THE ROLE OF RADIATION THERAPY IN MANAGEMENT OF PANCREATIC ADENOCARCINOMA

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RESECTABLE DISEASE

MANAGEMENT: RESECTABLE DISEASE

- Resection offers the only possibility of long term survival
- This possibility is not high:
  - 5 yr survival after R0 resection is ~20%
- Median survival for resectable disease is ~20 months

A TALE OF TWO CONTINENTS

United States (support for CRT)

- GITSG 91-73
- RTOG 97-04

Europe (support for chemo alone)

- EORTC 40891
- ESCPAC-1
- CONKO-1 (chemo alone study)
- ESPAC-3 (chemo alone study)

RTOG 97-04
SECONDARY ANALYSIS

Int J Radiat Oncol Biol Phys. 2012 February 1; 82(2): 809–816. doi:10.1016/j.ijrobp.2010.11.039.

Failure to Adhere to Protocol Specified Radiation Therapy Guidelines Was Associated With Decreased Survival in RTOG 9704 - A Phase III Trial of Adjuvant Chemotherapy and Chemoradiotherapy for Patients with Resected Adenocarcinoma of the Pancreas

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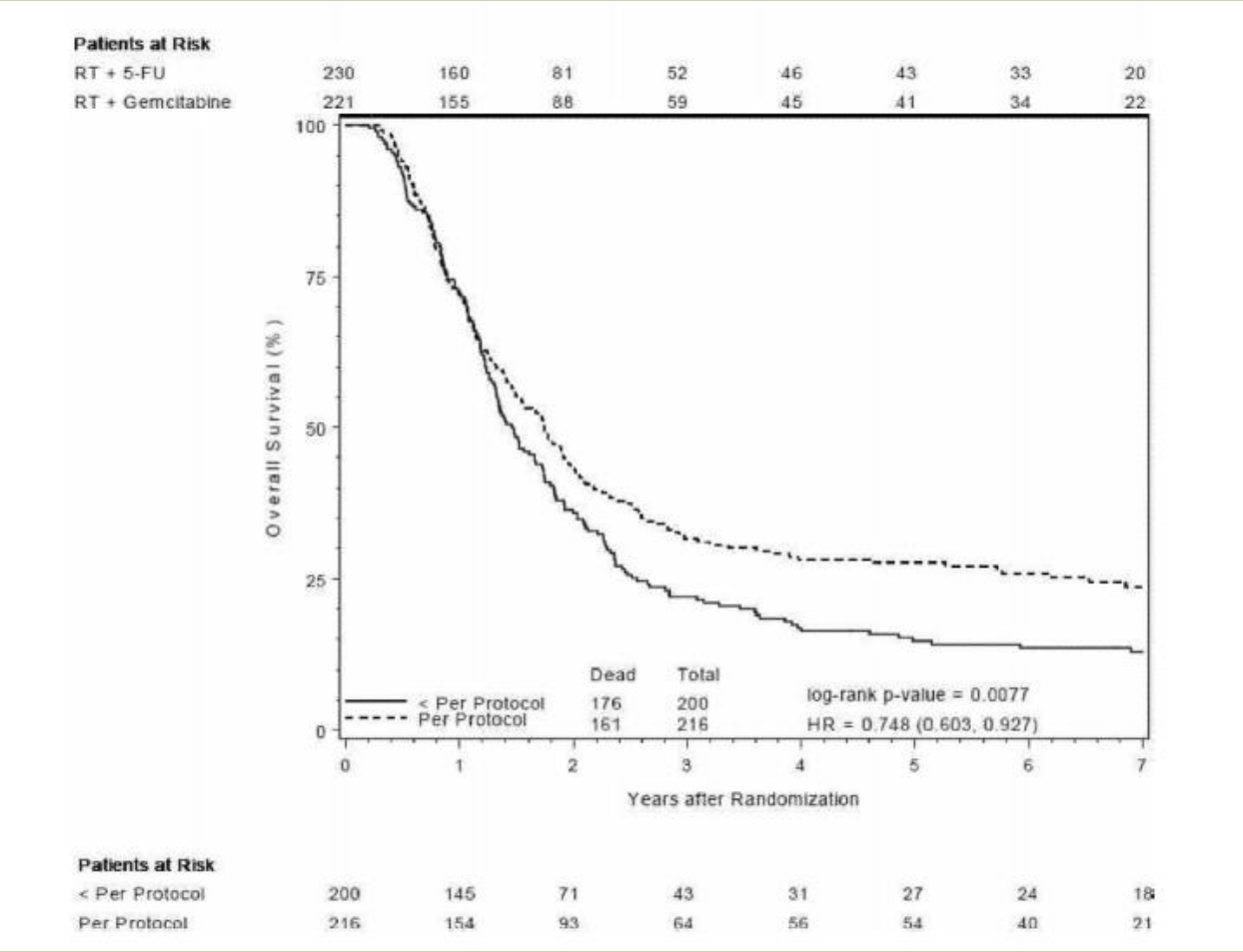
RTOG 97-04
SECONDARY ANALYSIS



RTOG 97-04
SECONDARY ANALYSIS

Head of Pancreas Patients Only (n=359)

Adjustment Variables	Comparison	Adjusted HR	p-value†
Treatment	Gemcitabine vs. 5-FU	0.79 (0.62, 0.99)	0.043
Nodal Involvement	No vs. Yes	1.47 (1.13, 1.91)	0.0036
Tumor Diameter	<3 vs. ≥ 3cm	1.25 (0.98, 1.59)	0.070
Surgical Margin Status	Negative	Ref level	--
	Positive	1.07 (0.82, 1.40)	0.64
	Unknown	0.94 (0.69, 1.27)	0.68
RT QA Score	< PP vs. PP	0.75 (0.60, 0.95)	0.016

Abbreviations: 5-FU, fluorouracil; HR, hazard ratio; C.I., confidence interval

Hazard Ratio (HR) > 1 indicates increased risk of death for the second variable; HR < 1 indicates decreased risk of death for the second variable

† p-value from Chi-square test using the Cox proportional hazards model.

RTOG 0848

STRATIFY

Nodal Status:
1: involved
2: uninvolved

CA19-9 result:
1: ≤ 90
2: > 90 – 180

Surgical margins:
1: positive (R1)
2: negative (R0)

Gemcitabine x 5 cycles

If no progression, then:

RANDOMIZE

Arm 3:
1cycle of chemotherapy

Arm 4:
1 cycle of chemotherapy followed by
XRT with either capecitabine or 5-FU

Accrual: 347/950

SEER REGISTRY ANALYSIS

- National Propensity-Adjusted Analysis of Adjuvant RT
- McDade et al., Cancer 2010
  - 1988-2005, 5676 patients, 40% received adjuvant RT
  - Predictors of improved OS on MVA: white race, married status, earlier stage, tumors < 2 cm, well-differentiated path, LN-, recent diagnosis (within 6 years) and receipt of adjuvant RT.
  - RT: HR of 0.587 (0.545 – 0.631, p<0.0001)
  - Benefit remained significant after propensity adjustment for the likelihood of receiving RT (HR 0.774; 0.719-0.834).
  - Median survival: 10 months no RT vs 18 months with RT (p<0.0001)
- Sugawara et al., Journal of Surgical Oncology 2014
  - 2004 – 2009, 2532 patients, 40% received adjuvant RT
  - On MVA RT associated with improved cause-specific survival (HR 0.654) and OS (HR 0.647)
  - Median survival: 16 months no RT vs 20 months with RT (p<0.0001)

LOCAL VS SYSTEMIC DISEASE

- Most, but not all, pancreatic cancers are metastatic
  - 12% of patients with no metastatic disease at autopsy
  - 18% of patients with limited metastatic burden, not deemed directly contributing to their cause of death
- Genetic markers may help distinguish pancreatic cancer with predilection for local progression vs systemic spread
- SMAD4 (Dpc4) tumor suppressor gene
  - Lost in up to 80% of pancreatic cancers
  - Immunohistochemical assessment of SMAD4 protein is a reliable predictor of gene status
  - Loss in a surgically resectable carcinoma corresponds to a relative risk of 3.3 of development of widespread mets compared to those with intact Dpc4 labeling.

Iacobuzio-Donahue et al., JCO 2009

SMAD4 GENE STATUS

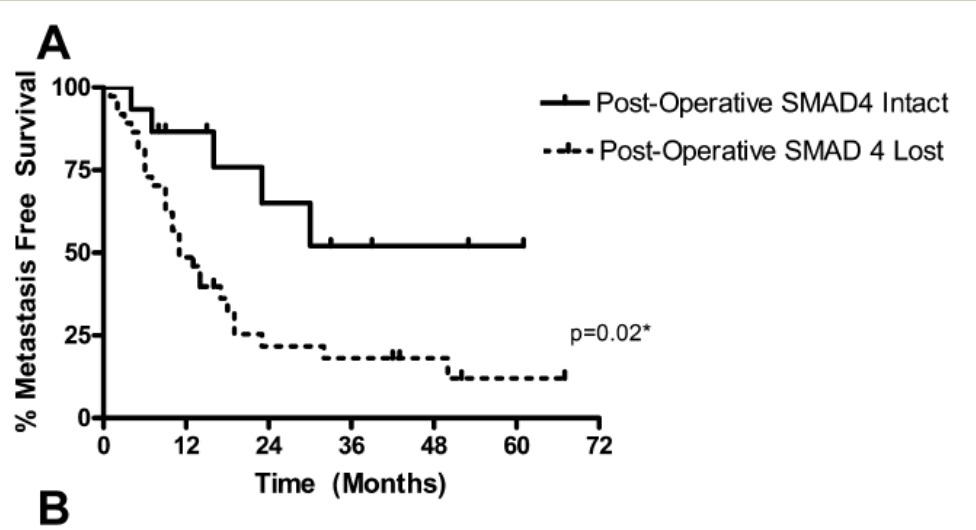
Table 3. Relationship of Genetic Features to Patterns of Failure in Advanced Stage Pancreatic Cancer

Metastatic Burden by Gene for Primary Carcinoma	Locally Destructive				Locally Confined				
	0		1-10		11-99		100s-1,000s		
	No.	%	No.	%	No.	%	No.	%	*P*
KRAS2 (n = 59)	6/7	86	11/11	100	19/21	90	20/20	100	.283
	17/18; 94%				39/41; 95%				.672
TP53 (n = 58)	6/6	100	6/11	54	16/21	76	18/20	90	.083
	12/17; 71%				34/41; 83%				.037
DPC4 (n = 65)	2/9	22	5/11	45	17/24	71	16/22	73	.032
	7/20; 35%				33/46; 72%				.007

Iacobuzio-Donahue et al., JCO 2009

SMAD4 GENE STATUS

- Boone et al., J of Surg Onc, 2014. Univ of Pittsburgh
  - Retrospective review of 117 patients undergoing resection
  - SMAD4 loss in 70%
  - Metastatic disease:
    - 13.3% vs 51.4% at 1 year
    - 36.8% vs 78.5% at 2 years
- On logistic regression analysis:
  - SMAD4 loss was associated with 6 times odds ratio of developing metastatic disease
  - Neoadjuvant treatment did not affect the predictive value of preoperative SMAD4



THE ROLE OF SBRT IN ADJUVANT SETTING

- 2006 – 2010, 24 patients at Univ of Pittsburgh
  - 8 patients with close margins of 1 – 2.5 mm
  - 16 patients with positive margins
- Single fraction SBRT 20-24 Gy
- Median target volume 11 cc (4.5 – 30 cc)

- Results:
  - Median followup 12.5 months
  - Median OS 26.7 months
  - OS1: 80%, OS2: 57%
  - Freedom from Local Progression:
    - at 6 mos: 95%, at 1 year 66%, at 2 years 44%
  - 19/24 patients resumed or started a 6-month course of gemcitabine at a median interval of 18 days (range, 9-31 days) post-SBRT
- Toxicity:
  - No grade 3 - 5 toxicity
  - 3 patients (12.5%) grade 1-2 acute GI toxicity
  - 2 patients (8.3%) grade 1-2 late toxicities

Rwigema, et al., Am J Clin Oncol 2011

THE ROLE OF SBRT IN ADJUVANT SETTING

- BIDMC, Boston
- 8 patients with pT3N0-1, positive margins
  - 7 head and 1 tail lesions
  - 10 Gy SBRT boost to positive margins, followed by 45-50.4 Gy of fractionated RT to pancreatic bed with concurrent capecitabine
  - With a median followup of 8.8 months:
    - PFS 75% (2 patients progressed systemically and died)
    - Remaining 6 patients were free of disease
    - 100% local control at death or last follow-up.

ASTRO 2007 abstract, IJROBP 2007; 69:S307

LOCALLY ADVANCED DISEASE

LOCALLY ADVANCED

- Median survival 7-12 months
- Ideally enroll on protocol

GERCOR

HUGUET et al. JCO. 2007

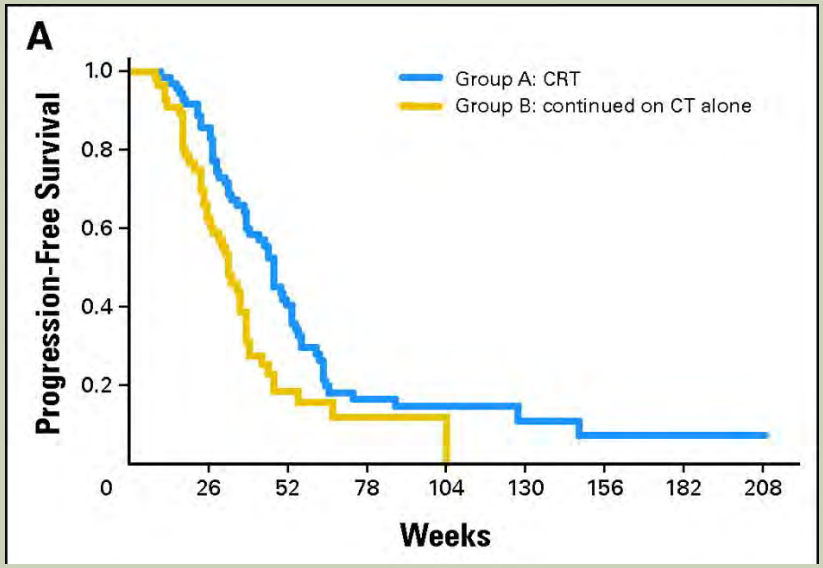
- Rationale: Management of locally advanced disease was controversial.

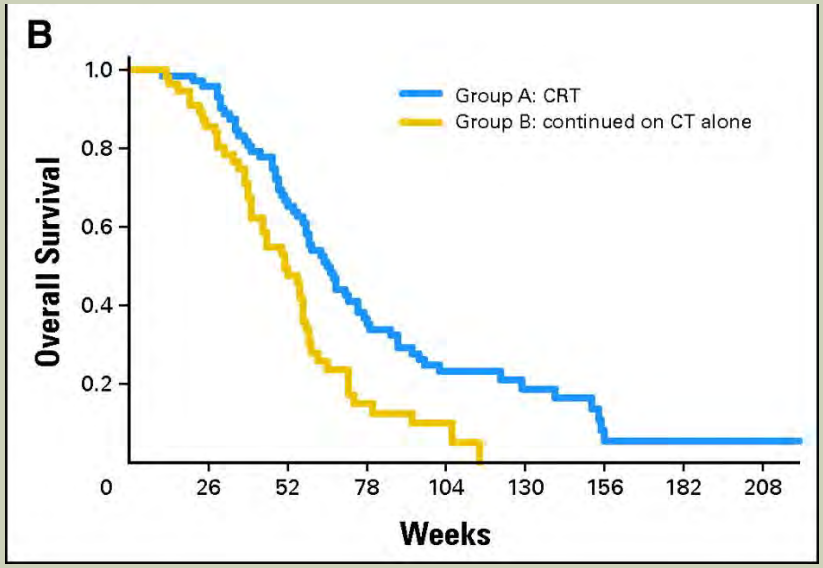
- Retrospective analysis of 181 pts from 4 prospective Phase II and III GERCOR studies
- Compared chemotherapy to chemoradiation (decision was investigator's choice)
  - Gem based chemo x 3 months → Chemo
  - Gem based x 3 months → chemoradiation (55 Gy + 10 Gy boost + 5-FU)

GERCOR

HUGUET et al. JCO. 2007

- 30% developed metastatic disease within 3 months of chemo
- 70% (128) eligible





GERCOR

HUGUET et al. JCO. 2007

	Chemo	CRT
PFS	7.4 mon	10.8 mon
OS	11.7 mon	15 mon
1 yr survival	47.5%	65.3%

Conclusions:

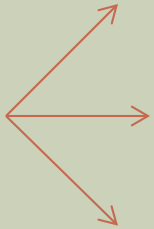
- Chemotherapy should be first line treatment for LAPC.
- If no progression of disease after three months, CRT could increase survival.

LOCALLY ADVANCED

- Median survival 7-12 months
- Ideally enroll on protocol
- Otherwise, FOLFIRINOX based chemo x 2-4 months → 5FU based chemoradiation
- Begin chemoradiation if:
  - Radiographic local progression
  - CA 19-9 increase
  - Symptoms
  - Chemo poorly tolerated

RTOG 1201

Gem/abraxane x 3



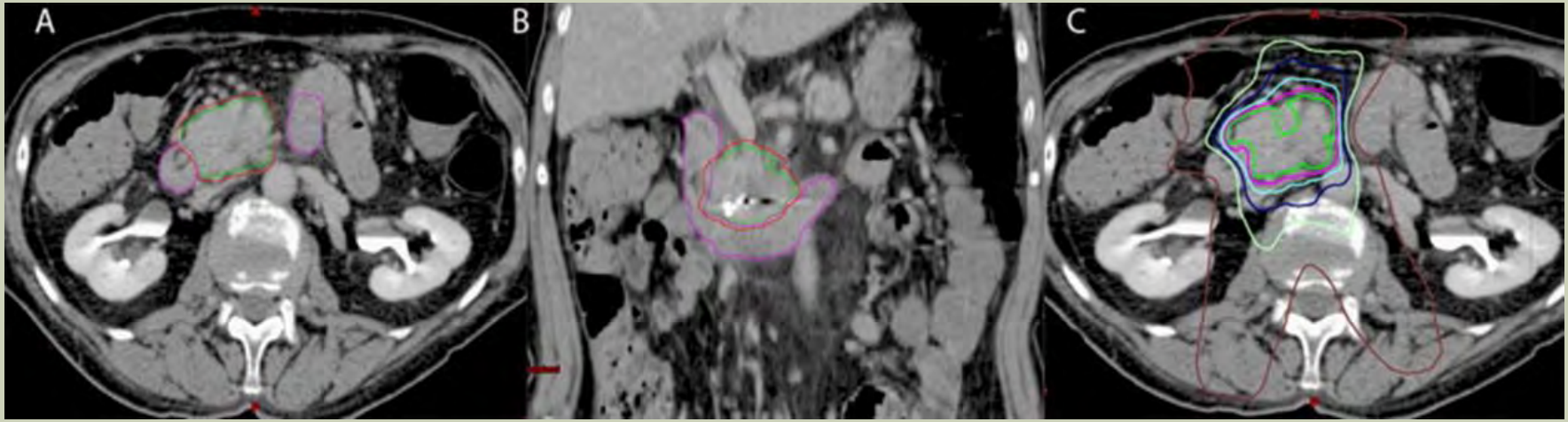
Gem/abraxane x 3

Gem/abraxane x 1 + IMRT 63 Gy

Gem/abraxane x 1 + RT 50.4 Gy

Stratify by:
Ca19-9 < 90
SMAD4 status

SBRT IN LOCALLY ADVANCED



Representative pancreatic SBRT plan:
(A) axial view showing pancreatic tumor (GTV: green), a typical PTV (red), and the duodenum (magenta);
(B) coronal view demonstrating tumor relationship with the duodenum;
(C) dose distribution for a plan treating to 33 Gy in 5 fractions. Isodose lines: green = 45 Gy; magenta = 40 Gy; cyan = 33 Gy; blue = 30 Gy; light green = 20 Gy; and brown = 10 Gy.

Trakul et al., Seminars in Radiation Oncology, 2014

Table Outcomes in Reported Studies of Pancreatic SBRT

References	Patients	Dose	Local Control (1 y Unless Specified)	Median Survival (mo)	Toxicity	Chemo
Koong et al[26]	15 LA or LR	15-25 Gy × 1	100%	11	33% Grades 1 and 2 0% ≥Grade 3	None
Koong et al[27]	16 LA	25 Gy × 1 (boost)	94%	8.3	69% Grades 1 and 2 12.5% ≥Grade 3	5-FU with EBRT prior to boost
Hoyer et al[34]	22 LA	15 Gy × 3	57%	5.4	79% ≥Grade 2 4.5% Grade 4	
Schellenberg et al[28]	16 LA	25 Gy × 1	100%	11.4	19% Acute 47% Late	1 Cycle induction GEM + post-SBRT GEM
Didolkar et al[35]	85 LA or LR	5-10 Gy × 3	92%	18.6	22.3% ≥Grade 3	Post-SBRT GEM
Mahadevan et al[30]	36 LA	8-12 Gy × 3	78%	14.3	33% Grades 1 and 2 8% Grade 3	Post-SBRT GEM
Polistina, et al[32]	23 LA	10 Gy × 3	82% 6 mo 50% 1 y	10.6	20% Grade 1 0% ≥Grade 2	6 wk induction GEM
Mahadevan et al[31]	39 LA	8-12 Gy × 3	85%	20	41% Grades 1 and 2 0% ≥Grade 3 (acute) 9% Grade 3 (late)	2 Cycles induction GEM
Rwigema et al[36]	71 LA, LR, RPM, and MD	24 Gy (med) × 1 (94%) 8-10 Gy × 2-3 (6%)	71.7% 6 mo 48.5% 1 y	10.3	39.5% Grades 1 and 2 4.2% Grade 3	90% Received chemo (various regimens)
Schellenberg et al[29]	20 LA	25 Gy × 1	94%	11.8	15% Grades 1 and 2 5% ≥Grade 3	1 Cycle induction GEM + post-SBRT GEM
Goyal et al[37]	19 LA or LR	20-25 Gy × 1 8-10 Gy × 3	81%	14.4	11% Grades 1 and 2 16% Grade 3	68% Received chemo (5-FU or GEM based)
Lominska et al[40]	28 LA or LR	4-8 Gy × 3-5	86%	5.9	7% Grade 3 (late)	5-FU or GEM prior to SBRT
Gurka et al[33]	10 LA	5 Gy × 5	40%	12.2	0% ≥Grade 3	1 cycle GEM prior, 6 cycles GEM total
Chuong et al[38]	73 BR or LA	5-10 Gy × 5	81%	16.4 BR 15 LA	5% Grade 3 (late)	3 cycles GTX

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THANK YOU!