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Title:

**Multidisciplinary Surgical Management with Chemotherapy and Transcatheter Arterial
Embolization for a Giant Hypervascular Pancreatic Neuroendocrine Tumor**

*Running title: Multidisciplinary Strategy for Giant pNET

Authors:

Kokoro Niwa, MD,* Shintaro Takeuchi, MD, PhD,*† Takahiro Tsuchikawa, MD, PhD,*† Toru Nakamura,
MD, PhD,* Satoshi Takeuchi, MD, PhD,†‡ Ryo Morita, MD, PhD,§ Daisuke Abo, MD, PhD,§ Kenji
Hirata, MD, PhD,†§ Tomoko Mitsuhashi, MD, PhD,|| and Satoshi Hirano, MD, PhD*

Affiliation:

*Department of Gastroenterological Surgery II, Division of Surgery, Faculty of Medicine, Hokkaido
University, Sapporo, Japan

†Center of Neuroendocrine Tumor, Hokkaido University Hospital, Sapporo, Japan

‡Department of Medical Oncology, Faculty of Medicine, Hokkaido University, Sapporo, Japan

§Department of Diagnostic Imaging, Faculty of Medicine, Hokkaido University, Sapporo, Japan

||Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan

Corresponding author:

Shintaro Takeuchi, MD, PhD

Department of Gastroenterological Surgery II, Division of Surgery, Faculty of Medicine, Hokkaido

University, West-7, North-15, Kita-ku, Sapporo 060-8638, Hokkaido, Japan

Phone: +81-11-706-7714

Fax: +81-11-706-7158

E-mail: takeuchishintaro979@med.hokudai.ac.jp

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Abstract

Pancreatic neuroendocrine tumors (pNETs) are rare and heterogeneous neoplasms occasionally presenting as giant, hypervascular, and anatomically complex tumors. In such cases, curative resection is often challenging, and multidisciplinary treatment is required. However, the clinical utility and optimal sequencing for these approaches remain unclear. We report a 39-year-old woman with a 130 mm hypervascular pNET occupying nearly the entire pancreas, complicated by portal vein tumor thrombus (PVTT) and extensive collateral circulation. The tumor was initially deemed unresectable by a multidisciplinary team. Streptozotocin (STZ)-based chemotherapy led to tumor regression and PVTT resolution. Preoperative transcatheter arterial embolization (TAE) was subsequently performed to reduce arterial inflow and facilitate surgical manipulation. Total pancreatectomy with segmental portal vein resection was successfully performed without transfusions. Histopathological examination confirmed a grade 2 pNET with a multifocal histological response which was consistent with radiological findings. The patient remained recurrence-free for 12 months postoperatively without adjuvant therapy. This case highlights the clinical utility of integrating STZ-based chemotherapy and selective TAE to achieve curative surgery for locally advanced giant pNETs. The unique clinical course and radiologic-pathologic correlation of this rare disease further contribute to the understanding of the treatment response.

Key Words: Pancreatic neuroendocrine tumor, locally advanced, conversion surgery, transcatheter arterial embolization, multidisciplinary treatment

Abbreviations: Pancreatic neuroendocrine tumors (pNETs), Streptozotocin (STZ), Transcatheter arterial embolization (TAE), Peptide receptor radionuclide therapy (PRRT), Computed tomography (CT), Portal vein tumor thrombus (PVT), 5-fluorouracil (5-FU), Parathyroid hormone-related peptide (PTHrP), Right gastric artery (RGA), Right gastroepiploic artery (RGEA), Posterior superior pancreaticoduodenal artery (PSPDA), Anterior superior pancreaticoduodenal artery (ASPDA), Left gastric artery (LGA), Left gastroepiploic artery (LGEA), Superior mesenteric artery (SMA)

Foot note: Not applicable

Introduction

Pancreatic neuroendocrine tumors (pNETs) are rare heterogeneous neoplasms with a wide spectrum of clinical presentations [1]. In some cases, their hypervascular nature can lead to the development of locally advanced giant tumors [2]. Although locoregional therapy remains a cornerstone for pNETs treatment, even in patients with metastatic disease [3], surgical resection of giant tumors is often technically challenging due to invasion of major vessels and extensive collateral circulation.

Unlike pancreatic ductal adenocarcinoma, the role of chemotherapy in localized pNETs remains undefined [4]. However, cytoreductive therapy may offer clinical benefits by reducing tumor volume and anatomical involvement, potentially facilitating curative pancreatectomy [5,6]. Systemic cytotoxic chemotherapy is commonly administered for symptom palliation and disease control in metastatic pNETs

[7]. Furthermore, previous studies have suggested the potential utility of cytotoxic chemotherapy in neoadjuvant settings for localized disease [8,9].

Herein, we describe a rare case of a giant hypervascular pNET that was successfully managed with streptozotocin (STZ)-based chemotherapy, followed by complete surgical resection.

Preoperative transcatheter arterial embolization (TAE) was also performed to reduce the tumor inflow and intraoperative bleeding risk. This case highlights the potential value of a multidisciplinary treatment strategy for achieving curative resection in initially unresectable cases. In the current era, when multiple induction strategies, such as cytotoxic chemotherapy, molecular targeted agents, and peptide receptor radionuclide therapy (PRRT) are available, they provide valuable insights into the management of locally advanced pNETs.

Case report

A 39-year-old woman presented to a local clinic with epigastric pain, and abdominal imaging studies revealed a large pancreatic mass. She had no remarkable past medical history and no significant family history, including neuroendocrine tumors. The patient was then referred to our institution for further evaluation and management. Contrast-enhanced computed tomography (CT) revealed a giant hypervascular mass measuring 130 mm in diameter involving the entire pancreas, except for part of the pancreatic head, along with a 30 mm segment of near-complete circumferential portal vein stenosis (Fig. 1A, B). Splenic vein occlusion resulted in prominent collateral circulation along the left retroperitoneum,

gastric veins, and colonic veins, as well as splenomegaly (Fig. 1C). The giant tumor enveloped major arteries and developed into venous collaterals (Fig. 1D). Abdominal ultrasonography revealed a portal vein tumor thrombus (PVTT) at the confluence of the splenic vein (Fig. 2A). Endoscopic ultrasound-guided fine-needle aspiration confirmed grade 2 neuroendocrine tumor [10]. Immunohistochemistry was positive for synaptophysin and chromogranin A, and the Ki-67 labeling index was 3.7% in hotspot areas. Somatostatin receptor scintigraphy using ^{111}In -pentetreotide (Octreoscan®) demonstrated diffuse uptake of the tumor, and ^{18}F -fluorodeoxyglucose positron emission tomography revealed a maximum standardized uptake value of 17.6 (Fig. 1E). Neither modality demonstrated definitive evidence of lymph node or distant metastasis.

The treatment plan for this patient was discussed in a multidisciplinary team meeting for neuroendocrine tumors. Our team concluded that the tumor was initially unresectable due to its anatomical complexity and oncological aggressiveness, as indicated by the PVTT. Tumor downsizing was considered essential to secure a sufficient surgical field for safe dissection around major vessels. As an initial treatment, the patient received four cycles of systemic chemotherapy with STZ and 5-fluorouracil (5-FU) every six weeks (STZ 500 mg/m² and 5-FU 400 mg/m², days 1–5). After the chemotherapy, the tumor size was reduced to 100 mm, which was classified as stable disease according to the Response Evaluation Criteria in Solid Tumors criteria [11] (Fig. 2C, D). Additionally, the previously noted PVTT showed a marked regression (Fig. 2B). On contrast-enhanced CT, the solid components at the center of

the tumor exhibited a marked low-density region (Fig. 2D), suggesting partial intratumoral degeneration. Although portal vein stenosis persisted, no distant metastases were identified on follow-up imaging. At diagnosis, the patient presented with mild hypercalcemia (serum calcium: 10.5 mEq/L) and elevated parathyroid hormone-related peptide (PTHrP: 4.4 pmol/L) levels, which normalized after the administration of zoledronic acid during chemotherapy. Given the tumor shrinkage and absence of distant disease, conversion surgery was planned.

Preoperative TAE was planned to reduce arterial inflow to the hypervascular tumor because an intraoperative artery-first approach was considered technically unfeasible owing to the limited working space, even after tumor shrinkage. Selective TAE was performed 1 day before surgery by an interventional radiology team under angiographic guidance. Arterial supplies to the tumor were the right gastric artery (RGA), right gastroepiploic artery (RGEA), posterior superior pancreaticoduodenal artery (PSPDA), anterior superior pancreaticoduodenal artery (ASPDA), and left gastric artery (LGA) (Fig. 3A). Selective coil embolization was performed to occlude the RGA, RGEA, PSPDA, and ASPDA while preserving proximal flow in the hepatic artery (Fig. 3B). Additionally, the peripheral branches of the RGA and left gastroepiploic artery (LGEA) were embolized with coils while preserving the main trunk of the LGA (Fig. 3B). Given that the arterial supply from the superior mesenteric artery (SMA) system was limited, no embolization was performed in that territory (Fig. 3C). As prophylaxis against ischemia-related symptoms and systemic inflammation, corticosteroids (hydrocortisone 100 mg every 8 hours from

the day of TAE through the following day and then tapered) and analgesics (fentanyl) were administered.

The patient remained afebrile and hemodynamically stable, with no evidence of pancreatitis or systemic inflammatory response. We performed total pancreatectomy with segmental portal vein resection (Fig. 3D, E). Intraoperatively, the tumor appeared softened, the collateral veins collapsed, possibly due to preoperative embolization, and inflammatory changes attributable to the embolization were minimal.

Dissection was initiated from anatomically accessible areas, regardless of the standard vascular control sequence. The tumor was successfully mobilized without significant bleeding from collateral vessels.

Segmental portal vein resection with primary end-to-end anastomosis was performed at the site previously occupied by a tumor thrombus. Operation time was 732 min, with an estimated blood loss of 1,440 mL, mainly due to oozing rather than major hemorrhage. No blood transfusions were required.

Pathological examination of the resected specimen revealed a 107 × 85 × 41 mm white solid tumor centered in the pancreatic body and tail (Fig. 4A). The central portion of the tumor appeared whitish and degenerated on cut specimens (Fig. 4B), corresponding to the preoperative CT findings. The tumor cells exhibited eosinophilic cytoplasm and nuclei with characteristic salt-and-pepper chromatin. In some areas, enlarged and variably sized nuclei with pale swellings were also observed, consistent with the features of a neuroendocrine tumor (Fig. 4C). Lymph node metastasis was positive (1/47), and the resection margins were completely free. Immunohistochemical staining revealed positive chromogranin A (Fig. 4D-1), synaptophysin, and CD56 expression in the tumor cells. Mitoses were absent (0 per 2 mm²), and the Ki-

67 index was 6.2% in hotspot areas (Fig. 4D-2), confirming the diagnosis of a grade 2 pNET. In the central degenerative area, histological responses were multifocally observed on hematoxylin and eosin staining by irregular hyalinization with heterogeneous density in otherwise uniform fibrotic areas representing a unique feature suggestive of treatment-related changes (Fig. 4E, F). The overall extent of degenerative change was <10%. Elastica–Masson staining revealed randomly disorganized collagen fibers associated with edema and proliferating endothelial cells, indicating reactive stromal remodeling (Fig. 4G). No tumor thrombus was identified in the portal vein, but a tumor thrombus was observed within the splenic vein, consistent with the imaging findings (Fig.4H). Her postoperative course was uneventful. The patient was discharged on postoperative day 25, and she remained recurrence-free for 12 months postoperatively without adjuvant therapy.

Discussion

pNETs exhibit diverse clinical and morphological characteristics. Giant hypervascular tumors involving the entire pancreas represent a challenging clinical scenario that compromises the efficacy of locoregional therapy. This case highlights the successful application of a multidisciplinary treatment strategy, including STZ-based chemotherapy and preoperative TAE, which resulted in substantial tumor shrinkage and enabled subsequent curative resection; however, such reports are scarce. The clinical course, radiological features, and pathological findings described herein provide valuable insights for the clinical management of pNETs.

Neoadjuvant strategies are beginning to attract increasing attention as potential options for tumor downstaging in selected cases of locally advanced pNETs [12,13]. Although not yet established as a standard treatment, recent retrospective cohort studies have reported favorable outcomes with systemic chemotherapy and PRRT as preoperative approaches for non-metastatic pNETs [9,14]. Similar to our case, Prakash et al. reported the use of STZ-based preoperative chemotherapy for localized pNETs, demonstrating its feasibility and disease control potential; however, they noted that significant reductions in tumor size or anatomical extent were uncommon [8]. More recently, Minczeles et al. and Partelli et al. demonstrated that induction of PRRT with ¹⁷⁷Lu-DOTATATE could serve as a neoadjuvant option in patients with locally advanced pNETs, with partial response rates reaching 45–60% [5,6]. Furthermore, the NETTER-2 trial demonstrated that PRRT may represent a new standard of care as first-line treatment for advanced gastroenteropancreatic neuroendocrine tumors [15]. Based on these findings, PRRT was initially considered as a first-line therapy in our case. Nonetheless, the tumor of our patient was G2 with a low Ki-67 index (3.7%) and would not have met NETTER-2 inclusion [15]. Given a conversion intent, the anticipated time-to-best-response was an important consideration; PRRT typically requires a longer interval to achieve its maximal effect, with previous reports indicating a median of approximately 8 months [5]. Therefore, we prioritized an induction strategy with proven and timely cytoreductive potential to facilitate surgery, selecting a cytotoxic agent as first-line treatment, with PRRT intentionally preserved as an effective option for potential recurrence. Fortunately, STZ-based chemotherapy resulted in tumor

shrinkage and successful control of massive PVTT, a known negative prognostic factor for PNETs [16]. As a result, a favorable response to chemotherapy alone allowed conversion to surgery. In Japan, the clinical benefits and disease control potential of STZ-based chemotherapy for unresectable pNETs have been well established in multicenter studies [17-19]. This regimen may be an option for induction chemotherapy for conversion surgery. If the tumor showed a poor response to chemotherapy, PRRT would have been considered as a second-line option for this patient. The first-line systemic treatment for locally advanced pNETs may be selected with the intention of conversion surgery, prioritizing modalities with proven cytoreductive potential rather than those used for metastatic cases.

Preoperative TAE has been utilized to facilitate surgery for hypervascular tumors such as hepatocellular carcinoma, renal cell carcinoma, and pNETs [20-22]. In the present case, significant collateral circulation developed owing to the splenic vein occlusion, with engorged mesocolic and retroperitoneal veins encasing the tumor. The artery-first approach is now widely recognized in pancreatic surgery as a strategy to reduce intraoperative blood loss through early vascular control [23]. In giant hypervascular tumors, the early interruption of arterial inflow is imperative for safe surgical treatment. However, despite tumor shrinkage following chemotherapy, dissection around the splenic, gastroduodenal, and gastric arteries was still a high risk because it required dissection around the tumor with limited operative space. Preoperative TAE allowed simulation of the effects of the artery-first approach in a controlled setting. This enabled mobilization and dissection to begin from anatomically

favorable locations rather than immediately confronting high-risk vascular zones. Although tumor downsizing after TAE could not be objectively evaluated, intraoperative findings demonstrated a softer and partially collapsed tumor, suggesting a hemodynamic benefit with a shrinkage following preoperative TAE. Ultimately, the procedure was completed safely without the need for blood transfusion. Preoperative TAE may be a key adjunct in the surgical management of giant hypervascular pNETs, offering a means to improve intraoperative safety.

A noteworthy feature of this case was the unique tumor shrinkage pattern observed after preoperative chemotherapy. On contrast-enhanced CT, the internal components of the giant tumor showed focal areas of regression accompanied by tumor downsizing. This radiological finding was mirrored histologically, with corresponding unique irregular hyalinization observed in the resected specimen. We speculate that this pattern of partial intratumoral regression may reflect a specific feature of treatment-related reactions of pNETs, possibly affected by the heterogeneous histological architecture of the tumor. Additionally, although the tumor demonstrated meaningful shrinkage, the disappearance of the PVTT was particularly striking. Similar patterns have been reported in other solid tumors following chemotherapy [24], and this phenomenon may represent a common response pattern associated with neoadjuvant treatment. To the best of our knowledge, no previous reports have provided a detailed pathological evaluation of the radiological response of pNETs to chemotherapy. This case report provides a deeper understanding of treatment response patterns in pNETs and informs future strategies for evaluating the

efficacy of chemotherapy.

Whether the treatment strategy described in this report can be universally applied remains unclear.

Currently, the optimal selection and sequencing of neoadjuvant therapies for locally advanced pNETs have not been standardized. Personalized approaches are required to manage this rare and heterogeneous disease. Furthermore, selective TAE requires advanced technical expertise and should be performed by experienced interventional radiologists at specialized centers. Adverse events such as tumor lysis or organ ischemia remain a concern; therefore, this approach should be reserved for technically demanding “giant” cases in which intraoperative artery-first dissection is not feasible. These complexities of the multidisciplinary treatment emphasize the limitations in generalizing our approach. However, as previously emphasized in the literature [25], it also highlights the importance of centralizing the care of patients with pNETs in high-volume centers with expertise.

In conclusion, this case illustrates the potential of combining cytotoxic chemotherapy with selective preoperative TAE to achieve curative resection of a giant hypervascular pNET that was initially deemed unresectable. Radiological and pathological findings provide valuable insights into treatment response patterns. Multidisciplinary strategies in specialized centers tailored to individual tumor characteristics are essential for managing clinically complex pNETs.

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Figure Captions

Fig. 1 a Contrast-enhanced axial CT showing a 130-mm giant hypervascular mass involving the entire pancreas, with encasement of the portal vein (arrow). **b,c** Coronal CT views demonstrating a 30-mm segment of near-complete circumferential stenosis of the portal vein (**b**, arrow), and extensive collateral vessels developing into the retroperitoneum, gastric veins, and colonic veins (**c**, arrowheads), along with splenomegaly (**c**, arrow). **d** Schematic illustration of the tumor and associated vasculature. The giant tumor enveloped major arteries and markedly developed venous collaterals. **e** Somatostatin receptor

scintigraphy using ^{111}In -pentetreotide (Octreoscan®) 24 hours after tracer injection (**e-1**). Diffuse uptake of the giant pancreatic tumor, consistent with its neuroendocrine nature (**e-1**, arrowhead). ^{18}F -fluorodeoxyglucose positron emission tomography revealing a maximum standardized uptake value (SUVmax) of 17.6 in the primary tumor (**e-2**, arrowhead). Abbreviations: CT, computed tomography; LGA, left gastric artery; CHA, common hepatic artery; PHA, proper hepatic artery; RGA, right gastric artery; GDA, gastroduodenal artery; RGEA, right gastroepiploic artery; SPA, splenic artery; SMA, superior mesenteric artery; PV, portal vein; GCT, gastrocolic trunk; SMV, superior mesenteric vein; RGV, right gastric vein; IVC, inferior vena cava; SPV, splenic vein; LRV, left renal vein.

Fig. 2 a,b Axial ultrasonography demonstrating a portal vein tumor thrombus (PVTT) connected to the tumor (**a**, arrow). After four cycles of chemotherapy with streptozotocin and 5-fluorouracil (5-FU), the PVTT resolved, and the portal vein was reopened on sagittal ultrasonography (**b**, arrow). **c,d** Coronal computed tomography images of the tumor before (**c**) and after (**d**) chemotherapy. The tumor showed marked size reduction, and multiple low-attenuation foci were observed within the tumor parenchyma (**d**, arrowhead).

Fig. 3 a-c Preoperative transcatheter arterial embolization (TAE). **a** Angiography demonstrated arterial feeders to the tumor originating from gastroduodenal artery (GDA)-related branches and the right gastric

artery (RGA). **b** Selective coil embolization was performed for the GDA-related branches, left gastroepiploic artery (LGEA), and peripheral branches of the RGA. **c** Arterial inflow from the superior mesenteric artery (SMA) system was limited. **d,e** Intraoperative findings. The bulky tumor involved most of the pancreatic body and tail, but the distention was relatively mild (**d**). Total pancreatectomy with portal vein resection was performed (**e**).

Abbreviations: PSPDA, posterior superior pancreaticoduodenal artery; ASPDA, anterior superior pancreaticoduodenal artery; LGA, left gastric artery; GDA, gastroduodenal artery; RGA, right gastric artery; RGEA, right gastroepiploic artery; LGEA, left gastroepiploic artery; SMA, superior mesenteric artery; PV, portal vein; SPA, splenic artery.

Fig. 4 a,b Gross appearance of the resected specimen (**a**) and macroscopic view of the maximal cut surface (**b**). A 107 × 85 × 41 mm white solid tumor occupying the pancreatic body and tail was identified. Degeneration and fibrosis were observed as whitish areas in the central portion of the tumor, corresponding to the computed tomographic findings (**b**, arrowhead). **c** Microscopic view showing tumor cells with eosinophilic cytoplasm and nuclei containing characteristic salt-and-pepper chromatin, consistent with a neuroendocrine tumor. **d-1,2** Immunohistochemical staining revealed positivity for chromogranin A (**d-1**) and a Ki-67 labeling index of 6.2% in hotspot areas (**d-2**), supporting the diagnosis of a grade 2 pancreatic neuroendocrine tumor. **e,f** Hematoxylin and eosin (H&E) staining of the

309 degenerative area corresponding to the black square indicated in **b**. Histological response to
310 chemotherapy was characterized by focal irregular hyalinization (**e**, arrowhead), distinct from the
311 surrounding uniform hyalinized areas, likely reflecting tumor regression. **g** Elastica–Masson staining of
312 the same area showed disorganized collagen fibers with associated edema and proliferating endothelial
313 cells, indicative of reactive stromal remodeling. **h** Neuroendocrine tumor cells invading the portal vein
314 wall but not extending into the lumen (**h**, arrowhead). No tumor thrombus was identified.







