

MINIREVIEW

ENDOSCOPIC RADIOFREQUENCY ABLATION IN BILIOPANCREATIC TUMOURS

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ABSTRACT

Bilio-pancreatic malignant neoplastic diseases are characterized by aggressive evolution and low 5-year survival rates. The only therapeutic method with curative potential remains surgical treatment. Unfortunately, a very high percentage of patients are diagnosed in advanced stages, no longer suitable for surgical resection. Studies in recent years have focused on identifying new therapeutic techniques to improve the quality of life and survival of these patients. One of these techniques is endoscopic radiofrequency ablation, that showed good results in terms of morbidity and mortality, with an acceptable rate of complications.

Keywords: biliopancreatic tumours, radiofrequency ablation, biliary stenoses, prognosis.

RÉSUMÉ

Ablation par radiofréquence endoscopique dans les tumeurs bilio-pancréatiques

Les maladies néoplasiques malignes bilio-pancréatiques sont caractérisées par une évolution agressive et à faible taux de survie à 5 ans. La seule méthode thérapeutique à potentiel curatif reste le traitement chirurgical. Malheureusement, un pourcentage très élevé de patients sont diagnostiqués en stades avancés, ne se prêtant plus à une résection chirurgicale. Les études de ces dernières années se sont concentrées sur l'identification de nouvelles techniques thérapeutiques pour améliorer la qualité de vie et la survie de ces patients. L'une de ces techniques est l'ablation endoscopique par radiofréquence, qui a montré de bons résultats en termes de morbi-mortalité, avec un taux de complications acceptable.

Mots-clés: tumeurs bilio-pancréatiques, ablation par radiofréquence, sténoses biliaires, pronostic.

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INTRODUCTION

Pancreas, liver, gallbladder and bile ducts have a common embryological origin, and malignancies originating in these organs are characterized by low 5-year survival rates¹. Bilio-pancreatic adenocarcinomas are among the most aggressive neoplasms. Despite their low incidence, they are currently one of the leading causes of cancer-related mortality worldwide^{2,3}. The prevalence of pancreatic cancer in the United States is 9 cases per 100,000 population, in all age groups, increasing to 68 cases per 100,000 population in the age group over 55 years old³. Despite the advances in the management of patients with malignant neoplastic diseases, the survival rate of patients with pancreatic cancer has remained almost unchanged over the past decades⁴. Currently, pancreatic cancer is the fourth leading cause of cancer death in both sexes in the United States, after lung, colorectal, and breast cancer, and the seventh leading cause of cancer death world-wide^{5,6}. The 5-year survival rate of patients with this malignancy is approximately 7%⁷. Unfortunately, only 10-20% of cases are suitable for surgical resection, about 75% of patients with pancreatic cancer being diagnosed in stages III-IV^{5,7}. One study showed that only 7% of pancreatic cancer patients are diagnosed in a stage of localized disease¹. This early diagnosis rate is much lower compared to other malignant diseases, such as prostate (91%), breast (61%), colon (40%), lung (16%), and ovarian cancer (19%)⁸⁻¹⁰. Over 95% of pancreatic tumours originate in the exocrine pancreas and less than 5% in the endocrine pancreas^{11,12}. The most widely used classifications of exocrine pancreatic tumours in the United States are those provided by the Armed Forces Institute of Pathology (AFIP) and the World Health Organization (WHO)¹². These classifications are based on histopathological aspects and divide pancreatic tumours into three categories: benign, premalignant and malignant lesions^{12,13}. Premalignant tumours have the potential to progress to malignancy, and therapeutic management currently requires imaging surveillance to detect early malignant transformation. The WHO recommends the use of three degrees of dysplasia to estimate the malignant potential of a tumour, namely low, intermediate and high¹⁴.

The local development of a pancreatic tumour can lead to the invasion or extrinsic compression of the bile ducts, with the appearance of cholestasis and the need to apply a treatment that decompresses the bile ducts. Malignant biliary stenoses can occur both in the evolution of pancreatic cancer and other neoplasms, such as cholangiocarcinomas or hepatocellular carcinomas¹⁵. Cholangiocarcinomas are a group of malignant bile tumours, very heterogeneous, which can occur at any level of the biliary system¹⁶.

Depending on the anatomical origin, they are divided into three subtypes: intrahepatic, perihilar, and distal cholangiocarcinomas¹⁷. Cholangiocarcinoma is the second most common type of primary liver tumour, after hepatocellular carcinoma, accounting for about 15% of all primary liver tumours and 3% of gastrointestinal cancers¹⁶. The incidence of these malignancies varies by geographical area, from 85 cases per 100,000 population in Thailand to 0.4 cases per 100,000 population in Canada¹⁸. These are, however, isolated regions, the global average incidence being estimated at 0.3-6 cases per 100,000 inhabitants per year¹⁶⁻¹⁸. Most often, these diseases are clinically asymptomatic in the early stages, in 70% of cases the diagnosis being established in advanced stages¹⁶⁻¹⁸. The direct consequence of the late diagnosis is the compromise of therapeutic possibilities and poor prognosis. Thus, the 5-year survival rate of these patients remains low, 7-20%¹⁶⁻¹⁸. Also, noteworthy is the high rate of tumour recurrence after surgical resection¹⁶.

ENDOSCOPIC RADIOFREQUENCY ABLATION

Most cases of pancreatic cancer or cholangiocarcinoma are diagnosed in advanced stages, which are not suitable for surgical resection. In addition, surgery involves very high risks, and advanced age or the association of comorbidities further decrease the percentage of patients who can benefit from this treatment. In addition, the percutaneous approach of bilio-pancreatic neoplasms is associated with high risks, because of the anatomical position of these organs. Chemotherapy and radiotherapy provided minimal benefits on the survival rate of patients with biliary-pancreatic neoplasms^{19,20}. The most used and effective palliative therapy, at present, remains the stenting of the biliary tract with self-expanding metal stents, for the treatment of biliary obstruction that occurs frequently in the evolution of these neoplasms²¹. In about 50% of cases, however, 6 months after the insertion of these stents, tumour growth leads to their invasion^{22,23}. Thus, readmissions are needed, with a negative impact on the quality of life and survival of these patients²⁴. Under these conditions, studies in recent years have focused on identifying new therapeutic methods used for curative or palliative purposes, which would improve the morbidity and mortality of patients with biliary-pancreatic neoplasms. The development of devices compatible with endoscopic instruments has led to the possibility of applying minimally invasive treatments, such as radiofrequency ablation. This technique uses high frequency alternating current to provide local thermal energy that induces coagulation necrosis and destruction of tumour tissue. The active thermal effect

is limited to a few millimeters (1.5-3.8 mm) around the electrode that provides the alternating current, but it is conducted over a larger area, which can cause damage to adjacent structures^{24,26}.

Radiofrequency ablation, percutaneously or intraoperatively, has been widely used in malignancies of several solid organs such as liver, breast, lung or kidney²⁷. The pancreas, however, because of its deep anatomical position, is difficult to visualize and approach therapeutically. Currently, the most sensitive and specific diagnostic method for pancreatic tumours is echo-endoscopy²⁸. As per treatment, the percutaneous application of radiofrequency energy is associated with the risk of thermal lesions in the duodenum or adjacent blood vessels. The surgical approach offers a better visibility and the ability to manipulate the anatomical structures adjacent to the pancreas more effectively. However, a very small percentage of patients with biliopancreatic malignancies may be candidates for surgery. In the case of bile duct tumours, the endoscopic access to the bile ducts through endoscopic retrograde cholangiopancreatography (ERCP) has proven to be the safest and most effective. The developments in the field of endoscopy and the working channel of an endoscope or through a needle compatible with an echoendoscope allowed a minimally invasive approach of bilio-pancreatic tumours, by ablation with radiofrequency under endoscopic guidance²⁹.

To perform this interventional treatment, a dedicated system of radiofrequency procedures for bilio-pancreatic pathologies is necessary, consisting of:

- a radiofrequency energy generator dedicated to echoendoscopy (EUS) and ERCP procedures in bilio-pancreatic pathologies (RF VIVA generator), that allows the control of power, impedance, temperature and time interval. It has attached a cooling system, which circulates cold saline solution through the needle, avoiding the extension of tissue necrosis during ablation of large-volume tumours. The generator is compatible with both endoscopic ultrasound-guided radiofrequency ablation electrode (EUSRA) and endoluminal radiofrequency ablation (ELRA).
- EUSRA: a 19-gauge needle with an electrode length of 140 cm, the thermal insulation of which is interrupted for the last 5-30 mm.
- ELRA with various lengths (11mm, 18mm, 22mm, and 33mm) for the different anatomy and geometry of the stricture²⁴.

Regarding pancreatic neoplasms, preliminary data in the literature support a significant efficiency of the use of ELRA. Thus, the use of this therapy in patients with locally advanced pancreatic adenocarcinoma has led to a significant cytoreduction, with

decreased tumour volume³⁰. The morbidity associated with echoendoscopic treatment was acceptable, with low rates of acute pancreatitis or pancreatic fistulas. Compared to surgical treatment, ablative techniques allow a better preservation of surrounding healthy tissues, shorter hospital stays and lower costs³¹. There are studies that have evaluated the effectiveness of radiofrequency ablation in the treatment of benign lesions, cystic focal lesions (intraductal papillary mucinous neoplasm, mucinous cystadenoma) or small neuroendocrine tumours with a low degree of dysplasia. The conclusion of these studies is that ELRA may be an alternative to surgical resection for small tumours, or may reduce the need for long-term surveillance of benign tumours^{26,32}. The thermal ablation of a pancreatic tumour can reduce the spread of pancreatic cancer and increase the effectiveness of chemo and neoadjuvant radiotherapy. This can be explained by thermally induced changes in the microenvironment of pancreatic cancer. Secondary to tumor necrosis, the local immune response is stimulated by infiltrating tumour margins with T and B lymphocytes, dendritic cells, neutrophils, macrophage and natural killer cells. Thermally mediated tissue damage also leads to the stimulation of the systemic antitumour immune response^{33,34}.

Regarding malignant biliary stenoses, radiofrequency ablation has been shown to be effective in ensuring a longer duration of biliary stent permeability, with a favourable impact on the quality and lifespan of these patients (Fig. 1,2). Currently, among the indications of this therapeutic method there are palliative treatment of malignant bile strictures, avoidance of bile stent occlusion or prolongation of their permeability, ablation of residual adenomatous tissue after endoscopic ampulectomy¹⁵. A study that included 40 patients with unresectable malignant biliary strictures, showed an increase in the life expectancy by about three months among those who underwent radiofrequency ablation³⁵. Another retrospective study followed 62 patients with malignant biliary obstructions, divided into two groups: a group of 30 patients who underwent endo-biliary radiofrequency ablation and metallic stent placement, and another group of 32 patients who had benefited only from metallic stent placement²⁹. This study demonstrated the potential of radiofrequency ablation in improving stents' patency and implicitly in the quality of life and survival of patients.

There are also some risks associated with endoscopic radiofrequency ablation:

- Hemorrhage – for which endoscopic hemostasis with coag grasper or the use of blood clots can be performed.



Figure 1. Endoscopic retrograde cholangiopancreatography (ERCP). Medio-distal choledochal stenosis, with sudden decalibration and irregular contour, highly suggestive of malignancy; dilated supra stenotic bile ducts (published with permission, from the collection of Clinical Emergency Hospital of Bucharest, Romania).



Figure 2. Endoscopic retrograde cholangiopancreatography (ERCP). Remodeling of the bile duct with partial recovery of patency immediately after performing radiofrequency ablation (published with permission, from the collection of Clinical Emergency Hospital of Bucharest, Romania).

- Perforation – risk minimized by the accuracy of the technique, the use of carbon dioxide, blood clotting and possibly surgery.
- The development of some forms of acute pancreatitis, pancreatic or pseudocyst fistulas, for which medical, endoscopic or even surgical treatment may be used.
- Sepsis, for which appropriate antibiotic therapy will be administered, according to antibiogram.
- Duodenal lesions, for which endoscopic or surgical intervention can be performed.
- Recurrence – monitoring according to standard protocols, resolution by endoscopic or surgical re-intervention.
- Uncommon complication: left bundle branch block, liver infarction, hepatic coma³⁶⁻³⁷.

CONCLUSIONS

Bilio-pancreatic neoplasms are diseases with low prevalence, but high mortality. The negative prognosis is due on one hand to the late diagnosis, in advanced stages of the disease, and on the other hand, to the absence of effective therapeutic methods. Currently, the only treatment with curative potential is the surgical treatment. However, the late diagnosis means that a small percentage of patients can benefit

from surgical treatment. Chemotherapy and radiation have shown minimal benefits in these patients.

Echoendoscopy is considered today the most sensible method for identifying pancreatic tumours, its sensibility reaching up to 94%²⁸. In addition, echoendoscopy allows therapeutic maneuvers such as drainage of pancreatic fluid collections or postsurgical abdominal collections, endoscopic ultrasound-guided angiotherapy, endoscopic ultrasound-guided liver interventions, celiac plexus block and celiac plexus neurolysis, etc.²⁸. One of the most innovative therapeutic procedures that can be performed under echoendoscopic guidance is radiofrequency ablation. In bilio-pancreatic tumours, this therapeutic method can be used for both curative and palliative purposes, with a relatively low rate of complications.

ERCP is commonly used in the diagnostic and therapeutic management of bilio-pancreatic disorders³⁸. Regarding malignant biliary stenoses, which appear in the evolution of surgically unresectable neoplasms, stenting of the biliary tract is generally accepted today as a standard of treatment, but its effectiveness may be reduced by tumour growth and stent dysfunction³⁹. In addition to biliary tract decompression, ERCP allows several therapeutic maneuvers, such as ERCP-guided naso-pancreatic drainage or radiofrequency ablation.

Endoscopic radiofrequency ablation of bilio-pancreatic tumours opens new perspectives in the therapeutic management of these diseases. These methods can be used for both curative and palliative purposes, improving the duration and quality of life of the patients. Thus, for premalignant tumours, the need of long-term follow-up can be reduced. For small tumours, endoscopic radiofrequency ablation may be an alternative to surgical treatment, with a curative result and reduction of the risks involved. In advanced stage tumours, it is possible to obtain an effective reduction of tumour volume, with decompression of adjacent structures, including the main bile duct, improving not only the quality but also the life span of these patients. The endoscopic application of radiofrequency energy is associated with lower risks compared to the percutaneous or surgical approach.

Bilio-pancreatic neoplasms usually affect adult patients who are socio-economically active⁴⁰. Among the major consequences of these diseases are the exclusion of the patient from the socio-economic circuit, decreased quality of life and high risk of mortality and morbidity. The life expectancy of these patients is very low and the therapeutic possibilities are limited. Thus, it is necessary to develop and implement new treatment methods that reduce both the negative impact on the individual and the negative impact on society in terms of cost-effectiveness. A therapeutic method with promising results and a good safety profile has proven to be radiofrequency ablation applied endoscopically^{38,39}.

Author Contributions:

V.A.I. and G.G. conceived the original draft preparation. G.C., C.C.D., and M.S.-I., were responsible for conception and design of the review. A.C., V.S., R.O. and O.M.P. were responsible for the data acquisition. V.A.I, G.G., and C.C.D. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. V.A.I., G.G., and M.S.-I. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

“The authors declare no conflict of interest regarding this article“

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