

University Health Network
guidelines for management of
resectable, borderline resectable and locally advanced
pancreatic ductal adenocarcinoma (PDAC)

Objective: A document to define institutional standard practice and guide discussions around the multidisciplinary management of PDAC patients at The University Health Network/Princess Margaret Cancer Centre focusing on surgical classifications of the disease (i.e. resectable, borderline and locally advanced PDAC).

Initial Draft by:

Dr Amélie Tremblay St-G., Fellow in HPB Surgical Oncology

Dr Natalie Cook, Fellow in GI Medical Oncology

Content Modified by:

Dr. Steve Gallinger (HPB)

Dr. Neesha Dhani (Med Onc)

as per Group Discussion Jun 11, 2015

Approved by Group at Large: November 2015

SUMMARY STATEMENTS

- Assuming no medical contraindications, upfront surgical resection when technically feasible (with negative margins) is standard of care.
- Neoadjuvant treatment should be considered (off trial) in patients who are unlikely to be resected with clear margins.
- Neoadjuvant treatment protocol includes systemic (combination) chemotherapy (generally 2 mths) followed by chemoradiotherapy.
- Current radiotherapy protocols are standard fractionation given with concurrent gemcitabine. 5FU may be substituted in patients intolerant of gemcitabine.
- All decisions re: neoadjuvant therapy prior to consideration of resection requires discussion at MCC with documentation of consensus opinion

I) DIAGNOSIS AND STAGING

a) Preliminary Evaluation

All patients with a suspected diagnosis of PDAC require:

- **HISTORY AND PHYSICAL EXAM INCLUDING FAMILY HISTORY OF CANCER**
- Performance status evaluation
- Liver function tests, Coagulation profile
- Serum CA 19.9
- Pancreatic protocol CT (biphasic pancreas protocol)
- Chest CT
- Consider IgG4 in selected cases without confirmed diagnosis

b) Multi-disciplinary cancer conference (MCC) discussions

- All suspected cases of PDAC should be presented for multi-disciplinary review at MCC to enable appropriate and efficient sequencing of investigations and treatment.
- MCC review involves contributions from HPB/Surgical Oncology, Radiation Oncology, Medical Oncology, Radiology, Pathology, Clinical Trials, Nursing and Allied Health (Nutrition, Social Work, Psychosocial)
- MCC discussion should be documented in pts' EPR record either by MRP or McCain attending staff for the week (HPB or Med Onc respectively)
- Where applicable, resectability status should be documented.

c) Surgical Classification: Determination of (technical) resectability

The following discussion is with the implicit understanding that apart from technical resectability, patients must also be medically fit with no contraindications to major surgery based on performance status, pre-existing co-morbidities and cardiopulmonary reserve.

In medically fit patients, the initial technical determination of resectability is based on pre-operative radiology: either (pancreatic protocol) computerized tomography (CT) or magnetic resonance imaging (MRI). The function of imaging is exclusion of (1) distant metastatic disease (liver, lungs, lymph nodes) and (2) extensive involvement of neurovascular structures, either of which would preclude resection. Definitive resectability is ultimately determined intra-operatively and is based on the ability to resect tumor with negative margins (R0) while preserving function and essential structures.

The following categories/classifications are used in discussions of technical resectability of PDAC.

- **Resectable (RES) tumour:** high probability of resection with negative margins (R0).
-
- **Borderline Resectable (BOR) tumour :** R0 resection may not be possible with standard resection techniques (i.e. without vascular resection and reconstruction). This is generally due to suspected involvement of major vascular structures based on pre-operative imaging.

BOR tumours include:

- *Borderline-Vein (BOR-V) tumour:* there is radiographic evidence of venous involvement (portal vein (PV) and/or superior mesenteric vein (SMV)). Although previously not the case, PV/SMV resection/reconstruction are now considered standard procedures in PDAC surgery. Consequently, BOR tumours with VENOUS involvement ONLY are considered resectable with a high likelihood of achieving an R0 resection.
- *Borderline-Artery (BOR-A) tumour:* there is radiographic suspicion of involvement of arterial wall (celiac, superior mesenteric (SMA), common or lobar hepatic arteries) with ≤ 180° of vessel circumference involvement. With standard resection techniques the chances of R0-resection are low-to-moderate (less than 50%). However, if the extent of arterial involvement has been over-estimated by pre-operative imaging and the arterial wall is not found to be involved intra-operatively, then an R0 resection might be achieved through dissection of tumour off the artery (i.e. w/o arterial resection). The ambiguity in this group stems from the extent to which arterial involvement can be estimated by imaging which means that resectability can only be determined intra-operatively. If at the time of surgery arterial resection is felt to be required, surgery is generally aborted

as arterial resection/reconstruction is currently not a standard approach in this disease.

- **Locally Advanced (LA) tumour:** these tumours are considered unresectable by standard definitions due to the extent of local disease particularly with respect to major arteries/veins. There is no surgical option that does not include extensive vascular resection and R0 margins are not possible in most cases despite major arterial resection.
 - **Locally Advanced-Vein (LA-V) tumour:** since venous resection/reconstructions are a standard aspect of PDAC surgery, LA-V tumours are those in which there is no technical option to reconstruct the PV or SMV.
 - **Locally Advanced-Artery (LA-A) tumour:** pre-operative imaging of these tumours demonstrates unambiguous arterial involvement. The only option for achieving an R0 tumour resection would also require arterial resection and reconstruction, which is currently not standard of care. These extended surgical resections should only be considered in the context of a clinical trial as the morbidity and oncologic sensibility of this approach are yet to be determined.
- ❖ **Additional comments on arterial involvement in PDAC:**

The primary controversies in considering the technical feasibility of PDAC resection revolve around the extent of arterial involvement in the *Borderline-Artery* (BOR-A) and the *Locally Advanced-Artery* (LA-A) groups. Much of this is related to the discordance between imaging-based and true arterial involvement. In addition, this remains a group at a high risk of (distant) failure and therefore several groups have routinely adopted the use of neoadjuvant therapy in order to expose pts to systemic chemotherapy earlier in their disease course.

❖ The UHN experience

Highly selected pts have proceeded to extended resections (+/- arterial reconstruction) as an institutional standard of practice since 2009. From 2009 to 2013, the resection rate was 44 % (11/25) in the BOR-A group with an overall R0 rate of 44%. This includes 6 patients who had arterial resection-reconstruction to achieve negative margins and 5 patients who did not require arterial resection-reconstruction to achieve negative margins.

❖ Definitions of arterial involvement at UHN:

- any abutment or encasement of the CHA, PHA or RepRHA over a length of 0 to 5 mm is considered Borderline.
- UHN consensus defines long segment as > 5 mm. Therefore, encasement of the CHA, PHA or RepRHA over a length of > 5 mm is to be considered *Locally Advanced-Artery*.

❖ The different surgical classification systems (NCCN, MD Anderson, AHPBA-SSAT-SSO and Intergroup Alliance) also vary with respect to the extent of vessel involvement that is considered resectable.

For the purpose of our policy, we will refer to the NCCN Guidelines version 2015.1.
(appendix)

d). Tissue Diagnosis

- A biopsy is not required in patients with a typical clinical presentation and imaging findings who are candidates for upfront surgical resection.
- Tissue diagnosis is necessary for patients with unresectable and metastatic disease who are being considered for chemotherapy +/- chemoradiotherapy.
- Biopsy can be obtained from primary pancreatic lesion or suspected liver metastasis at the discretion of interventional radiology. For the primary, tissue diagnosis can be obtained with brushings, EUS-FNA or percutaneous biopsy. A tissue biopsy is preferable to cytology wherever possible. Suspicious or unclear cytology should be reviewed by UHN pathology.
- EUS biopsy is preferred over percutaneous in patients who would be considered for surgical resection after a favourable response to chemotherapy.

II) MANAGEMENT

a) Management approaches at UHN according to surgical classification

General Comments:

- all patients should be considered for/offered participation in clinical trial/s (over standard of care: SOC) if appropriate for the stage of disease
- recommendations below are not meant to be prescriptive but provide guidelines re: UHN SOC best practice to guide discussion of cases

“Neoadjuvant therapy” at UHN generally implies 2 mths (combination) systemic chemotherapy (FOLFIRINOX or Abraxane/Gemcitabine (AG)) followed by chemoradiotherapy. Pts undergo re-staging every 2mths (i.e. after completing chemotherapy and prior to starting radiotherapy, and again after completing radiotherapy). There is usually a break of approximately 4 to 6 wks between systemic chemotherapy and radiotherapy and between radiotherapy and re-evaluation for surgery. Radiographic progression or functional deterioration are both indications for aborting neoadjuvant approach

RESECTABLE

- SOC is upfront surgery providing there are no medical contraindications (poor ECOG, cardiopulmonary reserve etc)
- If medically not eligible for surgery pt should be managed as per SOC for locally advanced disease (chemotherapy +/- radiotherapy)
- all resected pts should be considered for adjuvant chemotherapy (SOC: gemcitabine x 6 mths) within 12 wks of surgery
- pts with prolonged recovery post-surgery may have a delayed start to chemotherapy or it may be omitted altogether at the discretion of the medical oncologist

- adjuvant radiation therapy can be considered for R1 resections (microscopic positive margin: institutional standard is presence of cancer cells AT resection margin)
- there is currently no role for maintenance therapy outside of a clinical trial

BORDERLINE: VEIN ONLY

- SOC is primary surgery (+/- vein resection)
- adjuvant therapy should be considered as per resectable pts (above)
- neoadjuvant strategies only through clinical trial participation

BORDERLINE: ARTERY

- upfront surgery OR neoadjuvant therapy are both reasonable strategies¹ with neoadjuvant therapy preferred due to concern about margins.
- surgery may include vein resection BUT arterial resection/reconstruction should be avoided outside of a clinical trial
- resected pts who have not had prior chemoradiotherapy follow adjuvant guidelines as per resectable or borderline-vein cases (above)
- neoadjuvant strategies: 2 mths systemic chemotherapy (FOLFIRINOX or Gemcitabine/Nab-paclitaxel (AG), followed by chemoradiotherapy (current UHN SOC: 50Gy with biwkly Gemcitabine (40mg/m²))
- the role of SBRT (stereotatic radiation therapy) is still exploratory in this context and is not a standard approach at UHN
- if no progression on neoadjuvant treatment patient can proceed to surgical exploration
- if pts undergo R0 or R1 resection after neoadjuvant treatment they should be considered for a further 2 mths of adjuvant Gemcitabine (within 8 to 12 wks)

(LIMITED) LOCALLY ADVANCED: ARTERY

- single major artery involvement
- consider neoadjuvant treatment with chemotherapy and chemoradiation as per protocol
- ARCAP-GA trial eligibility

LOCALLY ADVANCED (ALL OTHERS)

- includes pts with unreconstructable vein or multiple artery involvement or not eligible or refuses ARCAP-GA
- systemic chemotherapy as per SOC (FOLFIRINOX or AG)
- radiotherapy can be considered for (local) progression on or intolerance of systemic chemo or palliation of pain
- considering trials of SBRT and novel therapies should be a priority for evaluation in this pt population

b) RADIOTHERAPY for PDAC at PMH

- need to specify iv contrast for planning
- planning: GTV + 0.5cm CTV and PTV based on 4D CT
- “definitive dose” conformal technique to 50Gy/25
- palliative dose (pain control): 30Gy/10
- SBRT not standard approach; trials pending

c) Biliary Decompression

- ❖ Pre-operative decompression should be used selectively and is not considered SOC unless BR levels > 350-400
- ❖ When deemed necessary, preference is for endoscopic stenting (often with brushings obtained simultaneously); if this fails, consideration is given to percutaneous stent
- ❖ All patients with unresectable disease should be effectively decompressed if jaundiced and symptomatic
- ❖ Indications for ERCP-stent:
 - Symptomatic jaundice/pruritus AND an expected delay to surgery of >1 week
 - Cholangitis, Sepsis
 - Malnutrition
 - Coagulopathy
 - Renal insufficiency
 - Candidate for neoadjuvant treatment AND bili > 50 (Short metal stent)

c) Surgical Bypass

Surgical biliary +/- gastric bypass are recommended at the time of exploration if the disease is deemed unresectable or metastatic and patient has an expected survival greater than 12 months (good performance status, absence of risk factors of poor survival). This procedure is also considered for those with unresectable disease who have symptoms related to biliary/gastric obstruction and are not considered stentable. Duodenal stenting should be considered for patients with expected survival <6 months.

DRAFT

Appendix I. NCCN Surgical Guidelines

CRITERIA DEFINING RESECTABILITY STATUS¹

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis, SMA, or common hepatic artery).	No tumor contact with the SMV or PV or $\leq 180^\circ$ contact without vein contour irregularity
Borderline Resectable ²	<p>Pancreatic head /uncinate process:</p> <ul style="list-style-type: none"> • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of $\leq 180^\circ$ • Presence of 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. <p>Pancreatic body/tail:</p> <ul style="list-style-type: none"> • Solid tumor contact with the CA of $\leq 180^\circ$ • Solid tumor contact with the CA of $>180^\circ$ without involvement of the aorta and with intact and uninvolved gastroduodenal artery [some members prefer this criteria to be in the unresectable category]. 	<ul style="list-style-type: none"> • Solid tumor contact with the SMV or PV of $>180^\circ$, contact of $\leq 180^\circ$ 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 IVC
Unresectable ²	<ul style="list-style-type: none"> • Distant metastasis (including non-regional lymph node metastasis) <p>Head/uncinate process:</p> <ul style="list-style-type: none"> • Solid tumor contact with SMA $>180^\circ$ • Solid tumor contact with the CA $>180^\circ$ • Solid tumor contact with the first jejunal SMA branch <p>Body and tail</p> <ul style="list-style-type: none"> • Solid tumor contact of $>180^\circ$ with the SMA or CA • Solid tumor contact with the CA and aortic involvement 	<p>Head/uncinate process</p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV <p>Body and tail</p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

¹Al-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. Gastroenterology. 2014 Jan; 146 (1):291-304.

²Solid 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. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions

Appendix II. Comparison of Surgical Guidelines

Table 1 Comparison of radiographic differences in common definitions for borderline resectable pancreatic cancer

Effected vessel	AHPBA/SSAT/SSO/NCCN ^[29]	MD Anderson ^[28]	Alliance ^[24]
SMV/PV	Abutment, impingement, encasement of the SMV/PV or short segment venous occlusion	Occlusion	Tumor-vessel interface $\geq 180^\circ$ of vessel wall circumference, and/or reconstructable occlusion
SMA	Abutment	Abutment	Tumor-vessel interface $< 180^\circ$ of vessel wall circumference
HA	Abutment or short segment encasement	Abutment or short segment encasement	Reconstructable short segment interface of any degree between tumor and vessel wall
CA	Uninvolved	Abutment	Tumor-vessel interface $< 180^\circ$ of vessel wall circumference

AHPBA/SSAT/SSO/NCCN: Americas Hepatopancreaticobiliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology/ National Comprehensive Cancer Network; SMV/PV: Superior mesenteric vein/portal vein; SMA: Superior mesenteric artery; HA: Hepatic artery; CA: Celiac artery.

Appendix III. Inclusion/Exclusion criteria of ARCAP-GA (for patients with locally advanced PDAC eligible for surgery with extended (arterial) resection

INCLUSION CRITERIA

Major Arterial Involvement (Surgical)

1. Patients medically fit for major pancreatic surgery as per the assessment of the treating surgeon
2. No evidence of metastases (*i.e.*, metastatic work-up negative including a CT scan of the chest and the abdomen (IV and oral contrast, 3 phase) and pelvis).
3. Index operation - no prior attempted resection
4. Arterial involvement limited to a single major vessel [i.e. reconstructable single artery involvement (therefore allows for encasement of one major and abutment (< 180°) or a second with the assumption that reconstruction of only 1 major artery will be completed]
 - a. Superior mesenteric artery or
 - b. Celiac axis (including major celiac axis branches eg common hepatic artery)
 - c. Replaced right hepatic artery (RRHA) as a special case. This will be based on the individual anatomical variant and the extent of associated SMA involvement. The SMA involvement accepted is the same as without the RRHA. The extent of the involvement of the RRHA will be within the technical ability to safely revascularize. > 5mm involvement of RRHA will be considered equivalent to SMA encasement
 - d. “long segment” (> 5mm) hepatic artery will be considered equivalent to celiac encasement) extent of arterial involvement will be assessed radiographically by 2 GI radiologists.
5. Arterial involvement that is potentially resectable confirmed by two Hepatobiliary surgeons
6. Hepato-Pancreato-Biliary (HPB) surgeons consider that tumour-free margins could be achieved based on a recent CT abdomen with IV and oral contrast, triple phase.

7. Length of vessel involved on CT
 - a. SMA - not extending into distal branches (beyond proximal jejunal artery)
 - b. Celiac – reconstruction of left and right supply possible
 - c. Hepatic – Not extending into distal branches (reconstruction of single lumen only)
8. Mass considered otherwise resectable by current standards
 - a. May include co-existent, resectable portal or superior mesenteric venous involvement
 - b. Short-segment occlusion permitted of the SMV/PV if suitable vessel above and below for reconstruction
 - c. May include other organ involvement by local extension

General Considerations

1. Age < 70
2. ECOG performance status of ≤ 1
3. Cytological or histological diagnosis of pancreatic adenocarcinoma
4. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20 mm with conventional techniques or as >10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.
5. Adequate bone marrow and organ function as evident by:
 - a. absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - b. platelet count $> 100 \times 10^9 /L$
 - c. hemoglobin $> 90 \text{ g/L}$
 - d. total bilirubin $\leq 26 \text{ umol/L}$
 - e. ALT and AST $\leq 2.5 \text{ X upper limit of normal}$
 - f. ALP $\leq 2.5 \text{ X upper limit of normal}$
 - g. serum creatinine $\leq 133 \text{ umol/L}$ OR CrCl $> 50 \text{ ml/min/1.73m}^2$ (if above institutional limits of normal)

- h. prothrombin time (PT) international normalized ratio (INR) < 1.5
6. Therapeutic anticoagulation with low molecular weight heparin is allowed
7. Patients taking chronic erythropoietin are permitted provided no dose adjustment is undertaken within 1 month prior to or during the study.
8. Women of childbearing potential (*i.e.*, those that are not surgically sterile or without documented menopause for 18 months) must have a negative pregnancy test (serum β -HCG) performed within seven days prior to the start of study drug.
9. Both men and women enrolled in this trial must use barrier birth control (*i.e.*, condoms) during the course of the trial and for three months after completing treatment.
10. Patients must be able to provide written informed consent

EXCLUSION CRITERIA

Major Arterial Involvement (Surgical)

1. Aortic involvement
2. Involvement of two major arterial trunks:
 - a. encasement (> 180°) of both SMA and celiac
 - b. encasement of SMA and > 5mm hepatic artery
 - c. encasement of celiac and > 5mm replaced hepatic artery
3. SMV or portal venous occlusion with no technical option for reconstruction
4. Extensive venous involvement without concurrent arterial involvement
5. Borderline resectable *i.e.* abutment (< 180°) single artery involvement
6. Evidence of significant disease progression (precluding resection) on neo-adjuvant treatment.

General Considerations

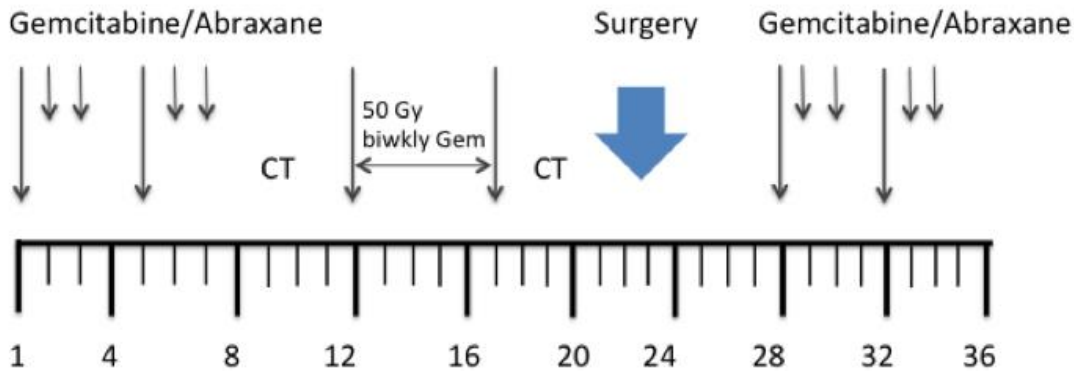
1. Previous or concurrent cancer that is distinct in primary site or histology from adenocarcinoma, except cervical carcinoma in situ, localized prostate cancer, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis & T1). Any cancer curatively treated 3 years prior to entry is permitted.
2. Previous treatment with radiotherapy to the pancreas and/or associated field
3. Previous chemotherapy within 3 years of presentation with pancreatic cancer.
4. Previous autologous bone marrow transplant or stem cell rescue
5. Major surgery within 4 weeks of start of chemotherapy
6. Disease with distant metastases
7. Renal dysfunction with an estimated creatinine clearance of < 50 cc/min
8. Pulmonary insufficiency (clinically evident history of chronic obstructive pulmonary disease)
9. History of cardiac disease including, but not limited to:
 - a. Congestive heart failure > New York Heart Association (NYHA) class 2
 - b. Active coronary artery disease
 - c. Uncontrolled hypertension
10. The patient cannot have any active systemic infection(s) or any other active major medical illnesses of the respiratory or immune system, uncontrolled psychiatric disorders, or other conditions that may affect patient compliance or safety on this trial
11. Known human immunodeficiency virus (HIV) infection or uncontrolled active hepatitis B (HBV) or Hepatitis C virus (HCV)
12. History of solid organ transplantation, collagen vascular disease, inflammatory bowel disease, or underlying neuropathy
13. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results
14. Known or suspected allergy to the investigational agent or any agent given in association with this trial
15. Pregnant or breast-feeding patients are excluded from this study as the

chemotherapy agents used in this study have been demonstrated or have the potential to be a teratogen and there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother

16. Patients who are being therapeutically anticoagulated with Coumadin

17. Prior diagnosis of malignancy allowed as long as all therapy has been completed and there is no evidence of disease for at least 3 years prior to enrollment. Exceptions are adequately treated in situ carcinoma of the prostate (Gleason score ≤ 7), cervix, uteri or non-melanomatous skin cancer (all treatment for these should be completed prior to enrollment).

Treatment schematic



References:

1. Lopez N et al. Borderline resectable pancreatic cancer: Definitions and management. *World Journal of Gastroenterology* 2014; 20 (31)
2. M. Katz, C. Crane, G. Varadhachary, et al. Management of Borderline Resectable Pancreatic Cancer. *Semin Radiat Oncol* 2014, 24:105-112
3. Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* June 2014.

DRAFT