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LPM

QMR Pancreatic cancer

Pancreatic cancer: best supportive care

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Abbreviations

APA: adapted physical activity

BMI: body mass index

CRP: C-reactive protein

ECOG: Eastern Cooperative Oncology Group

ESPEN: European Society of Clinical Nutrition and Metabolism

HRQoL: health-related quality of life

IL-6: interleukin-6

L3: third lumbar vertebra

LMWH: low molecular weight heparin

LSP: left splenopancreatectomy

OS: overall survival

PD: pancreaticoduodenectomy

PDAC: pancreatic ductal adenocarcinoma

PPI: proton-pump inhibitor

PS: performance status

TGF β : transforming growth factor β

WHO: World Health Organization

Abstract

Palliative and supportive care holds a major place in pancreatic ductal adenocarcinoma (PDAC) management. It aims to prevent and reduce symptoms and hospital admissions, while ensuring optimal health-related quality of life (HRQoL), which has been reported to be correlated with overall survival in PDAC. Best supportive care includes non-specific treatment of pain, anxiety and depression, chemotherapy-related toxicities, as well as thromboembolic disease treatment and prevention in high-risk patients. Moreover, nutrition and physical activity interventions are receiving increasing attention as they are crucial to optimize treatment tolerance and efficacy. Of note, they require adaptation to the specificities of PDAC setting and stage of the disease.

In this review, we propose an overview of palliative and supportive care interventions in PDAC, with a highlight on nutritional and physical activity management.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is expected to become the second cause of cancer-related death in the United States and in Europe by 2030 (1,2). It is the tumour of the digestive tract with the poorest prognosis, with 80% of patients having advanced disease at diagnosis and five-year overall survival (OS) rate not exceeding 7%-8% (3,4). Late diagnosis, due to an absence of specific symptoms, together with high metastatic potential, resistance to therapies, and lack of biomarkers and screening methods for early detection, are the main causes for PDAC poor prognosis (3,5). Over the past few years, the landscape of PDAC management has undergone major changes with the advent of the FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, and oxaliplatin combination) and gemcitabine plus *nab*-paclitaxel regimens, which yielded improved median OS compared to gemcitabine alone both in the advanced and adjuvant settings, thus making longer survival a reasonably achievable goal and raising some new clinical questions (5–8). However, not all patients are eligible for these combination chemotherapies (mainly reserved to patients with good performance status [PS], Eastern Cooperative Oncology Group [ECOG] PS 0-1) and therapeutic options remain limited (5–7).

Beside conventional antitumour treatments (*i.e.* surgery, chemotherapy, and radiotherapy), palliative and supportive care holds a major place in PDAC management. It aims to prevent and reduce symptoms and hospital admissions, while ensuring optimal health-related quality of life (HRQoL), which has been reported to be a surrogate prognostic indicator for survival in PDAC (9,10). Supportive care should be systematically implemented in all patients, from the time of diagnosis of PDAC and whatever the tumour stage, in order to improve patient general condition so that they can receive optimal treatment (11). Optimal treatment implies avoiding both undertreatment at initial management and inappropriate end-of-life aggressiveness (12,13). Best supportive care encompasses a broad spectrum of interventions from the treatment of pain, anxiety and depression, chemo(radio)therapy-related toxicities and surgery sequelae, thromboembolic disease, fatigue, malnutrition and cachexia, to psychological assistance to caregivers (14–17). These symptoms are complex and multifactorial in origin and thus their management requires a multidisciplinary therapeutic approach involving oncologists, surgeons, gastroenterologists, nutritionists and dieticians, radiologists, pain and palliative care specialists, nurses and

physical activity professionals (15). Of note, nutrition and physical activity interventions require adaptation to the specificities of PDAC setting and stage of the disease.

The aim of this review is to provide an overview of palliative and supportive care interventions in PDAC, with a highlight on nutritional and physical activity management.

2. Methods

We performed a systematic literature search in Pubmed using the keywords “nutrition AND pancreatic cancer”, “diet AND pancreatic cancer”, “physical activity AND pancreatic cancer”, “physical exercise AND pancreatic cancer”, “sarcopenia AND pancreatic cancer”, “cachexia AND pancreatic cancer”, “palliative care AND pancreatic cancer”, “supportive care AND pancreatic cancer”, and “quality of life AND pancreatic cancer” from 01/2015 to 04/2018. We reviewed all titles and abstracts and included reviews and meta-analyses, guidelines, clinical trials, and original articles, with the exception of study protocols and case reports.

3. Non-specific management of common symptoms

3.1. Pain

Pain is the most frequent symptom in PDAC, reported by 75% of patients at diagnosis and up to 90% at advanced stage (15). PDAC-related pain is multifactorial in origin, combining visceral (tissue destruction and inflammation, pancreatic duct obstruction) and neuropathic (nerve infiltration) mechanisms (15). Perineural invasion is quasi-constant in PDAC, resulting in neuropathic pain. Of note, intense abdominal pain (requiring morphinic analgesics), with posterior irradiation, is suggestive of an unresectable tumour by celiac invasion and is associated with a poor prognosis (18). Therefore, the addition of neuropathic agents (*e.g.* gabapentine, pregabalin, nortriptyline, duloxetine) should be systematically considered in patients with advanced PDAC, regardless of the pain intensity, in association to classical step-up approach based on World Health Organization (WHO) pain ladder scale (19,20). Drug combination aims at increasing the effectiveness of the analgesic treatment by acting on different targets of nociception, while reducing overall side effects (in particular, opioid-induced pruritus, nausea, and constipation) (15). In case of uncontrolled pain despite well-conducted medical treatment, interventional techniques (*i.e.* endoscopic ultrasound-

guided or image-guided percutaneous neurolytic celiac plexus block, or palliative radiotherapy) may be considered in selected patients (15,20,21) .

3.2. Anxiety and depression

Only few studies outside clinical trials assessed depression or anxiety in patients with PDAC, most of which had small sample sizes or were focused on particular patient subgroups (22). Most of them suggested that depression and anxiety were more prevalent in PDAC patients than in other cancer populations (17,22). Interestingly, anxiety, but not depression, is even more common in carers than in patients (39% vs. 15%, and 58% vs. 70%, respectively) (17). Similar to pain, anxiety and depression have a significant impact on HRQoL and PS (23). Questionnaires (*e.g.* Hospital Anxiety and Depression Scale, HADS and Beck Depression Inventory, BDI) may be useful tools for screening and evaluation of these symptoms. Psychological distress should be managed on an individual basis and relies on non-pharmacological interventions (psychotherapy, cognitive-behavioural therapy, support groups), other symptom control (*e.g.* pain), and, if required, antidepressant medication (23).

3.3. Thromboembolic events

Twenty to 35% of patients with PDAC (up to 60% in autopsy series) are affected by thromboembolic events during the course of the disease, making it one of the most thrombogenic tumours (15,24). Hypercoagulability is induced by systemic inflammation and cancer cell secretion of factors that trigger the clotting cascade (25). Parameters of blood cell count analysis (elevated leukocyte and platelet count and decreased haemoglobin) have turned out to be useful in risk prediction (26). The Khorana score provides guidance for preventive anticoagulation based on primary tumour site and clinico-biological parameters (27). In patients with PDAC, the presence of one factor among (i) haemoglobin < 10 g/dL or treatment with erythropoietin derivative, (ii) platelet count $\geq 350,000/\text{mm}^3$, (iii) white blood cell count $> 11,000/\text{mm}^3$, or (iv) body mass index (BMI) $\geq 35 \text{ kg/m}^2$ is sufficient to reach the high-risk threshold score of 3, at which primary thromboprophylaxis by low molecular weight heparin (LMWH) may be considered (27). The high efficacy and feasibility of primary pharmacologic prevention of symptomatic venous thromboembolic events in ambulatory patients with advanced PDAC using LMWH has been demonstrated (CONKO-004 study), suggesting that these indications might be widened (28). After the occurrence of a venous

thromboembolic event in a patient with advanced PDAC, the anticoagulation therapy should be prolonged indefinitely (29). Of note, direct oral anticoagulants are not yet approved for the prevention or treatment of thromboembolic disease in cancer (30). Finally, there is no consensus regarding the management of visceral thrombosis (*i.e.* involving portal, mesenteric or splenic veins) in PDAC (31).

4. Nutrition

4.1. Definitions, screening/evaluation, and physiopathology

Cachexia is a paraneoplastic multi-organ syndrome characterized by negative protein and energy balance driven by a variable combination of reduced food intake (anorexia) and abnormal metabolism, weight loss (including muscle and fat), and decreased physical function (32,33). Three phases of cachexia are classically described: (i) pre-cachexia, (ii) cachexia, and (iii) refractory cachexia; the latter cannot be reversed by conventional nutritional support, highlighting the importance of early diagnosis and therapeutic intervention for cancer-related cachexia (32,33). Reduction of muscle mass (also known as sarcopenia, initially described in elderly patients but also applied to muscle loss secondary to cancer), as assessed by various modalities of body composition analysis (*i.e.*, anthropometry, biphotonic absorptiometry, bioimpedance analysis, or, more often, muscle surface area evaluated at the level of the third lumbar vertebra [L3] on abdominopelvic computed tomography) is a hallmark of cachexia (32,34). Cancer-related malnutrition is classified into two grades of severity, whose clinico-biological definitions (based on body mass index [BMI], weight loss, and serum albumin level) take into account the age of the patient [Table 1]. The European Society of Clinical Nutrition and Metabolism (ESPEN) also introduced diagnostic criteria for malnutrition in 2015 combining BMI, unintentional weight loss, and fat free mass index (*i.e.* muscle mass) (35). Overall, there is an overlap between cachexia, sarcopenia, and malnutrition.

Besides these simple criteria that are used for malnutrition screening, other scales (*e.g.* Mini-Nutritional Assessment, Prognostic Nutrition Index, VEGA-GP) and laboratory tests (plasma proteins, blood urea, creatinine, plasma C-reactive protein [CRP], and immune function) may be useful for further comprehensive malnutrition evaluation and management (34). Body weight is not always reliable and may be overestimated in case of pathological increase in body water content, such as ascites or lymphoedema. Of note, none

of the above-mentioned clinico-biological scores for nutritional assessment meets the diagnostic performance criteria to predict surgical complications and outcomes (36). In contrast, radiologic evaluation of sarcopenia (muscle surface at L3 level) is gaining increasing interest, although optimal cut-offs remain to be defined (37–40). In addition, in the context of the obesity epidemics, and as this latter is a known risk factor for PDAC development, sarcopenic obesity is emerging as a new entity that may be associated with a poorer prognosis (41–45).

Malnutrition prevalence increases with PDAC stage (46). All stages taken together, it is experienced by about 70% of patients (including 30% of patients with severe malnutrition at diagnosis) (46). Malnutrition is multifactorial in origin, involving mainly inflammatory and hypercatabolic syndrome, as well as stenosis of the digestive tract, cholestasis, exocrine pancreatic insufficiency, diabetes mellitus, anxiety/depression, surgery sequelae, and chemotherapy/radiotherapy adverse effects (nausea/vomiting, mucitis, diarrhea, and loss of appetite) (35,46,47). Chronic systemic inflammation, through hypercatabolism, is a crucial driver of cancer-induced cachexia (32,33). PDAC is prototypical of cancer-induced inflammation and cachexia. High levels of inflammatory cytokines (*e.g.* interleukin-6 [IL-6] and its surrogate CRP) and imbalanced peripheral blood mononuclear cells (*i.e.*, high neutrophil-to-lymphocyte ratio) are observed in PDAC patients and correlate with reduced survival (32,48–52). The pancreas, through its endocrine and exocrine functions, plays key roles in metabolism (glucose regulation) and absorption of nutrients. PDAC development (either through parenchymal destruction or paraneoplastic effect) and treatment side effects (surgery, chemotherapy, radiotherapy) may then frequently impact the nutritional status of patients. Cholestasis and jaundice, causing malabsorption, as well as digestive tract obstruction can be due to compressing tumour in the pancreatic head or peritoneal carcinomatosis (53). Diabetes mellitus of recent onset (< 2 years), caused by PDAC (also known as type IIIc diabetes (54), *i.e.*, paraneoplastic or secondary to ductal obstruction with upstream pancreatic atrophy), or long-standing diabetes (risk factor for PDAC, better documented for type II diabetes), is present in more than 50% of cases and can contribute to malnutrition when decompensated (55,56).

Furthermore, sarcopenic muscle proteolysis induces an important efflux of muscle amino acids, which constitute “bricks and fuel” to boost tumour progression (57,58). This breakdown in muscle tissue proteins is an early event in PDAC carcinogenesis: indeed,

elevated plasma levels of branched-chain amino acids, derived from muscle catabolism, are detectable in blood samples collected two to five years before PDAC diagnosis, when occult disease is probably already present, and may feed PDAC tumour cells (59). In addition, skeletal muscle insulin resistance is a hallmark of PDAC (60). Overall, metabolic changes and secreted “atrophying” inflammatory cytokines (e.g. IL-6, transforming growth factor β [TGF β]) alter cell signaling and mitochondrial functioning in muscle fibers and result in imbalance between muscle protein synthesis and degradation, leading to sarcopenia (61,62).

Malnutrition, cachexia, and sarcopenia are responsible for a significant proportion of PDAC-related deaths and poor prognosis, at all stages of the disease, most probably because of increased morbidity of surgery, toxicity of anticancer treatments, and susceptibility to infections and other complications (33,63). In addition, sarcopenia and cachexia negatively affect HRQoL (64). Therefore, management of malnutrition in patients with PDAC, whatever the tumour stage, is crucial and, given its multifactorial origins, relies on a multidisciplinary approach, including nutritional support, as well as relief of biliary and digestive obstructions, insulin and enzyme replacement therapy, and prevention and symptomatic treatment of surgical complications and chemotherapy/radiotherapy toxicities, on a background of family-centered education.

4.2. Peri-operative care of resectable PDAC

Surgery, aiming at complete tumour resection with clear margins (R0), followed by adjuvant chemotherapy, is the only treatment with curative intent in PDAC (5).

Pre-operative biliary drainage is not systematic since it increases the rate of infectious complications, especially when plastic stents are used (65,66). If performed, the insertion of a short metal stent is preferred (67). Drainage is discussed in cases of: (i) acute cholangitis, (ii) elevated bilirubin level > 250 $\mu\text{mol/L}$, (iii) neoadjuvant treatment, or (iv) delayed surgery (> 3-4 weeks) (68,69).

Alcohol and smoking cessation are recommended, ideally for one month before surgery, to reduce post-operative morbidity (mainly, pulmonary infections and wound complications), although this duration may be decreased not to delay tumour resection (68,70).

Pre-operative immunonutrition for five to seven days should be prescribed to all patients, undernourished or not, undergoing pancreatic surgery as it reduces the risk of

infectious complications (57,59). Complementary oral supplements and other modalities of artificial nutrition (preferentially, enteral) should be administered in patients with malnutrition (68,71,72). Parenteral nutrition should be considered only when the enteral route is not accessible nor functional (69,73).

No oral bowel preparation is warranted, and preoperative fasting duration should be limited to six hours for solids and two hours for liquids (58,62). The use of nasogastric tube should be avoided since it increases the risk of pulmonary infectious complications. Early (24-48h) post-operative oral feeding is safe and feasible in most patients, with progressive increased intake over three to four days according to tolerance. Therefore, artificial nutrition is required only in selected cases (*e.g.* major complications, prolonged gastroparesia) and should rely on enteral feeding whenever possible (68,74,75). Somatostatin analogue pasireotide has been demonstrated to decrease the rate of clinically significant post-operative pancreatic fistula, leak, or abscess (76). A French multicenter study is ongoing to compare the efficacy of somatostatine vs. octreotide in the post-operative setting (NCT03000946).

Following pancreatic resection, patients should be regularly screened and treated for pancreatic insufficiency and its nutritional complications (77,78). Pancreatic exocrine insufficiency is observed in 64%-100% of patients after pancreaticoduodenectomy (PD) and 0%-42% after left splenopancreatectomy (LSP) (79). Diagnosis of pancreatic exocrine insufficiency is, however, challenging (80). Indeed, tests directly evaluating maldigestion are cumbersome and non-specific (such as coefficient of fat absorption) or have limited availability (such as ¹³C-mixed triglyceride breath test) (80). The fecal elastase test is widely used, but its correlation with fecal fat excretion in operated patients is low and the optimal cut-off point in this setting is unclear (80). In addition, exocrine insufficiency can be subclinical yet leading to vitamin (A, D, E, K, B12) and minerals (zinc, selenium, magnesium, calcium, iron) deficiencies and lipid maldigestion (79,80). Therefore, pancreatic enzyme replacement, along with proton-pump inhibitors (PPI), should be systematically considered after PD. Enzyme replacement therapy consists in oral administration of 50,000-75,000 IU of lipase in form of pancreatin enteric-coated minimicrospheres distributed throughout each main meal and 25,000-50,000 IU with snacks (81). PPIs can be co-administered to optimize the efficacy of pancreatic enzymes by decreasing intra-gastric pH. Of note, diarrhea due to

altered bowel motility following celiac denervation may also worsen malnutrition and may require treatment with loperamide.

Alternatively, as β -islets are mainly located within the pancreatic tail (90%), LSP is more frequently associated with diabetes mellitus than PD (54), which should be detected based on HbA1c and fasting glycaemia and treated if necessary. When hypoglycaemic agents are used, it is important to closely monitor glucose concentrations because diabetes (when paraneoplastic) can improve, and often resolve, in patients successfully treated with surgery (43). There are no direct studies to inform decisions regarding the choice of hypoglycaemic treatment. Because of its reported antineoplastic properties, metformin might be preferred as first-line therapy for mild hyperglycaemia, and insulin considered as second-line treatment (43).

4.3. Nutrition care in patients with advanced PDAC

The vast majority of patients with PDAC have unresectable disease at diagnosis, due to vascular involvement (locally advanced PDAC, 30%) or distant metastasis (50%) (23,82). Nutrition care is crucial in these patients to ensure optimal PS, tolerance of systemic treatments, and HRQoL.

Nutritional status should be assessed from diagnosis/treatment initiation and regularly reevaluated (14). Nutrition counseling should be provided to all patients; this includes, for example, encouraging good oral hygiene practices to prevent mucositis, adequate fluid intake, multiple small meals to stimulate appetite, and favouring cold food in case of nausea caused by cooking odours. Dieticians and nutritionists are expert in estimating calorie and protein intakes (83). Oral nutritional supplements, high in proteins and calories, are routinely proposed when oral intakes are insufficient to cover needs (84). Enteral nutrition, which is indicated when nutrient intakes remains inadequate and less than 50% of total energy needs, should be preferred to parenteral nutrition (84). Nasogastric tubes can be used for up to four to six weeks (14). According to the ESPEN guidelines, home parenteral nutrition has to be considered only when patient gastrointestinal tract is not functional due to obstruction, radiation enteritis, severe mucositis, or intestinal failure, in the absence of heavy lung or liver metastatic burden, and if the vital prognosis is conditioned by nutritional status rather than by neoplastic disease (84). Thus, parenteral nutrition should not be prescribed in near end-of-life setting.

Endoscopic treatment of biliary duct or duodenal obstruction (*i.e.* biliary and/or duodenal stenting) should be preferred over surgery in symptomatic patients. Metal stents are preferred but plastic stents can be considered when patient life expectancy is very short (< 3 months) (82,84). Surgical derivation to bypass an unresectable PDAC from the head of the pancreas in an asymptomatic patient (*i.e.* prophylactic gastrojejunostomy) is not recommended. In the event of intra-operative finding of a contra-indication to a curative surgical procedure, in a patient with a biliary stenosis requiring drainage, it is acceptable to perform a choledoco-duodenal anastomosis, which is simpler to perform and as effective as choledoco-jejunal anastomosis (86). In addition, ascites is a frequent complication of PDAC, due to peritoneal carcinomatosis and/or severe malnutrition (87–89). In case of compressing ascites, paracentesis can alleviate pain, improve respiratory function, and facilitate oral food and fluid intakes.

Pancreatic exocrine insufficiency is estimated to affect more than 50% of patients with advanced PDAC (90). As described earlier in the adjuvant setting, exocrine insufficiency may present with symptoms (fatty diarrhea, flatulence, and dyspeptic symptoms) or be subclinical. Based on this finding, some guidelines (NICE) propose to offer pancreatic enzymes to all patients with unresectable PDAC (91). Otherwise, replacement therapy using at least 25,000–50,000 IU of enteric-coated pancreatin with each meal should be started promptly once exocrine insufficiency is diagnosed or suspected (80,91).

Endocrine insufficiency (*i.e.* diabetes mellitus) may also develop and be decompensated by nutritional support (particularly, parenteral nutrition) or steroids, requiring hypoglycaemic agents.

Omega-3 fatty acids (fish oils), L-carnitine, amino acids, vitamins, and other minerals have not shown consistent efficacy data and require further research (22,92).

Anorexia is frequently multifactorial in cancer (involving pain, gastroparesia, early satiety, gastrointestinal obstruction, constipation, dysgeusia, mucositis, nausea, depression, and hypothyroidism) and is an important component of cachexia (94–96). Several drugs have been tested to increase appetite and food intakes. Drugs containing the active ingredient of cannabis (tetrahydrocannabinol, THC), such as dronabinol, have been proposed to reduce chemotherapy-related nausea and anorexia but are not recommended due to lack of high level evidence of efficacy and significant side effects (*e.g.* impairment of cognitive function, depression, somnolence) (97,98). Other agents have been tested

including ghrelin mimetics, neuroleptic drugs (mirtazapine, olanzapine), progesterone analogues, corticosteroids, and anabolic hormones; none of them has been properly clinically validated and they cannot be recommended in PDAC patients (97,99–102). Beside classical antiemetics, nausea or early satiety may be alleviated by prokinetics in the absence of digestive tract obstruction (96).

Anti-inflammatory agents (*e.g.* non-steroidal anti-inflammatory drugs, anti-COX2) may decrease the inflammatory syndrome and showed activity in mouse models of cachexia (103,104). Other drugs, such as anti-IL-6 or anti-TGF β agents, may also have anti-cachectic properties. However, no prospective trial has demonstrated their efficacy and inocuity in large number of patients, thus they are not validated for clinical routine practice (105–107).

Overall, no specific medication targeting cachexia or anorexia is validated to date, and they cannot be recommended in PDAC patients.

5. Physical activity

There is accumulating evidence that physical activity is beneficial for cancer patients during and after treatment by reducing disease and/or treatment-induced symptoms (including pain, fatigue, and anxiety/depression), improving physical fitness and muscle function (in a multimodal approach against sarcopenia in combination with nutritional support), and HRQoL (108–111). Cancer-related fatigue has a major impact on patient HRQoL; it is multifactorial and involves the disease itself, treatments, and bed rest leading to deconditioning. Deconditioning, *i.e.* loss of physical (cardiorespiratory function and muscle strength) and psychological fitness caused by reduced physical activity, is one of the main drivers of cancer-related fatigue. As an appearing paradox, rest may be deleterious in these patients, while physical exercise is the best way to reduce deconditioning and fatigue. Several studies have reported a 30%-decrease in cancer-related fatigue, maintained cardiorespiratory fitness and muscle strength, and potential benefit on HRQoL with physical activity practice, even in advanced-stage cancer (108,111,112). In contrast, no specific drug has shown efficacy for the treatment of fatigue in palliative care patients (112,113).

A beneficial effect of physical activity on OS has also been reported in case-control observational studies in two frequent cancers, *i.e.* breast and colorectal cancer (89–91). Exercise may reduce cancer-specific mortality through modulation of several pro-tumoral pathways (114,117). Indeed, exercise (i) reduces circulating estrogen and sex hormone

binding globulin (SHBG) levels in sex hormone-dependent cancers, (ii) improves insulin sensitivity and decreases insulin and insulin-related factors (including insulin-like growth factor 1, IGF-1) secretion, (iii) decreases inflammation and may reduce cancer-related cachexia, (iv) modulates muscle mitochondrial activity thereby counteracting muscle wasting, and (v) increases natural killer and T-cell-mediated immunity (62,114,117). Recent data also suggest that exercise can favorably modulate the MEK/MAPK and PI3K/mTOR/AMPK signaling pathway activity (117). Hence, physical activity may reduce the risk of cancer recurrence and progression. Moreover, physical activity may improve survival through its impact on HRQoL, as a surrogate indicator of OS (118). Finally, physical activity reduces treatment-related toxicity and improves treatment dose-intensity (119).

Implementation of an adapted physical activity (APA) program in cancer patients implies a multidisciplinary collaboration between the cancer-care medical team and an APA professional (109,120–122). The APA program should be individualized for each patient according to the person (physical fitness, exercise type preferences, psychological functions, and expectations), the cancer (stage, treatments, and tolerance), and the social environment. A combined aerobic exercise and resistance-training program is hypothesized to be the most efficient way to improve physical fitness and decrease fatigue and therefore should be favored (109,120–122). Patient adherence to the APA program is crucial for its efficacy. Performing exercise in groups of patients having similar physical capabilities and under the supervision of an APA professional trainer whenever possible is hypothesized to be the best way to ensure patient motivation. The APA program also requires the contribution of nutrition specialists (dietician or physician) to balance energy intake with energy expenditure. Indeed, cancer patients often display significantly increased basal resting energy expenditure and spontaneously reduced physical activity level compared with healthy individuals (123–125). Little is known about the optimal duration of exercise interventions and no specific recommendation from evidence-based guidelines exists (109).

Exercise interventions in cancer patients have been demonstrated to be safe and feasible both in the advanced setting and in the adjuvant setting following surgery (84,97–99). However, randomized controlled studies are warranted to adequately evaluate the efficacy and determine the optimal modalities of APA programs (*e.g.* mode, intensity, frequency, duration, timing) in each cancer type. Prospective data about APA interventions specifically in PDAC patients are limited (129–132). Patients with advanced PDAC are strongly

affected by fatigue, and are thus likely to benefit from an exercise intervention. However, an exercise intervention may appear challenging due to multiple PDAC-related symptoms such as fatigue, depression, pain, and malnutrition. We believe that an APA program taking into account specific features of PDAC may improve symptoms and HRQoL (133). Two multicenter randomized studies are ongoing in France to prospectively evaluate the efficacy of APA on HRQoL in patients with advanced (APACaP phase III trial, NCT02184663, (134)) and resected PDAC (APACaPOp-PRODIGE 56 randomized phase II trial, NCT03400072).

Overall, APA appears as a promising non-pharmacological intervention to improve HRQoL in PDAC patients.

6. Conclusion

Supportive care is inseparable from antitumour treatments in patients with PDAC, to ensure the best conditions for their efficacy and optimal HRQoL. PDAC patients suffer from numerous symptoms (pain, anxiety/depression, fatigue, malnutrition) of multifactorial origin, severely impacting their daily life. These symptoms require a global approach, involving joint action and complementary expertise from multidisciplinary cancer care team [Figure 1]. Future progress in PDAC management and survival benefits may come from improvements in supportive care as much as antitumour therapies.

FIGURE LEGENDS

Figure 1. Summary of main components of multidisciplinary palliative care management in patients with pancreatic ductal adenocarcinoma (PDAC).

TABLE

Table 1. Definitions of malnutrition, severe malnutrition, and cachexia.

Note : 1 criteria is sufficient.

Age	Malnutrition	Severe malnutrition	Cachexia
< 70	• BMI < 17 kg/m² • Weight loss ≥ 5% of BW in 1 month • Weight loss ≥ 10% of BW in 6 months • Albumin < 30 g/L	• Weight loss ≥ 10% of BW in 1 month • Weight loss ≥ 15% of BW in 6 months • Albumin < 20 g/L	• Weight loss > 5% over the past 6 months (in absence of simple starvation) • BMI < 20 kg/m² and any degree of weight loss > 2%
≥ 70	• BMI < 21 kg/m² • Weight loss ≥ 5% of BW in 1 month • Weight loss ≥ 10% of BW in 6 months • Albumin < 35 g/L • MNA < 17	• BMI < 18 kg/m² • Weight loss ≥ 10% of BW in 1 month • Weight loss ≥ 15% of BW in 6 months • Albumin < 30 g/L	• Muscle atrophy (<i>i.e.</i>, reduced muscle mass) and any degree of weight loss > 2%

BMI: body mass index; BW: body weight; MNA: Mini-Nutritional Assessment

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