En bloc distal pancreatectomy with transverse mesocolon resection strategy using the mesenteric approach for advanced pancreatic body and tail cancer

Running title: DP using mesenteric approach

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Abstract

Background

Pancreatic body and tail cancer easily invades the retroperitoneal tissue, including the transverse mesocolon. It is difficult to ensure a dissected peripancreatic margin using standard distal pancreatectomy for advanced pancreatic body and tail cancer.

Thus, we developed a novel surgical procedure to ensure dissection of the peripancreatic margin. This involved performing dissection deeper than the fusion fascia of Toldt and further extensive en bloc resection of the root of the transverse mesocolon. We performed distal pancreatectomy with transverse mesocolon resection (DP-TCR) using the mesenteric approach and achieved good outcomes.

Methods

There are two main considerations regarding the surgical procedure using the mesenteric approach: 1) dissection deeper than the fusion fascia of Toldt (securing the vertical margin) and 2) modular resection of the pancreatic body and tail, with the root of the transverse mesocolon and adjacent organs in a horizontal direction (ensuring the caudal margin).

Results
From 2017 to 2019, we performed DP-TCR using the mesenteric approach for six patients with advanced pancreatic body and tail cancer. Histopathological radical surgery was possible in all patients who underwent DP-TCR. No perioperative complications of grade IIIa or above in the Clavien–Dindo classification were observed in any patients.

Conclusions

We believe that DP-TCR is useful as a radical surgery for advanced pancreatic body and tail cancer with extrapancreatic invasions.

Key words: distal pancreatectomy, mesenteric approach, pancreatic body and tail cancer
Introduction

Pancreatic body and tail cancer easily invades the retroperitoneal tissue, including the transverse mesocolon, and is a major factor that hinders the curability of surgery.\textsuperscript{1-5} In standard distal pancreatectomy (anterior approach)\textsuperscript{6-9} for cancer invasion deeper than the fusion fascia of Toldt (generic term, including Gerota fascia) and for cancer invasion progressing toward the root of the transverse mesocolon, the principal problem is difficulty in ensuring that the dissected peripancreatic margin (DPM) and posterior peripancreatic margin (PPM)\textsuperscript{10,11} is cancer negative. In addition, it is difficult to perform en bloc resection of micro-lymph node metastasis and local dissemination. Therefore, we developed a novel surgical procedure to ensure dissection of the peripancreatic margin; to this end, we used the mesenteric approach performed in isolated pancreatoduodenectomy for advanced pancreatic head cancer that was proposed by Nakao.\textsuperscript{12-14} This involved performing dissection and cleaning deeper than the fusion fascia of Toldt and performing further extensive en bloc resection of the root of the transverse mesocolon.

Furthermore, we performed distal pancreatectomy with transverse mesocolon resection (DP-TCR) using the mesenteric approach and achieved good outcomes.

Patients and Methods

The present procedure is indicated for advanced pancreatic body and tail cancer that invades
the retroperitoneal tissue, including the transverse mesocolon, and without distal metastasis, other than controlled peritoneal dissemination within the omental bursa [stage I–IV (only presence of dissemination in the omental bursa)]\textsuperscript{10,15} (Fig. 1a, b). Furthermore, with regard to invasion into the superior mesenteric artery (SMA), surgery is indicated for patients in whom resection is deemed possible by dissection of the SMA nerve plexus. Depending on the patient, concurrent distal pancreatectomy with celiac axis resection is also possible.\textsuperscript{4,16,17} Moreover, while efforts are made to preserve the marginal vessel of the transverse colon and maintain blood flow of the transverse colon (Fig. 2), if blood flow in the transverse colon is poor after completing excision, concurrent resection of the transverse colon can be performed without hesitation. We decided to apply DP-TCR preoperatively, not during the surgery, when we diagnosed that cancer cells invaded to extra-pancreatic tissues in computed tomography. By contrast, we applied standard DP preoperatively or during surgery, when we diagnosed that cancer cells remained within pancreatic parenchyma.

There are two main considerations with regards to the surgical procedure. First, for extrapancreatic cancer invasion, the procedure aims to secure 1) the vertical margin and 2) the horizontal margin. Dissection by the mesenteric approach is appropriate to secure both margins.

1) Dissection deeper than the fusion fascia of Toldt using the mesenteric approach (securing the
vertical margin)

After elevating the transverse colon to the cranial side, dissection is initiated from the root of the transverse mesocolon. Using the mesenteric approach, dissect the root of the transverse colon (Fig. 3a) and then perform circumferential dissection of the superior mesenteric vein (SMV) and SMA on the ventral side of the horizontal portion of the duodenum. Proceed to dissect toward the root of the SMA and ligate and section the middle colic artery (MCA) to reach the celiac nerve plexus. The goal of dissection around the root of the MCA is not essentially lymph node dissection but to ensure the surgical margin for advanced pancreatic body and tail cancer.

Subsequently, proceed to dissect toward the left crus of the diaphragm from the left celiac nerve plexus as much as possible. Simultaneously, resect the ligament of Treitz that continues on the left side of the SMA nerve plexus from the abdominal aorta toward the celiac nerve plexus from the origin of the jejunum. The nerves, lymph nodes, and adipose tissue around the SMA dorsal to the fusion fascia of Toldt and surrounded by the ventral side of the SMA and ventral side of the ligament of Treitz are dissected, cleaned, and attached to the fusion fascia of Toldt (resected side) (Fig. 3b). Furthermore, the anterior surface of the abdominal aorta is dissected dorsal to the ligament of Treitz, and the nerves, lymph nodes, and adipose tissue surrounding the dorsal side of the ligament of Treitz and the ventral side of the abdominal aorta are cleaned. During surgery, proceed with circumferential dissection of the left renal vein, ligation and dissection of the left
adrenal vein, and dissection of the left adrenal gland. Thereafter, lift the left adrenal gland dorsally, enabling combined resection without dividing the ventral surface of the left adrenal gland and the fusion fascia of Toldt (Fig. 3c). This manipulation is an extremely important technique to ensure the most dorsal vertical margin.

2) Modular resection of the pancreatic body and tail with adjacent organs in a horizontal direction using the mesenteric approach (ensuring the caudal margin)

Considering extrapancreatic cancer invasion of the pancreatic body and tail in a horizontal direction, examination can be divided into the coronal direction and cephalocaudal direction (from head to tail). With regard to the coronal direction, the left side extends to the spleen and poses no clinical problem, while on the right side, there is no resection limit unless considering total pancreatectomy. However, if total pancreatectomy is to be avoided, the point up to the line connecting the gastroduodenal artery and intrapancreatic bile duct can be considered. With regards to the cephalocaudal direction (from head to tail), the common hepatic artery, celiac axis, and splenic artery (SA) form a protective wall on the cranial side. However, the caudal direction poses a problem. Cancer that has invaded dorsally outside the pancreas continues to invade the retroperitoneal tissue, where there are no large protective organs up to the transverse colon. To ensure a cancer-negative margin in such circumstances, en bloc resection of the root of the transverse mesocolon on the left side of the SMV, together with the body and tail of the pancreas
as the module, is the only suitable method.

In the anterior lobe of the transverse mesocolon, retroperitoneal tissue, and posterior lobe of the transverse mesocolon (in the bare area), en bloc dissection is completed by the layer reaching the ventral side of the left renal vein via the ventral side of the ligament of Treitz from the tissue on the ventral side of the SMA nerve plexus. In this situation, it is important that the dissected tissue be dissected en bloc with the body and tail of the pancreas as the module.

In the layer where the prepancreatic head-duodenal fascia is resected with the third portion of the duodenum as the starting point, the omental bursa is released from the cranial side of the pancreas. Skeletonization of the SMV and portal vein (PV) is performed, and with regard to branches flowing in from the left side of the main trunk of the SMV, only the inferior mesenteric vein and inferior pancreatoduodenal vein are preserved based on preoperative computed tomography. The splenic vein is ligated and dissected; however, the left of the inferior border of the pancreas and transverse mesocolon (all layers) are not separated (Fig. 4a). The area from the common hepatic artery to the SA should be cleaned as much as possible so as to determine the cranial margin of the resected specimen. The SA is then ligated and dissected, and upon cutting the pancreas at the anterior surface of the PV, the fusion fascia of Toldt remains, while the ventral and dorsal sides are completely dissected (Fig. 4b). Upon dissecting the fusion fascia of Toldt at the left margin of the PV, the anterior surface of the SMA nerve plexus, which has been dissected
to ensure the vertical margin, is exposed. As a result, the pancreas forming the right margin of the
resected specimen, the anterior lobe of the transverse mesocolon, the retroperitoneal tissue more
superficial than the fusion fascia of Toldt, the fusion fascia of Toldt, and the retroperitoneal tissue
deeper than the fusion fascia of Toldt are all resected en bloc (Fig. 4c).

The subsequent procedures proceed as per radical antegrade modular pancreatosplenectomy
(RAMPS), wherein dissection proceeds toward the left subphrenic space on the dorsal side
along the crus of the diaphragm.

Dissection on the left side of the origin of the jejunum was performed after elevating the
transverse colon to cranial side. To allow effective visualization of the surgical site of the
retroperitoneum, the inferior mesenteric vein was ligated and excised early. (Fig. 4d, 4e). The
pancreatic tail was excised together with a part of the left perirenal fat. If the transverse colon can
be preserved, we should pay careful attention not to injure the arc of Riolan.

Finally, en bloc resection is performed with the specimen as the module (Fig. 5).

From 2017 to 2019, we performed DP-TCR using the mesenteric approach for six patients with
advanced pancreatic body and tail cancer who satisfied the surgical indications. The staging of
pancreatic cancer was determined using the 8th Union for International Cancer Control (UICC)
TNM classification. Furthermore, to evaluate the cancer stump of the resected specimen and
implement radical surgery, we used the criteria described in the Classification of Pancreatic

We recommend neoadjuvant chemotherapy or chemoradiotherapy for patients who were diagnosed as T4 classification preoperatively.

This protocol was approved by the Ethics Committees of Nippon Medical School Musashikosugi Hospital (No. 5283157).

The distribution of two groups was compared using the Mann-Whitney U test and the \( \chi^2 \)-test. Significance was defined as \( p < 0.05 \). JMP version 9.0.0 (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis.

Results

The details of DP-TCR using the mesenteric approach included DP-TCR alone in three patients, transverse colon resection and DP-TCR in one patient, and DP-TCR and celiac axis resection (DP-TCR-CAR) in two patients (Table1). With regards to preoperative treatment, neoadjuvant chemoradiotherapy was administered to one patient who underwent DP-TCR-CAR (gemcitabine + 50 Gy) and was not administered to four patients. Furthermore, in the patient who underwent concurrent transverse colon resection, invasion in the retroperitoneal tissue and transverse colon with several disseminations in the omental bursa were observed at the initial examination.
Therefore, as an unresectable pancreatic cancer, six cycles of chemotherapy using gemcitabine + S1 were administered, after which partial response (Response Evaluation Criteria In Solid Tumor; RECIST) persisted, and conversion surgery was indicated (Fig. 6).

The median operative duration was 258.5 (229–360) min, and the median blood loss was 495 (150–1,110) mL for six patients who underwent DP-TCR. The median operative duration of the six patients who received standard DP (seventeen patients) over the same period was 195.0 (165–235) min. The median amount of blood loss was 357 (125–1,280) mL. Both the operative duration and amount of blood loss were significantly greater with DP-TCR (the Mann-Whitney U test: \( p < 0.05 \)).

An image of the entire resected specimen of Case 3 is presented in Fig. 7a. En bloc resection was performed from the main lesion margin to a distant site, including the transverse colon as the module. Observation of the sectioned surface on the cephalocaudal plane revealed that the cancer with extrapancreatic invasion had invaded the retroperitoneum at the root of the transverse mesocolon in a vertical and horizontal direction. Furthermore, direct invasion into the transverse colon was also suspected (Fig. 7b). On the sectioned surface A, the tumor center, extrapancreatic invasion of cancer cells, with tissue of mucinous adenocarcinoma extending to the fusion fascia of Toldt to the adipose tissue, was observed. The fusion fascia of Toldt was entangled midway and torn, making it difficult to observe (Fig. 7c). Furthermore, the tumor was enlarged and
compressed but did not penetrate the fusion fascia of Toldt (Fig. 7d). It is important to note that retroperitoneal tissue with sufficient thickness to provide a vertical and horizontal margin was observed (Fig. 7c, 7d); this is the result of using the mesenteric approach. On the basis of histopathological examination, for cancer with extrapancreatic invasion, it was confirmed that en bloc resection by DP-TCR contributes to ensuring DPM and PPM. Furthermore, in Case 3, there were multiple controlled local disseminations within the omental bursa; however, all were resected using DP-TCR with concurrent resection of the transverse colon. Moreover, pathology results revealed that there were no viable cancer cells in any of the disseminated lesions in the omental bursa. The staging was stage IB in one patient, stage IIB in three patients, and stage III in two patients (UICC classification). In all patients who underwent DP-TCR, histopathological radical operation (R0 surgery), including both DPM\textsuperscript{10} and PPM\textsuperscript{11}, was possible. In this retrospective study, the histopathological radicality of distal pancreatectomy without DP-TCR for fifteen patients who were diagnosed as the same stage as DP-TCR patients was 73% ($\chi^2$-test: $p < 0.05$).

No perioperative complications of grade IIIa or above in the Clavien–Dindo classification were observed in any patient. Furthermore, there was no significant difference in the rate of complications of postoperative pancreatic fistula compared to standard distal pancreatectomy. All patients completed adjuvant chemotherapy with S1, and the median postoperative observation
period was 610 days. With regard to the prognosis, hepatic recurrence was confirmed on postoperative day 595 in one patient who underwent DP-TCR-CAR; however, chemotherapy was refused, and the patient died on postoperative day 697. Furthermore, the patient who underwent conversion surgery developed intrapelvic peritoneal recurrence on postoperative day 470 and continues to receive chemotherapy with gemcitabine + nab-paclitaxel. The other four patients are alive and recurrence-free.

Discussion

The pancreatic body and tail has particular anatomical characteristics in that at 35–50 days after fertilization, the midgut rotates 270 degrees counter-clockwise, and the dorsal side of the pancreas changes into the ventral side. Therefore, there is no membrane forming a boundary between the pancreatic body and tail with the transverse mesocolon. As a result, when pancreatic body and tail cancer invades outside of the pancreas, it can easily invade the transverse mesocolon (Fig. 1a). Furthermore, the fusion fascia of Toldt is located at the dorsal side of the pancreatic body and tail in continuity with the anterior surface of the kidneys; even if the pancreatic body and tail spreads dorsally from the pancreas, the SMA, abdominal aorta, left renal vein, left adrenal gland, and other retroperitoneal tissue serve as a protective wall against invasion (Fig. 1b). Therefore, in patients with cancer confined to the pancreas, a cancer-negative margin in the dissected
peripancreatic margin (DPM0, PPM-) can be ensured if standard distal pancreatectomy is performed. However, when extrapancreatic invasion of cancer cells is present, the fusion fascia of Toldt, which serves as a protective wall, is penetrated, and invasion spreads further dorsally, resulting in DPM1 and PPM+, despite standard distal pancreatectomy, thereby making histologically radical surgery impossible. Strasberg et al. reported a procedure to achieve further thorough dissection of the retroperitoneum in such situations. The procedure involves antegrade en bloc resection of the retroperitoneal tissue extending from the pancreatic body toward the pancreatic tail and spleen, including the fusion fascia of Toldt, left adrenal gland, lymph nodes, adipose tissue, and nerve tissue dorsal to the pancreatic body and tail. The procedure was named “RAMPS,” and at present, it is performed extensively worldwide as the primary procedure for advanced cancer of the pancreatic body and tail.

RAMPS and our proposed DP-TCR procedure aim to achieve histologically radical surgery. Both procedures have the same philosophy in that they attempt to resect the retroperitoneum en bloc with the pancreatic body and tail and the spleen. However, our procedure differs greatly from that of RAMPS in that the retroperitoneum deeper than the fusion fascia of Toldt is dissected first, and the transverse mesocolon to the left of the PV is resected en bloc, with the pancreatic body and tail as the module (ensuring the caudal margin).

The advantage of first dissecting the retroperitoneum deeper than the fusion fascia of Toldt is that
the dorsal margin can be more accurately ensured by dissecting the dorsal infiltrative margin of the cancer tension-free. Furthermore, at the start of surgery, if the presence of cancer can be confirmed in the dissection stump in the deepest part of the retroperitoneum, unnecessary non-radical surgery can be avoided.

The advantage of concurrent resection of the transverse mesocolon is that for cancer invasion spreading laterally from the pancreatic body and tail (particularly in a cephalocaudal direction from the head to tail), i.e., cancer invasion into the retroperitoneal tissue in the root of the transverse mesocolon, DPM0 and PPM- can be ensured. For cancer of the pancreatic body, en bloc resection of the transverse mesocolon can be achieved by applying the mesenteric approach used in isolated pancretoduodenectomy for advanced cancer of the pancreatic head.\textsuperscript{12-14} The greatest advantage of the mesenteric approach is that the retroperitoneum dorsal to the fusion fascia of Toldt can be directly approached and that the transverse mesocolon can be resected en bloc in a systematic manner.\textsuperscript{13, 14, 27, 28} Incidentally, in the report by Strasberg et al., there is no mention of a specific procedure performed for cancer invading toward the root of the transverse mesocolon.

None of the patients who underwent DP-TCR underwent transverse colon resection due to poor blood flow to the transverse colon after extraction of the specimen. To avoid poor blood flow to the transverse colon, the marginal vessels should be accurately secured intraoperatively, and the
blood flow should be verified while performing experimental clamping of the proximal colic artery using bulldog forceps prior to commencing resection (Fig. 2). With regard to the fact that the operative duration and amount of intraoperative blood loss were significantly greater in DP-TCR compared with that in standard distal pancreatectomy, we believe that this is a natural result given the significant difference in the degree of localized cancer progression (T factor) between the two groups.

The fact that all patients were DPM0 and PPM- demonstrated excellent local control by DP-TCR (Table 1). The proactive combined use of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy\textsuperscript{29-33} should be addressed in the future. We believe that prognosis can be improved further by completing neoadjuvant chemotherapy and chemoradiotherapy, radical surgery, and adjuvant chemotherapy\textsuperscript{34, 35}.

Our study has several limitations associated with the errors and biases inherent to a small study, and future trials with larger numbers are recommended to further evaluate the effectiveness of DP-TCR in pancreatic body and tail cancer patients.

Conclusion

We believe that DP-TCR is useful as a radical surgery for advanced pancreatic body and tail
cancer with extrapancreatic invasions.

Conflict of interest

The authors declare that they have no conflict of interest.

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Figure legends

Figure 1

a: Cephalocaudal section of the upper abdomen. The root of the transverse mesocolon transitions into the retroperitoneal tissue without serous membrane. The fusion fascia of Toldt is located in the retroperitoneal tissue. For extrapancreatic cancer invasion, the fusion fascia of Toldt serves, to a certain extent, as a barrier on the dorsal side of the pancreas.

b: In distal pancreatectomy with transverse mesocolon resection, the region resected en bloc is shown in color as a module.

Figure 2

In the mesenteric approach, the middle colic artery and accessory right colic arteries are clamped using bulldog forceps to test the colonic blood flow. Arrow head: marginal vessel of the transverse colon

Figure 3

a: The serosa of the transverse mesocolon is sectioned from the third portion of the duodenum to the terminus of the ligament of Treitz (origin of the jejunum), thereby commencing the mesenteric approach
**Ligament of Treitz**

b: The dorsal side of the fusion fascia of Toldt is directly accessed using the mesenteric approach.

c: After sectioning the left adrenal vein, the anterior to the abdominal aorta and dorsal to the left adrenal gland were dissected.

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**Figure 4**

a: Skeletonization of the superior mesenteric vein was performed; however, the caudal side of the pancreatic body and tail on the left side of the superior mesenteric vein was not separated from the transverse mesocolon.

b: After dissecting the pancreatic neck, the remaining fusion fascia of Toldt was sectioned at the left side of the portal vein.

c: Upon sectioning the fusion fascia of Toldt, the anterior surface of the superior mesenteric artery was exposed. The pancreatic body, root of the transverse mesocolon, and retroperitoneal tissue of the right margin of the resected stump (dotted line area).

d: The root of the transverse mesocolon on the left side of the SMV was cut extensively (arrow head).

e: The left perirenal fat was exposed, and the pancreas body and tail covered by the fusion fascia.
of Toldt was mobilized to the cranial side (arrow head).

Figure 5

Completion of resection. En bloc resection of the resected organs, including the transverse mesocolon, was completed precisely.

Figure 6

CT image of Case 3 prior to the start of neoadjuvant chemotherapy. Extrapancreatic invasion of the main tumor is present, as is invasion into the fusion fascia of Toldt and deeper. The transverse mesocolon and transverse colon are suspected (arrow head). Furthermore, several disseminations within the omental bursa can be seen (arrow).

Figure 7

a: Overall image of the resected specimen of Case 3. En bloc resection was performed up to a site away from the main lesion as the module.

b: Macro image of the sectioned surface of the main lesion. The tumor invades outside of the pancreas, and marked shortening of the transverse mesocolon can be observed (dotted line region).

*Transverse colon.
c: On the sectioned surface A, the tumor invades into the adipose tissue on the caudal side of the fusion fascia of Toldt. Arrow head: fusion fascia of Toldt, arrow: Toldt fascia rupture (Elastica Masson-Goldner stain).

d: On the sectioned surface A, the fusion fascia of Toldt extends from the dorsal side of the splenic artery (cranial side) toward the transverse colon and serves as a protective wall against the cancer. Arrow head: fusion fascia of Toldt (Elastica Masson-Goldner stain).

Abbreviations

Fig. 1a
Fig. 3a

- T/mesocolon
- SMA

*
Fig. 3b

- T/mesocolon
- pancreas head
- SMV
- SMA
- *
Fig. 3c
Fig. 4a

- Stomach
- T/mesocolon
- Pancreas head
- MCV
- SMV
Fig. 4b

distal pancreatic stump

Toldt fusion fascia

SMV  SMA  T/mesocolon
Fig. 4c

- distal pancreatic stump
- CHA
- SV
- SMA
- SMV
- T/mesocolon

[Image of surgical anatomy]
Fig. 4d
Fig. 4e
Fig. 5

- stomach
- stump of SA
- Lt. diaphragm
- CHA
- Lt. perirenal fat
- Lt. renal vein
- proximal pancreatic stump
- SMV
- SMA
Fig. 6
Fig. 7a

- **stump of pancreas**
- **local dissemination**
- **main tumor**
- **Transverse colon**
Fig. 7b

Lt. adrenal grand
Fig. 7c

- tumor
- colic artery

The caudal margin (T/mesocolon)
Fig. 7d

← cranial side
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Abbreviations: OP; operation, BL; blood loss, NAC; neo-adjuvant chemotherapy, RFS; recurrence free survival, OS; over all survival