I Intracavitary Irradiation Combined with I Seeds Implantation for Treatment of Locally Advanced Pancreatic Head Cancer: A Retrospective Analysis of 67 Cases

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Background: Pancreatic cancer is an aggressive malignant tumor of the digestive system and the fourth leading cause of tumor-related death. Intracavitary I seed irradiation has been recently developed as a therapy for locally advanced pancreatic head carcinoma. However, there are still many limitations, and more investigations are needed in order to optimize this new treatment method.

Methods: Sixty-seven patients were included in our study; 41 cases treated by SEMS- CL-I intracavular irradiation (SEMS-CL-I group) and 26 cases treated by SEMS- CL-I intracavular irradiation combined with I particle implantation in the tumor body (the combined group). Among the 67 patients, 43 were males and 24 were females, with an average age of 69.64±8.84 years. Tumor site size was determined based on the MRI or CT imaging scans, and the number and radius of I particle placement were calculated according to a specific formula. I particles were inserted into the tumor with a radius of 1.5 cm and a row spacing of 1 cm. The main postoperative biochemical indexes, imaging analysis, postoperative analgesia degree, median survival time and rate of complications were compared between the two groups.

Results: Jaundice and liver function improved in both groups after treatment for 6 months. The combined group did better. Kaplan–Meier analysis showed that patients in the combined group had a significantly better overall survival than those in the SEMS-CL-I group. Patients in the combined group had less complications than those in the SEMS-CL-I group (23.1% vs 34.1%), and the postoperative pain status of the combined group was improved (26.8% vs 53.8%).

Conclusion: Compared with the SEMS-CL-I intracavular irradiation alone, the combination of I seed implantation with solid tumor I seed implantation had a better therapeutic effect in LAPHC patients, with improved biochemical indicators, survival prognosis, pain relief, and fewer complications.

Keywords: locally advanced pancreatic cancer, I, metal biliary stent

Introduction

Pancreatic cancer is an aggressive malignant tumor of the digestive system for which very limited therapeutic options exist. It is the fourth leading cause of cancer death and the 5-year survival rate of patients with pancreatic cancer is about 10%. Patients with early stage of pancreatic cancer show no obvious clinical symptoms, and in the majority of cases, the disease has progressed to an advanced stage at the time of
presentation. About 40% of the patients with pancreatic cancer are diagnosed with locally advanced pancreatic head cancer (LAPHC). LAPHC is defined as pancreatic cancer with extensive local invasion, severe vascular invasion, and no distant metastasis. The opportunity for radical excision is often missed in these patients.

In patients with pancreatic cancer who cannot be treated surgically, biliary stents can significantly relieve symptoms and improve their quality of life. However, stent implantation alone does not seem to significantly improve stent patency time and patient survival. 125I seeds have been shown to be effective in killing tumor cells without causing significant damage to the surrounding normal tissues. 125I seeds and postoperatively chemotherapy treatment in locally advanced pancreatic cancer has a better effect than chemotherapy alone. Patient complications and the OS life cycle increased. In comparison with the traditional surgery group, the effect of 125I implantation in the treatment of advanced local malignant pancreatic cancer is feasible. Biliary stent implantation alone for the treatment of LAPHC still has many limitations, since the rapid progression of the tumor can easily result in biliary obstruction again. SEMS-CL-125I has been used to treat LAPHC in many hospitals. However, so far, no literature has reported the comparison between SEMS-CL-125I and SEMS-CL-125I combined with intratumoral implantation of 125I seeds in the treatment of LAPHC patients. Here, we investigated the effect of combined treatment with intratumor implantation 125I seeds based on SEMS-CL-125I versus SEMS-CL-125I seeds alone in patients with LAPHC.

Methods

Patients

Patients with a diagnosis of LAPHC who were admitted to the First Affiliated Hospital of Bengbu Medical College between January 2015 and January 2020 were retrospectively analyzed. Inclusion criteria were as follows: 1) clinical and pathological diagnosis of LAPHC via imaging; 2) inability or unwillingness to undergo radical resection; 3) poor age or general condition, accompanied by serious co-morbidities, and unable to accept surgical treatment; 4) no previous treatments with SEMS-CL-125I or SEMS-CL-125I combined with intratumoral implantation of 125I seeds; 5) an expected survival time of more than 3 months. Exclusion criteria were as follows: 1) patient had received chemotherapy, radiotherapy or other treatment; 2) other stages of pancreatic head cancer (not locally advanced stage); 3) incomplete or lost follow-up data after surgery; 4) distant tumor metastasis or extensive abdominal cavity metastasis.

Our study complied with the Helsinki Declaration, and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Signed informed consent prior to treatment was obtained from all patients.

Physical Characteristics of 125I Seeds and Biliary Stents

The initial dose of 125I seeds (Beijing Atomic Energy High-tech Nuclear Technology Application Company, Beijing, China) was of 11.1–37 Mbq. The half-life of 125I seeds was 59.43 days and the main radiation was 31.4/27.4 keV X-ray and 35.5 keV ray. The diameter, length and wall thickness of 125I seeds were 0.8 mm, 4.5 mm and 0.05 mm, respectively. The metal biliary stent (Nanjing Minimally Invasive Medical Technology Co., Ltd) is made of nickel–titanium memory alloy. The specifications of the metal biliary stent were 8–10 mm in diameter and 4–10 cm in length. The intracavitary 125I seed donor catheter (P-type catheter) is a disposable double-chamber biliary catheter independently developed by our hospital, in which the 125I example is placed in the leading tube, while the side tube is used for external drainage.

Surgical Procedures

SEMS-CL-125I percutaneous transhepatic cholangial drainage (PTCD) was performed 1 week before surgery in LAPHC patients with biliary obstruction and malignant jaundice to reduce postoperative complications (such as biliary bleeding, biliary leakage, biliary infection, etc). If the digital subtraction angiography (DSA) results showed that the stent expansion was adequate, then the p-type tube was implanted for the implantation of 125I seeds in the lumen, otherwise DSA examination or balloon dilatation was repeated 1–2 weeks later. When expansion was found to be adequate, 125I seeds were implanted in the P-type canal cavity. The number of 125I seeds was calculated according to the preoperative image data of the patient and to the degree of stenosis measured by contrast. Then, 125I seeds were placed into the p-type tube, into the spacing of 0.4–0.6 cm; the spacing between each seed was maintained with sterile plastic tubes for medical use. If the tumor was too large, we adjusted the number of 125I seeds according to the tumor volume. After implantation of the last 125I particles, a long plastic spacer tube was placed to the end seal in order to prevent the particles from shifting and falling off. To
determine the position of the particles and whether the spacing was appropriate, a P-type tube was placed under the prospective probe. The P-type tube was sent through the lateral lumen guide wire and placed in the treatment site inside the stent cavity. The outer end of the tube was sutured and fixed on the skin, the main lumen was closed, and finally the lateral lumen was connected with the anti-reflux drainage bag.

**Implantation of \( ^{125} \text{I} \) Particles in the Tumor of the Pancreatic Head**

Two to three days after SEMS-CL-\( ^{125} \text{I} \) surgery, the size of the tumor was measured again via B-ultrasound or computed tomography. The location of the tumor and the surrounding vascular system were identified. The number of particles implanted was calculated according to the size of the tumor. After anesthesia, a special puncture needle was inserted into the tumor body, avoiding the main blood vessels, pancreatic duct and other tissues, and while checking for bleeding by back pumping. Then, the particles were implanted into the tumor body. The needle was removed about 1 cm at a time, and the particles were released in turn.

**Perioperative Data and Data Tracking**

Baseline and perioperative characteristics of LAPHC patients were obtained by querying case data and include: patient gender; age; tumor size; length of stay; hospitalization costs; and serum indicators. Serum test indicators included: total bilirubin (TBIL); direct bilirubin (DBIL); alanine aminotransferase (ALT); aspartate aminotransferase (AST); alkaline phosphatase (ALP); albumin (ALB); carbohydrate antigen 19–9 (CA19-9); carcinoembryonic antigen (CEA); and cancer antigen 125 (CA-125).

**Imaging Data**

Tumor size was calculated according to the results of MDCT images before and 3 months after surgery. The evaluation indicators (according to the WHO solid tumor evaluation criteria) were based on the comparison of the product of the maximum diameters of the two perpendicular tumors shown on MDCT, and were categorized as follows: 1) complete response (CR): the tumors completely disappeared and no residual tumor was found on imaging examinations, or only particle residues were found; 2) partial response (PR): tumor size was reduced by more than 50%; 3) no change (NC): tumor size was reduced by less than 50%; 4) progressive disease (PD): the sum of the maximum diameter of target lesions increased by at least 20%, or new lesions appeared. We used the following calculation formula: \((\text{CR} + \text{PR})/\text{total} \times 100\% = \text{effective rate}\).

**Assessment of Pain Status**

Pain was classified according to VRS method as follows: Level 0: no pain; Level 1: mild or tolerable pain, normal life and sleep cycles; Level 2: moderate or obvious pain, need to use analgesics, sleep is affected; Level 3: severe pain.

All patients were followed-up until January 2020 or until death. Data obtained during follow-up included: 1, 3, and 6 months of serum test indicators (including TBIL, DBIL, AST, ALT, ALP, ALB); multidetector computed tomography (MDCT) data; and color Doppler ultrasound data. If complications or other conditions are found in the patient during follow-up, follow-up treatment will be performed.

Because the half-life of \( ^{125} \text{I} \) seeds is of 59.43 days, a reduced effect after 6 months is anticipated. For this reason, patients were re-admitted to hospital 6 months after surgery, and the P-type tube and \( ^{125} \text{I} \) seeds used for intracavitary irradiation were replaced. Discarded \( ^{125} \text{I} \) seeds were sent to the nuclear supply’s treatment center.

**Statistical Analysis**

Continuous variables consistent with normal distribution are expressed as mean±SD and verified by \( T \)-test. If a variable did not conform with normal distribution, then the median (maximum–minimum) was used for verification, and the Wilcoxon test was used. Overall survival (OS) was calculated using the Kaplan–Meier method and the Log rank test. Only single factor analysis with \( P<0.05 \) were included in the multifactor analysis model. Statistical significance was considered only when \( P<0.05 \). All data were analyzed using the SPSS statistical software (version 22).

**Results**

**Patient Characteristics**

The basic information of all patients is shown on Table 1. This study evaluated eligibility of 112 LAPHC patients admitted in our hospital from January 2015 to January 2020. Sixty-seven of 112 (59.8%) patients met the inclusion criteria. Among them, 43 (64.2%) were males and 24 (35.8%) were females. There were 41 patients in the SEMS-CL-\( ^{125} \text{I} \) group and 26 patients in
the combined treatment group. There were not statistically significant differences in gender, age, CA19-9, CA-125 and ALB between the two groups (\(p>0.05\)). However, TBIL, DBIL, ALT, AST, ALP and CEA values, and the mean tumor diameter of the SEMS-CL-\(^{125}\)I group were lower than in the combination group (\(p<0.05\)). No statistically significant differences in the length of hospital stay between the two groups were observed, although the hospitalization costs in the SEMS-CL-\(^{125}\)I group were lower than those in the combined group (median: 40135.07 CNY vs 46991.745 CNY; \(p<0.01\)).

Perioperative Outcomes
All patients had successful implantation of \(^{125}\)I seeds and metal biliary stent. Jaundice, pain and other clinical symptoms have been partially improved. Liver function indexes at 1, 3 and 6 months after surgery decreased significantly in the SEMS-CL-\(^{125}\)I group compared with the preoperative level (\(p<0.05\)), although postoperative ALB values showed no difference (\(p>0.05\)). In contrast, TBIL, DBIL, ALT, AST and ALP were significantly reduced in the combined group (\(p<0.05\)) (Figure 1).

Comparative Evaluation of Clinical Effects and Postoperative Complications
Three months following surgery, CT imaging (Figure 2) suggested that the overall effective rate was 79.1% (53/67). The SEMS-CL-\(^{125}\)I group 75.6% (31/41) was lower than that of the combined group 84.6% (22/26) (\(p=0.018\)). Fifty-eight of 67 (86.6%) patients achieved a painless state or a state of mild pain without the need for analgesics. The combined group achieved better pain relief 3 months after surgery than the SEMS-CL-\(^{125}\)I group (\(p=0.035\)). Preoperative and postoperative pain scores were compared between the two groups, and the results showed that both methods improved postoperative pain (\(p<0.001\)) (Table 2). In the SEMS-CL-\(^{125}\)I group, there were three cases of biliary obstruction, five cases of P-type tube displacement,
two cases of biliary infection, and one case of postoperative pancreatitis. In the combined group, there were two cases of biliary obstruction, two cases of P canal displacement, one case of biliary tract infection, one case of needle canal metastasis, and one case of gastrointestinal discomfort (Table 3).

The overall postoperative complication rate was 29.9% (20/67), with no significant differences between the two groups ($P=0.601$). There were no serious complications such as bleeding, pancreatic leakage or particle displacement in either of the groups (Table 3).

Patients with biliary obstruction improved after biliary stent implantation. Patients with p-tube displacement were handled under the guidance of DSA. Patients with biliary tract infection were considered cured after 3–7 days of open P-type tube drainage and antibiotics. Patients with postoperative pancreatitis were treated with somatostatin and symptomatic treatment. The subcutaneous $^{125}$I seed implantation was effectively controlled in patients with needle-passage metastasis. Symptoms of digestive tract discomfort were improved upon administration of gastric protectors and antiemesis.
Overall Survival (OS)
As of the last follow-up in January 2020, 38 (56.7%) patients had died and 29 (43.3%) were alive. In the SEMS-CL-$^{125}$I group (n=26), 11 (16.4%) patients had died and 15 (22.4%) were alive. In the combined group (n=41), 27 (40.3%) patients died and 14 (20.9%) were alive. Compared with the SEMS-CL-$^{125}$I group, the combined group has a higher OS (median: 9 vs 17, \(p<0.001\)). Similarly, the 1-year survival rate of the SEMS-CL-$^{125}$I group was lower than that of the combined group (1-year survival rate: 72.7% vs 94.3%, \(p<0.001\)) (Figure 3).

Discussion
Current treatment options for patients with pancreatic cancer are very limited. About 40% of patients with pancreatic cancer have locally advanced pancreatic cancer at the time of diagnosis, with a 5-year survival rate less than 5%\(^1\). Standard of care has limited benefits for patients with LAPHC, and the majority of these patients will eventually

Table 2 Comparison of Pain Indexes (Based on VRS Scores) in the SEMS-CL-$^{125}$I Group and the Combined Group Preoperative and Postoperative

| Group                  | Preoperative | Postoperative | Z Value | \(P\) value |
|------------------------|--------------|---------------|---------|------------|
| SEMS-CL-$^{125}$I group (n=41) |              |               |         |            |
| Level 0                | 6            | 11            | −5.477  | \(<0.001\) |
| Level 1                | 12           | 24            |         |            |
| Level 2                | 17           | 5             |         |            |
| Level 3                | 6            | 1             |         |            |
| Combined group (n=26)  |              |               |         |            |
| Level 0                | 4            | 16            | −4.334  | \(<0.001\) |
| Level 1                | 9            | 7             |         |            |
| Level 2                | 11           | 2             |         |            |
| Level 3                | 2            | 1             |         |            |

Notes: Level 0, painless; Level 1, mild pain, tolerable, normal life and sleep; Level 2, moderate pain, significant pain, need to use analgesics, sleep disturbance; Level 3, severe pain, frequent use of analgesics, sleep seriously affected. The bold part is \(P<0.05\).

Table 3 Imaging Assessment, Pain Index and Complications Related Information of Postoperative Patients

| Characteristics                  | SEMS-CL-$^{125}$I Group (N=41) | Combined Group (N=26) | \(p\) value |
|----------------------------------|---------------------------------|------------------------|-------------|
| Imaging assessment               |                                 |                        | 0.018       |
| CR                               | 8                               | 14                     |             |
| PR                               | 23                              | 8                      |             |
| NC                               | 7                               | 3                      |             |
| PD                               | 3                               | 1                      |             |
| Postoperative pain relief (3 months after surgery) | | | 0.035 |
| Level 0                          | 11                              | 16                     |             |
| Level 1                          | 24                              | 7                      |             |
| Level 2                          | 5                               | 2                      |             |
| Level 3                          | 1                               | 1                      |             |
| Complications                    |                                 |                        | 0.601       |
| Biliary obstruction              | 4                               | 2                      |             |
| P-tube shift                     | 7                               | 3                      |             |
| Biliary tract infection          | 1                               | 0                      |             |
| Pancreatitis                     | 1                               | 0                      |             |
| Needle metastasize               | 0                               | 1                      |             |
| Digestive discomfort             | 1                               | 0                      |             |

Notes: Level 0: no pain; Level 1: mild pain; Level 2: moderate pain; Level 3: severe pain. The bold part is \(P<0.05\).
Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.
develop distant metastasis.\textsuperscript{12} Multidisciplinary therapy may be effective in improving patients’ clinical symptoms and induce local tumor shrinkage.\textsuperscript{13}

LAPHC is a relatively large type of cancer, which often compresses the bile duct and obstructs bile flow, causing jaundice, hyperbilirubinemia and other clinical manifestations. Self-inflating metal biliary stent implantation can rapidly reduce biliary pressure and reduce the level of total bilirubins, thus helping to maintain the metabolic function of the liver and increase its oxygen supply, to enhance the function of the digestive system, and overall to improve the diet and life quality of patients.\textsuperscript{14} However, stents themselves cannot inhibit the tumor progression. Due to the continuous tumoral growth and invasion, the incidence of stent re-obstruction is relatively high, which is a high risk factor affecting the prognosis.\textsuperscript{15} The efficacy of \textsuperscript{125}I seeds implanted in pancreatic cancer has been confirmed recently.\textsuperscript{16,17} \textsuperscript{125}I seeds continuously release low doses of X-rays and gamma rays, which can break the DNA double helix of cancer cells, resulting in their permanent and irreparable damage.\textsuperscript{17} Clinical studies have confirmed that metal biliary stents combined with \textsuperscript{125}I seeds brachytherapy can resist mucosal and intraluminal growth and kill tumor cells, delaying the recurrence of obstructive jaundice and extending patient survival.\textsuperscript{18,19} Treatment of pancreatic cancer by biliary stent combined with \textsuperscript{125}I seeds intraluminal irradiation has been previously shown to have promising therapeutic effects.\textsuperscript{8} In summary, \textsuperscript{125}I can treat pancreatic cancer, but the radiation radius of \textsuperscript{125}I was only 17–20 mm, and the size of local advanced pancreatic cancer was relatively large. Therefore, \textsuperscript{125}I seeds in the biliary tract could not effectively irradiate the tumor, reducing the overall therapeutic effect.

Our study found that compared with SEMS-CL-\textsuperscript{125}I alone, the combination of SEMS-CL-\textsuperscript{125}I with intratumor implantation of \textsuperscript{125}I seeds had a better effect in treating LAPHC (imaging data revealed a better effect, although no significant differences in stent patency time between the two groups were observed). Patients in the combined group had a better survival prognosis (median: 9 vs 17 months, \textit{P}<0.001). At the same time, the indexes of TBIL, DBIL, ALT, AST and ALP in the two groups were significantly decreased (\textit{P}<0.05) when comparing the indexes of liver function in 1, 3 and 6 months after surgery. Compared with patients in the SEMS-CL-\textsuperscript{125}I group, patients in the combined group had a higher painless rate 3 months after surgery (26.8\% vs 53.8\%, \textit{P}<0.001). The pain index before and after surgery was compared, and the postoperative pain was relieved in both groups (\textit{p}<0.001). These results suggest that SEMS-CL-\textsuperscript{125}I intracavity irradiation combined with \textsuperscript{125}I intracavity seed implantation is a promising approach to eliminate or alleviate compression or invasion of the tumor on the abdominal nerve plexus, resulting in overall better patient quality of life.

Importantly, intratumorally insertion of \textsuperscript{125}I seeds did not increase the risk of complications. Complication rates of the SEMS-CL-\textsuperscript{125}I group and the combination group were 34.1\% (14/41) and 23.1\% (6/26), respectively. One case of pancreatitis in the SEMS-CL-\textsuperscript{125}I group showed improvement of symptoms and gradual recovery of diet within 3 days after active symptomatic treatment to stimulate acid-inhibitory enzyme production. In six cases of biliary obstruction (four in the SEMS-CL-\textsuperscript{125}I group vs two in the combined group), successful recanalization through timely opening of p-type tube side flushing and drainage, combined with intracavity perfusion and chemotherapy, was performed, except for one patient who required stent implantation. Ten cases of p-type tube shift were reset under the guidance of digital subtraction angiography. There was one case of biliary tract infection in the SEMS-CL-\textsuperscript{125}I group, which was associated with biliary tract obstruction. This case was well controlled by timely opening of p-type lateral cavity drainage combined with the use of antibiotics. One patient had abdominal wall needle passage metastasis, which was effectively controlled after tumor particle implantation. One patient experienced digestive tract adverse reactions which
improved after drug intervention. No serious complications such as bleeding, pancreatic leakage, or particle displacement occurred in either of the groups.

This study has several limitations. Firstly, due to the small sample and single-center retrospective design, the findings could be considered as preliminary and therefore more multicenter data should be collected in order to confirm our findings. Secondly, relevant indicators (such as tumor markers) were not collected in a dynamic fashion, and therefore we were not able to assess the effect of these therapies on the biological behavior of tumors. Thirdly, in this retrospective study, no analysis on the correlation with combined chemotherapy was performed; such analysis would have reflected better the comprehensive treatment effects on the tumor. In addition, there may be residual confounding given that patients treated in the combination group had higher TBIL, DBIL, ALT, AST, ALP, CEA, and mean tumor diameter. Therefore, further studies to address the above-mentioned limitations and confirm the safety and efficacy of this novel therapeutic option are needed.

Conclusions
In conclusion, compared with the SEMS-CL\textsuperscript{125}I intracavity imaging alone, SEMS-CL\textsuperscript{125}I intracavity irradiation combined with \textsuperscript{125}I intracavity particle implantation improved the stent patency rate, resulted in better control of tumor progression, prolonged patient survival, and improved the general physical condition and quality of life of LAPHC patients. Since the \textsuperscript{125}I particles irradiated in the lumen can be replaced and renewed repeatedly with the P-type tube, and the \textsuperscript{125}I particles in the tumor can be supplemented and implanted several times according to the development of the tumor, the combination of the two methods can achieve longer treatment times and result in less pain for the patients with no increased rate of complications. Overall, based on our results, SEMS-CL\textsuperscript{125}I intracavity irradiation combined with \textsuperscript{125}I intracavity particle implantation appears safe and effective, and merits further clinical investigation.

Data Sharing Statement
The raw datasets generated during the current study are available from the corresponding author upon reasonable request.

Ethical Considerations
This study was complied with Helsinki Declaration and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. All patients signed informed consent prior to treatment.

Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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