Taipei Veterans General Hospital Practices Guidelines for

Pancreatic Adenocarcinoma

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Multidisciplinary Team

- Surgical Oncologists specialized in Pancreatic Cancer
- Gastroenterologists
- Medical Oncologists
- Radiation Oncologists
- Pathologists
- Diagnostic Radiologists
- Hospice Specialists
- Pharmacists
- Nurses (for specialized)
- Social Workers
- Dietitians (for Nutrition Support)

Taipei VGH Pancreatic Cancer Panel Members

- **Surgical Oncologist**

  石宜銘* ；王心儀* ；陳世欽*；石柏威*

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  于洪元*；吳佩珊

- **Endocrinologist**

  林亮羽*

- **Medical Oncologist**

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  邱乃祈*；陳蓉宣*；柳建安

- **Nuclear Medicine Specialist**

  林可瀚*；姚珊汎*

- **Pathologist**

  楊清越*

- **Pharmacist**

  胡晉嘉

* 核心成員

Pretreatment work-ups

- **History and physical exam**
- **CBC, platelets, chemistry profile and PT/APTT**
- **Abdominal CT with IV contrast (pancreatic protocol)**
- **Chest and pelvic imaging**
- **Tumor markers: CEA, CA19-9**
- **Biopsy confirmation (from a metastatic site preferred if metastatic disease)**
- **Optional studies**
  - Endoscopic ultrasonography (EUS) to confirm primary site or EUS-guided biopsy
  - Endoscopic retrograde cholangiopancreatography (ERCP) with stent placement
  - MRI/MRCP (if indeterminate liver lesions)
  - Whole body bone scan
  - Esophagogastroduodenoscopy (EGD, UGI-PES)
  - PET/CT scan in high-risk patients
  - Cardiac function (cardiac ultrasound and/or ejection fraction + wall motion)
  - Pulmonary function test (if age > 65 and prepare for surgery)
  - Germline testing (recommended for any patient with confirmed pancreatic cancer)
  - Gene profiling of tumor tissue for locally advanced/metastatic disease

TNM Staging System: UICC/AJCC 2017 (8th edition)

- **Primary Tumor (T)**

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma *in situ*

T1: Tumor ≦ 2cm in greatest dimesion

T1a: tumor ≦ 0.5cm

T1b: 0.5cm < tumor < 1cm

T1c: 1cm ≦ tumor ≦ 2cm

T2: 2cm < tumor ≦ 4cm in greatest dimension

T3: Tumor > 4cm in greatest dimension

T4: Tumor involves of the celiac,
superior mesenteric artery, and/or
common hepatic artery,
regardless of size

- **Regional lymph nodes (N)**

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in 1 to 3 regional lymph nodes

N2: Metastasis in ≧ 4 regional lymph nodes

- **Distant metastasis (M)**

M0: No distant metastasis

M1: Distant metastasis

TNM Staging System: UICC/AJCC 2017 (8th edition)

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	Any T	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Histological grade

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

References:

Giulianotti PC, *et al*. Int J Pancreatol. 1995 Jun;17(3):279-89.

Adsay NV, *et al*. Am J Surg Pathol. 2005 Jun;29(6):724-33.

Bosman FT, *et al*. WHO classification of tumors of the digestive system. World Health Organization; 2010

Principles of diagnostic imaging [NCCN guidelines 1.2022]

MDCT Pancreatic adenocarcinoma protocol

Parameters	Details
Scan type	Helical (preferably 64-multidetector row scanner or more)
Section thickness	Thinnest possible (<3 mm). Preferably submillimeter (0.5–1 mm) if available
Interval	Same as section thickness (no gap)
Oral contrast agent	Neutral contrast (positive oral contrast may compromise the three-dimensional [3D] and maximum intensity projection [MIP] reformatted images)
Intravenous contrast	Iodine-containing contrast agents (preferably high concentration [>300 mg I/L]) at an injection rate of 3–5 mL/sec. Lower concentration contrast can be used if low Kv setting is applied.
Scan acquisition timing	Pancreatic parenchymal phase at 40–50 sec and portal venous phase at 65–70 sec, following the commencement of contrast injection
Image reconstruction and display	- Axial images and multiplanar reformats (in the coronal, and per institutional preference, sagittal plane) at 2- to 3-mm interval reconstruction - MIP or 3D volumetric thick section for vascular evaluation (arteries and veins)

Principles of diagnostic imaging [NCCN guidelines 1.2022]

MRI Pancreatic adenocarcinoma protocol

Sequences	Plane	Slice Thickness
T2-weighted single-shot fast spin-echo (SSFSE)	Coronal +/- axial	<6 mm
T1-weighted in-phase and opposed-phase gradient echo (GRE)	Axial	<6 mm
T2-weighted fat-suppressed fast spin-echo (FSE)	Axial	<6 mm
Diffusion-weighted imaging (DWI)	Axial	<6 mm
Pre and dynamic post IV contrast administration (gadolinium[d]) 3D T1-weighted fat-suppressed gradient-echo (in pancreatic, portal venous, and equilibrium phases)	Axial	Thinnest possible 2–3 mm (4–6 mm if overlapping)
T2-weighted MR cholangiopancreatography (MRCP) (preferably 3D, fast relaxation fast spin-echo sequence [FRFSE])	Coronal	<3 mm

Criteria defining resectability status at diagnosis [NCCN guidelines 1.2022]

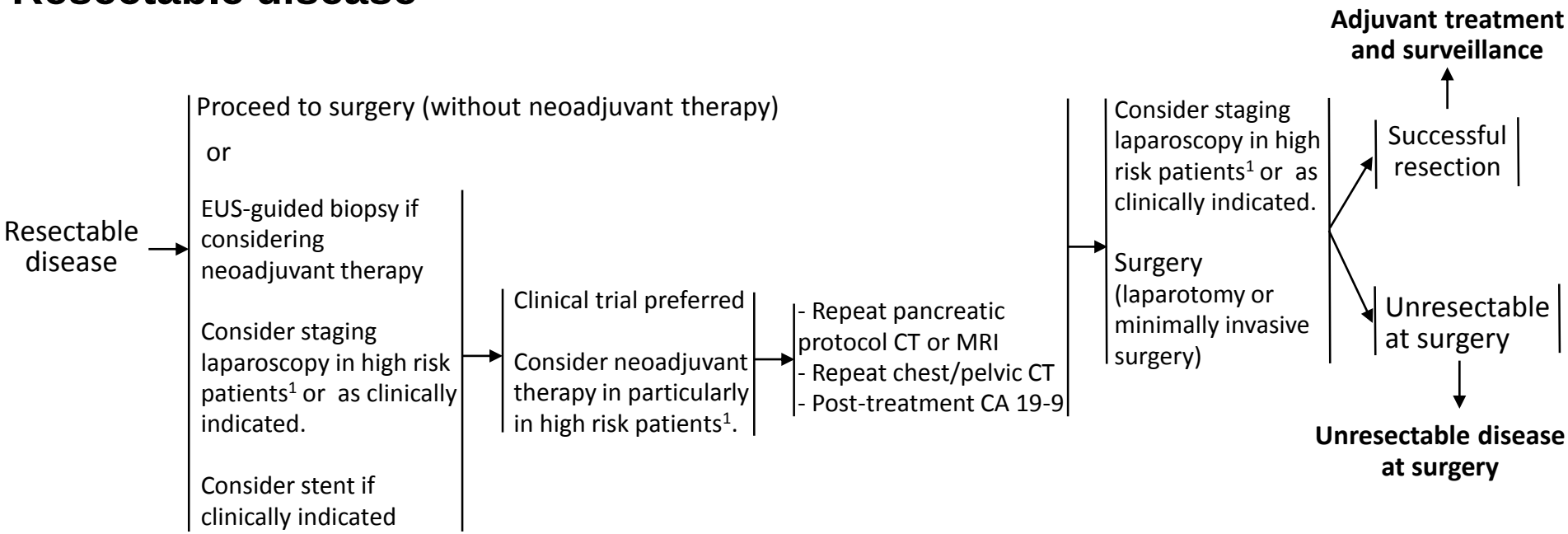
Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions

Resectability Status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180°. • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180°.	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced[b,c]	Head/uncinate process: • Solid tumor contact >180° with the SMA or CA. Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA. • Solid tumor contact with the CA and aortic involvement.	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus).

[a] Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270:248-260.
[b] Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans.
[c] Distant metastasis (including non-regional lymph node metastasis), regardless of anatomic resectability, implies disease that should not be treated with upfront resection.

Pancreatic Adenocarcinoma

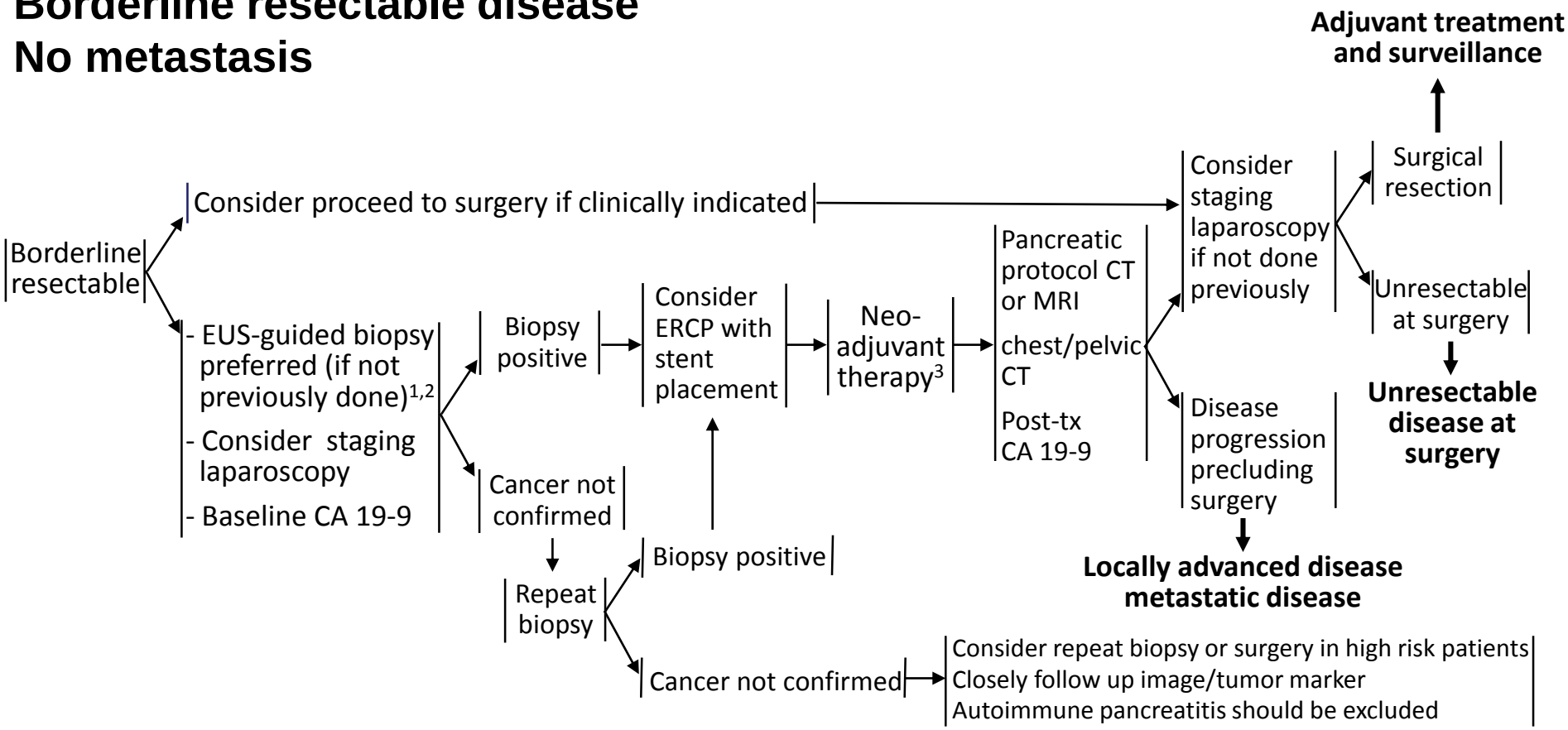
Resectable disease



1. High risk patients: imaging findings, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain
2. Consider frozen section analysis of pancreatic neck and bile duct during surgery (5mm from the transection margin).
3. Neoadjuvant regimens (limited evidence):
   -FOLFIRINOX/mFOLFIRINOX ± subsequent chemoradiation
   -Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation
   Only for BRCA 1/2 mutations
   -FOLFIRINOX/mFOLFIRINOX ± subsequent chemoradiation
   -Gemcitabine + cisplatin (≧2-6 cycles) ± subsequent chemoradiation

Pancreatic Adenocarcinoma

Borderline resectable disease
No metastasis



Neoadjuvant Therapy

Recommended regimens:

FOLFIRINOX/mFOLFIRINOX ± subsequent chemoradiation,
Gemcitabine + albumin-bound paclitaxel ± chemoradiation

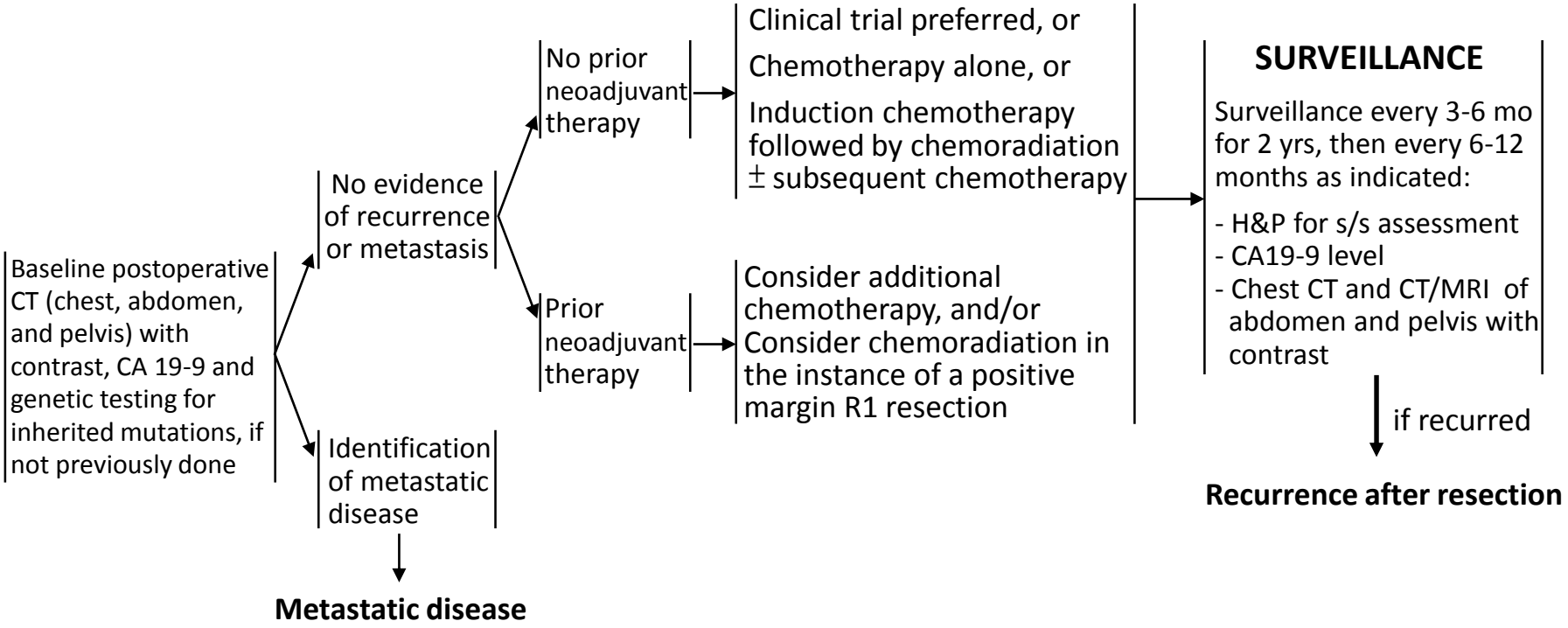
Only for *BRCA 1/2* or *PALB2* mutations:

FOLFIRINOX/mFOLFIRINOX ± subsequent chemoradiation,
Gemcitabine + cisplatin + chemoradiation

1. Core biopsy is recommended if possible.
2. Biopsy proof of malignancy is not required before surgical resection, and a non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high

Pancreatic Adenocarcinoma

Adjuvant treatment and surveillance (postoperative)



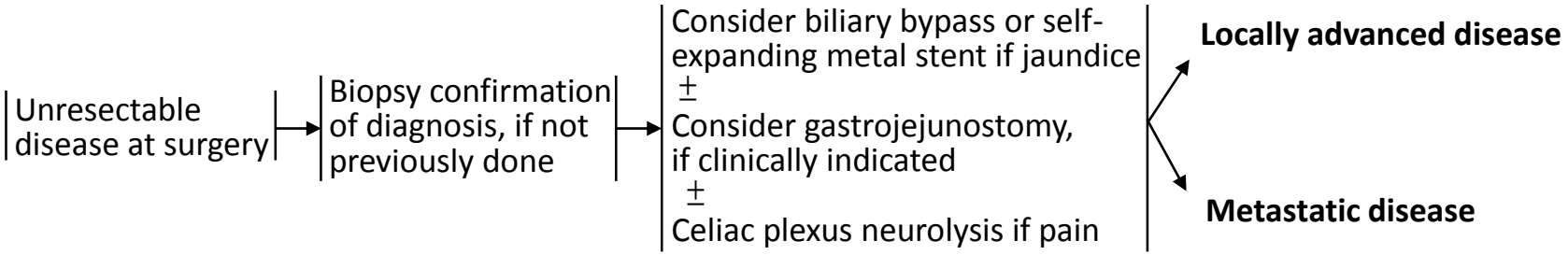
Adjuvant Therapy

Preferred Regimens—
- mFOLFIRINOX
- Gemcitabine + capecitabine

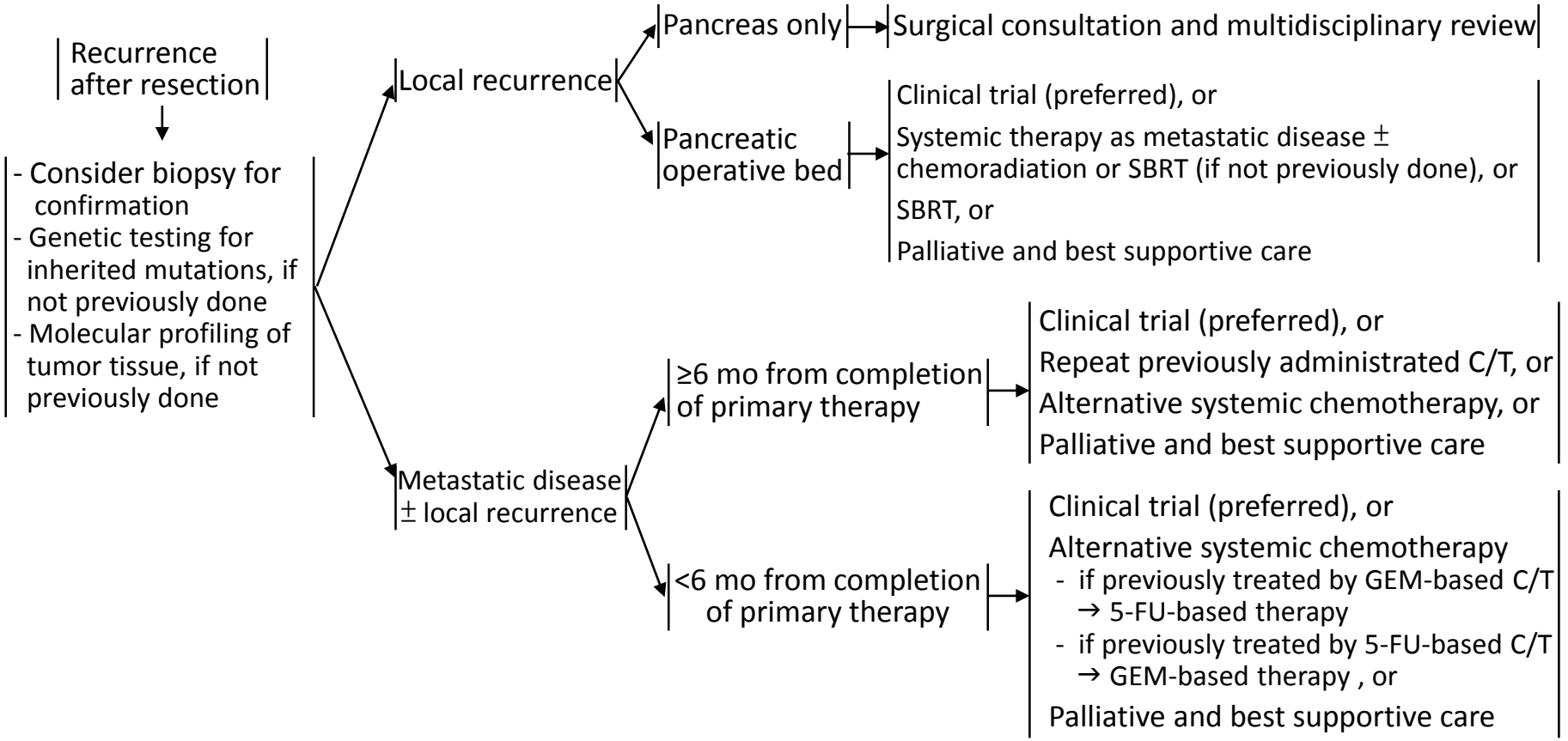
Other recommended regimens–
- Gemcitabine
- 5-FU + leucovorin
- Continuous infusion 5-FU
- Capecitabine
- Induction chemotherapy, followed by chemoradiation ± subsequent chemotherapy

Pancreatic Adenocarcinoma

Unresectable disease at surgery

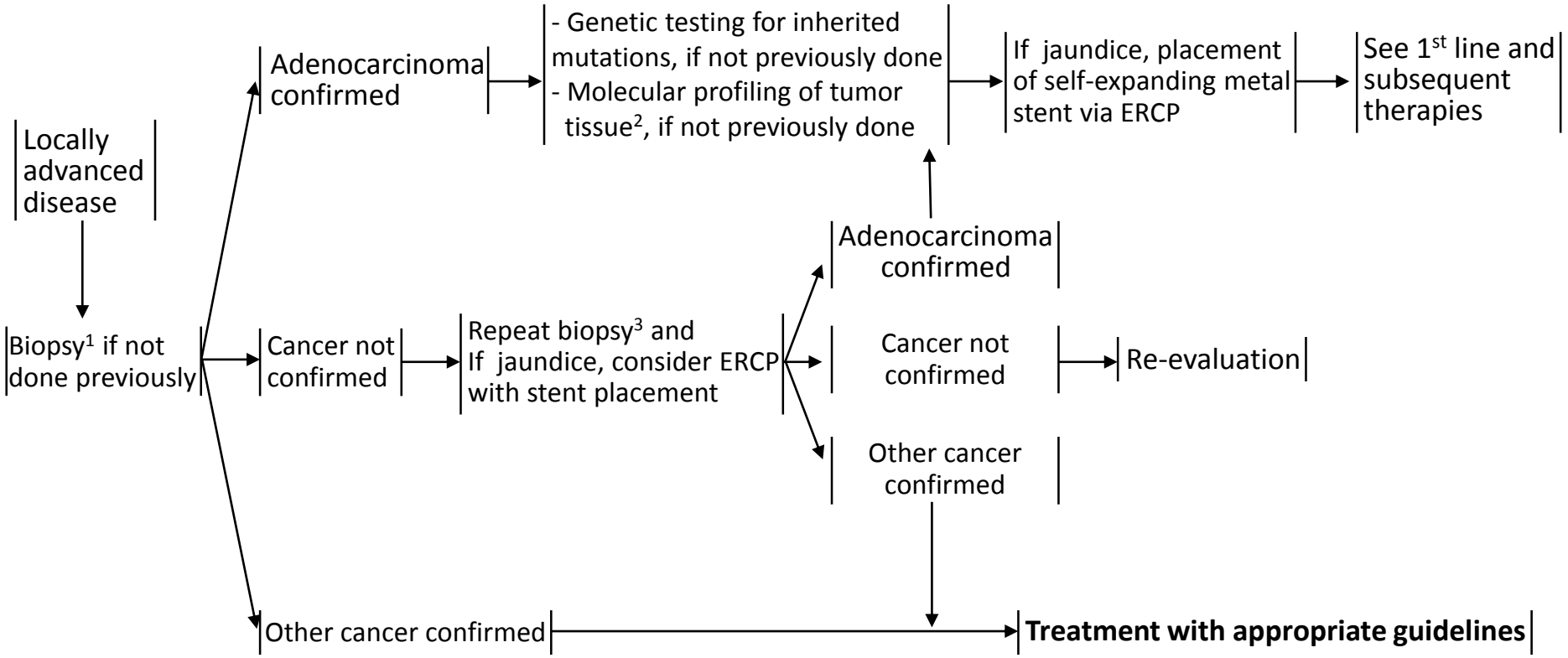


Recurrence after resection



Pancreatic Adenocarcinoma

Locally advanced disease
Workup

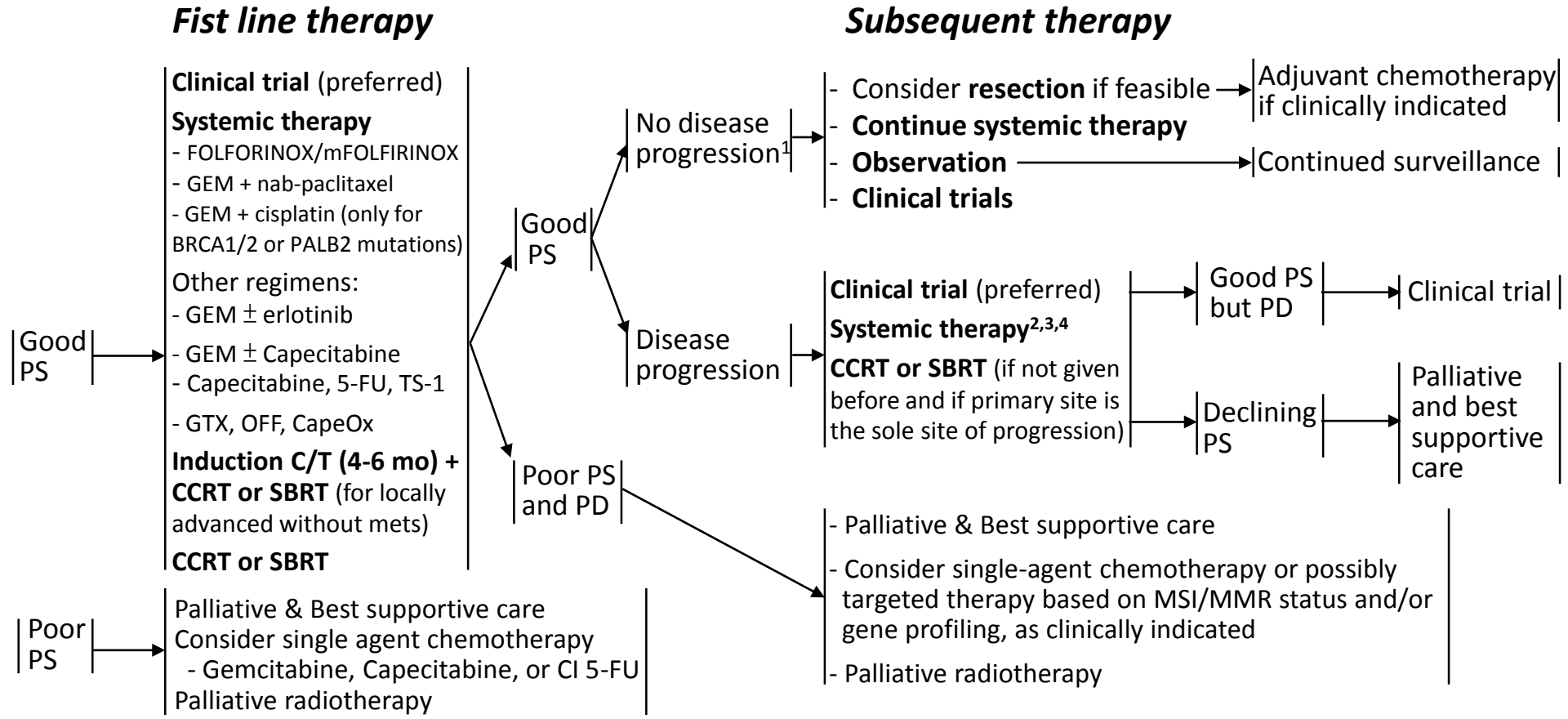


1. Core biopsy is recommended, if possible, to obtain adequate tissue for possible ancillary studies.
2. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, RET), mutations (BRAF, BRCA1/2, KRAS, PALB2), amplifications (HER2), microsatellite instability (MSI), and/or mismatch repair (MMR) deficiency. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible.
3. EUS-guided biopsy is preferred. When EUS-guided biopsy is not feasible, CT-guided biopsy can be done.

Pancreatic Adenocarcinoma

Locally advanced disease

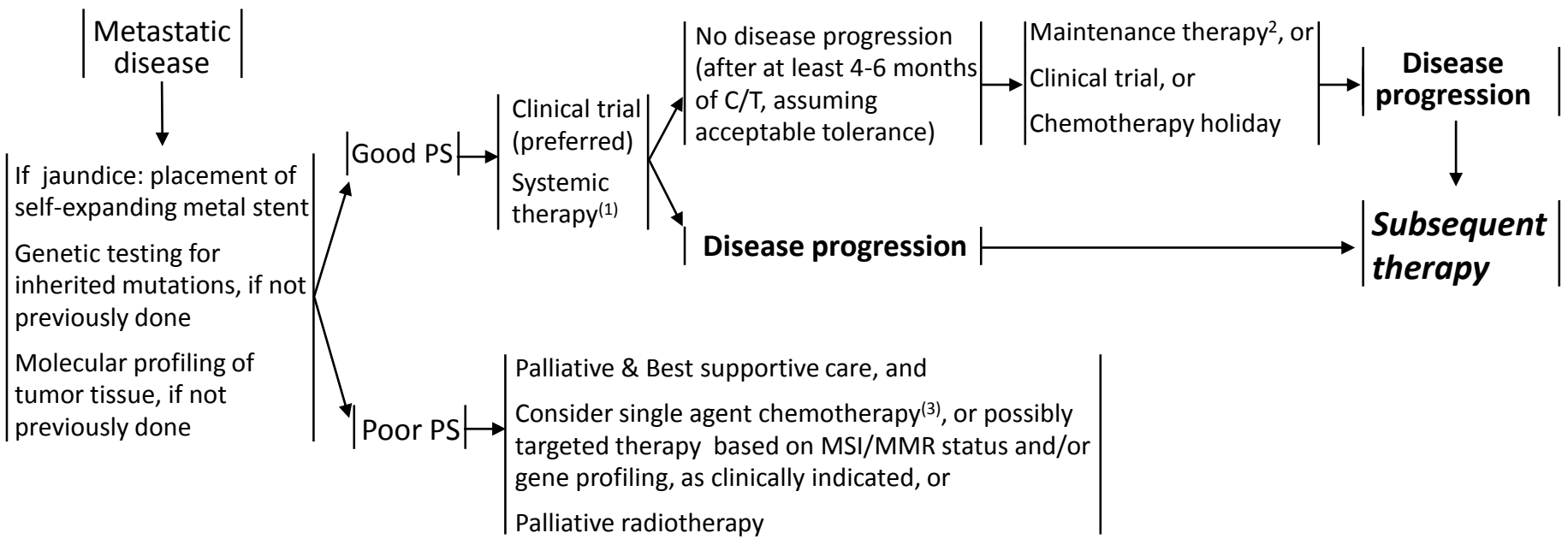
First line and subsequent therapies



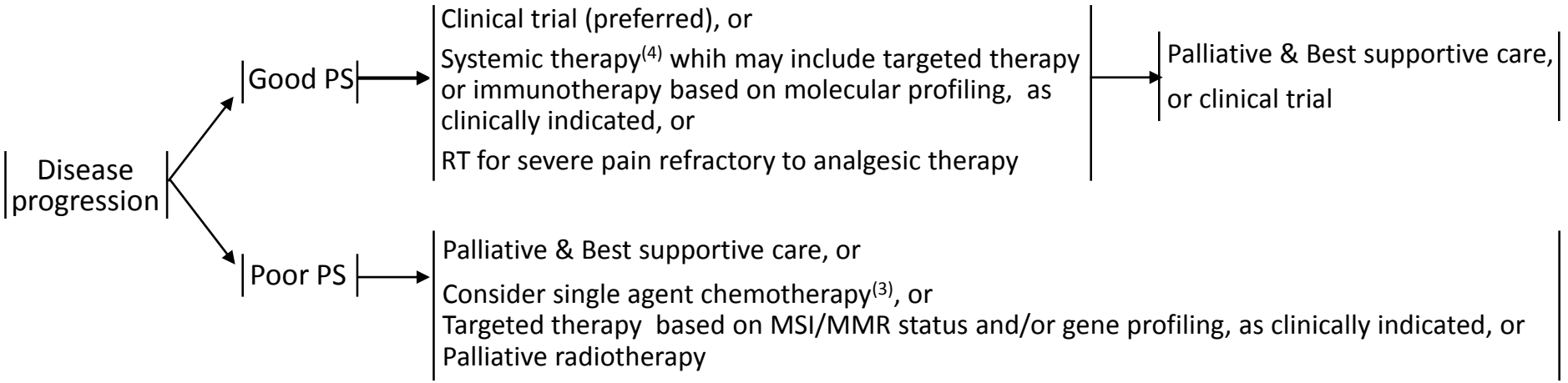
1. If radiographic improvement or radiographic stability with marked clinical improvement or decline in CA19-9 despite no regression radiographically
2. If prior GEM-based therapy:
   liposomal irinotecan +5-FU + LV; (m)FOLFIRINOX, OFF, FOLFIRI, FOLFOX, Capecitabine ± oxaliplatin; CI 5-FU.
3. If prior 5-FU based therapy:
   GEM ± albumin-bound paclitaxel; GEM ± erlotinib; GEM + cisplatin (only for known BRCA1/2 or PALB2 mutations); 5-FU + leucovorin + liposomal irinotecan (if no prior irinotecan)
4. Pembrolizumab (only for MSI-H or dMMR); Larotrectinib / Entrectinib(if NTRK gene fusion +)

Pancreatic Adenocarcinoma

Metastatic disease



Disease progression



Metastatic disease

[Good PS]

(1) First-line systemic therapy:

- FOLFIRINOX/mFOLFIRINOX
- Gemcitabine + albumin-bound paclitaxel,
- Gemcitabine + cisplatin: only for *BRCA1/2 or PALB2* mutations
- Other recommended regimens: GEM + erlotinib, GEM + capecitabine, GEM alone, GTX, OFF, CapeOx
- Pembrolizumab (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb])

(2) Maintenance therapy:

- If previous platinum-based chemotherapy: Olaparib (only for germline BRCA1/2 mutations)
- Clinical trial
- If previous 1st line FOLFIRINOX: Capecitabine; 5-FU ± irinotecan (allergy or neuropathy due to oxaliplatin); FOLFOX.
- If previous 1st line GEM + nab-paclitaxel: GEM+nab-paclitaxel modified schedule or GEM alone
- Prior platinum-based therapy: Rucaparib (for germline or somatic *BRCA1/2* or *PALB2* mutations)

[Poor PS]

(3) Single agent chemotherapy: Gemcitabine, Capecitabine, or continuous infusion (CI) 5-FU

(4) Useful in certain circumstances: Target therapy

- Pembrolizumab (only for MSI-H or dMMR tumors)
- Larotrectinib (if NTRK gene fusion positive)
- Entrectinib (if NTRK gene fusion positive)

(5) Second line systemic therapy:

If prior GEM-based therapy --

- 5-FU+leucovorin + liposomal irinotecan
- FOLFIRI
- FOLFIRINOX or mFOLFIRINOX
- OFF, FOLFOX, CapeOx, Capecitabine, CI 5-FU

If prior fluoropyrimidine-based therapy:

- GEM alone
- GEM + albumin-bound paclitaxel
- GEM + cisplatin (only for known BRCA1/2 or PALB2 mutatiions
- GEM + erlotinib
- 5-FU + leucovorin + liposomal irinotecan (if no prior irinotecan)

Principle of Chemotherapy

- **Gemcitabine** at 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days ± **Erlotinib** 100 mg PO QD.
- **Gemcitabine** at 1000 mg/m^2 over 30 minutes , weekly for 7 weeks and rest 1 week, then weekly for 3 weeks every 28 days ± **Erlotinib** 100 mg PO QD.
- **Gemcitabine** at 400-600 mg/m^2 over 30 minutes, weekly during radiotherapy.
- Fixed-dose rate **Gemcitabine** (10 mg/m^2/minute) may substitute standard infusion of gemcitabine over 30 minutes.
- **FOLFORINOX**: Oxaliplatin, 85 mg/m^2; irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2; and fluorouracil, 400 mg/m^2 given as a bolus followed by 2400 mg/m^2 46-hour continuous infusion, every 2 weeks.
- **Modified FOLFORINOX** (mFOLFIRINOX): Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and irinotecan 150 mg/m^2 at day 1, and 5-FU continuous IV infusion 2.4 g/m^2 over 46 hours. This was repeated. every 2 weeks for 12 cycles
- **TS-1** orally twice daily at a dose according to the body surface area (BSA) (< 1.25 m^2, 80 mg/d; ≥ 1.25 to < 1.5 m^2, 100 mg/d; ≥ 1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-day cycle.
- ***nab*-Paclitaxel** 125 mg/m^2, followed by gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks.
- **Liposomal irinotecan** (80 mg/m^2 over 90 min) with fluorouracil 2400 mg/m^2 over 46 h and folinic acid 400 mg/m^2 over 30 min every 2 weeks.
- **Gemcitabine** 1000 mg/m^2 Days 1, 8, 15 for 6 cycles + **Capecitabine** 1660 mg/m^2/day 21/28 days.

Principle of Chemotherapy

- **FOLFIRI regimen: 5-FU + leucovorin + irinotecan**
  irinotecan 180 mg/m^2 on day 1, leucovorin 400 mg/m^2 followed by 5-fluorouracil (5-FU) 400 mg/m^2 bolus, then 5-FU 2400 mg/m^2 as a 46-h infusion, biweekly

- **OFF regimen: Oxaliplatin + 5-FU + leucovorin**
  folinic acid 200mg/m^2 followed by 5-FU 2g/m^2 (24h) on d1, d8, d15, d22 and oxaliplatin 85 mg/m^2 on days 8 and 22. After a rest of 3 weeks the next cycle was started on d43.

- **FOLFOX regimen**
  oxaliplatin (85 mg/m2; day 1), leucovorin (400 mg/m2; day 1), followed by 5-fluorouracil (5-FU) (2000 mg/m2; days 1 and 2), biweekly.

- **GTX regimen: fixed-dose-rate gemcitabine + docetaxel + capecitabine**
  Days 1–14: Capecitabine 750mg/m2 orally twice daily
  Days 4 and 11: Gemcitabine 750mg/m2 IV + docetaxel 30mg/m2 IV.
  Repeat cycle every 21 days until disease progression

- **CapeOx regimen: Capecitabine + oxaliplatin**
  oxaliplatin 130 mg/m^2 given on Day 1 and capecitabine 1000 mg/m^2 BID for 14 days.

- **Continuous infusion 5-FU (CI 5-FU)**
  Fluorouracil 250mg/m2 continuous IV infusion over 24 hours for 28 days.
  Repeat each 42-day cycle until disease progression or unacceptable toxicity.

Specific target therapy / immunotherapy:

- **Olaparib** at 300 mg twice daily
- **Larotrectinib** at 100 mg twice daily
- **Entrectinib** at 600 mg orally once daily
- **Pembrolizumab** at 200mg every 3 weeks for adult

PRINCIPLES OF RADIOTHERAPY (1)

Resectable /Borderline Resectable (Neoadjuvant)

- RT in the neoadjuvant setting may increase the likelihood of a R0 resection and local control
- Should ideally be conducted in a clinical trial

Combination options: Neoadjuvant chemotherapy prior to RT

RT dose options:

- **36 Gy in 15 fractions** (2.4 Gy per fx)
- **45- 54 Gy in 18-25 fractions** (1.8-2.0 Gy per fx) (Dose > 54 Gy may be considered on a clinical trial)
- Role of elective nodal irradiation is controversial for resectable/ borderline resectable diseases.

Resectable (adjuvant)

- Treatment with chemotherapy is recommended
- May consider for patients with high risk features: pT3-4, N+, R1-2 resection[28]

Combination options: If no prior neoadjuvant therapy and no evidence of recurrence or metastasis after resection, RT is included: **adjuvant chemotherapy followed by chemoradiation +/- subsequent chemotherapy.**

RT dose options:

- **45- 50.4 Gy in 25-28 fractions** (1.8-2.0 per fx) to the tumor bed, surgical anastomosis (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate) and adjacent lymph node basins, with **potential dose escalation to the high-risk regions**, if clinically appropriate[32].

PRINCIPLES OF RADIOTHERAPY (2)

Locally advanced

- Goal: To prevent of delay local progression and facilitate local disease control

 # Combination options:

- **Induction chemotherapy followed by chemoradiation** or SBRT in select patients
- **Chemoradiation** or SBRT in selected patients

 # RT dose options:

For CCRT [11, 12, 33]

- **45-54 Gy in 25-28 fractions**

For SBRT [34]

- limited data to support specific RT dosing for SBRT; should utilized as a part of clinical trial
- **30-45 Gy in 3 fractions** (10-15 Gy per fx); **25-45 Gy in 5 fractions** (5-9 Gy per fx)

Palliation

- Goal: to relieve pain and bleeding and/or ameliorate local obstruction
- Non-metastatic disease: For elderly and/or not candidates for definitive therapy due to poor PFS.
- Metastatic disease: For local palliation for symptoms such as obstruction, pain or bleeding.

 # RT dose options: the burden of metastatic disease, normal tissue tolerance and expected survival should be considered.

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