



# Conversion surgery for initially unresectable pancreatic ductal adenocarcinoma with synchronous liver metastasis after treatment with FOLFIRINOX

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## Abstract

FOLFIRINOX is a highly effective anticancer treatment, even in advanced pancreatic cancer, which provides a potential cure in patients initially treated with a palliative strategy. A 47-year-old man was found to have an unresectable pancreatic cancer (4 cm in size) surrounding both the superior mesenteric artery and superior mesenteric vein. A simultaneous liver metastasis in Segment 8, with a diameter of 17 mm, was also detected. The pancreatic tumor markers CEA, CA19-9, and DUPAN-2 were significantly elevated to 21.7 ng/mL, 6224 ng/mL, and 1200U/mL, respectively. After 21 courses of FOLFIRINOX, the primary pancreatic tumor diminished in size (partial response) from 42 to 17 mm, and the liver mass almost disappeared. The tumor markers significantly decreased to almost normal levels. Fourteen months after the initial chemotherapy, conversion surgery was performed. Upon surgical resection, the pancreatic tumor was found to be Grade 1b, and a pathologically complete response was observed for the liver metastasis. The patient is still alive 32 months after initial treatment with no recurrence. This is an informative case of a locally advanced pancreatic cancer with a synchronous liver metastasis that had a significant response to FOLFIRINOX, allowing for subsequent curative resection.

**Keywords** Pancreatic cancer · Conversion surgery · FOLFIRINOX

## Abbreviations

MDCT	Multi-detector computed tomography
PET-CT	Positron emission tomography–computed tomography
UGT	Uridine diphosphate glucuronosyltransferase

## Introduction

Pancreatic duct carcinoma accounts for 90–95% of pancreatic cancers and has a poor prognosis [1, 2]. Pancreatic cancer is characterized as highly invasive, frequently metastatic, and chemo-resistant. Surgical resection is the only potentially curative treatment, with a survival rate of 20% at 5 years, but only 15–20% of newly diagnosed patients can benefit from it [3]. Unresectable and borderline resectable pancreatic cancers are often treated with neoadjuvant chemo- or chemoradio-therapy. A recent meta-analysis revealed that approximately one-third of patients with initially unresectable pancreatic cancer may convert to resectable cancer after neoadjuvant chemotherapy, with survival comparable to that of initially resectable patients [4]. Furthermore, even patients with R1 resections have prolonged survival with adjuvant chemotherapy [5]. FOLFIRINOX [6] and nab-paclitaxel plus gemcitabine [7] have demonstrated significant anticancer effects in patients with metastatic pancreatic cancer, with response rates between 20 and 30%. Complete responses on radiological images, however, were described in only 4% of patients in a FOLFIRINOX phase II

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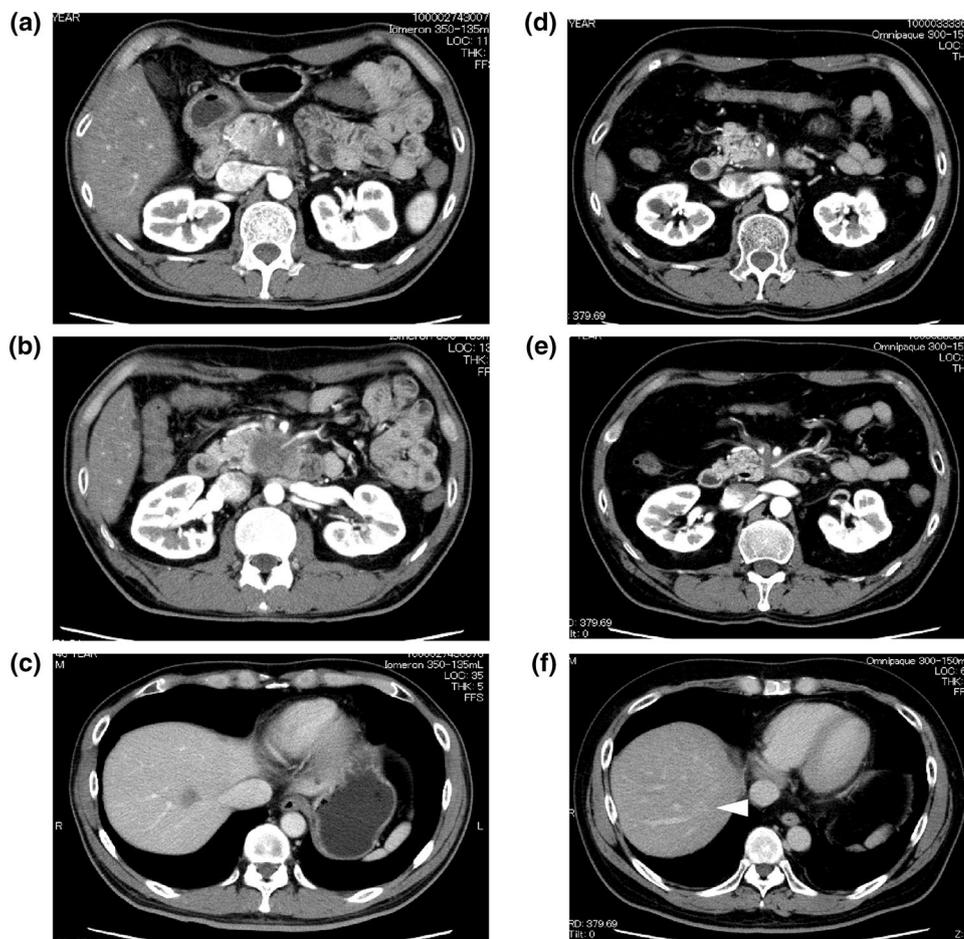
trial of patients with advanced pancreatic cancer [8]. Thus, a multi-disciplinary approach, including conversion surgery, is required to give a potential curative chance to patients with metastatic pancreatic cancer. Herein, we report a case of successful conversion resection of locally advanced pancreatic cancer with simultaneous liver metastasis after FOLFIRINOX chemotherapy.

## Case report

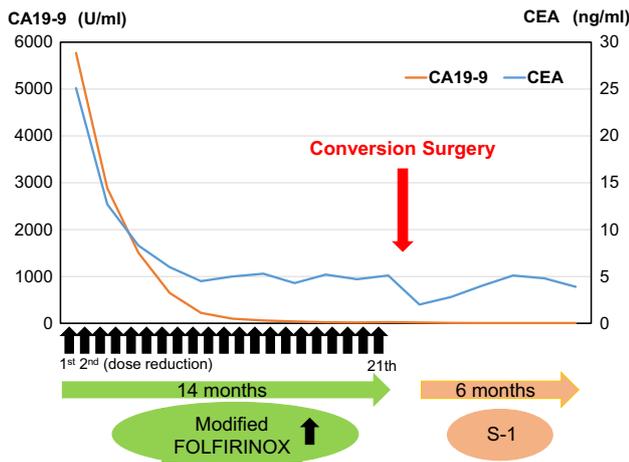
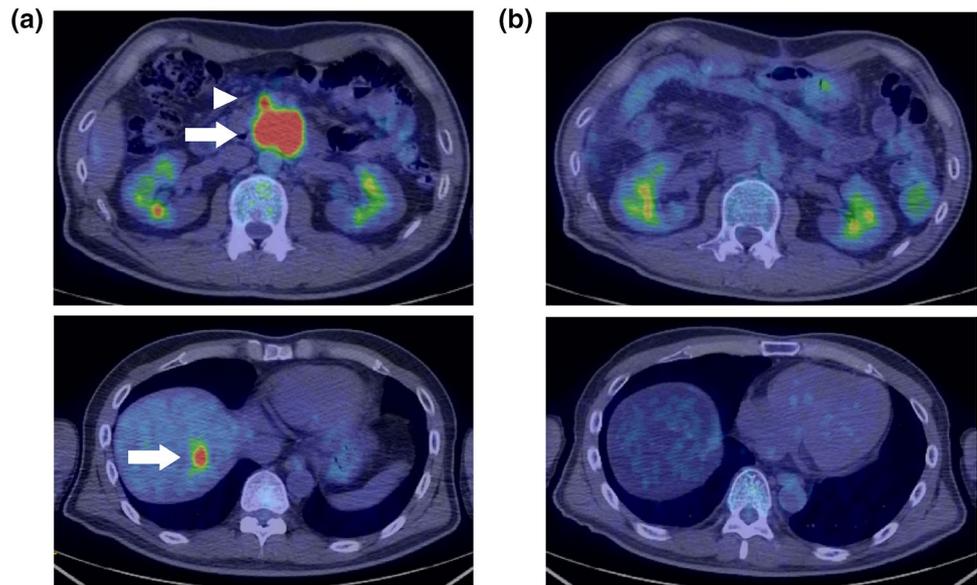
A 47-year-old man presented with epigastric pain. Abdominal ultrasound revealed a large (4 cm) irregularly shaped mass located in the uncinate process of the pancreas. The character of internal echo was hypoechoic and homogenous. Multi-detector computed tomography (MDCT) demonstrated that the pancreatic tumor surrounded both the superior mesenteric artery (the entire circumference of the vessel with extension to the first SMA branch) and superior mesenteric vein (focal vessel narrowing  $> 180^\circ$ ) (Fig. 1a, b). Additionally, a liver metastasis (17 mm in diameter) was detected in Segment 8 (Fig. 1c). FDG PET-CT revealed an abnormally high uptake of FDG in the primary tumor, the liver metastasis, and in a

lymph node at the origin of the jejunal arteries (#14d) with the SUV max (10.5, 6.8, and 4.2 at 60 min and 14.9, 9.5, and 6.3 at 120 min, respectively) (Fig. 2a). The pancreatic tumor markers CEA, CA19-9, and DUPAN-2 were significantly elevated at 21.7 ng/mL, 6224 ng/mL, and 1200 U/mL, respectively. Thus, according to these radiological findings and laboratory data, the patient was diagnosed with locally advanced pancreatic cancer with a liver metastasis (URLA/M). A pathological examination by EUS-FNA was not routinely carried out because of the risk of complications such as tumor implantation and bleeding in our institute. Especially in this case with radiologically solid findings of the pancreatic cancer with highly elevated tumor markers, the pathological examination by EUS-FNA was not performed. The liver function in the blood biochemical examination was normal, and the serum values of liver functional tests (AST, ALT, ALP,  $\gamma$ -GTP, CHE and T-Bil) were 15 IU/L, 12 IU/L, 163 IU/L, 15 IU/L, 307 IU/L and 1.4 mg/dL, respectively. The uridine diphosphate glucuronosyltransferase (UGT) 1A1 genetic polymorphism was *UGT1A1* (\*1/\*6). Chemotherapy with a modified FOLFIRINOX (oxaliplatin 85 mg/m<sup>2</sup>, irinotecan 150 mg/m<sup>2</sup>, 5-FU 2400 mg/m<sup>2</sup>, levofolinate 200 mg/m<sup>2</sup>) was initiated. Because of severe neutropenia (CTCAE grade III), a dose

**Fig. 1** Unresectable primary pancreatic cancer and synchronous liver metastasis on multi-detector computed tomography. **a** The pancreatic tumor contacted both the superior mesenteric artery (surrounding the entire vessel) and superior mesenteric vein (focal vessel narrowing  $> 180^\circ$ ). **b** Tumor involvement extended to the first SMA branch (J1). **c** A liver metastasis 17 mm in diameter was detected in Segment 8. **d, e** After 21 courses of FOLFIRINOX, the primary pancreatic tumor significantly decreased (partial response) from 42 to 17 mm in size. **f** After 21 courses of FOLFIRINOX, the liver metastatic mass almost completely disappeared (white arrow head)



**Fig. 2** Accumulation of FDG in the PET before (a) and after (b) chemotherapy Upper panels: Accumulation of FDG in the primary tumor and a lymph node at the origin of the jejunal arteries (#14d) (arrow and arrow head, respectively). Lower panels: Accumulation of FDG in the lesion of liver metastasis (arrow)



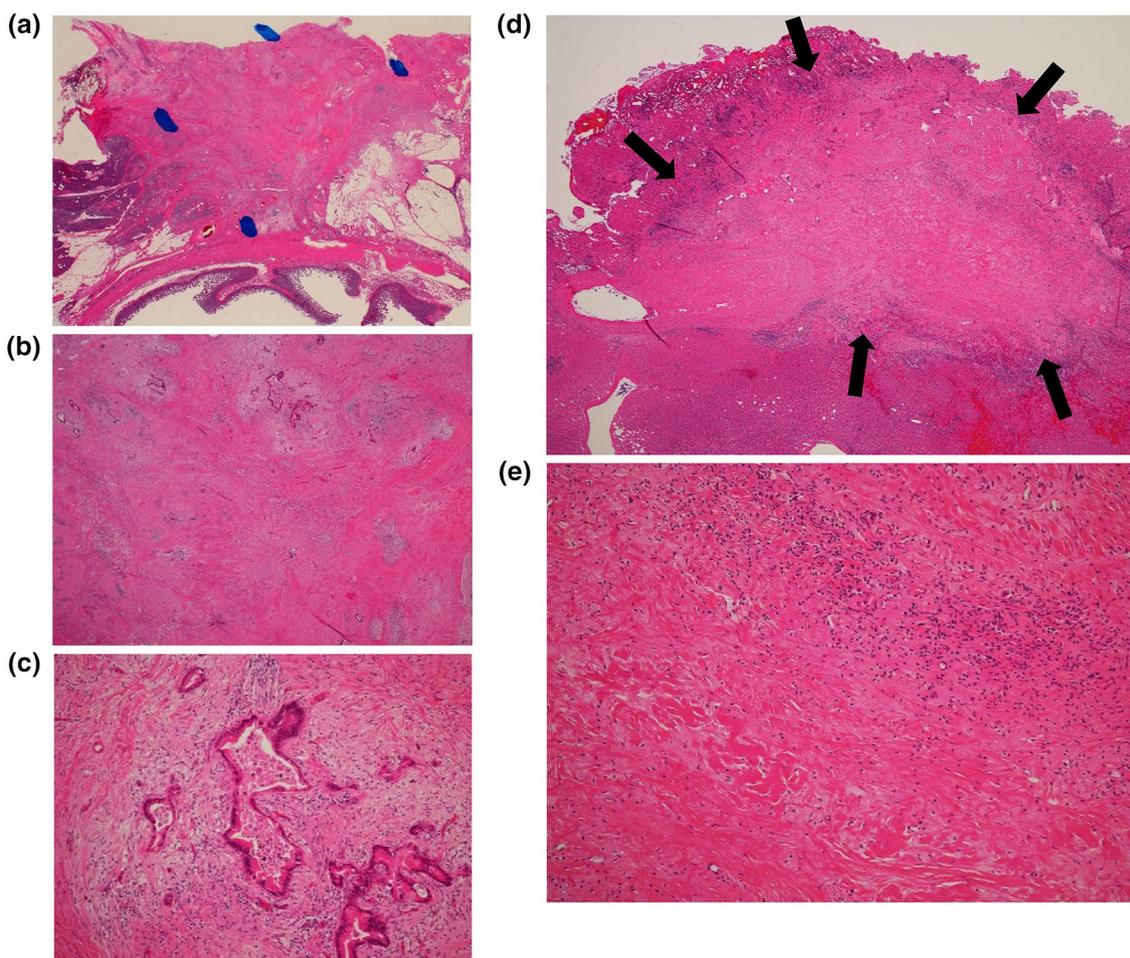
**Fig. 3** Clinical course during the period

reduction (oxaliplatin 65 mg/m<sup>2</sup>, irinotecan 120 mg/m<sup>2</sup>, 5-FU 2400 mg/m<sup>2</sup>, levofofolate 200 mg/m<sup>2</sup>) was required beginning with the second course. Additionally, a peripheral neuropathy (CTCAE grade II) was appeared in the third course. Thereafter, a peripheral neuropathy (CTCAE grade II) has persisted. After 21 courses over 14 months, the primary pancreatic tumor diminished (partial response) from 42 to 17 mm in size (Fig. 1d, e). The liver metastatic mass almost disappeared on MDCT (Fig. 1e). In addition, CEA and CA19-9 significantly decreased into normal level and those levels were maintained within normal level over 6 months (Fig. 3). The preoperative levels of CEA and CA19-9 were 5.1 ng/mL and 25 ng/mL, respectively. FDG PET-CT accumulation also disappeared (Fig. 2b). There was no new lesion during the chemotherapy. A cancer board meeting including medical

oncologist, gastroenterologist and the surgeon was hold about the surgical approach for this case. Thereafter, we explained the possibility of the surgical approach for the patient and his family, and they decide to do surgical approach for the pancreatic cancer. Fourteen months after the initial chemotherapy, stomach-preserving pancreaticoduodenectomy and portal vein resection with partial hepatectomy was performed. Contrast ultrasonography detected the liver metastasis as a hypoechoic tumor 2 mm in diameter in the kupffer phase. Pathological findings were tubular adenocarcinoma, moderately differentiated type, 1.3×1.0 cm, intermediate type, INIβ, ly 0, v 0, ne 1, mpd (-), CH (-), DU (-), S (-), RP (-), R0. In contrast to the preoperative image findings, the histology of the primary tumor according to General Rules for the Study of Pancreatic Cancer 2016, the 7th Edition, by Japan Pancreas Society was poor response to chemotherapy (Grade 1b) (Grade IIa according to Evans criteria [9]) (Fig. 4a–c). Interestingly, a pathologically complete response (Grade 4) was observed for the liver metastasis, and only fibrotic scar tissue remained (Fig. 4d, e). Collectively, FOLFIRINOX treatment down-staged the tumor to ypT1, ypN0, ypM0, ypStage I. Post-operatively, S-1 was administrated for 6 months as adjuvant chemotherapy, and he is now free from anti-cancer drug. The patient remains alive and without recurrence 32 months after initial treatment.

### Discussion

Several recent reports have described conversion surgery following FOLFIRINOX treatment of metastatic pancreatic cancer, with the hope of surgical cure [10–13]. In a retrospective analysis of 127 pancreatic cancer patients with synchronous liver metastases, Crippa et al. reported that



**Fig. 4** Microscopic findings of the primary and metastatic lesions after chemotherapy. **a–c** Microscopic findings of the primary pancreatic tumor after FORFIRINOX. The histological grade was Grade 1b.

surgical resection, chemotherapy with multiple agents,  $\leq 5$  liver metastases at diagnosis, and CA19-9 reduction  $\geq 50\%$  of baseline value were favorable and independent prognostic factors [14]. Furthermore, in their sub-analysis of 56 patients (44%) with a partial/complete response after neoadjuvant chemotherapy, disease-specific survival significantly improved for the 11 patients (8.5%) who underwent surgical resection, compared to the remaining 45 (1-year OS: 100% vs. 59% and 3-year OS: 57% vs. 9%) (MST was 46 and 11 months, respectively) [14]. They concluded that surgical resection of primary pancreatic tumor with or without residual liver disease can be considered in selected cases after primary chemotherapy and that resection is associated with improved survival [14]. In the present case, FOLFIRINOX demonstrated significant anti-cancer effects, such as tumor shrinkage (60% reduction in size), abatement of FDG accumulation, and normalization of tumor markers. The pathological findings, however, revealed that viable cancer cells remained (Grade 1b). On the other hand, the metastatic liver

Viable residual cancer cells were detected. **d, e** The liver metastatic lesion (black arrows) consisted of only fibrotic scar tissue. A pathologically complete response was obtained

lesion displayed a pathologically complete response. These findings suggest that the tumor microenvironment, such as a large amount of fibrotic tissue, might contribute to different anti-cancer effects in the primary and metastatic sites. As a limitation of the present case, the pathological examination of liver metastasis prior to chemotherapy was not performed. Therefore, we discussed with the pathological findings with a pathologist (TK). In this case, there were no underlying diseases such as liver cirrhosis and non-alcoholic steatohepatitis in the liver that could cause liver cancer, although there was mild adipose tissue deposition. In addition, infiltration of inflammatory cells was mildly observed around the fibrotic scar tissue, and the pathological finding was not a typical to suspect inflammatory pseudotumor. The pathologist diagnosed that the fibrotic scar tissue was due to a complete response of the metastatic liver cancer by chemotherapy. Since the liver tumor disappeared by chemotherapy, the possibility of a primary tumor was not be completely excluded.

It remains unclear how to determine eligibility for conversion surgery after chemotherapy in patients with locally advanced cancer. A retrospective cohort study found that the sensitivity and specificity of computed tomography/magnetic resonance imaging to detect vascular involvement were only 71 and 58%, respectively, after down-staging chemotherapy [15]. Vascular involvement on imaging after chemotherapy often involves tumor fibrosis rather than viable neoplastic cells. Multimodality neoadjuvant therapy may lead to a pathologically complete response in a small number of patients with borderline resectable/locally advanced pancreatic adenocarcinoma [16]. Several publications have reported successful resection of pancreatic cancer with distant metastases leading to long-term survival [17–20]. On the other hand, even in patients with a pathologically complete response of the primary lesion following neoadjuvant chemotherapy, the majority of patients still have the potential to relapse locally or systemically [16]. In another report of pancreatic cancer patients with synchronous liver metastases, ten of eleven patients who underwent conversion surgery developed tumor recurrence, including liver recurrence in seven cases [14]. The high rate of recurrence after curative resection suggests the presence of occult disease or micrometastases at the time of surgery. To achieve a surgical cure by conversion surgery, such occult disease or micrometastases should be treated with neoadjuvant chemotherapy. In the present case, the duration of chemotherapy from induction to conversion surgery was 14 months. In a Japanese multicenter survey of 58 patients who underwent conversion surgery for initially unresectable pancreatic cancer because of either locally advanced disease ( $n=41$ ) or metastasis ( $n=17$ ), the overall survival was favorable in patients receiving chemotherapy for more than 240 days compared to those receiving chemotherapy for fewer than 240 days [21]. However, this report did not include patients treated with powerful chemotherapeutic regimens such as FOLFIRINOX and nab-paclitaxel/gemcitabine [21]. Tumor markers are often used to evaluate the tumor response to therapy, and to estimate remaining occult disease or micrometastases. In the present case, the initially elevated tumor markers normalized and they were maintained within a normal level over 6 months by the time of conversion surgery. A few similar reports of conversion surgery and pathologically complete response following FOLFIRINOX indicated that tumor markers, especially CA19-9, normalized by the time of surgery [13, 22]. Due to the heterogeneity and small sample size of available retrospective series, it is difficult to definite the specific duration of neoadjuvant chemotherapy or timing of conversion surgery for these patients. Patient selection criteria and the timing of surgery should be examined in future studies.

There is no evidence of adjuvant therapy after conversion surgery for metastatic pancreatic cancer. For resectable pancreatic cancer, there are several reports about adjunctive therapy

such as 5-FU/ folinic acid [23], Gemcitabine [5, 24], and the combination of gemcitabine and capecitabine [25]. In Japanese patients, oral administration of S-1 for 6 months as an adjunctive therapy for resectable pancreatic cancer provided the significant improvement in recurrence free survival and overall survival [26]. In several case reports of conversion surgery for locally advanced or metastatic pancreatic cancer, the usage of S1 as adjuvant chemotherapy has been reported [27, 28]. Although there is no clear evidence about an adjunctive therapy after conversion surgery for metastatic pancreatic cancer, S1 oral administration for 6 months was performed as adjuvant chemotherapy in the present case. The clinical significance of adjuvant chemotherapy for conversion surgery for metastatic pancreatic cancer and its regimens should be elucidated in the future studies.

## Conclusions

We described an informative case of locally advanced pancreatic cancer with synchronous liver metastasis that regressed with FOLFIRINOX therapy, allowing for subsequent curative resection. A multi-disciplinary approach to locally advanced pancreatic cancer with synchronous liver metastasis is necessary, as a small and carefully selected number of patients with an excellent response to neoadjuvant chemotherapy may be candidates for potentially curative conversion surgery.

**Authors' contributions** KO, HH, YI, SA, and HT performed the operation. HH and HT determined the treatment plan. HB and TK provided critical review of clinical findings. All other authors made a round of visits after the operation. All authors read and approved the final manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest concerning this article.

**Human and animal rights** All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Ethical approval** Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

**Informed consent** Informed consent was obtained for this case report.

## References

- Hidalgo M, Cascinu S, Kleeff J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. *Pancreatol.* 2015;15:8–18.
- Cid-Arregui A, Juarez V. Perspectives in the treatment of pancreatic adenocarcinoma. *World J Gastroenterol.* 2015;21:9297–316.

3. Garrido-Laguna I, Hidalgo M. Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. *Nat Rev Clin Oncol*. 2015;12:319–34.
4. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med*. 2010;7:e1000267.
5. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *Jama*. 2013;310:1473–81.
6. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817–25.
7. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691–703.
8. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer—a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol*. 2005;23:1228–36.
9. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg*. 1992;127:1335–9.
10. Buc E, Orry D, Antomarchi O, et al. Resection of pancreatic ductal adenocarcinoma with synchronous distant metastasis: is it worthwhile? *World J Surg Oncol*. 2014;12:347.
11. Schneitler S, Kropil P, Riemer J, et al. Metastasized pancreatic carcinoma with neoadjuvant FOLFIRINOX therapy and R0 resection. *World J Gastroenterol*. 2015;21:6384–90.
12. Sasaki T, Isayama H, Aoki T, et al. A R0 resection case of initially unresectable metastatic pancreatic cancer downstaged by FOLFIRINOX therapy. *Pancreas*. 2014;43:972–4.
13. Neofytou K, Giakoustidis A, Smyth EC, et al. A case of metastatic pancreatic adenocarcinoma with prolonged survival after combination of neoadjuvant FOLFIRINOX therapy and synchronous distal pancreatectomy and hepatectomy. *J Surg Oncol*. 2015;111:768–70.
14. Crippa S, Bittoni A, Sebastiani E, et al. Is there a role for surgical resection in patients with pancreatic cancer with liver metastases responding to chemotherapy? *Eur J Surg Oncol*. 2016;42:1533–9.
15. Donahue TR, Isacoff WH, Hines OJ, et al. Downstaging chemotherapy and alteration in the classic computed tomography/magnetic resonance imaging signs of vascular involvement in patients with pancreaticobiliary malignant tumors: influence on patient selection for surgery. *Arch Surg*. 2011;146:836–43.
16. Hashemi-Sadraei N, Gbolahan OB, Salfity H, et al. Clinical characteristics of patients experiencing pathologic complete response following neoadjuvant therapy for borderline resectable/locally advanced pancreatic adenocarcinoma. *Am J Clin Oncol*. 2018;41:982–5.
17. Shimada K, Kosuge T, Yamamoto J, et al. Successful outcome after resection of pancreatic cancer with a solitary hepatic metastasis. *Hepato-gastroenterology*. 2004;51:603–5.
18. Spinelli GP, Zullo A, Romiti A, et al. Long-term survival in metastatic pancreatic cancer. A case report and review of the literature. *JOP Journal Pancreas*. 2006;7:486–91.
19. Ibusuki M, Hiraoka T, Kanemitsu K, et al. Complete remission of pancreatic cancer after multiple resections of locally pancreatic recurrent sites and liver metastasis: report of a case. *Surg Today*. 2008;38:563–6.
20. Klein F, Puhl G, Guckelberger O, et al. The impact of simultaneous liver resection for occult liver metastases of pancreatic adenocarcinoma. *Gastroenterol Res Pract*. 2012;2012:939350.
21. Satoi S, Yamaue H, Kato K, et al. Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepato-Biliary-Pancreat Sci*. 2013;20:590–600.
22. Luu AM, Herzog T, Hoehn P, et al. FOLFIRINOX treatment leading to pathologic complete response of a locally advanced pancreatic cancer. *J Gastrointest Oncol*. 2018;9:E9–12.
23. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200–10.
24. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *Jama*. 2010;304:1073–81.
25. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011–24.
26. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016;388:248–57.
27. Ariake K, Motoi F, Mizuma M, et al. Locally advanced pancreatic cancer successfully treated by distal pancreatectomy with celiac axis resection (DP-CAR) after S-1 with radiation therapy followed by gemcitabine/nab-paclitaxel therapy: a case report. *Surg Case Rep*. 2017;3:15.
28. Shimura M, Mizuma M, Hayashi H, et al. A long-term survival case treated with conversion surgery following chemotherapy after diagnostic metastasectomy for pancreatic cancer with synchronous liver metastasis. *Surg Case Rep*. 2017;3:132.

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