Chapter 17
Pancreatic Cancer

Ronald S. Arellano and Ryan Nipp

Epidemiology and Pathophysiology

Pancreatic cancer is highly lethal, and surgery remains the only potentially curative approach. Pancreatic cancer is the third leading cause of cancer death in the United States, and estimates suggest it will emerge as the second leading cause of cancer death by 2030 [1]. In 2017, over 50,000 new diagnoses of pancreatic cancer were expected in the United States, and projections expect over 40,000 deaths will be attributed to pancreatic cancer each year [2]. Incidence rates for this cancer increased at a rate of 1.2% per year between 2000 and 2012, and death rates increased by 0.4% [3]. Pancreatic cancer represents a particularly aggressive and lethal malignancy, with approximately 93% of pancreatic cancer patients dying within 5 years of diagnosis [3, 4]. Historically, 5-year survival rates for patients with pancreatic adenocarcinoma were below 6%, and those with metastatic disease had approximately 3–6-month median life expectancy [5–7]. Metastatic pancreatic cancer is incurable, but for patients with disease localized to the pancreas, surgical resection represents a potentially curative option. Unfortunately, many patients with pancreatic cancer present with initially unresectable disease, and thus oncologists frequently employ preoperative treatment to try to shrink the tumor and improve resectability [8, 9].

R. S. Arellano (✉)
Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
e-mail: rarellano@mgh.harvard.edu

R. Nipp
Department of Hematology/Oncology, Massachusetts General Hosptial, Harvard Medical School, Boston, MA, USA

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Role of Surgery

Pancreatic cancer remains highly lethal despite incremental gains with the use of multi-agent chemotherapy in the metastatic setting. Surgery remains the best opportunity for cure, but historically only 15–20% of patients with pancreatic cancer present with upfront, resectable disease. Recently, the combination regimens of FOLFIRINOX [10] and gemcitabine/nab-paclitaxel [11] have demonstrated encouraging results for patients with metastatic disease and also for patients with locally advanced and potentially resectable disease [12]. In the metastatic setting, median survival has been pushed out to beyond 11 months, and we are now seeing approximately 10% of patients alive at 2 years [10, 11, 13]. Several institutions have now published data about their ability to convert locally advanced or borderline resectable disease to resectable by using FOLFIRINOX [8, 12, 14, 15].

A Paradigm Shift Is Occurring in the Management of Potentially Resectable Pancreatic Cancer

Recent advances in combination chemotherapy regimens for pancreatic cancer have led to innovative strategies using these agents as preoperative therapy for patients with upfront unresectable disease [8–11, 14, 15]. Oncologists frequently introduce these therapies preoperatively to help convert locally advanced or borderline resectable disease to resectable and ensure a more successful operation. However, although surgery represents the only potentially curative approach for patients with pancreatic cancer, studies historically demonstrated 5-year survival rates of only 10–20% for patients with resected disease [13, 16–19].

Future Directions

Based on promising clinical results in other cancer types, the use of immunotherapy has been tested in pancreatic adenocarcinoma. Results to date are limited, but efforts remain to understand how best to harness the improved outcomes seen with immunotherapy in other malignancies. In addition, preliminary data of resected pancreatic adenocarcinoma from patients on angiotensin system inhibitors suggest enhanced T-cell activation and antigen presentation pathways, with analysis of mouse model tumors treated with an angiotensin receptor blocker (ARB) revealing suppression of tumor-associated macrophages [20, 21]. Collectively, these data underscore the potential for ARBs to modulate the immune microenvironment toward a permissive environment for immunotherapy. Future work will also continue to investigate how best to target available treatment options to patients most likely to benefit. For example, future studies will seek to demonstrate predictive biomarkers that will help guide clinicians and patients toward choosing a

gemcitabine versus a 5FU-based regimen. Moreover, the addition of other agents to known therapies will continue to emerge. For example, a regimen such a gemcitabine plus Abraxane in combination with cisplatin will have data in the coming years. Furthermore, studies of circulating tumor DNA (ctDNA) and circulating tumor cells will help identify patients with recurrent/progressive disease earlier while also helping identify patients for whom novel treatment paradigms may prove beneficial. Importantly, ongoing work is critically needed to investigate how best to provide supportive care to patients with pancreatic cancer. In the metastatic setting, understanding the role of palliative care and symptom monitoring interventions are urgently needed [22]. For patients with potentially resectable pancreatic cancer, additional research should seek to determine how best to help with the complex shared decision-making for these patients while also helping to support these patients along their journey of neoadjuvant treatment.

Patients receiving neoadjuvant therapy often experience numerous side effects, including nausea, vomiting, diarrhea, fatigue, fever, neuropathy, and loss of appetite [8, 10, 11]. Frequently, patients require hospital admissions to help address uncontrolled symptoms related to their cancer and side effects related to the treatment [8, 23]. A prior study demonstrated that nearly one-third of patients receiving combination chemotherapy for locally advanced pancreatic cancer required hospital admissions while receiving treatment. In addition, when patients complete their preoperative therapy and are able to undergo resection, the surgical operation is fraught with postoperative morbidity and occasional mortality [17, 24, 25]. Therefore, it is critically important that patients understand the risks and benefits when considering preoperative treatment for pancreatic cancer.

Another area of need within the field of pancreatic cancer includes the opportunity to help patients develop accurate understanding of their prognosis. Despite patients' general preference for accurate information regarding their prognosis, data suggest that the majority of patients misunderstand the curability of their cancer [26–28]. Patients often report a more optimistic assessment of their prognosis than their oncologist [29]. Importantly, research suggests that patient-clinician communication about prognosis does not take away patients' hope but rather enables patients to make informed treatment decisions and prepare for the future [28]. Thus, improving patient-clinician communication about prognosis and treatment options should be a priority for enhancing the quality of cancer care and improving informed treatment decision-making [30–35].

Pain Management for Patients with Pancreatic Carcinoma

Pain management represents one of the most challenging aspects of treating pancreatic carcinoma and often requires chronic high-dose narcotics [36, 37]. Because of the high risk of dependency and adverse effects of chronic narcotic use, an alternative approach to pain control is by neurolysis of the celiac ganglion. Pain from upper abdominal visceral organs, including the pancreas, is relayed via visceral afferent fibers through the splanchnic nerves and celiac plexus [38]. The celiac ganglion is

located deep in the retroperitoneum and typically overlies the anterolateral abdominal aorta, near the origins of the celiac plexus and superior mesenteric artery [38]. Tumor infiltration and/or desmoplastic reaction from pancreatic carcinoma often leads to an increased in nociceptive impulses to the celiac ganglion, resulting in excruciating pain. Kappis first described neurolysis of the celiac ganglion as a means of controlling upper abdominal visceral pain [39]. Anesthesiologists or interventional radiologists use imaging guidance to target the celiac ganglion for neurolysis. Because of the superior anatomic resolution offered by computed tomography (CT) versus fluoroscopic guidance of ultrasound, celiac neurolysis is often performed with CT guidance.

Computed Tomography-Guided Celiac Ganglion Neurolysis

Patient Selection

Pain associated with abdominal malignancies may be multifactorial; thus careful patient selection and elucidation of pain sources are essential in order to maximize the potential benefit of celiac neurolysis. While pain associated with pancreatic cancer is often the result of perineural or duodenal invasion, somatic pain from musculoskeletal involvement of tumor can contribute to the overall pain profile and will not be alleviated by neurolysis of celiac ganglion. Careful review of cross-sectional imaging and detailed patient history will help to identify patients who will receive maximum benefit from the neurolysis procedure.

Patient Preparation

Preliminary evaluation included patient education and discussion of the goals of care associated with neurolysis. Many patients who qualify for celiac ganglion neurolysis are on chronic opioid usage; thus an important goal of the procedure is to reduce the opioid usage with reduction of opioid-related side effects. Once appropriate patients are identified, imaging review and assessment of coagulation profile is necessary. A thorough neurological exam is essential in order to establish a baseline level of pain and to assess for post-procedure complications. Patients should be fasting for 8–10 hours prior to the procedure, and any correctable coagulopathies should be addressed prior to the procedure. Neurolysis can be performed with intravenous procedural sedation, monitored anesthesia care, or general anesthesia. Continuous hemodynamic monitoring is essential throughout the procedure.

Patient Positioning

Various approaches can be utilized to target the celiac ganglion, depending on patient body habitus, patients' overall condition, and the best percutaneous access to the ganglion. The most commonly used positions are prone, lateral decubitus, or supine.

Prone The prone position is the most commonly used approach, as it facilitates access to the celiac ganglion from a posterior approach. This allows a transcrural trajectory to target the para-aortic soft tissues at the level of the celiac axis (Fig. 17.1). When tumor infiltration precludes a transcrural approach, the prone position allows a retrocrural trajectory that targets neurolysis of preganglionic splanchnic nerves in the retrocrural space.

Lateral Decubitus When patients are unable to lie prone, a lateral decubitus position can be used for either retrocrural or antecrural approaches to the celiac ganglion. Because the independent lung is often more inflated than the dependent lung, this position may increase the risk of procedure-related pneumothorax.

Supine When either the lateral decubitus or supine position is not feasible, an anterior approach with the patient in the supine position is possible. This approach often necessitates a transhepatic or transgastric approach, which is usually of no clinical consequence.

Targeting

Antecrural The antecrural approach targets the soft tissue anterior to the diaphragmatic crura and the abdominal aorta in which the celiac ganglia reside. Injection of neurolytic agent in this space is most effective in achieving pain relief.

Retrocrural When the antecrural space is replaced by tumor, a retrocrural injection of neurolytic agent can be used to achieve splanchnic nerve block. In this targeting approach, the neurolytic agent spreads along the retroaortic space and treats the splanchnic nerves.

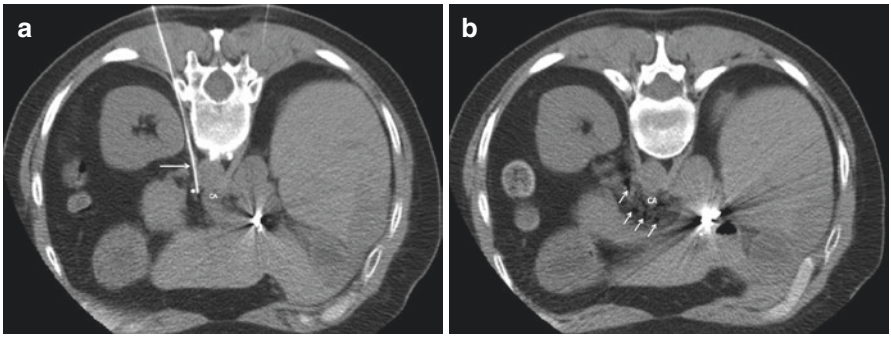

Fig. 17.1 (**a**) Axial unenhanced CT scan of the abdomen with the patient in the prone position. White arrow indicates 22-gauge needle on the celiac ganglion (white asterisk) via an antecrural approach. CA indicates origin of the celiac axis. (**b**) Axial unenhanced CT scan of the abdomen with the patient in the prone position. White arrows indicate distribution of ethanol in the retroperitoneal space. CA indicates origin of the celiac axis

Neurolytic agents Absolute alcohol is the most common neurolytic agent used for neurolysis. It acts by causing immediate precipitation of lipoproteins and mucoproteins of the neural elements. When an antecrural approach is used, approximately 20 ml of 95–100% absolute ethanol is injected on either side of the aorta at the level of celiac ganglion. When a retrocrural approach is chosen, the confined space limits the amount of neurolytic agent to approximately 5–10 ml. Phenol is an alternative agent that has been used to achieve celiac neurolysis. At a concentration of 3–20%, phenol acts as a protein coagulant and causes necrosis of neural elements. The data are limited comparing the effectiveness of ethanol versus phenol, but ethanol is considered to be more effective than phenol and is thus more commonly used [40].

Recovery Post-procedure care involves overnight observation for treatment response and potential complications. Hypotension may be encountered in the immediately post-procedure; therefore, patients should adhere to strict bed rest for a minimum of 12 hours post-procedure. Hemodynamic monitoring should continue in the post-procedure observation period for up to 24 hours. If necessary, acute hypotension can be treated with fluid replacement and medications if needed. A neurological examination should be performed immediately after the procedure to assess the changes in lower extremity function, especially when a retrocrural approach is used. Subjective evaluation of pain relief and changes in opioid requirement should be assessed the following day and compared with pre-procedure baseline to assess effectiveness.

Follow-up Follow-up care is carried out by the interventional team in collaboration with anesthesia, oncology services for inpatients. Outpatients typically follow up with pain control specialists for ongoing management of pain control if needed.

Complications Overall, celiac plexus neurolysis is a safe procedure with major complications occurring in fewer than 2% of patients. Most patients experience some transient back pain, especially when ethanol is used, that is likely the result of the neurolytic effect of the ethanol on sensory fibers within the ganglion. Orthostatic hypotension may result from diminished sympathetic tone that in turn leads to vasodilation [36, 40]. Transient self-limiting diarrhea can occur in up to 44% of patients who undergo celiac plexus neurolysis [36]. Neurologic complications are extremely rare and can include anal and bladder dysfunction. Inadvertent injection of neurolytic agent into or near the spinal artery can result in ischemia and subsequent lower extremity paralysis. With CT guidance, these complications are uncommon.

Outcomes Reported clinical efficacy of celiac plexus neurolysis is up to 90% of patients with upper abdominal malignancy [36]. With regard to patients with pancreatic cancer, celiac plexus neurolysis can eliminate pain in 10–20% when used without other therapies and up to 80–90% when combined with other therapies [41]. Even for patients who achieve partial relief, the major benefit of celiac plexus neurolysis is an overall reduction in opioid requirements and its associated adverse effects.

Locoregional Therapy for Pancreatic Carcinoma

Irreversible Electroporation

Irreversible electroporation (IRE) is an emerging nonthermal ablative technology with potential application in treating pancreatic carcinoma [42, 43]. With IRE cell death is achieved by subjecting tumor cell to high-voltage electrical pulses. The high electrical pulses result in permanent disruption of the phospholipid bilayer of the cellular membrane, resulting in multiple nanometer size pores. As a result, the normal homeostasis that exists between extracellular and intracellular environments is disrupted, ultimately leading to cell death by apoptosis. Because of its nonthermal mechanism of action, IRE may have a role in local control of pancreatic carcinoma. Early experiments in animals suggested that IRE achieves significant tissue destruction while maintaining vessel patency [44, 45]. In a retrospective analysis of 221 patients with 325 tumors, including 69 with pancreatic carcinoma, Scheffer et al. found that when IRE was combined with surgical resection of pancreatic carcinoma, overall survival was extended to 20 months from 13 months. In three patients, significant complications of bile leak and portal vein thrombosis were identified, despite early reports that suggested IRE preserved vasculature [46]. In contrast, Manson enrolled 24 patients in a prospective study in which ultrasound-guided percutaneous IRE was used as first-line therapy. The results showed that overall survival was 13.3 months in the IRE group compared to 9.9 months in patients identified through a registry. Because the overall survival between the two groups was not significant, the authors advocated against the use of IRE as first-line therapy. More recently, Flak et al. reported on a series of 33 patients with locally advanced pancreatic cancer who underwent 44 open IRE procedures. These authors found that the 30-day mortality was only 5% and the median overall survival was 10.7 months from the initial IRE procedure and 18.5 months from the time of diagnosis [47]. Despite a growing body of literature, more level I and II evidence are necessary to help define the potential role of IRE in the management of pancreatic carcinoma.

Transarterial Chemoembolization (TACE)

Pancreatic Adenocarcinoma Data regarding the use of transarterial chemoembolization for treatment of locally advanced pancreatic carcinoma is limited. Early studies proposed that locoregional delivery of chemotherapy should result in high concentrations of cytotoxic agents directly to tumors [48]. They studied 22 patients divided into 2 groups. Group A consisted of 12 patients who were treated with transarterial delivery of epirubicin, folic acid, and f-fluorouracil. Group B consisted of ten patients treated with transarterial delivery of mitoxantrone, 5-fluorouracil, and folic acid. For these two cohorts, Group A showed 33.3% 1-year survival rate, compared to 20% 1-year survival rate for Group B. A more recent study evaluated the

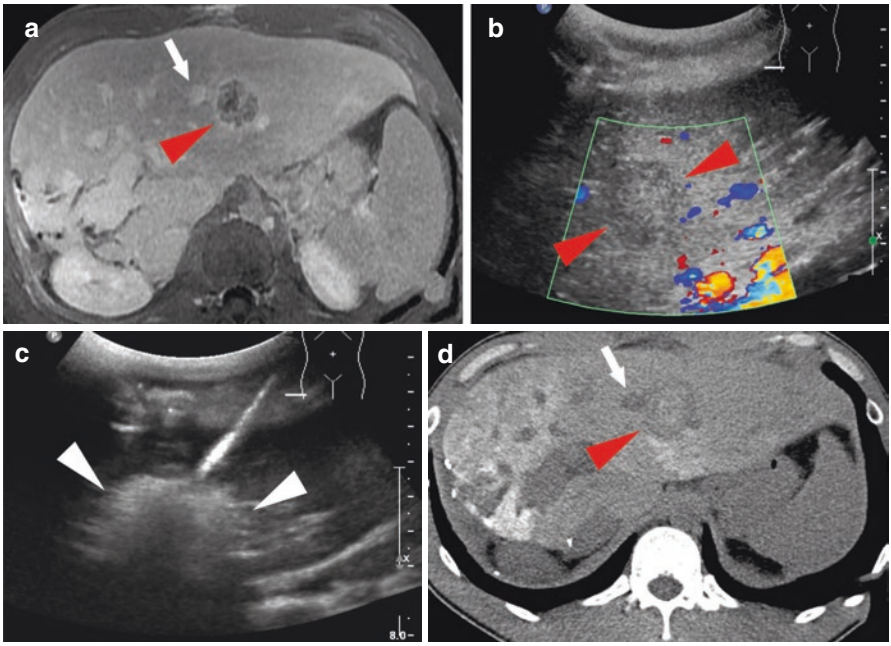

Fig. 17.2 72-year-old female with metastatic pancreatic adenocarcinoma s/p Whipple. Despite systemic chemotherapy, the single hepatic lesion grew, and a multidisciplinary team opted for percutaneous ablation. Contrast-enhanced MR image (**a**) shows the lesion (red arrowhead) in the left lobe near a portal vein branch (white arrow). Ultrasound examination (**b**) shows the same lesion (red arrowheads). Toward the end of microwave ablation (**c**), the lesion is completely obscured by gas (white arrowheads) as a result of tissue heating. Post-ablation non-contrast CT (**d**) shows the ablation zone (red arrowhead) covering the entire lesion and now extending to the portal vein branch (white arrow). Studies confirm excellent imaging responses for pancreatic metastatic lesions to the liver smaller than 3 cm; however we lack high-level studies as to any survival benefit

safety and efficacy of locoregional therapy for metastatic pancreatic adenocarcinoma. This study included 20 patients with hepatic metastatic pancreatic adenocarcinoma that were treated with thermal ablation (Fig. 17.2), chemoembolization (Fig. 17.3), or radioembolization. While the authors report a median overall survival of 25 months from the time of diagnosis, there were only three patients who underwent transarterial chemoembolization [49]. Thus, the clinical impact of TACE to treat metastatic pancreatic adenocarcinoma is limited. Sun et al. evaluated 27 patients with liver metastases from pancreatic cancer treated with TACE and found that the median survival time was 13.6 months and that the 1-, 3-, and 5-year survival rates were 70.4%, 22.2%, and 11.1%, respectively [50]. To date, there are no strong levels 1 or II data that advocate the use of TACE as primary treatment for locally advanced pancreatic carcinoma.

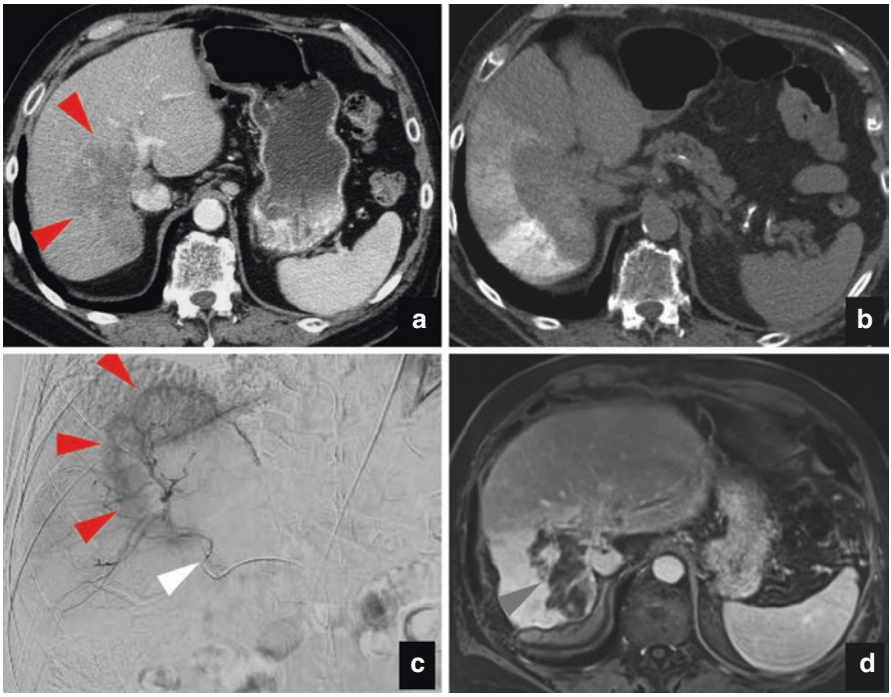

Fig. 17.3 62-year-old male with liver metastatic pancreatic adenocarcinoma. Axial contrast-enhanced CT (**a**) shows an infiltrating lesion in the right posterior liver lobe (red arrowheads). Post-chemoembolization CT (**b**) shows Lipiodol distribution peripheral to the lesion. Unlike in hepatocellular carcinoma where Lipiodol shows selective uptake by tumors, in pancreatic adenocarcinomas, Lipiodol distribution is preferentially seen in the tumors' periphery. This is despite the fact that during chemoembolization (**c**) with a superselective microcatheter (white arrowhead), the target lesion appears hypervascular (red arrowheads). Eighteen-month follow-up with contrast-enhanced MRI (**d**) shows complete devascularization of the slightly smaller lesion (red arrowhead). As with ablation, despite the encouraging imaging responses, high-level studies on oncologic outcomes after intra-arterial therapies are lacking

Radioembolization Emerging data suggests a possible role of radioembolization for treatment of liver metastases from pancreatic adenocarcinoma. Kim et al. reported on a series of 33 patients with hepatic metastases treated with yttrium-90 microspheres and showed post-treatment imaging findings consistent with partial response in 42%, stable disease in 37%, and progressive disease in 21%. Importantly, radioembolization produced only grade 3 or less toxicities up to 12 weeks post-procedure and a survival benefit of up to 20.8 months [51]. As with transarterial chemoembolization, additional clinical trials are necessary to further evaluate the efficacy and clinical outcomes of radioembolization for metastatic pancreatic adenocarcinoma.

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74:2913–21.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67:7–30.
3. American Cancer Society. Cancer facts & figures 2016. Atlanta: American Cancer Society; 2016.
4. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277–300.
5. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006;56:106–30.
6. Hawes RH, Xiong Q, Waxman I, Chang KJ, Evans DB, Abbruzzese JL. A multispecialty approach to the diagnosis and management of pancreatic cancer. Am J Gastroenterol. 2000;95:17–31.
7. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25:2607–15.
8. Faris JE, Blaszkowsky LS, McDermott S, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist. 2013;18:543–8.
9. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg. 2015;261:12–7.
10. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
11. 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.
12. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: a phase 2 clinical trial. JAMA Oncol. 2019;5:1020–7.
13. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371:2140–1.
14. Boone BA, Steve J, Krasinskas AM, et al. Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer. J Surg Oncol. 2013;108:236–41.
15. Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer. 2012;12:199.
16. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg. 1993;165:68–72; discussion −3.
17. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg. 1990;211:447–58.
18. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg. 1997;226:248–57; discussion 57–60.
19. Perysinakis I, Avlonitis S, Georgiadou D, Tsipras H, Margaris I. Five-year actual survival after pancreatoduodenectomy for pancreatic head cancer. ANZ J Surg. 2015;85:183–6.
20. Cortez-Retamozo V, Engblom C, Pittet MJ. Remote control of macrophage production by cancer. Onco Targets Ther. 2013;2:e24183.
21. Cortez-Retamozo V, Etzrodt M, Newton A, et al. Angiotensin II drives the production of tumor-promoting macrophages. Immunity. 2013;38:296–308.
22. Temel JS, Greer JA, El-Jawahri A, et al. Effects of early integrated palliative care in patients with lung and GI cancer: a randomized clinical trial. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35:834–41.
23. Smyth EN, Bapat B, Ball DE, Andre T, Kaye JA. Metastatic pancreatic adenocarcinoma treatment patterns, health care resource use, and outcomes in France and the United Kingdom between 2009 and 2012: a retrospective study. Clin Ther. 2015;37:1301–16.

24. Dias-Santos D, Ferrone CR, Zheng H, Lillemoe KD, Fernandez-Del CC. The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. Surgery. 2015;157:881–7.
25. Barugola G, Falconi M, Bettini R, et al. The determinant factors of recurrence following resection for ductal pancreatic cancer. JOP. 2007;8:132–40.
26. Greer JA, Pirl WF, Jackson VA, et al. Perceptions of health status and survival in patients with metastatic lung cancer. J Pain Symptom Manag. 2014;48:548–57.
27. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367:1616–25.
28. Epstein AS, Prigerson HG, O'Reilly EM, Maciejewski PK. Discussions of life expectancy and changes in illness understanding in patients with advanced cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34:2398–403.
29. Gramling R, Fiscella K, Xing G, et al. Determinants of patient-oncologist prognostic discordance in advanced cancer. JAMA Oncol. 2016;2(11):1421–6.
30. Steinhauser KE, Christakis NA, Clipp EC, et al. Preparing for the end of life: preferences of patients, families, physicians, and other care providers. J Pain Symptom Manag. 2001;22:727–37.
31. Steinhauser KE, Christakis NA, Clipp EC, McNeilly M, McIntyre L, Tulsky JA. Factors considered important at the end of life by patients, family, physicians, and other care providers. JAMA. 2000;284:2476–82.
32. Steinhauser KE, Clipp EC, McNeilly M, Christakis NA, McIntyre LM, Tulsky JA. In search of a good death: observations of patients, families, and providers. Ann Intern Med. 2000;132:825–32.
33. Lundquist G, Rasmussen BH, Axelsson B. Information of imminent death or not: does it make a difference? J Clin Oncol Off J Am Soc Clin Oncol. 2011;29:3927–31.
34. Smith TJ, Dow LA, Virago E, Khatcheressian J, Lyckholm LJ, Matsuyama R. Giving honest information to patients with advanced cancer maintains hope. Oncology. 2010;24:521–5.
35. Zhang B, Wright AA, Huskamp HA, et al. Health care costs in the last week of life: associations with end-of-life conversations. Arch Intern Med. 2009;169:480–8.
36. Eisenberg E, Carr DB, Chalmer TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg. 1995;80:290–5.
37. Kaugman M, Singh G, Das S, Concha-Parra R, et al. Efficacy of endoscopic ultrasound guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol. 2010;44:127–34.
38. Loukas M, Klaasen A, Merbs W, Tubbs RS, Gielecki J, Zurada A. A review of the thoracic splanchnic nerves and celiac ganglia. Clin Anat. 2010;23(5):512–22.
39. Fujita Y, Sari A. Max Kappis and the celiac plexus block. Anesthesiology. 1997;86:508.
40. Wang PJ, Shang MY, Qian Z, Shao CW, Wang JH, Zhao XH. CT-guided percutaneous neurolytic celiac plexus block technique. Abdom Imaging. 2006;31(6):710–8.
41. Sachev AH, Gress FG. Celiac plexus block and neurolysis: a review. Gastrointest Endosc Clin N Am. 2018;28(4):579–86.
42. Silk M, Tahour D, Srimathveeravalli G, Solomon SB, Thornton RH. The state of irreversible electroporation in interventional oncology. Semin Intervent Radiol. 2004;31:111–7.
43. Scheffer HJ, Nielsen K, de Jong MC, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol. 2014;25:997–1011.
44. Charpentier KP, Wolf F, Noble L, Winn B, Resnick M, Dupuy DE. Irreversible electroporation of the pancreas in swine: a pilot study. HPB (Oxford). 2010;12:348–51.
45. Bower M, Sherwood L, Li Y, Martin R. Irreversible electroporation of the pancreas: definitive local therapy without systemic effects. J Surg Oncol. 2011;104:22–8.
46. Narayanan G, Bhatia S, Echenique A, Suthar R, Barbery K, Yrizarry J. Vessel patency post irreversible electroporation. Cardiovasc Intervent Radiol. 2014;37:1523–9.
47. Flak RV, Stender MT, Jensen TM, Andersen KL, et al. Treatment of locally advanced pancreatic cancer with irreversible electroporation; A Danish single center study of safety and feasibility. Scand J Gastroenterol. 2019;54(2):252–8.

48. Meyer F, Grote R, Lippert H, Ridwelski K. Marginal effects of regional intra-arterial chemotherapy as an alternative treatment option in advanced pancreatic carcinoma. Langenbeck's Arch Surg. 2004 Feb.;389:32–9.
49. Bailey RE, Srapanemi PK, Core J, Vidal LLC, LeGout J, et al. Safety and efficacy of locoregional therapy for metastatic pancreatic ductal adenocarcinoma to the liver: a single-center experience. J Gastrointest Oncol. 2019;10:688–94.
50. Sun JH, Zhou TY, Zhang YL, Zhou GH, et al. Efficacy of transcatheter arterial chemoembolization for liver metastases arising from pancreatic cancer. Oncotarget. 2017;8:39746–55.
51. Kim AY, Frantz S, Bower J, Akhter N. Radioembolization with Yttrium-90 microspheres for the treatment of LIver metastases of pancreatic adenocarcinoma: a multicenter analysis. J Vasc Interv Radiol. 2019;30:298–304.