SEPTEMBER 2019

RECOMMENDATIONS AND GUIDELINES

/Summary

INITIAL MANAGEMENT OF PANCREATIC ADENOCARCINOMA CASES

ACHBT
ASSOCIATION DE CHIRURGIE
HEPATO-BILIO-PANCREATIQUE
ET TRANSPLANTATION

LABEL
INSTITUT NATIONAL DU CANCER

The French National Cancer Institute (INCa) is the health and scientific expertise agency in the field of cancer care responsible for coordinating cancer control in France.

This document was drafted by ACHBT (French Association of hepatobiliary surgery and transplantation) in partnership with SIAD (French Society of abdominal and digestive imaging, a body of the French Society of radiology (SFR), the French Society of gastroenterology (SNFGE), the French Society of digestive endoscopy (SFED), the French Federation of digestive oncology (FFCD), the French Society of digestive surgery (SFCD), the French Society of nuclear medicine (SFMN), the French Society of pathology (SFP) and the French-language Association for oncology supportive care (AFSOS) for the purposes of obtaining INCa accreditation.

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This means that the expert group received guidance from the Institute's departments and that the document was produced in compliance with the accreditation procedure and quality, methodological, and ethical rules.

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It is available to download on website **e-cancer.fr**

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INTRODUCTION

The incidence of pancreatic adenocarcinoma (PADC) is on the rise in mainland France, estimated at 14,220 cases in 2017 (7101 female cases and 7119 male cases).[1] PADC is associated with a very poor prognosis (the age-standardised net survival was 10% for females and 9% for males over the 2005-2010 period, in mainland France).[2] These 2 factors could explain why PADC is set to become the second cause of cancer-related mortality in 2030.[3]

One of the specific aspects of PADC is the complexity of the care pathway which involves a multidisciplinary team: general practitioner, radiologist, gastroenterologist, interventional endoscopist, digestive surgeon, medical oncologist, supportive care specialist, radiation oncologist. Failure of stakeholders to work together, a care pathway in an illogical order, or incomplete investigations require further testing, thereby prolonging the time to treatment.

Alongside vital challenges, the prolongation of survival has now brought with it other specific aspects of care (undernourishment, prevention of thromboembolic disease which is particularly frequent in this disease, pain management, diabetes, etc.) for which guidelines are needed.

The purpose of the project is to provide practitioners with national best practice guidelines for the diagnosis, treatment and follow-up of pancreatic adenocarcinoma patients in order to:

- standardise technical procedures in respect of diagnostic tests and disease staging, reading criteria and resectability criteria,
- define non-resectability criteria,
- standardise sampling techniques and define quality and reading criteria for anatomo-cyto-pathological tests,
- define the indications and technical procedures in respect of biliary drainage,
- define therapeutic response evaluation criteria,
- define the role of specific treatments in treating undernourishment, impaired general health, thromboembolic disease, pain management and diabetes in order to optimise cancer treatments throughout the care pathway,
- standardise monitoring frequency.

[1] Les cancers en France, 2017 edition, collection Les Données, Institut national du cancer, April 2018
[2] Les cancers en France, 2016 edition, collection Les Données, Institut national du cancer, April 2017
[3] Rahib L et al. Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. Cancer Res 2014;74(11):2913-2921.

TARGETS

These guidelines apply to adult pancreatic adenocarcinoma patients. Intraductal papillary mucinous neoplasms (IPMN), precancerous lesions with a high incidence but subject to specific literature and guidelines, are not covered in this document.

These guidelines are intended for healthcare professionals involved in the early detection, diagnosis, treatment and follow-up of pancreatic adenocarcinoma patients: digestive surgeons, hepato-gastroenterologists, medical oncologists, anatomo-pathologists, general practitioners, pain consultants, radiologists, radiotherapists, anaesthetists, molecular biologists (oncogenomic platform), oncogenetics consultants, oncogeriatrics consultants, nutritionists, nuclear medicine physicians, psychiatrists, hospital or dispensing pharmacists, and nurses.

This document summarises the main findings based on the data developed in the thesaurus, available to download on the e-cancer site. In this thesaurus, the reader will find all the justifications supporting these findings.

The methodology is described on page 35. A list of abbreviations is available on page 6.

It should be noted that all cases of pancreatic adenocarcinoma, prior to any therapeutic decision, must be reviewed as part of a Multidisciplinary Consultative Meeting (RCP). All major treatment changes and treatments for relapse must also be reviewed as part of an RCP review.

ABBREVIATIONS

CEA: carcinoembryonic antigen

PADC: pancreatic adenocarcinoma

GDA: gastroduodenal artery

HA: hepatic artery

SMA: superior mesenteric artery

CA 19-9: carbohydrate antigen 19-9

FPC: familial pancreatic cancers

MCRP: magnetic resonance cholangiopancreatography

ERCP: endoscopic retrograde cholangiopancreatography

PBD: percutaneous biliary drainage

NBD: nasobiliary drain

CDP: cephalic duodenopancreatectomy

DPD: dihydropyrimidine dehydrogenase

EE: echoendoscopy

EUS: endoscopic ultrasound

EUS-FNA: endoscopic ultrasound fine needle aspiration

FNA: fine needle aspiration

FNB: fine needle biopsy

5 FU: 5 fluoro-uracil

MRI: magnetic resonance imaging

LAPC: locally advanced pancreatic cancer

PanIN: pancreatic intraepithelial neoplasia

RAMPS: radical anterograde modular pancreatosplenectomy

RCP: multidisciplinary consultative meeting

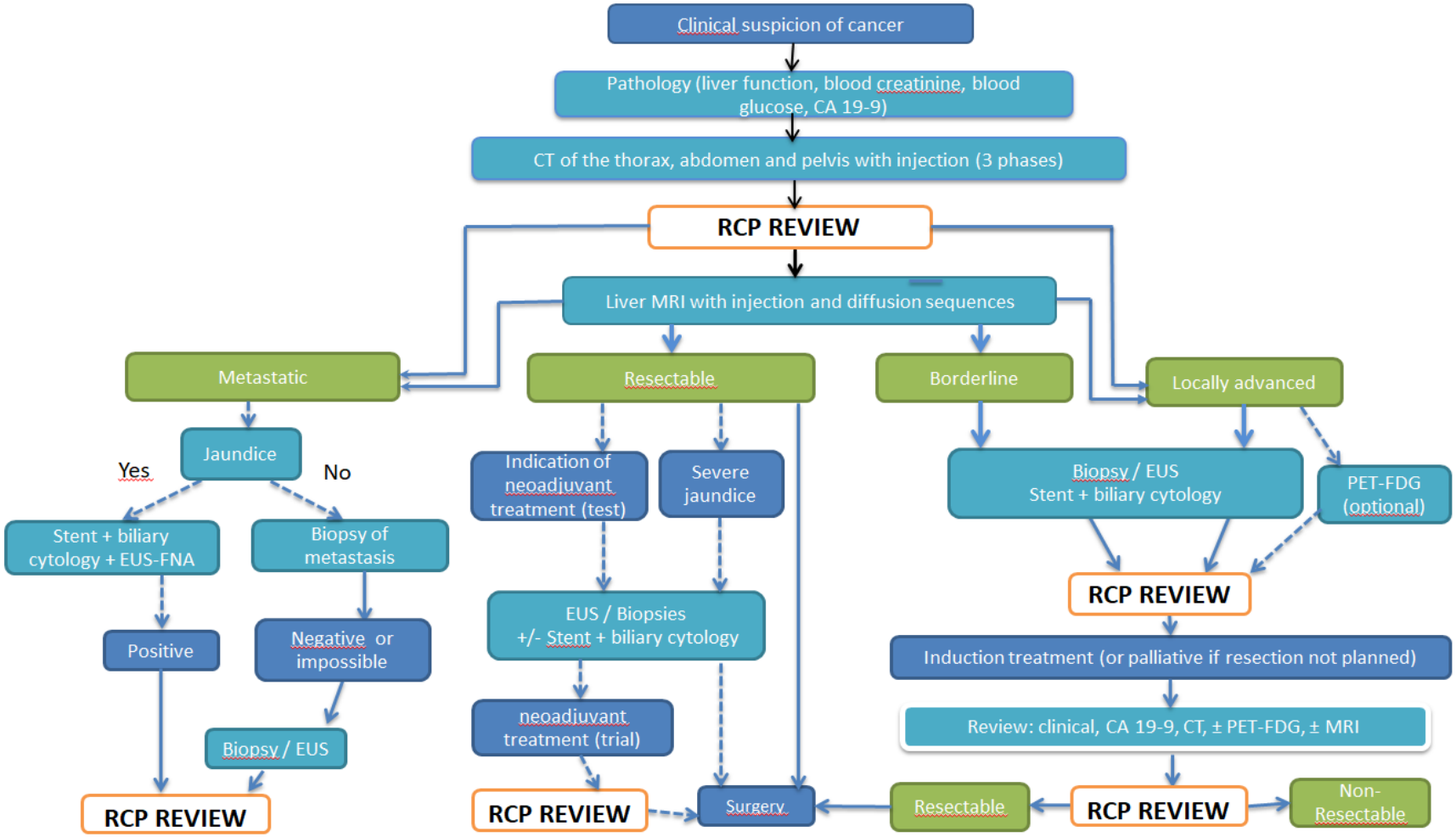
CT: computed tomography

CT TAP: computed tomography of the thorax, abdomen and pelvis

PET-FDG: fluorodeoxyglucose positron emission tomography

IPMN: intraductal papillary mucinous neoplasms

ALGORITHM


Clinical suspicion of cancer
Pathology (liver function, blood creatinine, blood glucose, CA 19-9)
CT of the thorax, abdomen and pelvis with injection (3 phases)
RCP REVIEW
Liver MRI with injection and diffusion sequences
Metastatic
Resectable
Borderline
Locally advanced
Jaundice
Yes
No
Stent + biliary cytology + EUS-FNA
Biopsy of metastasis
Positive
Negative or impossible
Biopsy / EUS
RCP REVIEW
Indication of neoadjuvant treatment (test)
Severe jaundice
EUS / Biopsies +/- Stent + biliary cytology
neoadjuvant treatment (trial)
RCP REVIEW
Surgery
Biopsy / EUS Stent + biliary cytology
PET-FDG (optional)
RCP REVIEW
Induction treatment (or palliative if resection not planned)
Review: clinical, CA 19-9, CT, ± PET-FDG, ± MRI
Resectable
RCP REVIEW
Non-Resectable

GUIDELINES

KEY

- **recommended courses of action**
- **unadvised courses of action or no recommendation possible due to a lack of data or insufficient data.**

SCREENING

IMPLEMENTATION OF SCREENING MEASURES

- It is recommended to implement screening measures due to an increased risk of pancreatic cancer in patients with:

A) chronic pancreatitis (Grade B)

- genetic form associated with PRSS1 mutations;
- idiopathic or genetic form associated with SPINK1, CTRC or CFTR mutations with abnormal pancreatic imaging (CT and MRI with MCRP).

B) a familial pancreatic cancer (FPC) context (with or without identified genetic anomaly) (Grade A):

- all first-degree relatives of index cases of FPC families (at least 2 first-degree cancers or 3 second-degree cancers);
- any patient with Peutz–Jeghers syndrome, i.e. carrier of a constitutional LKB1/STK11 mutation;
- any carrier of a constitutional mutation of the BRCA2 or PALB2 genes with a first-degree relative who has had pancreatic cancer or at least 2 relatives of any degree;
- any patient carrying a constitutional mutation of the CDKN2A/p16INK4 gene, or with Lynch syndrome with at least one case of pancreatic cancer in one first-degree relative.

- It is not recommended to screen for pancreatic cancer:

A) in cases of chronic pancreatitis (Grade C):

- of the auto-immune form as the increased risk is not known and evaluated to date;
- of the alcoholic form as the absolute increased risk of cancer is low in this population.

B) in cases of associated risk factors such as obesity, diabetes and tobacco consumption (Grade C).

ONCOGENETIC COUNSELLING

FOR ALL PANCREATIC ADENOCARCINOMA PATIENTS

- It is recommended to refer, for oncogenetic counselling, all patients with pancreatic adenocarcinoma and:

1) suspected hereditary syndromic form (Grade A)
   - Hereditary forms of breast and ovarian cancers, associated with a constitutional BRCA1/2 gene mutation (Hereditary Breast Ovarian Cancer, HBOC) identified in the family or presence of breast or ovarian cancers in ≥ 2 first-degree relatives (parents, children, siblings) or ≥ 3 relatives of any degree.

   - Hereditary forms of breast and ovarian cancers, associated with a constitutional PALB2 gene mutation identified in the family or presence of breast cancers in ≥ 2 first-degree relatives (parents, children, siblings) or ≥ 3 relatives of any degree.

   - Hereditary forms of skin melanoma with a constitutional CDKN2A/p16 gene mutation (Familial Atypical Multiple Mole Melanoma, FAMMM syndrome) identified in the family or presence of melanoma in ≥ 2 first-degree relatives (parents, children, siblings) or ≥ 3 relatives of any degree.

   - Peutz-Jeghers syndrome; constitutional STL11/LKB1 gene identified in the family.

   - Lynch syndrome; constitutional MMR (MLH1, MSH2, MSH6, PMS2) gene identified in the family.

   - Familial adenomatous polyposis, constitutional APC gene mutation identified in the family.

2) hereditary/familial non-syndromic form, defined by the validation of the following criteria (Grade B):
   - pancreatic adenocarcinomas diagnosed in ≥ 2 first-degree relatives (parents, children, siblings), regardless of their ages at diagnosis;
   - pancreatic adenocarcinomas diagnosed in ≥ 3 relatives regardless of the degree of relationship and the ages at diagnosis.

3) in isolated cases of pancreatic adenocarcinoma, if:
   - age at diagnosis ≤ 50 years (Grade C);
   - association with grade 2/3 multifocal pancreatic intraepithelial neoplasia (Pan-IN) lesions at a distance from the tumour, regardless of the age at diagnosis (expert opinion).

FOR ANY NON-DISEASED SUBJECTS

- It is recommended to refer any non-diseased subject meeting all of the following criteria for oncogenetic counselling:

- from an FPC (familial pancreatic cancers) family;
- first-degree relative with 1 or 2 index cases;
- index case of the family deceased therefore unable to undergo oncogenetic counselling (Grade C).

Screening methods

Examinations

- For pancreatic cancer screening in an at-risk patient, it is recommended to use endoscopic ultrasound and MRI, including MCRP and diffusion sequences (Grade C).
- CT is recommended in cases of contraindication to MRI, in cases where MRI is not technically satisfactory (motion artefacts) or is not suitable for analysing the pancreatic parenchyma satisfactorily, or to investigate an anomaly detected by MRI (expert opinion).
- It is recommended to conduct these examinations from the age of:

- 40 years for cases of hereditary pancreatitis;
- 50 years or 10 years prior to the index case in FPC (familial pancreatic cancers) cases (expert opinion).

FREQUENCY

- It is recommended to carry out (expert opinion):

- One examination per year in the absence of pancreatic anomalies (cystic lesion or parenchymal anomaly), using alternating MRI and endoscopic ultrasound.
- One examination every 6 months in cases of pancreatic anomalies, using alternating MRI and endoscopic ultrasound.

EARLY DIAGNOSIS

IN PATIENTS OVER 50 YEARS

- It is recommended to screen for pancreatic cancer, in patients aged over 50 years presenting with (Grade B):

- impaired general health associating asthenia, anorexia and weight loss;

- epigastric or abdominal pains, with impaired general health, or unexplained after upper digestive tract endoscopy;

- retention jaundice associating dark urine coloration, discoloured stools and frequently pruritus.

IN DIABETIC PATIENTS

- It is recommended to screen for pancreatic cancer in diabetic subjects in cases of:

1 - recent onset of diabetes (< 12 months) in a patient over 50 years of age with no family history of diabetes, and who is not overweight (BMI < 25 kg/m²) (expert opinion).

2 - recent onset of diabetes (< 12 months) in a patient with weight loss > 10% of their body weight (expert opinion).

- It is recommended to perform CT or MRI pancreatic screening (performed according to a dedicated technique) (expert opinion).

- In cases of recent decompensation of previous diabetes with no intercurrent disease explaining the decompensation, no guidelines can be formulated.

In patients with known chronic pancreatitis

- It is recommended to screen for pancreatic adenocarcinoma in patients with known chronic pancreatitis in the following circumstances:

A) In cases of chronic pancreatitis of genetic origin (Grade B):

- genetic chronic pancreatitis associated with PRSS1 mutations,

- idiopathic or genetic chronic pancreatitis associated with SPINK1, CTRC or CFTR mutations with abnormal pancreatic imaging (CT and MRI with MCRP).

B) In the following clinical scenarios (expert opinion): onset of diabetes, decompensated diabetes, onset or resurgence of chronic pancreatic pain, onset of acute pancreatitis, significant weight loss (> 10%), increased exocrine insufficiency, and cholestasis of recent onset or jaundice.

- To identify adenocarcinoma in cases of chronic pancreatitis, it is recommended to use:

a) as a first-line choice, CT and MRI;

b) in the event of a lack of anomalies typical of cancer or in the event of persistent doubt, endoscopic ultrasound (EUS) fine needle aspiration (if possible guided by contrast-enhanced endoscopic ultrasound) (Grade B).

- PET-FDG may be proposed, after inconclusive CT, MRI and endoscopic ultrasound (EUS) + biopsies, to perform a differential diagnosis between chronic pancreatitis and pancreatic adenocarcinoma (Grade C).

In patients with so-called idiopathic acute chronic pancreatitis

- In cases of so-called idiopathic (particularly non-alcoholic and non-biliary) acute pancreatitis in patients over 40 years, it is recommended to screen systematically for cancer with an initial workup including CT and MRI with MCRP initially, followed by endoscopic ultrasound if the cause is unclear on cross-sectional imaging (Grade C). This endoscopic ultrasound should not be too early as the inflammation may take on a tumour-like appearance (expert opinion).
- In the presence of necrotic fluid, it is recommended to defer the imaging assessment for a few weeks to improve its diagnostic value (expert opinion).
- In the absence of a tumour (or anomaly explaining the pancreatitis) displayed by CT, MRI and endoscopic ultrasound (EUS), it is recommended to continue cancer screening by repeating CT and MRI scans at 3 months, 6 months and 12 months:

- followed by annually for 4 years, for patients over 40 years of age (expert opinion);

- without continuing after that time for patients under 40 years of age (expert opinion).

POSITIVE DIAGNOSIS

CT METHODS IN CASE OF SUSPECTED PANCREATIC TUMOUR

- Multiphase CT scanning of the abdomen and pelvis, with contrast medium injection, in response to a structured request, including standardised instrumentation, a late arterial phase in respect of multiphase acquisitions and multiplanar reconstructions is recommended for pancreatic adenocarcinoma diagnosis (Grade B).
- In cases of pancreatic lesions, it is recommended to perform a CT scan of the thorax at the same time (see page 16). (Grade B)
- The CT report structure helps optimise diagnostic accuracy and resectability assessment. (Grade C).

ROLE OF CA 19-9 AND OTHER CIRCULATORY MARKERS

- The serum CA 19-9 assay is recommended in the following circumstances:

a) symptomatic patient with a pancreatic mass suggestive of cancer (Grade C),

b) chronic pancreatitis with suspected tumour mass (expert opinion),

c) pretherapeutic testing of a resectable or borderline/locally advanced tumour with prospect of surgery after induction treatment (expert opinion),

d) post-therapeutic follow-up (or postoperative follow-up) (Grade C).

- Exceptionally, in the presence of a pancreatic mass clinically and radiologically suggestive of cancer, very high CA 19-9 thresholds may be an alternative to obtaining histological evidence, if this proves to be impossible or has failed after several attempts, following approval as part of an RCP review in order to commence chemotherapy without delay (expert opinion).
- Serum CA 19-9 quantification is not recommended for screening in an at-risk subject (Grade B).
- Failing a suspected image of cancer, quantification of CEA (Grade A) and other markers (expert opinion) is not recommended outside clinical studies.

INDICATIONS OF MRI

- MRI is recommended for the positive diagnosis of pancreatic adenocarcinoma in cases of suspected lesions that fail to show up on CT scans due to their isodensity in the pancreas (Grade C).
- For patients for whom surgical resection is planned, either immediately or after induction treatment, it is recommended to carry out CT and MRI scans prior to biliary prosthesis insertion due to artefacts and inflammatory rearrangements associated with prosthesis insertion (expert opinion).

ENDOSCOPIC ULTRASOUND INDICATIONS AND METHODS

- It is recommended to carry out an endoscopic ultrasound examination associated with a biopsy:

- In the case of a questionable lesion detected by CT+MRI, even if it appears to be resectable, in order to reduce the risk of inappropriate pancreatectomy (Grade B).

- In cases of lesions suggestive of cancer, that is not accessible for immediate excision (borderline or locally advanced tumour) and non-metastatic, if an induction or palliative treatment is decided as part of an RCP review (Grade A).

- In cases of lesions suggestive of cancer accessible for immediate excision if neo-adjuvant treatment (therapeutic trial) is decided as part of an RCP review (Grade A).

- Rarely in cases of metastatic tumours, if the metastases are not accessible or if the biopsy has failed, prior to palliative chemotherapy (Grade A).

- It is recommended to carry out endoscopic ultrasound after CT +/- MRI in order to reduce biopsy-related artefacts (expert opinion).

- It is recommended to give the findings of the endoscopic ultrasound following a standardised report format (expert opinion).

- The use of contrast-enhanced endoscopic ultrasound (EUS) is recommended in cases of diagnostic difficulties with endoscopic ultrasound without contrast or difficulties locating the lesion to be biopsied (expert opinion).

- To obtain histological evidence, a maximum number of 3 biopsy attempts is recommended (expert opinion).

INDICATIONS OF BIOPSY AND SITES TO BE BIOPSIED

- In cases of imaging typical of pancreatic adenocarcinoma, but requiring first-line or exclusive chemotherapy treatment, it is recommended to carry out a pretherapeutic biopsy (Grade A).

- in the case of a non-metastatic pancreatic tumour, it is recommended to carry out a pancreatic biopsy by endoscopic ultrasound (Grade A). Percutaneous pancreatic biopsies are not recommended in this case (Grade C).

- in the case of a metastatic pancreatic tumour, it is recommended to carry out a biopsy under local anaesthetic of the metastatic site offering the easiest access (Grade C). Endoscopic ultrasound biopsies should be reserved for cases in which percutaneous metastasis biopsies have failed (Grade C). Percutaneous pancreatic biopsies may be used as an alternative as a last resort option (Grade C).

- In cases of pancreatic adenocarcinoma suitable for immediate resection and having a typical diagnosis in cross-sectional imaging in an operable patient, it is not recommended to perform a biopsy of the primary tumour, unless a neoadjuvant treatment is selected (Grade C).

HISTO/CYTOLOGICAL SPECIMEN PROCESSING

- For endoscopic ultrasound-guided FNA (EUS-FNA) processing, hybrid techniques enabling a cytological (monolayer or cytoblock) and histological approach are recommended (Grade C).

- Rapid on-site evaluation (ROSE) is not recommended due to the organisational problems generated, its limited diagnostic benefit and its cost (Grade C).
- Immunohistochemistry is not recommended in routine practice due to the minor improvement of the positive diagnosis of pancreatic adenocarcinomas provided (Grade C).

IN CASES OF NEGATIVE ENDOSCOPIC ULTRASOUND-GUIDED BIOPSIES

- The decision to repeat a biopsy depends on the context and must be taken as part of an RCP review:

- the decision not to carry out a further attempt should be approved as part of an RCP review (Grade C);

- in cases of diagnostic uncertainty between a tumour and a benign lesion not requiring surgery, it is recommended to make a further attempt (Grade C);

- in the case of a negative first attempt with an FNA type needle or in a difficult location (anterior part of the head or uncus) in a patient who would potentially benefit from effective treatment, it is recommended to repeat a further attempt with an FNB type sharp needle, carrying out 3 passages, if possible by a more experienced operator and using techniques optimising the findings (fanning, slow pull, contrast-enhanced guidance or elastometry) until a tissue specimen of macroscopic quality is obtained (Grade B).

ROLE OF PET

- PET-FDG is not recommended for characterising a pancreatic lesion or performing a differential diagnosis between chronic or autoimmune pancreatitis and pancreatic adenocarcinoma (Grade C).

Order of testing

See algorithm page 7.

DISEASE STAGING

TESTING AND TIME-FRAMES

- For the initial disease staging of pancreatic adenocarcinoma, it is recommended to carry out CT scanning of the abdomen and pelvis meeting specific acquisition criteria associated with CT scanning of the thorax at the same time (Grade B).
- It is recommended to carry out CT scanning prior to any endoscopic procedure (expert opinion) and within 4 weeks prior to any surgical resection. (Grade B).
- Prior to any decision in respect of surgical resection, MRI of the liver with diffusion-weighted imaging is recommended (Grade B.)

METASTATIC DISEASE

DIFFERENTIATING LIVER METASTASIS AND ABSCESSES

- MRI is recommended in cases of one or more focal liver lesions, in the event of uncertainty between abscesses and metastases (Grade B).
- If uncertainty persists, a needle biopsy of the lesions should be proposed (Grade B).

LYMPH NODE DISEASE STAGING

- In cases of radiological suspicion of periaortic lymph node involvement (group 16), it is recommended to carry out surgical lymph node excision biopsies (with extemporaneous or standard histological testing) prior to any decision to resect the primary tumour (Grade B).
- PET-FDG is an option for assessing the metastatic nature of periaortic lymph nodes visible in CT scanning (expert opinion).

SCREENING FOR LUNG, BONE OR OTHER METASTASES

- A recent CT scan of the thorax (< 4 weeks) is recommended to detect lung metastases and serve as a reference examination (Grade C).
- Regardless of the findings of the CT of the thorax, abdomen and pelvis and MRI (tumour resectable or not, metastatic disease), it is not recommended to screen for bone metastases or other extra-abdominal sites systematically. (expert opinion)

RESECTABILITY OF ADENOCARCINOMA (RESECTABLE, BORDERLINE, LOCALLY ADVANCED)

- It is recommended to carry out CT scanning prior to any treatment, biliary drainage and any pancreatic biopsy due to the risk of pancreatitis associated with endoscopic procedures and of artefacts associated with a biliary prosthesis (expert opinion).
- It is recommended to use the most recent NCCN classification to define resectable, borderline or locally advanced adenocarcinoma (expert opinion).
- It is recommended to use a structured report for the CT scan assessing local resectability (expert opinion).
- For the therapeutic decision, made as part of an RCP review, it is recommended not to use the NCCN classification result obtained from CT scanning as the sole factor in the decision, but also to take into account the patient's general health, the tumour pathology (tumour marker assay, likely course if available) and a geriatric assessment for elderly patients (> 75

years) (expert opinion).

ROLE OF PET-FDG IN INITIAL STAGING

- In cases of locally advanced, potentially resectable cancer based on the CT findings, PET-FDG may be proposed to screen for any metastases undetected by the CT scan and to serve as a reference when assessing the tumour response to the induction treatment (expert opinion).
- PET-FDG is not recommended systematically for the initial disease staging of non-metastatic pancreatic cancer with CT and MRI (Grade C).

ROLE OF LAPAROSCOPY OR EXPLORATORY COELIOSCOPY

- Laparoscopy including the investigation of "blind" zones may be indicated selectively, decided as part of an RCP review, for a patient having a high likelihood of liver or peritoneal metastasis undetectable with imaging (large or locally advanced or corporeocaudal tumour and/or associated with CA 19-9 elevation) (Grade C).
- Systematic laparoscopy prior to pancreatic adenocarcinoma resection is not recommended due to its poor cost-effectiveness (approximately 10-15%) after disease staging based on CT scanning of the thorax, abdomen and pelvis and liver MRI of good quality and the existence of false negatives (metastases detected during laparotomy) (Grade B).
- Failing sufficient data, it is not possible to formulate any guidelines in respect of cytology and perioperative ultrasound.

TREATMENTS OF OBSTRUCTIVE SYMPTOMS

BILIARY DRAINAGE PRIOR TO CURATIVE SURGERY

INDICATIONS

- It is recommended to reserve biliary drainage for patients with jaundice associated with at least one of the following conditions: hyperbilirubinaemia (variable threshold, between 130 and 250 µmol/l depending on the studies) (Grade C), angiocholitis, kidney failure associated with hyperbilirubinaemia and need to postpone surgery (operability evaluation, refeeding, neoadjuvant chemotherapy) (expert opinion).
- For patients with a bilirubin count between 130 and 250 µmol/L, indications of biliary drainage are dependent on the expected time to surgery and the patient's nutritional status (expert opinion).
- In cases of pancreatectomy in patients with a biliary prosthesis, it is recommended to sample bile perioperatively for bacteriological testing and to adapt the antibiotic prophylaxis regimen (expert opinion).
- Systematic preoperative transtumoral biliary stent drainage is not recommended due to the significant increase in the risk of postoperative complications, in particular for non-jaundiced patients or those with moderate jaundice (< 130 µmol/L) provided that the nutritional status is satisfactory and that the patient can undergo surgery without delay (Grade C).

PROCEDURE

- ERCP biliary drainage is recommended as the first-line approach (Grade B).
- In cases of endoscopic retrograde drainage, it is recommended to use a short metal stent ≤ 6 cm, in preference to long stents and plastic stents (Grade C).
- In cases of diagnostic uncertainty during biliary drainage, it is recommended to use an extractible covered metal stent in preference to a non-extractible non-covered metal stent, despite a greater risk of migration, pancreatitis and cholecystitis (expert opinion).
- If cases where the endoscopic retrograde approach has failed, it is not possible to formulate any guidelines for choosing between the endoscopic ultrasound route or the percutaneous route.

BILIARY DRAINAGE PRIOR TO NEOADJUVANT OR INDUCTION TREATMENT

INDICATIONS

- Biliary drainage prior to neoadjuvant chemotherapy is indicated:

- in the event of clinical symptoms (angiocholitis, pruritus) (Grade C);
- if bilirubin exceeds 1.5 times the upper limit of the normal and if irinotecan is to be used (Grade C).

- In the event of cholestasis at normal bilirubin levels or in the event of biliary duct dilatation without cholestasis, biliary drainage must not be performed (expert opinion).

METHODS

- Endoscopic retrograde biliary drainage is recommended as the first-line approach (Grade B).
- It is recommended to reserve stent insertion by the endoscopic ultrasound or percutaneous route to cases of endoscopic retrograde route failure (Grade B).
- It is recommended to insert a short metal stent ≤ 6 cm in preference to long stents and plastic stents (expert opinion).
- In cases of diagnostic uncertainty during biliary drainage, it is recommended to use an extractible covered metal stent in preference to a non-extractible non-covered metal stent, despite a greater risk of migration (Grade C).
- There is a lack of data available to recommend a particular type of metal prosthesis except in the absence of a formal cancer diagnosis — in these circumstances, it is recommended to a use a fully covered metal prosthesis, due to the easy extractability, enabling repeat samples (expert opinion).

BILIARY DRAINAGE IN CASES OF PALLIATIVE TREATMENT

INDICATIONS AND METHODS

- Biliary drainage by the endoscopic retrograde route is recommended as the first-line approach, except in cases of isolated jaundice (no pruritus) and in the absence of a treatment plan (Grade B). During this procedure, it is recommended to insert a metal stent in preference to a plastic prosthesis due to the shorter duration of permeability of the latter (Grade A).
- In the event of failure of the endoscopic retrograde route, it is recommended to use an endoscopic ultrasound-guided approach in preference to the percutaneous route (Grade C).
- It is not possible to make any recommendations between uncovered, covered or partially covered metal stents (Grade A).

INDICATIONS OF ENDOSCOPIC OR SURGICAL TREATMENT OF DUODENAL STENOSIS

- It is recommended to insert a duodenal stent in preference to surgical gastrojejunostomy in cases of predicted poor life expectancy (metastatic disease) or poor general health incompatible with laparotomy or prolonged chemotherapy (Grade C).
- Surgical gastrojejunostomy (if possible via the laparoscopic route) may be an option, in preference to a duodenal stent in cases of good life expectancy (locally advanced disease) and good general health compatible with prolonged palliative chemotherapy (Grade C).

ONCOLOGICAL TREATMENT OF LOCALISED FORMS

PREOPERATIVE TREATMENT: INDICATIONS, METHODS

- In cases of venous borderline pancreatic cancer, neoadjuvant treatment is recommended even if pancreatic and vascular resection is technically possible as immediate venous resection is associated with poorer prognosis (Grade C).
- In cases of arterial borderline pancreatic cancer, neoadjuvant treatment is recommended rather than immediate resection given the high morbimortality and the lack of oncological benefit of pancreatectomies with arterial resection (Grade C).
- In routine practice, if the patient is not included in a trial, chemotherapy (optionally followed by radiochemotherapy) is recommended. In cases of disease control and for selected patients, secondary resection must be proposed. There is, however, no consensus on the optimal induction treatment in this context (Grade C).
- Biliary drainage is recommended in cases of neoadjuvant or induction treatment for patients having biliary symptoms or if bilirubin exceeds 1.5 times the upper limit of the normal and if irinotecan is to be used (Grade C).
- Endoscopic metal prosthesis drainage is recommended, in preference to a plastic prosthesis (Grade B).
- Immediate surgery is not recommended in cases of borderline pancreatic cancer due to the high risk of positive margin(s), involving a proven negative prognostic impact (Grade C).

EVALUATION OF SECONDARY RESECTABILITY

- To evaluate the secondary resectability of a borderline or locally advanced tumour pre-treated by chemotherapy and/or radio-chemotherapy, it is recommended to carry out a CT scan of the thorax, abdomen and pelvis (Grade C) and a liver MRI with diffusion sequences (expert opinion).
- Evaluation of the biological response by assaying the CA19-9 level after neoadjuvant treatment for pancreatic adenocarcinoma is a useful indicator of prognosis, but it is not possible to recommend its use as an isolated criterion in terms of therapeutic orientation, due to the limited data available (Grade C).
- It is recommended to propose surgical investigation with a view to resection to all patients having a response or disease stability in a CT scan and a normalised or significantly reduced serum CA19-9 level (Grade C). This decision must be made as part of an RCP review with comparative imaging review.
- CT is the gold-standard examination for evaluating secondary resectability. PET-FDG may, compared to pretherapeutic PET conducted under identical conditions, be proposed to evaluate the tumour response (Grade C).
- Surgical investigation with a view to resection is not recommended in cases of local or loco-regional or distant radiological progression or if resection appears not to be technical feasible with an acceptable risk (locally advanced tumour) (Grade C).

IN CASES OF LOCALLY ADVANCED TUMOURS NOT SUITABLE FOR IMMEDIATE RESECTION OR REMAINING UNSUITABLE FOR RESECTION DESPITE INDUCTION TREATMENT

CHEMOTHERAPY

- In cases of locally advanced cancer, systemic chemotherapy is recommended (Grade C). Folfirinox-based chemotherapy is recommended for patients capable of tolerating it (Grade C).

CONSOLIDATION RADIOCHEMOTHERAPY

- Chemoradiotherapy is an option as a consolidation treatment after 3 to 6 months of induction chemotherapy for locally advanced pancreatic cancer in the absence of metastatic progression, with the aim of improving local control and increasing the treatment-free interval (Grade B).
- Radiotherapy must be sensitised with concomitant chemotherapy based on 5FU continuous IV 200 mg/m²/day or capecitabine 830 mg/m² X 2/day on radiotherapy treatment days (Grade A). In cases of DPD deficiency, concomitant gemcitabine at a weekly dose of 300 to 600 mg/m2 may be proposed (expert opinion).
- It is recommended that the radiotherapy dose delivered be between 50 and 54 Gy in a volume limited to the pancreatic tumour, using the 3D conformal or conformal intensity-modulated technique, accounting for pancreas movements (Grade B).
- Stereotactic radiotherapy is not recommended (outside clinical trials) due to the lack of standardisation of stereotactic radiotherapy regimens and the weak level of evidence of the studies published.

OTHER TREATMENTS UNDER EVALUATION

- For patients with locally advanced adenocarcinoma, ablative treatments are not recommended, outside clinical studies (Grade C).

SURGERY

ROLE OF PREOPERATIVE BILIARY DRAINAGE

- It is recommended to reserve drainage indications for patients presenting with clinical jaundice associated with the following conditions: hyperbilirubinaemia (variable threshold, between 130 and 250 µmol/l depending on the studies), severe undernourishment, angiocholitis, liver and/or kidney failure associated with hyperbilirubinaemia and need to postpone surgery (operability evaluation, refeeding, neoadjuvant chemotherapy) (Grade C).
- It is recommended to use endoscopic biliary drainage as the first-line approach. The percutaneous route and the endoscopic ultrasound route should be reserved for cases of endoscopic retrograde failure (Grade B).
- It is recommended to prefer a short metal stent ≤ 6 cm to long metal stents and plastic stents. In cases of diagnostic uncertainty during biliary drainage, an extractible covered metal stent should be preferred to a non-extractible non-covered metal stent, despite a greater risk of migration. Nasobiliary drainage is a possible alternative (Grade C).
- After biliary drainage, surgery is only recommended for patients if the blood bilirubin level has returned to a low value (twice the normal), regardless of the interval. (expert opinion)
- If biliary drainage is not sufficiently effective (persistent significant hyperbilirubinaemia), diagnostic investigations must be performed +/- associated with repeat endoscopic drainage procedures (Grade C).
- Systematic preoperative transtumoral biliary stent insertion is not recommended due to the significant increase in the risk of postoperative complications (Grade A).

NUTRITIONAL ASSESSMENT PRIOR TO PANCREATIC EXCISION

- Evaluation of the preoperative nutritional status is recommended (Grade C).
- Failing pancreatic cancer-specific data, no guidelines can be formulated on the refeeding strategy in pancreatic cancer.

ROLE OF ANTIBIOTIC PROPHYLAXIS/PERIOPERATIVE ANTIBIOTIC THERAPY

- Perioperative antibiotic prophylaxis based on third-generation cephalosporins is recommended for all pancreatic cancer surgery patients (Grade C).
- Perioperative antibiotic therapy for at least 5 days, adapted to the local epidemiology/bacterial ecology and following perioperative bile samples, is recommended for patients pre-treated with preoperative biliary drainage (Grade C).

EVALUATION OF IMMUNOLOGICAL STATUS

- Prescribing preoperative immunonutrition (nutrition enriched with fatty acids rich in omega-3, arginine and RNA) is recommended prior to pancreatic adenocarcinoma resection, regardless of the initial nutritional and immune status (Grade B).
- No guidelines can be formulated as to the parameters to be used for preoperative immune evaluation.
- No change of perioperative strategy (neoadjuvant treatment, exploratory coelioscopy,

perioperative nutrition or immunonutrition) can be recommended in cases of impaired immune response (Grade C).

- No validated preoperative sarcopenia treatment can be recommended at the present time.

ROLE OF PREHABILITATION

- No guidelines can be formulated as to the administration of a prehabilitation programme prior to surgical pancreatic cancer excision.

GERIATRIC ASSESSMENT

- It is recommended to screen for frailty using the G8 questionnaire in patients aged 75 years or over prior to surgical pancreatic cancer excision (Grade B).

GENERAL CONTRAINDICATIONS TO CDP AND TO SPG

- It is recommended to carry out a stricter selection of patients prior to cephalic duodenopancreatectomy than prior to left pancreatectomy, due to the higher morbi-mortality of the former procedure (Grade B).
- Age alone is not a contraindication but an oncogeriatric assessment is required if age > 80 years (or > 75 years with a G8 score < 14/17) along with a full operability evaluation to identify aggravating comorbidities (cardiovascular, pulmonary and renal) and functional and cognitive status (Grade B).
- In the case of a high ASA score (3), it is recommended to assess the benefit-risk ratio of the procedure very specifically, particularly for cephalic duodenopancreatectomy (Grade C).
- CDP is not recommended in cases of decompensated cirrhosis and/or cirrhosis with severe portal hypertension complications (oesophageal varices, splenomegaly) (Grade C). SPG is not recommended in cases of decompensated cirrhosis (expert opinion).
- Due to the lack of data in the literature, no guidelines can be formulated in respect of the (probably higher) risk of SPG non-compensated cirrhosis.
- In the event of the onset of impaired general health prior to any treatment or during the induction treatment, it is not recommended to carry out pancreatectomy as it is associated with a poor survival benefit (Grade C).

TECHNICAL CDP METHODS FOR ADENOCARCINOMA

- The first vessel approach is recommended for borderline tumours, whether pretreated or not (Grade B).
- Regional lymphadenectomy is recommended during CDP (Grade A).
- Pylorus preservation may be proposed as an alternative to CDP with distal gastrectomy (Grade A).
- Systematic bile sampling for bacteriological purposes is recommended, particularly in the case of prostheses, to adapt the perioperative antibiotic therapy (Grade C).
- It is recommended to prescribe a somatostatin analogue, initiated perioperatively, for patients at a high risk of fistula (thin Wirsung, soft pancreas) (Grade A).

- After CDP, systematic drainage is recommended if the estimated pancreatic fistula risk is high (soft pancreas, lack of Wirsung's duct dilatation) (Grade C). Absence of drainage is an option if the pancreatic fistula risk is low (Grade C).
- Laparoscopy is not recommended for CDP outside expert centres and prospective trials (Grade B).
- Lymphadenectomy extended to the left preaortic and periaortic lymph nodes is not recommended (Grade A).
- Systematic histological pancreatic slice testing is not recommended (Grade C).
- No type of anastomosis (pancreaticojejunal or pancreaticogastric) can be recommended to lower the pancreatic fistula risk (Grade A).
- No cancer-specific technique can be recommended for treating the slice, in particular in respect of pancreaticodigestive anastomosis

TECHNICAL SPG METHODS FOR ADENOCARCINOMA

- Despite a lack of formal evidence of its oncological equivalence, laparoscopy may be proposed as an alternative to laparotomy to carry out left splenopancreatectomy as laparoscopy lowers overall morbidity (Grade B).
- Splenectomy is recommended in left pancreatectomy for adenocarcinoma. (expert opinion).
- The resection technique according to the "RAMPS" procedure may be proposed as an alternative to "standard" left splenopancreatectomy (expert opinion).
- If abdominal drainage is used, early removal (D3 at the latest) is recommended in the absence of fistula (Grade C).
- No cancer-specific technique can be recommended for treating the pancreatic slice (Grade B).
- After left splenopancreatectomy, systematic abdominal drainage is not recommended. (Grade B).

INDICATIONS OF VASCULAR RESECTIONS DURING CDP AND SPG

VENOUS RESECTIONS

- Venous resection associated with pancreatectomy is recommended if R0 resection can be envisaged in cases of limited lateral or circumferential involvement but with no venous occlusion and in the absence of arterial contact with the coeliac trunk (cephalic tumours) of the superior mesenteric artery (all tumour sites) (Grade B).
- It is recommended to select patients in good general health as mortality and morbidity are higher than after pancreatectomy without venous resection (Grade B).
- In cases of scheduled venous resection, induction treatment is recommended due to the improvement in the rate of R0 resections and the survival provided (Grade B).

ARTERIAL RESECTIONS

- Due to their complexity and their specificities, CDPs with arterial resection (other than SMA) should be reviewed as part of a referral RCP review (expert opinion).
- CDP with scheduled arterial resection (with the exception of the SMA) may be proposed for selected patients whose tumour is stable or at best responding after induction treatment. This approach should be qualified according to the tumour site and the type of arterial extension (Grade B):

- in the case of an accessory right hepatic artery situated near the tumour, preoperative embolisation followed by "en bloc" resection is recommended (expert opinion),
- in cases of right HA - total liver: resection after induction treatment, with artery bypass reconstruction, may be proposed (expert opinion),
- in cases of invasion of a short segment of the common HA (invasion of GDA origin): resection after induction treatment with arterial reconstruction may be proposed (expert opinion).

- In cases of corporeocaudal cancer with coeliac trunk invasion, induction treatment is recommended. In cases of tumour stabilisation or response, distal pancreatectomy with coeliac trunk resection without arterial reconstruction may be proposed after radiological embolisation of the branches of the coeliac trunk (expert opinion).
- In cases of SMA invasion, induction treatment is recommended, followed in cases of tumour stability or response, by laparotomy with peri-arterial tissue dissection and biopsy (Grade C).
- If the results of extemporaneous peri-arterial tissue testing are positive, CDP with arterial resection is not recommended (Grade C).

INDICATIONS OF TOTAL PANCREATECTOMY AND/OR EXTENDED VISCERAL RESECTION DURING PANCREATECTOMY

- Total pancreatectomy may be proposed in cases of tumour extension to the entire pancreas in order to obtain R0 resection but must be reserved for selected patients due to high morbi-mortality, functional effects and poorer long-term survival than after partial pancreatectomy (expert opinion).
- Partial pancreatectomy extended to the adjacent organs may be proposed if it is necessary to obtain R0 resection (expert opinion).

IN CASES OF PERIOPERATIVE DETECTION OF LIVER METASTASES, PERITONEAL CARCINOSIS OR RETROPERITONEAL LYMPH NODE EXTENSION

LIVER METASTASES

- Excision of liver metastases detected perioperatively (synchronous metastases) is not recommended and this detection is a contraindication to pancreatectomy (Grade C).

PRECAVAL LUMBAR/PARA-AORTIC LYMPH NODE SAMPLING

- It is recommended to take a systematic para-aortic lymph node sample with extemporaneous testing regardless of the tumour site (Grade C).
- In cases of metastatic para-aortic lymph nodes, pancreatectomy is not recommended

(Grade B).

PERITONEAL CARCINOSIS

- In cases of peritoneal carcinosis proven by extemporaneous histology, pancreatectomy is not recommended (Grade B).
- Peritoneal cytology is not recommended in routine clinical practice due to the difficulties in performing extemporaneous testing (Grade B).

NON-RESECTABLE PANCREATIC CANCER

- Gastrojejunal bypass surgery may be proposed (Grade C).
- No guidelines can be formulated in respect of performing biliary bypass surgery.

R2 PALLIATIVE EXCISION SURGERY

- Palliative excisions (i.e. on macroscopically invaded margin) (R2) are not recommended (Grade B).

INDICATIONS OF SCHEDULED PALLIATIVE SURGERY

- Digestive bypass surgery (if possible by laparoscopy) is an option for patients with duodenal stenosis, a considerable life expectancy on the grounds of locally advanced disease and good general health (expert opinion).
- In cases of known metastatic disease, scheduled biliary bypass surgery is not recommended and endoscopic drainage should be preferred (Grade A).
- In cases of known metastatic disease, scheduled digestive bypass surgery is not recommended and an endoscopically guided duodenal stent should be preferred (Grade B).

FUNCTIONAL EFFECTS OF PROCEDURE

- Exocrine and endocrine pancreatic insufficiency screening and treatment after pancreatectomy due to cancer are recommended (Grade B).
- undernourishment screening and treatment after pancreatectomy due to cancer are recommended (Grade B).
- For the diagnosis of postoperative exocrine insufficiency, it is recommended to use functional investigations (the simplest being the faecal elastase assay) or a therapeutic test (pancreatic enzymes) (Grade B).
- Post-CDP, questionnaire-based screening and antimotility agent treatment of motility-related diarrhoea are recommended, especially if the CDP procedure included vascular resection or if treatment with pancreatic extracts alone is not effective on the diarrhoea. (Grade B).
- Post-total duodeno-pancreatectomy, it is recommended to prevent undernourishment (Grade C), and stabilise diabetes by particularly reducing the risk of hypoglycaemia (Grade

C).

- It is recommended to prevent ulcers on the gastro- or duodeno-jejunal anastomosis post-duodenopancreatectomy with PPIs; this prevention must be continuous and definitive post-total duodenopancreatectomy (expert opinion).

ANATOMO-PATHOLOGY OF THE SURGICAL SPECIMEN

TREATMENT OF SURGICAL SPECIMEN BY SURGEON AND PATHOLOGIST

- It is recommended to ink (by the surgeon) the CDP specimen and use an axial cross-section method for improved assessment of margin invasion. (Grade C)

MINIMUM ITEMS OF THE ANATOMO-PATHOLOGICAL REPORT

- It is recommended to draft a standardised report as this improves its overall quality, particularly in terms of exhaustiveness (Grade C).
- It is recommended to include the following anatomopathological items in the report (Grade B):

- Macroscopy protocol (inking, axial cross-sections).

- Histological tumour type, specifying the histological variants.

- Tumour size.

- Tumour differentiation.

- After neoadjuvant treatment, tumour regression assessment (CAP score).

- Presence of perineural invasion.

- Presence of vascular embolus and vessel invasion.

- Invasion of the various resection margins and for each, the distance between the boundary and the closest tumour cell.

- For each lymph node group, the number of lymph nodes tested and the number of metastatic lymph nodes.

- 2017 UICC 8th edition pTNM stage.

- Items not associated with the prognosis but which it is advised to mention (expert opinion).

- Appearance of adjacent parenchyma, presence of associated preneoplastic lesions (IPMN, cystic mucinous tumour or PanIN and grade).

- Calculation of ratio of positive lymph nodes (Lymph node ratio = LNR) to lymph nodes in the specimen.

DEFINITION OF R0 VS R1 RESECTION

- It is recommended to consider as R1 resections having a margin-tumour distance < 1 mm (Grade B), including after preoperative treatment (expert opinion).
- It is recommended to record the exact value of the margin (if < 5 mm) for each of the margins (impression of superior mesenteric vein/vena porta, retroportal slide/impression of superior mesenteric artery, posterior face, pancreatic, biliary, upper and lower digestive tract resections) (expert opinion).

SPECIFIC ASPECTS OF ANATOMO-PATHOLOGICAL REPORT POST-ANTITUMOUR TREATMENT

- For the macroscopic handling of a surgical specimen after preoperative treatment, the axial section technique and inclusion of the entire specimen (or at least of all of the "non-normal zones") are recommended (expert opinion).
- After preoperative treatment, it is recommended to assess "conventional" microscopic items (tumour size, tumour differentiation, perineural invasions, vascular emboli, measurement of margins (< 1 mm), lymph node invasion) in the same way as for untreated patients (expert opinion).
- To assess the tumour response to the preoperative treatment, it is recommended to use a tumour regression score, the most commonly used being the CAP score (expert opinion).
- To assess the pTNM stage, it is recommended to use that of the 2017 UICC 8th edition (ypTNM).

ADJUVANT TREATMENT

AFTER CURATIVE RESECTION

- In pancreatic adenocarcinoma, adjuvant chemotherapy improves survival significantly and is recommended over monitoring alone regardless of disease stage (Grade A).
- The benefit of this treatment is to be reviewed as part of an RCP review, particularly in cases of severe postoperative morbidity (expert opinion).
- In pancreatic adenocarcinoma, 6 months of mFolfirinox chemotherapy is standard regardless of disease stage, for patients in good general health (WHO 0-1) with no contraindications to 5FU + folinic acid, irinotecan or oxaliplatin (Grade A).
- For exceptional cases of subcentimetric tumours with no lymph node extension, monitoring alone or a reduced chemotherapy regimen may be discussed as part of an RCP review.
- If triple chemotherapy cannot be administered (poor general health or contraindication to one of the chemotherapy drugs), it is recommended to administer mono-chemotherapy based on 5FU+folinic acid or gemcitabine (which offer equivalent efficacy levels), or a gemcitabine+capecitabine combination (Grade A).
- It is not recommended to propose targeted therapy as none of these therapies have shown any benefit as an adjuvant in post-surgery pancreatic adenocarcinoma (Grade A).
- It is not recommended to propose postoperative radiotherapy or radio-chemotherapy, outside clinical trials (Grade A).
- Based on current knowledge, no guidelines can be formulated in respect of the adjuvant treatment to be used after induction treatment followed by pancreatectomy (expert opinion).

ADJUVANT TREATMENT REGIMEN BASED ON R0 OR R1 RESECTION TYPE

- In resected pancreatic adenocarcinoma, adjuvant chemotherapy for 6 months (mFolfirinox

or failing that gemcitabine or 5FU alone or gemcitabine+capecitabine) is recommended and improves survival significantly compared to monitoring alone regardless of resection type (R0 or R1) and the definition used (Grade A).

- For patients having had R1 resection, it is not recommended to propose postoperative radiotherapy or radio-chemotherapy, outside clinical trials (Grade A).

TIME-FRAME AND EVALUATION PRIOR TO COMMENCING TREATMENT

- In pancreatic adenocarcinoma, chemotherapy is recommended over monitoring alone regardless of disease stage (Grade A).
- It is recommended to commence postoperative chemotherapy within 12 weeks post-surgery (Grade B). During this phase, all necessary measures must be taken to optimise the patient's general health and thus enable the completion of the 6 months of treatment (Grade C).
- Prior to adjuvant chemotherapy, the patient assessment should include at least a CT scan of the thorax, abdomen and pelvis and a serum CA19-9 assay to ensure the absence of early recurrence of the disease (expert opinion).

PREDICTIVE BIOMARKERS OF RESPONSE

- In pancreatic adenocarcinoma, it is not possible to recommend any predictive biomarker of the efficacy of adjuvant chemotherapy, regardless of the type (gemcitabine, fluoropyrimidine, folfirinox) at the present time.

OTHER HISTOLOGICAL TYPES ON SURGICAL SPECIMEN: AMPULLOMA, CHOLANGIOCARCINOMA, OTHER PANCREATIC CARCINOMA

- In cases of cholangiocarcinoma of the primary biliary duct, capecitabine for 6 months is the recommended adjuvant treatment (Grade B).
- In cases of degenerated ampulloma, adjuvant chemotherapy for 6 months is recommended:

- based on gemcitabine for excreto-biliary or indeterminate phenotypes (Grade A);
- based on gemcitabine or folfox for intestinal phenotypes (expert opinion);
- by reviewing the benefit/risk balance as part of an RCP review for early forms (N0) (expert opinion).

- No guidelines can be formulated for other histological pancreatic carcinoma types.

TREATMENT OF METASTATIC FORMS AND RECURRENCES

FIRST-LINE SYSTEMIC TREATMENTS

- For patients in good general health (PS 0-1), with no jaundice, who have metastatic pancreatic adenocarcinoma, the use of first-line chemotherapy based on folfirinox or gemcitabine-nabpaclitaxel is recommended (Grade A).
- For patients in poor general health (PS 2) or over 75 years of age, the recommended treatment is gemcitabine or the gemcitabine +/- nabpaclitaxel combination (Grade A).
- No prospective data are available validating the use of folfirinox in patients over 75 years of age. An oncogeriatric assessment is recommended to aid the therapeutic decision in this context (Grade C).
- For patients presenting with cholestasis (total bilirubin > 1.5 times the normal value), there is no recommended chemotherapy treatment; an adapted-dose chemotherapy regimen may be envisaged after optimising the biliary drainage (Grade C).
- For patients showing significantly impaired general health (PS 3), palliative care alone, without chemotherapy, is recommended (expert opinion).
- The blood uracil level must be assayed (DPD phenotyping) prior to any 5 fluoro-uracil chemotherapy.

IN CASES OF TUMOUR PROGRESSION: SECOND-LINE TREATMENT SELECTION CRITERIA

- The use of a second-line treatment is recommended for patients in good general health (PS 0-1). However, evidence of its benefit has only been obtained for patients treated with gemcitabine as a first-line approach (Grade A).
- After progression under gemcitabine treatment:

1) a combination of 5FU and oxaliplatin is recommended for patients in good general health, (WHO 0-1) (Grade B). The OFF regimen should be preferred over the FOLFOX-6 regimen (Grade C);

2) the 5FU-leucovorin-liposomal irinotecan may be proposed for patients in good general health (PS 0-1) (Grade A). Liposomal irinotecan (Onivyde) is not included in the supplementary list. Access to this drug is dependent on the patients' treatment facilities.

3) the use of folfiri as a second-line treatment is not recommended due to a lack of prospective data (Grade C);

4) folfirinox is not recommended as a second-line treatment due to a lack of prospective data (Grade C).

- After progression under folfirinox treatment, the use of a second-line regimen based on gemcitabine may be recommended for patients in good general health (PS 0-1) (Grade C).
- The blood uracil level must be assayed (DPD phenotyping) prior to any 5 fluoro-uracil chemotherapy.

STEP-DOWN THERAPY

AFTER FOLFIRINOX-BASED INDUCTION CHEMOTHERAPY

- Maintenance chemotherapy based on 5FU monotherapy (LV5FU2 or capecitabine) is an option for patients having received 4 to 6 months of folfirinox (Grade B).

AFTER GEMCITABINE-NAB-PACLITAXEL-BASED INDUCTION CHEMOTHERAPY

- No step-down therapy can be recommended for cases of gemcitabine-nabpaclitaxel-based first-line chemotherapy. In cases of nabpaclitaxel-related limiting toxicity, gemcitabine may be continued until progression (expert opinion).

FACTORS FOR IDENTIFYING CANDIDATE PATIENTS FOR STEP-DOWN THERAPY

- Obtaining a significant tumour response after induction treatment, CA19-9 marker reduction or normalisation, and the asymptomatic nature of the disease are the factors to be taken into account to decide on step-down therapy (expert opinion).
- In view of the lack of formal evidence supporting step-down therapy, a treatment break is another option that may be envisaged after 6 months of folfirinox (expert opinion).

INDICATIONS FOR SURGERY AND ABLATIVE TREATMENTS FOR LOCOREGIONAL RECURRENCES AND METASTATIC FORMS

- Percutaneous radiofrequency ablation may be proposed as a treatment combined with palliative chemotherapy for selected patients presenting with single, exclusively liver metastatic involvement, < 2 cm in size (expert opinion).
- Surgical treatment may be proposed for cases of isolated metachronous lung metastases (Grade C).
- In cases of major biological response and well-documented full radiological response, the indication of treatment of the primary tumour and/or residual liver metastases may be proposed on a case-by-case basis (expert opinion).
- In cases of locoregional recurrence proven to be isolated, local treatments are to be discussed. The assessment of the course of the tumour disease should be taken into account in the therapeutic decision (assessment of response, median time to recurrence compared to initial surgery, induction chemotherapy treatment) (Grade C).
- No guidelines can be formulated on the surgical treatment of metachronous liver metastases of pancreatic adenocarcinoma due to the limited data available.

PALLIATIVE PHASE CARE

- It is recommended to detect, assess and treat the main debilitating symptoms such as pain, depression, impaired nutritional status early (Grade C).
- It is recommended to apply an iterative assessment involving the patient and those close to them, awareness-raising measures among all the professionals involved in the care

pathway, their inclusion in the multidisciplinary design of the care plan along with follow-up by a specialised supportive care-palliative care team helping address the patient's situation in an appropriate manner (expert opinion).

- It is recommended to treat debilitating symptoms early to improve palliative treatment compliance and tolerance (expert opinion).
- It is recommended to use folfirinox, gemcitabine or gemcitabine-nabpaclitaxel type chemotherapy regimens for which evidence of efficacy in improving symptoms such as pain and depression (Grade A).
- Combining supportive care and palliative chemotherapy should always be discussed in order to provide and maintain a superior quality of life for the patient (expert opinion).
- Early, active treatment, as per WHO guidelines, of pain, which is frequent and has a significant impact on the patient's quality of life, is recommended. (Grade B).
- Should these treatments be ineffective and/or give rise to significant adverse effects, it is recommended to discuss interventional techniques which have proven to be effective in reducing analgesic doses and improving the patient's general health as part of a multidisciplinary review (Grade C).
- Early screening for and treatment of depression are recommended (Grade C).
- Early, multidisciplinary treatment of anorexia, undernourishment and cachexia is recommended (Grade B).
- In advanced cancers or recurrences, LMWH prevention is recommended (Grade B).
- It is recommended to treat jaundice by biliary obstruction, as this treatment forms part of supportive care and the regimen should be determined as part of an RCP review (expert opinion).
- The treatment of pruritus and the prevention of skin lesions from scratching, its consequence should be managed with advice and treatments to be reviewed on a case-by-case basis (Grade B).

ONCOLOGICAL MONITORING

MONITORING PROCEDURE AFTER CURATIVE RESECTION

- After curative resection for pancreatic adenocarcinoma, it is recommended to screen for tumour recurrence prior to the onset of symptoms to enable the most effective treatment of this recurrence and improve long-term survival (Grade C).
- To screen for tumour recurrence, it is recommended to conduct a CT scan of the thorax, abdomen and pelvis and CA19-9 assay periodically (except for patients with an undetectable preoperative level: Lewis negative group) (Grade C).
- The recommended monitoring schedule is one postoperative check-up prior to commencing chemotherapy (expert opinion), followed by every 3 months for 2 years, then every 6

months for 3 years (Grade C).

- PET-FDG is not recommended systematically for detecting pancreatic adenocarcinoma recurrence, except as a second-line treatment if uncertainty remains on the conventional assessment (CT and CA19-9) (Grade C).

MONITORING METHODS FOR PATIENTS SURVIVING OVER 5 YEARS

- Post-pancreatectomy for IPMN cancer, it is recommended to continue monitoring the remaining pancreas after 5 years (expert opinion).
- For patients surviving more than 5 years post-pancreatectomy for cancer (excluding IPMN), no guidelines can be formulated in respect of monitoring of the remaining pancreas which is exposed to a second site risk of between 3 and 5%.
- As regards metastatic risk, a very low, essentially pulmonary, risk of recurrence remains after 5 years, for which no guidelines can be formulated (expert opinion).

FOLLOW-UP METHODS FOR LOCALLY ADVANCED OR METASTATIC CANCER

- CT scanning of the thorax, abdomen and pelvis may be proposed at 3-monthly intervals during chemotherapy (expert opinion):

- after initiating the first line of chemotherapy;

- in cases of tumour progression, after initiating a second line of chemotherapy.

- In the case of a treatment break, follow-up at 3-monthly intervals may be proposed (expert opinion).
- In cases of progression under second-line chemotherapy treatments (and subsequent lines) resulting in discontinuation of an antitumour treatment, no morphological monitoring is recommended (expert opinion).

METHODOLOGY

Guideline formulation methodology

The guidelines formulation methodology is detailed in the thesaurus, available to download on the INCa website.

It is based on:

- critical analysis of the best scientific data available used to assign a level of evidence to the findings from the literature;
- and the justified opinion of the experts of the working group.

A systematic bibliographic search was conducted over the period between 1 January 2007 and December 2018. The bibliographic search, methodological analysis and summary of the scientific data were conducted by the working group. The guidelines were formulated by the multidisciplinary working group. They were subsequently reviewed by a panel of independent reviewers from the working group by means of quantitative (grading) and qualitative (observations) reviews. The members of the working group finally reviewed the compiled observations with a view to finalising the document at a final meeting.

Recent publications, in 2019, were included prior to the final meeting of the working group.

Levels of evidence

The level of evidence consists of the ranking of the data of the literature on which the formulated guidelines are based. It is dependent on the type and quality of the studies available, as well as the consistency or lack of consistency of their findings. Details of the levels of evidence used are provided in the thesaurus. The findings of the literature were subsequently summarised and assigned a level of evidence according to the scale described in the thesaurus.

Grading of guidelines

Each guidelines is associated with a grade according to the scale described in the thesaurus and based on the level of evidence of the literature and the expert review by the working group and the reviewers.

In respect of the medicinal product

It should be noted that the marketing authorisations of some older drugs (particularly oxaliplatin, capecitabine, irinotecan), for which generic versions are now available, have never been reviewed despite changes in knowledge and practices. In this way, some of the courses of action recommended by the expert group for these medicinal products are based on the findings of trials conducted after the marketing authorisations were granted and on the ensuing clinical practices.

The adverse effects of medicinal product treatments are mostly mentioned in the summary of product characteristics of the marketing authorisation of the corresponding drugs. Some adverse

effects occurring after the drug was introduced on the market and not yet mentioned in the marketing authorisation are reported on the ANSM website.
In cases of severe (serious) adverse reactions that could be attributed to the cancer treatment, the treatment may be discontinued and the temporary discontinuation must be confirmed by the oncologist within 24 hours. As a general rule, temporary or permanent discontinuation of a cancer treatment as well as dose modifications fall within the remit of the medical oncologist and may give rise to a further multidisciplinary consultative meeting for a further therapeutic proposal if relevant.

Healthcare professionals are required to report any suspected adverse effects (online via the dedicated portal **http://solidarites-sante.gouv.fr/soins-et-maladies/signalement-sante-gouv-fr**, information also available on the ANSM website).

Working group set-up

These national guidelines were formulated by the multidisciplinary working group, representing the medical fields involved in the care pathway of pancreatic adenocarcinoma patients, practice methods and geographic divisions. It was formed by ACHBT (French Association of hepatobiliary surgery and transplantation) in partnership with SIAD (French Society of abdominal and digestive imaging, a body of the French Society of radiology (SFR), the French Society of gastroenterology (SNFGE), the French Society of digestive endoscopy (SFED), the French Federation of digestive oncology (FFCD), the French Society of digestive surgery (SFCD), the French Society of nuclear medicine (SFMN), the French Society of pathology (SFP) and the French-language Association for oncology supportive care (AFSOS).

The professional members of the national review group were proposed by the learned societies concerned by the scope of these guidelines and the regional oncology networks (detailed in the thesaurus).

WORKING GROUP, COORDINATION AND EXPERT REVIEWERS

The experts of the working group were contacted intuitu personae and not as a representative of an organisation, learned society or group of professionals.

INCa ensured that the experts proposed by the sponsor availed of the independence needed to carry out the expert reviews required based in particular on a review of their declarations of interest, published on the dedicated DPI-SANTE website.

Within the scope of the accreditation procedure, the review of the connections of interest was submitted by INCa's Expert Review Commission.

Coordination

Accreditation coordinator:

SAUVANET Alain, digestive surgery, CHU Beaujon, Clichy (ACHBT)

Working group

Theme 1: Screening (coordinator: REBOURS Vinciane)

BORIES Erwan, hepato-gastroenterology, Institut Paoli-Calmettes, Marseille
REBOURS Vinciane, pancreatology, gastroenterology, CHU Beaujon, Clichy
VULLIERME Marie-Pierre, radiology, CHU Beaujon, Clichy

Theme 2: Early diagnosis (coordinator: REBOURS Vinciane)

BORIES Erwan, hepato-gastroenterology, Institut Paoli-Calmettes, Marseille
REBOURS Vinciane, pancreatology, gastroenterology, CHU Beaujon, Clichy
VULLIERME Marie-Pierre, radiology, CHU Beaujon, Clichy

Theme 3: Positive diagnosis (coordinator: KOCH Stéphane)

BELLE Arthur, hepato-gastroenterology, Hôpital Brabois (CHRU Nancy), Vandoeuvre-lès-Nancy
GARCIA Stéphan, pathological anatomy, Hôpital Nord, Marseille
KOCH Stéphane, gastroenterology, Hôpital Minjoz (CHRU Besançon), Besançon
LUCIANI Alain, radiology, Hôpital Henri Mondor, Créteil (SIAD)
SAUVANET Alain, digestive surgery, CHU Beaujon, Clichy
WARTSKI Myriam, nuclear medicine, Hôpital Cochin, Paris

Theme 4: Disease staging (coordinator: TASU Jean-Pierre)

SAUVANET Alain, digestive surgery, CHU Beaujon, Clichy
TASU Jean-Pierre, radiology, medical imaging, Hôpital de la Milétrie (CHU Poitiers), Poitiers
WAGNER Mathilde, radiology, medical imaging, Hôpital Pitié-Salpêtrière, Paris
WARTSKI Myriam, nuclear medicine, Hôpital Cochin, Paris

Theme 5: Treatment of obstructive symptoms (coordinator: BORIES Erwan)

BORIES Erwan, hepato-gastroenterology, Institut Paoli-Calmettes, Marseille
RONOT Maxime, radiology, CHU Beaujon, Clichy
SAUVANET Alain, digestive surgery, CHU Beaujon, Clichy

Theme 6: Oncological treatment of localised forms (coordinator: SCHWARZ Lilian)

CASSINOTO Christophe, medical imaging, Hôpital Haut-Lévêque (CHU Bordeaux), Pessac
CROS Jérôme, pathological anatomy, CHU Beaujon, Clichy
HUGUET Florence, oncology, radiotherapy, Hôpital Tenon, Paris
MICHEL Pierre, hepato-gastroenterology, Hôpital Charles Nicolle (CHU Rouen), Rouen
SCHWARZ Lilian, digestive surgery, Hôpital Charles Nicolle (CHU Rouen), Rouen
TRUANT Stéphanie, digestive surgery, Hôpital Claude Huriez (CHRU Lille), Lille
VENDRELY Véronique, oncology, radiotherapy, Hôpital Haut-Lévêque (CHU Bordeaux), Pessac

Theme 7: Surgery (coordinator: DELPERO Jean-Robert)

BUC Emmanuel, digestive surgery, CHU Estaing (CHU Clermont-Ferrand), Clermont-Ferrand
DELPERO Jean-Robert, surgery, Institut Paoli-Calmettes, Marseille
SAUVANET Alain, digestive surgery, CHU Beaujon, Clichy
SCHWARZ Lilian, digestive surgery, Hôpital Charles Nicolle (CHU Rouen), Rouen
TRUANT Stéphanie, digestive surgery, Hôpital Claude Huriez (CHRU Lille), Lille

Theme 8: Pathological anatomy of surgical specimen (coordinator: CROS Jérôme)

BUC Emmanuel, digestive surgery, CHU Estaing (CHU Clermont-Ferrand), Clermont-Ferrand
CROS Jérôme, pathological anatomy, CHU Beaujon, Clichy
GARCIA Stéphane, pathological anatomy, Hôpital Nord, Marseille

Theme 9: Adjuvant treatment (coordinator: DAHAN Laetitia)

BACHET Jean-Baptiste, gastroenterology, digestive oncology, Hôpital Pitié-Salpêtrière, Paris
DAHAN Laetitia, gastroenterology, digestive oncology, Hôpital La Timone, Marseille
FARSI Fadila, oncology, Centre Léon Bérard, Lyon
HUGUET Florence, oncology, radiotherapy, Hôpital Tenon, Paris
VENDRELY Véronique, oncology, radiotherapy, Hôpital Haut-Lévêque (CHU Bordeaux), Pessac

Theme 10: Treatment of metastatic forms and recurrences (coordinator: DE LA FOUCHARDIERE Christelle)

BLANC Jean-Frédéric, hepato-gastroenterology, medical oncology, Hôpital Haut-Lévêque (CHU Bordeaux), Pessac
CROISE-LAURENT Valérie, medical imaging and radiodiagnostics, CHRU Nancy, Nancy
DE LA FOUCHARDIERE Christelle, medical oncology, Centre Léon Bérard, Lyon
FARSI Fadila, oncology, Centre Léon Bérard, Lyon
HUGUET Florence, oncology, radiotherapy, Hôpital Tenon, Paris
SCHWARZ Lilian, digestive surgery, Hôpital Charles Nicolle (CHU Rouen), Rouen
VENDRELY Véronique, oncology, radiotherapy, Hôpital Haut-Lévêque (CHU Bordeaux), Pessac

Theme 11: Oncological monitoring (coordinator: CROISE-LAURENT Valérie)
CROISE-LAURENT Valérie, medical imaging and radiodiagnostics, CHRU Nancy, Nancy
DAHAN Laetitia, gastroenterology, digestive oncology, Hôpital La Timone, Marseille
WARTSKI Myriam, nuclear medicine, Hôpital Cochin, Paris

Project follow-up by INCa

FERRAND Gabriel, project manager in Best Practices Department (until December 2018)
DUPERRAY Marianne, head of Best Practices Department
DAHAN Muriel, director of Guidelines and Medicines Division (until January 2019)
VERMEL Christine, head of Expert review quality and conformity team

National review

The list of all 70 reviewers is available in the thesaurus available to download on the INCa website e-cancer.fr.

/Summary
INITIAL MANAGEMENT
OF PANCREATIC ADENOCARCINOMA CASES

INSTITUT NATIONAL DU CANCER

52, avenue André Morizet
92100 Boulogne-Billancourt
France

Tel. +33 (1) 41 10 50 00
diffusion@institutcancer.fr

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