

CASE REPORT

Conversion Therapy for Locally Advanced Pancreatic Cancer: A Case Series and Literature Review

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Abstract: Patients with locally advanced pancreatic cancer account for a large proportion of patients with pancreatic cancer. According to the National Comprehensive Cancer Network guidelines, the patients with good performance status can undergo chemotherapy or chemoradiotherapy. However, a growing number of clinical studies suggested that aggressive surgical treatment after chemotherapy may lead to longer survival. In this case series, we report the effect of conversion therapy in four patients with locally advanced pancreatic cancer who visited Zhejiang Provincial People's Hospital from January 2015 to October 2020. The clinical evaluation and prognosis of these patients after conversion therapy were analyzed and discussed in conjunction with relevant literature. The median overall survival time of the patients was 21.5 months. One patient who underwent surgery after chemotherapy achieved R0 resection. Another patient gave up the opportunity of surgery in the process of conversion therapy, but has been living with the tumor since. Taken together, the patients with locally advanced pancreatic cancer can benefit from conversion therapy in achieving R0 resection or long-term survival if surgery is not implemented.

Keywords: Conversion therapy, Chemotherapy, Locally advanced unresectable pancreatic cancer, Surgery

1. Introduction

Pancreatic cancer is one of the most common solid malignant tumors with the worst prognosis, and pancreatic ductal adenocarcinoma (PDAC) is one of the most common forms of the cancer. According to the statistics of China National Cancer Center in 2015, pancreatic cancer ranked fifth in the mortality rate of malignant tumors among the Chinese urban population^[1]. Based on the National Comprehensive Cancer Network (NCCN) guidelines (version 2017), pancreatic cancer can be classified as resectable, borderline resectable-locally advanced unresectable, and metastatic disease^[2]. In general, at initial diagnosis, locally advanced and borderline resectable tumors account for 30–40% of

the cases, whereas metastatic diseases are diagnosed in most of the rest of patients^[3]. The concepts of locally advanced pancreatic cancer and borderline resectable pancreatic cancer can be easily confused with each other. Locally advanced unresectable tumors are defined as those that encase the adjacent arteries (celiac axis, superior mesenteric artery, or both) or that occlude the superior mesenteric vein, portal vein, or both confluence^[4]. Borderline resectable tumors are defined as tumors with limited involvement of the adjacent vascular structures where vascular reconstruction options are feasible^[4]. For locally advanced unresectable diseases, the 5-year overall survival rate remains <5%^[5].

The unique anatomical location of pancreatic cancer, aggressive biological characteristics, and resistance to chemotherapeutic drugs have led to problems in the treatment and prognosis of pancreatic cancer^[6]. Radical resection is the only treatment that is potentially able to provide a long-term survival, while only around 10 – 20% of people have access to an upfront tumor resection^[7]. A single-center study showed that the overall median survival of patients with pancreatic adenocarcinoma who had undergone curative resection was 19 months, and their 1-year, 3-year, and 5-year survival rates were 72.5%, 28.0%, and 23.4%, respectively^[8]. In addition to surgery, chemotherapy is another important treatment for pancreatic cancer. However, the choice of chemotherapy drugs for pancreatic cancer is limited. Gemcitabine, nab-paclitaxel, oxaliplatin, irinotecan, fluorouracil, and S-1 are regarded as the vital therapeutic drugs for unresectable pancreatic cancer^[9-11]. The NCCN panel of experts on pancreatic cancer believed that multidisciplinary team (MDT) is the basis of pancreatic cancer treatment^[12]. Combining each patient's physical condition and tumor size, location, and scope of invasion, the doctor formulates individualized comprehensive treatment plan for patients through multidisciplinary discussion and cooperation. Conversion therapy mainly adopts the MDT model, which treats patients with appropriate chemotherapy, radiotherapy, targeted, and other comprehensive treatment methods, then the initially unresectable tumor can be transformed into a resectable tumor, thereby facilitating radical surgical resection subsequently. According to the current literature, conversion therapy had improved the R0 resection rate and overall survival rate of pancreatic cancer patients to a certain extent^[12-14].

Here, we present four cases of patients with locally advanced pancreatic cancer who received conversion therapy. This case series explores the clinical application of conversion therapy in patients with locally advanced pancreatic cancer, and together with the literature review, highlights the favorable outcome of using conversion therapy in the aspect of survival.

2. Case presentation

2.1. Case 1

A 76-year-old male was admitted to Taizhou Central Hospital, Zhejiang, China, in December 2017 after a physical examination on the patient revealed a mass between the body and tail of the pancreas. Serum carbohydrate antigen 19-9 (CA 19-9) level was 7417.24 U/ml. Abdominal-enhanced computed tomography (CT) showed that the splenic vein was involved, and multiple small retroperitoneal lymph nodes were displayed (**Figure 1A**). Surgery is not applicable on the account of tumor's invasion of the surrounding blood vessels. AG regimen (albumin-bound paclitaxel 200 mg on days 1 and 8; gemcitabine 1400 mg on days 1 and 8, every 3 weeks) was selected as conversion therapy for the patient in December 2017. After 5 cycles, the level of CA 19-9 decreased to 176.9 U/ml. Positron emission tomography-CT (PET-CT) showed that the lesions were slightly smaller than before, local splenic vein was not clear (**Figure 1B**). Enhanced magnetic resonance indicated that the tumor is surrounded by the splenic vessels for <180° (**Figure 1C**). Following the decrease of tumor index, the mass of tumor became smaller and no distant metastasis was found, suggesting that surgery is feasible for tumor resection. Therefore, radical antegrade modular pancreatosplenectomy was performed in June 2018. Histopathological findings showed moderately differentiated adenocarcinoma with nerve involvement (**Figure 1D**). The negative margin of pancreatectomy as well as transection of the artery and vein indicates the achievement of R0 resection. After operation, the patients were treated with single-drug chemotherapy of S-1. Regular re-examination showed no recurrence. The overall survival time of the patient was 24 months.

2.2. Case 2

A 68-year-old female was admitted to the Zhejiang Provincial People's Hospital, Zhejiang, China in October 2015 after complaining of pain in her upper right abdomen and back pain on the right side for 2 months. Serum CA 19-9 level of the patient was 65.4 U/ml. PET-CT indicates active fluorodeoxyglucose (FDG) metabolism in the mass of the head of pancreas and infiltration of the surrounding fat space (**Figure 2A**). Enhanced CT showed a low-density mass in the head of pancreas, and the proximal superior mesenteric artery might be involved. The findings of endoscopic ultrasound-guided fine-needle aspiration biopsy of the pancreas showed that cancer could not be ruled out (**Figure 2B**). The patient was diagnosed with malignant tumor of pancreas, T4N0M0, stage III. Following a discussion in the department, the patient was given conversion therapy first. Subsequently, the patient began to receive 23 cycles of GS regimen (gemcitabine 1, 400 mg on days 1 and 8, S-1 60 mg twice daily on days 1–14, every 3 weeks). Then, single-agent capecitabine maintenance therapy replaced the GS regimen as treatment. During the period of chemotherapy, CT showed that the pancreatic

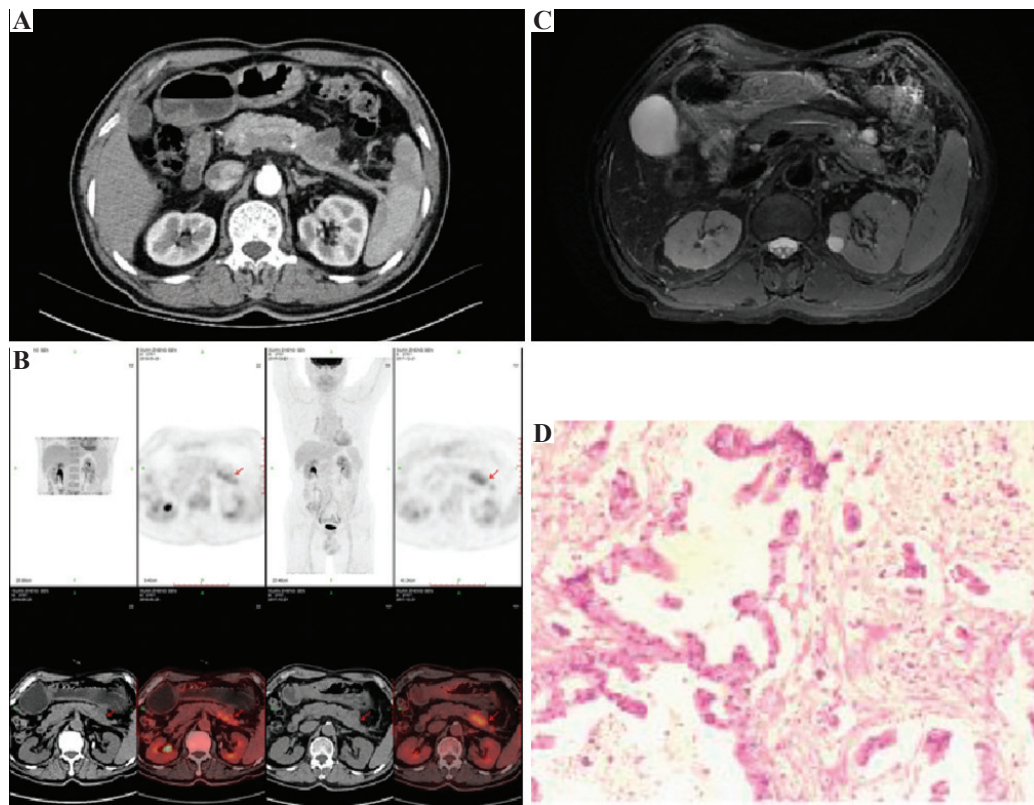


Figure 1. Comparison of imaging and histopathological findings of Case 1 after conversion therapy. (A) Enhanced computed tomography (CT) showed irregular low-density foci in the tail of the pancreas. (B) Positron emission tomography-CT indicated reduced fluorodeoxyglucose metabolism and no distant metastasis. (C) Enhanced magnetic resonance indicated that the tumor is surrounded by the splenic vessels for $<180^\circ$. (D) Post-operative histopathological test revealed a moderately differentiated adenocarcinoma. The specimens obtained from surgery were fixed, embedded, and thinly sliced, stained with hematoxylin and eosin, and photographed under an optical microscope ($200\times$ magnification).

lesions gradually shrank (**Figure 2C**) and the serum CA 19-9 level was within the normal range. In September 2017, the findings indicated that the lesion could achieve complete response to the treatment (**Figure 2D**). The condition of the patient was stable, with an overall survival of 60 months at the end of follow-up (**Figure 3**).

2.3 Case 3

A 50-year-old male was admitted to the Zhejiang Provincial People's Hospital, Zhejiang, China in March 2019 with upper abdominal discomfort for more than 1 year and aggravation for 2 weeks. PET-CT revealed increased FDG metabolism in the mass (48×25 mm) of the head of pancreas, invasion of the duodenum by the mass, and the possibility of metastasis to lymph nodes around the lesion and retroperitoneum. Enhanced CT angiography (CTA) of the mesenteric artery indicates local invasion of the superior mesenteric vein. Pathological biopsy under ultrasound gastroscopy revealed PDAC. The patient was diagnosed with locally advanced pancreatic cancer and surgery was not feasible at that time. The AS regimen (albumin-bound paclitaxel 200 mg on days 1 and 8, S-1 60 mg twice daily on days 1–14, every 3 weeks) was prescribed in March 2019. After 4 cycles, the lesion

shrank significantly (25×24 mm). However, the patient refused to undergo the operation for tumor resection. After the fifth cycle, the patient voluntarily stopped chemotherapy for 1/2 year, during which the patient's condition was evaluated to be stable. In December 2019, PET-CT revealed that the metabolism of pancreatic tumor is still active after treatment, and implantation metastasis occurred in the pelvic cavity. Considering that pancreatic cancer invaded the bile duct and caused obstructive jaundice, percutaneous transhepatic cholangial drainage was performed. Since January 2020, the FOLFIRINOX regimen (oxaliplatin 120 mg on day 1; irinotecan 210 mg on day 1; 5-fluorouracil 3330 mg 46 h) was applied as the chemotherapy for the patient, and the condition of the disease has achieved stability afterward. The overall survival time was 19 months at the end of follow-up.

2.4. Case 4

A 63-year-old male was admitted to the Zhejiang Provincial People's Hospital, Zhejiang, China in September 2017 with recurrent epigastric pain for 3 months. PET-CT showed increased FDG metabolism in the soft tissue mass (32×25 mm) of the uncinate process of the pancreas, and increased FDG metabolism in enlarged lymph nodes

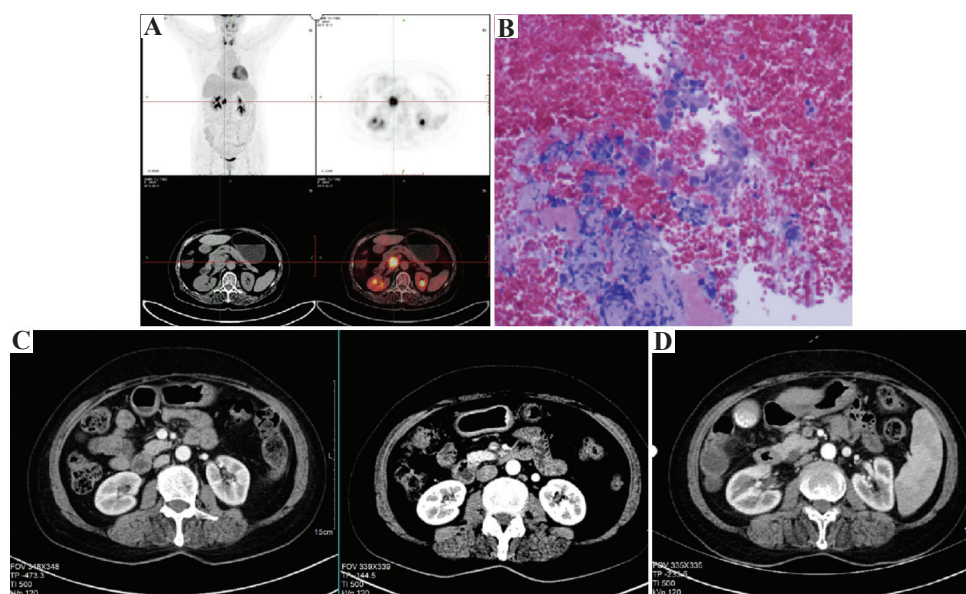


Figure 2. Comparison of imaging data of Case 2 after conversion therapy. (A) Positron emission tomography computed tomography (CT) indicated high fluorodeoxyglucose metabolism and no distant metastasis. (B) The finding of endoscopic ultrasound-guided fine-needle aspiration biopsy suggested the development of carcinoma in the pancreas. (C) Enhanced CT indicated partial response of the lesion (13×11 mm vs. 22×26 mm). (D) Enhanced CT indicated complete response of the lesion to the treatment.

around the lesion and retroperitoneum. Enhanced CTA of the mesenteric artery indicated that the first jejunal artery was partially embedded by the pancreatic mass. Endoscopic ultrasound-guided fine-needle aspiration biopsy showed that the lesion was adenocarcinoma. The patient was diagnosed with locally advanced pancreatic cancer and treated with conversion therapy initially. FOLFIRINOX regimen (oxaliplatin 100 mg on day 1; irinotecan 210 mg on day 1; 5-fluorouracil 3280 mg 46 h) was started in October 2017. Four cycles later, abdominal-enhanced CT showed a 20×23 mm companion shadow in uncinate process of pancreas. Mesenteric angiography showed no obvious abnormality. After MDT discussion, the physicians decided that the FOLFIRINOX regimen should be continued. After 8 cycles, CT indicated that the tumor in the uncinate process of the pancreas had disappeared, and surgical treatment was recommended. However, the patient refused to undergo surgery. After 11 cycles, abdominal-enhanced CT showed a 23×26 mm, round, and slightly low-density shadow in uncinate process of pancreas. GEMOX regimen (gemcitabine 1,500 mg on days 1 and 8; oxaliplatin 200 mg on day 1, every 3 weeks) was changed in October 2018. After 2 cycles, bone marrow suppression occurred and the platelet count was as low as $11 \times 10^9/L$. The condition improved after blood transfusion. Then, the patient was lost to follow-up after receiving 7 times of bio-immunotherapy. The overall survival time of the patient was 17 months.

3. Discussion

The median survival time of locally advanced pancreatic cancer is 5–11 months, and the standard treatment is still

controversial^[15,16]. For patients with pancreatic cancer who had no opportunity to undergo surgical resection initially, the guidelines recommended systemic treatment with chemotherapy as the primary treatment^[2,5]. The FOLFIRINOX regimen was reported to have significantly prolonged the overall survival of the patients with locally advanced unresectable pancreatic cancer, with a median survival time of 24.2 months^[17]. In a phase II study, albumin-bound paclitaxel combined with gemcitabine achieved 77.6% disease control rate as well as a total response rate of 33.6% and resulted in a median total survival time of 18.8 months in locally advanced unresectable pancreatic cancer^[18]. The recent studies found that about one-third of initially unresectable tumors that were expected to be transformed into resectable tumors after conversion therapy were associated with survival rates comparable to those of patients with initially resectable tumors^[19,20]. A large retrospective study showed that the median survival time of patients with locally advanced unresectable pancreatic cancer who underwent primary tumor resection was significantly different from that of patients without resection (35.3 vs. 16.2 months)^[21]. Combining drugs with higher response rates in conversion therapy may allow an increasing number of patients with locally advanced unresectable patients to be reoperated. The drugs include gemcitabine, nab-paclitaxel, 5-fluorouracil, irinotecan, oxaliplatin, and S-1^[11,18,22,23].

Here, the four cases presented in this case series were all initially diagnosed with locally advanced pancreatic cancer but not amenable to surgeries. We selected a conversion treatment plan for the patient based on the patient's Eastern Cooperative Oncology Group score and

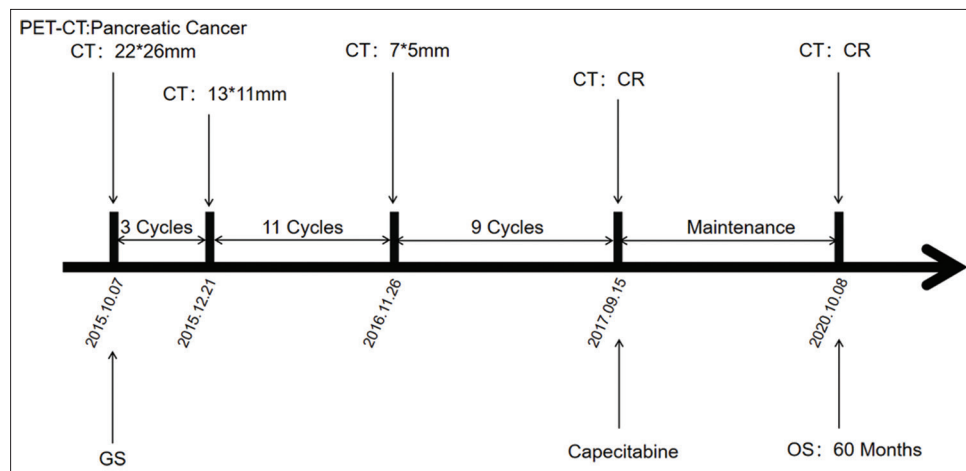


Figure 3. The treatment timeline for Case 2 from the initial diagnosis to the end of follow-up. GS, gemcitabine plus S-1; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; PR, partial response; CR, complete response; OS, overall survival.

condition assessment. In the process of conversion therapy, we evaluated the patient's condition every 3–4 cycles. One of the 4 patients successfully completed radical surgical resection after conversion therapy. The other 3 patients were evaluated for the possibility of surgical resection during chemotherapy, but failed to complete the surgery due to their own reasons. One of the 3 patients who did not receive surgical treatment achieved clinical complete remission. At the last reexamination, the patient was in stable condition with no signs of recurrence, and overall survival was up to 60 months. During the treatment, it is beneficial to the prognosis of patients to seize the opportunity to perform radical surgical resection or adjust the treatment plan in time. PET-CT combined with detection of CA 19-9 levels can significantly improve the sensitivity and accuracy of pancreatic cancer detection, thus helping to monitor the disease progression^[24]. The median survival time of conversion therapy (21.5 months) was between that of the FOLFIRINOX regimen (24.2 months) and that of the albumin-bound paclitaxel combined with gemcitabine regimen (18.8 months).

The eventual aim of conversion therapy is to prolong the survival time and improve the prognosis of patients, rather than to achieve radical surgical resection. Even if the potential radical resection is completed, most patients relapse within 2 years, and more than 80% of patients eventually die due to local recurrence or distant metastasis^[25-27]. The FOLFIRINOX regimen is the first option to be considered, with advantages in both R0 resection rate and survival^[22,28,29]. Compared with gemcitabine, FOLFIRINOX has more obvious grade 3 and 4 toxicity, which limits its application^[10,30,31]. We still need to explore chemotherapy regimens that are more appropriate for conversion therapy.

So far, findings regarding the efficacy of conversion therapy are scarce. In the future, we will carry out clinical trials with larger sample size to provide more clinical

evidence for corroborating the conclusion of this case series.

4. Conclusion

In this study, 4 cases of locally advanced unresectable pancreas were reported, and the patients achieved a median survival time of 21.5 months after conversion therapy. One of the patients is still alive. The overall survival period is as long as 60 months, which is longer than that of patients who underwent radical surgery after chemotherapy. In the clinic, we should choose the treatment plan tailored to the biological differences of patients. Although surgery is the first choice for radical treatment of pancreatic cancer, we have observed that some patients are more sensitive to chemotherapy. How to formulate the best comprehensive treatment for patients depends on the experience of clinicians. In general, for locally advanced pancreatic cancer with good biological behavior, conversion therapy is a good treatment option that could prolong survival of the patients, irrespective of the implementation of surgery.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Ethics statement

These case studies were based on the principles outlined in the Declaration of Helsinki. The protocol was approved by

the ethics committee of the Zhejiang Provincial People's Hospital (2017KY007).

Patient anonymity and consent

The study received informed written consent from all participants.

Author contributions

L.Y. and Z.C. contributed to the conception of the study. M.W. integrated all information and wrote the manuscript. L.Y., Z.C., and J.J. provided critical guidance, revisions for M.W. throughout the writing process. Y.X., M.Y., D.J., and Y.C. compiled information and revised the manuscript. All authors read and approved the final manuscript.

References

- Chen W, Zheng R, Baade PD, *et al.*, 2016, Cancer Statistics in China, 2015. *CA Cancer J Clin*, 66:115–32.
- Tempero MA, Malafa MP, Al-Hawary M, *et al.*, 2017, Pancreatic Adenocarcinoma, Version 2. 2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*, 15:1028–61.
- Strobel O, Büchler MW, 2016, Pancreatic Cancer: Clinical Practice Guidelines-What is the Evidence? *Nat Rev Clin Oncol*, 13:593–4. DOI: 10.1038/nrclinonc.2016.127.
- Varadhachary GR, Tamm EP, Abbruzzese JL, *et al.*, 2006, Borderline Resectable Pancreatic Cancer: Definitions, Management, and Role of Preoperative Therapy. *Ann Surg Oncol*, 13:1035–46. DOI: 10.1245/aso.2006.08.011.
- Balaban EP, Mangu PB, Khorana AA, *et al.*, 2016, Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*, 34:2654–68. DOI: 10.1200/jop.2016.017376.
- Grossberg AJ, Chu LC, Deig CR, *et al.*, 2020, Multidisciplinary Standards of Care and Recent Progress in Pancreatic Ductal Adenocarcinoma. *CA Cancer J Clin*, 70:375–403. DOI: 10.3322/caac.21626.
- Hidalgo M, 2010, Pancreatic Cancer. *N Engl J Med*, 362:1605–17.
- Lin H, Ma Y, Wang JZ, *et al.*, 2016, Analysis of 300 Consecutive Cases of Pancreatic Adenocarcinoma in a Single-Center in China. *Hepatobiliary Pancreat Dis Int*, 15:189–97.
- von Hoff DD, Ervin T, Arena FP, *et al.*, 2013, Increased Survival in Pancreatic Cancer with Nab-Paclitaxel Plus Gemcitabine. *N Engl J Med*, 369:1691–703.
- Conroy T, Desseigne F, Ychou M, *et al.*, 2011, FOLFIRINOX Versus Gemcitabine for Metastatic Pancreatic Cancer. *N Engl J Med*, 364:1817–25.
- Ueno H, Ioka T, Ikeda M, *et al.*, 2013, Randomized Phase III Study of Gemcitabine Plus S-1, S-1 Alone, or Gemcitabine Alone in Patients with Locally Advanced and Metastatic Pancreatic Cancer in Japan and Taiwan: GEST Study. *J Clin Oncol*, 31:1640–8. DOI: 10.1200/jco.2012.43.3680.
- Maggino L, Malleo G, Marchegiani G, *et al.*, 2019, Outcomes of Primary Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Ductal Adenocarcinoma. *JAMA Surg*, 154:932–42. DOI: 10.1001/jamasurg.2019.2277.
- Furuse J, Shibahara J, Sugiyama M, 2018, Development of Chemotherapy and Significance of Conversion Surgery after Chemotherapy in Unresectable Pancreatic Cancer. *J Hepatobiliary Pancreat Sci*, 25:261–8. DOI: 10.1002/jhbp.547.
- Hank T, Strobel O, 2019, Conversion Surgery for Advanced Pancreatic Cancer. *J Clin Med*, 8:1945.
- Yeo TP, Hruban RH, Leach SD, *et al.*, 2020, Pancreatic Cancer. *Curr Probl Cancer*, 26:176–275.
- Huguet F, Mukherjee S, Javle M, 2014, Locally Advanced Pancreatic Cancer: The Role of Definitive Chemoradiotherapy. *Clin Oncol (R Coll Radiol)*, 26:560–8. DOI: 10.1016/j.clon.2014.06.002.
- Suker M, Beumer BR, Sadot E, *et al.*, 2016, FOLFIRINOX for Locally Advanced Pancreatic Cancer: A Systematic Review and Patient-Level Meta-Analysis. *Lancet Oncol*, 17:801–10. DOI: 10.1016/s1470-2045(16)00172-8.
- Philip PA, Lacy J, Portales F, *et al.*, 2020, Nab-Paclitaxel Plus Gemcitabine in Patients with Locally Advanced Pancreatic Cancer (LAPACT): A Multicentre, Open-Label Phase 2 Study. *Lancet Gastroenterol Hepatol*, 5:285–94. DOI: 10.1016/s2468-1253(19)30327-9.
- Gillen S, Schuster T, Büschenfelde CM, *et al.*, 2010, Preoperative/Neoadjuvant Therapy in Pancreatic Cancer: A Systematic Review and Meta-Analysis of Response and Resection Percentages. *PLoS Med*, 7:e1000267. DOI: 10.1371/journal.pmed.1000267.
- Strobel O, Berens V, Hinz U, *et al.*, 2012, Resection after Neoadjuvant Therapy for Locally Advanced, “Unresectable” Pancreatic Cancer. *Surgery*, 152:S33–42. DOI: 10.1016/j.surg.2012.05.029.
- Gemenetis G, Groot VP, Blair AB, *et al.*, 2019, Survival in Locally Advanced Pancreatic Cancer after Neoadjuvant Therapy and Surgical Resection. *Ann Surg*, 270:340–7. DOI: 10.1097/sla.0000000000002753.
- Hackert T, Sachsenmaier M, Hinz U, *et al.*, 2016, Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. *Ann*

- Surg*, 264:457–63. DOI: 10.1097/sla.0000000000001850.
23. Napolitano F, Formisano L, Giardino A, *et al.*, 2019, Neoadjuvant Treatment in Locally Advanced Pancreatic Cancer (LAPC) Patients with FOLFIRINOX or Gemcitabine NabPaclitaxel: A Single-Center Experience and a Literature Review. *Cancers (Basel)*, 11:981. DOI: 10.3390/cancers11070981.
 24. Sun Y, Duan Q, Wang S, *et al.*, 2015, Diagnosis of Pancreatic Cancer using ¹⁸F-FDG PET/CT and CA19-9 with SUVmax Association to Clinical Characteristics. *J BUON*, 20:452–9.
 25. Smeenk HG, Tran TC, Erdmann J, *et al.*, 2005, Survival after Surgical Management of Pancreatic Adenocarcinoma: Does Curative and Radical Surgery Truly Exist? *Langenbecks Arch Surg*, 390:94–103. DOI: 10.1007/s00423-004-0476-9.
 26. Suenaga M, Fujii T, Kanda M, *et al.*, 2014, Pattern of First Recurrent Lesions in Pancreatic Cancer: Hepatic Relapse is Associated with Dismal Prognosis and Portal Vein Invasion. *Hepatogastroenterology*, 61:1756–61.
 27. Kleeff J, Reiser C, Hinz U, *et al.*, 2007, Surgery for Recurrent Pancreatic Ductal Adenocarcinoma. *Ann Surg*, 245:566–72. DOI: 10.1097/01.sla.0000245845.06772.7d.
 28. Ferrone CR, Marchegiani G, Hong TS, *et al.*, 2015, Radiological and Surgical Implications of Neoadjuvant Treatment with FOLFIRINOX for Locally Advanced and Borderline Resectable Pancreatic Cancer. *Ann Surg*, 261:12–7. DOI: 10.3410/f.725318150.793554053.
 29. Yoo C, Hwang I, Song TJ, *et al.*, 2020, FOLFIRINOX in Borderline Resectable and Locally Advanced Unresectable Pancreatic Adenocarcinoma. *Ther Adv Med Oncol*, 12:1758835920953294. DOI: 10.1177/1758835920953294.
 30. Gunturu KS, Yao X, Cong X, *et al.*, 2013, FOLFIRINOX for Locally Advanced and Metastatic Pancreatic Cancer: Single Institution Retrospective Review of Efficacy and Toxicity. *Med Oncol*, 30:361. DOI: 10.1007/s12032-012-0361-2.
 31. Chiorean EG, Cheung WY, Giordano G, *et al.*, 2019, Real-World Comparative Effectiveness of Nab-Paclitaxel Plus Gemcitabine Versus FOLFIRINOX in Advanced Pancreatic Cancer: A Systematic Review. *Ther Adv Med Oncol*, 11:1758835919850367. DOI: 10.1177/1758835919850367.