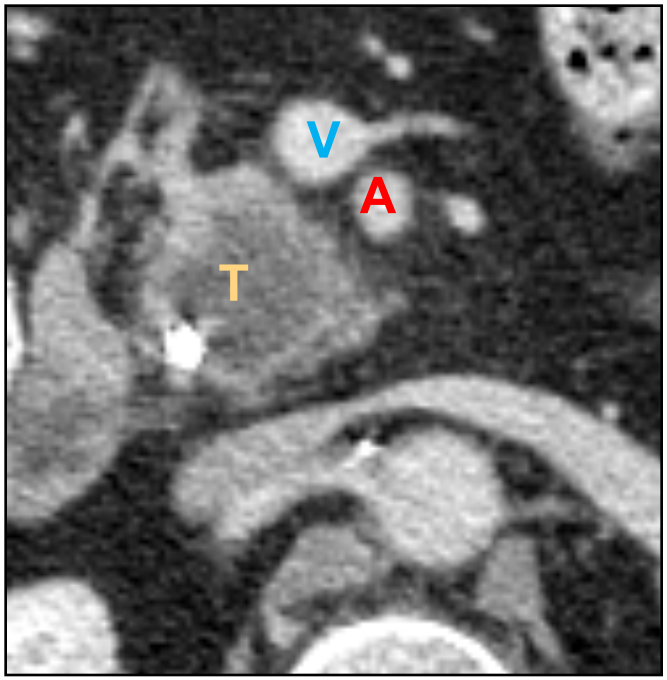
Preoperative chemotherapy and chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas

Alliance A021501

Alliance – SWOG – ECOG/ACRIN - NRG

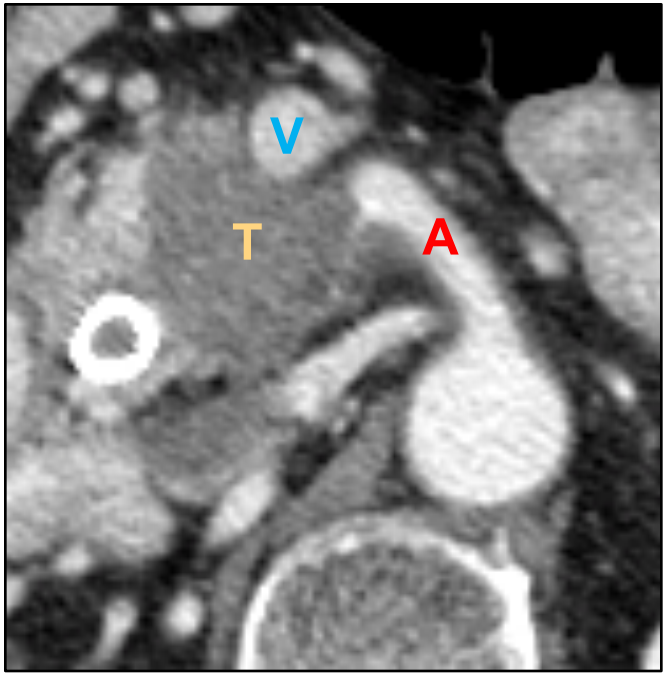
Clinical spectrum of resectability

Resectable



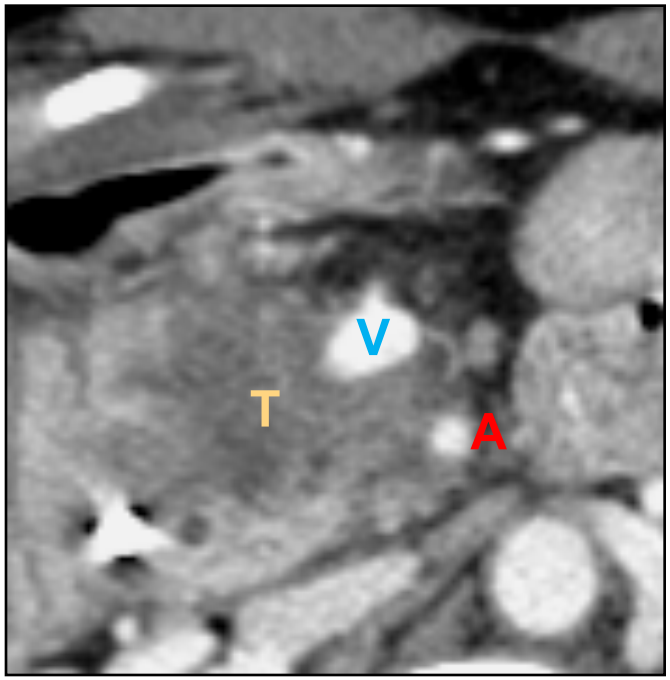
R0 likely
Surgery/adjuvant tx standard

Borderline Resectable



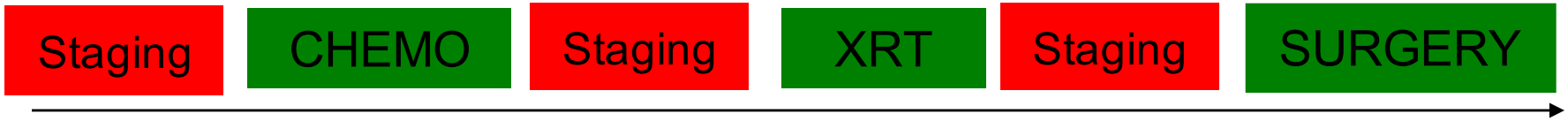
R1 likely
Surgery possible but results suboptimal

Unresectable



R2 likely
Surgery not a technical option

Borderline resectable PDAC: Treatment based on consensus not data



- ***CHEMO:*** *Cytotoxic effect on systemic disease*
- ***XRT:*** *Sterilization of surgical margins (R0)*
- ***Time:*** *Selection of tumor biology and patient physiology for surgery*

Provides an opportunity to impact the natural history of the disease

Callery, Ann Surg Onc 2009

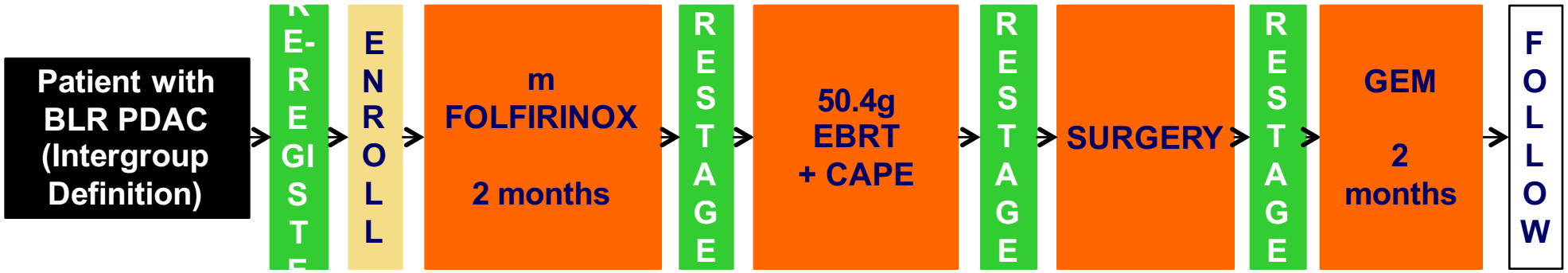
JAMA Surgery

Original Investigation

Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer

Alliance for Clinical Trials in Oncology Trial A021101

Matthew H. G. Katz, MD; Qian Shi, PhD; Syed A. Ahmad, MD; Joseph M. Herman, MD; Robert de W. Marsh, MD; Eric Collisson, MD; Lawrence Schwartz, MD; Wendy Frankel, MD; Robert Martin, MD; William Conway, MD; Mark Truty, MD; Hedy Kindler, MD; Andrew M. Lowy, MD; Tanios Bekaii-Saab, MD; Philip Philip, MD, PhD; Mark Talamonti, MD; Dana Cardin, MD; Noelle LoConte, MD; Perry Shen, MD; John P. Hoffman, MD; Alan P. Venook, MD



- *Centralized radiographic review of pretreatment and restaging studies*
- *Prospective QC of all modalities*
- *Protocol-mandated operative indications and procedures*
- *Analysis and reporting of survival rates and objective response metrics*

What did we learn from A021101?

- Complex trials in this population feasible in the cooperative group setting
- 27% RECIST response
- R0 operations possible in 64% patients…but vascular resection 80%
- 33% resections <5% viable cells, 13% pCR
- 1/3 resected patients did not start postop tx, emphasizing need for preloading
- median OS of all enrolled patients: 22 months

Katz, JAMA Surg 2016

The clinical problem

- This approach of CTX -> CXRT is **based on consensus** and **subsequently weakly "supported"** by retrospective data
- Consensus proposed when gemcitabine– an agent with a response rate < 10%-- was standard therapy[1]
- Sequential administration of gem-based chemo then CXRT -> RECIST response 12%[2]
- FOLFIRINOX response rate 32% in metastatic setting[1]
- Standard CXRT is long (5.5 weeks), limits administration of full-dose systemic therapy, and deters patients from enrolling in trials at tertiary centers

[1]Conroy NEJM 2011
[2]Katz Cancer 2012

Pancreas SBRT

- Pioneered for locally advanced PDAC
- Patient convenience
- Shorter time away from full dose chemo (e.g. FOLFIRINOX)
- Prospective multicenter study showed SBRT safe and improves pain/QoL in LAPC
- Retrospective single institution data (e.g. Moffitt, Hopkins) suggests SBRT for BR PDAC:
  - Does not compromise potential surgery option
  - Does not increase postoperative complications
  - Is associated with high rate of R0 resection
  - Is very well tolerated

Herman et al, Chuong et al.

What else do we know?

- Role of CXRT unclear in LA PDAC
  - Pts who received CXRT alone: median OS 9-12 months (Moertel 1981)
  - 269 of 442 patients with LAPC who received systemic tx and subsequently randomized: median OS 16.5 months (chemo) and 15.3 months (CXRT) – note that 40% progressed prior to first randomization (Hammel 2013)

- Neoadjuvant therapy for resectable PDAC reasonable with chemo +/- CXRT
  - Pts who received CXRT: median OS 22.7mo (Evans 2008)
  - Pts who received gem-CIS and gem-CXRT: median OS 17.4mo (Varadhachary 2008)
  - Pts who received gem-OX: median OS 27.2 months (O'Reilly 2014)
  - Pts who received FFX: median OS 33 months (Marsh 2016)

- Local control with as few as 5d XRT then surgery. Tumorcidal doses unnecessary!
  - 30Gy/10 compatible with local control and favorable OS in resectable (Evans 2008)
  - 25Gy/5 safe and favorable local control after surgery in resectable (Hong 2014)
  - 33Gy/5 SBRT following induction chemo for BLR: 56% resected, 97% R0 (Chuong 2013)
  - 80% of 61 pancreatic surgeons, med oncs, rad oncs surveyed would enroll on a trial utilizing SBRT

Primary objective

To estimate the 18 month OS rate of patients with borderline resectable PDAC receiving neoadjuvant therapy consisting of one of the following regimens prior to intended surgical resection and adjuvant therapy with 4 cycles of FOLFOX:

1) 8 cycles of systemic FOLFIRINOX,
2) 7 cycles of systemic FOLFIRINOX followed by short-course XRT (SBRT/HIGRT)

Secondary Objectives

- To estimate R0 resection rates
- To estimate event-free survival rates (including local recurrence)
- To estimate pCR rates
- To assess AE profiles
- To evaluate and compare QOL
- To evaluate a novel, image-based risk classification

Inclusion

- Borderline resectable – Intergroup Criteria
- ECOG 0-1
- No prior treatment or second malignancy
- No sensory neuropathy, PE, Gilbert's
- Bili <=2
- No CA 19-9 limit

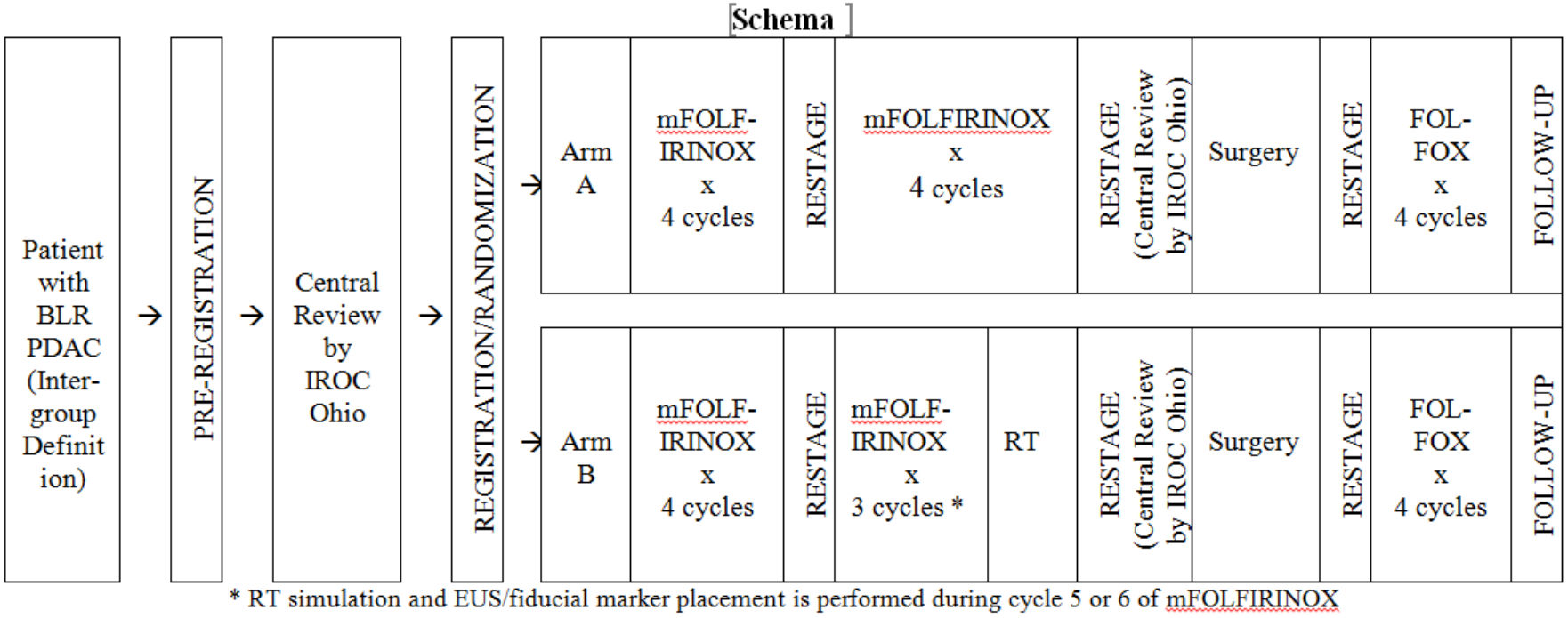
Local Disease Staging

Intergroup radiographic criteria

	Potentially Resectable	BORDERLINE RESECTABLE	Locally Advanced
SMV-PV	T-V-I < 180º	**T-V-I ≥ 180º and / or reconstructable occlusion**	Unreconstructable Occlusion
SMA	No T-V-I	**T-V-I < 180º**	T-V-I ≥ 180º
CHA	No T-V-I	**Reconstructable short-segment T-V-I of any degree**	Unreconstructable
Celiac Trunk	No T-V-I	**T-V-I < 180º**	T-V-I ≥ 180

T-V-I: tumor-vessel interface

Pancreas SBRT, A021501 Schema



Statistics

- Total targeted accrual 134 patients

- Interim analysis after only 30 patients/arm: if R0 resection performed in 11 or fewer patients in either arm, that arm closes

IMPORTANT NOTES

- Chemotherapy may be administered outside the enrolling institution but XRT and surgery must be performed at the enrolling institution
- Sites will decide whether to utilize either SBRT or HIGRT on this trial, but *SBRT is recommended and preferred*
- Radiation plans must be prospectively reviewed prior to treatment
- Trial employs a two-phase registration process with real-time central radiographic review of imaging

IMPORTANT NOTES RE: SBRT

- Centers delivering SBRT must be **credentialed** for SBRT prior to the delivery of radiation therapy on any protocol patient.
- SBRT requires the ability to perform **daily image guidance**.
- SBRT is recommended to be done at **high volume pancreatic cancer centers**.
- Patients with **active duodenal or gastric ulcers** are not acceptable for SBRT. Patients with previous ulcers that have resolved are acceptable for SBRT.
- Patients with **direct tumor invasion of the bowel or stomach** are not acceptable for SBRT, but may be considered for HIGRT.
- Patients should not be treated with SBRT if **SBRT-specific organ at risk (OAR) constraints** cannot be met; these patients should be considered for HIGRT.
- Patients should be treated with SBRT only if tumor motion can be minimized using **motion management techniques**, when applicable.

IMPORTANT NOTES RE: HIGRT

- Expected to be used for <10% of cases
- Centers that are **not credentialed for SBRT** may treat with HIGRT if appropriately credentialed.
- **Direct tumor invasion of the bowel or stomach** (loss of fat plane) is acceptable for HIGRT.
- **Active duodenal or gastric ulcers** are not acceptable for HIGRT. Patients with previous ulcers that have resolved are acceptable. This must be confirmed at the time of fiducial placement.
- HIGRT should be considered at centers that **do not have motion management** techniques such as respiratory gating, active breathing control, or abdominal compression.

EduCase Modules

- Combining modules and videos (EduCase) can decrease deviations, improve compliance, safety

- We have developed a comprehensive **instructive module** that demonstrates protocol requirements/steps to assist each participant: physician who contours, dosimetrist, physicist, radiation therapist.