Development of Proton Therapy in GI Cancers

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Disclosures

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Why protons for gastrointestinal cancers?

- Disease sites where VOLUME irradiated is important for toxicity
  - Liver
- Disease sites where there is a compelling reason for a shorter treatment course
  - Pancreas
- Diseases large volumes and high toxicity chemotherapy
  - Anal cancer
- Limited prospective clinical data

Protons and GI Sites

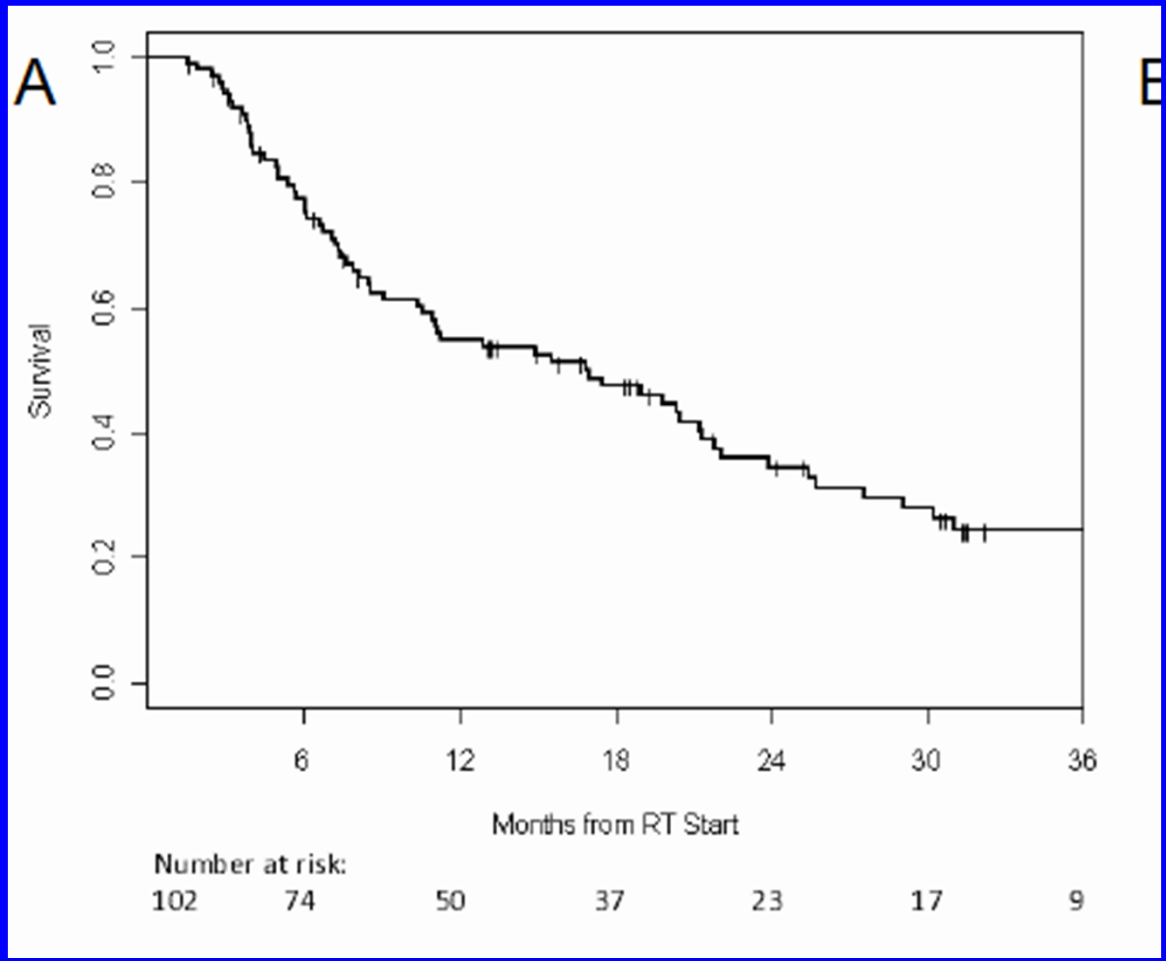
- Liver
- Pancreas
- Anal Canal

Photon (non-proton) radiation- PMH Ph II- HCC

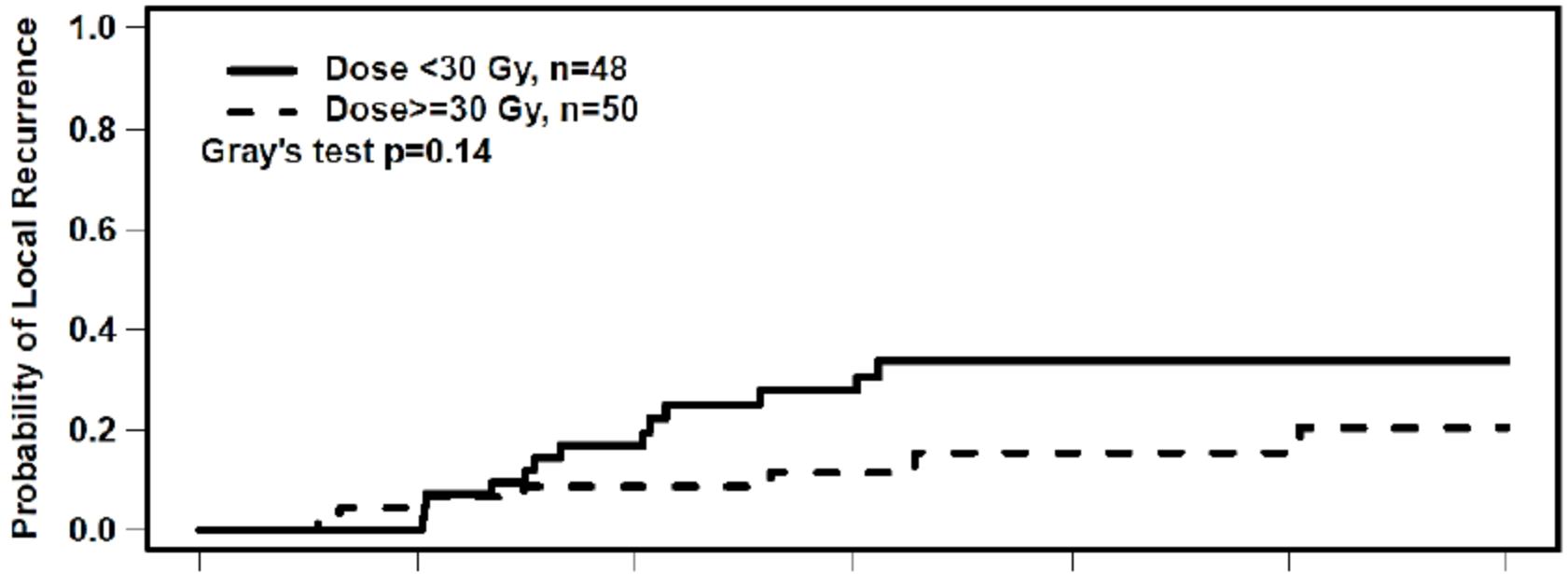
- 6 fraction SBRT
- 102 patients
- Individualized dosing based on Veff
- High risk patients
  - 55% with portal vein thrombus
  - 61% with multiple lesions
  - 52% CLIP $\geq$ 2

Bujold A, et al. JCO 2013

OS


A
B
Survival
0.0
0.2
0.4
0.6
0.8
1.0
6
12
18
24
30
36
Months from RT Start
Number at risk:
102
74
50
37
23
17
9

Local Control as a Function of Dose



Number of Patients at Risk:

<30:	48	34	16	9	4	3	1
>30:	50	36	24	17	10	8	4

Why Protons for Liver Tumors?

Table 1 The Estimated 5% RILD for Uniform Irradiation of One Third, Two Thirds, and the Whole Liver From Different Publications (in 1.5 Gy bid equivalent dose unless otherwise stated)

Reference, Year	No. Patients With RILD	Total	NTCP Model	5% Risk of RILD 1/3 Liver	2/3 Liver	Whole Liver
9, 1986	1	11	None	35 Gy†	NA	NA
2, 1991	27*	407*	None	50 Gy‡	35 Gy‡	30 Gy‡
22, 1991	27*	407*	Lyman	43 Gy‡	34 Gy‡	30 Gy‡
9, 1992	9	79	Lyman	72 Gy§	45 Gy	35 Gy
27, 1995	9	93	D-I	No limit	52 Gy	35 Gy
28, 2001	19	183	Lyman	90 Gy§	47 Gy	31 Gy
28, 2001	19	183	D-I	99 Gy§	43 Gy	32 Gy
28, 2001	19	183	Mean dose	—	—	31 Gy
Liver metastases						
11, 2002	3	85	Lyman	107 Gy§	54 Gy	37 Gy
23, 2004	3	85	Mean dose	—	—	37 Gy
Primary liver cancer						
11, 2002	11	84	Lyman	93 Gy§	47 Gy	32 Gy
23, 2004	11	84	Mean dose	—	—	32 Gy

Dawson LA, et al. Semin Radiat Oncol 2005;15:279-283

HCC: Clinical Data

- Efficacy
- Bridge to transplant
- Central tumors/venous thrombosis

Tsukuba Proton Liver Historical Experience

- Treatments
  - 165 patients
  - 192 tumors
  - Median dose - 72 Gy
  - Median dose/fraction – 4.5 Gy
- Outcomes
  - LC-5 – 86.9%
  - OS-5 – 23.5%
- Toxicity
  - 5 pts with Gr 2 or greater late sequelae
  - 2 Mucosal Ulceration
  - No RILD

Tsukuba Prospective Experience

- 51 pts
- > 2 cm from porta hepatis
- 66 GyE in 10 fractions
- 45 pts < 5 cm in diameter
- 80% Child's A, 20% Child's B
- 33 pts had prior treatment (TACE, RFA, Surgery)

Fukumitsu, et al.
IJROBP 2009.

Outcomes

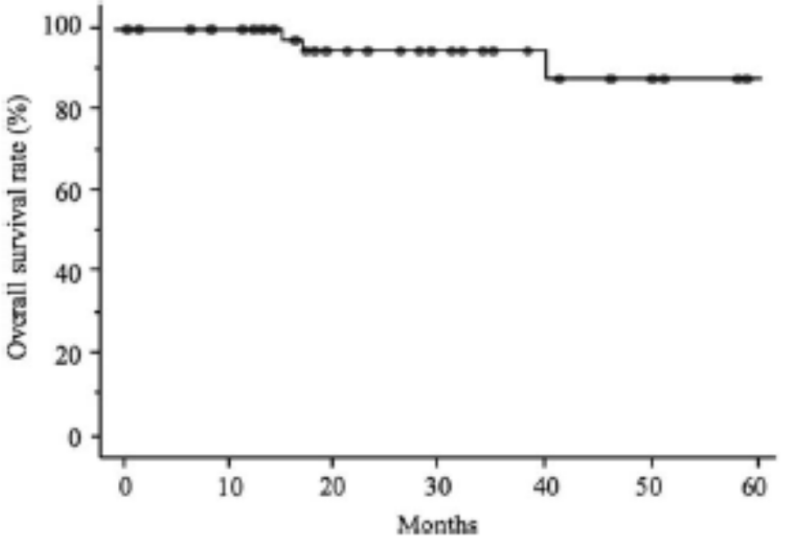


Fig. 2. Local control rate for all 51 patients. The 5-year local control rate was 87.8%.

Local Control

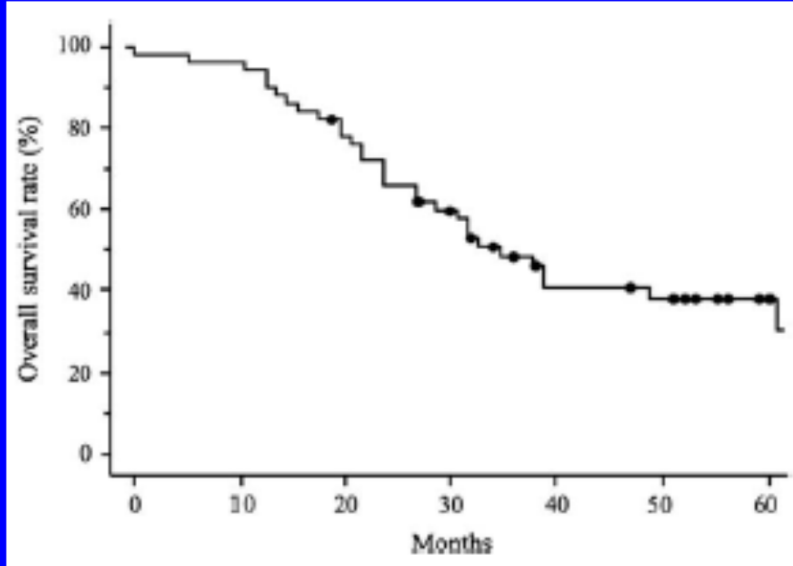


Fig. 1. Overall survival rate for all 51 patients. The 5-year overall survival rate was 38.7%.

Overall Survival

Loma Linda –Proton therapy as bridge to transplant

- 76 patients
- Mean tumor size 5.5 cm
- 63 GyE in 15 fractions
- 18 pts transplanted- 6 had pCR
- mPFS 36 mo
- PFS-3 for pts in Milan criteria – 60%

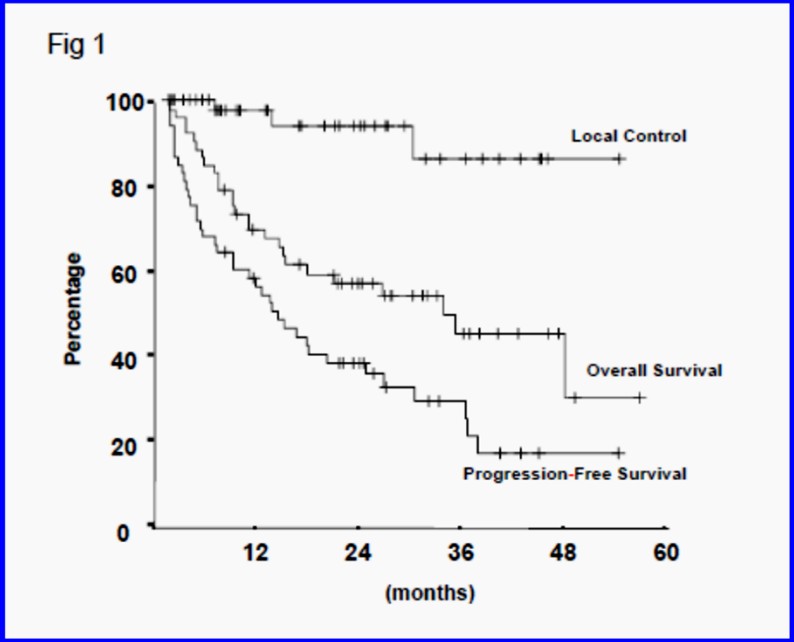
Bush et al. Cancer 2011

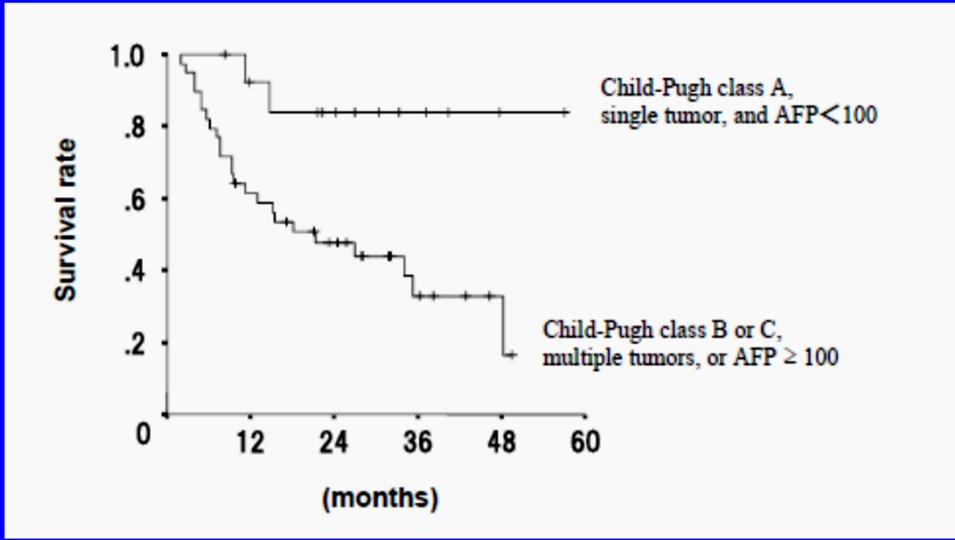
Central HCC

- 53 patients
- Tumors within 2 cm of porta hepatis
- 28% vascular invasion
- Tumor 5-10 cm in size – 18 (34%)
- Tumors >10 cm – 4 (8%)
- 66 Gy in 22 fractions

Mizumoto, et al.
IJROBP 2009.

Outcomes with central tumors

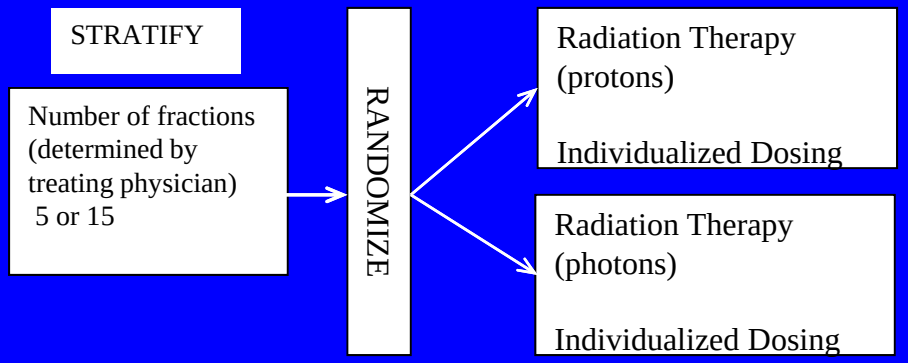




Protons vs. Photons for Unresectable, Liver Confined HCC

- Hypothesis:
  - Protons will result in superior local control compared to photons
- Rationale
  - Protons may allow for higher radiation dosing in an individualized, Veff based dosing strategy
  - Prospective Phase II study of photons for HCC from PMH shows dose-response relationship for local control
  - Tumor vascular thrombus may be harder to treat with passively scattered protons, but may be feasible with pencil-beam scanning protons

- Schema

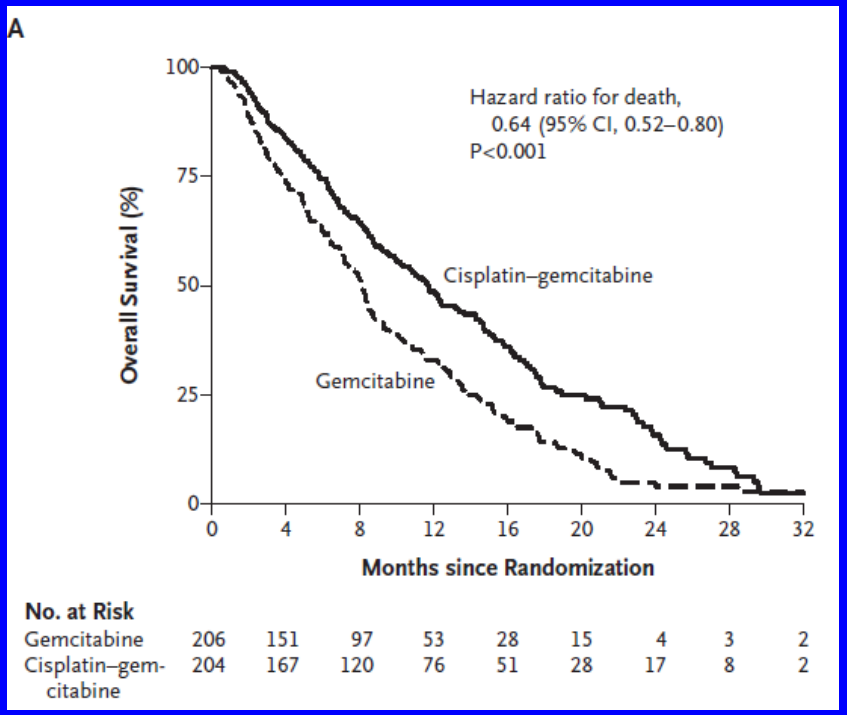


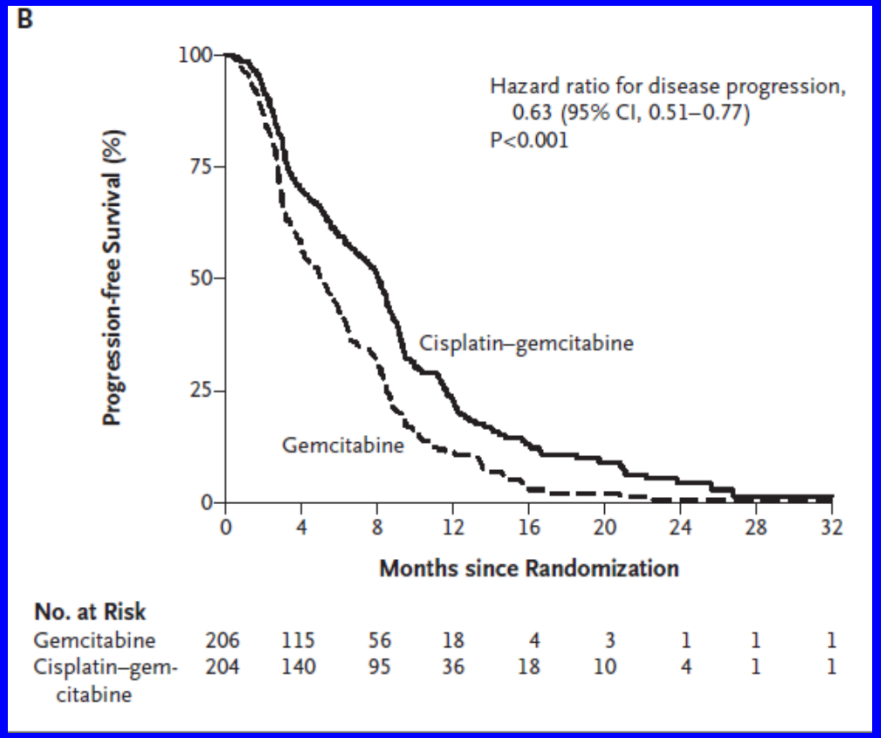
- Endpoints
  - Primary- Local Control
  - Secondary
    - PFS
    - OS
    - Toxicity
    - Exploratory evaluation of tissue/blood based biomarkers for disease control/liver toxicity

Intrahepatic cholangiocarcinoma

- Standard of care for unresectable cholangiocarcinoma is chemotherapy
- Gem/cis chemotherapy per ABC-2
- Protons have been associated with high rates of local control in HCC
- Can protons lead to long term local control, and thus survival in intrahepatic cholangiocarcinoma (ICC)?

Chemotherapy for Cholangiocarcinoma ABC 2





OS

PFS

Valle J, et al. N Engl J Med 2010;362;1273-81

Design

- Multicenter, single arm ph II study (MGH/MDACC/UPenn)
- Sample size calculated to demonstrate >80% LC at 2 yrs
- Eligibility
  - No cirrhosis or Child's A/B
  - ECOG PS 0-2
  - No extrahepatic disease
  - No Prior RT
  - Max tumor size 12 cm

Hong TS, et al. ASCO 2015

Treatment

- 15 Fractions
- Peripheral - 67.5 Gy
- Central (within 2 cm porta hepatis) – 58 Gy

Results

- 43 patients
  - 41 ICC, 2 mixed HCC/ICC
- 4 did not receive treatment
  - 3 could not meet dosing constraints
  - 1 became ineligible due to ECOG
  - Median longest tumor diameter (N=3):
    - 6.9 cm (range 4.4 - 9.0 cm)

Results

- 39 analyzed
  - 37 ICC, 2 mixed HCC/ICC
  - Median age – 66 years (range 29-87 years)
  - Cirrhosis
    - None- 1 (3%)
    - Childs A – 34 (87%)
    - Childs B – 4 (10%)
  - Prior systemic therapy – 24 pts (62%)
  - Number of tumors
    - 1 lesion – 33 (85%)
    - 2 lesions – 4 (10%)
    - 3 lesions – 2 (5%)

Results

Variable	Minimum	Median	Maximum
Longest tumor dimension (cm)	2.2	5.8	10.9
CA 19-9 at baseline (u/mL)	0	72	10,549
Dose prescribed (Gy)	45	58	67.5
Dose received (Gy)	15.1	58	67.5

Gr 3 Radiation-Related Toxicity 3 pts (8%)

- Hyperbilirubinemia – 1 pt
- Stomach ulcer – 1 pt
- Liver failure – 1 pt
- Ascites – 1 pt

1 patient had both liver failure and ascites.

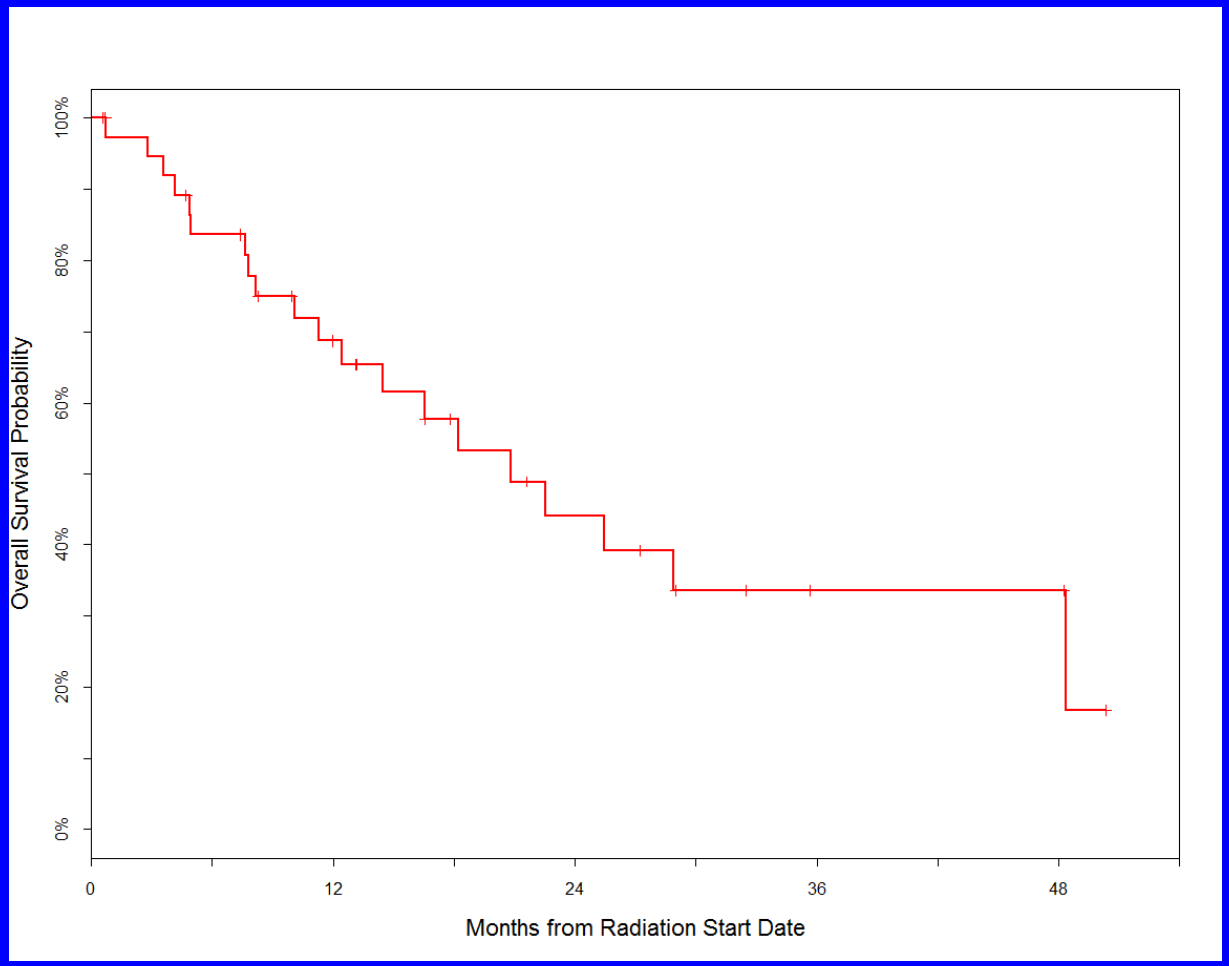
No grade 4 radiation-related toxicities.

Outcomes

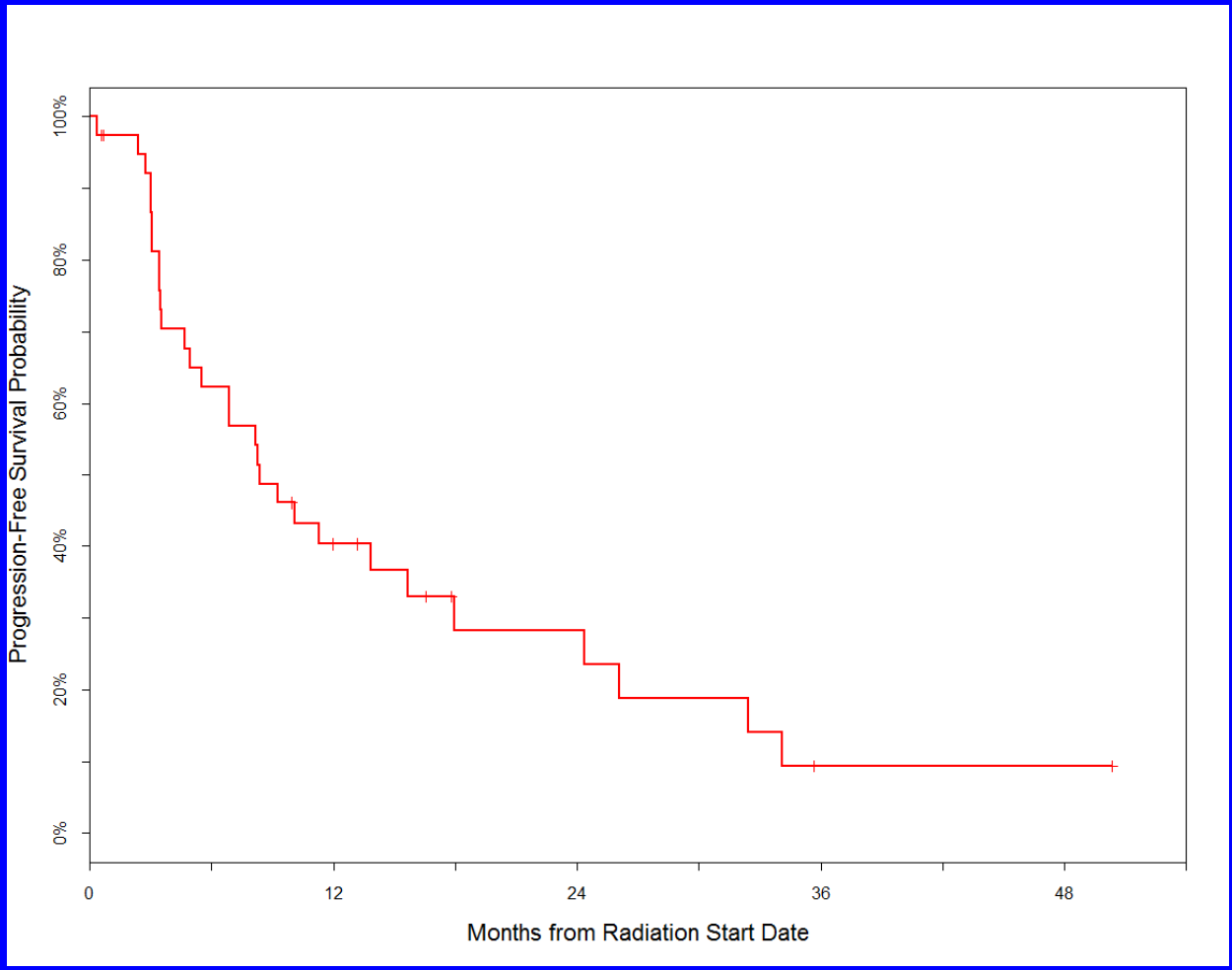
Median follow up duration among 19 survivors:
13.2 months (range 0.6 – 50.4 months)

Endpoint	1-year	2-year
Local Control	97%	90%
Overall Survival	69%	44%
Progression-Free Survival	40%	28%

OS – All Treated Subjects n=39



PFS – All Treated Subjects n=39



PFS status

Site of First Progression	N	%
Local only	5	12.8%
Local + hematogenous	1	2.6%
Hematogenous	19	48.7%
Death, no progression	4	10.3%
Alive, no progression	10	25.6%

Predictors of Local Control

Variable	Level	N	Median Time to Local Failure (months)	Log-Rank Test P-value
Size of longest tumor diameter	<6 cm	21	32.4	0.9561
	≥6 cm	18	30.1	
CLIP score	0-1	33	32.4	0.8259
	2+	5	--	
Tumor vascular thrombosis	No	28	34.1	0.0873
	Yes	11	--	
Prior chemotherapy	No	15	--	0.1288
	Yes	24	26.1	
CA 19-9	<72 u/mL	18	34.1	0.7751
	≥72 u/mL	19	32.4	
Dose Prescribed	<58 Gy	9	--	0.4927
	≥58 Gy	30	32.4	
Dose Received	<58 Gy	11	--	0.4927
	≥58 Gy	28	32.4	

-- Median time not reached

Predictors of OS

Variable	Level	N	Median Overall Survival (months)	Log-Rank Test P-value
Size of longest tumor diameter	<6 cm	21	25.5	0.2169
	≥6 cm	18	14.5	
CLIP score	0-1	33	18.2	0.1979
	2+	5	--	
Tumor vascular thrombosis	No	28	28.9	**0.0022**
	Yes	11	14.5	
Prior chemotherapy	No	15	25.5	0.7255
	Yes	24	20.8	
CA 19-9	<72 u/mL	18	28.9	0.2337
	≥72 u/mL	19	12.4	
Dose Prescribed	<58 Gy	9	25.5	0.5424
	≥58 Gy	30	20.8	
Dose Received	<58 Gy	11	14.5	0.9154
	≥58 Gy	28	20.8	

-- Median time not reached

Conclusions

- High dose, hypofractionated radiation (with protons) is associated with high rates of local control in ICC
- Radiation is safe
- Long term survival is possible
- These data form the foundation for NRG GI-001

NRG GI-001

Unresectable Cholangiocarcinoma

- -liver confined
- -no cirrhosis or CPC A
- -solitary lesion
- - 12 cm or less

→ Gem/Cis x 4 →

Re-staging AND Randomization after cycle 3
Radiation Planning during cycle 4

→ **Liver Directed Radiation Therapy**

Followed by maintenance Gem/Cis x 4

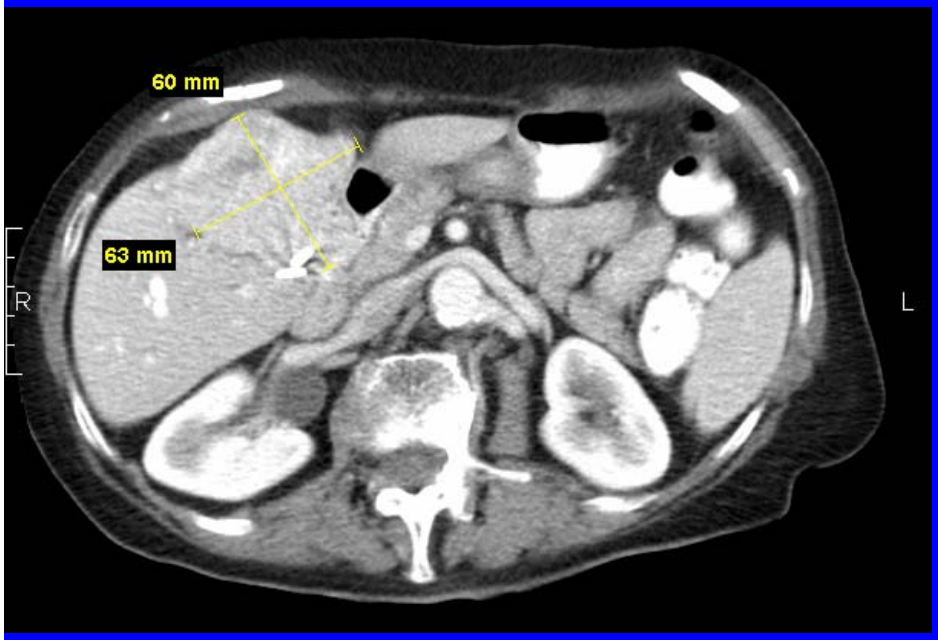
→ **Gem/Cis x 4**

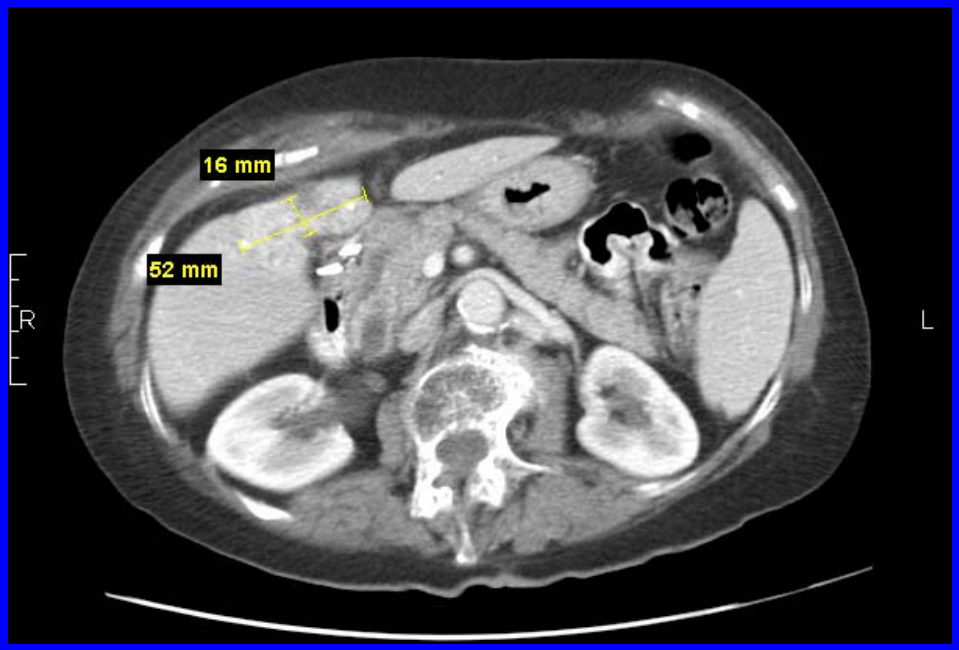
Stratify:

- -Largest tumor > 6 cm
- -Nodal involvement

Maintenance gemcitabine allowed at physician's discretion

Pre/Post Radiation
58.05 Gy





Liver Metastases

- Phase II of stereotactic protons or photons
- 5 fractions over 2 weeks
  - Veff<0.22 – 50 Gy
  - Veff 0.22-0.51- 40 Gy
  - Veff > 0.51- 30 Gy
- Endpoint- LC-1 >75%
- Outcomes will be presented at ASTRO 2015

Protons and Preoperative Therapy for Pancreas Cancer

- Can we challenge conventional paradigm of radiation fractionation
- If we can render local control in 1 week- makes decision to use RT less controversial

The Controversy of Radiation and Resectable Pancreatic Cancer

- Local Failure is a problem after surgery alone
- Early randomized trials showed a benefit to chemoradiation
- One controversial trial did not
- One chemotherapy alone trial showed a benefit to gemcitabine
- Standard chemoradiation is associated with significant toxicity, takes 6 weeks

Advantages of Short Course

- It works (rectal data)
- Cost-effective
- Less delay to surgery

Is it feasible in the pancreas?

Hypo-fractionation

Professional Charges	CPT	3D-CRT 50.4Gy	IMRT 50.4 Gy	Proton 25 Gy
Clinical plan	77263	1	1	1
IMRT Plan	77301		1	
Simulation: simple	77280	1	1	1
Simulation: 3D	77295	1		1
Dosimetry calc	77300	7	9	2
Plan complex	77315	1		
Device simple	77332			1
Device complex	77334	6	9	4
Weekly mngmt	77427	6	6	1
Special procedure	77470		1	
Consult: comps	99245	1	1	1
Total Prof.		**$2,600**	**$3,100**	**$1,200**

Technical Charges	CPT	3D-CRT 50.4 Gy	IMRT 50.4 Gy	Proton 25 Gy
CT guidance	76370	1	1	1
Simulation: simp	77280	1	1	1
Simulation: 3D	77295	1		1
Dosimetry calcs	77300	7	9	2
IMRT plan	77301		1	
Plan: complex	77315	1		
Device: simple	77332			1
Device: complex	77334	6	9	4
Physics consult	77336	5	6	1
Treatment γ	77414	28		
IMRT treatment	77418		28	
Port film	77417	5	5	1
Special proc	77470		1	
Treatment:p	77523			5
Consult: comp	99245	1	1	1
Total Technical		**$7,500**	**$13,700**	$8,000
Overall Cost		**$10,000**	**$16,700**	**$9,200**

Differentiate between cost to institution and cost to patient!

PHYSICS CONTRIBUTION

DOSIMETRIC FEASIBILITY OF HYPOFRACTIONATED PROTON RADIOTHERAPY FOR NEOADJUVANT PANCREATIC CANCER TREATMENT

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CLINICAL INVESTIGATION

PHASE I STUDY OF PREOPERATIVE SHORT-COURSE CHEMORADIATION WITH PROTON BEAM THERAPY AND CAPECITABINE FOR RESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA OF THE HEAD

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Phase I study of preoperative short course chemoradiation with early surgery

- Pancreatic head/neck adenocarcinoma
- Deemed resectable by surgeon
  - No SMA/Celiac involvement
  - Venous involvement allowed at discretion of surgeon
- Negative metastatic work up
  - CT C/A/P
  - Diagnostic Laparoscopy

Hong TS, et al. IJROBP, in press

Treatment Regimen

- Proton beam radiation for 5 fractions
- 2 weeks of concurrent capecitabine 825 mg/m2 BID
- Dose level 1-3: Surgery 4-6 weeks after therapy
- Dose level 4: Surgery 1-3 weeks after therapy
- 3 patients at dose levels 1-3, 6 at dose level 4

Phase I
Dose Escalation Schema

Dose Escalation Schema

Dose Level	Step 1 Lead-in Phase	Dose/fraction	# Tx	Fractionation Schedule	Total Dose	Week 1 Schedule	Week 2 Schedule	Total Days
1	1	3 GyE	10	QD	30	M T W Th Fri	M T W Th Fri	12
	Step 2	**Dose/fraction**	**# Tx**	**Fractionation Schedule**	**Total Dose**	**Week 1 Schedule**	**Week 2 Schedule**	**Total Days**
2	1	5 GyE	5	QD	25	M W F	T Th	11
3	2	5 GyE	5	QD	25	M T Th Fri	M	9
4	3	5 GyE	5	QD	25	M T W Th Fri	-	5

Hong TS, et al. IJROBP, 2014

Adjuvant chemotherapy

- Gemcitabine x 6 cycles

Correlative Studies

- Mutational Status- MGH SNaPShot
  - KRAS, BRAF, NRAS, PIK3CA, CTNNB1, PTEN, TP53, IDH1, FLT3, JAK1, FLT3, EGFR, KIT, NOTCH1
- SMAD4 Status
- Circulating biomarkers

Screening and Enrollment

- 57 patients screened
- 50 patients enrolled*
- 49 patients (29 patients at MTD) eligible for analysis
  - -2 patients found to have a distal cholangiocarcinoma
- 7 patients found to have positive laparoscopy (gross metastases or positive cytology)- 12%

Patient Characteristics

Table 1. Patient Characteristics (N=50 patients)

Gender		
Female	N=23	(46%)
Male	N=27	(54%)
Age, years		
Median	65	
Range	49-92	
CA19-9 at baseline		
Median	136.5	
Range	0-15,151	
Tumor size on abdominal/pelvic CT		
Median	2.9 cm	
Range	1.1-4.3	

Toxicity- Grade 2 or worse

Table 2. Preoperative chemoradiation-related toxicity, grade 2 or worse (N=35 phase II patients)

Toxicity	Grade 2 N (%)	Grade 3 N (%)
Colitis	0	1 (3%)
Nausea & Vomiting	3 (9%)	0
Constipation	1 (3%)	0
Dehydration	1 (3%)	0
Diarrhea, no prior colostomy	1 (3%)	0
Flatulence	1 (3%)	0
Chest wall pain	0	1 (3%)
Abdominal pain	1 (3%)	0
Limb pain	1 (3%)	0
Weight loss	2 (6%)	0

Resection Rate

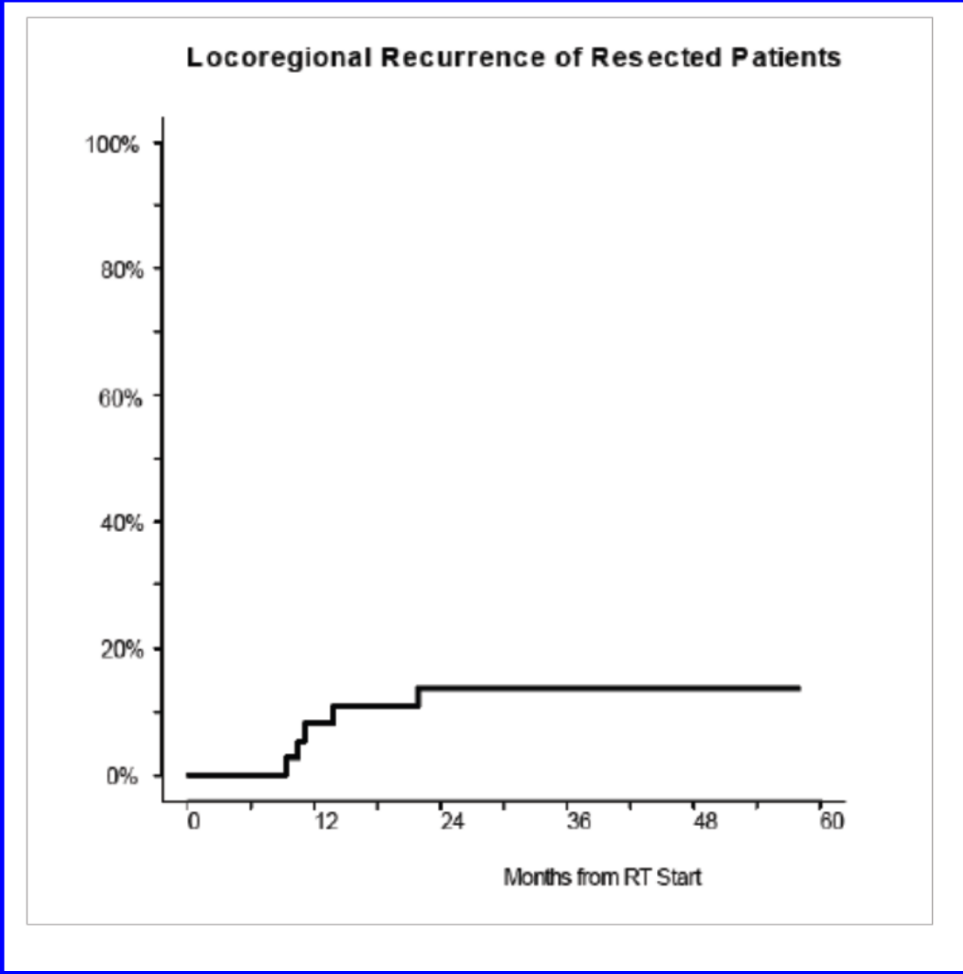
- 38/48 underwent resection
- 10/48 did not
  - Metastasis at exploration- 9
  - Unresectable tumor- 1

Pathologic Response

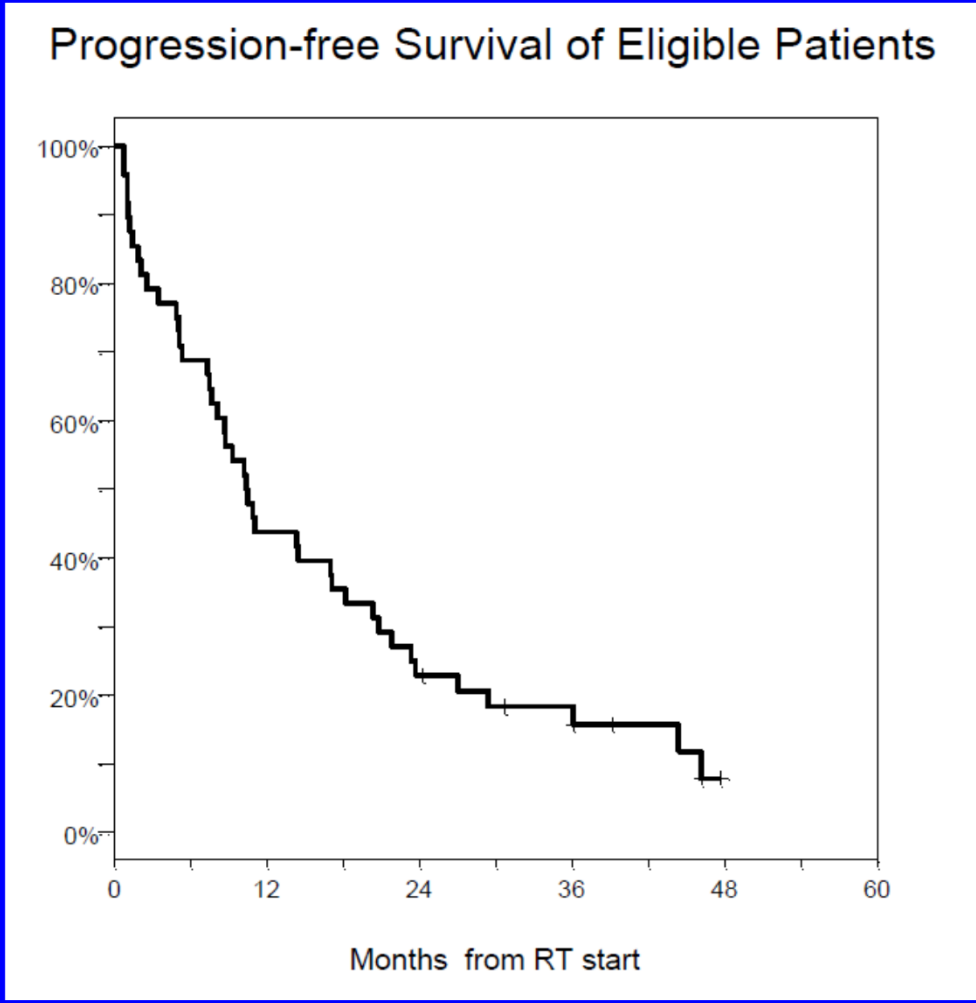
Table 3. Pathologic Response

Primary tumor (N=37 eligible resected patients)	
Tumor size	
Median	2.9 cm
Range	1.3-4.8
Histologic grade	
Moderate differentiation	17 (46%)
Poor differentiation	20 (54%)
Margin status	
Negative	31 (84%)
Positive	6 (16%)
Nodal Involvement	
No	7 (19%)
Yes	30 (81%)

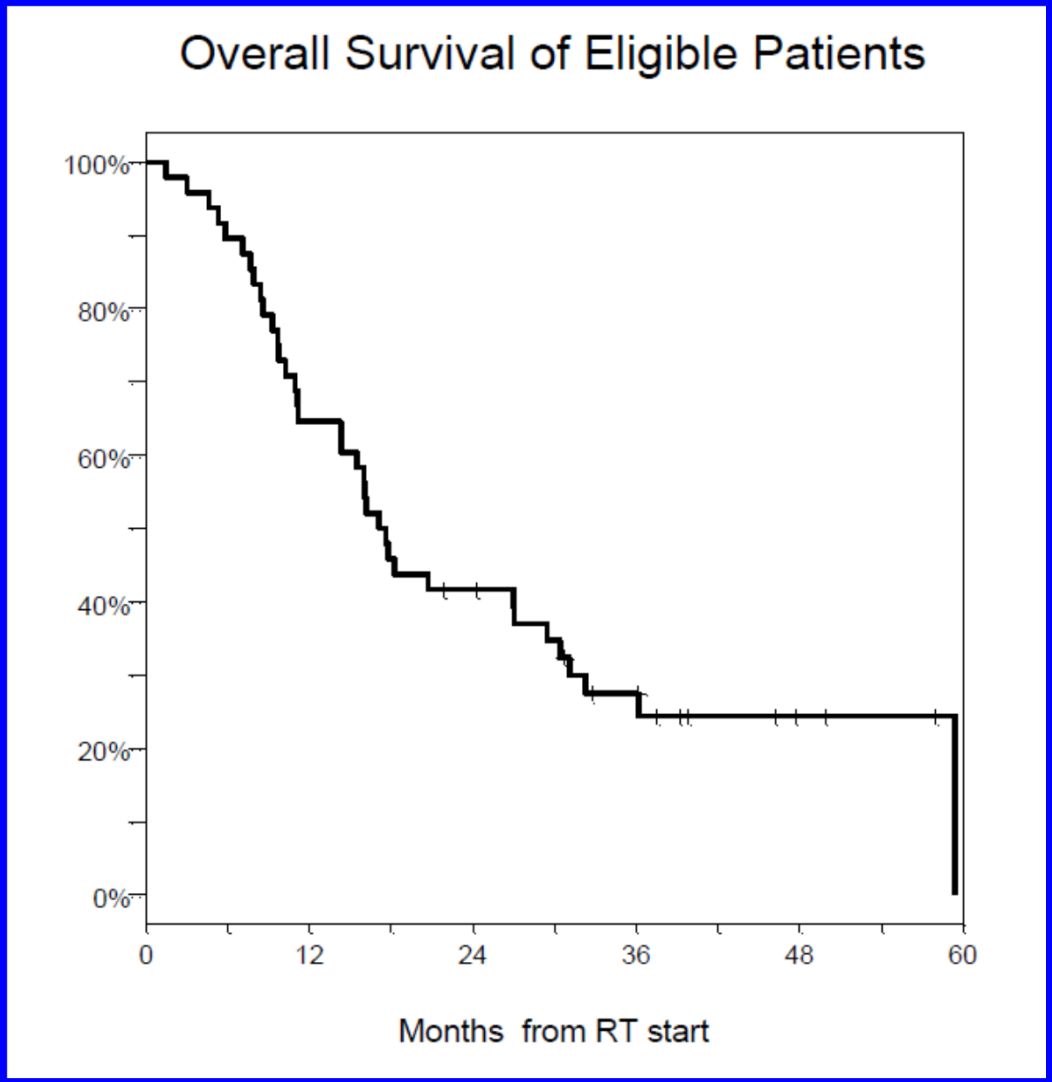
Local Recurrence



PFS


Progression-free Survival of Eligible Patients
100%
80%
60%
40%
20%
0%
0
12
24
36
48
60
Months from RT start

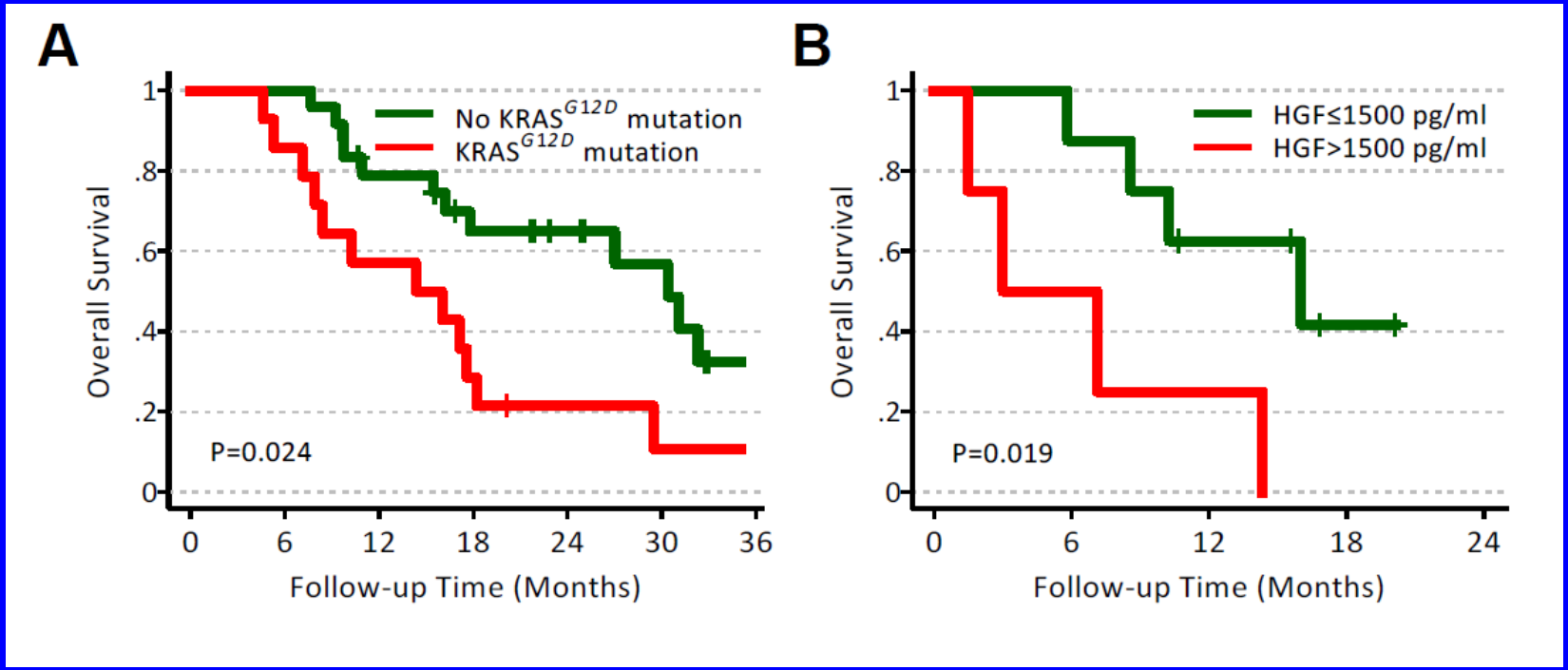
OS



MS- All patients- 17 mo

MS- Resected patients- 27.7 mo

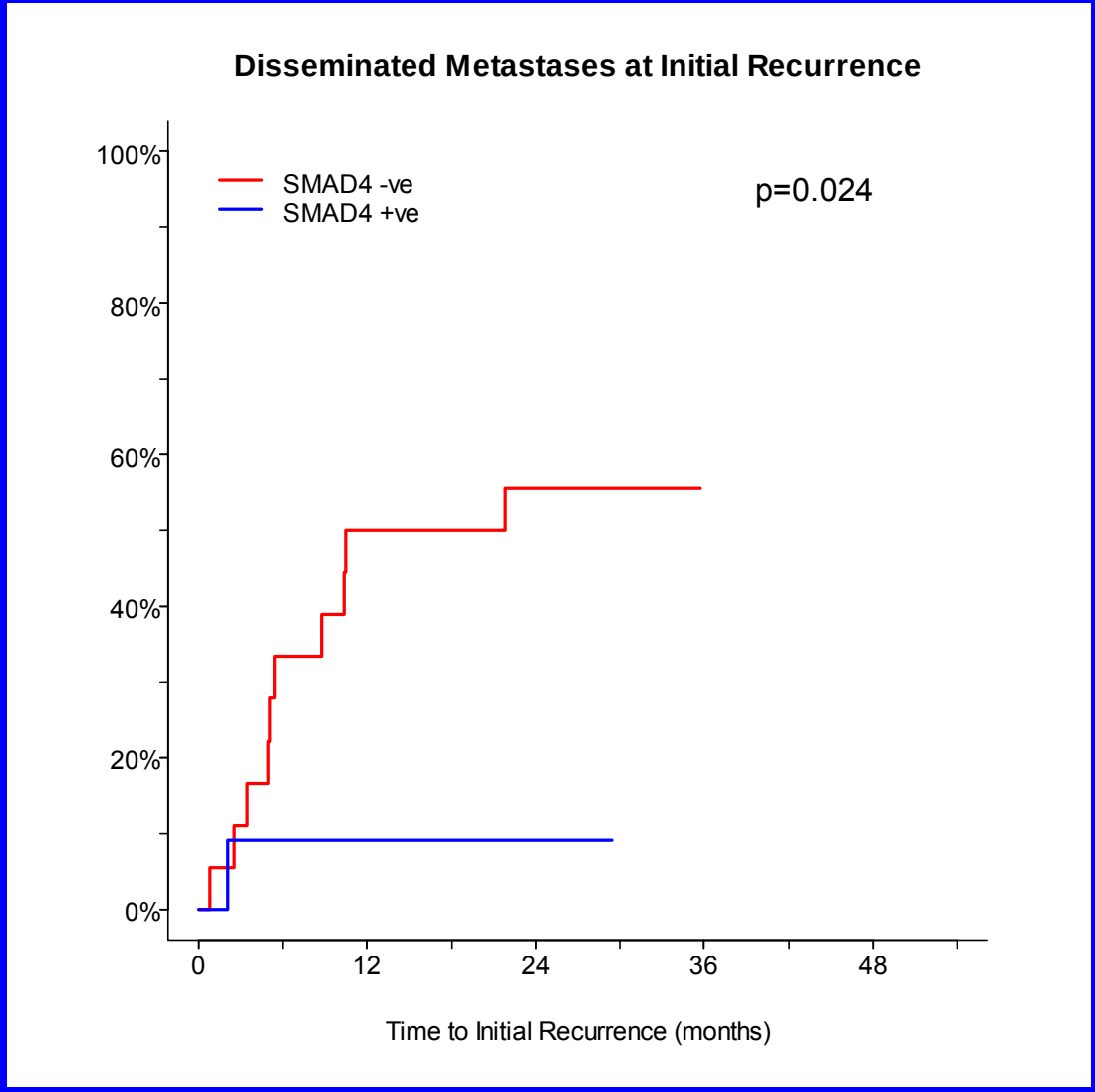
OS by Genotype and Serum HGF



Outcomes by circulating biomarkers

Biomarker/ Time-point	Pre-treatment		Post-treatment		Change post-treatment	
	OS	PFS	OS	PFS	OS	PFS
Plasma HGF	**5.56 [1.26,24.64] n=12**	2.57 [0.73,9.11] n=12	**10.12 [0.74,138.3] n=12**	**2.53 [1.03,6.21] n=12**	**78.72 [0.69,9022] n=12**	**8.70 [0.66,114.3] n=12**
P value	**0.0057**	0.13	**0.0002**	**0.015**	**0.0073**	**0.033**
Plasma TNF-α	3.72 [0.84,16.46] n=12	3.87 [0.92,16.26] n=12	**1.86 [0.95,3.65] n=12**	**3.28 [1.11,9.64] n=12**	1.95 [0.59,6.41] n=12	4.53 [0.51,39.88] n=12
P value	0.071	0.054	**0.048**	**0.0074**	0.23	0.052
Serum CEA	**1.43 [1.08,1.90] n=43**	**1.34 [1.02,1.76] n=43**	**2.02 [1.36,3.01] n=12**	**2.12 [1.37,3.29] n=23**		
P value	**0.021**	**0.034**	**0.0001**	**0.0002**		
Serum CA19-9	**1.21 [1.04,1.41] n=45**	1.13 [0.97,1.31] n=45	**1.20 [1.06,1.38] n=42**	**1.20 [1.04,1.38] n=42**		
P value	**0.014**	0.12	**0.0057**	**0.014**		

Patterns of Failure by SMAD4 status



Conclusion

- Short course proton-based chemoradiation followed by early surgery is feasible and appears safe
- Local control is encouraging
- Survival remains driven by systemic progression
- Exploratory analysis shows prognostic impact of KRAS G12D and circulating HGF
- Confirms SMAD4 as a marker of patterns of failure

Pancreas and Protons

- Short course preop for resectable disease is feasible
- Have not pushed SBRT because protons don't address duodenal toxicity issues and limitations of imaging (Arvold et al, Int J Radiat Oncol Biol Phys 2011;80:1383-90)
- Currently is the platform of our pancreatic cancer program

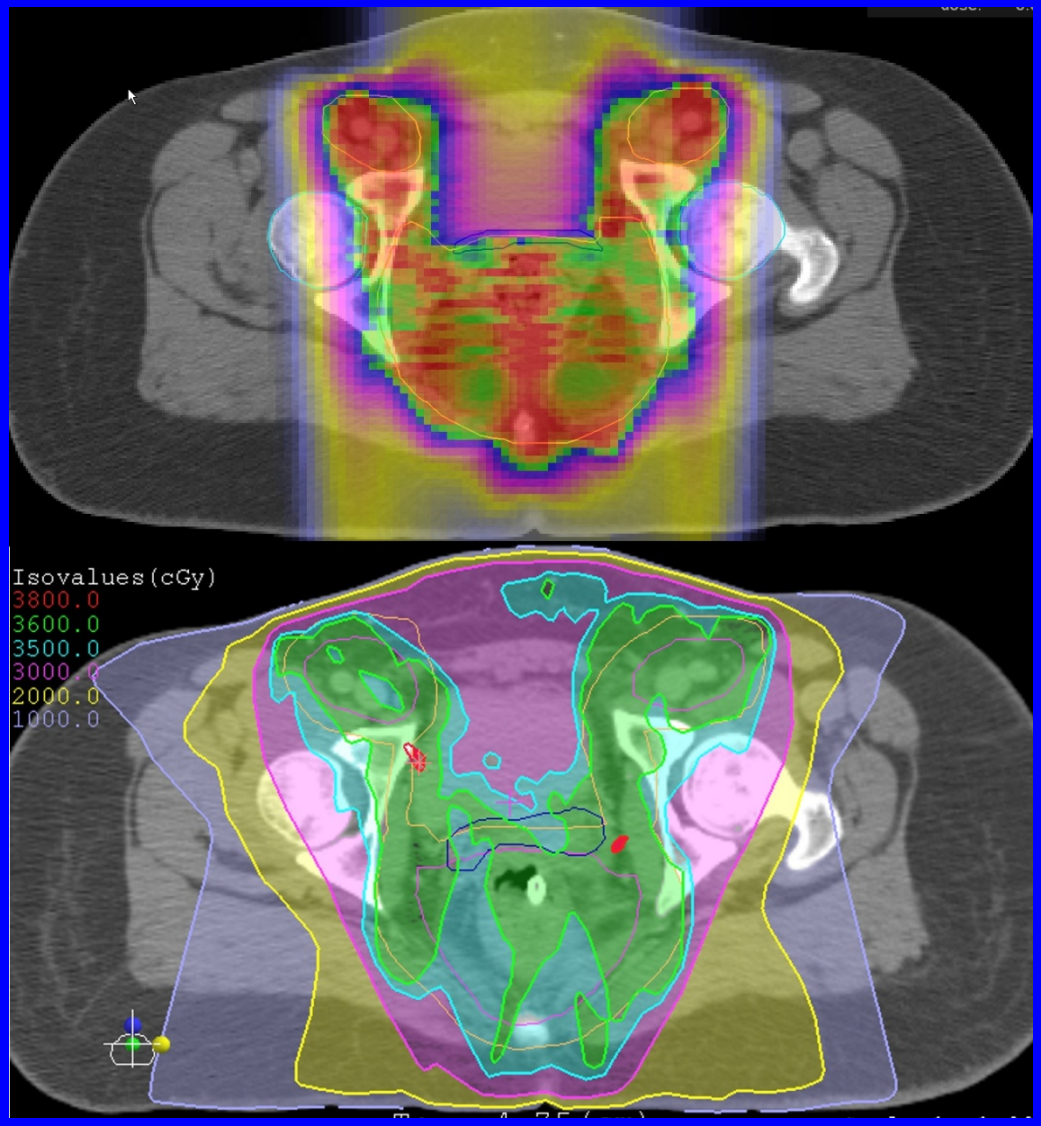
Ongoing Protocols

- Resectable
  - Short course protons with hydroxychloroquine
  - Gem/nab-paclitaxel vs. FOLFIRINOX followed by short course protons and surgery
- Borderline resectable
  - FOLFIRINOX x 8 followed by short course protons and surgery
- Locally advanced
  - FOLFIRINOX/losartan followed by dose-painted short course protons

Anal Cancer
Pencil Beam Scanning

- 20 patients
- Feasibility/QOL study

Anal Nodes p PBS v IMRT



- PBS: AP + PA Fields
  - ~10 mm spot (1 σ)
  - ~3,000 spots
  - Automated planning (computation time ~20 min)
- IMRT: 7 Fields
  - IMRT is not well suited to this problem
- Dose
  - Genitals constrained by minimum CTV dose of 35Gy(RBE)
  - PBS dose (obviously) conforms better. Inhomogeneity is set by constraint of CTV dose between 35 and 42 Gy (RBE).

Conclusions

- Protons unequivocally provide improved dosimetry
- Clinical benefit remains unproven
- Allows for novel fractionation schedules that clinically make more sense
  - Also consistent with the surgical model of “center of excellence”
- Future directions should acknowledge the limited resource and high cost of facility
- May be a platform to develop proof of concept before transitioning to standard photon therapy

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