Pathological Complete Remission of Pancreatic Cancer Following Neoadjuvant Chemoradiation Therapy; Not the End of Battles

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Abstract: In spite of controversial issues, pancreatectomy following neoadjuvant chemoradiation therapy (NeoCRT) has been applied in treating advanced pancreatic cancer. Cases of pathological complete remission (pCR) following NeoCRT is rare, and its long-term follow-up data are still lacking.

From January 2000 to December 2012, medical records of the patients who underwent pancreatectomy for pancreatic ductal adenocarcinoma were retrospectively reviewed. Characteristics of the patients with pCR were summarized and their long-term follow-up data were analyzed.

Among 86 patients with pancreatic cancer who underwent radical pancreatectomy following NeoCRT, 10 patients (11.6%) were reported to pCR. Nine out of 10 patients received gemcitabine-based chemoradiation therapy. Median pre-NeoCRT serum CA 19-9 was 313.5 U/ml, and post-NeoCRT serum CA 19-9 was 9.9 U/ml, which was shown to be significant difference between 2 serum CA 19-9 level (P = 0.005). Pylorus-preserving pancreatectoduodenectomy was done in 8 patients, and the others received distal pancreatectomy. Postoperative chemotherapy was received in 6 patients. Disease-free survival was statistically superior in patients with pCR than patients without pCR (P < 0.05). However, 5 patients experienced cancer recurrence and no clinicopathologic variables including preoperative resectability could not predict the potential recurrence of tumor in patients with pCR (P > 0.05).

pCR is rarely reported following NeoCRT, but this condition is not telling the cure of the disease. Early recurrence in the pattern of liver metastasis and peritoneal seeding can be expected. However, long-term survival could be maintained in patients without recurrence. Further investigation is necessary for predicting failure of treatment.

(INTRODUCTION)

Pancreatic cancer is regarded as one of the lethal malignant diseases arising in gastrointestinal tract. Margin-negative resection is an essential step for cure of disease, but only 20% of the patients with pancreatic cancer can be treated by surgical resection. However, most patients who underwent pancreatectomy usually experience tumor recurrence, especially in liver, within 2 years after surgery, resulting in disease-specific survival, 15% to 20%. Therefore, surgery alone is not enough for cure of pancreatic cancer. Postoperative adjuvant chemotherapy should be applied for improving oncologic outcomes. Unfortunately, it is reported as many as 50% of the patients who underwent curative resection of pancreatic cancer cannot receive proper postoperative adjuvant chemotherapy due to delayed recovery and major surgical morbidity.

There are several rationales of neoadjuvant therapy (Neo-Tx) in pancreatic cancer. It can convert an initial unresectable pancreatic cancer to a resectable one. It can avoid unnecessary laparotomy if the pancreatic cancer progresses during preoperative treatment. It provides complete cancer treatment in case of surgical resection. The effect of preoperative anticancer treatment can be enhanced because tissues are well vascularized. Recent large volume series suggest that pancreatectomy following Neo-Tx is safe and effective in treating advanced pancreatic cancer.

Onologic role of pancreatectomy following Neo-Tx in treating pancreatic cancer is sum of following effects: patients selection, potential down-staging effect, and complete cancer treatment.

Pathologic complete remission (pCR) after Neo-Tx has been reported in treating other gastrointestinal cancer. In rectal cancer patients who have received Neo-Tx, approximately 15% of the patients are reported to be pCR, and patients with esophageal cancer who received Neo-Tx, up to 40% of them have been reported to have pCR in their surgical specimens. It was shown that pCR improved oncologic outcomes including lower incidence of local recurrence, distant metastasis, and better survival rate.

However, there are a few case reports on pCR following Neo-Tx in treating pancreatic cancer. According to literatures, about 1.3% to 7% of the patients with pancreatectomy following Neo-Tx are reported to be complete remission (pTO). The prognostic value of pCR in pancreatic cancer is not still clearly identified. In this study, we identified 9 patients with pCR among 86 patients who underwent pancreatectomy following...
Neo-Tx for pancreatic cancer. We investigated prognostic impact of pCR on oncologic outcome of the pancreatic cancer.

**MATERIALS AND METHODS**

**Patients and Data Collection**

This study was approved by the Institutional Review Board of Severance hospital. From January 2000 to December 2012, we retrospectively evaluated the patients who underwent surgical resection following neoadjuvant treatment for pancreatic cancer from our cohort database. Demographic and clinico-pathologic factors were acquired from database and the information for disease-free and disease-specific overall survival period were also included.

**Neoadjuvant Treatment for Pancreatic Cancer**

Neoadjuvant treatments were applied for borderline resectable pancreatic cancer in most cases. After the pathologic confirmation regarding pancreatic ductal adenocarcinoma using cytology via endoscopic retrograde cholangiography, patients received gemcitabine-based chemotherapy including or not additional radiotherapy of which total radiation dose was usually from 5040 to 6000 cGy. Pancreatectomy was performed after evaluation for treatment effect in radiologic evaluations.

**Statistics**

All statistical analyses were performed by using IBM® SPSS® Statistics version 20. Continuous variables were indicated as mean ± standard deviation or range and categorical variables as frequency and percentage. Student t test and Mann–Whitney U test were used for comparing continuous variables between pCR and non-pCR group and Chi-square and Fisher exact were used for comparing categorical data between 2 groups. Kaplan–Meier method was applied for survival analysis of disease-free and disease-specific overall survival period. $P$-value < 0.05 was considered as statistical significance.

**RESULTS**

**Patients Demographics of PCR Confirmed by Pancreatectomy Following Neo-CRT**

Among 86 patients who underwent pancreatectomy following Neo-CRT, 9 patients (10.4%) were reported to have no residual pancreatic cancer cells in final pathologic examination (Figure 1, Table 1). Six patients were female and 3 were male.

![Figure 1](image-url)
| Patients Number | Gender/Age | Tumor Location | R-Tumor Size (cm) | Resectability | Tumor Condition | Biopsy-Proven | NeoCRT | Radiologic Response | Surgery | Combined Resection | POAT | Recurrence Pattern | Follow-Up (months) | Current Status |
|-----------------|------------|----------------|------------------|---------------|----------------|---------------|--------|-------------------|---------|-------------------|------|-------------------|-----------------|---------------|
| 1               | M/55       | U              | 2                | BR            | r/o SMV invasion r/o liver mets, LN+ r/o CHA invasion | PDA FL, RT 5040cGy | SD     | PPPD              | No      | No                | No   | No                | 10              | Alive         |
| 2               | M/55       | H              | 2                | BR            | PDA GEM, RT 5842cGy | GEM + Tarceva | PR     | PPPD              | No      | GEM               | Liver | 15              | Alive, disease progress |
| 3               | F/74       | H              | 5.5              | LA            | r/o SMV invasion with mesenteric root invasion | PDA GEM, RT 4500cGy | SD     | PPPD              | SMV-PV segmental resection | GEM + Tarceva | Remnant pancreas body mass, paraaortic LN, ascites with peritoneal thickening | 13              | Death         |
| 4               | F/64       | B              | 2.6              | BR            | SMV-SV confluence and SA abutting | PDA GEM, RT 5842cGy | PR     | DPS SMV-PV segmental resection | GEM | No                | 33              | Alive         |
| 5               | F/64       | H              | 3                | BR            | SMV invasion, paraaortic LN mets | PDA GEM/DDP RT5588cGy | PR     | PPPD              | SMV segmental resection | FP | No                | 34              | Alive         |
| 6               | F/55       | H              | 2                | BR            | SMV invasion, paraaortic LN mets | PDA GEM RT 5040cGy | SD     | PPPD              | SMV wedge resection | GEM | No                | 50              | Alive         |
| 7               | F/69       | H              | 6.9              | LA            | major vascular invasion, liver mets, LN mets peritoneal seeding | PDA GEM/DDP | PR | PPPD              | No | No                | Peritoneal seeding | 14             | FU loss        |
| 8               | F/67       | U              | 3.5              | LA            | SMA invasion, SMV obliteration | PDA GEM RT 5994 | PR | SSPPD SMV-PV segmental resection | No | No                | No             | 63              | Alive         |
| 9               | M/57       | H              | 2.4              | R             | No | GEM RT 5040cGy | PPPD | No | GEM/DDP | Liver | 15               | Death         |

BR = borderline resectable; CHA = common hepatic artery; DDP = cisplatin; FL = 5-FU/leucovorin; FU = follow-up; GEM = gemcitabine; LA = locally advanced; LN = lymph node; NeoCRT = neoadjuvant chemoradiation therapy; PDA = pancreatic ductal adenocarcinoma; POAT = postoperative adjuvant treatment; PPPD = pylorus preserving pancreaticoduodenectomy; PR = partial response; PV = portal vein; R = resectable; RT = radiotherapy; SA = splenic artery; SD = stable disease; SMA = superior mesenteric artery; SMV = superior mesenteric vein; SSPPD = subtotal stomach-preserving pancreaticoduodenectomy; SV = splenic vein.
with median age, 64 (range, 55–74) years. Most patients (8 out of 9 patients) received gemcitabine-based chemotherapy or chemoradiation therapy. Initial CA 19-9 was noted to be 685.1 ± 1024.7, which was decreased to 20.1 ± 30.1 following neoadjuvant chemoradiation therapy (NeoCRT) \( (P = 0.008) \). Ten patients had pancreatic head cancer requiring pancreaticoduodenectomy. Five patients required combined venous vascular resection such as 4 segmental resections of SMV-SV-PV confluence and 1 wedge resection of SMV.

**Comparison of Clinicopathologic Factors Between pCR and Non-pCR**

In comparative analysis, there were no clinicopathologic differences between pCR and non-pCR group \( (P > 0.05) \), however, CA19-9 after Neo-CRT \( (P = 0.053) \), pT stage \( (P < 0.001) \), and pN stage \( (P = 0.024) \) were significantly different between 2 groups (Table 2). During follow-up period (median 21 months (range, 10–63)), 4 patients experienced tumor recurrence (2 in liver and 2 in peritoneum), and the rest 5 patients (5.8%, 5 out of 86) still have no evidence of tumor recurrence in pCR group. Most recurrence was found within 1 year after surgery. Among them, 4 patients have been in disease-free condition for more than approximately 3 years. There was no difference in disease-free survival (mean 37.1 months vs. 25.3 months, \( P = 0.269 \)) between 2 groups (Figure 2A). Disease-specific survival in pCR group was shown to be superior to that of non-pCR group with marginal significance (mean, 56.3 months vs. 41.9 months, \( P = 0.066 \)), Figure 2B.

**DISCUSSION**

The current results showed that even 4 patients with pCR showed systemic recurrence in liver and peritoneum within 1

| TABLE 2. Comparison of Clinicopathologic Factors Between pCR and Non-pCR |
|--------------------------|--------------------------|--------------------------|
| Variables                | pCR (n = 9)              | Non-pCR (n = 77)          | P-Value     |
| Age                      | 62.8 ± 8.2               | 60.4 ± 9.7               | 0.483       |
| Gender                   |                          |                          |             |
| Female                   | 6                        | 30                       |             |
| Male                     | 3                        | 47                       | 0.156       |
| Symptom                  |                          |                          |             |
| No                       | 2                        | 13                       |             |
| Yes                      | 7                        | 64                       |             |
| Tumor size               | cm                       |                          |             |
| 3.1 ± 1.6                | 2.9 ± 0.9                | 0.412                    |
| CA19-9                   |                          |                          |             |
| Before Neo-Tx            | 685.1 ± 1024.1           | 1132.4 ± 2334.3          | 0.573       |
| After Neo-Tx             | 20.1 ± 30.1              | 206.9 ± 767.4            | 0.052       |
| Resectability            |                          |                          |             |
| Resectable               | 2                        | 35                       |             |
| Borderline resectable    | 5                        | 28                       |             |
| Locally advanced         | 2                        | 14                       | 0.385       |
| Tumor location           |                          |                          |             |
| Head                     | 7                        | 60                       |             |
| Body                     | 1                        | 10                       |             |
| Tail                     | 1                        | 5                        |             |
| Body-Tail                | 0                        | 2                        | 0.696       |
| Operation                |                          |                          |             |
| PD                       | 0                        | 8                        |             |
| PPPD                     | 7                        | 51                       |             |
| DPS                      | 2                        | 17                       |             |
| TP                       | 0                        | 1                        | 0.88        |
| Combined VVR             |                          |                          |             |
| No                       | 5                        | 52                       |             |
| Yes                      | 4                        | 25                       | 0.478       |
| pT stage                 |                          |                          |             |
| T0                       | 10                       | 0                        |             |
| T1                       | 0                        | 11                       |             |
| T2                       | 0                        | 5                        |             |
| T3                       | 0                        | 60                       |             |
| T4                       | 1                        | <0.001                   |             |
| pN stage                 |                          |                          |             |
| N0                       | 9                        | 47                       |             |
| N1                       | 0                        | 30                       | 0.024       |
| EBL                      | 705.5 ± 834.7            | 1023.2 ± 835.0           | 0.286       |
| Transfusion              |                          |                          |             |
| No                       | 7                        | 39                       |             |
| Yes                      | 2                        | 37                       | 0.17        |
| POAT                     |                          |                          |             |
| No                       | 3                        | 26                       |             |
| Yes                      | 6                        | 50                       | 0.714       |
| Morbidity                |                          |                          |             |
| No                       | 3                        | 42                       |             |
| Yes                      | 6                        | 35                       | 0.299       |
| Mortality                |                          |                          |             |
| No                       | 9                        | 76                       |             |
| Yes                      | 0                        | 1                        | 1           |

DPS = distal pancreatectomy with splenectomy; EBL = estimated blood loss; PD = pancreaticoduodenectomy; POAT = postoperative adjuvant treatment; PPPD = pylorus preserving pancreaticoduodenectomy; TP = total pancreatectomy; pCR = pathological complete remission; VVR = venous vascular resection.
It is extremely difficult to determine the viability of residual carcinoma cells and systemic nature of disease in pCR group, this observation is strongly suggesting pCR, it is real in clinical setting of Neo-Tx for pancreatic cancer. Zhao et al. recently reported that 100% of disease-specific overall survival in patients with pCR (n = 10), which showing a significant better than those of posttreatment stage I or stage IIA disease in resected pancreatic cancer following Neo-Tx (P < 0.001). Their reported incidence of pCR is 2.5% indirectly shows strict and meticulous evaluation of pathologic examination of resected specimen.

Retrospective study design and small number of patients with pCR are inevitable limitations in our study. And, study period was relatively long and a number of pathologists were involved in pathologic examination for pancreatectomy specimen. Nevertheless, this study can be valuable evidence for evaluating clinical meaning of pCR following neoadjuvant treatment in pancreatic cancer in limited clinical references.
In conclusion, pCR can be achieved from neoadjuvant treatment in pancreatic cancer. Postoperative adjuvant treatment, however, may be required even in pCR because pCR can be contaminated with potential residual cancer cells and pancreatic cancer is systemic disease which can have metastatic foci in early phase. Further investigation for predicting failure of neoadjuvant treatment is mandatory.

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