Chapter 20
Pancreatic Cancer

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PEARLS

- Fifth leading cause of cancer mortality, although only the ninth most common cancer.
- Found primarily in Western countries. Known risks include tobacco use, diets high in animal fat, ionizing radiation, chemotherapy, and exposure to 2-naphthylamine, benzene, and gasoline. Possible links between alcohol use, coffee use, chronic pancreatitis, and diabetes are less clear.
- Four parts: head (including uncinate process), neck, body, and tail. Two-third cancers present in the head.
- Most common presenting symptoms = jaundice (due to common bile duct obstruction), weight loss (due to malabsorption from pancreas exocrine dysfunction), diabetes (related to pancreas endocrine dysfunction), gastric outlet obstruction, and abdominal pain. Jaundice is most common in patients with lesions in the head. Patients with lesions arising in the body or tail typically present with midepigastric or back pain. May infrequently present with Trousseau's sign (migratory thrombophlebitis) or Courvoisier's sign (palpable gallbladder).
- Primary LN drainage includes the pancreaticoduodenal, suprapancreatic, pyloric, and pancreaticosplenic LN with the porta hepatic, infrapyloric, subpyloric, celiac, superior mesenteric, and paraaortic areas being involved in advanced disease.
- Most common type is of ductal origin. Cystadenocarcinomas, intraductal carcinomas, and solid and cystic papillary neoplasms (also known as *Hamoundi tumors*) have a more indolent course. Acinar cell cancers and giant cell tumors are aggressive and have poor survival. Five percent are tumors of the endocrine pancreas – these tumors are rare, slow growing, and have a long natural history.
- Seventy to hundred percent contain k-*ras* oncogene. TP53 mutation present in approximately 50%.

- Peritoneal and liver mets are most common. Lung is most common location outside the abdomen.
- Postresection CA19-9 levels prognostic in patients treated with chemorad per RTOG 9704 (Berger et al. 2008).

WORKUP

- Main purpose of the workup is to determine resectability, establish a histologic diagnosis, reestablish biliary-tract outflow, and circumvent gastric outlet obstruction. Various diagnostic approaches exist.
- H&P, upper GI, CT scan, US, and ERCP, laparoscopy, or CT-guided biopsy.
- Laboratories: CBC, CEA, CA19-9, glucose, amylase, lipase, bilirubin, alkaline phosphatase, LDH, and LFTs.
- Endoscopy of the upper GI tract is extremely valuable with endobiliary stent placement. Endoscopic ultrasound can also be performed.

STAGING (AJCC 7TH ED., 2010): PANCREATIC CANCER

- The definition of TNM and anatomic stage/prognostic groupings has not changed from the sixth edition (2002) for exocrine pancreas.
- Pancreatic neuroendocrine tumors (including carcinoid tumors) are now staged by a single pancreatic staging system.

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ*
T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanInIII" classification.

Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

continued

Anatomic stage/prognostic groups

0:	Tis N0 M0
IA:	T1 N0 M0
IB:	T2 N0 M0
IIA:	T3 N0 M0
IIB:	T1-T3 N1 M0
III:	T4 Any N M0
IV:	Any T Any N M1

- For practical purposes, tumors are generally classified as resectable (Stage I, II), unresectable (Stage III), and metastatic (Stage IV).
- Definition of resectability varies by institution, but generally includes no encasement (<180° involvement) of the celiac artery or superior mesenteric artery, and patency of portal vein and superior mesenteric vein. Splenic vein involvement does not necessarily mean a tumor is unresectable. Borderline resectable cases- tumor abutment (≤180 or ≤50%) of celiac artery or SMA circumference, or >180° or >50% common hepatic artery that is amenable to resection and repair, or SMV or portal vein occlusion amenable to resection and interposition grafting.
- Prognostic markers: surgical margins, nodal status, tumor grade.

TREATMENT RECOMMENDATIONS

Stage	Recommended treatment
Resectable (10–15% of patients)	■ Pancreaticoduodenectomy. Mortality <5% when performed by experienced surgeons. Pylorus-preserving pancreaticoduodenectomy improves GI function and does not appear to compromise efficacy. Body/tail cancers (when resectable) should have a distal pancreatectomy with en bloc splenectomy ■ Recommendations about adjuvant treatment are controversial. Options include ■ Clinical trial ■ Systemic gemcitabine followed by concurrent chemo-RT (5-FU based, 50.4 Gy) ■ Chemotherapy alone (gemcitabine based) ■ Due to post-op complications ~25% of patients do not receive intended post-op therapy ■ *Open areas of investigation include* ■ RT dose-escalation with IORT, radiosurgery, brachytherapy, proton therapy, IGRT

	■ Pre-op chemo-RT to decrease treatment toxicity, increase potential for negative margins, decrease risk of intraoperative tumor seeding, and ensure that operative complications do not cause omission of adjuvant therapy ■ Prophylactic hepatic irradiation in favorable patients due to the high incidence of liver metastasis. This has been tested and determined feasible by an RTOG study in patients with unresectable lesions which showed a 13% liver metastasis rate (lower than historic controls). Other RTOG trials pending. ■ Radiosensitizers, radioprotectants, and Yttrium-90 have also been studied
Borderline resectable	■ Staging laparoscopy. If negative, neoadjuvant therapy (concurrent 5-FU based chemo-RT ± systemic gemcitabine) followed by restaging and surgical resection if feasible.
Unresectable	■ Clinical trial preferred. Alternatively, definitive concurrent chemo-RT (5-FU based, 50–60 Gy) ± gemcitabine, or gemcitabine based chemotherapy alone. Multiinstitution cooperative ECOG and RTOG trials ongoing palliation with stents or surgical bypass
Metastatic	■ Palliation with stents, surgical bypass, chemo, RT, supportive care, or some combination of the above. Most randomized studies favor the use of gemcitabine over the use of 5-FU based chemo in the treatment of metastatic disease. Celiac nerve block is an effective palliative tool for local pain
Endocrine	■ Treatment surgical. Chemo for unresectable or metastatic disease. Effects of RT unknown, although anecdotal responses exist

STUDIES

RESECTABLE ADJUVANT TREATMENT

In favor of postoperative chemo-RT

- *GITSG 91-73* (Kalser and Ellenberg 1985): 43 patients with resectable pancreatic cancer were randomized to surgery followed by EBRT (40 Gy split course) with concurrent 5-FU vs. surgery alone. Adjuvant chemo-RT improved OS (2-year/5-year OS 43%/14% vs. 18%/5%).
  - Updated (GITSG 1987): additional 30 nonrandomized patients entered into adjuvant therapy group. Two-year OS 46%
  - Although touted by many as "the gold standard," few radiation oncologists currently use this split course regimen
- *Mayo Clinic* (Corsini 2008): retrospective review of 472 patients with R0 resection of T1-3N0-1M0 pancreatic cancer who

received adjuvant chemoradiation (50.4 Gy, 98% of patients received concurrent FU-based chemotherapy) or observation. Adjuvant chemoradiation cohort improved OS (MS 25.2 vs. 19.2 months, 2/5-year OS 50%/28 vs. 39%/17%).

- *Johns Hopkins* (Herman et al. 2008): review of 616 patients treated with pancreaticoduodenectomy. Patients who received adjuvant 5-FU based chemo-RT had improved MS (21 vs. 14 months), 2-year OS (44 vs. 32%), and 5-year OS (20 vs. 15%) compared to those who did not receive chemo-RT.
- *SEER* (Hazard et al. 2007): 3,008 patients receiving pre-op/post-op RT or surgery alone were reviewed. Patients (1,224) received RT. Majority of RT patients received post-op RT; only 23 patients got pre-op RT. Patients receiving RT (either pre or post-op) had improved survival (MS 17 vs. 12 months, 5-year OS 13 vs. 9.7%). RT improved OS in patients with direct extension of tumor beyond pancreas or positive regional nodes, but not T1-2N0M0. RT improved CSS in patients with positive regional nodes. No difference in OS between patients receiving pre-op or post-op RT. (Note that reanalysis of SEER database by Stessin showed improved OS in patients receiving pre-op RT. See Sect. "Neoadjuvant treatment").
- *Johns Hopkins-Mayo Clinic Collaborative Study* (Hsu 2009): retrospective OS was longer among patients receiving chemo-RT (50.4 Gy with concurrent 5-FU based chemo) vs. surgery alone (MS 21.1 vs. 15.5 months; 2/5-year OS 44.7%/22.3 vs. 34.6%/16.1%, $p < 0.001$). Adjuvant chemo-RT also improved survival 33% when propensity score analysis used and stratified by age, margins, nodes, and T stage (RR = 0.57–0.75, $p < 0.05$). Matched-pair analysis demonstrated OS was longer with chemo-RT vs. observation (MS 21.9 vs. 14.3 months; 2/5-year OS 45.5%/25.4 vs. 31.4%/12.2%, $p < 0.001$).

In favor of chemo

- *ESPAC-1* (Neoptolemos et al. 2001, 2004): 2 × 2 factorial design, 541 patients with resected pancreatic or periampullary carcinoma (only 289 of which were randomized). Arms were chemo-RT (40 Gy split course with 5-FU), adjuvant chemo alone (5-FU/leucovorin), both chemo-RT and chemo, or observation alone. Results contradictory when looking at randomized vs. nonrandomized patients in initial analysis. For all patients, chemo improved MS (19.7 vs. 14 months). For randomized patients only, chemo had no effect on MS (17.4 vs. 15.9 months). In final analysis (Neoptolemos et al. 2004) of the randomized patients,

authors concluded that chemo was of benefit (5-year OS 21 vs. 8%), while chemo-RT was detrimental (5-year OS 10 vs. 20%).
  - Criticisms: no RT quality assurance. Only 128 patients with RT details available, of whom only 90 patients got the prescribed dose of 40 Gy. Use of split-course RT. Progressive disease in 19% of patients precluded RT.
- *ESPAC metaanalysis* (Neoptolemos et al. 2009): 822 patients received either adjuvant 5-FU/folinic acid or observation after resection. Adjuvant 5-FU/FA improved MS (23.2 vs. 16.8 months).
- *CONKO-OO1* (Oettle et al. 2007): 368 patients with R0/R1 resection randomized to observation vs. gemcitabine × 6c. Adjuvant gemcitabine improved DFS (13.4 vs. 6.9 months, $p < 0.001$), but not OS (22 vs. 20 months, $p = 0.06$). Excluded patients with postop CEA/CA19-9 levels ≥2.5 × upper limit of normal.
- *Metaanalysis* (Stocken et al. 2005): 875 patients with resected pancreatic cancer on six trials. Chemo improved MS (14→19 months) and 5-year OS (12→19%). No significant survival benefit for chemo-RT (MS 15.2–15.8 months). Subgroup analyses estimated that chemo-RT was more effective (and chemo less effective) for patients with positive resection margins.

In favor of observation

- *EORTC 40891* (Klinkenbijl et al. 1999; Smeenk et al. 2007): 218 patients with resectable pancreatic or periampullary cancer status postresection randomized to chemo-RT (40 Gy split course with 5-FU) vs. observation. Adjuvant treatment resulted in no significant difference in 10-year OS (18% overall, 8% pancreatic head group, 29% periampullary group) or PFS (median PFS 1.2 years in observation arm vs. 1.5 years in treatment arm). Criticisms: only 119 patients had pancreatic cancer, no maintenance therapy was given, and the study included patients with positive margins without stratification. No RT quality assurance.

Beyond adjuvant 5-FU chemo-RT

- *RTOG 97-04/SWOG/ECOG* (Regine et al. 2008): 451 patients with GTR of pancreatic cancer randomized to weekly gemcitabine vs. protracted venous infusion 5-FU for 3 weeks before and for 12 weeks after concurrent chemo-RT (5-FU, 50.4 Gy). Trend for improved MS (20.5 vs. 16.9 months) and 3-year OS (31 vs. 22%, $p = 0.09$) with gemcitabine. Patterns of failure similar in both arms: distant (71–77%) > local (23–28%) > regional (nodes associated with tumor site) 7–8%.

- *ACOSOG Z05031* (Picozzi 2008): multicenter phase II trial of 89 patients with R0/1 resection of pancreatic head carcinoma treated with 50.4 Gy RT with concurrent cisplatin, 5-FU, and alpha-interferon followed by additional 5-FU chemotherapy. Ninety-six percent of patients had grade 3+ toxicity, but no toxicity-related deaths were noted. MS is 27 months and 2-year OS is 55% after surgery. Local recurrence 46%, systemic recurrence 35%.

Ongoing trials

- ESPAC-3 (phase III): resected pancreatic adenocarcinoma randomized to adjuvant 5-FU vs. gemcitabine
- EORTC 40013 (phase II/III): resected pancreatic head adenocarcinoma randomized to gemcitabine vs. gemcitabine for 2c followed by gemcitabine and concomitant RT (50.4 Gy)

Neoadjuvant treatment

- No completed phase III studies.
- Krishnan et al. (2007): of 323 patients, 247 patients received neoadjuvant chemo-RT (30 Gy/10 fx or 50.4 Gy/28 fx with 5-FU, gemcitabine, or capecitabine), 27 patients received induction gemcitabine-based chemo → chemorad. RT encompassed regional nodes in 69% patients. Median follow-up 5.5 months. MS 8.5 months (chemo-RT group) vs. 11.9 months (induction chemo → chemo-RT group). No significant difference in patterns of failure between groups.
- Evans et al. (2008): phase II, 86 patients. Chemo-RT (30 Gy/10 fx and weekly gemcitabine × 7 weeks) → surgery. RT included pancreaticoduodenal, portahepatic, superior mesenteric, and celiac axis LN. All patients restaged after chemo-RT. Eighty-five percent patients went on to surgery. MS 22.7 months, 5-year OS 27%. Of patients who received surgery, MS 34 vs. 7 months for unresectable patients.
- *SEER* (Stessin et al. 2008): reanalysis of SEER database, 3,885 patients. Seventy patients (2%) pre-op RT, 1,478 patients (38%) post-op RT, 2,337 patients (60%) surgery alone. MS 23 months (pre-op RT), 17 months (post-op RT), 12 months (surgery alone).

UNRESECTABLE

- *GITSG* (Moertel et al. 1981): 194 patients with unresectable pancreatic cancer randomized to split course EBRT (40 Gy) with concomitant bolus 5-FU vs. split course EBRT (60 Gy) with concomitant bolus 5-FU vs. EBRT (60 Gy) alone. Both

concomitant chemo arms prolonged MS vs. EBRT alone (42.2, 40.3, and 22.9 weeks, respectively).

- *GERCOR* (Huguet et al. 2007): reviewed 181 patients with locally advanced disease treated with 5-FU or gemcitabine based chemo × 3 months without evidence of progression who then received either additional chemotherapy vs. chemo-RT (physician choice). Chemo-RT improved median PFS (7.4→10.8 months) and OS (11.7→15 months).
- *RTOG 9812* (Tyvin 2004): phase II study of 109 patients with unresectable pancreatic cancer treated with EBRT 50.4 Gy and weekly paclitaxel. All patients were restaged 6 weeks after completion of chemo-RT. If marked shrinkage, resection was attempted. MS 11.2 months with 1-year OS 43% and 2-year OS 13%. Forty percent grade III and 5% grade IV toxicity with 1 death due to treatment.
- Tempero et al. (2003): 92 patients with locally advanced and/or metastatic adenocarcinoma of the pancreas randomized to 2,200 mg/m^2 gemcitabine over 30 min or 1,500 mg/m^2 over 150 min on days 1, 8, and 15 of a 4-week cycle. Slow infusion resulted in increased median survival (5 vs. 8 months, $p = 0.031$) and decreased toxicity.
- Ko et al. (2007): phase II, 25 patients. Gemcitabine and cisplatin × 6c→chemo-RT (50.4 Gy/28 fx with capecitabine). Patients restaged during and after chemotherapy, and after chemo-RT. If progressed on chemo, then spared chemo-RT. Forty-eight patients completed treatment, 32% patients progressed during chemo. Well tolerated. Median time to progression 10.5 months, MS 13.5 months, and MS of patients completing treatment 17 months.
- Murphy et al. (2007): 74 patients with locally advanced pancreatic cancer treated with chemo-RT (36 Gy/15 fx) with full-dose gemcitabine (1,000 mg/m^2 on days 1, 8, and 15). PTV = GTV + 1 cm. Six-month OS 46%/13%, median OS 11.2 months.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Treat tumor (or tumor bed) and nodal groups at risk using pre-op and post-op imaging studies as well as the findings at surgery. Three-dimensional planning is necessary to optimize dose distribution while minimizing dose to liver, kidneys, small bowel, and spinal cord.
- Sim supine, arms up, with oral contrast. Use gastrografin (proprietary name) oral contrast, not barium, if CT is planned within 2 days. Give renal contrast or use CT to identify kidneys.

- Pancreas lies at L1–L2. Celiac axis is at T12. SMA is at L1.
- Lesions at the pancreatic head: treat pancreaticoduodenal, suprapancreatic, and celiac nodes, porta hepatis, the entire duodenal loop, and the tumor with 2–3 cm margin on gross disease.
- Lesions in the body/tail: treat pancreaticoduodenal, portal hepatic, lateral suprapancreatic nodes, the nodes of the splenic hilum, and the gross tumor with 2–3 cm margin. Porta hepatis and duodenal bed do not need to be covered.
- In general, patients are treated with a three or four field design – AP (50–80% of dose), two laterals or slightly off-axis superior/inferior obliques (20% of dose), plus or minus a posterior field. High energy photon fields (e.g., 18 MV) are useful particularly for the lateral/oblique fields.
- In general, for tumors of the pancreatic head treated with AP/PA fields: superior border = T10/T11; inferior border = L3/4; left border = 2 cm to the left of the edge of the vertebral body or 2 cm from the tumor; right border = pre-op location of the duodenum. On the laterals, anterior margin = 1.5–2 cm beyond the gross disease (being sure to include the duodenum); posterior margin = blocks the cord but covers 1.5–2 cm of the vertebral body.
- 4DCT or fluoroscopy is useful at the time of simulation to evaluate organ movement during respiration, which can have an impact on the position of the target volume and the kidneys. Some groups use respiratory gating, and abdominal compression to limit organ motion and decrease field size.
- Conedown to gross tumor (or preoperative tumor extent) + 2 cm margin at 45 Gy.
- For unresectable/palliative cases, consider using smaller field sizes, particularly if giving concurrent chemo-RT: GTV = primary tumor excluding draining LN, CTV = GTV ± 0.5 cm, PTV = CTV ± 0.5 cm.

DOSE PRESCRIPTIONS

- Treat to 45 Gy at 1.8 Gy/fx followed by conedown to 50.4 Gy. In definitive chemo-RT setting, consider boosting to 54–59.4 Gy if feasible, respecting normal tissue tolerance.
- Multiple dose-escalation studies with hyperfractionation, brachytherapy, IORT, radiosurgery, hypofractionation, and other methods are under investigation.

DOSE LIMITATIONS

- Doses up to 50 Gy are tolerated by small volumes of stomach and intestine. Most common late effects are mucosal ulceration and bleeding. Perforation is rare.

- Limit the equivalent of at least one kidney to <20 Gy.
- Limit the whole liver to <20 Gy and 70% of liver to <30 Gy to prevent radiation hepatitis. Small volumes of liver can be treated to high doses.

COMPLICATIONS

- Critical normal tissues include liver, small bowel, stomach, cord, and kidney.
- Because the pancreas is a gland with both exocrine and endocrine secretions, both can decrease acutely or chronically following treatment. Adequate monitoring for diabetes is integral to treatment as is supplementation with pancreatic enzymes if exocrine insufficiency is suspected (pancrealipase with each meal).
- Acute – nausea and vomiting (use antiemetics, proton pump inhibitor, or H2 blocker). Diarrhea less common. If jaundice develops during RT or following treatment, ascending cholangitis must be considered as a potential etiology.
- Late – possible side effects include ulceration, stricture formation, obstruction, and (less commonly) perforation of GI tract. Side effects to cord, kidney, liver should not occur if normal tissue tolerances are followed.

FOLLOW-UP

- H&P, laboratories, and abdominal CT every 2 months to evaluate for disease recurrence/progression.

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