












## REVIEW ARTICLE

# The Brazilian Society of Surgical Oncology (SBCO) Guidelines for the Treatment of Exocrine Pancreatic Insufficiency in Cancer Patients

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## ABSTRACT

Exocrine pancreatic insufficiency (EPI) in oncology patients requires careful attention due to its clinical significance and frequent underdiagnosis. This narrative review and Guideline established by the Brazilian Society of Surgical Oncology suggest a practical approach to diagnosis and pancreatic enzyme replacement therapy (PERT). This promising approach can improve symptoms, nutritional status, and quality of life, potentially positively impacting survival in unresectable pancreatic cancer and postsurgical settings.

## 1 | Introduction

Exocrine pancreatic insufficiency (EPI) in surgical and clinical oncology patients is a condition characterized by inappropriate secretion of pancreatic enzymes and bicarbonate. It is often underdiagnosed and undertreated despite its high clinical relevance [1–3].

EPI can be multi-causal, including conditions that lead to loss of parenchyma, obstruction of its main duct, decreased stimulation, or inactivation of its enzymes in an intraluminal acidic environment. In cancer patients, especially those with pancreatic cancer, EPI is

common due to impairment of the pancreatic parenchyma by the tumor itself or by surgical resections [2–5].

The clinical symptoms of EPI include abdominal cramps, changes in bowel function, steatorrhea, and progressive weight loss, not all of which must be present. This symptomatic triad can lead to varying degrees of malnutrition, which is associated with high morbidity and mortality. The complications of malnutrition resulting from EPI include increased susceptibility to infections, impaired healing, deficiencies in fat-soluble vitamins, calcium, and micronutrients, osteopenia, and an increased risk of cardiovascular events [2, 6].

There is no widely available test to diagnose EPI accurately. Diagnosis is usually late and requires high suspicion, recognition of risk groups, evaluation of symptoms, nutritional markers, and noninvasive pancreatic function tests such as fecal fat quantification. Fecal elastase-1 is often used as an indirect marker of pancreatic exocrine function [1, 6].

The treatment of EPI includes the oral administration of exogenous pancreatic enzymes, which should be taken with meals. The dose should be proportional to the fat content of the meal, with adjustments as necessary. Pancreatic enzyme replacement therapy (PERT) improves symptoms, nutritional status, and quality of life (QoL) in patients and may be associated with improved survival in unresectable pancreatic cancer and after surgery for pancreatic cancer [1–4, 6, 7].

Patient education on the correct use of enzymes can optimize results [4–6]. It is essential to raise awareness about EPI in different clinical conditions, and nutritional counseling and adequate PERT are mandatory to improve outcomes [1–3].

## 2 | Objective

This guideline aims to guide and assist in the treatment of exocrine pancreatic insufficiency in the context of cancer patients.

## 3 | Method

The guidelines for the treatment of exocrine pancreatic insufficiency endorsed by the Brazilian Society of Surgical Oncology (SBCO) were developed by a multidisciplinary panel of renowned specialists.

The process started with wide-ranging discussions among the experts at one of the society's congresses, in which the possible key topics to be debated were addressed. Subsequently, these key topics were identified and distributed to the specialist group. This group carried out a narrative review of the relevant literature in databases such as MEDLINE/PubMed and, also with the assistance of the OpenEvidence 2024 tool (Available at <https://www.openevidence.com>), drew up preliminary recommendations, which were submitted for analysis and discussed in a brainstorming model.

Suggestions for standardizing and aligning these recommendations were debated, revised, and incorporated into the final version of the text.

An adapted version of the Infectious Diseases Society of America—the United States Public Health Service Grading System [8] was used to define the level of evidence and to classify each recommendation proposed by the panel (Table 1).

Level of evidence and recommendation grading (Table 1) [8].

The recommendations were then evaluated in terms of their degree of recommendation and level of evidence. Throughout the process, agreement among the participants was defined, with a consensus threshold of more than 80% for approval of the recommendation.

## 4 | Which Groups of Patients Are Most Affected by Exocrine Pancreatic Insufficiency?

The most affected groups include patients with chronic pancreatitis, patients with cystic fibrosis, and patients with pancreatic neoplasms, who often have obstruction of the main

**TABLE 1** | Level of evidence and recommendation grading [8].

Quality of evidence	
I	Evidence from at least one large randomized, controlled trial by sound methodological rigor (indicating low potential for bias) or from meta-analyses of well-executed randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with suspicion of bias (indicating lower methodological quality) or from meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, or expert opinions
Grade of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence indicates efficacy, although with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweighing the risk or the disadvantages (such as adverse events or costs), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

pancreatic duct, pancreatic atrophy, and adverse effects from treatments such as chemotherapy and, less frequently, radiotherapy [9, 10].

Patients with pancreatic cancer alone and those who are not resectable have 50% to 92% EPI, while those with resectable cancer have rates of 40% to 50% before treatment and close to 75% after it [9]. The high postoperative prevalence of EPI in pancreatic resections, such as pancreatoduodenectomy and distal pancreatectomy, is around 74% and 67% to 80%, respectively [11].

Patients with tumors of the pancreatic head, distal bile duct, or ampulla of Vater are often present with EPI at diagnosis, with a prevalence that can increase significantly within a few months [12], which is associated with serious nutritional complications that can negatively impact the quality of life and survival [10, 13]. The proper management of these patients, including PERT, can optimize nutritional status and improve clinical outcomes [14].

## 5 | Physiopathology

The physiopathology of EPI involves several causes, which act in four scenarios:

- Decreased production of digestive enzymes due to loss of pancreatic parenchyma.
- Reduced pancreatic stimulation (signaling process that triggers pancreatic secretion).
- Obstruction of the pancreatic drainage pathways (e.g., obstruction of the main pancreatic duct).
- Inactivation of pancreatic enzymes by increased gastric-duodenal acidity and/or reduced bicarbonate production [3, 9, 15, 16].

EPI is frequently observed in cancer patients and is particularly common in individuals with pancreatic cancer or in those who have undergone surgical resections of the pancreas. It can occur due to the damage caused to the pancreas by the disease or due to surgical resections that reduce the organ's exocrine capacity [3, 9, 15, 17]. In addition, obstruction of the pancreatic duct, especially noted in reconstruction with pancreatogastrostomy, can limit the release of enzymes into the intestine [9, 17–19].

EPI leads to significant clinical manifestations, such as steatorrhea, weight loss, and malnutrition, which are particularly

worrying in the oncology context with negative impacts on quality of life and survival [3, 15, 16, 20]. Pancreatic enzyme replacement therapy (PERT) is essential for improving digestion and nutrient absorption, relieving symptoms, and improving nutritional status, as well as being part of perioperative prehabilitation care in patients who are candidates for cancer treatment [16, 20].

## 6 | EPI Classification

EPI can be classified into four stages (Table 2) [21].

In patients with chronic pancreatitis, 46% show potential EPI (without steatorrhea), while 31% have definite EPI (with steatorrhea), suggesting that a significant proportion of them may not have steatorrhea [22]. Also, for patients in Stages I and II, where steatorrhea is not present, PERT can be beneficial.

## 7 | Diagnosis

The definitive diagnosis of EPI involves a combination of laboratory tests, imaging, and clinical evaluation. We describe the most relevant methods for diagnosis, including asymptomatic patients:

### 7.1 | Clinical and Physical Examinations

Clinical assessment includes observation of symptoms such as steatorrhea, weight loss, and signs of malnutrition. In asymptomatic patients, the presence of risk factors, such as a history of chronic pancreatitis or pancreatic resections, may justify diagnostic investigation [23].

### 7.2 | Laboratory Tests

#### 7.2.1 | Fecal Elastase Test

This is the most widely used indirect test due to its simplicity and non-invasiveness. Fecal elastase levels below 200  $\mu\text{g/g}$  of faeces are considered abnormal, with values below 100  $\mu\text{g/g}$  strongly indicating the presence of EPI. This test is less sensitive for mild cases of EPI but is useful for identifying moderate to severe cases [9].

**TABLE 2** | EPI classification [21].

Stage	Dysfunction
Stage I (mild dysfunction)	Fecal elastase between 100–200 mcg/g, without steatorrhoea
Stage II (moderate dysfunction)	Fecal elastase < 100 mcg/g, without steatorrhoea
Stage III (severe EPI without nutritional deficiency)	Marked fecal elastase and fat absorption reductions, but normal vitamins levels
Stage IV (severe EPI with nutritional deficiency)	All parameters abnormal

### 7.2.2 | Fecal Fat Quantification

This method assesses digestive capacity by measuring fat in the feces and is one of the most accurate tests for EPI [24, 25]. Qualitative analysis can also be carried out using Sudan III staining.

### 7.2.3 | Serum Trypsinogen and Fecal Chymotrypsin Test

These are other tests for evaluating EPI, but they have not been used due to their lower sensitivity and specificity compared to the fecal elastase test [9, 22, 25].

## 7.3 | Imaging Tests

### 7.3.1 | Magnetic Resonance Imaging (MRI) and MRI With Secretin Stimulation

MRI can assess the volume of the pancreatic parenchyma, pancreatic duct obstruction, and parenchymal atrophy, and additionally the response to secretin, which helps to identify exocrine dysfunction. MRI with secretin (if available) can be particularly useful for detecting subtle ductal changes and assessing exocrine secretion. The degree of duodenal filling determined on MRI pancreatography after secretin stimulation allows a specific estimate of pancreatic exocrine function [26, 27].

### 7.3.2 | Computerized Tomography (CT)

Used to assess pancreatic morphology, including atrophy, calcifications, ductal dilation, and other structural changes [25].

For asymptomatic or oligosymptomatic patients, diagnosis can be challenging, as indirect tests such as fecal elastase may not detect mild and chronic cases. In these cases, the assessment should be based on a combination of risk factors, imaging findings, and laboratory tests, with a focus on preventing long-term nutritional complications.

## 7.4 | Recommendation

Clinical assessment and physical examination should be carried out on all patients with pancreatic conditions that could lead to EPI. If suspected, laboratory and imaging tests should be conducted.

[level of evidence IV/grade of recommendation B]

## 8 | Treatment

The treatment of EPI mainly involves PERT, which is essential for improving digestion, relieving symptoms such as abdominal pain, improving nutrient absorption, reducing steatorrhea, and

weight loss. PERT is administered in the form of capsules, which are usually coated to resist gastric acidity and release the enzymes in the small intestine [3, 9, 28–30]. The dosage of PERT should be adjusted according to the fat content of the meals.

In Brazil, the Clinical Protocol and Therapeutic Guidelines (PCDT) for Exocrine Pancreatic Insufficiency, approved by Ministerial Order 112/2016 of the Ministry of Health, provides a structured basis for the management of this condition within the National Health System (SUS). This protocol guides the diagnosis and use of PERT, including initial doses and adjustments according to the patient's clinical response and nutritional status. It also provides for the use of Pancreatin in doses of 10 000 to 50 000 lipase units per meal, with the possibility of individual adjustments [31].

## 8.1 | Recommendation

It is recommended to have an initial dose of 25 000 to 50 000 units of lipase per meal, which can be increased to 75 000 to 80 000 units, depending on the clinical response and the severity of the EPI [3, 28, 31]. For snacks, the dose is usually half that of the main meals. In cases of inadequate response, a dose increase or the addition of proton pump inhibitors may be considered to improve the effectiveness of therapy [3, 27, 28].

Nutritional guidance is relevant to ensure adequate intake and avoid deficiencies. Restricting fat in the diet is usually not necessary but can be considered in specific cases [3, 28, 32].

[level of evidence II/grade of recommendation A]

## 9 | What Are the Most Common Side Effects Associated With PERT in Cancer Patients?

The most common side effects associated with PERT include gastrointestinal symptoms such as diarrhea, dyspepsia, abdominal pain, flatulence, constipation, and nausea [9]. These effects are generally mild and can be managed by adjusting the dosage.

Rarer but potentially serious adverse reactions include fibrosing colonopathy, which is associated with prolonged use of high doses of pancreatic enzymes, especially in children [9]. In addition, hypersensitivity reactions such as anaphylaxis, asthma, urticaria, and pruritus have also been reported [9]. Hyperuricemia is another possible side effect, particularly in patients with gout or kidney impairment.

### 9.1 | Recommendation

It is essential to monitor patients for these side effects and adjust treatment as necessary to minimize the impact on quality of life and ensure treatment effectiveness.

[level of evidence IV/grade of recommendation B]

## 10 | Impact of PERT on QoL, Survival, and Symptom Control?

EPI, when not properly treated, can lead to malabsorption, negatively affecting quality of life and the ability to tolerate cancer treatments [9].

Evidence suggests that improving dysabsorption with PERT relieves symptoms and promotes weight maintenance or gain [4, 33]. In patients with advanced pancreatic cancer, these benefits are associated with a possible increase in overall survival [34, 35]. A retrospective analysis including 160 patients with unresectable pancreatic cancer showed an independent and significant association for both PERT and chemotherapy treatment concerning survival benefit, especially in those with weight loss >10% in 6 months [13]. Other retrospective and observational publications have shown the same [36]. Replacement therapy is considered an important part of EPI management in cancer patients, helping to mitigate nutritional complications and improve tolerance to systemic treatments [9].

### 10.1 | Recommendation

PERT improves quality of life and symptom control in patients with pancreatic cancer and EPI. Its early and appropriate implementation should be encouraged in treating these patients.

[level of evidence III/grade of recommendation A]

## 11 | Are There Any Benefits to Adding PERT During Chemotherapy Treatment?

In patients with metastatic pancreatic cancer, PERT associated with nutritional support has been linked to improved overall survival and the prevention of weight loss during chemotherapy [36]. Furthermore, it can improve nutritional status, which is crucial for tolerating systemic treatment and maintaining performance status [36, 37]. Its proper administration can also mitigate muscle loss/sarcopenia, which is common in patients with advanced cancer [38].

### 11.1 | Recommendation

PERT improves the quality of life and symptom control and can also contribute to an increase in survival in patients with pancreatic cancer and EPI, highlighting the importance of its early and appropriate implementation in the management of these patients [14, 34, 36].

[level of evidence IV/grade of recommendation B]

## 12 | Which Drugs Can Cause EPI-Related Side Effects?

In the context of oncology patients with pancreatic cancer undergoing chemotherapy, some drugs can cause side effects

related to exocrine pancreatic insufficiency (EPI). The medical literature highlights that immune checkpoint inhibitors, such as those used in immunotherapy, can induce EPI secondarily as an immune-mediated event. One study described the incidence of EPI in patients treated with immune checkpoint inhibitors, noting that the condition is rare but clinically significant and often associated with symptoms such as steatorrhea and weight loss, which improve with PERT [39].

Although not directly related to EPI, chemotherapy regimens for pancreatic cancer, such as FOLFIRINOX and gemcitabine-based combinations, are known for their significant toxicity, which can include gastrointestinal effects that complicate patients' nutritional management [40, 41]. These effects can exacerbate nutrient malabsorption in patients already predisposed to EPI due to underlying pancreatic disease.

It is therefore important to carefully monitor and manage gastrointestinal side effects in pancreatic cancer patients undergoing chemotherapy, especially those that can aggravate EPI.

### 12.1 | Recommendation

Pancreatic cancer patients treated with immunotherapy or chemotherapy regimens such as FOLFIRINOX and gemcitabine-based should be monitored to identify EPI-related symptoms, such as steatorrhea and weight loss, considering early interventions, including PERT, to mitigate gastrointestinal effects and optimize nutritional management.

[level of evidence IV/grade of recommendation B]

## 13 | How Can PERT Adherence be Improved in Cancer Patients?

To improve adherence to enzyme replacement therapy in cancer patients, various strategies can be implemented. Initially, provide educational measures for both the patient and the healthcare professional. Many patients do not receive detailed information about how and when to take PERT, which can lead to a failure in adherence [42]. Raising awareness about the importance of therapy at all meals and snacks can improve treatment effectiveness and adherence [43].

The implementation of dosing and titration algorithms can help standardize and facilitate the administration of appropriate doses [44]. Regular reviews by specialized professionals can help adjust doses as necessary and resolve persistent symptoms [44].

Another important factor is the continuous follow-up of patients. Loss of follow-up has been identified as a significant barrier to effective adherence [42]. Establishing a regular follow-up system can help identify and resolve adherence problems, such as inappropriate dosage adjustments or side effects.

Finally, it addresses socioeconomic barriers such as cost and access. Patients with lower levels of education and income were

associated with lower adherence to PERT [45]. Personalizing treatment strategies to meet patients' individual needs can help overcome these barriers and improve treatment.

### 13.1 | Recommendation

To improve PERT adherence in cancer patients, detailed education on the correct use of therapy is recommended, with an emphasis on intake with all meals and snacks, implementation of standardized dosing and titration algorithms, regular reviews for individual adjustments, ongoing follow-up to resolve adherence problems and specific strategies to overcome socio-economic barriers such as cost and accessibility, ensuring personalized and effective management.

[level of evidence IV/grade of recommendation B]

### 14 | Conclusion

Pancreatic enzyme replacement therapy (PERT) improves symptoms, nutritional status, and quality of life (QoL) in patients. It may be associated with improved survival in unresectable pancreatic cancer and after surgery for pancreatic cancer. Patient education on the correct use of enzymes can optimize results. Raising awareness about EPI in different clinical conditions is essential, and nutritional counseling and adequate PERT can improve outcomes.

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#### Data Availability Statement

The data supporting this study's findings are available from the corresponding author, Rodrigo N. Pinheiro, upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of research authors.

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