Diagnostic and therapeutic recommendations in pancreatic ductal adenocarcinoma. Recommendations of the Working Group of the Polish Pancreatic Club

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Abstract

These recommendations refer to the current management in pancreatic ductal adenocarcinoma (PDAC), a neoplasia characterised by an aggressive course and extremely poor prognosis. The recommendations regard diagnosis, surgical, adjuvant and palliative treatment, with consideration given to endoscopic and surgical methods. A vast majority of the statements are based on data obtained in clinical studies and experts' recommendations on PDAC management, including the following guidelines: International Association of Pancreatology/European Pancreatic Club (IAP/EPC), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and Polish Society of Gastroenterology (PSG) and The National Institute for Health and Care Excellence (NICE). All recommendations were voted on by members of the Working Group of the Polish Pancreatic Club. Results of the voting and brief comments are provided with each recommendation.

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Introduction

Diagnostics and treatment of pancreatic cancer represent a great challenge for contemporary medicine. Year by year, the incidence of pancreatic ductal adenocarcinoma (PDAC) is increasing. Currently, pancreatic ductal adenocarcinoma is the 12th most common malignancy which occurs worldwide [1]. Its incidence is as follows: 8–12.5/100 000 males and 6–7/100 000 females. It mostly affects populations in the developed countries: the Unites States, Europe (mostly Central and Northern), Australia and Argentina [2, 3].

Pancreatic cancer is highly malignant, characterised by rapid local progression and formation of distant metastases. Due to its aggressive course, late diagnosis and resistance to treatment, PDAC represents the cancer with the lowest survivability. Currently, it occupies 4th place with regard to malignancy-related mortality (7% of deaths) [3].

The most common management of early stage PDAC is radical surgery. However, upon making the diagnosis, surgical treatment of the carcinoma can be implemented only in 9.7% of cases [4]. In the event of a tumour involving only the pancreas, the 5-year survival is 32%; for tumours infiltrating nearby structures, the survival is 12% and for PDAC with distant metastases it is only 3% [3]. The overall 5-year survival for pancreatic cancer is up to 8% [3].

If we do not improve the diagnostics of PDAC in its early stage and implement adequate therapy, we can estimate that in 2020, this malignancy will become the 2nd cause of mortality of all neoplasms [5]. Early detection of this disease and implementation of adjuvant therapy are options which may improve the disease management.

Intensive studies on improving the survival of pancreatic cancer patients have been conducted for many years. The studies involve searching for new mechanisms of carcinogenesis as well as specific diagnostic and prognostic markers, improving surgical techniques and implementing new methods of adjuvant therapy. Unfortunately, the results of clinical studies published between the years 1986 and 2016 indicate that the median overall survival for this carcinoma increased by only 3 months [6].

Guideline development methods

This study contains 25 statements regarding diagnostics and therapy as well as palliative management in pancreatic cancer. The vast majority of these statements are based on data obtained in clinical studies and experts' recommendations on management of pancreatic cancer. The level of acceptance of the statements was determined on the basis of results of voting, carried out by the Polish Pancreatic Club Expert Working Group. The acceptance level for each statement was expressed in a five-step scale, presented in Table I. Next, the researchers determined the reliability of the clinical studies on which they based the statements, as presented in Table II.

Recommendations on the diagnostics of pancreatic ductal adenocarcinoma (PDAC)

> 1. Patients who demonstrated pancreatic focal lesions, confirmed with imaging techniques, should be referred to reference centres for further diagnostics. Assessment I – 100% full acceptance, data reliability C

Decisions on a diagnosis and tumour resectability should be made in reference centres, offering appropriate diagnostic methods, including e.g. multidetector-row computed tomography and endoscopic ultrasound with fine-needle aspiration biopsy. Details regarding elective treatment should be discussed conjointly by specialists in gastroenterology, radiology, pathology and oncology.

Implementation of imaging examinations according to the pancreatic protocol in a high-volume reference centre improves preoperative evaluation of the disease stage, which allows its management to be modified in the majority of patients with PDAC (56%). Therefore, in high-quality reference centres, repeated CT according to the pancreatic protocol and evaluated by radiologists experienced in pancreatic imaging is recommended [7].

Table I. Five-step scale

Category	Acceptance level
I	Full acceptance
II	Acceptance with minor reservation
III	Acceptance with major reservation
IV	Rejection with minor reservation
V	Full rejection

Table II. Scale of evidence

Category	Data reliability
A	High (based on meta-analyses and randomised clinical trials)
B	Moderate (based on clinical studies and observational studies)
C	Low (mainly based on expert opinions)

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> 2. In the event of clinical suspicion of pancreatic adenocarcinoma, ultrasound of the abdominal cavity is not recommended in diagnostics and evaluation of disease progression. Assessment I – 76.5%, II – 23.5%, moderate acceptance, data reliability C

Ultrasound (US) represents the common preliminary screening examination in abdominal symptoms diagnostics. Its common use is caused by the fact that US is widely accessible, non-invasive and cost-effective. In this examination, performed for other indications, not infrequently focal pancreatic lesions are detected, including relatively early changes, requiring further diagnostics. On the other hand, many such lesions are benign.

Pancreatic adenocarcinoma, in its early stage, is asymptomatic or its symptoms are atypical. Hence, the disease is usually diagnosed in its advanced stage. Due to its limitations, US is not recommended to detect PDAC or to evaluate the disease progression [8–10]. The sensitivity of the examination is highly operator-dependent and ranges between 67% and 90% [11]. The examination poorly visualises the body and tail of the pancreas, particularly in obese patients. It enables, however, one to visualise a hypoechogenic mass, dilatation of the main pancreatic and bile duct, the enlarged pancreatic head and metastases to the liver – changes which require further, more accurate diagnostics [10, 12]. Ultrasound poorly visualises the topography of changes, their localization related to the surrounding organs, and the degree of local progression, and does not show small abnormalities (< 2 cm). Overall, transabdominal US is an acceptable first imaging method, although not reliable for a confident diagnosis or the exclusion of small pancreatic tumours, which are the only ones with a chance for cure.

> 3. For diagnostic purposes and in order to evaluate the degree of progression of PDAC, a contrast-enhanced computed tomography (CT) scan of the abdominal cavity and pelvis according to the pancreatic protocol is recommended, and in unclear cases, magnetic resonance imaging (MRI) is also advisable. Assessment I – 100% strong acceptance, data reliability B

According to the pancreatic protocol, multidetector-row contrast-enhanced CT of the abdominal cavity should be performed in each patient suspected with PDAC in order to evaluate the disease progression [9, 13–16].

Spiral tomography, preferably with the application of a 64-row or above scanner, with slice thickness up to 3 mm, should be performed [9, 15, 17]. Both a neutral oral contrast agent (e.g. water) and an intravenous iodinated contrast agent at a dose of 3–5 ml/s are recommended. The two-phase technique includes the pancreatic parenchymal phase (40 to 50 s after contrast administration) and the portal venous phase (after 65 to 70 s). This pancreatic protocol allows for making an appropriate evaluation of morphological, arterial, venous and extrapancreatic changes, which is crucial to determine the disease progression [17].

The sensitivity of multidetector-row CT in pancreatic cancer detection is high, i.e. 89–97%, but lower for smaller (< 1.5 cm) lesions – 67% [12, 18, 19]. An extensive meta-analysis comparing various imaging techniques in PDAC revealed the sensitivity and specificity of CT of 89% and 90%, respectively, which were equivalent to those of MRI [20].

The PDAC is usually visualised in a CT scan as a lesion poorly demarcated and poorly enhanced after contrast application, and therefore hypodense in scans of the arterial phase. In delayed scans, it can become isodense [15]. Changes which might imply suspicion of PDAC also include (from the lowest to the highest specificity): pancreatic duct dilatation (sensitivity 50% and specificity 78%), hypo-attenuation (sensitivity 75% and specificity 84%), ductal interruption (sensitivity 45% and specificity 82%), distal pancreatic atrophy (sensitivity 45% and specificity 96%), pancreatic contour anomalies (sensitivity 15% and specificity 92%) and common bile duct dilatation (sensitivity 5% and specificity 92%) [21].

The CT is also crucial in evaluation of the disease stage and prediction of tumour unresectability. This examination allows one to accurately determine the size of the tumour, its localization, infiltration of large vessels, involvement of lymph nodes and presence of distant metastases [9, 22]. Recent studies indicate that sensitivity of CT in determining tumour unresectability ranges from 52% to 91%, and specificity from 92% to 100% [22].

The MRI is recommended in patients with strong suspicion of pancreatic neoplasm and uncertain results of a CT scan [23–25]. In most MRI examinations, PDAC is seen as a hypointense lesion, both in T1- and T2-weighted images [25]. Sensitivity and specificity of MRI in detection and evaluation of progression of the disease is comparable to those obtained in CT, i.e. 89% and 89%, respectively [20]. Therefore, MRI is not widely used as the primary imaging modality in most centres due to issues of its high cost and relatively low availability [9].

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> 4. Positron emission tomography (PET) is not applied in PDAC diagnostics as it does not differentiate this disease from chronic pancreatitis. This examination can be used in selected clinical cases in order to detect distant metastases or cancer recurrence. Assessment I – 82.4%, II – 17.6%, moderate acceptance, data reliability C

The PET-CT is an imaging technique which combines functional PET imaging with anatomical images of CT [16]. Fluorodeoxyglucose 18F (18F-FDG), a glucose analogue, is the most commonly applied radiotracer. PDAC is in most cases associated with overexpression of glucose 1, which is demonstrated by increased uptake of 18F-FDG in PET-CT results [26]. This technique sensitivity ranges from 85% to 95% and specificity 61% to 94% in PDAC detection [27]. A great advantage of visualising a patient's anatomy by PET-CT is that it allows one to see the whole body, which is helpful in evaluation of the stage of metastatic disease. A meta-analysis showed that the sensitivity of a 18-FDG PET examination in PDAC diagnostics and evaluation of metastases to lymph nodes and the liver was 91%, 64% and 67% respectively, and specificity 81%, 81% and 96%, respectively [28]. Unlike other imaging techniques, PET allows for monitoring after chemotherapy, and detection of recurrence of malignancies as well as distant neoplastic metastases, particularly to the bones [29, 30].

The main limitation of this technique is the low spatial resolution and possibility of false-positive uptake in healthy structures or mild disturbances, such as inflammatory processes [31]. This examination does not differentiate inflammatory changes from malignant tumours because both conditions manifest with increased accumulation of the tracer. As a diagnostic tool, PET-CT is similar to CT and does not bring any further benefits [32, 33].

Currently, according to the NCCN guidelines, PET-CT is recommended as a complementary examination for CT in patients with borderline resectable disease, with a high CA19-9 level, in large primary tumours or large regional lymph nodes [9].

On the other hand, a combination of PET and MRI reveals higher sensitivity than PET-CT in detection of PDAC due to better resolution in visualization of soft tissues and more accurate visualization of the pancreatic duct [34, 35]. A PET-MRI scan is much more reliable than a PET-CT scan – respectively 96.6% vs. 86.6% [35]. In the event of cystic tumours, PET-MRI enables one to detect also structures located inside lesions, such as mural nodules or intracystic septa.

It can be concluded that currently PET-CT plays no role in standard PDAC diagnostics, but can be applied as a complementary examination in selected cases, e.g. for the purpose of diagnosing distant metastases and recurrence of neoplastic process [9].

> 5. Endoscopic ultrasound (EUS) with fine-needle aspiration biopsy is a recommended diagnostic method in PDAC. Biopsy is not required in patients with resectable PDAC but indicated in candidates for chemo- or chemoradiotherapy, including neoadjuvant therapy. Histopathological samples have to be analysed by an experienced pathologist. Assessment I – 100% strong acceptance, data reliability B

Endoscopic ultrasound is recommended as one of the most accurate methods for the detection of pancreatic focal lesions [36–39]. In the diagnostics of pancreatic tumours, this method is more sensitive than CT, particularly for small lesions of diameter smaller than 2 cm [12, 40–43]. In EUS, PDAC is usually visualised as a poorly outlined, non-homogeneous hypoechogenic mass [12].

Endoscopic ultrasound is indicated in tumour staging, particularly in patients with an unclear result of a CT examination [9]. The EUS is the most reliable examination evaluating local PDAC progression, particularly infiltration of large visceral vessels and lymph node involvement [9, 39, 44]. Sensitivity and specificity for prediction of tumour resectability are 90% and 86%, respectively [39, 44].

Endoscopic ultrasound with fine-needle aspiration biopsy (EUS-FNA) allows for PDAC diagnosis with accuracy of about 96%, sensitivity 85–95% and specificity 95–99% [38, 41, 45–49]. The EUS-FNA is required in patients considered for chemo- or chemoradiotherapy in order to obtain the cytopathological diagnosis [9, 16]. Biopsy is also indicated in tumours of unclear nature, with no malignancy suspicion, i.e. inflammatory or neuroendocrine tumours. In EUS, iodine contrasting agents are not applied, which is an advantage, particularly in patients with renal failure or allergies.

According to the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE), published in 2017, it is recommended to use 25-gauge or 22-gauge needles for routine collection of biological material from solid tumours and lymph nodes [50]. Use of both needles for cytological (FNA) and histological material (fine needle biopsy – FNB) collection are being recommended [50]. For the purpose of tissue biopsy collection, it is advisable to use the following needles: 19-gauge FNA or FNB or 22-gauge FNB. If it is not possible to conduct the cytological material analysis immediately after EUS-FNA, it is recommended to perform three or four biopsies with FNA needles or two or three biopsies with an FNB needle [50].

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It should be pointed out that this procedure is invasive and there is a possibility, however minimal, of complications, such as pain (0.38%), bleeding (0.10%), fever (0.08%), infection (0.02%) and acute pancreatitis (0.44%) [51, 52]. Routine antibiotic prophylaxis before the biopsy of solid lesions and lymph nodes is not required [50].

> **6. Failure to obtain the histological confirmation of malignant neoplasm does not exclude it; therefore in those cases the surgical treatment of potentially resectable lesions should not be delayed. Assessment I – 100% strong acceptance, data reliability A**

Histological confirmation of malignant neoplasm is not required for resectable tumours [9, 10, 16]. Identification of the tumour pathology is necessary in patients with locally advanced and metastatic PDAC – prior to implementation of neoadjuvant therapy or palliative chemo- or chemoradiotherapy [9, 10, 16].

In most cases, a histopathological diagnosis is made based on the post-operative or biopsy specimen evaluation. A histopathological analysis of post-operative material allows for identification of the histopathological type, its local progression and grade. The PDAC grows in a highly dispersed fashion, which makes macroscopic and histopathological identification of the tumour margins difficult. Thus both performing a radical resection and obtaining its histopathological evaluation are difficult [53, 54]. An accurate identification of the margin status of a surgical resection specimen is crucial because it bears a significant prognostic value and allows one to select those patients who will most benefit from the adjuvant therapy [55].

> **7. Percutaneous ultrasound/CT-guided pancreatic biopsy is not recommended in patients with potentially resectable PDAC. In comparison to EUS-guided biopsy, this procedure is less safe and the risk of cancer cells seeding along the needle path is higher. Assessment I – 100% strong acceptance, data reliability B**

Percutaneous ultrasound-guided pancreatic biopsy allows one to detect PDAC with 92–98.7% accuracy; the sensitivity is 94–98.7% and specificity is 97%, whereas the accuracy in a EUS-guided biopsy is about 96%, sensitivity is 85–95% and specificity is 95–100% [38, 41, 45–49, 56–62].

Percutaneous pancreatic biopsy, in comparison to a EUS-guided biopsy, bears a higher risk of complications, equal to 0.8–1.6%, including serious complications, such as pseudoaneurysm and acute pancreatitis [57, 60]. The EUS-guided biopsy, in comparison to the percutaneous technique, carries a low risk of cancer cells seeding, since the potential dissemination site along the needle path is limited to the area of the surgical resection [51, 52, 63, 64].

Percutaneous CT-guided pancreatic biopsy is characterised by low sensitivity, equal to 88.8%, specificity 100% and accuracy 90%. The percentage of complications is high, ranging from 9% to 20% [65, 66]. The procedure entails a lot of technical problems and is rarely performed.

Percutaneous biopsy of PDAC may be performed only for unresectable lesions or if EUS is not available. Percutaneous biopsy of metastatic lesions in the liver is recommended for metastatic PDAC and may be sufficient for revealing the tumour pathology.

> **8. CA19-9 antigen is a recognized PDAC marker. It is not useful for either early diagnostics or screening. Nevertheless, it may be useful as a prognostic and predictive PDAC marker. Assessment I – 88.2%, II – 11.8%, moderate acceptance, data reliability B**

CA19-9 antigen, determined in the blood serum, is the most common marker applied in PDAC diagnostics [67–70]. An increased level of CA19-9 can be observed in 75–85% of PDAC patients. The sensitivity and specificity of CA19-9 in PDAC detection in symptomatic patients is respectively 79–81% and 82–90% [10, 71].

In early stages of PDAC, the marker CA19-9 is usually not elevated. Thus, this marker does not appear to be useful in early diagnostics or PDAC screening [8, 71]. In most cases, an increased serum level of CA19-9 serum indicates advanced malignancy and its increased preoperative level is associated with worse post-operative prognosis [16, 72–74]. The level of serum CA19-9 above 100 U/ml increases the possibility that PDAC is unresectable, highly advanced and metastatic [71]. A cohort study recently published in the United States, conducted in PDAC patients in the years 2004–2012 confirmed that the level of CA19-9 > 800 U/ml before the treatment was associated with advanced PDAC and indicated shorter survival [75].

The marker may be useful in the evaluation of treatment efficacy (predictive value) because a post-operative CA19-9 decrease and normalization after implementation of adjuvant therapy are associated with better prognosis [76–78]. It was shown that a low postoperative level of CA19-9 < 90 U/ml was associated with a better response to gemcitabine adjuvant chemotherapy and higher median survival [79].

According to the ESMO guidelines, in patients with a high preoperative CA19-9 level, after the operation, this marker should be monitored every 3 months for 2 years along with an abdominal CT scan every 6 months. Then, an increased level of the marker will have prognostic value and allow one to identify patients with disease progression [16].

Management of PDAC

> 9. The decision on the management of PDAC should be taken by a multi-specialist team (gastroenterologist, surgeon, radiologist, oncologist and pathologist) in a high-level reference centre. Assessment I – 100% strong acceptance, data reliability C

A decision on the management of PDAC should be taken by a multidisciplinary specialist team, consisting of a gastroenterologist, surgeon, radiologist, pathologist and oncologist [13, 80]. The therapeutic management should be consulted with the patient and accepted by him after he/she has obtained detailed information on the degree of disease progression, types of available therapies, their benefits and complications [8].

The PDAC patients should be operated on in high-level reference centres [8]. Interdisciplinary management of PDAC appeared to have modified therapeutic recommendations for almost every fourth patient [81].

> 10. Radical surgery is the only effective method of PDAC treatment and it should be performed in high-volume centres, by surgeons well experienced in pancreatic surgery. Assessment I – 100% strong acceptance, data reliability C

Primary surgical resection of the primary tumour and regional lymph nodes is recommended for patients with potentially curable pancreatic cancer with no clinical evidence for metastatic disease and a performance status and comorbidity profile appropriate for a major abdominal operation.

Radical resection of a pancreatic malignant tumour is feasible only in 20% of patients [8]. The type of surgery depends on the location of the tumour. In the case of pancreatic head tumour, Kausch-Whipple pancreato-duodenectomy or Traverso-Longmire pylorus-preserving pancreatoduodenectomy with lymphadenectomy is performed [82]. A large literature review was published in 2016, comparing those two operation techniques, considering survival, postoperative mortality, complications and postoperative quality of life, and no significant differences were found [82]. Tumours localized in the pancreatic body or tail require distal pancreatectomy, including the resection of the body and the tail of pancreas and the spleen. In some multi-focal tumours total pancreatectomy is carried out [83].

According to the NCCN guidelines, criteria for tumour resectability include absence of distant metastases, no tumour contact with the superior mesenteric vein and/or portal vein in imaging examinations or ≤ 180° contact without vein contour irregularity and no arterial tumour contact (celiac axis, superior mesenteric

artery or common hepatic artery) (all criteria must be fulfilled). These criteria are presented in Table III [9].

Involvement of lymph nodes in patients with operable PDAC is a significant prognostic factor [84]. Studies confirmed that extended lymphadenectomy, compared to the standard one, is not beneficial in terms of survival, complications number, postoperative mortality or the quality of life [85]. Hence, extended lymphadenectomy is not currently recommended [13].

Reference centres experienced in performing pancreatic resections, achieve the best treatment results [84, 86–88]. High-volume centres have reported decreased complication and postoperative mortality rates, shorter hospital stay, lower cost and longer postoperative stay compared with low-volume institutions [84]. Studies show that the centres performing less than 5 pancreatic procedures per year, in comparison to those performing at least 40 pancreatic procedures per year, have significantly higher mortality rates [89].

In 2016, results of a population study on all patients who underwent surgical treatment of pancreatic cancer in Italy, between 2010 and 2012, were published [88]. The probability of performing palliative surgery in Italian hospitals was much higher in low-level reference centres than in high-level centres [88]. One reason for such a difference might be the poor quality of CT scans obtained in smaller hospitals as well as their evaluation by less experienced radiologists.

Nevertheless, the long-term results of surgical treatment of PDAC are not satisfactory yet. In patients who underwent radical surgery, the median overall survival is 14–17 months, and 5-year survival is observed in only 10–27% [8, 9, 90–93].

> 11. Obtaining R0 resection is crucial for survival. Assessment I – 100% strong acceptance, data reliability A

The aim of surgical therapy is to obtain a radical resection which is microscopically free from disease, i.e. R0 resection. A macroscopically clear resection is defined as R0 if there are no tumour cells within 1 mm of any surface in the pathologic examination. If one or more tumour cells are visible within 1 mm of any surface, we obtain R1 resection [55]. R2 resection is defined as macroscopically incomplete. Obtaining R0 resection is the basic factor affecting the prognosis [8]. In the event of involvement of the portal vein or the superior mesenteric vein, a radical resection with reconstruction of those vessels is feasible. Such a procedure is not associated with higher morbidity or mortality, but then R0 resection is obtained less frequently and the survival is poor, probably due to the tumour's inherent aggressiveness.

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Table III. Criteria defining respectability status according to NCCN guidelines [9]

Resectability status	Arterial	Venous
Resectable	No arterial tumour contact (celiac axis (CA), superior mesenteric artery (SMA) or common hepatic artery (CHA))	No tumour contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤ 180° contact with vein contour irregularity
Borderline resectable	Pancreatic head/uncinate process: • Solid tumour contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumour contact with the SMA of < 180° • Solid tumour contact with variant arterial anatomy (e.g. accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumour contact should be noted if present as it may affect surgical planning Pancreatic body/tail: • Solid tumour contact with the CA of < 180° • Solid tumour contact with the CA of > 180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery permitting modified Appleby procedure (some panel members prefer these criteria to be in the unresectable category)	• Solid tumour contact with the SMV or PV > 180°, contact of ≤ 180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal or distal to the site of involvement allowing for safe and complete resection and vein reconstruction • Solid tumour contact with the inferior vena cava (IVC)
Unresectable	• Distant metastases (including non-regional lymph node metastases) Pancreatic head/uncinate process: • Solid tumour contact with the SMA of > 180° • Solid tumour contact with the CA of > 180° Pancreatic body/tail: • Solid tumour contact of > 180° with the SMA or CA • Solid tumour contact with the CA and aortic involvement	Pancreatic head/uncinate process: • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) • Contact with the most proximal draining jejunal branch into SMV Pancreatic body/ tail: • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

In 561 surgically treated PDAC patients subsequently subjected to adjuvant therapy, longer median survival was obtained in cases with R0 resection compared to others. Moreover, a multifactor analysis confirmed the significant prognostic value of the resection [94].

> **12. Neoadjuvant therapy (induction) is not recommended in resectable tumours but can be implemented in selected cases. Assessment I – 94.1%, II – 5.9%, strong acceptance, data reliability B**

Administration of neoadjuvant therapy in resectable PDAC is controversial due to conflicting data regarding its effectiveness [95].

In recent years, more and more patients have been administered preoperative systemic chemotherapy alone or in combination with radiotherapy. The main aim of the therapy is to extend the survival period in patients, by means of tumour size reduction and obtaining R0 resection [96–98].

Currently, there are no clear recommendations regarding administration of a particular chemotherapeutic drug in neoadjuvant therapy [10]. The majority of patients who undergo neoadjuvant chemotherapy or radiotherapy are administered oral or intravenous drugs for a period of 3–6 months prior to the operations [99].

Neoadjuvant therapy in resectable PDAC should be considered in patients whose condition or concomitant diseases, potentially reversible, do not allow for performing prompt surgery, in large tumours, in cases with high levels of CA19-9 and in patients with extreme pain [8].

In patients with primarily resectable PDAC, the frequency of resections and post-neoadjuvant therapy survival are similar to those after tumour resection and adjuvant therapy [99].

> **13. In borderline resectable PDAC, we should consider combined neoadjuvant (induction) chemotherapy with or without radiotherapy, and next, after exclusion of disease progression based on imaging examinations – surgery. Assessment I – 100% strong acceptance, data reliability B**

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The role of neoadjuvant therapy in patients with borderline resectable PDAC is well documented [9]. This treatment aims at reducing the tumour size, diminishing the disease stage and increasing the chance of obtaining R0 resection. Before implementation of induction treatment, histopathological identification of the neoplasm is required [9]. The definition of borderline resectable PDAC, according to the most recent NCCN guidelines, is presented in Table III [9].

In 2016, the results of a meta-analysis of 18 clinical studies, conducted from 1966 to 2015, regarding implementation of neoadjuvant therapy in patients with borderline resectable PDAC, were published [100]. It was concluded that the overall percentage of resections and R0 resections and the estimated survival period of patients with borderline resectable PDAC after neoadjuvant therapy are similar to those in patients with resectable PDAC. The percentage of patients who were administered induction therapy, and subsequently underwent an operation, ranges from 385 to 80.8% with the percentage of R0 resection up to 75–100% [101–105].

There are numerous retrospective analyses of various options of induction treatment, including chemo- and chemoradiotherapy in borderline resectable PDAC, confirming high efficacy of this kind of treatment and good tolerance [101–106].

According to the ESMO guidelines, a patient with borderline resectable PDAC should be included in chemotherapy clinical trials whenever possible. If those are unavailable, gemcitabine-based chemotherapy or FOLFIRINOX-based chemotherapy, being a combination of 5-fluorouracil (5-FU) and leucovorin (calcium folinate), irinotecan and oxaliplatin, should be administered. Subsequently chemoradiotherapy and then surgery appear to be the best option [16]. The role of radiation therapy, the duration of chemotherapy and the optimal regimen of systemic therapy remain to be elucidated.

Recently, neoadjuvant therapy has been applied also in locally advanced pancreatic adenocarcinoma, followed by surgical treatment. In 2016, a meta-analysis of 325 patients, gathered from 12 studies, with locally advanced PDAC, was conducted. Implementation of the FOLFIRINOX therapy resulted in resections, which were performed in 28% of patients. R0 resection was carried out in 78.4% of the patients who underwent operations [97]. It is estimated that about one third of patients with an initially unresectable neoplasm will develop resectable tumours after neoadjuvant therapy, with a survival period comparable to that in initially resectable tumours. Thus, patients with locally unresectable neoplasm should be included in neoadjuvant protocols and then reassessed for resection [99].

> **14. After R0 and R1 resections of PDAC, in the event of no preoperative treatment (neoadjuvant), adjuvant chemotherapy (complementary) is recommended. Implementation of adjuvant chemoradiotherapy is still controversial. Assessment I – 94.1%, II – 5.9% strong acceptance, data reliability B**

Adjuvant therapy is applied after a radical surgical procedure in order to decrease the risk of local recurrence or to prevent distant metastases, and as a consequence, extend overall survival [8].

Many prospective, randomized studies have revealed that adjuvant therapy, implemented after a radical PDAC resection, extends patients' survival in comparison to the surgery alone [107–111].

According to the ASCO, NCCN and ESMO guidelines, if neoadjuvant therapy has not been implemented in resectable PDAC, adjuvant chemotherapy should be initiated within 8–12 weeks following the operation. Therapeutic options are: 6-month gemcitabine monotherapy or therapy with 5-FU and leucovorin [8–10, 16].

Implementation of adjuvant chemoradiotherapy in resectable PDAC is still controversial [8, 9, 16]. It was previously confirmed that implementation of chemoradiotherapy with chemotherapy does not improve survival and is more toxic than chemotherapy alone [112, 113]. Recently, some studies confirmed that in resectable PDAC, adjuvant chemoradiotherapy is more useful than adjuvant chemotherapy [114–117].

According to the ASCO guidelines, adjuvant chemoradiotherapy can be considered in patients who did not receive neoadjuvant treatment, in the event of positive resection margin (R1), occurrence of metastases to lymph nodes and after administering 4–6-month adjuvant chemotherapy [8]. In the ESMO guidelines it is stated that no chemoradiation should be given to patients after surgery except in clinical trials.

> **15. In the event of diagnosing local recurrence, chemotherapy, chemoradiotherapy, or a combination of both are indicated. In the event of generalized recurrence, following PDAC resection, chemotherapy is indicated. Assessment I – 100% strong acceptance, data reliability B**

In the event of PDAC recurrence after a radical surgical procedure, management of the disease depends on the time elapsed since the systemic therapy, conducted within adjuvant or neoadjuvant therapy. If the disease recurred not later than 6 months following the chemotherapy treatment, the patient is administered different drugs than before (the second-line chemotherapy). If the disease recurred later than 6 months following the

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systemic treatment, the same therapy can be repeated or the patient can be administered alternative chemotherapy. If local recurrence or distant metastases are detected, a biopsy may be required in order to confirm the recurrence. In a local recurrence without distant metastases, chemoradiotherapy can be implemented, provided it has not been administered before or systemic chemotherapy. In the event of occurrence of distant metastases with or without local recurrence, the patient receives maintenance therapy [9].

> **16. Routine preoperative insertion of biliary stents in patients with PDAC is not recommended since it does not improve the complication or post-resection mortality rate. Assessment I – 100% strong acceptance, data reliability B**

Routine pre-operative stenting of the biliary tract in patients with potentially resectable PDAC is not indicated because it increases the percentage of complications, including inflammation of the biliary tract, serious intra-abdominal infections and post-operative pancreatic fistula [10, 118–120]. On the other hand, stenting should be considered in active inflammation of the biliary tract, extensive hepatic damage, severe skin itchiness or when the surgery has to be delayed over 2 weeks [16]. Metal stents applied in the procedure of pre-operative stenting of the biliary tract are more effective than plastic stents due to the lower number of repeated endoscopic interventions [121, 122]. In addition, the incidence of post-operative pancreatic fistula is lower for metal than plastic stents [121, 122]. Studies which reveal no significant differences between these two procedures were also published [123].

The procedure of endoscopic stenting of the biliary tract significantly outperforms the percutaneous method in terms of patient tolerability and effectiveness of the therapy [10].

Palliative treatment

> **17. Chemotherapy is a treatment of choice for locally advanced PDAC. Application of chemoradiotherapy is currently recommended by some groups of experts. Assessment I – 100% strong acceptance, data reliability C**

Chemotherapy is a treatment of choice for locally advanced PDAC [9, 16, 124]. Definition of unresectable PDAC, according to the most recent NCCN guidelines, is presented in Table III [9].

The type of administered chemotherapeutic drug is still controversial [10, 124]. According to the ESMO guidelines, 6-month gemcitabine therapy is recommended [16], whereas, according to the NCCN guidelines, patients in good general condition should be administered the FOLFIRINOX programme or gemcitabine monotherapy or in combination with other cytostatics, e.g. with albumin-bound paclitaxel, erlotinib, capecitabine or cisplatin (only for known BRCA1/2 mutations) [9]. Patients in poor general condition should be administered gemcitabine or capecitabine or 5-FU monotherapy or maintenance treatment alone [9]. Gemcitabine chemotherapy (if fluoropyrimidine was previously applied) or fluoropyrimidine chemotherapy (if gemcitabine was previously applied) is recommended as the second-line therapy.

According to the ESMO guidelines, chemoradiotherapy in locally advanced PDAC is only rarely advisable and it may be used in combination with capecitabine. According to the NCCN and ASCO guidelines, it can be considered in the event of local progression after induction chemotherapy, and if there are no distant metastases [9, 124]. Also, chemoradiotherapy can be applied in patients who responded to preliminary 6-month chemotherapy or have stable disease or have developed unacceptable chemotherapy-related toxicities [124].

> **18. In disseminated PDAC, chemotherapy apart from symptomatic treatment is a treatment of choice. Assessment I – 100% strong acceptance, data reliability A**

Chemotherapy, apart from maintenance treatment, is a treatment of choice in disseminated PDAC. For decades, gemcitabine was a standard of care for first line treatment of unresectable and metastatic PDAC. In 2007 erlotinib with gemcitabine was approved, but more recently FOLFIRINOX and gemcitabine with nab-paclitaxel have become the two upfront standards of the care regimen [9, 125]. The patient's condition is a factor determining the choice of therapy. The treatment basically aims at extending the patient's life and relieving symptoms of the advanced neoplastic disease. Patients in good general condition most benefit from systemic therapy. Such patients are administered more aggressive treatment strategies which contribute to longer overall survival. Patients in poor general condition, demonstrating intense symptoms of neoplastic disease, require less aggressive treatment, which should focus more on relieving bothersome symptoms of the disease [125].

In patients in good general condition, more aggressive treatment, consisting of the FOLFIRINOX programme or gemcitabine in combination with nab-paclitaxel (albumin-bound paclitaxel), should be used. This formulation of paclitaxel increases the drug concentration in pancreatic cancer cells by 30%.

Application of FOLFIRINOX extends the median overall survival, free from progression, despite an increase in toxicity. However, this treatment is associated with considerable toxicity [9, 10, 16, 125]. In the first-line treatment, patients in good general condition can also be administered gemcitabine in combination with other cytostatics or targeted drugs (erlotinib, capecitabine, cisplatin) and gemcitabine, capecitabine or 5-FU monotherapy.

Patients who are in poor general condition are administered gemcitabine monotherapy or maintenance treatment alone. In the second-line treatment, patients are administered either 5-FU or capecitabine-related programmes if they were previously treated with gemcitabine or programmes based on gemcitabine if the patients previously received 5-FU, capecitabine or maintenance therapy. Very recently combination of nanoliposomal encapsulation of irinotecan, and 5-FU, folinic acid can be offered to the patients with first line treatment with gemcytabine plus NAB-paclitaxel [9, 16]. No data regarding the third-line therapy are available in professional literature [9, 10, 16, 97, 125].

A programme set forth by the Ministry of Health in Poland is available. The programme concerns the therapy of disseminated PDAC with albumin-bound nab-paclitaxel in combination with gemcitabine. Patients who cannot be treated with FOLFIRINOX and fulfil other criteria, i.e. normal hepatic and renal function, low bilirubin and creatinine levels and haemoglobin level equal or higher than 10 g/dl, may be qualified for this programme [126].

> **19. Mechanical jaundice in patients with inoperable PDAC is an indication for the procedure of stenting the biliary tract during endoscopic retrograde cholangiopancreatography (ERCP), EUS-guided choledochoduodenostomy or percutaneous drainage of the biliary tract when endoscopic treatment is not possible. Assessment I – 100% strong acceptance, data reliability B**

Patients with inoperable pancreatic cancer and biliary tract obstruction undergo ERCP with insertion of stents into the biliary tract. Coated metal self-expanding stents are recommended because they contain a special coating to prevent stent occlusion [9, 13, 127, 128]. Commonly used plastic stents have a narrower lumen than metal ones and require frequent replacement, every 3–4 months, due to their occlusion. However, unlike metal stents, they have hooks at their ends to prevent their migration [128].

If the ERCP procedure is not feasible, EUS-guided endoscopic drainage or percutaneous drainage of the biliary tract should be considered. It is possible to perform endoscopic drainage of the extrahepatic and intrahepatic biliary ducts, through the stomach or duodenum. The method should be adjusted to the particular patient, depending on anatomical conditions. It should be pointed out that endoscopic drainage of the biliary tract requires considerable experience from an endoscopist and is associated with a high risk of complications: 3.4–38.6% [129]. On the other hand, the incidence of complications of percutaneous drainage of the biliary tract may be higher than that of EUS-guided technique [130].

Patients with mechanical jaundice, in whom the tumour was intraoperatively unresectable, may also undergo the procedure of common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) bypassing anastomosis with the intestine [13, 118]. An alternative method is gall bladder and jejunum anastomosis (cholecystojejunostomy), easier from the technical point of view and possible to perform laparoscopically [118]. Nevertheless, ERCP with insertion of stents into the biliary tract, in comparison with surgical procedures, is associated with a smaller number of complications, shorter hospitalization period, better quality of life of the patients and lower costs [131].

> **20. Duodenal occlusion in patients with inoperable PDAC is an indication for a surgical bypassing anastomosis or endoscopic implantation of a metal self-expandable prosthesis. Assessment I – 100% strong acceptance, data reliability C**

Duodenal occlusion occurs in about 10–25% of pancreatic cancer patients and is caused by an infiltration of the coeliac plexus and impaired motoric activity of the stomach and duodenum, tumour pressure or direct duodenum infiltration [101, 132–134].

According to the ESMO guidelines, a procedure of endoscopic insertion of a metal self-expandable stent prosthesis in the stenosis is a preferred management method in duodenal stenosis [16, 134]. Endoscopic procedures are characterized by high therapeutic effectiveness, a low morbidity rate and low costs in comparison to surgical methods [134]. Biliary tract occlusion, requiring percutaneous or endoscopic drainage in 40% of patients, is a common problem, occurring during the procedure of duodenal stenting [132, 135]. One way of avoiding this complication is placing a stent in the main biliary duct before duodenal stenting [136]. Insertion of the prosthesis to the duodenum is associated with a risk of complications, including intestinal perforation, bleeding, inappropriate stent position and/or migration or fistula formation [132, 136].

However, according to the NCCN guidelines, in occlusion in patients with life expectancy over 3–6 months, laparoscopic or open gastrointestinal anastomosis should be performed. Similarly, patients with

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inoperable tumour, confirmed at laparotomy, without current occlusion but with at a higher risk of occlusion, can be offered the prophylactic bypassing anastomosis [9, 133]. In the most recent NICE guidelines, the proposed management is similar [13]. A surgical procedure is still effective and represents the best therapeutic tool in properly selected patients. Patients not qualified for a surgical procedure may undergo endoscopic techniques [133].

> **21. Pain is observed in most patients with advanced PDAC and analgesic treatment should be conducted according to the analgesic ladder. Assessment I – 100% strong acceptance, data reliability B**

Upon PDAC diagnosis, over 50% of patients experience pain [137, 138]. The pain is mostly localized in the epigastrium, umbilical and frequently in the lumbar area. It is a cachexia-producing symptom which negatively affects the quality of life of patients. Pain in pancreatic cancer has three components: coeliac, somatic and neuropathic [138].

In most cases PDAC-related pain is controlled by oral pharmacological treatment. Pharmacological treatment of pain is conducted according to the analgesic ladder based on the World Health Organization (WHO) guidelines. In the first stage, the patient is administered non-steroid anti-inflammatory drugs. If they appear to be ineffective, the patient receives drugs of the second level of the analgesic ladder, including weak opioids (codeine, dihydrocodeine, tramadol). If the weak opioids, applied in maximum doses, are ineffective, they are replaced with strong opioids, which include morphine, oxycodone, fentanyl and buprenorphine (stage III) [139, 140]. Morphine is commonly applied to control chronic neoplasm-related pain, particularly in moderate and severe pain [138, 139]. It should be emphasized that opioid use is associated with severe side effects, such as sedation, respiratory depression, pruritus, nausea and constipation [138].

Antidepressants (amitriptyline, sertraline) as well as antiepileptic drugs (gabapentin, pregabalin, carbamazepine, valproic acid) are auxiliary agents in treating neuropathic pain [140–142]. For coeliac pain, steroids proved to be particularly useful. They inhibit synthesis of prostaglandins, a precursor of the inflammatory state cascade, and decrease vascular permeability, thus decreasing the tissue oedema [143].

One method of relieving pain and improving the quality of life is the implantation of a prosthesis in the pancreatic duct, improving its patency, which completely eases the pain in 60% of patients or at least partly alleviates it in 25% [144, 145].

> **22. EUS-guided celiac plexus neurolysis is moderately effective in alleviating pancreatic pain. Nevertheless, it should be considered in patients with poor opioid tolerance or limited response to pharmacotherapy. Assessment I – 100% strong acceptance, data reliability C**

In persistent pain unresponsive to pharmacological treatment or in patients with poor opioid tolerance, celiac plexus neurolysis may be considered [146–149]. Decreased visceral plexus conduction may be obtained by blocking it with EUS-guided local injection of alcohol, phenol, bupivacaine or steroid in the coeliac plexus region [9, 13, 150].

Studies reveal that the effectiveness of EUS-guided neurolysis in reducing PDAC pain is 70–80% which endures for a limited time [150, 151]. Surgery-related complications include transient pain exacerbations, hypotension, diarrhoea and inebriation. Most of the complications are not severe, but at times serious adverse effects are observed, such as bleeding in the extraperitoneal space, abscess and ischaemic complications [151].

Such management most often decreases pain but does not eliminate it completely. Hence, most of the patients still require analgesics [10].

> **23. Supplementation with pancreatic enzymes is not recommended in PDAC, unless exocrine pancreatic insufficiency has been diagnosed. Assessment I – 94.1%, II – 5.9%, strong acceptance, data reliability C**

Exocrine pancreatic insufficiency occurs in 68% to 92% of PDAC patients before and in 80% of PDAC patients after surgery [152]. In the event of symptoms of exocrine pancreatic insufficiency, the therapy involves supplementation with pancreatic enzymes [9, 152]. The aim of the pancreatic enzyme therapy is to restore normal fat absorption by providing a sufficient amount of active lipase in the duodenum and the proximal jejunum simultaneously with the release of nutrients from the stomach [153].

Exocrine insufficiency leads to malabsorption syndrome, which causes fatty stools, weight loss and undernutrition. It is associated with a deficit of fat-soluble vitamins (vitamins A, D, E and K), magnesium, calcium and essential fats and amino acids [152].

According to the NCCN guidelines, supplementation should be administered only in the event of symptoms of pancreatic insufficiency [9], whereas according to the most recent NICE guidelines, supplementation should be applied prior to and after PDAC resection [13]. However, fatty diarrhoea is a late symptom of exocrine pancreatic insufficiency and many patients demonstrate serious malabsorption, weight loss and undernutrition

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not accompanied with any abdominal symptoms [154]. Evaluation of the symptoms alone does not allow one to exclude pancreatic insufficiency. Hence, only a combined evaluation of the symptoms, nutrition state and appropriate tests may provide a reliable assessment of the exocrine function of the pancreas [154]. Determination of faecal elastase concentration is widely used for exocrine pancreatic insufficiency estimation [155].

In clinical practice, administration of replacement therapy with pancreatic enzymes is difficult because their optimal dose is highly variable, depending on the remaining active pancreatic parenchyma, postoperative anatomy and fat content in the diet. Patients after pancreatic resection are routinely recommended to take pancreatic enzymes at initial doses of 75,000 lipase units with main meals and between 25,000 and 50,000 units with snacks [154]. Patients who have undergone extensive pancreatic resection should be individually evaluated for exocrine pancreatic insufficiency in the postoperative period. Patients who will not respond to supplementation with pancreatic enzymes should be referred to a dietician, informed of the requirement to adjust doses and undergo examinations in order to exclude other gastrointestinal pathologies, including small intestinal bacterial overgrowth (SIBO) and bile acid malabsorption [154].

Screening examinations

24. Patients who are in high risk groups of PDAC – with hereditary pancreatitis, congenital syndrome with high risk of pancreatic cancer (HNPCC, Peutz-Jeghers syndrome, FAMMM, congenital breast and ovarian cancer) and family history of pancreatic cancer (occurrence of the cancer in at least two family members) – require monitoring in reference centres. Annual EUS scan and serum CA19-9, starting at the age of 35, are recommended. Assessment I – 100% strong acceptance, data reliability C

Genetic disorders characterised by an increased risk of PDAC include Lynch syndrome (HNPCC), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, familial atypical multiple mole melanoma (FAMMM), hereditary breast and ovarian cancer (HBOC), Fanconi anaemia, Hippel-Lindau disease, Li-Fraumeni syndrome and ataxia telangiectasia [156–159]. Patients from high risk groups of PDAC require monitoring in reference centres and a multidisciplinary approach.

Presence of a mutated PRSS1 gene in a patient with chronic pancreatitis (CP) is identified with an occurrence of hereditary pancreatitis. If the mutation respon-

sible for hereditary pancreatitis has not been confirmed, recurrent acute pancreatitis (AP) or CP of unknown etiology observed in two first-degree relatives or in three second-degree relatives, in at least two generations, is a proof of hereditary pancreatitis [160]. It was revealed that patients with hereditary pancreatitis are at increased risk of pancreatic cancer. In children and young adults, the risk of developing PDAC is almost zero; it rapidly increases about the age of 50 and at 80 years its percentage reaches 40% [161].

Patients who do not meet the above criteria but more than one relative of the same generation is affected by CP are diagnosed with familial pancreatitis [161]. This type of pancreatitis occurs in about 3–10% of patients affected by pancreatitis [162, 163]. Familial occurrence of pancreatitis refers to families where at least two first-degree relatives were diagnosed with pancreatitis with no genetic syndrome occurring [164].

All patients with a positive history of hereditary pancreatitis should undergo genetic tests. According to the guidelines of the American College of Gastroenterology, genetic tests conducted in patients with suspicion of familial pancreatitis should include the following mutations: BRCA1 and BRCA 2, CDKN2A, PALB2 and ATM [156].

According to the most recent guidelines on chronic pancreatitis of the Working Group of the National Consultant for Gastroenterology and the Polish Pancreatic Club, patients with hereditary pancreatitis family history of pancreatitis should each year undergo an EUS examination, and have serous CA19-9 marker determined, starting at the age of 35 [165].

According to the guidelines of the American College of Gastroenterology, screening for PDAC in patients with confirmed mutations characteristic for genetic syndromes should involve conducting EUS or MRI of the pancreas each year, starting at age 50 or 10 years prior to the earliest occurrence of pancreatitis in the family [166]. Patients with Peutz-Jeghers syndrome should start screening at age 35. According to the same guidelines, due to a lower risk of PDAC in family members with the confirmed mutations BRCA1, BRCA2, PALB2, ATM and LS, the screening should be limited to mutation carriers and to first- or second-degree relatives of PDAC patients [156].

According to the NICE guidelines, screening for PDAC is recommended in patients with hereditary pancreatitis and PRSS1, BRCA1, BRCA2, PALB2 or CDKN2A (p16) mutations as well as in patients with Peutz-Jeghers syndrome who have at least one relative with PDAC [13]. It should also be considered in subjects who have two or more first-degree relatives with PDAC, in Lynch syndrome (mutations: MLH1, MSH2, MSH6 or PMS2) and other first-degree relatives of a pancreatic cancer

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patient. In such a group of patients, the NICE guidelines recommend performing MRI/MRCP (magnetic resonance cholangiopancreatography) or EUS of the pancreas. In patients with hereditary pancreatitis and PRSS1 mutation, it is recommended to conduct contrast-enhanced abdominal CT according to the pancreatic protocol [13].

> **25. Non-genetically related chronic pancreatitis (PC) is not an indication for routine examinations for potential detection of PDAC. Assessment I – 82.4%, II – 17.6%, moderate acceptance, data reliability C**

Long-term chronic pancreatitis (CP) is a significant factor of PDAC development [167–169]. In patients with CP, the risk of PDAC increases 14-fold [168]. It increases with the disease duration and reaches about 2% after 10 years after its onset and about 4% after 20 years. The incidence of PDAC as a consequence of chronic pancreatitis is 5% [168]. The percentage is higher (40–55%) in patients affected by hereditary pancreatitis [161, 170, 171]. According to the most recent guidelines of the Working Group of the National Consultant for Gastroenterology and the Polish Pancreatic Club on chronic pancreatitis, long-lasting, non-genetically related chronic pancreatitis is not an indication for routine examinations for potential detection of PDAC. However, in the event of occurrence of new worrying symptoms in patients with CP, it is crucial to conduct an adequate diagnostics [165].

Conclusions

Improving survival in PDAC is strongly needed but still not achieved. Recent scientific advantages targeting the stroma, immune system and blocking different signalling pathways provided some optimism in this area. Wide use of new biomarkers, a personalized approach and surrogate endpoints may also help in improving the therapeutic efficacy. Nevertheless, survival in PDAC remains poor and extensive patient enrolment in clinical trials is encouraged with the hope of improved outcomes from novel therapeutic regimens.

Conflict of interest

The authors declare no conflict of interest.

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