

SURGICAL TECHNIQUES IN THE TREATMENT OF INSULINOMAS: A COMPREHENSIVE REVIEW OF APPROACHES, EFFECTIVENESS AND IMPACTS ON QUALITY OF LIFE

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Abstract: Objective: Analyze and synthesize the surgical approaches used in the treatment of insulinomas, highlighting their effectiveness, complications and impacts on patients' quality of life. **Methods:** A Literature Review was carried out through searches in the PubMed database. Among the 93 articles identified, 11 studies were selected that met the established inclusion criteria. **Results:** The various research modalities analyzed converge to the conclusion that complex surgeries are the only curative treatment option for insulinoma. The location of the tumor, its proximity to vital pancreatic structures and the functionality of the mass represent crucial criteria that guide the choice of surgical techniques. Open surgery, with enucleation of the tumor, using palpation and intraoperative ultrasound to identify the mass, stands out as the most effective alternative in the treatment of insulin-producing pancreatic tumors. This approach aims to optimize clinical results and quality of life for patients. **Conclusion:** There is a pressing need to expand the scope of research into the treatment of insulinoma, especially in cases of multiple tumors, aiming to provide a more in-depth understanding of the best therapeutic options and the establishment of appropriate guidelines.

Keywords: insulinoma; neuroendocrine tumor; pancreas; surgical technique; treatment.

INTRODUCTION

Insulinoma is a rare endocrine pancreatic tumor characterized by autonomous secretion of insulin and proinsulin by beta cells of the pancreas, leading to hypoglycemia (Burghardt et al., 2019). Its annual incidence can reach 4-6 people per million and, although insulinomas represent the most common cause of Endogenous Hyperinsulinemic Hypoglycemia (EHH) in adults, most cases of EHH in children fall into the category of

familial hyperinsulinism (Christ et al., 2023).

The disease is a challenge with regard to clinical presentation, diagnostic investigation, choice of surgical procedure and pathological classification (Andreassen et al., 2019). According to Andreassen et al. (2019), the initial symptoms of hypoglycemia are nonspecific, with a wide spectrum of possible differential diagnoses. In certain cases, the drop in the amount of glucose in the peripheral blood circulation can present symptoms such as sweating, tremors, fatigue, hunger and neurological symptoms, such as irritability, transient focal cognitive and neurological deficits, which can progress to convulsions and coma (Christ et al, 2023).

The basis of the diagnosis of HHE is related to Whipple's triad, which includes symptoms consistent with hypoglycemia such as those related to the autonomic nervous system, a history of low glucose concentration, and the relief of symptoms after ingestion of carbohydrates (Christ et al., 2023). Unfortunately, many localization procedures for endocrine pancreatic tumors in general, and for insulinomas in particular, have a rather low diagnostic sensitivity and will produce negative results even when used in patients with a clearly biochemically proven insulinoma (Burghardt et al., 2019).

For Delguete et al. (2018), the management of patients with neuroendocrine tumor diseases requires a multidisciplinary approach, and the diagnosis must take into consideration the patient's condition, histological type, location, size, degree of extension and the character of functioning or not. of the tumor.

As most of these insulin-producing endocrine tumors are single and approximately 90% are benign, surgical treatment can lead to a cure of the disease if the tumor can be completely removed (Burghardt et al., 2019). Complete resection (R0) of the primary tumor and its potential metastases is the

only possibly curative treatment and must always be considered (Delguete et al., 2018). Knowing the size, nature and location of the tumor is useful to support the decision for surgery by both the surgeon and the patient, as well as directing the most appropriate treatment when it comes to the appropriate surgical strategy (Burghardt et al., 2019).

Pancreaticoduodenectomy (PD) and distal pancreatectomy (DP) are standard operations for tumors located in the proximal portion of the pancreas. However, these techniques are associated with a significant risk of long-term endocrine and exocrine impairment (Huang et al., 2009). Macroscopically incomplete surgery may be exceptionally discussed to control a refractory hormonal syndrome, prevent or treat local complications, and/or limit the risk or extension of the tumor to the liver (Delguete et al., 2018). There has been increasing interest in conservative surgery in an attempt to preserve as much as possible the pancreatic parenchyma and the integrated anatomy of the digestive system (Huang et al., 2009).

The objective of this literature review article is to analyze and summarize the surgical approaches used in the treatment of insulinomas, highlighting their effectiveness, complications and impacts on patients' quality of life. We aim to provide a comprehensive overview of available surgical strategies, evaluating their indications, advantages and disadvantages, in order to guide clinicians and surgeons in selecting the most appropriate approach for the effective management of these insulin-producing pancreatic tumors.

METHODOLOGY

The present study is a bibliographical review developed in accordance with the criteria of the PVO strategy, whose acronym represents: Population or Research Problem, Variables and Outcome. This methodological

approach aims to answer the following guiding question: “What are the most effective surgical strategies for the treatment of insulinomas, insulin-producing pancreatic tumors, aiming to optimize clinical results and patients’ quality of life?” In the context of this methodology, the population or research problem addressed specifically refers to patients with insulinomas, that is, pancreatic tumors that produce insulin. We sought to analyze the surgical approaches used to treat these patients, evaluating their indications, advantages and disadvantages.

The searches were carried out by searching the PubMed Central (PMC) database. We used descriptors combined with the Boolean term “AND”, resulting in the following combination: (Insulinoma [MeSH] AND “Surgical Procedures, Operative” [MeSH]). From this initial search, we identified a total of 93 articles, which were subsequently subjected to selection criteria.

The inclusion criteria considered for the selection of articles were the following: articles published in English, Portuguese and Danish; published between 2018 and 2023; studies that addressed the themes proposed for this research, of the review or meta-analysis type and made available in full. On the other hand, the exclusion criteria cover: studies that did not directly address the study proposal and that did not meet the other inclusion criteria. After applying these criteria, a total of 11 articles were selected to compose the present study, contributing to the analysis of surgical strategies used in the treatment of insulinomas and their impact on clinical results and quality of life of patients affected by this condition.

DISCUSSION

SURGICAL CHALLENGES IN PANCREATIC NEUROENDOCRINE TUMORS

Pancreatic neuroendocrine tumors (P-NET) represent a highly challenging category of pathologies due to their clinical diversity and heterogeneity. Addressing these neoplasms requires a complex surgical approach, with the location of the primary tumor, the type of hormone or neuropeptide produced and the presence of metastases being crucial factors in surgical planning (Belotto et al., 2019). Complete resection of resectable NET-P is essential for successful treatment. Even in smaller tumors, surgical precision is crucial due to the risk of lymph node metastases (Beek et al., 2020).

As discussed by Beek et al. (2020), NET-P stands out for its variety and complexity, representing a substantial challenge in the field of surgery. Smaller tumors can be monitored in patients without multiple endocrine neoplasia type 1 (MEN-1), while larger tumors require specific surgical interventions, such as enucleation or pancreaticoduodenectomy. Accuracy in tumor location, proximity to vital pancreatic structures and tumor functionality are crucial criteria that guide the choice of surgical techniques.

A detailed review revealed that surgical precision is the determining factor for successful treatment of NET-P. Regardless of tumor size, complete resection remains the main goal. We have found that less invasive techniques such as enucleation can be equally effective in single tumors. However, in cases of multiple MEN-1-related tumors, personalized surgical strategies are crucial to preserve pancreatic function and reduce recurrence rates (Beek et al., 2020).

The only curative treatment option available for insulinomas is surgical resection

(Beek et al., 2020). In cases of insulinomas smaller than 2 cm, especially in patients without multiple endocrine neoplasia type 1 (MEN-1), immediate surgical intervention may not be necessary. The standard approach for treating insulinomas is still open surgery, which involves palpation and the use of intraoperative ultrasound to identify tumors. Ultrasonography often reveals homogeneous, hyperechoic masses.

The procedure of choice is tumor enucleation, performed in 56% of cases, especially when dealing with small tumors (<2.5 cm), superficial, single and located at least 2 mm away from the pancreatic duct or large tumors. Larger tumors, suspected of malignancy or metastases, are treated using techniques that aim to preserve as much pancreatic tissue as possible, with only 0.6% of cases resulting in total pancreatectomy (Giannis et al., 2020).

Among the options for preserving pancreatic tissue, depending on the location of the tumor, are Whipple surgery (3% of cases), partial pancreatectomy (3%) and distal pancreatectomy (32%) (Giannis et al., 2020). Combined procedures demonstrated good curative potential and a low complication rate in a study from the "International MEN1 Insulinoma Study Group". In this study, the majority of 33 patients with type 1 endocrine neoplasia and multifocal insulinomas underwent distal pancreatectomies with enucleation of the tumor in the head of the pancreas, with only one patient experiencing postoperative hypoglycemia (Beek et al., 2020).

On the other hand, laparoscopic procedures correspond to 5.5% of surgeries, being more indicated for tumors in distal masses. Laparoscopic surgery has the advantage of reduced hospitalization time, lower morbidity and mortality and lower risks of postoperative fistula. However, the precise location of the

tumor is compromised in this procedure, as it does not allow direct palpation or high-quality intraoperative imaging. Furthermore, minimally invasive surgery has considerable surgical conversion rates, ranging between 17% and 25%. Due to these limitations, the minimally invasive approach remains relatively unpopular in clinical practice (Giannis et al., 2020).

The choice between open, laparoscopic and minimally invasive surgery must be carefully considered based on the characteristics of the tumor, its location and the patient's clinical condition. Open surgery remains the most common approach, allowing accurate identification of the tumor and application of appropriate resection techniques. Laparoscopic surgery, although it offers benefits in terms of reduced length of stay and morbidity and mortality, faces limitations in accurately identifying the tumor. This can be especially problematic in cases of small or deep tumors, where direct palpation and intraoperative ultrasound are crucial (Belotto et al., 2019). Although minimally invasive surgery is an attractive option, considerable surgical conversion rates indicate that not all cases can be successfully completed using this approach. Therefore, the choice of surgical technique must be individualized, taking into consideration the size, location and extension of the tumor, as well as the surgeon's experience (Giannis et al., 2020).

Enucleation, a technique that involves removing the tumor while preserving pancreatic tissue, offers higher survival rates compared to more extensive resections. It is also associated with a shorter length of hospital stay and fewer abdominal wall injuries. However, complications are possible, with slightly higher fistula rates, especially when the distance between the insulinoma and the main pancreatic duct is less than 3 mm. Fistulas are more common in the head

of the pancreas and in patients with a body mass index (BMI) above 25 kg/m² (Deguéte et al., 2018).

In studies, enucleation has been reported to rarely cause postoperative diabetes (less than 1% of patients) and no exocrine insufficiency. Furthermore, exocrine and endocrine pancreatic insufficiency is less common after enucleation compared to other resection techniques such as pancreaticoduodenectomy (Deguéte et al., 2018).

Pancreaticoduodenectomy, despite its advantages in some cases, is associated with a higher postoperative mortality rate due to the volume of resection. This puts the patient at risk of pancreatic insufficiency, especially exocrine insufficiency. Furthermore, the need for a bilioenteric anastomosis may contraindicate or increase risks for future procedures such as chemoembolization, radiofrequency, or ablation. Pancreaticoduodenectomy also increases the risk of liver abscesses as a result (Deguéte et al., 2018).

Regarding distal pancreatectomy, there is evidence of an association with pancreatic insufficiency, mainly endocrine, which may require further treatment. Furthermore, the rate of developing diabetes is 15% of patients undergoing this technique. The anatomical proximity and common vascular supply between the pancreas and spleen increase the frequent need for splenectomy, and there is a greater risk of infection (Deguéte et al., 2018).

Current studies investigate several ablation techniques, including injectable ethanol ablation, radiofrequency ablation (RFA), photodynamic therapy, and laser ablation, with the aim of treating pancreatic tumors (Matsumoto K. et al., 2022). Two of these techniques, injectable ethanol ablation and RFA, are widely used in the treatment of pancreatic tumors.

Injectable ethanol ablation, guided by endoscopic ultrasound, has shown promising

results in functional pancreatic tumors, with an effective complete response of approximately 60 to 80%. This procedure involves the application of heat through a water-cooled needle, reaching temperatures of up to 85°C. However, ablation efficacy is less pronounced in nonfunctional tumors, with lower response rates. Furthermore, treatment can result in adverse events, such as abdominal pain, pancreatic duct stenosis, acute pancreatitis, hemorrhage, and transient fever (Jansen C. et al., 2022).

To prevent the occurrence of postoperative pancreatitis, non-steroidal anti-inflammatory drugs (NSAIDs) are administered in the postoperative period (Jansen C. et al., 2022). The main indications for endoscopic ultrasound-guided ablation therapy in pancreatic solid neoplasms include tumors with a diameter of up to 2 cm, patients with hormone-related symptoms, and those who are not candidates for surgery (Matsumoto K. et al., 2022).

With regard to pancreatic cystic tumors (PCN), the effectiveness of endoscopic ultrasound-guided ablation varies across studies. Complete response to treatment has been reported in a range of 9% to 41%. To improve the treatment of cystic tumors, paclitaxel, a chemotherapy agent, has been used in combination with ethanol ablation. This resulted in higher complete response rates, ranging from 50% to 79%, with limited adverse events such as abdominal pain and acute pancreatitis (Matsumoto K. et al., 2022).

A comparative study was carried out to evaluate the need for the use of ethanol in the ablation of cystic tumors. It was concluded that ethanol was not essential, as the complete response rate was similar between the groups using ethanol and normal saline. Furthermore, removal of ethanol reduced the occurrence of complications (Matsumoto K. et al., 2022). In addition to ethanol ablation,

ultrasound-guided radiofrequency (EUS-RFA) is another treatment technique. It works through a high-frequency alternating current that raises the local temperature, leading to coagulative necrosis of the tissues. Studies have reported success rates ranging from 55% to 100%, with no additional treatment-related adverse events (Matsumoto K. et al., 2022). Comparatively, EUS-RFA has been shown to have better results compared to injectable ethanol ablation and other ablatives.

OUTCOMES, PROGNOSIS AND QUALITY OF LIFE IN PANCREATIC NEUROENDOCRINE TUMORS

In the treatment of pancreatic neuroendocrine tumors (P-NET), the surgical approach plays a crucial role. However, as with any surgical procedure, it is essential to consider the risk ratios. Precisely determining the location of the tumor is extremely important for the success of the procedure. These tumors are associated with significant complications, with an occurrence rate of approximately 45-52%, similar to other pancreatic surgeries. Furthermore, a lower incidence of complications is observed in patients already hospitalized or with long-term coexistence with the disease (Hoskovec et al., 2023).

In large insulinoma surgical series, mortality rates range from 0 to 6%, with a morbidity of 33-56%. Pancreatectomy, in particular pancreateoduodenectomy, is associated with the highest mortality rate (Carbonnières et al., 2021).

A common complication in pancreatic surgeries, both open and laparoscopic, are pancreatic fistulas. Treatment includes percutaneous drainage, parenteral nutrition with somatostatin analogues (SSAs) and, in more severe cases, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy or even reoperation (Giannis

et al., 2019).

According to Giannis et al. (2019), approximately 90-95% of NET-P are benign, with a 5-year survival after almost total resection of the tumor. However, there is the possibility of metastatic disease in lymph nodes, liver and, in rare cases, in bone or other tissues. Grade G2 tumors have a greater likelihood of recurrence. For patients with malignant insulinomas, the prognosis is unfavorable, with an average survival of up to 2 years. Those who resist surgical treatment must undergo follow-up with reexaminations at intervals of 3, 6 and 12 months, which can be extended annually over time. Remission of the disease is observed in asymptomatic patients within a period of 6 months.

FINAL CONSIDERATIONS

Surgical resection, through enucleation of the primary tumor and its potential metastases, currently represents the only curative treatment option available for insulinomas. The conventional surgical approach, through an open procedure with tumor enucleation, employs palpatory and intraoperative ultrasound techniques for the precise identification of the mass. This method stands out as the most effective alternative in the treatment of insulin-producing pancreatic tumors, aiming to optimize clinical results and improve patients' quality of life. However, recent research shows that alternative techniques, such as injectable ethanol ablation, radiofrequency ablation (RFA), photodynamic therapy and laser ablation, present promising results, achieving significant success rates. The effectiveness of these therapeutic procedures has been recognized as a standard of excellence, indicating a more diverse and personalized therapeutic approach. Despite evident advances, investigations related to the surgical approach in cases of multiple tumors associated with Multiple Endocrine Neoplasia

type 1 (MEN-1) emerge as necessary for the formulation of guidelines that guide the treatment of this complex condition.

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