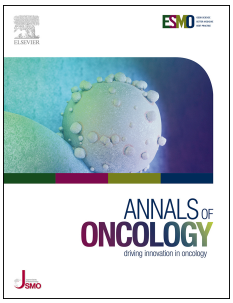

Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up†

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Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up†

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Highlights (online only; 3-5 bullet points of 125 characters each, including spaces):

- The guideline covers diagnosis, staging, risk assessment, treatment, disease monitoring and follow-up.
- The multidisciplinary expert author group is from different institutions and countries in Europe, Asia and the USA.
- Recommendations are based on available scientific data and the authors' collective expert opinion.
- ESMO-MCBS and ESCAT scores provide levels of evidence for treatment choices, including targeted therapies.
- In clinical practice, all recommendations provided need to be discussed with patients in a shared decision-making approach.

INCIDENCE AND EPIDEMIOLOGY

Details on incidence and epidemiology are covered in the **Supplementary Material Section 1**, available at *Annals of Oncology* online.

Risk factors

The opportunity to detect pancreatic cancer (PC) when potentially curable depends on early diagnosis and an ability to identify and screen high-risk populations before symptoms arise. Identification of a high-risk population is challenging and optimal screening tools remain unclear.[1] Older age is the strongest risk factor; incidence peaks at 65-69 years in males and 75-79 years in females.[2] A pooled analysis of 117 meta-analyses assigned a relative risk to a number of common risk factors (**Supplementary Table S1**, available at *Annals of Oncology* online).[3]

The vast majority (>80%) of PCs arise due to sporadically occurring somatic mutations. Only a small proportion are due to inherited deleterious germline mutations.[1] Familial PC, defined as at least two first-degree relatives with PC, accounts for only 4%-10% of all cases. Variants in *BRCA2* are the most common genetic abnormalities seen in familial PC. Other familial syndromes linked to PC are listed in **Supplementary Table S2**, available at *Annals of Oncology* online.

Individuals from families at risk should receive genetic counselling and be considered for enrolment in investigational screening registries. Currently, in high-risk individuals, annual endoscopic ultrasound (EUS) and/or pancreatic magnetic resonance imaging (MRI) are the procedures of choice for surveillance.[4] Surveillance programmes usually begin at age 50 (or 10 years earlier than the age of the youngest affected relative). Prospective surveillance data in high-risk individuals demonstrated high rates of resectability and encouraging observations of long-term survival.[5-9]

In sporadic PC, the major risk factors are tobacco, *Helicobacter pylori* infection and factors related to dietary habits (high red meat, high alcohol intake, low fruit and vegetable intake, overweight/obesity and type 2 diabetes mellitus).[2,3,10] Chronic pancreatitis, whatever the cause (alcohol abuse, smoking, genetic mutations), is a risk factor for PC. A proportion of the risk factors associated with PC are potentially

modifiable, affording a unique opportunity for primary prevention that is yet to be realised.

Recommendations

- Not smoking, limiting alcohol intake and reaching and maintaining a healthy weight are highly recommended to reduce the risk of PC [III, A].
- Individuals from families at risk should receive genetic counselling and be considered for enrolment in investigational screening registries [III, A].
- Surveillance in expert centres, usually beginning at age 50 years (or 10 years earlier than the age of the youngest affected relative), is recommended in high-risk individuals to detect early PC [III, A].
    - Annual EUS and/or pancreatic MRI are preferred for surveillance [IV, B].

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Approximately three quarters of PCs arise in the head of the pancreas, 17%-26% in the body and tail and the remaining 5%-8% in multiple pancreatic locations.[11,12] Tumours located in the body and tail are likely to be diagnosed at a more advanced stage relative to head tumours, as these latter tumours develop symptoms related to obstruction of the common bile duct and/or the pancreatic duct. Common presenting symptoms of PC include jaundice (head tumours), abdominal pain, weight loss, steatorrhoea and new onset or worsening of pre-existing diabetes. Tumours can grow locally into the duodenum (proximal for head tumours and distal for body/tail tumours) and result in duodenal obstruction.

Imaging

The imaging work-up aims to assess:

- Tumour location and size;
- Peripancreatic venous and arterial vascular involvement; and

- Locoregional involvement and metastatic extent (liver, lymph nodes, peritoneum and lung).

Computed tomography (CT) is the main modality for diagnosing PC. CT staging should include chest, abdomen and pelvis. In case of jaundice due to an obstructive head PC, the presence of bile duct dilation is an important landmark for delineation of these head PCs.

Technical optimisation is essential and key factors for high-quality CT are: i) multiphase thin-section images including pancreatic, arterial and portal venous phases; and ii) intravenous iodinated non-ionic contrast agent injection at 1.5 ml/kg and at a rate of 4-5 ml/sec. Diagnostic criteria for PC include direct signs such as a hypovascular tumour and indirect signs such as main pancreatic and/or common bile duct dilation, segmental atrophy of the parenchyma and abnormalities in pancreatic contour. The attenuation gradient between the tumour and the adjacent pancreas is greater in the pancreatic phase than in subsequent phases, and this phase performs best for tumour detection.[13] Delayed-phase CT increases the sensitivity for detecting small primary tumours.[14] CT should be carried out in the 4 weeks before starting therapy.

Abdominal MRI is usually used when CT is inconclusive, such as for isoattenuating tumours or when a contrast-enhanced CT is contraindicated; staging must include chest CT. The proportion of isoattenuating PC ranges from 5% to 17%.[13] MRI sequences should include T2-, fat suppressed T1- and diffusion-weighted sequences and magnetic resonance cholangiopancreatography (2D and/or 3D), followed by multiphasic contrast-enhanced sequences.

Several studies have demonstrated that MRI, including diffusion-weighted sequences, is more sensitive than CT for depicting small liver metastases. According to three series and a meta-analysis, MRI identified liver metastases that were not visible with CT in 10%-23% of cases. Thus, the rate of unnecessary laparotomy in potentially operable patients may be reduced.[15]

The imaging reports should detail tumour characteristics, tumour-to-vessel contact for each peripancreatic vessel, locoregional involvement (liver, lymphadenopathy,

omentum) and the presence/absence of distant metastases. The use of standardised reporting templates proposed by a multispecialist group of experts in PC[16] is recommended, as it has been shown that structured reports for PC staging significantly reduce the number of missing morphological and vascular features compared with free-text reports.[17]

A pathognomonic finding is the presence of a double duct sign identified at endoscopic retrograde cholangiopancreatography (ERCP) or on imaging related to obstruction of the bile and pancreatic ducts. ERCP, however, has little diagnostic value over CT or MRI for the evaluation of patients with PC. Positron emission tomography (PET)–CT is not routinely recommended for the diagnosis of PC, in view of the overlap of PC findings with autoimmune and chronic pancreatitis.[18] Furthermore, a meta-analysis of 17 clinical studies that recruited 1343 patients showed that PET–CT had no superiority over CT in identifying distant metastasis, with a 7.8% false-positive rate and a 9.8% false-negative rate.[19]

EUS is indicated for tumour staging in selected cases, e.g. isodense tumour at CT or when assessing venous involvement. EUS can also be used to biopsy pancreas, lymph nodes and lesions in the left liver or to sample ascites.

Biopsy is indicated for patients requiring differential diagnosis with benign chronic pancreatitis or a histological diagnosis, such as patients initiating chemotherapy (ChT); biopsy, however, is not routinely advised if surgical resection is planned. For localised disease, EUS-guided fine-needle biopsy is preferred, allows tissue confirmation of malignancy and is recommended over CT-guided biopsy. It is advised that at least one attempt be carried out unless unsafe for the patient. After two inconclusive attempts, treatment may begin without histological proof, provided multidisciplinary tumour board (MDTB) discussion, imaging and carbohydrate antigen (CA) 19-9 are consistent with a diagnosis of malignancy. Percutaneous biopsy of the most easily accessible tumour site can be carried out to confirm metastatic disease.

PET–CT can be considered for staging in the presence of non-metastatic disease on CT for patients who will receive local cancer treatment [surgery or radiotherapy (RT)].

The use of staging laparoscopy to evaluate peritoneal metastasis in resectable PC or borderline resectable PC (BRPC) has been advocated by some authors but is not routinely carried out.[20] Findings from a meta-analysis suggest that laparoscopy could be useful in this case.[21] Peritoneal lavage cytology in PC remains controversial due to its low sensitivity but is increasingly used, especially in Japan and Korea. Current studies are evaluating its prognostic impact.[22]

Pathology

PCs arise from both the exocrine and endocrine parenchyma; however, ~95% arise within the exocrine portion from ductal epithelium, acinar cells or connective tissue. Only 2% of tumours of the exocrine pancreas are benign. The most common type of PC is pancreatic ductal adenocarcinoma (PDAC), which accounts for ~80% of all PCs. Microscopically, these neoplasms vary from well-differentiated duct-forming carcinomas (that may mimic non-neoplastic glands) to poorly differentiated carcinomas, with epithelial differentiation demonstrable only on immunolabelling. PDAC typically elicits an intense stromal reaction.[23] Other variants of PC, such as adenosquamous carcinoma and undifferentiated carcinomas with osteoclast-like giant cells, are associated with a poorer prognosis. Conversely, pancreatic acinar-cell carcinomas have a slightly better prognosis than PDAC.[24] Pancreatic neuroendocrine tumours and neuroendocrine carcinomas are the second most frequent PC, a topic which is covered elsewhere.[25]

Cystic neoplasms represent 10%-15% of cystic lesions of the pancreas. The most commonly encountered cystic neoplasms include serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (either cystadenoma or cystadenocarcinoma). Mucinous lesions have potential for malignant progression and/or may harbour a malignancy at the time of diagnosis.[26] The non-mucinous lesions have no malignant potential.

The most frequent precursor lesions for PC are pancreatic intraepithelial neoplasia (PanIN), followed by IPMN and mucinous cystic neoplasm. PanIN are microscopic (<5 mm) mucinous papillary lesions, which lead to invasive carcinoma through an adenoma–carcinoma sequence.[23] Similarly, IPMN and mucinous cystadenoma become neoplastic by stepwise gene alterations.

Molecular biology

Genetic mutations. Multiple combinations of genetic mutations are commonly observed in PCs and can be classified as follows:

- Mutational activation of oncogenes, predominantly *KRAS*, is found in >90% of PCs;
- Inactivation of tumour suppressor genes such as *TP53*, *p16/CDKN2A* and *SMAD4*;
- Inactivation of genome maintenance genes, such as *hMLH1* and *MSH2*, which control DNA damage repair (DDR). Most of these mutations are somatic aberrations; and
- Alterations in genes specifically involved in the homologous recombination repair (HRR) pathway, such as *BRCA1* and *BRCA2*. Most of these mutations are germline.

Patterns of structural variation in chromosomes classify PC into four subtypes with potential clinical utility. The subtypes are termed ‘stable’, ‘locally rearranged’, ‘scattered’ and ‘unstable’. In the unstable group, a high rate of DNA variations is associated with significant defects in DDR, particularly in the HRR system. Additionally, genomic instability cosegregates with inactivation of DNA maintenance genes (*BRCA1*, *BRCA2* or *PALB2*) and a mutational signature of DDR deficiency. Overall, alterations in DDR/HRR pathways are observed in 24% of patients.

PC has also been classified using transcriptional networks. Two main clinically relevant subtypes have been identified. Squamous and ‘basal-like’ phenotypes share important aspects including high tumour grade, metastatic disease, chemo-resistance and poor prognosis. The ‘classical’ subtype has a more favourable outcome.[27] The genomics-driven COMPASS trial has provided the first evidence that ChT response rates differ among patients with advanced PDAC according to the transcriptomic profile.[27]

Genomic biomarkers. *KRAS*-wild type (wt) metastatic PDAC has been established as a unique molecular entity, for which therapeutic opportunities exist that extend beyond gene fusion events. Multigene sequencing is a useful tool to screen for rare, potentially actionable findings.[28,29]

Serum biomarkers. CA 19-9 is not useful for screening for PC. An increase in serum levels is identified in almost 80% of patients with advanced PC, which makes CA 19-9 significant as a prognostic factor. However, CA 19-9 is undetectable in patients with Lewis antigen-negative phenotypes. A preoperative serum CA 19-9 level ≥500 IU/ml indicates a worse prognosis after surgery and immediate surgery should be considered with caution in these cases.[30]

An algorithm for diagnostic work-up of suspected PC is given in **Figure 1**.

Recommendations

Imaging

- Multiphasic contrast-enhanced thoracic-abdominal and pelvic CT, including late arterial phase and portal venous phase, should be used as the first-line imaging modality for suspected PC [III, A].
- It is recommended that, in case of jaundice due to an obstructive head PC, imaging should be carried out before biliary drainage or stenting [IV, A].
- Imaging should be carried out in the 4 weeks before starting treatment [III, A].
- Abdominal MRI may be used when CT cannot be carried out, is inconclusive or for pancreatic cystic lesions [IV, C]; chest CT is mandatory [III, A].
- Dedicated imaging protocols are suggested [IV, B]. Comprehensive analysis of imaging findings should be incorporated in standardised reporting templates [IV, A].
- PET–CT is not recommended for diagnosis of primary tumours [III, D] but may be useful for staging localised tumours and in cases where the presence of distant metastases is uncertain (doubtful imaging or high CA 19-9) [III, B].
- Hepatic MRI is recommended before surgery to confirm the absence of small liver metastases [III, B].
- Cytology or biopsy proof of PC should be obtained before initiation of ChT, preferably by EUS guidance [III, A].

- All patients with localised disease should have imaging reviewed at an MDTB with experts in pancreas imaging, pancreas surgery and oncology [III, A].

Molecular biology

- Patients with family history and high-risk individuals should undergo genetic counselling [III, A].
- *KRAS* and *BRCA* testing are generally recommended [IV, B].
- If a *KRAS*-wt tumour is identified with next-generation sequencing, additional profiling can be carried out to evaluate for rare, potentially actionable findings [IV, B].
    - For patients with metastatic PC and *KRAS*-wt tumours, microsatellite instability (MSI) status, *NTRK* fusion status and other rare fusions should be assessed [III, B].
    - If multigene sequencing is not carried out, MSI and *NTRK* fusions can be detected using standard methods [IV, B].
- CA 19-9 can be used as a serum marker to measure disease burden and potentially guide treatment decisions [III, B].

STAGING AND RISK ASSESSMENT

Resectable or borderline resectable tumours

The prognosis of PC is primarily determined by tumour-related factors captured in the Union for International Cancer Control (UICC) 2017 tumour–node–metastasis (TNM) staging system. In the eighth edition, the T stage is based on size (except for pT4 tumours), as shown in **Supplementary Tables S3 and S4**, available at *Annals of Oncology* online. Furthermore, the N stage is subdivided into N1 and N2 according to the number of positive regional lymph nodes.

Aside from the UICC TNM and the National Comprehensive Cancer Network (NCCN) criteria[31], several studies have indicated the importance of tumour biology and host-related conditional factors. In 2017, the International Association of Pancreatology (IAP) released a definition of BRPC based on three dimensions: i) anatomical; ii) biological, including serum CA 19-9 level >500 IU/ml and regional

lymph node metastases diagnosed by biopsy or PET–CT; and iii) conditional, including Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2.[30] The author panel believes that these factors are also important for evaluating the tumour resectability.

Another major factor determining the prognosis of patients with resected tumours is the feasibility to receive and complete adjuvant treatment.[32,33]

Advanced disease

In advanced disease, the factors defining a worse prognosis are determined from the key phase III studies. Impaired general condition (ECOG PS ≥2), age >65 years, albumin <35 g/l, presence of synchronous metastases, liver metastases, number of metastatic sites and high serum CA 19-9 are negatively associated with survival.[33,34]

On completion of staging procedures and discussion in an MDTB, tumours should be categorised as resectable, borderline resectable, locally advanced or advanced/metastatic. A treatment decision must be taken in accordance with these findings, accounting for factors such as nutritional status, PS and comorbidities.

Recommendations

- Tumours should be staged according to the UICC TNM 8th edition staging system [III, A].
- Resectability can be assessed using both anatomical NCCN criteria and biological and conditional features following the IAP consensus [III, B].
- MDTB discussion in expert centres is required to define a recommended treatment strategy for patients with PC [III, A].

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

A treatment algorithm for local and locoregional disease is provided in **Figure 2**.

Treatment of resectable PC

Surgical resection is the only potentially curative treatment for PC. Following radiological evaluation, only patients with a high probability of surgical resection with

no tumour at the margin (R0; defined as no cancer cells within 1 mm of all resection margins) are good candidates for upfront surgery.

Anatomical resectability criteria. An expert consensus group has developed criteria to define tumour resectability, to improve patient selection and the rate of R0 resections.[20,35] According to the degree of contact between the tumour and the peripancreatic vessels [superior mesenteric vein (SMV) or portal vein (PV), superior mesenteric artery (SMA), coeliac trunk and common hepatic artery], tumours are classified as resectable, borderline resectable, locally advanced or advanced/metastatic. For resectable tumours, initial surgery remains the standard of care. These criteria have been adopted in the NCCN guidelines.[31] Although there are several other classification systems that assess tumour resectability, the NCCN criteria: i) are the most commonly used by far; ii) are regularly updated—the authors refer to NCCN Guidelines Version 2.2022 here;[31] and iii) have been extensively validated; the latest update was shown to be more accurate than prior versions.[36]

Resection and margins. The location and size of the tumour determine the type of surgery. Patients with tumours in the head of the pancreas undergo pancreatoduodenectomy (Whipple procedure). Dissection of the right hemi-circumference of the SMA to the right of the coeliac trunk is recommended to obtain a good medial clearance and to improve the rate of R0 resection.[37] In the event of vein involvement, complete venous resection (PV or SMV) followed by reconstruction to obtain R0 resection is possible. PV or SMV resection, however, is associated with a lower rate of R0 resection and poorer survival, likely due to the inherent aggressiveness of the tumour.[38] Arterial resections during pancreatoduodenectomy are associated with increased morbidity and mortality.

The International Study Group of Pancreatic Surgery (ISGPS) has recommended adhering to the guidelines of the British Royal College of Pathologists for specimen examination and microscopic tumour at the margin (R1) definition (i.e. margin <1 mm).[35] They advise surgeons to identify the following margins (when appropriate): anterior, posterior, medial or superior mesenteric groove, SMA, pancreatic transection, bile duct and enteric.

For patients with tumours in the body or tail, distal pancreatectomy, including resection of the body and tail of the pancreas and spleen, is usually undertaken. Radical anterograde modular pancreatosplenectomy with dissection of the left hemi-circumference of the SMA to the left of the coeliac trunk ensures R0 resection.[39]

Minimally invasive techniques can reduce the morbidity of pancreatectomies. Data relating to these techniques, however, are insufficient, particularly in relation to oncological results.[40] Therefore, open surgery remains the standard of care.

Lymphadenectomy. Standard lymphadenectomy should involve the removal of ≥16 nodes and is presented in **Supplementary Table S5**, available at *Annals of Oncology* online. In PC, extended lymphadenectomy is not recommended by the ISGPS.[41]

Age and pancreatectomy. Age alone is not a determinant for selecting patients for pancreatectomy. The definition of 'elderly patients' is not standardised and different cut-offs (70, 75 or 80 years) have been used.[42,43] A comprehensive systematic review and meta-analysis concluded that chronological age is not a contraindication for resection in experienced centres.[42] In cases of severe comorbidities (impaired ECOG PS >2) or severe malnutrition despite optimal supportive care, however, avoidance of surgery—even though technically feasible—may be justified. A surgical outcomes pancreatectomy score has been proposed that is calculated based on preoperative factors and accurately predicts the risk of perioperative mortality in patients undergoing PC resection.[44]

Preoperative biliary drainage. A randomised trial demonstrated an increased complication rate associated with routine preoperative biliary drainage in patients with a total bilirubin level ≤250 µmol/l (146 mg/l).[45] When the bilirubin level is >250 µmol/l, for patients planned to receive neoadjuvant treatment or for those for whom surgery will be delayed for longer than 2 weeks, endoscopic drainage is recommended; otherwise (e.g. bilirubin level ≤250 µmol/l), it should be considered on a case-by-case basis.

Neoadjuvant strategies. In this guideline, the authors define neoadjuvant therapy as preoperative treatment for patients with upfront resectable PC (preoperative

treatment for patients with BRPC or LAPC is referred to as induction therapy in this guideline). Three main approaches have been developed: neoadjuvant ChT, neoadjuvant chemoradiotherapy (CRT) and neoadjuvant ChT followed by neoadjuvant CRT.

Limited high-level evidence supports neoadjuvant therapy; literature-based meta-analyses compared neoadjuvant treatment with upfront surgery followed by adjuvant ChT and reported conflicting data on R0 resection rate and potential survival benefit.[46-48]

A small number of well-powered randomised trials comparing neoadjuvant therapy with initial surgery and adjuvant therapy have been completed in selected patients with resectable PC or BRPC (**Supplementary Table S6**, available at *Annals of Oncology* online).

The benefit of adjuvant ChT following neoadjuvant therapy and pancreatectomy remains to be established and randomised trial data to answer this question are lacking.

Criteria for resection following neoadjuvant or induction therapy. Performance of CT, EUS and MRI to assess resectability following ChT or CRT is lower compared with treatment-naïve settings.[49] The most common reasons are an overestimation of tumour size and extent of vascular invasion.[13] In particular, persistence of perivascular soft tissue is not synonymous with residual tumour and can be related to post-therapy changes. In a pooled analysis of 17 studies and 2242 patients, CA 19-9 decrease of >50% or a normalisation of CA 19-9 after neoadjuvant treatment were significantly associated with better overall survival (pOS; $P < 0.0001$).[50]

A decision on resectability status should be made in consensus at an MDTB based on imaging findings, serum CA 19-9, PS and clinical response.[51]

For BRPC and locally advanced PDAC, arterial resection after induction therapy is not recommended but can be considered in experienced centres on a case-by-case basis in selected patients. The most frequent procedure is resection of the common or proper hepatic artery with a direct or graft reconstruction. If technically feasible,

the common hepatic artery and celiac axis can be resected during distal pancreatectomy *en bloc* without reconstruction. Resection and reconstruction of the SMA are carried out occasionally and is an acceptable option if radical tumour removal can be achieved.[52,53]

Adjuvant therapy after surgical resection. The ESPAC-1 trial provided the first evidence that a survival benefit can be obtained from adjuvant ChT in resected PC, despite notable critics.[54] Results are summarised in **Supplementary Table S7**, available at *Annals of Oncology* online.

Supplementary Table S8, available at *Annals of Oncology* online, summarises additional trials conducted in the adjuvant setting for resected PC.

The CONKO-001 phase III trial demonstrated the efficacy of gemcitabine compared with observation.[55] The ESPAC-3 trial showed a similar survival benefit for either adjuvant gemcitabine or 5-fluorouracil (5-FU) and leucovorin (LV).[56] The ESPAC-4 trial built on the modestly improved OS signal for the combination of gemcitabine and capecitabine in the advanced-disease setting and randomised patients to gemcitabine or to gemcitabine–capecitabine.[57] This trial established gemcitabine–capecitabine as an adjuvant therapy option, although typically this combination is now reserved for patients not eligible for the modified LV–5-FU–irinotecan–oxaliplatin (mFOLFIRINOX) regimen.

Adjuvant mFOLFIRINOX has been established as the reference standard adjuvant therapy for fit patients who have undergone curative surgery for PC based on the results of the PRODIGE 24/CCTG PA.6 trial.[32,58] Both ESPAC-3 and PRODIGE 24/CCTG PA.6 trials identified completion of all cycles of adjuvant ChT as a favourable prognostic factor for OS.[58,59]

The APACT trial results provided insight into the role of gemcitabine–nab-paclitaxel (GN) in the adjuvant setting.[60] The study did not meet its primary endpoint [independently assessed disease-free survival (DFS)] and there is no role for GN in the adjuvant setting.

Adjuvant CRT.

Three randomised trials evaluated adjuvant CRT after pancreatic resection compared with surveillance alone. The first trial by the Gastrointestinal Tumour Study Group evaluating CRT (40 Gy and 5-FU) was stopped prematurely after the enrolment of 40 patients.[61] An interim analysis revealed a significant difference in survival in favour of the CRT arm.[62] An European Organisation for Research and Treatment of Cancer trial including 114 patients did not confirm a survival benefit for adjuvant CRT.[63] ESPAC-1 suggested a significant deleterious effect of adjuvant CRT (P = 0.05).[54] Additionally, in R1 patients, no benefit was observed with adjuvant CRT.[54]

Further details on the treatment of resectable PC are available in **Supplementary Material Section 2**, available at *Annals of Oncology* online.

Treatment of BRPC

In the event of BRPC, there is evidence supporting the use of induction treatment over upfront surgery.

In a recent meta-analysis of five studies of induction treatment in BRPC, there was a significant improvement in OS [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.44-0.85; P = 0.004].[46]

The PREOPANC-1 phase III trial reported outcomes for a total of 113 patients with BRPC and showed a significantly improved OS, DFS and locoregional failure-free interval in favour of induction CRT over upfront surgery.[65,66]

In summary, induction treatment for BRPC provides benefit for increasing the R0 resection rate and allows identification of patients most likely to benefit from surgical strategies; impact on OS seems promising.

The most appropriate induction strategy, ChT and/or CRT, is a controversial issue[67] and results from head-to-head comparisons in phase III trials are not yet available. Therefore, patients with BRPC should be enrolled into clinical trials whenever possible. If unfeasible, a period of induction ChT followed by CRT on a case-by-case basis and subsequent surgery appears to be a preferred option.

The multi-agent ChT regimens preferred in this setting are LV–5-FU–irinotecan–oxaliplatin (FOLFIRINOX)[68] or GN; otherwise, gemcitabine combined with oxaliplatin or capecitabine.

Regarding CRT strategies, most studies used full-dose RT paired with either capecitabine, 5-FU or gemcitabine. The addition of stereotactic RT following seven cycles of mFOLFIRINOX did not show benefit compared with mFOLFIRINOX alone.[69]

Optimal adjuvant therapy following induction treatment for BRPC is unclear with respect to both type and duration of treatment.

A small number of well-powered randomised trials comparing neoadjuvant therapy with initial surgery and adjuvant therapy have been completed in selected patients with resectable PC or BRPC (**Supplementary Table S6**, available at *Annals of Oncology* online).

Treatment of locally advanced PC

Locally advanced PC (LAPC) represents a spectrum of disease. In 30%-40% of patients, the tumour unresectable due to vascular involvement.[64]

In LAPC, the purpose of conversion (or induction) therapy is to induce tumour downsizing to facilitate resection in patients with initial unresectable disease. Reviews have demonstrated that induction therapy increases the possibility of an R0 resection and that OS is prolonged.[64,70,71] There are only a few randomised trials, however (**Supplementary Table S9**, available at *Annals of Oncology* online).

CRT. In the LAP-07 trial, CRT or maintenance ChT was tested in 449 patients without progressive disease following ChT alone.[72] Patients were treated with 4 months of gemcitabine–erlotinib or gemcitabine alone (first randomisation) and then randomised (269 patients) to continue with two months of ChT or CRT. The median OS (mOS) did not improve in the CRT group, but CRT was associated with delayed locoregional progression. The CONKO-007 trial produced very similar results using mainly FOLFIRINOX as induction treatment. The addition of CRT increased the

pathological complete response rate without any effect on progression-free survival (PFS) or OS.[73]

Systemic therapy. In a meta-analysis of 13 trials, mostly retrospective, that evaluated the efficacy of FOLFIRINOX ± RT in 315 patients with LAPC,[70] the pooled mOS from initiation of FOLFIRINOX was 24 months. The pooled proportion of patients who underwent resection was 26% (range 0%-43%).

In a recent review of optimal management of LAPC, resection was undertaken in ~30% of patients following FOLFIRINOX treatment and in ~20% following GN treatment.[64] A meta-analysis demonstrated that conversion surgery improved long-term survival of patients with initially unresectable PC who had a favourable response to induction therapy.[74]

Further details on the treatment of LAPC are available in **Supplementary Material Section 2**, available at *Annals of Oncology* online.

Recommendations

- **Treatment of resectable PC**Frozen section analysis of pancreatic neck transection and of common bile duct transection margins is suggested [IV, B].
- Tumour clearance should be defined for all margins identified by the surgeon [III, B].
- For patients with tumours in the body or tail, radical anterograde modular pancreatosplenectomy with dissection of the left hemi-circumference of the SMA to the left of the coeliac trunk is recommended [IV, A].
- The UICC TNM eighth edition staging system should be used to classify the anatomical spread of the tumour [III, A].
- Standard lymphadenectomy is recommended and should involve the removal of ≥16 lymph nodes to allow adequate pathological staging of the disease [IV, A].
- The total number of lymph nodes examined and lymph node ratio (number of involved lymph nodes as a proportion of the number of lymph nodes examined) should be reported in the pathological analysis [IV, A].

- Patients undergoing surgery should receive perioperative thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin (LMWH), unless contraindicated [I, A].
- If the bilirubin level is >250 µmol/l, endoscopic drainage is recommended in patients with cholangitis, those planned to receive neoadjuvant treatment or those in whom surgery will be delayed for longer than 2 weeks [I, B].
- Neoadjuvant therapy is not recommended for resectable PC due to limited phase III evidence, except in the context of clinical trials [II, E].
- Following resection of PC, completion of 6 months of adjuvant ChT is strongly recommended [I, A].
- Adjuvant mFOLFIRINOX is recommended for patients with resected PC and ECOG PS 0-1 [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A].
- In patients who are not candidates for mFOLFIRINOX (age >75 years, ECOG PS 2 or contraindication to mFOLFIRINOX), gemcitabine–capecitabine is an alternative option [I, B; ESMO-MCBS v1.1 score: A].
- Adjuvant gemcitabine or 5-FU−LV should be limited to frail patients [I, B].
- Adjuvant CRT is not recommended and should not be given to patients following surgery outside the setting of a clinical trial [I, E].

Treatment of BRPC

- Patients with BRPC have a high probability of an R1 resection and should be considered for induction treatment [III, A].
- Patients should be included in clinical trials whenever possible [III, A].
- If inclusion in a clinical trial is not feasible, induction therapy is recommended over initial surgery [II, A].
- A period of induction ChT (FOLFIRINOX or GN) followed by CRT on a case-by-case basis and subsequent surgery, is suggested, although GN is not EMA or FDA approved in this setting [III, B].
- Gemcitabine combined with oxaliplatin or capecitabine may be considered, when FOLFIRINOX or GN are not feasible [II, C].
- CRT with capecitabine may be considered after induction ChT [III, C].

- Following induction therapy, medically fit patients without disease progression and with a decrease in CA 19-9 should undergo surgical exploration, unless contraindicated [III, A].

Treatment of LAPC

- All patients must be evaluated by the local MDTB for resectability every 2-3 months [III, A].
- Patients with LAPC should be included in clinical trials whenever possible [III, A].
- A conversion surgery strategy utilising the standard of care of (up to) 6 months of combination ChT (FOLFIRINOX or GN) can be chosen [I, B]; GN is not EMA or FDA approved in this setting.
- Exploration for resection could be discussed if there is a significant decrease in CA 19-9 level, clinical improvement and tumour downstaging [IV, B].
- Arterial resection after induction therapy is not recommended but can be considered as a possibility in experienced centres on a case-by-case basis in selected patients [IV, D].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

First-line treatment

In 1997, gemcitabine monotherapy was established as the standard of care, after demonstrating some clinical benefit over 5-FU therapy. Gemcitabine-, capecitabine- and cisplatin-based combination regimens have produced limited benefits and the addition of targeted agents to gemcitabine have also been disappointing.[67]

A major improvement in the treatment of metastatic disease came with demonstrated superior efficacy of FOLFIRINOX over gemcitabine alone in patients with ECOG PS 0-1 and bilirubin level <1.5 times the upper limit of normal (ULN).[34]

Another trial demonstrated that GN is superior to gemcitabine alone in patients with metastatic disease.[33]

There are no prospective randomised data comparing FOLFIRINOX and GN in the metastatic setting. Numerous centres have published retrospective real-world data that suggest greater activity but also higher toxicity for FOLFIRINOX.[75,76] Recently, NALIRIFOX (liposomal irinotecan–5-FU–LV–oxaliplatin) was compared with GN in the randomised NAPOLI-3 phase III study including 770 patients. The PFS and OS were significantly improved in the NALIRIFOX arm [mOS: 11.1 months versus 9.2 months in the GN arm (HR 0.84, 95% CI 0.71–0.99, *P* = 0.04)]; however, the full results have not yet been published.[77]

A treatment algorithm for management of advanced/metastatic PC is provided in **Figure 3**. Further details on the first-line treatment of advanced and metastatic disease are available in **Supplementary Material Section 3**, available at *Annals of Oncology* online.,

Second-line treatment

In patients who have received a prior gemcitabine-based treatment, the combination of nanoliposomal irinotecan with 5-FU–LV showed an improvement in OS (6.1 versus 4.2 months; HR 0.67, *P* = 0.012), PFS and objective response rate (ORR) over 5-FU–LV in the randomised phase III NAPOLI-1 trial.[78] For fit patients with metastatic disease, this combination constitutes an active and tolerable second-line treatment option. In patients with advanced, gemcitabine-refractory PC, randomised trials of oxaliplatin combinations with 5-FU–LV have generated conflicting data. In the CONKO-003 trial, the addition of oxaliplatin to 5-FU–LV (OFF) led to improved OS compared with 5-FU–LV.[79] The modified LV–5-FU–oxaliplatin (mFOLFOX6) regimen had a detrimental effect on OS compared with 5-FU–LV.[80] The addition of oxaliplatin to tegafur–gimeracil–oteracil (S-1) compared with S-1 alone did not improve OS.[81] The author panel did not reach consensus regarding the benefit of oxaliplatin and 5-FU–LV in the second-line setting. There are no randomised data informing optimal second-line therapy selection following fluoropyrimidine-based first-line regimens.

Findings from the randomised phase III PRODIGE 65 - UCGI 36 - GEMPAX UNICANCER study showed that paclitaxel–gemcitabine provided no OS benefit over

gemcitabine alone as second-line therapy in patients with metastatic PDAC, but the combination did significantly improve both PFS and ORR.[82]

Third-line treatment

Most patients are considered unsuitable for third-line treatment due to poor nutritional status and/or poor PS, and no standard regimen can be recommended. In such cases, best supportive care (BSC) is the appropriate treatment choice. In patients with good PS, inclusion in a clinical trial is the first option when available.

Precision medicine in metastatic PC

A summary of biomarker and molecular targets for precision medicine in metastatic PC is provided in **Supplementary Table S10**, available at *Annals of Oncology* online.

***BRCA* mutations.** About 5%-7% of Caucasian patients harbour a germline *BRCA* (g*BRCA*) pathogenic variant that can be identified by germline testing after genetic counselling. Somatic testing may identify additional *BRCA* mutations.[83] The tumours of these patients are more susceptible to treatment with DNA crosslinking agents such as platinum compounds and poly (ADP-ribose) polymerase (PARP) inhibitors.[67] A randomised phase II trial in patients with g*BRCA* mutations demonstrated a high response rate for gemcitabine–cisplatin but failed to demonstrate a benefit for the addition of veliparib.[84] The POLO trial examined the efficacy of maintenance treatment with olaparib compared with placebo in patients with metastatic PC and g*BRCA* variants.[85] The study included 154 patients with disease that had not progressed following a 16-week platinum-containing regimen. The primary endpoint of median PFS (mPFS) was significantly improved by olaparib versus placebo (7.4 months versus 3.8 months, respectively; HR 0.53, $P = 0.004$). mOS, however, was not different between arms. The incidence of grade ≥3 adverse events was doubled in the olaparib arm (49% versus 25%).

There are no direct comparative data to inform whether FOLFIRINOX or cisplatin–gemcitabine is a preferred treatment strategy in patients with a *BRCA* mutation and

the choice should be guided by feasibility, potential toxicities and patient preferences.

Microsatellite instability high/ mismatch repair deficient. The frequency of MSI-high (MSI-H)/mismatch repair deficient (dMMR) in PC is ~0.8%,[86] with most occurrences being a Lynch syndrome, although sporadic cases occasionally occur. In the case of dMMR, treatment with checkpoint inhibitors has demonstrated some benefit.[87] In a prospective non-randomised trial, 22 patients with MSI-H/dMMR PC were treated with pembrolizumab. There was one complete responder and three partial responders (ORR 18.2%). mPFS was 2.1 months and mOS was 3.7 months.[88]

Pancreatic acinar-cell carcinomas contain *RAF* fusions and frequent inactivation of DNA repair genes,[89] which may be potentially targetable.[90]

NTRK fusions occur in *KRAS*-wt tumours and in >1% of all PCs. They are targetable with specific inhibitors, e.g. larotrectinib or entrectinib.[91]

A treatment algorithm for the use of precision medicine in metastatic disease is provided in **Figure 4.**

Recommendations

First-line treatment

- Options to treat patients with metastatic PC are dependent on PS:
  - In patients with ECOG PS 0-1 and bilirubin level <1.5 times the ULN, two regimens should be considered: FOLFIRINOX [I, A; ESMO-MCBS v1.1 score: 5] or GN [I, A; ESMO-MCBS v1.1 score: 3].
  - For patients with ECOG PS 2, Karnofsky PS (KPS) ≥70 and bilirubin level ≤1.5 times the ULN, GN can be considered [II, B; ESMO-MCBS v1.1 score: 3].
  - For patients with ECOG PS 2, KPS <70 and/or bilirubin level >1.5 times the ULN, gemcitabine monotherapy should be considered [I, A].
  - For patients with ECOG PS 3-4, symptom-directed care should be considered, as the risks of any ChT likely outweigh any benefit in this setting [IV, A].

- The efficacy of treatment should be typically evaluated every 8-12 weeks and should be based on clinical status, CA 19-9 trajectory and imaging [III, A].
- Patients with *BRCA* mutations should receive platinum-based ChT [III, A].

Second-line treatment

- After FOLFIRINOX treatment, GN (not EMA or FDA approved as second-line therapy) or gemcitabine alone may be offered to patients with ECOG PS 0-1 and a favourable comorbidity profile [III, C].
- In patients with, or who have recovered to, ECOG PS 0-1 and who have been pretreated with a gemcitabine-based regimen, nanoliposomal irinotecan–5-FU–LV (EMA and FDA approved in metastatic PC) can be considered [I, B; ESMO-MCBS v1.1 score: 3].
- Oxaliplatin-based second-line treatment (mFOLFOX6 or OFF) remains controversial but may be considered as an alternative in patients with ECOG PS 0-2 if not given previously [II, C].
- For patients with ECOG PS 3-4, symptom-directed care is recommended as the risks of any ChT likely outweigh any benefit [IV, A].

Third-line treatment

- Most patients are considered unsuitable for third-line treatment due to poor nutritional status and/or PS
    - In such cases, no standard regimen can be recommended and BSC is the appropriate treatment choice
- In patients with a good PS, inclusion in a clinical trial is the first option when available

Precision medicine in metastatic PC

- *BRCA* genetic testing should be offered to all patients with metastatic PC to determine eligibility for selection of platinum-based ChT, followed by maintenance with olaparib [I, B; olaparib ESMO-MCBS v1.1 score: 2].
    - Olaparib maintenance treatment is an option for patients with a g*BRCA1/2* variant whose disease is stable or responsive to platinum-based ChT [I, B; ESMO-MCBS v1.1 score: 2; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A].
- In patients with MSI-H/dMMR pancreatic tumours, pembrolizumab can be proposed as second- or later-line treatment [II, B; ESMO-MCBS v1.1 score: 3;

ESCAT score: I-C; Food and Drug Administration (FDA) approved; not EMA approved as a dMMR/MSI-H tumour-agnostic indication but for specific tumour types (excludes PC)].

- In patients with an *NTRK* fusion, larotrectinib or entrectinib is recommended [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C].

FOLLOW-UP, SUPPORTIVE CARE, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Follow-up

There is scant evidence that regular follow-up after initial therapy with curative intent has an impact on outcome. Patients within active surveillance programmes may be more likely to have their recurrence detected at an asymptomatic stage and to receive treatment for recurrence;[92] the impact on OS, however, remains unclear.

Supportive and palliative care

Exercise. Patients with PC are at high risk of developing sarcopenia and cachexia.[93] Exercise has been recommended as an effective therapy for patients to manage fatigue, psychological distress, mitigate muscle loss and decline in physical function and quality of life.[94] It has been postulated that exercise normalises tumour vasculature and may lead to increased ChT delivery.[95] Exercise also promotes immune mobilisation and interleukin (IL)-15 axis stimulation.[96] Interesting data are emerging from small studies evaluating the role of prehabilitation in the management of resectable PC[97]; formal evidence, however, is pending.

Thromboprophylaxis. The reported prevalence rate of venous thromboembolism in PC was shown to be ~25%.[98] The occurrence of these thrombotic events is not limited to the peripheral venous system; it can also occur in deep venous trunks and in the visceral system. The mechanism is multifactorial,[98] with the risk further increasing with ChT administration.[99] Three trials demonstrated the safety and efficacy of primary prevention for venous thromboembolic events with prophylactic

LMWH, apixaban or rivaroxaban in outpatients with advanced PC undergoing ChT.[98] A randomised trial of patients with cancer and acute venous thromboembolism (VTE) found that 6 months of direct oral anticoagulants was noninferior to LMWH therapy for preventing VTE recurrence over a 6-month follow-up. Rate of major bleeding was not significantly different between groups.[100]

Other interventions. Patients with PC may need intervention to provide relief of biliary and/or duodenal obstruction, malnutrition and pain. In the event of biliary obstruction due to the tumour, endoscopic placement is safer than percutaneous insertion and is as successful as surgical hepaticojejunostomy.[101] Duodenal obstruction is preferentially managed by endoscopic placement of an expandable metal stent, whenever possible, and favoured over digestive bypass.[101]

Pancreatic enzyme replacement therapy can help manage the symptoms of exocrine insufficiency, such as weight loss, abdominal discomfort or steatorrhoea.

Effective pain palliation is a major priority in many patients with advanced PC. Pain must be managed aggressively following standard guidelines on pain treatment.[102] The input of a pain control specialist is often mandatory. A coeliac plexus block (CPB) can effectively relieve pain and, as a result, frequently lead to a decrease in the total amount of narcotic drugs and their associated side-effects. The preferred way to carry out a CPB is via EUS guidance. CPB should be used for persistent pain and only if the PS is adequate.

Recommendations

Follow-up

- For patients with resected PC, regular follow-up is suggested, although there is insufficient evidence of an impact on OS [IV, B].

Supportive and palliative care

- Primary thromboprophylaxis should be considered in advanced PC patients receiving ChT [I, B].

- In the event of biliary obstruction, endoscopic placement of a fully covered, self-expandable metallic biliary stent is suggested [II, B].

- Duodenal obstruction can be preferentially managed by endoscopic placement of an expandable metal stent instead of surgery [IV, B].

- Effective pain control is strongly recommended and should involve a pain control specialist when required [III, A].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the authors. A table of ESCAT scores is included in **Supplementary Table S10**, available at *Annals of Oncology* online. ESCAT scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[103] A table of ESMO-MCBS scores is included in **Supplementary Table S11**, available at *Annals of Oncology* online. ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in **Supplementary Table S12**, available at *Annals of Oncology* online.[105] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/pancreatic-cancer.

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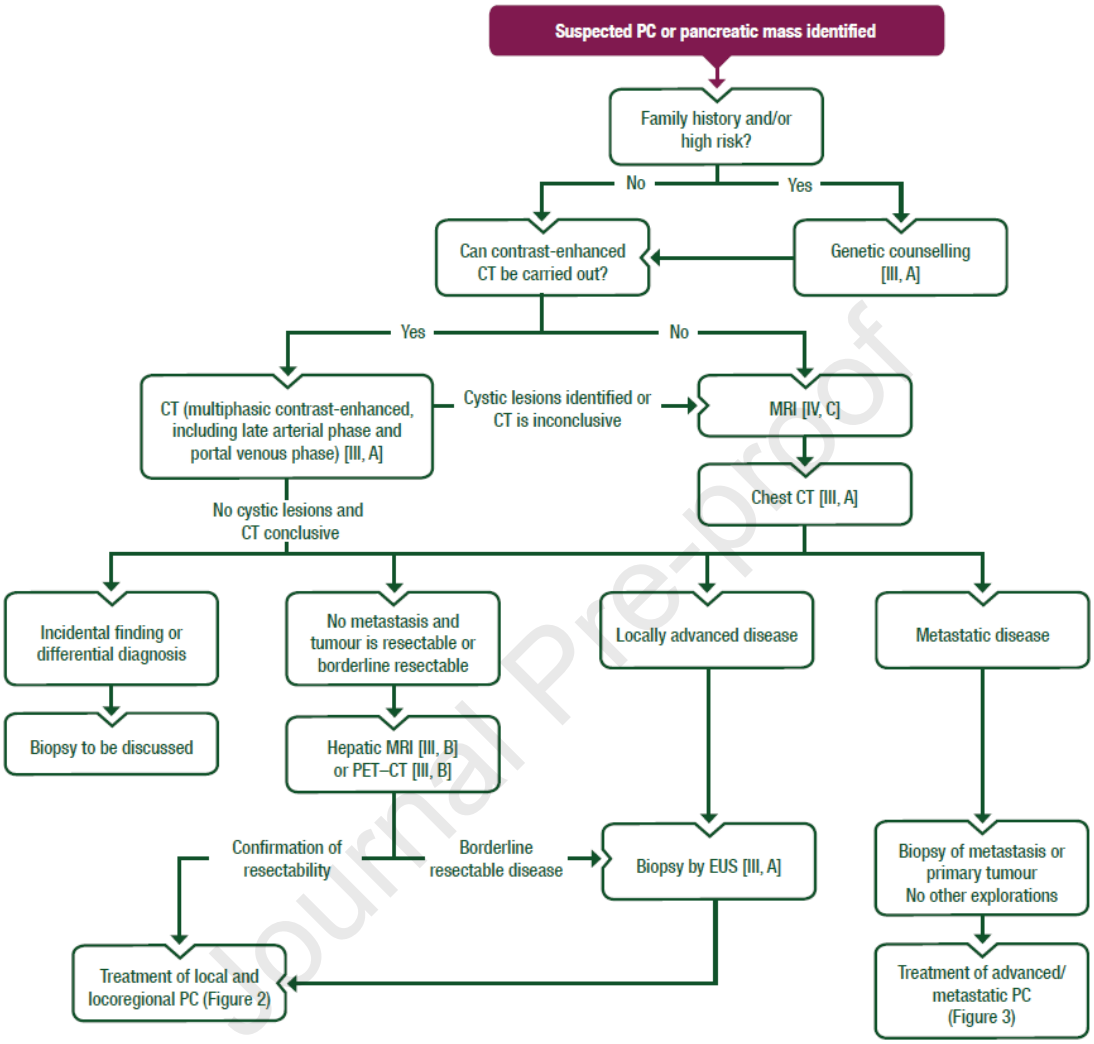
FIGURES

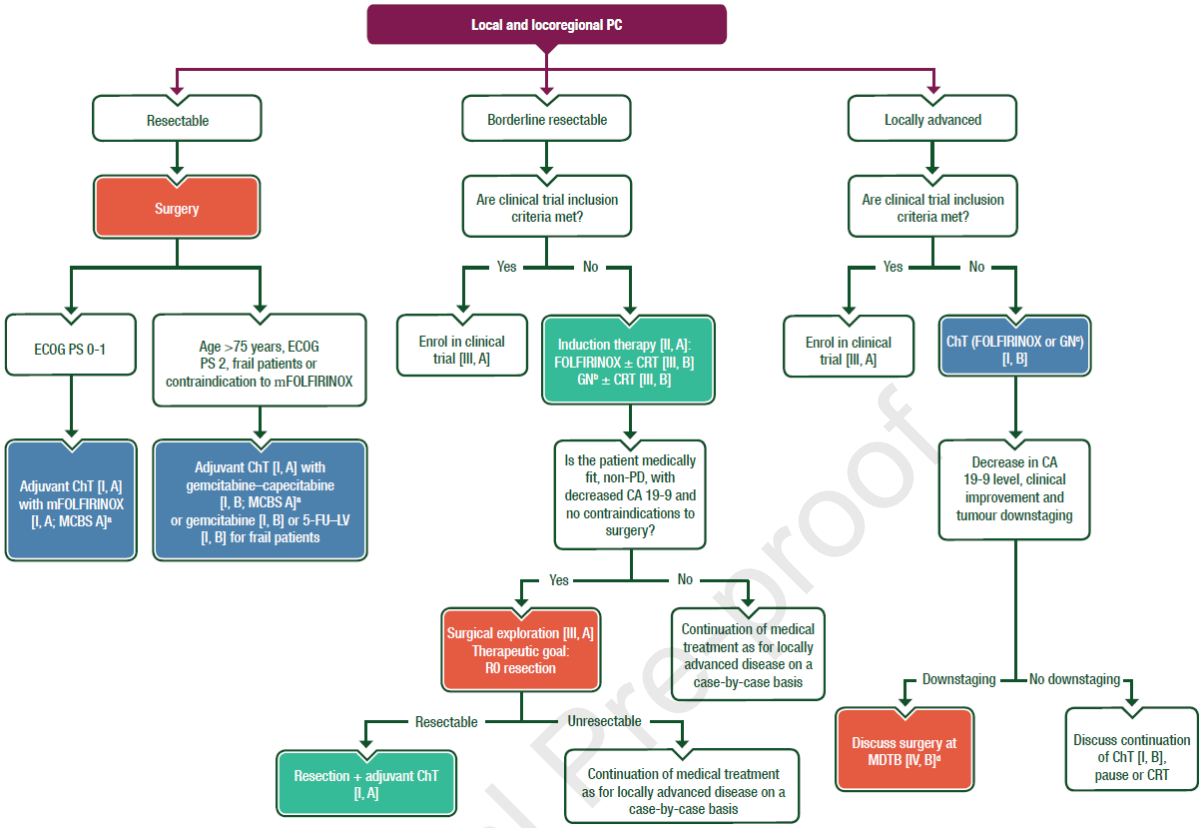
Figure 1. Diagnostic work-up of suspected PC.



Purple: general categories or stratification; white: management.

CT, computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; PC, pancreatic cancer; PET, positron emission tomography.

Figure 2. Treatment algorithm for local and locoregional PC.



Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments; white: other aspects of management.

CA 19-9, carbohydrate antigen 19-9; ChT, chemotherapy; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin–5-fluorouracil–irinotecan–oxaliplatin; GN, gemcitabine–nab-paclitaxel; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MDTB, multidisciplinary tumour board; mFOLFIRINOX, modified leucovorin–5-fluorouracil–irinotecan–oxaliplatin; PC, pancreatic cancer; PD, progressive disease; PS, performance status; R0, no tumour at the margin; defined as no cancer cells within 1 mm of all resection margins.

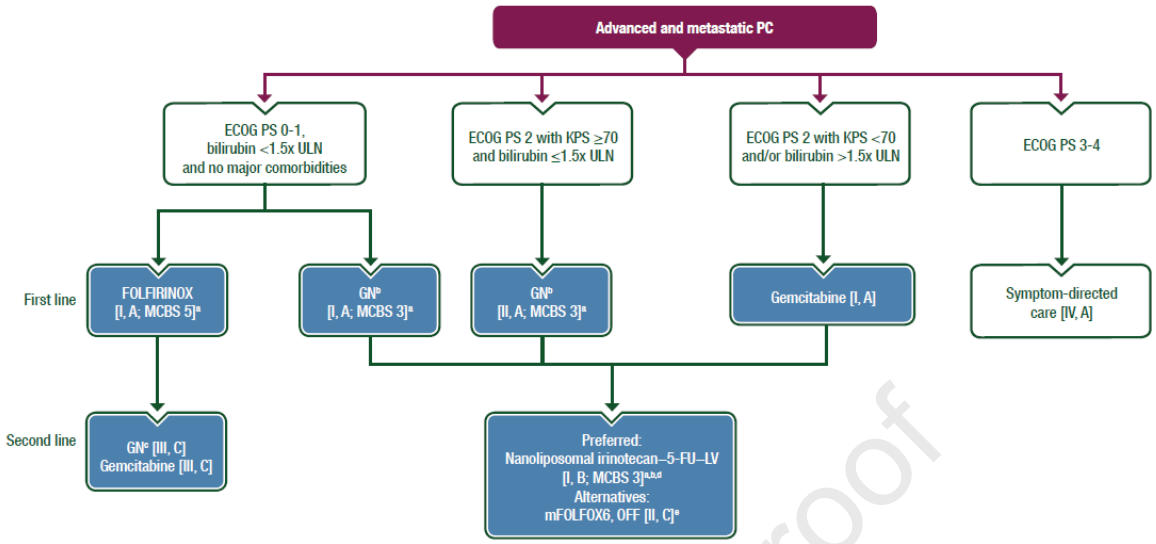
[a]ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[b]Not EMA or FDA approved as induction therapy.

[c]Not EMA or FDA approved for locally advanced disease.

To be discussed if significant decrease in CA 19-9 level, clinical improvement and tumour downstaging.

Figure 3. Systemic treatment of advanced and metastatic PC.



Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin–5-fluorouracil–irinotecan–oxaliplatin; GN, gemcitabine–nab-paclitaxel; KPS, Karnofsky performance status; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MDTB, multidisciplinary tumour board; LV, leucovorin; mFOLFOX6, modified leucovorin–5-fluorouracil–oxaliplatin; OFF, oxaliplatin–fluorouracil–leucovorin; PC, pancreatic cancer; PS, performance status; ULN, upper limit of normal.

[a]ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

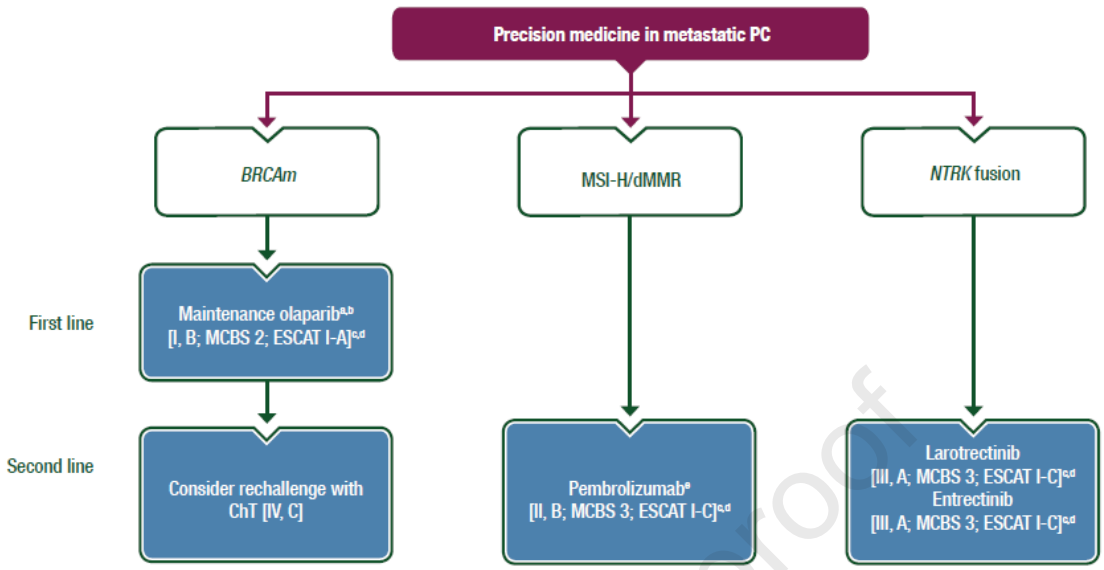
[bb]EMA and FDA approved in metastatic PC only (not advanced PC).

[c]Not EMA or FDA approved as second-line therapy.

[d]Only in patients with, or who have recovered to, ECOG PS 0-1.

[ce]If not given previously.

Figure 4. Precision medicine in metastatic PC.



Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

ChT, chemotherapy; dMMR, mismatch repair deficient; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; g, germline; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability high; m, mutated; PC, pancreatic cancer.

[a]EMA and FDA approved in patients with metastatic PC and *gBRCA* mutations.

[b]For patients whose disease is stable or responsive to platinum-based ChT.

[c]ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[d]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO

Translational Research and Precision Medicine Working Group.[103] See **Supplementary Table S10** for more information on ESCAT scores.

[e]FDA approved; not EMA approved as a dMMR/MSI-H tumour-agnostic indication but for specific tumour types (excludes PC).

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