Original article

Perioperative high dose rate (HDR) brachytherapy in unresectable locally advanced pancreatic tumors

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Abstract

Purpose: The aim of the study was to present an original technique of catheter implantation for perioperative HDR-Ir192 brachytherapy in patients after palliative operations of unresectable locally advanced pancreatic tumors and to estimate the influence of perioperative HDR-Ir192 brachytherapy on pain relief in terminal pancreatic cancer patients.

Material and methods: Eight patients with pancreatic tumors located in the head of pancreas underwent palliative operations with the use of HDR-Ir192 brachytherapy. All patients qualified for surgery reported pain of high intensity and had received narcotic painkillers prior to operation. During the last phase of the surgery, the Nucletron® catheters were implanted in patients to prepare them for later perioperative brachytherapy. Since the 6th day after surgery HDR brachytherapy was performed. Before each brachytherapy fraction the location of implants were checked using fluoroscopy. A fractional dose was 5 Gy and a total dose was 20 Gy in the area of radiation. A comparative study of two groups of patients (with and without brachytherapy) with stage III pancreatic cancer according to the TNM scale was taken in consideration.

Results and Conclusions: The authors claim that the modification of catheter implantation using specially designed cannula, facilitates the process of inserting the catheter into the tumor, shortens the time needed for the procedure, and reduces the risk of complications. Mean survival time was 5.7 months. In the group of performed brachytherapy, the mean survival time was 6.7 months, while in the group of no brachytherapy performed – 4.4 months. In the group of brachytherapy, only one patient increased the dose of painkillers in the last month of his life. Remaining patients took constant doses of medicines. Perioperative HDR-Ir192 brachytherapy could be considered as a practical application of adjuvant therapy for pain relief in patients with an advanced pancreatic cancer.

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Key words: brachytherapy, catheter implantation, HDR, pancreatic cancer.

Purpose

Prognosis for exocrine pancreas caner is one of the worst among all malignant gastrointestinal tract neoplasms; it is one of the main causes of death [1-3]. Neoplastic changes usually develop in pancreatic duct epithelium (about 80%) and in acinar epithelium (about 13%). 75-80% of glandular pancreatic cancers are localized in the head of the pancreas, while 20-25% in the body or in the tail [4]. Pancreatic cancer etiology is not known. The list of risk factors for pancreatic cancer includes: age over 60, male gender, smoking, alcoholism, drinking too much coffee, wrong dietary habit, obesity, lack of physical activity, exposure to ionizing radiation, chronic pancreatitis, resection of the pancreas, diabetes, contact with certain chemicals and genetic factors [1, 5]. Malignant pancreatic tumors develop secretly. Most of the patients consult the physician only in advanced stages of the disease, therefore only 10-20% of cases qualify for radical treatment. At the moment of diagnosis, the neoplasm is limited only to pancreas in 10% of patients. In almost 40% of patients neoplasms are locally advanced, and in over 50% distant metastases are observed [3, 6, 7]. Untreated patients with cancers localized in the head of pancreas usually survive only 3 months. A bit longer survival times are reported in cases of cancers located in the body or in the tail of pancreas [8]. In patients with stage I and II pancreatic cancer (according to the TNM scale), radical surgery is the only chance of complete recovery. Occasionally, radical treatment can be satisfactory applied also in stage III patients [2, 3].

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The progression of pancreatic cancer promptly causes an ileus and obstruction of bile duct. In unresectable tumors palliative surgeries are performed. The type of the operation performed depends on tumor placement and main ailments of the patient. The most frequently performed procedures are: gastroenterostomy (which prevents high obstruction) combined in the case of jaundice with: cholecystojejunostomy, choledochoduodenostomy, and Roux-en-Y choledochoduojejuostomy, which achieves superior results. Nonsurgical procedures performed in case of jaundice are external drainage or endoscopic placement of a stent into the bile duct. According to most retrospective researches, palliative operations extend the survival time of patients to 6-12 months [3, 8-12]. A dominant symptom of progressing pancreatic cancer after surgery is a strong pain in epigastrium. Therefore, one of the main clinical problems of palliative treatment in terminal patients is pain management. Usually pain can be relieved by pharmaceuticals: analgesics and adjuvants. Unfortunately, an inevitable progress of the disease forces us to increase the drug doses, which dramatically intensifies side effects. The search for supportive procedures which would allow reduction in painkiller doses could decrease the side effects without impairing the analgesic efficacy.

Brachytherapy performed perioperatively finds its application both in radical and palliative treatment of pancreatic cancer [13, 14]. It is either applied as low dose rate (LDR) permanent implants (mainly Iodine-125 seeds) or high dose rate (HDR) temporary implants (Iridium-192) [12, 14]. Brachytherapy seems to decelerate the tumor growth and, therefore, decrease the pain associated with the cancer.

The aim of the present study was: 1) to present an original technique of catheter implantation for HDR-Ir192 brachytherapy in patients after palliative operations of unresectable locally advanced pancreatic tumors; 2) to determine the influence of HDR-Ir192 brachytherapy on pain sensitivity in terminal patients who underwent palliative operations due to unresectable pancreatic cancer.

Material and methods

In 2004, eight patients with pancreatic tumors located in the head of pancreas underwent palliative operations with the use of HDR-Ir192 brachytherapy at the Chair and Clinical Department of General and Gastrointestinal Surgery in Bytom (Silesian Medical Academy, Poland). The subjects were 6 men and 2 women, aged 45-65 years (mean age 55 years), all of them addicted to cigarettes, two patients with stage II and six patients with stage III pancreatic cancer (according to the TNM scale). In order to determine the performance of cancer patients, the Zubrod assessment scale was used. All patients qualified for surgery reported pain of high intensity and had received narcotic painkillers prior to operations. All the patients met the criteria qualifying them for perioperative brachytherapy (Table 1). During palliative operations choledochoenteroanastomosis and gastrointestinal bypass utilizing a Roux-en-Y loop were performed. In the course of surgery, samples were taken and histopathological analyses were carried out intraoperatively. During the last phase of the operation, the Nucletron® catheters were implanted in patients, in order to prepare them for later perioperative brachytherapy. The difficulties met by the surgical team during the first implantation of a catheter into the tumor mass, caused the introduction of a modification of the implantation procedure. We worked out an original method of passing a catheter through the abdominal wall and transverse mesocolon, and placing it into the tumor mass, using our own cannula (Fig. 1). The cannula was made of an appropriate diameter puncture needle 30 cm × 0.6 cm, with a bit truncated end, and a millimeter scale. The catheter was stabilized in the tumor and transverse mesocolon with soluble sutures, catgut plain 4/0. The catheter was sewn into the skin with monofilament non-absorbable sutures. To prevent potential relocation or damage, the catheter of the third patient was additionally stabilized along its entire length with a sticking plaster, attached to the skin.

Table 1. Patients inclusion criteria

Up to 65 years of age
Tumor unresectability
No distant metastasis (liver, peritoneum, mesenteric lymphonodes)
I and II group in Zubrod's scale

Since the 6th day after surgery an after-loading HDR brachytherapy was performed at Brachytherapy Department, Institute of Oncology, Gliwice. It lasted for 4 consecutive days. Each time patients were transported from the Clinic to the Brachytherapy Department (a distance of around 20 kilometers). HDR brachytherapy planning was based on computer tomography (CT) (Fig. 2). Precise radiation areas were contoured based on CT images, which were directly sent to the Nucletron's Plato Inverse Treatment Planning Software®. Catheters in neoplasmic tumors were reconstructed and 3D dose calculations were received (Figs. 3 and 4). A fractional dose was 5 Gy and the total dose was 20 Gy in the area of radiation. Before each brachytherapy fraction, the locations of implants were checked using fluoroscopy. After the surgery, patients were given a subcutaneous injections of morphine (5 mg every 4 hours) and double night doses while in hospital. At home they took a dose of 10 mg every 4 hours orally, and a double late evening dose (a morphine syrup). In cases of stabbing pain patients themselves were able to increase the morphine doses by 10 mg. Regular follow-up visits at the outpatient clinic were recommended. At 15-days intervals (later at 30-days intervals) the clinical conditions of patients were determined and interviews were carried out to establish the pain level according to 10 point Numerical Rating Scale (NRS).

At all time, patients were provided with medical attention at the Pain & Palliative Clinic (permanent telephone contact was also available). During the first month since leaving the Clinic, a sustained-release (SR) morphine was administered to all patients. In the incidents of stabbing pain patients were recommended that they should take an immediate-release morphine (morphine syrup) as a supportive therapy. Based on the documentation gathered both in the Surgical Clinic and in the Pain & Palliative Clinic, an amount of pain-killers taken by the patients during post-hospital treatment was estimated. A comparative study of two

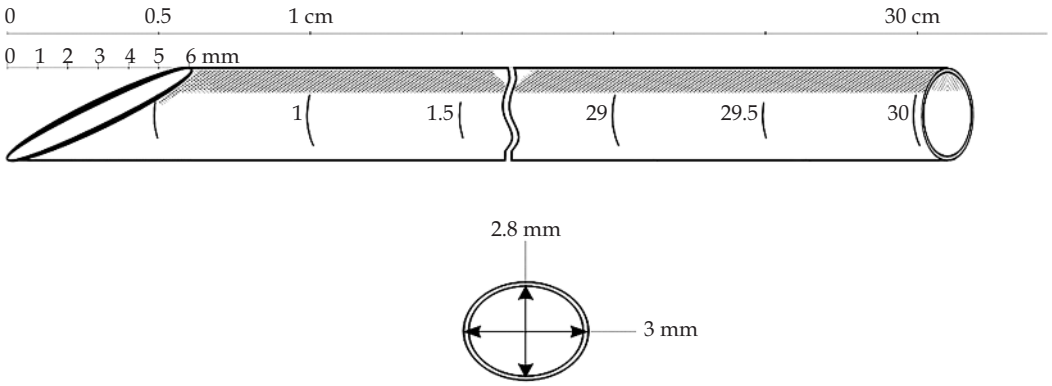

Fig. 1. Our specially designed cannula

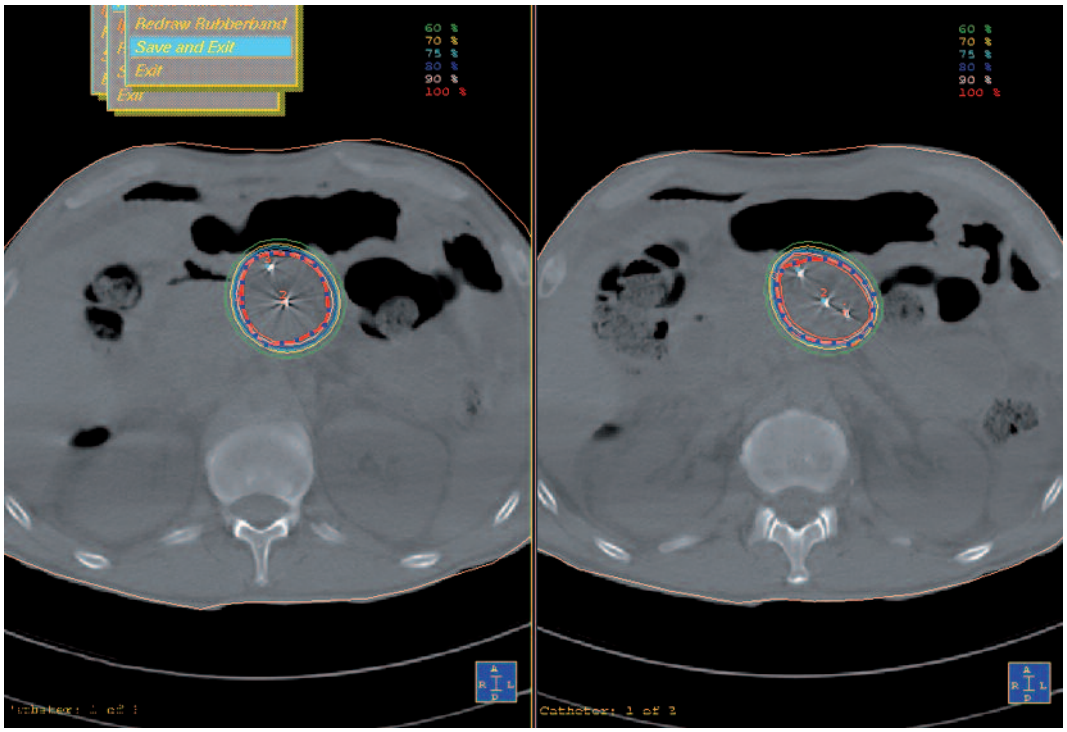

Fig. 2. HDR brachytherapy planning based on computing tomography. Catheters for brachytherapy, area exposed to radiation, and visible isodose distribution

groups of patients with stage III pancreatic cancer according to the TNM scale was undertaken. Group A consisted of 3 men aged 53, 57, and 65 years (mean age 58 years) who underwent perioperative brachytherapy. Group B consisted of 3 patients: a woman, aged 45, and 2 men, aged 60 and 62 years (mean age 55.7 years) who did not undergo brachytherapy (Table 2).

Results

Only 4 of 8 operated patients underwent a full cycle of treatment, including perioperative brachytherapy. Three of them were patients with stage III pancreatic cancer, one of the was a stage II patient. In the first patient with an implanted catheter for brachytherapy a complication occurred in the form of duodenal fistula. The patient was reoperated and the catheter was removed on the third day after the first surgery. In the second case (woman), on the second day after the operation, the catheter protruded and broke when the patient was asleep. In two cases catheters were removed due to bad clinical condition of the patients (respiratory failure at early postoperative stage). The patients resumed oral nutrition on 6th-10th day after the surgery. Hospitalization time varied from 12 to 28 days (mean 22). The cannula with a millimeter scale, which was applied by the surgical team, facilitated the process of inserting the catheter into the pancreatic tumor and shortened the time needed for the last phase of the procedure. At the same time, due to the cannula, implanted catheters for brachytherapy were not damaged, as it had happened in the case of the first operation. Flexible and springy catheter was difficult to manipulate with. Unfortunately, during the first operation, a duodenum was probably damaged.

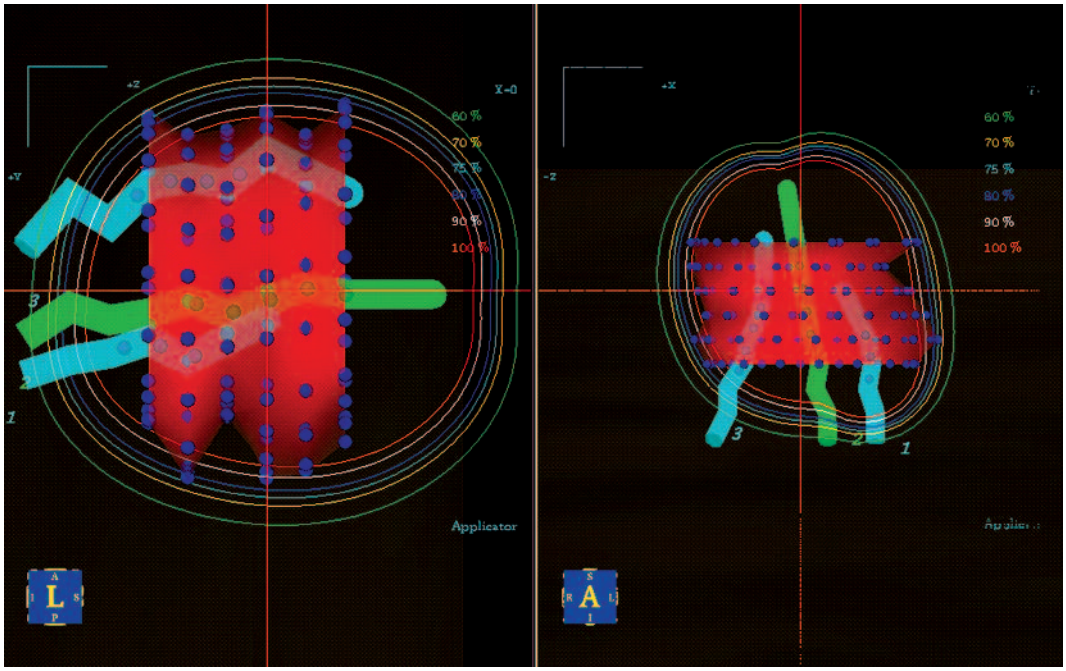

Fig. 3. Catheters reconstruction in PLATO brachytherapy planning system with isodose distribution

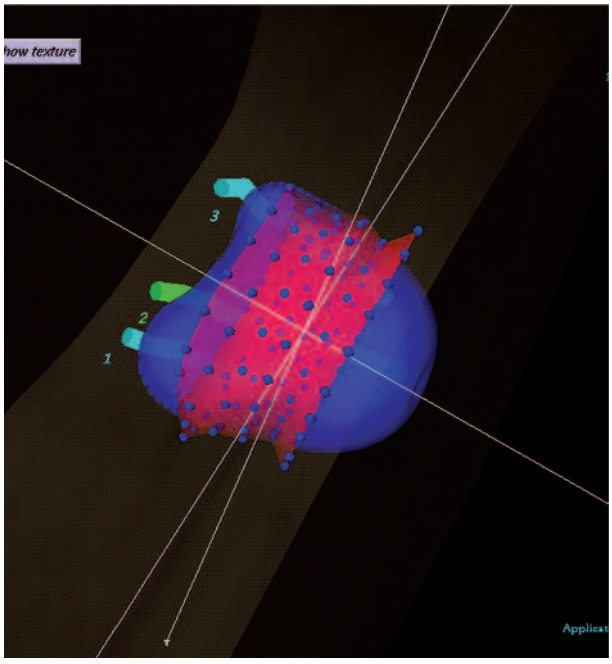

Fig. 4. Three-dimensional isodose distribution

In comparison with "plastic" catheter for brachytherapy, stiff and metal cannula with a rounded end, enabled more precise perforation of tumors, that were often very hard and of cohesive consistency. Smaller number of injections into the tumor structure limited the possibility of bleeding.

The length of life of all patients did not exceed 12 months. Mean survival time was 5.7 months. In group A (brachytherapy performed) mean survival time was 6.7 months, while in group B (no brachytherapy performed) 4.4 months (Table 3). To maintain group B patients on pain level between 1-4 according to 10 point NRS scale, a gradual increase of narcotic painkillers doses was necessary. One patient was given Fentanyl plasters every third day and immediate subcutaneous morphine injections (doses of 10 mg) due to persistent vomiting and lack of appetite in the last month of his life. In the group A (brachytherapy performed) only one patient increased the dose of painkillers in the last month of his life. Remaining patients (also the one with stage II pancreatic cancer) took constant doses of medicines (Table 2).

Discussion

Pancreatic cancer still poses a difficult diagnostic and therapeutic challenge. To treat it correctly one has to reach a correct diagnosis, precisely define the localization of the tumor, and, finally, determine the stage of the disease. Survival time of pancreatic cancer patients depends on the tumor resectability [2, 3, 15]. Resection of the neoplasm remains the basic medical treatment. The type and extensiveness of surgical procedure depend on the size of the tumor, portal vein infiltration, and metastasis in lymph nodes and liver [2, 5]. At the moment of diagnosis, only 15-20% of the patients qualify for radical resection, therefore in majority of cases the main aim is to maximally utilize palliative treatment in order to achieve the best quality of life [3]. The basic objectives of palliative treatment are to prevent mechanical jaundice, duodenal obstruction, and pain. At the moment, there are many possible surgical and nonsurgical procedures that aim at optimal reduction of patients discomfort. Thus, in majority of cases medical treatment can be individually adjusted to the medical prognosis and both clinical and general condition of a pancreatic cancer patient. In cases of unresectable tumors, a bypass operations can prevent mechanical jaundice and ileus.

Table 2. Sustained-release morphine doses (in milligrams) administered to group A (1-7) and B (8-12) patients during consecutive follow-up visits after hospitalization (till the 6th month after leaving hospital)

Patients	2 weeks	1 month	2 months	3 months	4 months	5 months	6 months
1. I.T	2 × 30	2 × 30	2 × 30	2 × 30			
2. K.J.	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	2 × 60
3. P.B.	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30
4. R.P.	2 × 30	2 × 30	2 × 30	2 × 30	2 × 15	2 × 30	2 × 30
5. M.W.	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	
6. C.W.	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30	2 × 30
7. P.M.	2 × 30	2 × 30	2 × 60	2 × 60	2 × 90		
8. H.W.	2 × 30	2 × 60	2 × 90	2 × 120	phentanyl patch + MF *s.c.*		
9. K.C.	2 × 30	2 × 30	2 × 60	2 × 90			
10. P.P	2 × 30	2 × 30	2 × 30	2 × 30	2 × 60	2 × 60	2 × 60
11. M.N.	2 × 60	2 × 60	2 × 120	2 × 120	2 × 90	2 × 120	
12. K.W.	2 × 30	2 × 30	2 × 30	2 × 30	2 × 60		

Apart from surgery, there are some other medical procedures that also aim at deterring an aggressive process of neoplasm development, extending the survival time, and eliminating or reducing the pain. Coexistence of early local and distant metastases, which is very characteristic of pancreatic cancer, makes the choice of the combination of adjuvant or neoadjuvant chemotherapy with radiotherapy very rational [3, 11, 14, 16, 17]. In the advanced stages of the disease, it is recommended to apply intraoperative radiotherapy alone [18-20] or combined with immunotherapy [18]. A combined treatment with postoperative radiochemotherapy and alpha-interferon immunotherapy is also carried on [21, 22]. All the above mentioned procedures often result in improving the quality of life and extending the survival time in patients with pancreatic cancer. To reduce pain, following procedures are used: neurolysis of celiac plexus [23-25] left-sided or bilateral thoracoscopic splanchnicectomy [9, 25-27] or EUS-guided splanchnicectomy [28]. However, these methods do not always bring satisfactory analgesic effects, especially in late stages of the disease [23-27]. Many clinical researches proved a positive influence of radiotherapy on pain intensity in patients with an advanced pancreatic cancer.

Radiotherapy acts locally at the tumor site, it reduces the neoplastic infiltration, and stops the primary tumor development. It seems that these are the main mechanisms of its analgesic effect. In 50% of patients with pancreatic cancer, a neoplastic infiltration of celiac plexus was observed [3]. Hirai *et al.* demonstrated a substantial tendency of neoplastic tissue to migrate to retroperitoneum, also to plexuses that were not directly subjected to neoplastic process [29]. Van Gen *et al.* analyzed the efficacy of different treatment methods in patients with palliative bypass surgery [30]. Their study did not demonstrate the benefits of celiac plexus neurolysis. However, a significant decrease in pain was observed when additionally radiotherapy was applied. Similarly, Yamaguchi *et al.* remarked that pain in patients with unresectable locally advanced pancreatic cancer after bypass operation disappeared after radiation therapy

Table 3. Mean survival time of patients (hospitalization time included)

Group A		Group B	
Patient	Number of months	Patient	Number of months
1.	4	8.	5
2.	6	9.	4
3.	11	10.	7
4.	8	11.	5
5.	6	12.	4
6.	7		
7.	5		

alone or with celiac plexus block [25]. Kovach *et al.* obtained postoperative pain reduction in patients with unresectable pancreatic cancer who underwent intraoperative crioablation [31]. Also a local chemotherapy performed in patients with inoperable pancreatic cancer, in most of the cases seemed to effectively diminish the pain [32].

Mohhiudin *et al.* used LDR brachytherapy in combined treatment [7]. They intraoperatively introduced I-125 implant. At first, apart from using brachytherapy they also practiced external radiotherapy. Finally, an introduction of adjuvant chemotherapy and perioperative and preoperative radiotherapy increased the mean survival time of the patients. In all groups of patients they showed positive results as far as tumor growth control was concerned. CT examinations demonstrated no signs of tumor enlargement or even tumor regression. Similarly, Peretz *et al.* received 30% tumor size reduction in 45% of patients and pain reduction lasting for at least 6 moths in 65% of patients [12]. Whittington *et al.* provided an evidence that in the case of radiotherapy alone, local control on tumor development was achieved in 22% of patients, while with the additional brachytherapy performed the results grew to 81% [33]. A similar influence on tumor growth was confirmed by Shipley *et al.* [34]. Percutaneous I-125 implants used by

Joyce *et al*. caused partial tumor regression in over 50% of patients and temporary pain reduction (lasting for 2-4 months) in about 25% of patients [34]. No positive brachytherapy influence in terms of survival time was found [7, 12, 33-35].

In our study the main criteria for patients selection were tumor unresectability and serious pain in patients that were poorly responding to pharmacologic treatment. There were several other criteria, which are listed in Table 1. Application of HDR-Ir 192 brachytherapy used in the therapy could play a part in reducing pain in terminal patients after palliative operations as well as decreasing the primary tumor development. At the very beginning, due to technical problems that occurred while placing the catheter in a hard tumor mass, we damaged the catheter. That probably could have been the reason of duodenum damage, which unfortunately we did not notice. A cannula with a millimeter scale, applied by the surgical team, made the procedure of catheter implantation easier and, therefore, significantly shortened the time needed of the procedure. At the same time the catheters for brachytherapy were no longer damaged. In comparison with "plastic" catheter for brachytherapy, stiff and metal cannula with a rounded end, enabled more precise perforation of tumors, that were often very hard and of cohesive consistency. Smaller number of injections into the tumor structure limited the possibility of bleeding and therefore reduced the risk of complications related to this part of surgery.

In our second patient, on the second day after the operation the catheter broke when the patient was asleep. It was properly adjusted to the skin with sutures and a sticking plaster. However, stiff and at the same time flexible catheter protruded from its original place and finally broke. Simple additional stabilization of the catheter (attaching it to the skin with a sticking plaster along its entire length – around 45 cm) enabled us to prevent this complication for the future. Being one of the complimentary methods for palliative treatment, brachytherapy provides some risks. Although well tolerated by patients, it prolongs the time of surgical procedure and can be the cause of some intra- and postoperative complications [7, 33]. An increase of morbidity rate and even death rate could have been noticed especially during the first phase of introducing new procedure. The results of treatment improved with experience acquired [7, 33]. Our specially designed cannula technically facilitated the process of passing a catheter through an abdominal wall and enabled placing it at the precisely determined depth in the tumor. It significantly reduced the risk of intraoperative complications and damage of catheters. Owing to proper stabilization of the catheter (along its entire length), the tips of the catheters placed in a tumor mass did not change their position. Therefore, it was possible to move patients to another health center for radiation therapy (since the sixth day after the surgery). The proper fixation of the catheter also allowed nursing of the patient and did not restrict in a significant way his ability to move.

End-of life pain management is the main aim of palliative treatment in patients with pancreatic cancer. It is estimated that about 90 percent of pancreatic cancer patients suffer an intense pain. In order to reduce pain, pharmacological treatment and chemical neurolysis of celiac plexus are practiced. In most pancreatic cancer patients, death is directly attributed to the spread of neoplastic process (mainly to liver metastasis). However, one cannot underestimate the destructive effect of total pain on the body. In our studies interviews with patients were carried out to establish their subjective assessment of pain intensity. Patients who had not been subjected to brachytherapy, reported considerably higher level of pain intensity and had to be administered larger doses of morphine with time. In the patients who had undergone HDR brachytherapy, the level of pain did not change. It seems that perioperative HDR Ir-192 brachytherapy would find an application in unresectable pancreatic tumors treatment [13, 14]. Performed in combined treatment, brachytherapy causes statistically significant improvement in the rate of remote survivals. However, the most important factor is that it brings pain relief to the patients and, therefore, improves their quality of life [7, 36].

Based on our study, we cannot confirm the influence of brachytherapy on reduction in tumor mass, which was reported by some authors, since our clinical material used in imagining procedures was not very extensive [33]. We think that the pain treatment in patients with aggressive cancer should be adjusted individually, depending on the tumor location and the stage of the disease. The efficacy of HDR brachytherapy in pain management requires further study.

Conclusions

1. It seems that perioperative HDR brachytherapy could find an application in unresectable pancreatic tumors treatment.
2. A specially designed cannula used for catheter implantation facilitates the process of inserting the catheter into the tumor.
3. Postoperative brachytherapy could be used as a supportive therapy in pain management in patients with an advanced pancreatic cancer.

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