Scientific summary

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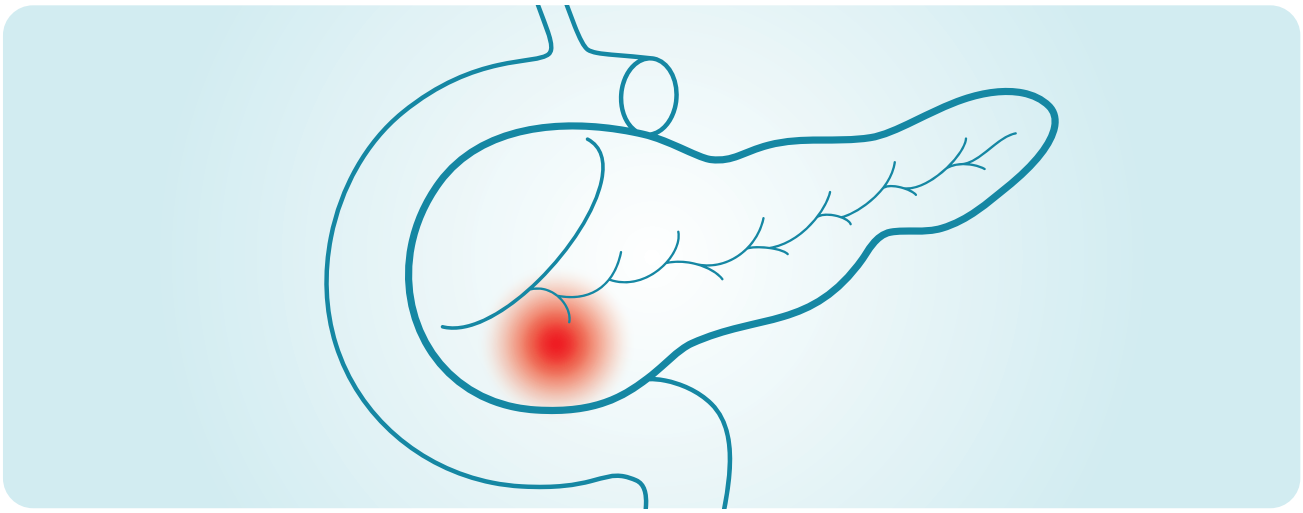
Malnutrition and pancreatic exocrine insufficiency in pancreatic cancer:

Towards the optimal management of a lethal condition



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Nutritional and metabolic dysfunctions in pancreatic cancer: **Relevance and therapeutic approach**

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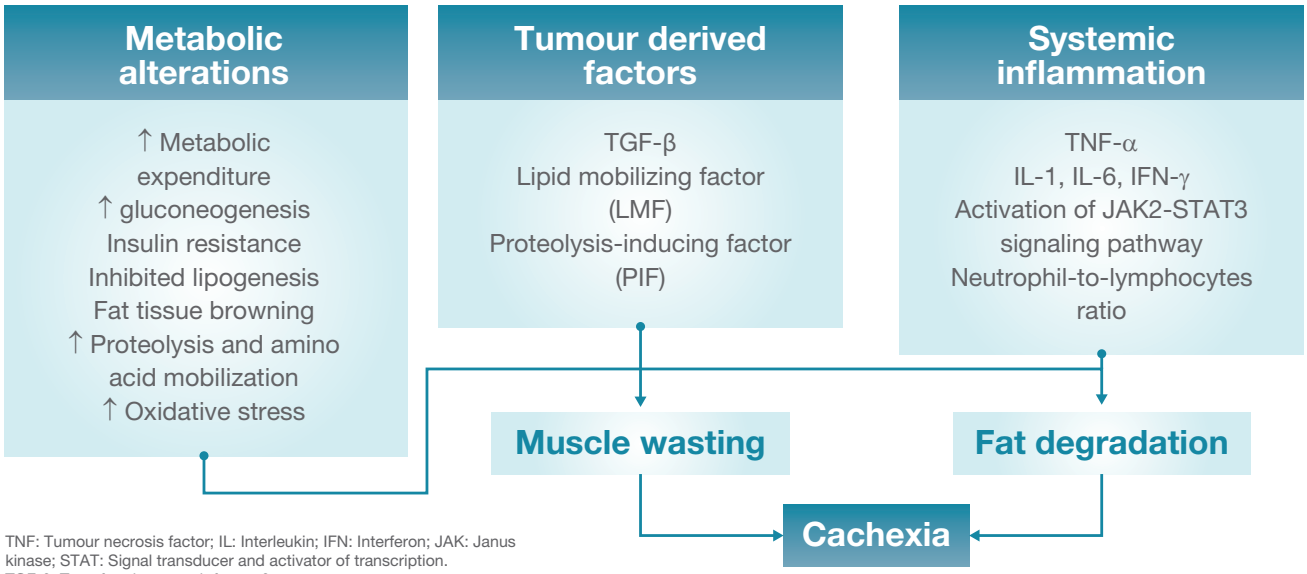
About 80% of patients with pancreatic cancer (PC) report a significant weight loss at the time of diagnosis. Pancreatic cancer, surprisingly, shows the highest rate of sarcopenia and cachexia among all malignancies.

Sarcopenia and cachexia are two different concepts. Sarcopenia is defined as the loss of skeletal muscle mass that can be mild, moderate, or severe. On the other hand, cachexia is an involuntary weight loss, progressively refractory to supportive interventions, with worsening physical inability and poor life expectancy. Sarcopenia and cachexia are the consequence of an imbalance between catabolism and nutritional intake and absorption (Figure 1). With regard to pathophysiology and management, sarcopenia and cachexia are two links of the same chain.

Figure 1: Mechanism of cachexia in patients with pancreatic cancer.



TNF: Tumour necrosis factor; IL: Interleukin; IFN: Interferon; JAK: Janus kinase; STAT: Signal transducer and activator of transcription.
TGF-β: Transforming growth factor-β

Reduced food intake in pancreatic cancer is multifactorial, including anorexia, early satiety, depression /anxiety, abdominal pain, diarrhoea, nausea and vomiting, duodenal obstruction, and pancreatic exocrine insufficiency (PEI), the leading cause of maldigestion and malnutrition in patients with PC).

Most patients have PEI at the time of tumour diagnosis, and the prevalence of PEI increases with the duration of the disease. In a study, 66% of patients had PEI at the time of diagnosis, which increased to 92% at the end of the 2-months follow-up. Notably, if the tumour is located at the head of the pancreas, 80% of the patients present PEI at the time of tumour diagnosis, suggesting the correlation between the tumour location and the severity of PEI.

In patients with a resectable tumour, the increase in the prevalence of PEI after duodenopancreatectomy (Figure 2 and 3) is attributed to:

- Reduced pancreatic secretion
  - o Reduced cholecystokinin release
  - o Loss of pancreatic parenchyma
- Asynchrony between gastric emptying of nutrients and biliopancreatic secretion

Figure 2: Prevalence of PEI after surgery.

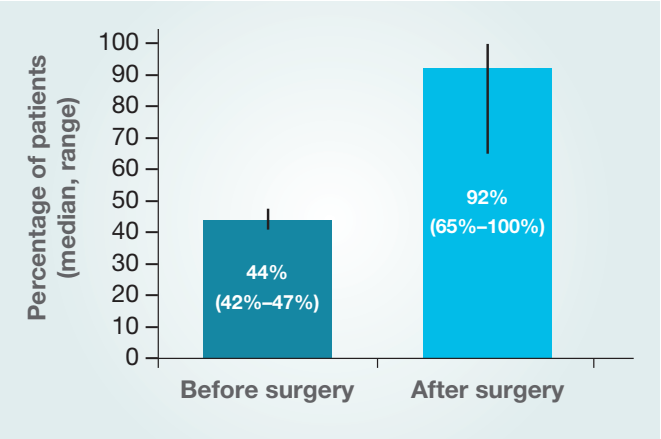
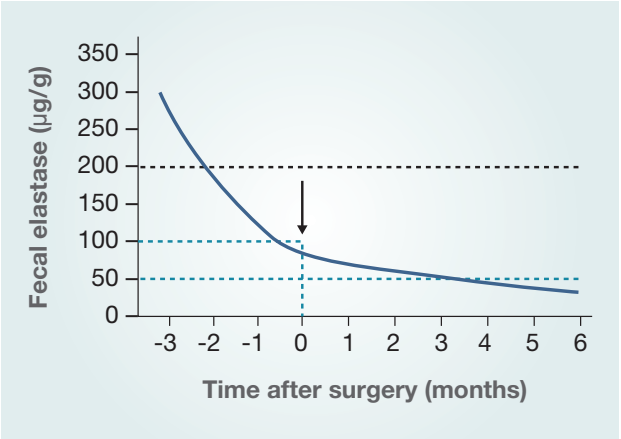


Figure 3: Pancreatic secretion after surgery.



Cachexia negatively impacts pancreatic cancer therapy. Several studies describe the cachectic, sarcopenic and malnourished patients as follows:

- Patients are poor surgical candidates and are less likely to undergo surgery as compared to non-cachectic patients.
- If operated upon, they have more postoperative complications, higher needs of intensive care, longer hospital stay, and increased mortality.

Besides, these patients have limited tolerance and response to chemotherapy and radiation. Altogether, these patients have a poor quality of life (QoL) and short survival.

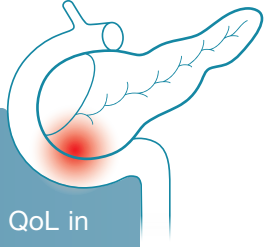
Pancreatic exocrine insufficiency in patients with PC is a major cause of weight loss, associated with poor QoL, complications, and limited tolerance to treatment and is associated with short survival.

A multifactorial approach is required to manage cachexia and PEI in these patients. This includes antagonism of tumour-secreted proteins, modulation of the inflammatory responses, the reverse of metabolic alterations, and improvement in the absorption of nutrients (Figure 4).

Figure 4: Therapeutic approach for nutritional and metabolic dysfunctions in PC.

Antagonism of tumour secreted proteins	Modulation of inflammatory response	Reversing metabolic alterations	Improving absorption of nutrients
• TGF-β antagonists *Trabedersen* • Monoclonal myostatin antibodies *Landogrozumab* • Anti-ActR II B monoclonal antibodies *Bimagrumab*	• Jak2 inhibitors *Ruxolitinib* • Anti-IL-6 *Tocilizumab* *Clazakizumab* • Anti-TNF-α *Infliximab* *Lenalidomide* *Etanercept* • Inhibition of fat tissue browning	• Ketogenic diet • Ghrelin receptor agonists *Anamorelin* • Silibinin • ω-3 polyunsaturated fatty acids	• Dietary advice • Pancreatic enzyme replacement therapy

TGF-β: Transforming growth factor-β; Jak: Janus kinase; IL6: Interleukin 6; TNF: Tumor necrosis factor



Key takeaway messages:

- Malnutrition and sarcopenia negatively impact the response to cancer therapies, survival, and QoL in patients with PC.
- Pancreatic exocrine insufficiency is a frequent complication of pancreatic cancer and pancreatic surgery, which leads to malnutrition, weight loss, and short survival.
- It is important to not just to treat the tumour. A holistic treatment of patients is important.
- Treatment of PEI, sarcopenia, and cachexia is critical in the prognosis of the disease and should follow a multifactorial approach. In this context, nutritional advice and pancreatic enzyme replacement therapy play a relevant role.

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Improving outcomes in resectable pancreatic cancer
– the roles of PEI and PERT

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Surgical treatment for PC has not gained immense interest among doctors. There are preconceived theories/notions on the existence of poor therapeutic approaches for cancers leading poor outcomes with high rates of complications and mortality. However, significant progress has been made in the past 5–10 years. Chemotherapies yield remarkable outcomes. Moreover, centralised pancreatic surgical services have reduced the mortality rates to an acceptable level.

We have embraced change to improve outcomes in patients with PC, but this has come at a cost. Treatments such as chemotherapy are toxic and expensive, and the centralisation of surgical services requires national reorganisation.

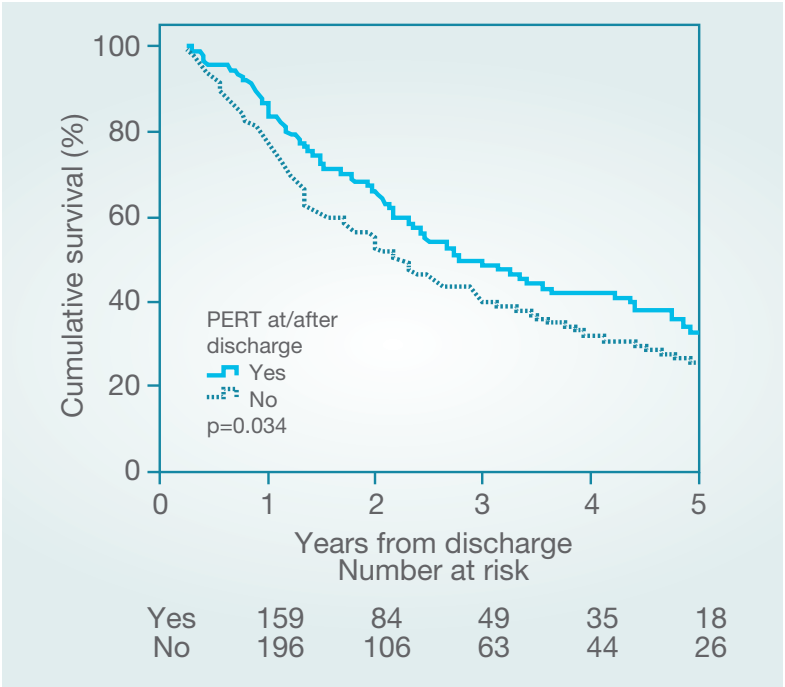
Although PEI is quite common among patients with PC, treatment of PEI among these patients has been a widespread failure. It is well known that treatment of PEI is beneficial in improving survival rates similar to other mainline therapies such as chemotherapy.

Malnutrition is a highly prevalent concern among cancer patients. Malnutrition in pancreatic cancer is fundamentally associated with PEI as well as other ubiquitous mechanisms of malnutrition in cancer. Pancreatic exocrine insufficiency in patients with PC is attributed to structural alterations caused by pancreatic surgery or by the tumour itself.

Most patients with tumours in the pancreatic region requiring pancreatic resection either had exocrine insufficiency at diagnosis or became exocrine-insufficient soon after surgical resection. In a study, preoperative PEI evaluated using the 13C-MTG breath test was present in 20.5% of patients, which increased to 64% postoperative. Several studies showed that almost 100% of patients had PEI after 6 months of pancreaticoduodenectomy, regardless of the surgery type.

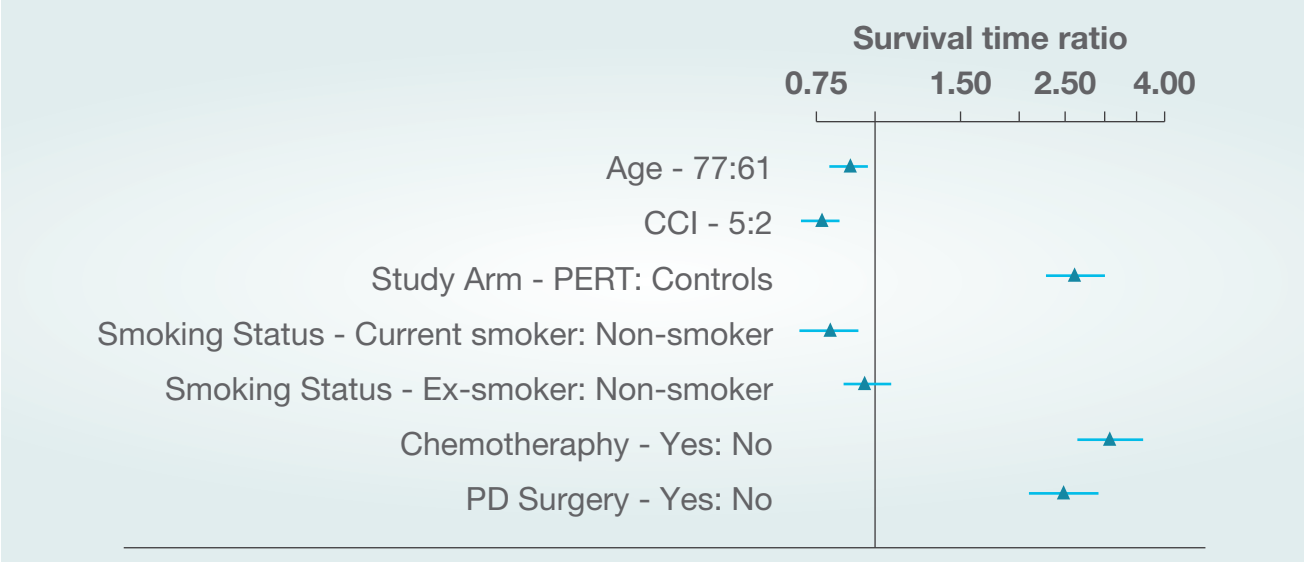
In a 2017 study, the effect of enzyme supplementation was evaluated on the survival of patients with PC in Birmingham. Around 43% of patients received PERT, and they lived 6 months llonger than those who did not receive PERT.

Figure 1: Survival of the whole cohort grouped using PERT or not.



Another 2019 UK-based population study showed that patients who received PERT lived twice as long as those who did not receive PERT. The strength of survival benefit with PERT is remarkably significant, similar to other established therapies such as chemotherapy or surgery.

Figure 2: Adjusted analysis of variables affecting survival.



There is a lack of evidence on the role of PERT in patients receiving neoadjuvant treatment. Though recent publications demonstrate the association between weight loss and skeleton muscle loss and very poor survival, they do not mention/discuss PEI and PERT. All these data demonstrate that despite high prevalence, PEI in patients with PC remains neglected and undertreated.

In the UK, the National Institute for Health and Care Excellence recommends that every patient with PDAC should receive PERT. However, RICOCHET audit 2018 showed that less than 50% receive PERT. The early data of RICOCHET audit show that patients with resectable cancer are more likely to be prescribed PERT. Interestingly, the patient's demographics have no significant impact on whether the patient received PERT or not. Patients were more likely to be on PERT if they were prescribed proton pump inhibitors (PPIs) or nutritional supplements or consulted a dietician. Patients who consulted pancreatic specialists were also more likely to receive PERT.

Key takeaway messages:

- Pancreatic exocrine insufficiency is prevalent among patients following pancreatoduodenectomy, particularly for PDAC, where its incidence approaches 100%. Yet there is widespread undertreatment.
- Pancreatic exocrine insufficiency generally progresses from diagnosis.
- Pancreatic enzyme replacement therapy improves symptoms, quality of life, and survival among patients with resectable disease.
- It is important to prescribe PPI along with PERT.

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Clinical relevance of pancreatic enzyme replacement therapy and nutritional support in unresectable ductal adenocarcinoma (PDAC)

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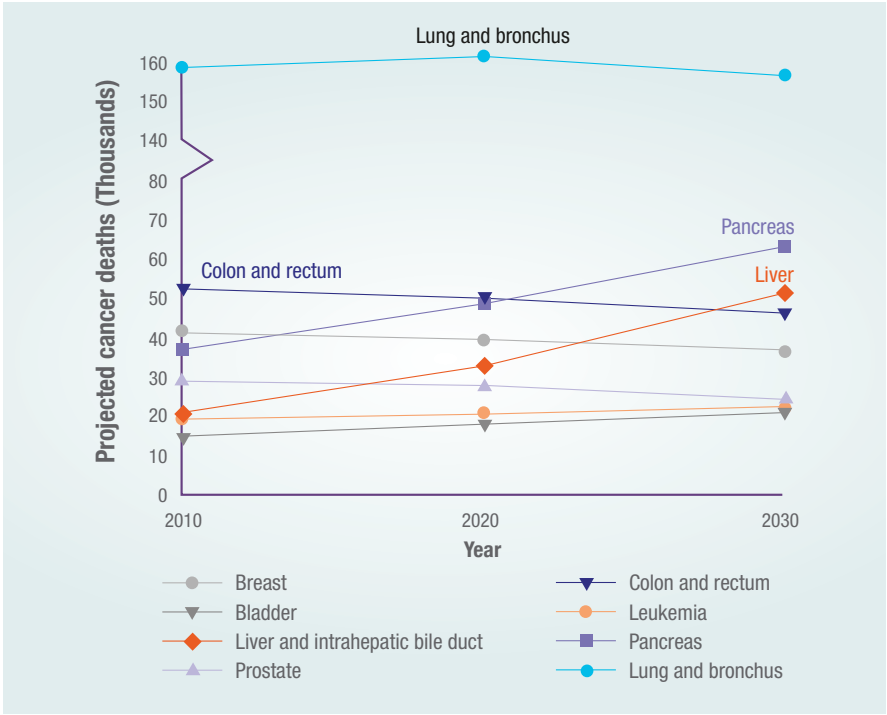
The incidence of pancreatic cancer may increase to become the second leading cause of cancer-related death by 2030 (Figure 1). The median survival of patients with PC has increased in the past two decades, thanks to the research advancements and the availability of new treatment options. However, the longer the survival, the higher the risk of developing PEI.

Figure 1: Projected cancer deaths in 2030.



The nutritional status of patients with PC significantly influences the response to tumour treat -ment, quality of life, as well as survival. Malnutrition in PDAC patients, is multifactorial in origin, involving, PEI, diabetes, pain, fatigue, loss of appetite, sorrow, anxiety/ depression, social issues and family support, chemotherapy/ radiotherapy adverse effects, and bile duct and duodenal obstructions.

The diagnosis of PEI relies on the evaluation of maldiges-tion-related symptoms, nutri-tional markers, and a noninva-sive pancreatic function test in the appropriate clinical context.

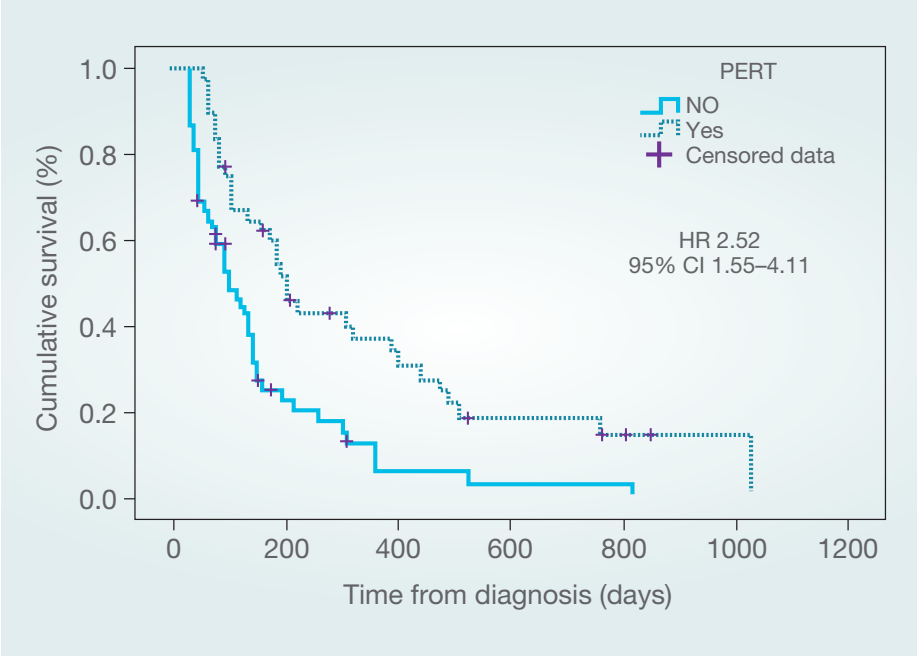
- Patients who underwent antitumoural treatment
  - o Differential diagnosis of diarrhoea: may be due to 5-FU or irinotecan
  - o Signs of PEI (bloating and sticky stools) with faecal elastase <100 mg/g of stool): prescribe pancreat-ic enzymes
  - o Check glycaemia: if diabetic, prescribe metformin ± insulin

- Patients who underwent surgery
  - o Differential diagnosis of diarrhoea (anatomic changes, vagal resection, etc.)
  - o Assessment of weight and nutritional parameters (prealbumin, vitamins B9, B12, D, calcium, etc.): Consult a dietitian; fraction feeding (≥5 small meals) is recommended
  - o Supplementation with pancreatic enzymes
  - o Follow-up of glycaemia (risk of diabetes, particularly after left pancreas resection)

As mentioned earlier, with an increase in survival in patients with PDAC, the risk of PEI also increases. This is due to the aggressivity of modern treatment (surgery, chemotherapy, and radiation therapy), precancerous conditions (such as chronic pancreatitis), and cancer itself.

In a 2017 study conducted by Keith Roberts and colleagues, it was shown that PERT is associated with increased survival following pancreatoduodenectomy for periampullary malignancy. Similarly, Domínguez-Muñoz and colleagues (2018) demonstrated that PERT significantly improves the survival in patients with unresectable PC, even among those with a significant weight loss at diagnosis (Figure 2). A 2019 population-based study showed that the median survival was significantly greater among those patients receiving PERT, regardless of the treatment modality.

Figure 2 Survival curves in patients with unresectable PC and a significant weight loss.



HR: Hazard ratio; CI: Confidence interval.

The currently available studies discussing the role of PERT in patients with PDAC have a few limitations – retrospective nature, non-homogeneous diagnostic methods, and lack of data on QoL. However, despite a limited level of evidence, PEI in patients with PDAC should be taken into consideration and treated appropriately. For surgeons, gastroenterologists, and oncologists, a cautious/exhaustive analysis of diarhhoea in PDAC patients is very important for the precise diagnosis of PEI and to rule out other causes.

Key takeaway messages:

- Aggressive anti-PDAC treatments have increased the survival rates; hence, more PEI cases will be diagnosed.
- Nutritional support plays an essential role in the management of PDAC patients.
- Pancreatic enzyme replacement may improve diarrhoea and nutritional status and may balance diabetes.
- Patients with PC, regardless of the treatment modality, develop PEI and hence require nutritional support and PERT.

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