Original article

The outcome of cryoablation in treating advanced pancreatic cancer: A comparison with palliative bypass surgery alone

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OBJECTIVE: This study aimed to investigate the efficacy and safety of palliative bypass surgery combined with cryoablation in treating patients with advanced pancreatic cancer and compare this combination therapy with palliative bypass surgery alone.

METHODS: Medical records of 118 patients with advanced pancreatic cancer who received palliative bypass surgery combined with cryoablation (the combination treatment group) or bypass surgery alone (the bypass surgery alone group) at the Department of Pancreatic Cancer, Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) were retrospectively reviewed. Their baseline and peri-operative parameters were collected and compared.

RESULTS: In both groups abdominal distension and pain was significantly ameliorated after treatment. Preoperative jaundice was more common in the bypass surgery group while backache was more frequent in the combination treatment group, which were both relieved by treatment. The pre-operative serum bilirubin level was higher in the bypass surgery group and was decreased significantly after treatment. However, a significant reduction in tumor size and serum carbohydrate antigen 19-9 level was found only in the combination treatment group. There was no significant difference in the incidence of postoperative complications and prognosis between the two groups.

CONCLUSIONS: Cryoablation can reduce tumor size and relieve the patients’ symptoms and signs such as abdominal discomfort and backache, although it could not improve the patients’ prognosis significantly. It is a safe and efficient modality when combined with bypass surgery for patients with advanced pancreatic cancer.

KEY WORDS: bypass surgery, complication, cryosurgery, pancreatic neoplasms.

INTRODUCTION

Pancreatic cancer is a malignant neoplasm which originates from the transformed cells that arise in the pancreatic tissues. Pancreatic adenocarcinoma is the most common type, which accounts for 85% of these tumors among all pancreatic cancers, exhibiting glandular architecture arising within the exocrine component of the pancreas under the light microscopy.1 Patients with pancreatic cancer usually manifest as
abdominal distention and pain, jaundice, backache and cachexia, etc. Most patients are found to have unresectable tumors by the time they are diagnosed, leading to a poor prognosis and a low 5-year survival rate. In 2013 pancreatic cancer was the fourth leading cause of cancer death in both man and woman in the USA and the 5-year survival rate was only 6% among all races.

Patients with advanced pancreatic cancer are usually treated palliatively, mainly with symptomatic treatment, chemotherapy and molecular-targeted therapy to ameliorate their symptoms and enhance the quality of life as well as to improve their survival rate. Palliative surgery consists of Roux-en-Y cholangioenterostomy and gastrojejunostomy, the former of which is performed to relieve jaundice and the latter to treat gastrointestinal (GI) obstruction. However, pancreatic cancer cannot be resected even with these surgeries.

Recently, the efficacy of cryoablation on the treatment of advanced pancreatic cancer has attracted much attention. It has been suggested that cryoablation can freeze and kill the tumor cells, thus reducing tumor growth in advanced pancreatic carcinoma. Since 2008 our team has adopted bypass surgery combined with intraoperative cryoablation in treating advanced pancreatic cancer. In this study, we aimed to investigate the efficacy and safety of palliative bypass surgery combined with cryoablation in treating patients with advanced pancreatic cancer compared with palliative bypass surgery alone.

PATIENTS AND METHODS

Patients

The medical records of patients with pancreatic cancer who were treated at the Department of Pancreatic Cancer, Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) from 30 June 2008 to 31 December 2010 were retrospectively reviewed. Inclusion criteria were: (i) patients with unresectable pancreatic carcinoma that invaded the superior mesenteric artery or celiac axis, bilateral stenosis of the portal vein, or local or distant metastasis, as identified with radiological and histopathological evidence; (ii) those who underwent bypass surgery (gastroenterostomy and/or cholangiojejunostomy) combined with cryoablation due to symptoms and signs such as jaundice and upper GI obstruction. Patients with severe systemic diseases or mental disorders were excluded from the study. All patients were informed with the detailed information on the operation and cryoablation as well as the peri-procedure complications before their treatment. Those who provided their written informed consent were divided into two groups, the bypass surgery combined with cryoablation group or the bypass surgery alone group, based on the patients’ decision. The study was approved by the Institutional Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (Tianjin, China).

The medical records of the patients were reviewed and their characteristics including age, gender, clinical symptoms, laboratory examination results such as peripheral bilirubin and carbohydrate antigen 19-9 (CA19-9), the size of the tumor, tumor stage according to the American Joint Committee on Cancer (AJCC), local and distant tumor metastases, peri-operation complications such as pancreatic leakage, bile leak, infection, GI or intra-abdominal bleeding, gastroparesis and GI obstruction, as well as the mortality and survival of the patients, were collected.

Bypass surgery and cryoablation

The surgery was performed with a midline or bilateral subcostal incision and the gastrocolic ligament was incised to expose the pancreas. After a careful exploration, the specimens of the pancreatic tumor were obtained with fine needle aspiration. Briefly, gastroenterostomy was performed on the stomach and jejunum with an end-to-side or side-to-side anastomosis, whereas cholangiojejunostomy was applied on either the common bile duct or the gallbladder and jejunum with an end-to-side or side-to-side anastomosis. Double bypass surgery was defined as performing both of the abovementioned surgical procedures at the same time.

The tumor was isolated from the normal pancreatic tissues before cryoablation, and the surrounding organs and vessels (stomach, duodenum, portal vein, superior mesenteric artery and vein) at the area of the pancreatic head or tail were protected and isolated carefully using gauze. The Ar-He targeted CryoSystem (Endolare, Irvine, CA, USA), a system providing cold or hot Ar-He gas source, was applied in cryoablation. Probes of 2–3 mm in diameter were inserted into the tumor; if the tumor was 3–5 cm in diameter, two to four probes were used. The tumor was frozen at −90 °C to −150°C for 8 min, depending on the size of the tumor, and was then rewarmed.
to 37°C. Generally, −150°C is the lowest temperature that the tumor center can bear, whereas the peripheral temperature should not be too low, especially for tumor tissues near the stomach, duodenum and vessels. The surrounding tissues and the blood circulation of the liver and spleen were observed closely, and cryoablation at one site was discontinued once the surrounding organs had ischemia or cold injury, which was diagnosed as the livid and dark color of the organs and a low tissue temperature. When the tumor was larger than 5 cm in diameter, one to two freeze–thaw cycles of the procedure in different sites of the tumor were required until the ice balls covered the whole tumor. An absorbable gelatin sponge was applied to the location of the cryoprobe and Prolene 4-0 (Johnson & Johnson, Shanghai, China) was used to suture the surface of the bleeding point. Then the bypass surgery was undertaken based on the relevant situation.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation, and discrete data were expressed as numbers and percentages. Differences in categorical variables between the combination treatment group and the bypass surgery alone group or between pre-operation and post-operation were analyzed using χ² and Fisher's exact tests. Survival and univariate analysis were performed by using the Kaplan–Meier method and log–rank test. A Cox regression was applied in the multivariate prognostic analysis. A two-sided \( P \leq 0.05 \) was regarded as statistically significant.

RESULTS

Characteristics of the patients

Finally, 118 patients with advanced pancreatic cancer were enrolled in the study, with a median age of 64 years (range 37–86 years) and a slight male predominance (72/118, 61.0%). Among them, 42 (35.6%) patients received bypass surgery combined with cryoablation (the combination treatment group) and the other 76 underwent bypass surgery alone (the bypass surgery alone group). The tumor was located at the pancreatic head in 26 (61.9%) and 43 (56.6%), at the pancreatic body and tail in 13 (31.0%) and 28 (36.8%), respectively, in the combination treatment group and the bypass surgery alone group, respectively; while the other 3 (7.1%) in the combination group and 5 (6.6%) in the bypass surgery alone group had diffuse lesions in the whole pancreas.

In the combination treatment group, 25 (59.5%) patients underwent both gastroenterostomy and cholangiojejunostomy, and 13 (31.0%) and 4 (9.5%) underwent gastroenterostomy or cholangiojejunostomy alone, respectively. In the bypass surgery alone group the numbers of patients who underwent double bypass surgery and gastroenterostomy or cholangiojejunostomy alone were 42 (55.3%), 28 (36.8%) and 6 (7.9%), respectively.

Clinicopathological features of the two groups

Among the patients, 76.1% (89/117) were confirmed to have arterial and/or venous tumor invasion, 70.4% (81/115) had lymph node metastasis, 16 (13.6%) had neural invasion and 19.5% (23/118) had distant tumor metastasis to the liver, lungs or bone. According to the AJCC Pancreatic Cancer Staging System (6th edition), 80 (67.8%) patients were classified as having stage III tumors and the other 38 (32.2%) as stage IV. Altogether, 37 patients received chemotherapy, including 19 received intraoperative regional chemotherapy with 5-fluorouracil (5-FU) and 18 received postoperative chemotherapy with gemcitabine combined with oxaliplatin for 2–8 cycles. No differences in these clinicopathological features were observed between the two groups (Table 1).

Comparison of pre-operative and postoperative clinical symptoms, laboratory results and tumor size between the two groups

Clinical symptoms and laboratory results of the patients and the tumor size were evaluated both before and 20–30 days after the surgery in the two groups (Table 2). After having been treated with surgery combined with cryoablation or surgery alone, the proportions of patients with abdominal distension and pain were significantly decreased, although there were no significant differences in the prevalence of this symptom between the two groups either before or after surgery. Preoperative jaundice was more commonly seen in the bypass surgery alone group, whereas backache was more frequent in the combination treatment group. Jaundice was relieved after the surgery, although no significant difference between the two groups after surgery was observed \( (P = 0.143) \), while the proportion of patients with backache was even slightly increased in the bypass surgery group after the treatment.
In both groups most patients had elevated serum bilirubin levels before treatment; only 86 patients had a bilirubin level of <200 μmol/L, while the bilirubin level in 12 patients was elevated to >300 μmol/L. Patients in the bypass surgery group had a higher pre-operative serum bilirubin level than those in the combination treatment group, but the postoperative serum bilirubin levels did not differ between the two groups. In the combination treatment group the pre-operative bilirubin level was relatively low and did not change significantly after treatment; while in the bypass surgery group the pre-operative bilirubin level was relatively high, making it easier to observe a difference. The baseline CA19-9 level was elevated in 90 patients; however, there were no statistical differences between the combination treatment group and the bypass surgery alone group. This level was significantly decreased after treatment in the combination treatment group, whereas in the bypass surgery group it did not change much.

The intraoperative exploration showed that 85 patients had a tumor ≥3 cm in diameter, but the post-operative tumor size was smaller in the combination group than in the bypass surgery group. A significant reduction in tumor size after operation compared with that of pre-operation was observed only in the combination treatment group, but not in the bypass surgery alone group.
Table 2. Pre-operative and postoperative clinical symptoms, laboratory results and tumor size of the bypass surgery combined with cryoablation group and the bypass surgery alone group

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Combination treatment group</th>
<th>Bypass surgery group</th>
<th>Combination treatment vs bypass surgery alone</th>
<th>Pre-operation vs postoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operation</td>
<td>Postoperation</td>
<td>Pre-operation</td>
<td>Postoperation</td>
</tr>
<tr>
<td></td>
<td>χ²</td>
<td>P value</td>
<td>χ²</td>
<td>P value</td>
</tr>
<tr>
<td>Abdominal distension and pain†</td>
<td>30 (71.4)</td>
<td>5 (11.9)</td>
<td>45 (59.2)</td>
<td>16 (21.1)</td>
</tr>
<tr>
<td>Jaundice‡</td>
<td>5 (11.9)</td>
<td>40 (95.2)</td>
<td>33 (43.4)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>Backache§</td>
<td>18 (42.9)</td>
<td>5 (11.9)</td>
<td>18 (23.7)</td>
<td>22 (28.9)</td>
</tr>
<tr>
<td>Laboratory examination</td>
<td>Bilirubin (μmol/L)</td>
<td>41 (97.6)</td>
<td>46 (60.5)</td>
<td>66 (86.8)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>40 (95.2)</td>
<td>41 (97.6)</td>
<td>46 (60.5)</td>
<td>66 (86.8)</td>
</tr>
<tr>
<td>200–300</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
<td>19 (25.0)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>300–500</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td>11 (14.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CA19-9¶</td>
<td>Elevated (&gt;39 U/mL)</td>
<td>30 (71.4)</td>
<td>15 (35.7)</td>
<td>60 (81.6)</td>
</tr>
<tr>
<td>Normal (≤39 U/mL)</td>
<td>12 (28.6)</td>
<td>27 (64.3)</td>
<td>14 (18.4)</td>
<td>12 (15.8)</td>
</tr>
<tr>
<td>Tumor size††</td>
<td>&lt;3 cm</td>
<td>3 (7.1)</td>
<td>15 (35.7)</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td>≥3 cm</td>
<td>30 (71.4)</td>
<td>18 (42.9)</td>
<td>55 (72.4)</td>
<td>56 (73.8)</td>
</tr>
</tbody>
</table>

†Abdominal distension and pain are diagnosed according to the patients' self-report. ‡Jaundice is defined as yellow sclera by the naked eye. §Backache is identified according to the visual analogue scale (VAS), defined as yes when the VAS grade is more than 4. ¶Altogether 116 patients were examined for carbohydrate antigen 19-9 (CA19-9). ††Altogether 96 patients enrolled in this analysis. The tumor size is measured by the maximum diameter in three-dimensions by imaging examination, including computed tomography and ultrasound 1–2 weeks pre-operation and 4–8 weeks postoperation.
Comparison of postoperative complications in the combination treatment group and the bypass surgery group

The main postoperative complications included pancreatic leakage \((n = 2)\), bile leak \((n = 3)\), infection \((n = 1)\), GI bleeding \((n = 5)\), intra-abdominal bleeding \((n = 1)\), gastroparesis \((n = 3)\) and GI obstruction \((n = 6)\). There were no significant differences in the incidences of these complications between the two groups (Table 3). All the symptoms were treated conservatively and most patients recovered soon after the therapy, while only one with pancreatic leakage died of cardiac arrest.

Prognostic analysis of advanced pancreatic cancer

Median survival was 4 months for all patients with advanced pancreatic cancer (5 months in the combination treatment group vs 4 months in the bypass surgery alone group, \(P > 0.05\)). The 1-year survival rate of the combination treatment group and the bypass surgery alone group was 4.8% and 2.6%, respectively (\(P > 0.05\)).

In the univariate analysis the AJCC stage of the tumors, lymph node metastasis and distant metastasis were prognostic factors for advanced pancreatic cancer (\(P < 0.05\), Figs 1,2). The Cox regression revealed that the AJCC stage and lymph node metastasis were independent prognostic factors, with a relative risk of 1.608 (95% CI 1.061–2.436) and 1.682 (95% CI 1.061–2.669), respectively (Table 4).
DISCUSSION

Pancreatic cancer is a common GI malignancy with a poor prognosis and an extremely low survival rate, especially in those having an advanced tumor. Abdominal distension and pain is one of the most common symptoms presenting in patients with pancreatic cancer, which may be severe in those who also have jaundice and digestive insufficiency.9 In our study most patients experienced abdominal distension and pain, which might be attributed to GI effusion, pneumatosis and peristaltic disorder caused by partial GI obstruction. However, GI obstruction as well as jaundice was relieved after bypass surgery alone or in combination with cryoablation, showing that GI function might, to some extent, recover and the abdominal symptoms could subsequently be relieved. Jaundice and elevated serum bilirubin level were observed in most of the patients in the current study, and were more severe in the bypass surgery alone group, which might contribute to their significant alteration after therapy. After cholangioenterostomy the bile can flow directly into the intestine, thus relieving both cholestasis and jaundice.

Pancreatic cancer has been found to invade the peripheral nerves, retroperitoneal and myenteric plexuses, and so on, although the mechanism of neural invasion in pancreatic cancer remains unclear. Backache, which is usually attributed to neural invasion in pancreatic cancer, is closely associated with tumor progression and recurrence and neuropathic pain.10 Kayahara et al.11 suggested that neural invasion might be a pathway to lymphatic involvement.

Ceyhan et al.12 suggested that neuro–cancer interactions started before pancreatic cancer cell migration and led to evident cancerous and neural biological changes. In this study, 30.5% of all patients complained of backache before the treatment, which was higher in the combination treatment group than in the bypass surgery alone group (42.9% vs 23.7%), suggesting that such patients might prefer cryoablation; and after receiving bypass surgery and cryoablation, a significant reduction in the complaint of backache could be observed. Cryoablation may relieve backache by damaging the tumor cells and subsequently inhibiting neural invasion. The mechanism in the efficacy of cryoablation on backache needs further investigation.

Serum CA19-9 examination has been applied clinically in the diagnosis and surveillance of pancreatic cancer, with a sensitivity of 70–90% and a specificity of 68–91%, respectively.13,14 It is also a good indicator for evaluating prognosis as well as predicting the chemotherapeutic efficacy and recurrence in patients with pancreatic cancer.15 In our study CA19-9 level was increased in both groups but was only decreased significantly in the combination treatment group after therapy, showing that cryoablation was effective in damaging the pancreatic cancer cells, and CA19-9 might be a potential marker to assess the therapeutic effect of cryoablation. Nevertheless, CA19-9 might not be a good prognostic indicator in advanced pancreatic cancer and it might be useless in predicting the patients’ quality of life, as its non-specific expression in several benign and malignant diseases, the low sensitivity in the diagnosis of asymptomatic pancreatic cancer and increased false positivity in patients with severe obstructive jaundice limit its applicability in the management of pancreatic cancer.13 CA19-9 is not a prognostic factor in our survival analysis, which is in line with the previous studies. Therefore, it is essential to find a more sensitive and specific tumor marker for the early diagnosis of and the predication of prognosis for pancreatic cancer.16 Ikenaga et al.17 demonstrated that S100A4 mRNA could be a new diagnostic and prognostic marker for pancreatic malignancy.

In our study, the intraoperative exploration showed that most patients (85/118) had a tumor ≥3 cm in diameter, and a significant reduction in tumor size was achieved in the combination group after treatment compared with the bypass surgery group, suggesting that cryoablation had a potential ability to shrink tumors.
The intraoperative exploration also showed that 89 patients had vessel invasion, including that involving the superior mesenteric artery and the portal vein. Müller et al. demonstrated that vascular resection in patients with vascular invasion could not achieve a favorable long-term survival for all patients because distant metastases or local recurrence of the tumor was frequently seen. Our intraoperative exploration also found that most patients (81/115) had lymph node metastasis. The most common metastatic sites are known to be the 8th, 9th, 12th, 14th and 16th lymph nodes. Even the large and multinodular confluent retroperitoneal metastasis lymph nodes can be explored in some patients. For these patients surgical resection is not recommended because the improvement of prognosis is not so obvious.

It has been reported that the incidence of neural invasion in pancreatic cancer is up to 70.8%, which is much higher than that in some other tumors. In our study, all pancreatic cancers were unresectable; therefore, the diagnosis of neural invasion was mainly via intraoperative exploration, leading to a potentially low positive diagnostic rate and a poor accuracy.

The main postoperative complications in our patients included pancreatic leakage, bile leak, infection, GI obstruction, GI bleeding, intra-abdominal hemorrhage and gastroparesis. All complications were mild and were managed by conservative treatment, confirming that cryoablation is a safe treatment modality.

Chemotherapy with 5-FU and gemcitabine is the main treatment modality in advanced pancreatic cancer. Postoperative chemotherapy has been found to be an independent factor for the prognosis of pancreatic cancer at stages I–II. However, it did little to retard advanced pancreatic cancer, which was also perceived in our patients. Thus, it is urgent to develop a new treatment option for advanced pancreatic cancer. A study by Moody et al. revealed that adjuvant radiotherapy for pancreatic cancer was associated with a survival benefit primarily in patients with stage IIb cancer, while its efficacy was uncertain in pancreatic cancer at stages III and IV. A better therapeutic efficacy was achieved in combination with cryosurgery and iodine seed implantation for locally advanced pancreatic cancer.

All patients in this study were at stage III and IV, including 23 patients with distant metastasis. In these patients, the relief of discomfort symptoms is the main goal of treatment because limited benefits can be achieved in prolonging their survival time. In our research, patients managed by bypass surgery in combination with cryoablation did not experience significantly prolonged survival time.

In our multivariate analysis, it was demonstrated that AJCC stage and lymph node metastasis were independent prognostic factors, showing that tumor progression was the crucial factor determining the prognosis of advanced pancreatic carcinoma. There is often lymph node metastasis in advanced pancreatic carcinoma, which was also verified as an important prognostic factor in our study.

In conclusion, cryoablation could freeze and kill the tumor cells and shrink the tumor size in advanced pancreatic carcinoma, although it could not improve the patients’ prognosis significantly. Furthermore, it could inhibit the cancer cell invasion in the peripheral nerve to relieve the patient’s symptoms.

Table 4. Univariate and multivariate prognostic analysis of advanced pancreatic cancer patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis RR (95% CI)</th>
<th>P value</th>
<th>Multivariate analysis RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC stage III vs IV</td>
<td>1.843 (1.235–2.751)</td>
<td>0.003</td>
<td>1.608 (1.061–2.436)</td>
<td>0.025</td>
</tr>
<tr>
<td>Lymph node metastasis Yes vs. no</td>
<td>1.908 (1.224–2.975)</td>
<td>0.004</td>
<td>1.682 (1.061–2.669)</td>
<td>0.027</td>
</tr>
<tr>
<td>Distant metastasis Yes vs no</td>
<td>1.700 (1.045–2.765)</td>
<td>0.033</td>
<td>1.008 (0.254–2.075)</td>
<td>0.257</td>
</tr>
<tr>
<td>Grouping Combination treatment vs bypass surgery</td>
<td>1.671 (0.754–1.978)</td>
<td>0.196</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee on Cancer; CI, confidence interval; RR, relative risk.

REFERENCES
