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The Role of Radio-Frequency and Stereotactic Ablation in the Treatment of Pancreatic Cancer

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Rezumat

Rolul ablației cu radiofrecvență și al stereotaxiei corporeale în tratamentul cancerul pancreatic

Adenocarcinomul pancreatic este o formațiune tumorală malignă foarte agresivă cu o rată de supraviețuire foarte scăzută. Prognosticul şi tratamentul acestei afecțiuni sunt strâns interconectate şi dependente de criteriul de resectabilitate al formațiunii tumorale primare, din punct de vedere terapeutic standardul de aur fiind rezecția chirurgicală în scop curativ. În cazul tumorilor nerezecabile sau în cazul bolii avansate local, cu sau fără metastaze la distanță, se poate lua în considerare ca terapie adjuvantă, pe lângă chimioterapie, radiochirurgia. Acest articol este un review narativ care îşi propune descrierea celor două tehnici de radiochirurgie utilizate în tratamentul cancerului pancreatic: ablația cu radiofrecvență şi stereotaxia corporeală. Pe lângă descrierea tehnicilor propriu zise, acest articol îşi propune sublinierea beneficiilor aduse de acestea, precum şi posibilele complicații postintervenționale apărute în managementul cancerului pancreatic.

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Cuvinte cheie: adenocarcinom pancreatic, ablație cu radiofrecvență, stereotaxie corporeală, rată de supraviețuire, chimioterapie

Abstract

Pancreatic adenocarcinoma is a very aggressive tumor with a low overall survival rate. The prognostic and the treatment of this disease are strongly interconnected and highly dependent on the resectability criteria of the tumor, surgical excision being the golden standard. For local advance disease or for unresectable tumors, with or without metastasis we can take into consideration as adjuvant therapy, together with chemotherapy, the radiofrequency ablation or stereotactic ablation radiotherapy of the solid tumor mass. This article is a narrative review that aims to describe these two interventional techniques: radiofrequency ablation and stereotactic ablation radiotherapy. We will discuss the techniques themselves, benefits that they bring and also, about the possible complications that can appear when using them in the management of pancreatic cancer.

Key words: pancreatic adenocarcinoma, radiofrequency ablations, stereotactic ablations radiotherapy, survival rate, chemotherapy regimes

Introduction

Pancreatic cancer is one of the most lethal malignant tumors with an overall survival rate around 10%. Unfortunately, in the last decades, the treatment of this condition has seen only little improvement. Although it has a relatively low incidence (3%), pancreatic cancer is the fourth leading cause of mortality in cancer patients (1).

Most malignant pancreatic tumors are located at the level of the pancreatic head. It is known that cephalic duodenopancreatectomy (DPC) is the surgery of choice for this location, this type of surgery being first described in 1898 by Alessandro Codivilla, and improved only years after, in 1935 by Allen Whipple. Although, over the years this surgical technique has undergone multiple improvements, it is still considered a major surgery with high morbidity (2).

The most common histopathological subtype of pancreatic cancer is the pancreatic ductal adenocarcinoma (PDAC), almost 80% (3). PDAC has the worst prognosis regarding the survival rate from all pancreatic cancers (4).

One of the characteristics of PDAC is the fact that at the time of diagnosis 80-85% of cases are unresectable and classified as locally advanced tumors (5). According to NCCN guidelines a locally advanced pancreatic carcinoma (LAPC) is a solid pancreatic tumor mass that is in contact with more than 180° of the circumference of the superior mesenteric artery or celiac trunk, no reconstruction options available when superior mesenteric vein (SMV) and/ or the portal vein (PV) are invaded due to tumor occlusion or presence of thrombus. The presence of distant metastasis is defined as advanced disease and the surgical removal of the tumor is not to be taken into account as the first treatment of choice (6).

The overall 5-year survival rate of the PDAC depends on the TNM stage and varies between 7-25% (7). For the early-detected pancreatic lesions, which were treated with surgical resection, the median survival rate was 17-23 months (8). Even if the survival rate is still low after resection, the surgical regiment is the only treatment option that improves it, but, unfortunately, only 20 % of the patients can benefit from it. Thus, the

resectability criteria at the time of diagnosis determine the prognosis and treatment strategy (9-12) A resectable tumor has no arterial contact with celiac trunk, superior mesenteric artery, or common hepatic artery, and no tumor contact with the superior mesenteric vein or portal vein or less than 180° contact without vein contour irregularity. There is another group in term of resectability status, borderline resection tumors which include the tumors embedding the superior mesenteric artery less than 180°, tumors in contact with the common hepatic artery but allowing safe and complete resection and reconstruction. In this group are also included the solid tumors which are in contact with the inferior vena cava and tumors embedding less than 180° the superior mesenteric vein or portal vein (6).

Current Oncological Treatment

Chemotherapy and radiotherapy represent treatment options for patients with advanced pancreatic cancer. Approximately one third of these patients will have resectable tumors after neoadjuvant treatment and the survival will be comparable with those who received oncologic, curative surgery from the beginning (13,14). Patients with locally advanced lesions, but with a good performance status benefit from oncological treatment with FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) (15).

Suker et al. conducted a meta-analysis where they demonstrated a median overall survival of 24.3 months and a progression-free survival of 15.0 months for patients with unresectable LAPC that were treated with FOLFIRINOX regimen. For the patients who cannot tolerate this treatment the combination between gemcitabine and nab-paclitaxel could be a second-line option (16). Despite the use of new chemotherapy regimens, many of the patients with LAPC will continue to have unresectable tumors (17).

Nowadays, new treatment methods considered to be non-invasive such as radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, irreversible electroporation (IRE) and stereotactic ablation radiation therapy (SART) can be taken into account, along with chemotherapy, in a multimodal therapeutic approach for unresectable pancreatic adenocarcinoma that is locally advanced and without metastases.

This paper is a narrative review which was done by a systematic research approach carried out in PubMed database using the key words: "radiofrequency ablation", "pancreatic cancer", "stereotactic ablation". We selected the results published in the last 5 years and identified a number of 240 articles, which, after applying the selection criteria, were narrowed down to only 18, two being published in 2022.

Our aim is to emphasize the existence of these therapeutic methods, and to compare them with other tumor downstaging techniques used for pancreatic cancer, so that we can highlight the benefits of radiofrequency ablation (RFA) and stereotactic ablation radiation therapy (SART) in terms of overall survival rates.

RFA – Why Choose this Technique?

The parallel development of ultrasound techniques and the appearance of high-performance transducers have improved the results of RFA. The operating principle of the RFA is based on the application of alternating current in the radio frequency range. This will cause a chaotic movement of the ions inside the tumor, which, by friction, will generate a heat with an ablative effect. When the target temperature is reached a process of coagulative necrosis occurs, and by that cell death is produced (18).

In fact, the effect of this technique is more a tumor debulking rather than ablation of the lesion. Considering the close relation of the tumor with vital anatomical structures the temperature cannot be raised too high, as is in the case of liver tumor ablation. An oncological treatment (chemotherapy) should be given after the use of RFA, this way improving the local effect (19).

Although percutaneous techniques have been described, the procedure for applying RFA remains a surgical one. In this case, the

patient has to have a good performance status and requires an adequate preoperative preparation. The patient needs a staging CT that has to be performed with a maximum of 4 weeks before surgery. Preoperative treatment involves antibiotic prophylaxis to prevent surgical wound infections (cephalosporin/ metronidazole) and administration of a somatostatin analog. If the placement of a metal stent was needed in the preoperative period, it is preferable to remove it before surgery in order to prevent an inadequate extension of the thermal effect. A laparoscopic evaluation of the peritoneal cavity is initially performed in order to detect possible peritoneal or hepatic metastatic lesions. If metastases are not confirmed, the procedure continues by a laparoscopic, robotic or classic approach where a Kocher dissection maneuver is performed. If the tumor lesion is resectable, after exploration and intraoperative ultrasound, the surgical excision is performed. On the other hand, when the presence of LAPC is confirmed, and the case is considered feasible for RFA, measures are taken to stop the extension of the thermal effect by covering the inferior vena cava with cold wet gauze and continuous perfusion of the duodenum with cold saline liquid. At the level of the proximal jejunum a clamp will be placed to prevent the saline solution to advance at the level of the entire small intestine. The RFA probe will be inserted into the tumor under ultrasound guidance, taking into account the safety zone in order to prevent the damage of the adjacent anatomical structures and to have a tumor debulking effect, this meaning less than a complete ablation of the tumor. It is also indicated to take tissue biopsy from the center of the tumor, under ultrasound guidance, before and after the ablation procedure. Venous blood should also by drawn from the portal vein in order to evaluate the immunomodulatory factors (19).

Indications for the use of radiofrequency ablation are divided into two groups: main indication: stage III ductal adenocarcinoma without distant metastasis and relative indication: lack of response to standard systemic treatment and stage IV disease - for local control. Stage III is defined according to AJCC as tumors between 2- 4 cm in greater diameters with more than four regional lymph nodes positive or a tumor that invades the celiac trunk, superior mesenteric artery, and /or common hepatic artery, but, very important, there are no distant metastases at the time of the procedure. Stage IV includes patients with distant metastases (7).

Regarding the eligibility criteria for RFA, the anticipated edge of the ablation area should be at a distance of at least 5 mm from the vital anatomical structures: SMA, SMV, PV, common hepatic artery, celiac trunk, inferior vena cava or duodenum. Therefore, the device comes with several types of electrodes, where the diameter of action varies between 6-8 mm for T9 electrode, 8-10 mm for T15 or 20 mm for T20. Thus, the specialist can choose the correct electrode after several ultrasound measurements of the tumor and the distance from the important anatomical structures - this example is for CelonLab® POWER System generator, Celon Aquaflow®, and bipolar Celon-ProSurge® (micro) applicators with exposure lengths of 9/15/20/30/40 mm (Olympus Surgical Technologies Europe, Teltow, Germany). Recent studies have established several parameters for the RFA technique: a temperature of 90˚C, for a period of 5 minutes. The device has a temperature sensor that will start the timer when the set temperature is reached. Also, the accepted distance between the electrode and the duodenum or the portomesenteric complex must be 10 mm, in order to benefit from a peripheral area in which there were no thermal changes - the so-called “safety ring” (20). After the procedure and ultrasound check, the surgeon must perform a hepaticojejunostomy if the lesion was located in the pancreatic head, and a gastrojejunostomy if an obstruction in the duodenum is foreseen.

Stereotactic Ablation Radiation Therapy (SART) - Definition and Indications

SART is an alternative treatment for pancrea-

tic cancer and implies administration of high doses of radiation delivered in 1 to 5 fractions for 1 to 2 weeks. The use of SART in the neoadjuvant context is also supported by several advantages as condensing radiotherapy treatment cycles can help prevent a delay in the administrations of systemic chemotherapy. Another important advantage of this technique is that it enables accurate high-dose radiation delivery to the tumor while reducing dosage to other organs that are at risk (21).

According to ASTRO (American Society for Radiation Oncology) guidelines, SART is strongly indicated for patients with locally advanced pancreatic cancer (22). Patients selected for SART should ideally be seen in a multidisciplinary team where factors such as imaging, pathology, patient requests, and performance status are taken into account. It is crucial to establish the patient's staging and also based on anatomical considerations, to decide if is a surgical candidate or not. Regarding the dosage used for SART, the most common protocol used in many of the previous study available is the literature is up to 50 Gy in 5 fractions with an acceptable toxicity (23-26). To obtain an ablative effect for long time, local control of the tumor a biological effective dose of at least 100 Gy is recommended. Therefore, at this dose range, the frequency of gastrointestinal side effects as bleeding, ulcerations, and necrosis is high (27,28).

In order to achieve good results using SART, the oncologist or the radiologist should take into considerations some anatomical features such as primary tumor dimension, tumor vessel interface (major vessels in direct contact or nearby, the gross tumor volume (GTV), and the proximity of the stomach, duodenum, and small bowel. The gross tumor volume is the fibrotic area near vessels, which surrounds the tumor stroma; the sterilization of this area using SBRT is likely to result in clean surgical margins and better local control. Patients with invasion of the stomach and duodenum by the pancreatic tumor are not considered suitable for SART because they are at high risk of ulcerations and bleeding (29).

DPC for Pancreatic Cancer - How Can We Improve the Results?

Improving surgical techniques, diagnostic and staging methods led to a decrease of mortality after DPC from 25% in the 1960s to 5% today. However, postoperative morbidity varies between 40% and 70% even in centers with experience and high volume of patients. Pancreatic cancer is a disease with a poor prognosis in general, and the grade of resectability is quite limited. Thus, good preoperative management and rigorous complication control is perhaps the most important thing after a DPC. After multiple organ resections the reconstruction time begins; from all the anastomosis the pancreatic one continues to be a challenge. The most common complication following this surgery is pancreatic fistula (30,31). Taken this into account, over the years, pancreatic anastomosis was performed in two main ways: with the jejunal loop or with the posterior wall of the stomach, the choice of the anastomotic partner being fully dependent on the local conditions: diameter of the Wirsung duct and consistency or firmness of the pancreatic parenchyma. Each of these anastomoses can be achieved in multiple ways. One of these subtypes is the insertion of the pancreatic stump into the stomach through a posterior gastrostomy. The diameter of the gastrostomy is smaller than the diameter of the pancreatic stump, this way the pancreas is kept in place by the tightening of the gastrostomy, without the necessity of suturing the pancreas to the stomach; if the surgeon does not feel comfortable with the compression done at the level of the pancreas, a bursa can be done at the level of the gastrostomy. For the same purpose, a study published in 2020 evaluates pancreatic-digestive anastomosis, in the case of soft pancreatic tissue, by two methods: classical and by using a biological mesh mounted around the pancreatic stump. They achieved promising and statistically significant results in favor of the use of biologic mesh (32).

Another possible complication of this surgery is the delayed gastric emptying,

patients will have a prolonged hospitalization period and will require mounting a naso-gastric tube and administration of parenteral nutrition. With an incidence between 2%-8%, postoperative hemorrhage can have a major negative impact on patient outcome. Thus, the mortality associated with this complication can vary between 18% and 47% (33,34).

Complications in elderly patients may be even more harmful, the literature stating a morbidity of 46.6% in patients <75 years compared to 61.9% in those over 75 years. On the same series of patients over 75 years old the perioperative mortality was of only 2.2% and an overall survival rate of 31-32.7 months.

Efficiency and Complications of RFA

The most common ablation technique used for pancreatic cancer is radiofrequency ablation. It produces focal thermal injury in the pancreatic tissue. The results of using RFA are promising, it produces both a local effect and a humoral one: an increasing of pro-inflammatory cytokines, serum interleukins, tumor necrosis factors or even tumor-specific T cells (35). There are studies in the literature that describe better clinical outcomes when using neoadjuvant RFA than neoadjuvant treatments. The same studies highlighted the effect of RFA in downstaging the pancreatic cancer by reducing the tumor size and by that obtaining negative resection margins (36). Onofrio et al. observed a decrease in the CA19-9 marker following RFA, the value being inversely proportional to the ablation area (37).

Other studies attempted to evaluate the efficacy of RFA alone or in combination with other systemic treatments, reaching an overall survival rate of over 25.6 months in patients with LAPC (38). Others reported an excellent result with a median OS of 30 months, but slightly less after the combination with other systemic therapies. However, there are only a few randomized controlled trials that study these combined therapies (39).

Like any surgical procedure, several complications related to the RFA technique have been described: pancreatic fistulae, portal vein thrombosis, gastrointestinal bleeding, and acute pancreatitis, with a rate of overall complications ranging from 10% to 43% (40).

Efficiency and complications of SART

Another ablation technique is SART. The main advantage of this technique is that it can be given earlier than conventional radiotherapy, in 1-2 weeks without having any delay in starting systemic chemotherapy. Beside this advantage, the use of neoadjuvant SART may transform some unresectable tumors into resectable ones (41).

Even if SART is used worldwide for therapeutic purposes, the biological mechanism of its effect is not yet totally understood. The 5R (reoxygenation, repair, repopulation, and radioresistance) principle of radiobiology is considered to be involved in the efficiency of this technique. One of the target tissues of high radiation dose is the vascular endothelium, this is due to the fact that it served as a barrier to regulate immune cell rolling on the vascular surface and also because the tumor endothelial cells are more radiosensitive. Damaging the endothelial cell using a dose higher that 10 Gy, can lead to changes in the tumor environment and finally lead to hypoxia. The destroyed endothelial cells release TNF cytokine, which activate macrophages; the CX-C motif chemokine ligand 6 (CXCL6) chemokine, which recruit immune cells and activate Toll-like receptors on dendritic cells (42,43).

Several studies from the literature have strongly suggested that besides the cellular apoptosis induced by RT at high dose per fraction (more than 10 Gy), some indirect biological effects called abscopal effects, like antitumor immunity, vascular damage or immunogenic tumor cells death may appear (44-47).

It seems that ablative therapies change the tumor microenvironment, which directly or indirectly determined cell death. Moreover, dead tumor cells released antigens, which stimulate antitumor immunity and, in this way, decrease the risk of metastasis or local relapse (48). The immune system plays an important role in cancer control and for this

task functional lymphocytes are needed. Thus, it has been demonstrated that SBRT spare the circulating lymphocytes of the patient with pancreatic adenocarcinoma, and by that, helping to decrease the rate of metastatic disease and recurrence (49).

High radiations delivered using SART in patients with pancreatic tumors increase the oligoclonality of the T cell response, likely by causing T cell responses against a larger variety of tumor antigens and also inducing the synthesis of myeloid cell attracting chemokines such as CCL2, this leading to an immunosuppressive microenvironment (50).

Conclusions

In conclusion, even if the surgical treatment is the gold standard in PDAC management, due to the low resectability rate, the difficulty of the technique and the occurrence of complications, we can say that interventional-ablative techniques find their place more frequently as part of the management of this condition.

Thus, although surgical resection is the gold standard for the treatment of pancreatic cancer, different ablation techniques used for LAPC have been developed in the last decades. RFA is a safe and feasible technique performed either in an open, laparoscopic, endoscopic or percutaneous way; if chemotherapy is also associated, it can lead to an increased overall survival rate in patients with LAPC.

Pancreas SART is a promising treatment modality requiring prospective evaluation in randomized studies. Given the high level of precision required and the potential for significant toxicity, pancreas SART should be performed in selected cases, in centers with high experience in this technique and by using a multidisciplinary approach.

In conclusion, RFA together with SART must be evaluated in future prospective multicentric studies, followed by a standardized protocol for case selection and therapeutic conduct.

Conflicts of Interests

The authors declare no conflict of interest.

Ethical Statement

No funding or ethical committee approval was required/obtained for the performance of this study.

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