact between tumor and vessels may predict a likely R0 resection, and thus should prompt to perform surgical exploration [101]. The absence of metastatic progression is another important efficacy criterion. Decrease or even normalization of serum level of CA19-9 and clinical improvement may also guide the decision; however, only intra-operative biopsy and/or examination of the resected specimen allows conclusions regarding the efficacy of induction therapy [97,104]. There is no consensus on the pathological criteria for defining tumor response and their prognostic value is controversial. The College of American Pathologists score is the most widely used tumor regression grading system [105,106].

4.3. Locally advanced tumors

4.3.1. Chemotherapy

The reference treatment for locally advanced PDAC is chemotherapy. It should be named “induction chemotherapy” rather than “neoadjuvant chemotherapy” since secondary resection is often not feasible, although it may be considered in some highly selected cases. Gemcitabine remains a weak but best-validated chemotherapy regimen in this setting, based on the results of past studies in “advanced PDAC”, pooling together patients with metastatic and locally advanced tumors. The addition of erlotinib to gemcitabine did not improve survival in the LAP07 phase III study [107].

In view of their efficacy in metastatic setting, FOLFIRINOX and gemcitabine plus *nab*-paclitaxel combinations have been tested in patients with locally advanced PDAC, with interesting results [100,108–111]. Nevertheless, there is no prospective validation in comparison with gemcitabine (the LAPACT study evaluating the gemcitabine plus *nab*-paclitaxel combination is a single-arm phase II study, and the NEOPAN phase III study evaluating FOLFIRINOX is in progress). Concerns about radiological and pathological examination after induction treatments are similar to those for borderline tumors [100,106].

4.3.2. Radiation therapy

Its role in the management of locally advanced PDAC is not consensual. The randomized phase III LAP07 study did not show superiority of chemoradiation over continuation of initial chemotherapy alone in terms of OS [107]. A secondary analysis showed that the administration of chemoradiotherapy was associated with better local control and a longer treatment-free period [112]. Thus, chemoradiotherapy could be proposed following a three- to six-month course of induction chemotherapy (to rule out patients with rapid metastatic progression), with concomitant administration of capecitabine as radiosensitizer [113–117]. Thus, chemoradiotherapy is an option to be discussed at MTB meeting in patients with controlled disease after induction chemotherapy, especially those who wish to have a chemotherapy break.

4.3.3. Surgery

Prophylactic gastrojejunostomy to bypass unresectable PDAC from the head of the pancreas in an asymptomatic patient is not recommended. In case of biliary stenosis requiring drainage in a patient in whom a contra-indication to a curative-intent surgical resection is found intra-operatively, it is acceptable to perform a choledoco-duodenal anastomosis; this is simpler to perform and as effective as choledoco-jejunal anastomosis.

Endoscopic treatment (biliary and/or duodenal stenting) should be preferred to surgery in symptomatic patients.

4.4. Metastatic PDAC

4.4.1. First-line chemotherapy

Gemcitabine was established as the reference first-line treatment of advanced PDAC in 1997 [118]. Multiple phase II and III studies attempted to improve the results of gemcitabine either by pharmacokinetic modulation or by combination with other agents. However, neither gemcitabine infusion at a fixed rate [119] nor its drug-lipid conjugated form [120] showed survival benefit. Combinations with various other agents were also disappointing, with a benefit of chemotherapy doublets (in particular, combination with platinum or capecitabine) restricted to patients with ECOG PS 0–1 [121–125]. A phase III study using the PEFG regimen (cisplatin, epirubicin, fluorouracil, and gemcitabine) was positive for its primary criteria (4-month PFS) [126]. However, PFS is not a validated surrogate of OS in PDAC and sample size was limited ($n = 104$). Evidence supporting the use of anthracyclines in PDAC remains scarce. Targeted therapies combined with gemcitabine did not provide any OS benefit vs. gemcitabine alone except for erlotinib, which yielded a statistically significant but clinically very modest OS improvement (<1 month) [127–142]. The inefficacy of erlotinib in patients with locally advanced PDAC in the LAP07 trial is an additional argument against its use in this indication [107].

In 2011, the PRODIGE-4/ACCORD-11 phase III study demonstrated the superiority of the FOLFIRINOX regimen over gemcitabine (median OS: 11.1 vs. 6.8 months, $p < 0.001$) in patients <75 years with ECOG PS 0–1 and bilirubin level <1.5 ULN [39]. A higher incidence of adverse events was observed in the FOLFIRINOX group, including 5.4% of febrile neutropenia. Modified FOLFIRINOX (without bolus of 5-FU \pm irinotecan dose reduction at 150 mg/m²) appears to have a better safety profile with maintained efficacy in retrospective studies [108]. The question of how and when the FOLFIRINOX regimen and doses can be deescalated after a period of tumor control (*i.e.*, maintenance therapy) remains to be answered; the results of the PANOPTIMOX randomized phase II study presented at ASCO meeting 2018 suggest that 5-FU/FA maintenance after four months of induction FOLFIRINOX chemotherapy may be an option [143].

In 2013, the combination of gemcitabine with *nab*-paclitaxel was also shown to significantly increase OS (median: 8.5 vs.

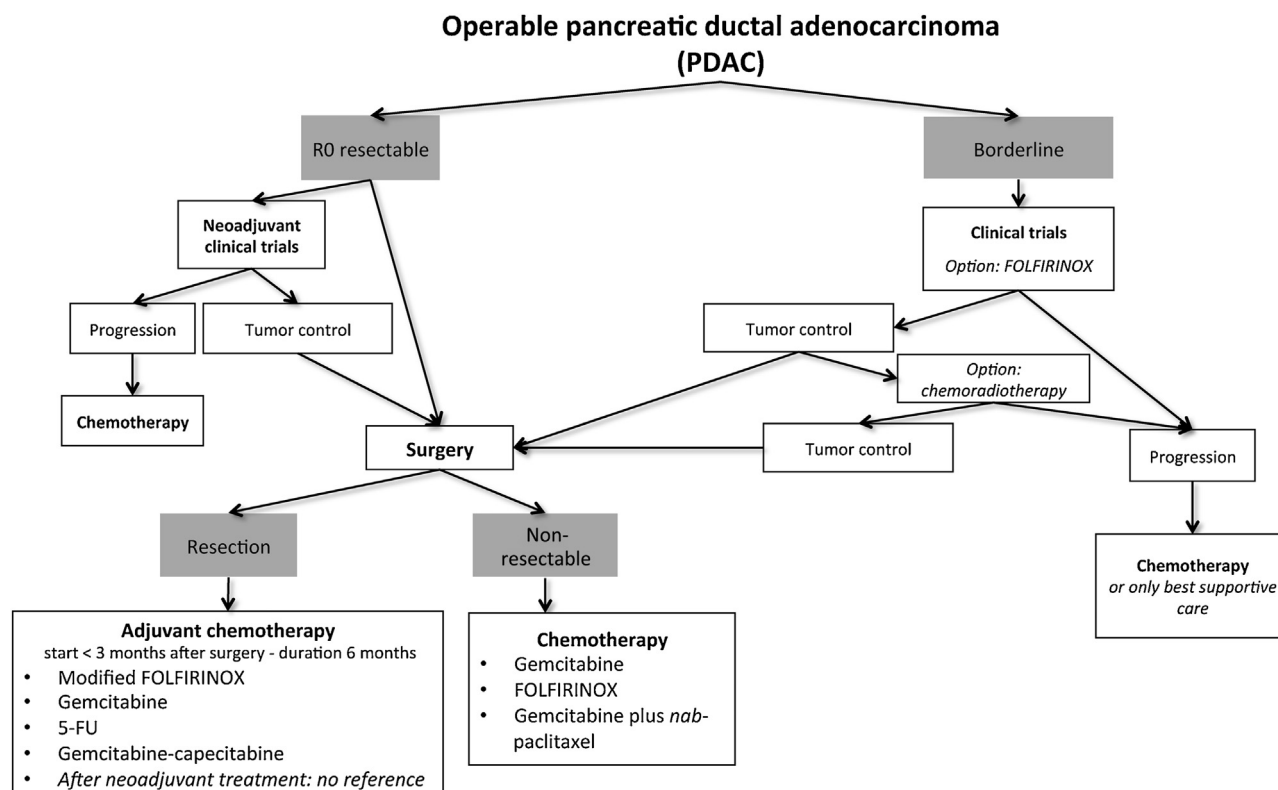


Fig. 1. Treatment algorithm for resectable and borderline resectable pancreatic ductal adenocarcinoma (PDAC).

6.7 months, $p < 0.001$) compared with gemcitabine alone in the MPACT phase III study [144].

This regimen has not been compared to FOLFIRINOX and validated predictive biomarkers to guide the therapeutic decision are lacking.

4.4.2. Second-line chemotherapy

Beyond progression under first-line treatment, about half of metastatic PDAC patients remain in sufficiently good clinical condition to receive subsequent line(s) of chemotherapy [145]. Only those with good performance status (ECOG PS 0–1) seem to benefit from second-line chemotherapy.

Combinations of 5-FU with platinum (oxaliplatin or cisplatin) or irinotecan (standard or nanoliposomal form) were mainly studied [146–153]. The combination of nal-IRI (MM-398) with 5-FU and FA was shown to be superior to 5-FU/FA alone (median OS: 6.1 vs. 4.2 months, $p = 0.012$) in a phase III trial (NAPOLI-1) [152]. Benefit of 5-FU and platinum combinations is controversial: a randomized phase III trial (CONKO-003) showed significant improvement in OS (median: 5.9 vs. 3.3 months, $p = 0.010$) with the OFF regimen (oxaliplatin, 5-FU, FA) compared to 5-FU/FA [147]. In contrast, the modified FOLFOX6 regimen was not superior to 5-FU/FA in the PANCREOX phase III trial possibly due to a higher toxicity [153].

Data about second-line treatment beyond progression under FOLFIRINOX or gemcitabine plus nab-paclitaxel are limited to retrospective studies [154–156].

4.5. Particular situations

Patients with PDAC and germline *BRCA1* or *BRCA2* gene mutation are sensitive to agents that cause DNA damage (e.g. platinum salts). PARP inhibitors are currently tested [49,157].

The same recommendations apply to treat histological variants of pancreatic cancer (e.g. cystadenocarcinomas, acinar or adenosquamous cell carcinomas).

4.5.1. Supportive care

It holds a major place in the management of PDAC patients to improve the quality of life and tolerance/adherence to anti-tumor treatments. It includes the treatment of: (i) biliary and/or digestive obstructions, (ii) pain, (iii) anxiety and depression, (iv) malnutrition and sarcopenia (including adapted physical activity), and (v) thromboembolic events [158,159]. Primary prevention of the latter may be indicated in high-risk patients according to the Khorana score [159–161]. Hypofractionated irradiation for analgesic or haemostatic purposes may be considered.

5. Therapeutic indications

5.1. Resectable tumor

Treatment algorithm is summarized in Fig. 1. Recommendations

- Curative surgery (R0):
 - PDAC of the head: PD by laparotomy in a high-volume expert center (recommendation: grade A) with dissection of ≥ 15 lymph nodes (recommendation: grade B). The retro-arterial resection (retro-arterial margin) of the pancreas, up to the right edge of the AMS is highly recommended (expert opinion). Extended lymphadenectomy and bulk arterial resection are not recommended.
 - PDAC of the body or tail: LSP (recommendation: grade A) by laparotomy with lymph node dissection (recommendation: grade B). A right-to-left RAMPS approach is strongly recommended (expert opinion).
- Adjuvant chemotherapy recommended (to be started within three months postoperatively if possible) in all patients after AP resection, regardless of T, N and R status, using modified FOLFIRINOX (ECOG PS 0–1), and in those not eligible for FOLFIRINOX

Locally advanced pancreatic ductal adenocarcinoma (PDAC)

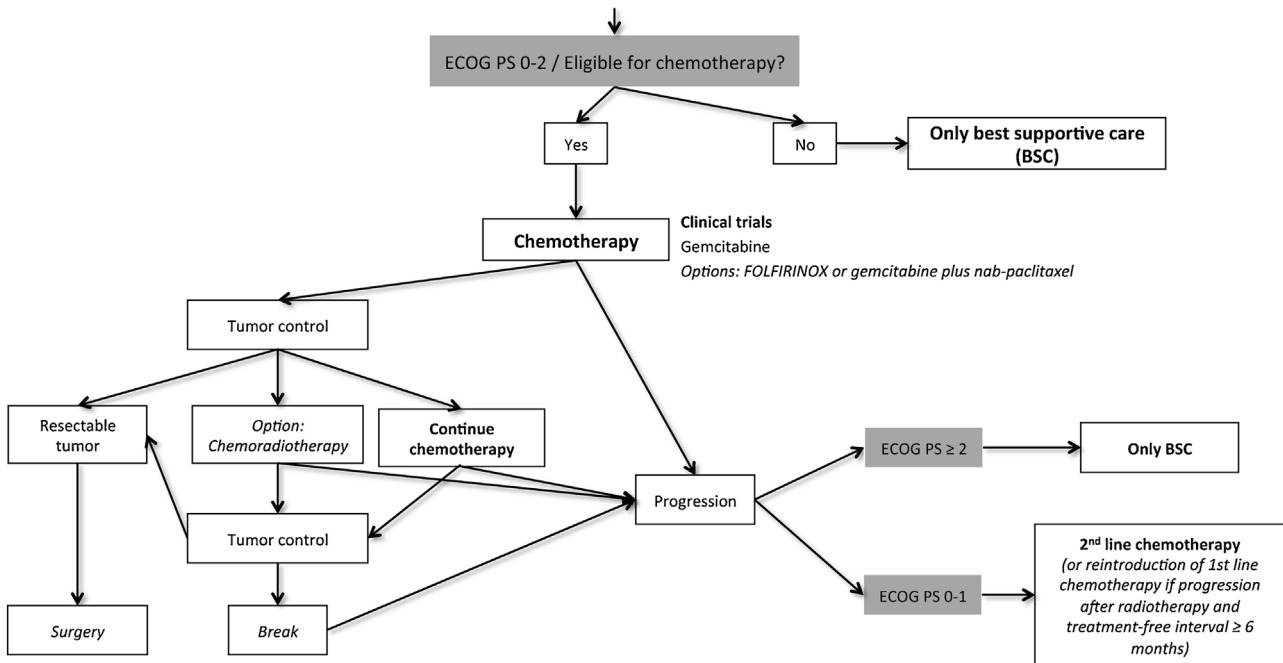


Fig. 2. Algorithm for treatment of locally advanced tumor pancreatic ductal adenocarcinoma (PDAC). ECOG PS: Eastern Cooperative Oncology Group performance status.

using gemcitabine, 5-FU or gemcitabine plus capecitabine, on a case-by-case basis, for a duration of six months (recommendation: grade A).

- Chemoradiotherapy: clinical trials only (expert agreement).

Options

- Biliary drainage (ERCP, preferably short metal stent) before surgery when cholangitis, bilirubin level >250 μmol/L (recommendation: grade A), neoadjuvant treatment, or delayed surgery (expert agreement).
- Laparoscopic LSP: optional for small tumors of the body and tail (expert opinion).
- Tumor resectable but not operable: management adapted to general condition similar to that of a locally advanced tumor (expert agreement).

Clinical trials

- PRODIGE 48 (PANACHE-01) trial (NCT02959879): neoadjuvant chemotherapy (FOLFIRINOX or FOLFOX) versus frontline surgery in resectable PDAC (randomized phase II study).
- PRODIGE 56 (APACaPOp) trial (NCT03400072): evaluation of adapted physical activity (APA) programs in patients with resected PDAC (randomized phase II study).

5.2. Borderline tumor

Treatment algorithm is summarized in Fig. 1.

Recommendations

- No reference.
- Inclusion in clinical trials.

Options

- Induction chemotherapy with FOLFIRINOX (recommendation: grade B).

- Preoperative chemoradiation with capecitabine after induction chemotherapy (expert agreement).
- Secondary surgery if controlled tumor and operable patient (expert agreement).
- Adjuvant chemotherapy (expert agreement).
- Biliary drainage (cf. resectable PDAC) (expert agreement).

Clinical trials

- PRODIGE 44 (PANDAS) trial (NCT02676349): neoadjuvant chemotherapy with mFOLFIRINOX, followed or not by concomitant radiochemotherapy before surgery of borderline PDAC (randomized phase II study).
- PRODIGE 56 (APACaPOp) trial.

5.3. Locally advanced tumor

Treatment algorithm is summarized in Fig. 2.

Recommendations

- Supportive care from diagnosis (recommendation: grade A): treatment of symptomatic biliary and/or duodenal stenosis, pain and anxiety/depression, malnutrition, and thromboembolic events.
- ECOG PS 0–2: induction chemotherapy with gemcitabine (recommendation: grade A).
- ECOG PS 3–4: best supportive care (expert agreement).
- Reconsideration for potential resection at each imaging evaluation in case of tumor response (expert agreement).

Options

- Induction chemotherapy with FOLFIRINOX (ECOG PS 0–1) (recommendation: grade B) or gemcitabine plus nab-paclitaxel (ECOG PS 0–2) (expert opinion).

Metastatic pancreatic ductal adenocarcinoma (PDAC)

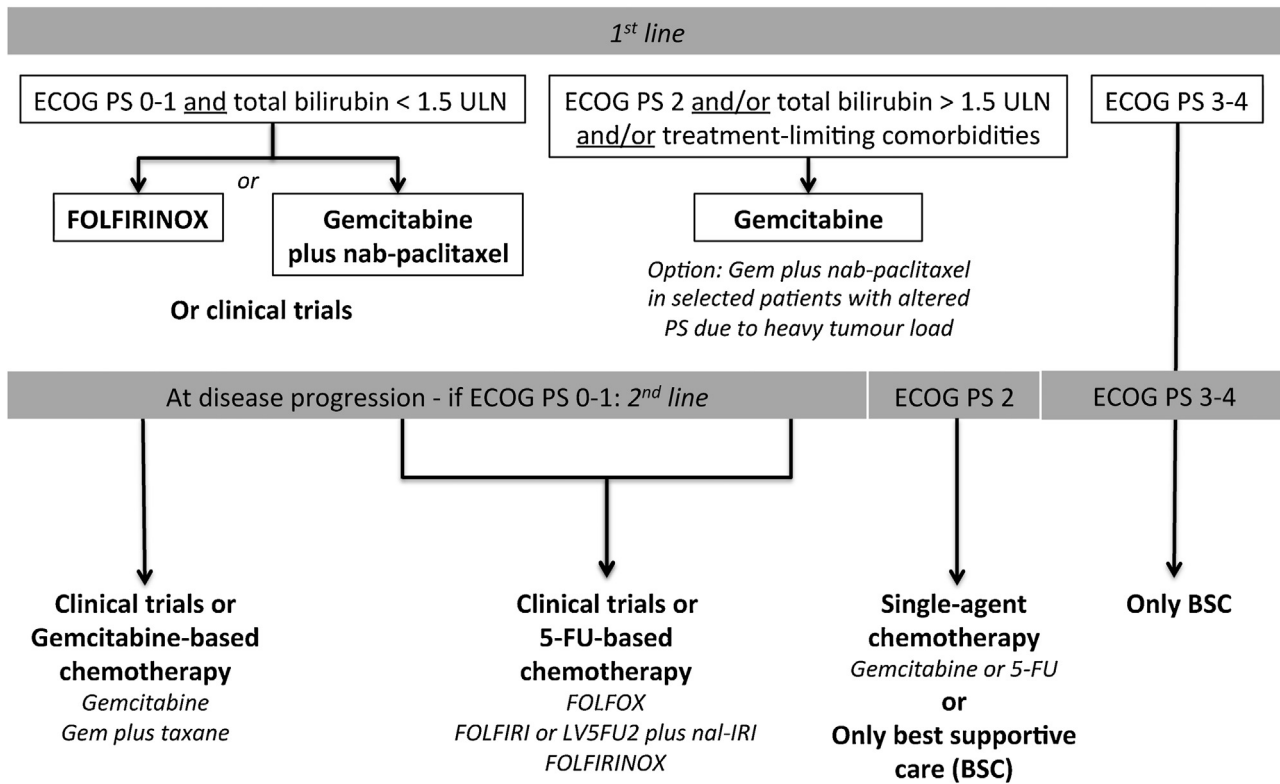


Fig. 3. Algorithm for treatment of metastatic pancreatic ductal adenocarcinoma (PDAC). ECOG PS: performance status; ULN: upper limit of normal.

- Chemoradiotherapy with capecitabine after at least three months of tumor control with systemic chemotherapy (recommendation: grade B).
- Secondary surgery if very good response, no metastasis, and operable patient (expert agreement).

Clinical trials

- PRODIGE 29 (NEOPAN) trial (NCT02539537): FOLFIRINOX versus gemcitabine in locally advanced PDAC (phase III study).
- PRODIGE 63 (TEDOPaM) trial: maintenance treatment with OSE2101 vaccine alone or in combination with nivolumab, or with FOLFIRI after FOLFIRINOX induction chemotherapy for locally advanced or metastatic PDAC (randomized phase II study).
- APACaP trial (NCT02184663): APA in patients with locally advanced or metastatic pancreatic cancer (phase III study).

5.4. Metastatic tumor

Treatment algorithm is summarized in Fig. 3.

5.4.1. First line

Recommendations

- Supportive care from diagnosis (recommendation: grade A) (same as locally advanced PDAC).
- ECOG PS 3–4: best supportive care (expert agreement)
- Age <75 years, ECOG PS 0–1 and bilirubin <1.5 ULN: FOLFIRINOX or gemcitabine plus nab-paclitaxel (recommendation: grade A).
- ECOG PS 2 and bilirubin <1.5 ULN: gemcitabine plus nab-paclitaxel (recommendation: grade B) or gemcitabine (recommendation: grade A).

- ECOG PS 0–2 and bilirubin ≥ 1.5 ULN or comorbidities: gemcitabine (recommendation: grade A).

Options

- ECOG PS 0–1: gemcitabine plus platinum or gemcitabine plus 5-FU (or capecitabine) (recommendation: grade B)
- ECOG PS 2 and/or bilirubin ≥ 1.5 ULN: FOLFOX (expert opinion).

Clinical trials

- PRODIGE 63 (TEDOPaM) trial.
- APACaP trial.
- URGENCE Pancreas Study (NCT02979483): prospective cohort evaluating an early supportive care program for symptomatic (ECOG PS 2) advanced PDAC.
- PRODIGE GEMFOX trial: first-line FOLFOX versus gemcitabine in patients with metastatic PDAC who are not eligible for FOLFIRINOX (phase III study).

5.4.2. Second line

Recommendations

- Chemotherapy if ECOG PS 0–1 (recommendation: grade A).
- FOLFOX (recommendation: grade B) after failure of gemcitabine.
- 5-FU/FA plus nal-IRI (recommendation: grade B) after failure of gemcitabine.

Options

- FOLFIRI after failure of gemcitabine (recommendation: grade C).
- Gemcitabine after failure of FOLFIRINOX (expert agreement).

- Gemcitabine plus nab-paclitaxel after failure of FOLFIRINOX if ECOG PS 0–1 (expert opinion).
- Gemcitabine or 5-FU single agent if ECOG PS 2 (expert opinion).
- Paclitaxel alone or with gemcitabine (expert opinion).

Clinical trials

- PRODIGE GEMPAX trial: gemcitabine plus paclitaxel versus gemcitabine alone after failure of FOLFIRINOX (phase III study).

6. Evaluation and surveillance

6.1. After treatment

Recommendations

- No reference.

Options

May be useful after curative surgical resection to detect recurrence at an early stage [162,163].

Proposal: (i) clinical examination, (ii) serum CA19-9 measurement when elevated at diagnosis, (iii) thoraco-abdomino-pelvic MDCT, every 3 months during 2–3 years, then every 6–12 months up to 5 years (expert opinion).

6.2. During treatment

Recommendations

- No reference.

Options

No data in the literature to define optimal surveillance modalities.

Proposal: same modalities as “after treatment” (expert agreement):

- Neoadjuvant or induction setting: every 2 months
- Adjuvant setting: every 3 months
- Advanced setting: every 2–3 months.

7. Treatment of tumor relapse

7.1. Metastatic relapse

Recommendations

- No reference.

Options

- Chemotherapy (recommendation: grade B). Type depends on: (i) patient’s general condition, (ii) extension of the disease and associated symptoms, (iii) residual toxicity of previous treatments, (iv) initial efficacy, (v) and treatment-free time interval.
- In very selected cases of long time interval between tumor resection and recurrence, oligometastatic pulmonary involvement, prolonged disease control with chemotherapy, and possibility of R0 resection: surgery or local destruction can be discussed (expert opinion). In patients who underwent PD and biliary digestive anastomosis, surgery recommended rather than local destruction (risk of liver abscess on ischemic cholangitis secondary to the reduction of the biliary arterial blood supply).

7.2. Loco-regional relapse

Recommendations

- No reference.

Options

- Treatment similar to that of unresectable PDAC (recommendation: grade B).
- In case of prolonged tumor control with chemotherapy ± chemoradiotherapy, and technical possibility of R0 resection, surgery may be discussed [164] (expert opinion).
- Occurrence of a second PDAC should be distinguished, particularly in case of predisposing condition (e.g. germline mutation or diffuse IPMN): it could be managed as a first tumor when resectable, taking into account patient’s general condition/comorbidities and morbidity of total pancreatectomy (expert opinion).

Conflicts of interest

C. Neuzillet: OSE Immunotherapeutics, Bristol-Myers Squibb, AstraZeneca.

N. Williet: Chugai Pharma, Sanofi.

J.B. Bachet: Amgen, Bayer, Celgène, Merck Serono, Roche, Sanofi, Servier, Shire.

T. Conroy: Roche.

L. Dahan: Sanofi, Amgen.

L. de Mestier: Ipsen, Pfizer, Novartis.

B. Napoléon: Boston Scientific, Maunakéa Technologies, Ipsen, Olympus.

F. Portales: Servier, Sanofi.

A. Sa Cunha: Merck Serono, Roche, Olympus, Eumedica, Novartis, Celgene.

O. Bouché: Roche, Merck, Amgen, Lilly, Novartis, Pierre Fabre, Bayer.

P. Hammel: Amgen, AstraZeneca, Celgene, Servier.

The other authors have reported no conflict of interest related to this work.

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