This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Resected Pancreatic Cancer
GI Practice Guideline

Background/Incidence

- Pancreatic cancer is one of the most treatment-resistant malignancies
- Only 15-20% of cancers are resectable at presentation
- Five-year survival rates for patients with resected pancreatic cancer are 10 to 30% (node positive and node negative respectively)
- There is no consensus on the interpretation of the available evidence, and as of 2007, there are still important questions unanswered by clinical trials. ESPAC-3 (PA.2) trial result pending – may change this guideline
- Approximately 50 patients per year are seen at LRCP

Investigations

- ERCP
- CT Scan
- Needle biopsy
- Open biopsy at surgery
- Ca 19-9

Staging

- See AJCC sixth edition
- Important post-surgical considerations for treatment are positive resected margins
Treatment

Adjuvant

R0 (no residual evident) Resection N0-1
1. FUFA: 5FU 400 mg/m$^2$ + Folinic Acid 20 mg/m$^2$ IV OD x 5 q4wk times 6 months

R1 (microscopic residual) or R2 (gross residual) Resection, N0-1
2. FUFA: 5FU 400 mg/m$^2$ + Folinic Acid 20 mg/m$^2$ IV OD x 5 q4wk times four months, with 5FU 200 mg/m$^2$ concurrent with radiation treatment between first and last two cycles of chemotherapy. 28 fractions, total dose variable (individualized) but desired range 50.4 – 59.4 Gy.

R2 (gross residual) or metastatic disease
3. Gemcitabine 1000 mg/m$^2$ IV - Three weeks out of four as palliative therapy

Treatment Benefits

Chemoradiotherapy Approach

GITSG study: Observation vs. 40Gy EBRT + bolus 5FU x 6 doses, then 5FU bolus 3 doses/month until progression or 2 years, whichever was earlier. MS 11 vs. 20 months, 43 pts. R1 excluded [2]

EORTC study: Observation vs. 40 Gy EBRT in split course + infusional 5FU. MS not different; 2YS 26 vs. 34%, 114 pts (but ~20% of pts in Rx arm did not receive it) R1 included [3]

RTOG 9704 study: 50.4 Gy + infusional 5FU followed by 2 months 5 FU infusion, vs. 50.4 Gy + infusional 5FU, preceded and followed by gemcitabine (1 cycle pre-, 3 cycles post). 16.9 vs 20 mos MS; 3 YS 32 vs 21 % for patients with pancreatic head tumours (n=380). Negative for all pancreatic tumours combined analysis. [4]

Johns Hopkins series: "standard" chemoradiation (40-45 Gy + 3 days 5FU, followed by 4 months weekly 5FU) vs "intensive" chemoradiation (50.4 Gy + hepatic irradiation + infusional 5FU then 5FU/LV x 4 months) vs observation. Patient choice. Postoperative Rx better MS 20 vs 14 months. 99 / 21 / 53 pts. [5]

SEER database: 29 vs 12.5 months MS; 3YS 45 vs 30 % for pts treated with chemoradiation. [6]

Picozzi 2003: Radiation 50-54 Gy + Interferon/Cisplatin/5FU (42pts; 84% LN +ve) 55% 5YS. [7]
Gemcitabine as radiation sensitizer tolerated, alone or with cisplatin (phase II studies only so far).

**Chemotherapy Approach**
Norwegian Trial 1984-7: Adjuvant 5FU/Doxorubicin/Mitomycin-C (AMF) vs observation. 23 vs 11 months MS but 3YS same (30 vs 27%), 61 pts, significant number did not complete therapy (37%). **R1 excluded [8]**

CONKO Trial: Adjuvant gemcitabine x 6 months vs observation. DFS 13.4 vs 6.9 months, but MS not different (22.1 vs 20.2 months). 368 pts, 17% LN+. **R1 included [9]**

**Radiation Therapy Approach**
Series only; most including intra-operative radiotherapy. Some suggest survival benefit. Others: EBRT may improve local control, not OS.

**Comparison of Approaches**
ESPAC-1: Three separate randomizations (physician choice):
- Chemoradiation (40 Gy + 2 x 3 days 5FU [split course]) vs observation
- Chemotherapy (Mayo regimen x 6 months) vs observation
- Chemoradiation vs chemotherapy vs chemoradiation + chemotherapy vs observation
  “Background” chemoradiation or chemotherapy allowed

Pooled analysis: Chemoradiation of no benefit (15.5 vs 16.1 months MS); chemotherapy of benefit (19.7 vs 14 months MS) [not intention-to-treat].

3rd schema only analyzed: chemoradiation or chemoradiation + chemotherapy, vs observation or chemotherapy alone: 2YS 29 vs 41%, also worse recurrence-free survival.

3rd schema only analyzed: chemotherapy alone vs no postoperative chemotherapy: 20.1 vs 15.5 months MS.

However: not sufficient power to analyze each arm individually. Difficult to draw firm conclusions. [10]

**Follow Up Recommendations**
As many patients will relapse, or be treated for on-going disease, regular follow-up for patients at the cancer centre is necessary. Those patients with RO resections who undergo adjuvant therapy are good candidates to be returned to their family doctors and surgeons for ongoing follow-up.
References

3. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Klinkenbijl JH; Jeekel J; Sahmoud T; van Pel R; Couvreur ML; Veenhof CH; Arnaud JP; Gonzalez DG; de Wit LT; Hennipman A; Wils J. Ann Surg 1999 Dec;230(6):776-82; discussion 782-4.
5. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Yeo CJ; Abrams RA; Grochow LB; Sohn TA; Ord SE; Hruban RH; Zahurak ML; Dooley WC; Coleman J; Sauter PK; Pitt HA; Lillemoe KD; Cameron JL. Ann Surg 1997 May;225(5):621-33
9. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. Oettle H; Post S; Neuhaus P; Gellert K; Langrehr J; Ridwelski K; Schramm H; Fahlke J; Zuelke C; Burkart C; Gutberlet K; Kettner E; Schmalenberg H; Weigang-Koehler K; Bechstein WO; Niedergethmann M; Schmidt-Wolf I; Roll L; Doerken B; Riess H. JAMA. 2007 Jan 17;297(3):267-77
**Pancreatic Adenocarcinoma**

**CLINICAL PRESENTATION**

- No jaundice
  - Preoperative CA 19-9 (category 2B)

- Jaundice
  - Symptoms of cholangitis or fever present
    - Temporary stent
  - No symptoms of cholangitis and fever
    - Preoperative CA 19-9 (category 2B)

**WORKUP**

- Resectable or borderline resectable
  - See Workup and Treatment (PANC-3)

- Locally advanced, unresectable, no metastases
  - See Workup and Treatment (PANC-5)

- Locally advanced, unresectable, no metastases
  - See Workup and Treatment (PANC-6)

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**Notes:**

a Consider testing for CA 19-9 if biliary decompression is complete and bilirubin is within normal range.

b See Principles of Surgery (PANC-A).

c See Criteria Defining Resectability Status (PANC-B).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Pancreatic Adenocarcinoma

CLINICAL PRESENTATION

Resectable, b, c no jaundice → Laparotomy

Unresectable at surgery →

TREATMENT

See Adjuvant Treatment and Surveillance (PANC-4)

See Locally Advanced Unresectable (PANC-5)
or Metastatic Disease (PANC-9)

Biopsy, EUS directed biopsy (preferred) d
+ Staging laparoscopy e (category 2B)

Candidate for neoadjuvant chemoradiation →

Biopsy positive → Laparotomy

Biopsy negative f → Laparotomy

Unresectable at surgery →

Surgical resection →

See Adjuvant Treatment and Surveillance (PANC-4)

See Locally Advanced Unresectable (PANC-5)
or Metastatic Disease (PANC-9)

Borderline resectable, b, c no jaundice →

Staging laparoscopy e (category 2B) →

Resectable → Laparotomy

Unresectable at surgery →

Surgical resection →

See Adjuvant Treatment and Surveillance (PANC-4)

See Locally Advanced Unresectable (PANC-5)
or Metastatic Disease (PANC-9)

b See Principles of Surgery (PANC-A).

c See Criteria Defining Resectability Status (PANC-B).
d See Surgical Principles #1 and #3 (PANC-A).
e See Surgical Principle #4 (PANC-A).
f A negative biopsy should be confirmed by at least one repeat EUS biopsy.

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Pancreatic Adenocarcinoma

**ADJUVANT TREATMENT**

- No evidence of recurrence or metastatic disease
  - Clinical trial preferred or Chemoradiation (5-FU-based) \(^a\) ± additional chemotherapy (gemcitabine-based) or Chemotherapy alone (5-FU or gemcitabine) (category 2B)

**SURVEILLANCE**

- Surveillance every 3-6 mo for 2 years, then annually:
  - H&P for symptom assessment
  - CA19-9 level (category 2B)
  - CT scan (category 2B)

**Metastatic disease**

(See PANC-9)

\(^a\) Adjuvant treatment should be considered for patients who have not had neoadjuvant therapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, consider restaging with a CT scan prior to radiation.

Note: All recommendations are category 2A unless otherwise indicated.

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