Case report

Use of intraoperative radiotherapy as part of the combined treatment of borderline resectable locally advanced pancreatic cancer

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ABSTRACT

Cancer remains a disease with a poor prognosis, due to late diagnosis, the progression of the disease, and the need for radical treatment. The specific risks associated with marginal resection margins, where radical resection is performed, are challenging and often involve additional microscopic resection margins. The objective of the present study was to evaluate the efficacy of intraoperative radiotherapy (IORT) as a component of multimodal cancer treatment. A 70-year-old patient with a tail tumor, classified as borderline resectable, received first-line chemotherapy according to the FOLFIRINOX regimen. This was followed by preoperative chemoradiotherapy, adjuvant therapy, and IORT. The treatment was well tolerated, with no postoperative complications related to IORT. A partial response to treatment was achieved, along with local control, thereby preventing disease progression and metastasis. The extant literature indicates that intraoperative radiotherapy may be a concomitant modality with multimodal therapy in patients with resectable cancer, particularly in cases of high-risk disease. This technique facilitates the irradiation of the tumor bed while concomitantly limiting exposure to critical risks. Whilst the benefits in terms of local control are recognized, the impact of IORT on overall survival remains unclear and requires further research.

Key words: borderline resectable pancreatic cancer, intraoperative radiotherapy, pancreatic cancer treatment

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INTRODUCTION

Pancreatic cancer is a relatively rare malignant neoplasia, but it accounts for the 6th cause of death from oncological causes [1]. Due to its non-specific symptoms, late diagnosis and anatomical location in close proximity to large vessels, it has the worst prognosis of all solid tumors. The 5-year survival rate is estimated at 12.8% [2]. Fewer than 15% of patients can undergo surgery, which is currently the only available option for achieving a permanent cure. The incidence of pancreatic cancer increases with age, and nearly 50% of patients have distant metastases at the time of diagnosis [3].

Non-modifiable factors that increase the risk of pancreatic cancer include age over 55, male gender, gastrointestinal microbiota, blood type other than 0 [4]. The microbiome of the oral cavity likely plays an important role in the pathogenesis of pancreatic malignancy. According to Fan et al. carrying *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans,* was associated with a higher risk, while *Fusobacteria* types and its type *Leptotrichia* were correlated with a reduced risk of developing pancreatic cancer [5]. The gut microbiota in cancer patients is fundamentally different compared to healthy individuals. Ren et al. demonstrated that pancreatic cancer patients have a less diverse microbiota compared to those without the disease. Cancer patients showed an increase in some pathogens (*Veillonella, Klebsiella, Selenomonas*) and lipopolysaccharide-producing bacteria (*Prevotella, Hallella, Enterobacter*) and a reduced amount of probiotic bacteria (*Bifidobacterium*), in addition to bacteria with the ability to produce butyrate (*Coprococcus, Clostridium IV, Blautia, Flavonifractor and Anaerostipes*) [6]. Ethnicity is also an important factor. It was found that African-Americans, Native Americans and Japanese Americans presented higher rates of disease [7].

On the other hand, modifiable risk factors that increase the likelihood of the disease include tobacco smoking, alcohol consumption, a diet rich in red meat and animal products, obesity, chronic pancreatitis, and *Helicobacter pylori* infection. A significant correlation was observed between low socioeconomic status and impaired access to health care, and poorer treatment outcomes and prognosis.

The research also revealed a number of genetic mutations that increase the risk of pancreatic cancer [4]. The most common of these is a mutation within KRAS, which occurs in about 93–95% of patients with pancreatic ductal adenocarcinoma (PDAC) [8, 9]. Other common mutations include TP53 (72% of patients), SMAD4 (22%) and CDKN2A (18%), respectively [9]. Furthermore, mutations of such genes as STK11/LKB1, BRCA1/2, PRSS1/SPINK1/CFTR, mispaired base repair genes (MLH1/MSH6/MSH2/PMS2), ATM and PALB2 contribute. Pancreatic cancer occurs with increased frequency in certain familial syndromes such as familial atypical multiple melanoma (CDKN2A), hereditary breast and ovarian cancer syndrome (BRCA1/2), Peutz–Jeghers syndrome (STK11/LKB1), and hereditary nonpolyposis colorectal cancer syndrome (MLH1/MSH6/MSH2/PMS2) [4, 10].

Despite the development of modern oncology, the therapy of pancreatic cancer does not yield satisfactory results. The fundamental issue when undertaking therapeutic decisions remains the estimation of the resectability of lesions.

Based on the NCCN anatomical criteria along with biological features, a resectable tumor is considered one that does not give rise to distant metastases and does not infiltrate the arteries, superior mesenteric vein (SMV) and/or portal vein on imaging studies, as well as the fatty tissue around the visceral trunk, hepatic artery and superior mesenteric artery (SMA). The line of borderline resectability for head and uncinate process of the pancreas carcinoma includes tumor contact with the common hepatic artery (CHA) without expansion to the visceral trunk (CA) or hepatic artery bifurcation, and tumor contact with the SMA ≤180°. For pancreatic body or tail carcinoma, the limit of resectability is tumor contact with the visceral trunk (CA) ≤180°. The venous criteria list tumor contact with the SMV or portal vein (PV) >180° and inferior vena cava (IVC), as well as contact ≤180° contour with a change in vein shape or venous thrombosis, but with the possibility of complete resection with vein reconstruction.

Locally advanced neoplasm, located in the head of the pancreas or the uncinate process, with reference to the periphery of the arterial vessels, means solid tumor contact >180° with the SMA or the visceral trunk (CA). With regard to the location in the body and tail, we specify the contact of the solid tumor >180° with the SMA or CA, or the contact of the tumor with the visceral trunk (CA) and aortic infiltration. When referring to the venous vessels, we do not condition the procedure based on the location of the tumor in the pancreas. Reconstruction of the SMV/peripheral portal vein (PV) is impossible due to tumor infiltration or closure of the lumen of the venous vessel by tumor or thrombus [11].

In primary resectable tumors, the standard procedure is classical pancreatoduodenectomy (PD) using the Kausch–Whipple procedure or pylorus-sparing PD using the Traverso-Longmire method in order to remove the head of the pancreas. In the case of resectable tail or pancreatic body tumor, removal of the distal segment of the affected organ along with the spleen is performed [12].

Then, after resection, 6 months of follow-up chemotherapy is recommended. First-line treatment is the FOLFIRINOX regimen, consisting of leucovorin, fluorouracil, irinotecan and oxaliplatin. This regimen is recommended for patients with ECOG 0–1, while in patients who are ineligible for treatment with the above-mentioned regimen (age >75 years, ECOG 2 or contraindications to mFOLFIRINOX treatment), gemcitabine–capecitabine is an alternative

option [13]. For borderline resectable tumors, 3 main approaches based on induction treatment have been developed, i.e., neoadjuvant chemotherapy with subsequent surgery, neoadjuvant chemoradiotherapy preceding surgery, or neoadjuvant chemotherapy followed by neoadjuvant chemoradiotherapy in case of partial regression, followed by surgery. The preferred regimen for induction treatment is FOLFIRINOX or gemcitabine/nab-paclitaxel (GN). The standard of care for locally advanced tumors is FOLFIRINOX or GN chemotherapy for up to 6 months. In advanced disease, management depends on the patient's general condition, which determines specific chemotherapy or symptomatic treatment [13, 14].

An interesting therapeutic option for the treatment of borderline resectable pancreatic cancer is the addition of intraoperative radiotherapy as part of a combination treatment. Intraoperative radiotherapy (IORT) involves the application of a single high dose of radiation during surgery. The target volume is usually the tumor bed in the case of complete resection or the remaining residual disease if complete resection was not possible [15]. This method has the potential to improve the efficiency of radiation therapy for pancreatic cancer by reducing the radiation dose directed at healthy tissues. The surgeon's ability to move adjacent healthy organs during the procedure makes it possible to protect them, while simultaneously increasing the radiation dose to the tumor bed during its direct visualization. As a result, intraoperative radiotherapy, as a component of combination treatment, carries the potential for improved local control and a trend toward improved patient survival rate [16, 17].

CASE REPORT

A 70-year-old male presented to the Oncology Outpatient Clinic due to abdominal pain and weight loss of about 8–10 kg in the span of 6 months, in addition, laboratory tests showed elevated tumor markers: CA-19-9 had a value of 186.00 U/mL (normal 0–37 units/mL), CEA reached 5.1 ng/mL (normal 0–5.0 ng/mL). The patient was found to have many years of nicotinism and a burden of chronic diseases, including hypertension, type 2 diabetes, hypercholesterolemia. Family history revealed the patient's grandmother's incidence of colorectal cancer. In addition, the patient had undergone oncological treatment for Gleason 7 (3 + 4) prostate adenocarcinoma. The patient underwent radical prostatectomy and bilateral obturator lymphadenectomy in 2009, and radiation therapy to the area of the prostate locus, seminal vesicles and obturator lymph nodes for local recurrence in 2015. Since then, he has remained under constant follow-up with an oncologist. In 2019, a control computed tomography (CT) scan of the abdomen and pelvis was performed, which did not visualize lesions in the pancreatic region. In October 2021, laboratory and imaging tests were performed on the patient due to the reported symptoms. After finding elevated tumor markers, the patient was referred for a CT scan of the chest, abdomen and pelvis, where a tumor infiltration of the tail of the pancreas was visualized. The tumor described was 65 × 25 mm with possible infiltration of the greater curvature of the stomach and adherence to the splenic artery and obstruction of the splenic vein, and perigastric circulation was present. No metastatic lymph nodes were visible. A fine-needle biopsy of the lesion confirmed infiltration of tumor cells. Tumor staging was defined as T3/4NxM0, and the tumor was considered borderline resectable.

Due to the patient's good general condition (ECOG 1), induction chemotherapy with the FOLFIRINOX regimen was started. After the initiation of chemotherapy, a control CA-19.9 marker was ordered, whose level was 456.1 U/mL and CEA 8.83 ng/mL. After the 5th course of chemotherapy, a follow-up CT scan was performed, in which the described tumor of the tail of the pancreas was reduced to 56 × 28 mm in size. With the partial regression of the lesion, the patient was qualified for radical preoperative radiochemotherapy. In the first stage of treatment, a dose of 50.4 Gy in 28 fractions of 1.8 Gy each was administered to the area of the pancreatic tail tumor with margin and regional lymph nodes, then in the second stage, the dose to the area of the pancreatic tail tumor with margin was increased to a total dose of 54 Gy in 30 fractions. During radiotherapy, 4 of 6 courses of gemcitabine chemotherapy were administered due to thrombocytopenia.

After preoperative treatment, the dimensions of the tumor reduced to approximately 44 × 26 mm, and the CA 19-9 marker dropped to 72.62 U/mL. Two months after chemoradiotherapy, surgery was performed with intraoperative radiotherapy using IntraOpp's Mobetron accelerator. After the surgical team removed the tumor, a dose of 15 Gy at 90% isodose (energy 6 MeV, 6 cm diameter applicator) was administered to the area of the surgical locus. The postoperative course was uncomplicated. The use of intraoperative radiotherapy did not hinder the healing process and did not prolong hospitalization. Histopathological examination of the postoperative material confirmed G2 ductal carcinoma of the pancreas with a maximum dimension of 3.5 cm, with a partial response to preoperative treatment – more than 50% of the tumor tissue remained, without features of angioinvasion and perineural infiltration. No tumor cells were found in the incision lines from the pancreas and posterior gastric wall, while the presence of cancer cells was detected in the retroperitoneal margin. No metastasis was confirmed in the lymph nodes. TNM based on histopathology was determined as: ypT2, ypN0, PR, R1. Two months after the operation with IORT, the CA-19.9 level rose to 1273 U/mL. A follow-up CT scan noted disease progression

with intraperitoneal implants present. The patient received systemic treatment, but died 2 years after diagnosis due to disease dissemination.

DISCUSSION

Treatment of borderline resectable pancreatic cancer is multifaceted and allows individualization of the therapeutic approach depending on the clinical situation. It includes a combination of chemotherapy and radiotherapy with subsequent resection. Despite the use of multiple treatment modalities, achieving negative surgical margins (R0 treatment) is technically difficult, and many patients will have microscopic disease (R1) found in the surgical margin, which is associated with an increased likelihood of local recurrence and worse overall survival rate. We can achieve better locoregional control by using IORT. In the context of pancreatic cancer, this technique is well tolerated by patients. It is characterized by fewer complications, is better targeted to the area of the tumor lesion and demonstrates better local control.

According to the ESTRO IORT/ACROP Task Force recommendations for intraoperative radiation therapy for borderline resectable pancreatic cancer, IORT is a technique that works well for personalized treatment relying on patient selection based on resection conditions. According to ESTRO recommendations, the dose applied varies between 10 Gy and 20 Gy, depending on the stage. For low-risk resections, it is recommended to use a dose of 10–12.5 Gy, if positive margins are suspected the dose should be increased to 12.5–15 Gy, while in case of complications or residual infiltration, a dose of 15–20 Gy should be considered [18].

In a retrospective study conducted by Harrison et al. involving 158 patients, progression-free survival (PFS) and overall survival (OS) were 21.5 and 46.7 months in patients who underwent resection and IORT, and 14.7 and 23 months in the IORT-only group. Local progression occurred in 12.7% of patients after resection combined with IORT and in 15% of patients who received IORT alone. Serious complications occurred in 13% of patients after resection and IORT and in 5% of patients after IORT alone, including one death. R0 resection was achieved in 81.7% after surgery by Whipple or total pancreatectomy and in 85.3% by Appleby or distal pancreatectomy. In 25% of patients, recurrence at the primary resection site was observed, accounting for 12.7% of all patients undergoing total resection with IORT. In 57% of patients with R0 resection, there was no sign of disease progression [19].

Jin et al. analyzed 1,095 studies, from which 15 studies were selected. The systematic review compared 2 groups: patients who underwent pancreatic resection with IORT (n = 401) and patients who underwent surgery without IORT (n = 433). It was found that therapy with IORT significantly reduced the rate of locoregional recurrence compared to surgery without IORT, relative risk (RR) 0.70; 95% CI: 0.51–0.97, P = 0.03 [20].

Another retrospective study compared disease-free survival (DFS) and overall survival (OS) in patients with borderline resectable pancreatic cancer or locally advanced pancreatic cancer. 201 patients received neoadjuvant FOLFIRINOX therapy with chemoradiotherapy, followed by resection. 88 patients received IORT, with 69 patients undergoing R0 resections and 19 undergoing R1 resections. In terms of both clinical and pathological factors, there was no difference in patients with and without IORT. A significant difference was noted only in patients with R0 or R1 resection status. Patients without IORT for R1 resection showed worse DFS and OS compared to patients who received intraoperative radiotherapy. In their conclusion, the researchers note that the use of IORT may reduce the adverse impact in resections with positive microscopic margins (R1) [21].

The poor prognosis of pancreatic cancer is due to factors related to screening, detection, treatment, as well as genetic mutations. It is expected that by 2040, pancreatic ductal adenocarcinoma will be the second cause of cancer deaths, just after lung cancer [22]. Li et al. noted the lack of sensitive screening methods and specific biomarkers. An additional challenge is the late appearance of the first symptoms of the disease, which often occur at the advanced stage of the cancer. Typically (about 80%), cancer is detected when the surrounding lymphatic and blood vessels are infiltrated, and with the presence of distant metastases that disqualify the patient from surgery [23]. Many current studies are finding breakthroughs in the analysis of pancreatic cancer biology, as well as genetic factors and proteins such as HDAC2, HDAC4 involved in the tumor cascade [24, 25]. Pitarresi et al. also demonstrated the role of blocking parathormone-related protein (PTHrP), which is part of the KRAS aplicon, in shrinking the primary tumor, preventing metastasis and prolonging survival in a mouse study [26]. The above-mentioned studies provide a promising perspective for innovative approaches in the treatment and prevention of pancreatic cancer metastasis.

RESULTS

Pancreatic cancer remains a formidable challenge for the scientific world. Despite the rapid development of new therapeutic approaches, breakthroughs are still lacking, and treatment results are unsatisfactory.

Intraoperative radiotherapy seems to be an interesting option to improve local control. Very meticulous selection of patients who are likely to benefit from this method seems necessary. In view of the high risk of failure associated with tumor dissemination,

in parallel with the search for methods to improve local control, there is an urgent need to seek new methods of systemic treatment.

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