PTCOG 54 Educational Session

Proton Re-irradiation

Charles B. Simone, II, MD
Assistant Professor
Chief, Thoracic Oncology
Director, Penn Mesothelioma and Pleural Program
Department of Radiation Oncology
Hospital of the University of Pennsylvania

May 19, 2015

Penn Radiation Oncology

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Disclosures

- National Institutes of Health
  - P01 5-P01-CA-087971
  - R01 5-R01-CA-154562
- Department of Defense
  - W81XWH-09-2-0174

Rationale for Reirradiation

- As systemic therapy has improved, local control is becoming increasingly important and can influence overall survival
- Isolated local or regional recurrences can occur after definitive radiation therapy or multimodality therapy for a variety of malignancies
- Alternatives to reirradiation
  - Surgery is often difficult after prior RT course and as monotherapy may not control microscopic disease
  - Chemotherapy is generally not a curative modality

Rationale for Reirradiation

- Potential benefits of reirradiation
  - Symptomatic control
  - Durable local/locoregional control
  - Only chance of cure in select circumstances
- Concerns
  - Risks of toxicity with high cumulate irradiation doses
- Questions
  - What recovery from the prior RT course do normal tissues achieve?
  - Are recurrent tumors more resistant to RT?
  - Are RT-induced tumors more resistant to RT?

Hesitation to Reirradiate

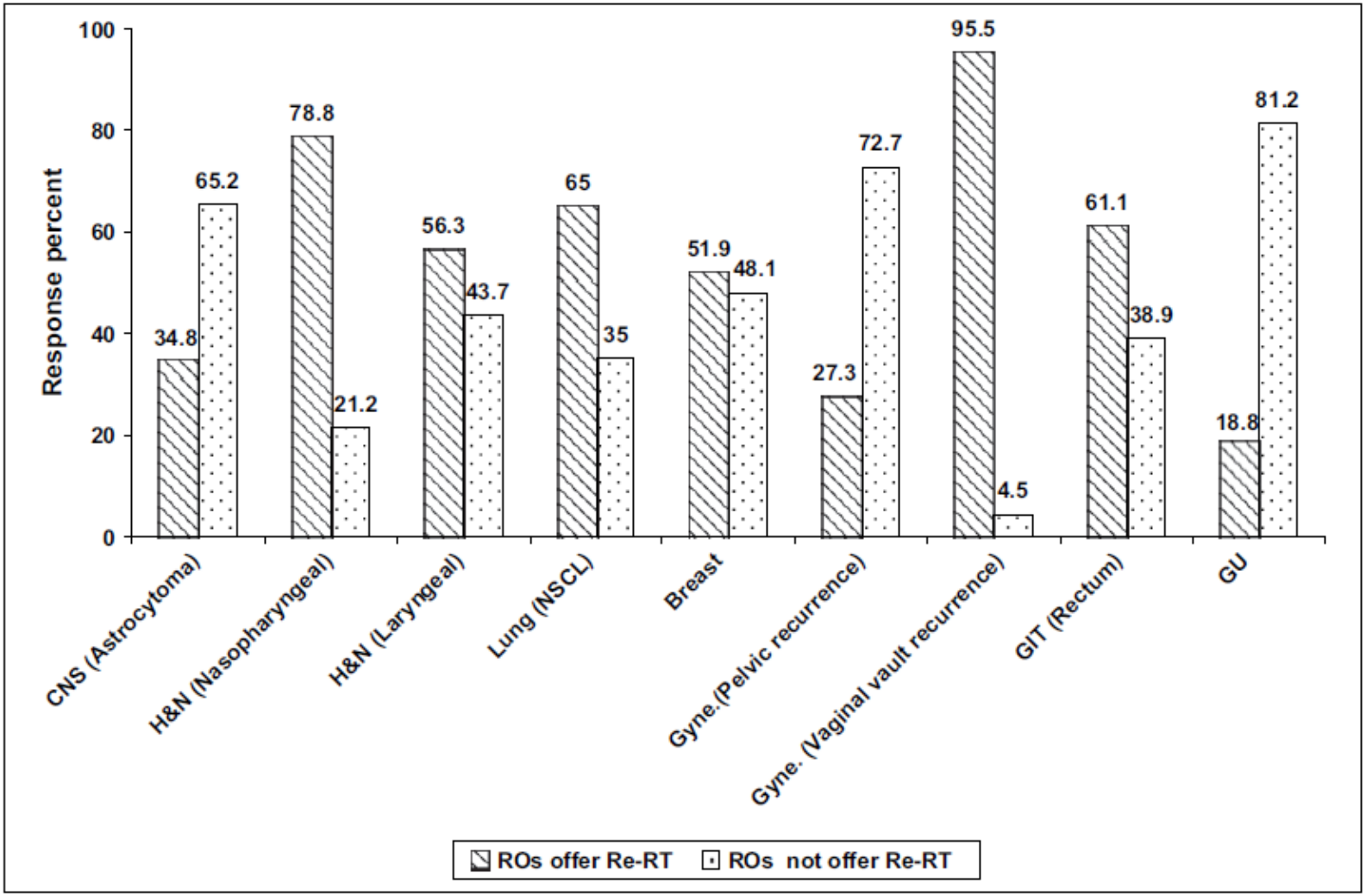

Fig. 1. Poll of radiation oncologists' (ROs) opinions for case scenarios of patients referred for reirradiation (Re-RT). *Abbreviations:* CNS = central nervous system; H&N = head and neck; NSCL = non–small-cell lung cancer; gyne = gynecologic; GIT = gastrointestinal; GU = genitourinary.

Reasons for Hesitation to Reirradiate

- Toxicity concerns
  - Acute or subacute fatal toxicities
    - Bleed, bowel perforation/ulceration
  - Late severely morbid toxicities
    - Myelopathy, necrosis, fistula, fibrosis
- Liability concerns
- Success rates are thought to be low, high rates of uncertainty
- Retreatment planning is more complicated and time consuming

Tools to Aid in Reirradiation

- Early detection of recurrence
  - Improvements in and use of advanced imaging surveillance
  - Biomarkers, circulating tumor products, or other means to detect recurrence at an early time point to allow for smaller PTVs
- Target definition
  - Advanced imaging (PET/CT, MRI)
  - Generally no elective nodal reirradiation
- Surgery
  - Debulking to allow smaller PTVs
  - Spacers to separate OARs from PTV
- Conformal RT techniques
  - Brachytherapy, IMRT, SBRT, Proton therapy

Options for Reirradiation

	IMRT	SBRT	Brachytherapy	Protons
Conformality	+	++	+++	++
Integral Dose			+++	++
Ease of Use	+++	++		++
Target Motion Sensitivity	++	+	+++	
Cost	+	++	+++	

Rationale for Proton Reirradiation

- Proton radiotherapy is well suited to the problem of reirradiation
  - Highly spatially conformal treatment
  - No exit dose may allow for complete sparing of structures that have been “maxed out” by prior RT course
  - Early report of the success of proton reirradiation to salvage recurrences and preserve useful vision in 31 patients with recurrent uveal melanoma

	Primary tumor	Recurrent tumor
Useful vision	*39–67 at 3 yrs	27% at 5 yrs
Local control	96% at 5 yrs	69% at 5 yrs
Eye retention	†76–99% at 5 yrs	55% at 5 yrs
Metastasis-free survival	‡58–97 at 4 yrs	73% at 5 yrs
Overall survival	80% at 5 yrs	64% at 5 yrs

OAR Constraints: Spinal Cord

- Cord dose often is dose limiting when retreating for lung/thoracic, head and neck, upper GI malignancies
- Safe spinal cord dose often considered 45-50 Gy
- Recovery of prior cord dose with increasing time interval?
  - RTOG 0421: phase III reirradiation head and neck trial
    - Cord lifetime dose max 54 Gy
- Low risk of myelopathy if (Nieder C, et al. *IJROBP*. 2006;66(5):1446-9):
  - >6 month interval between courses
  - Each course is of modest dose (<BED 98-102 Gy_2)
  - Total dose is limited to BED <135.5 Gy_2

Table 4. Risk score for development of radiation myelopathy from reference (1)

Factor	0 points	1 point	2 points	3 points	4 points	5 points	6 points	7 points	8 points	9 points
Cumulative BED in Gy_2	≤120	120.1–130	130.1–140	140.1–150	150.1–160	160.1–170	170.1–180	180.1–190	190.1–200	>200
Interval <6 months					× (4.5)					
BED of one course ≥102 Gy_2					× (4.5)					

Group	Points	Myelopathy 2005 (1)	**Myelopathy updated**	% Myelopathy 2005 (1)	**% Myelopathy updated**
Low risk	≤3	0/24	**1/30**	0	**3**
Intermediate risk	4–6	2/6	**2/8**	33	**25**
High risk	>6	9/10	**9/10**	90	**90**

Multi-institutional Trial of Proton Radiotherapy for Reirradiation of Recurrent Tumors

Started a prospective reirradiation trial in March 2010

Principal Investigator: John P. Plastaras, MD PhD (UPenn)

[1] Department of Radiation Oncology, University of Pennsylvania
[2] Procure Proton Therapy Center, Oklahoma City
[3] CDH Proton Center, Warrenville, IL

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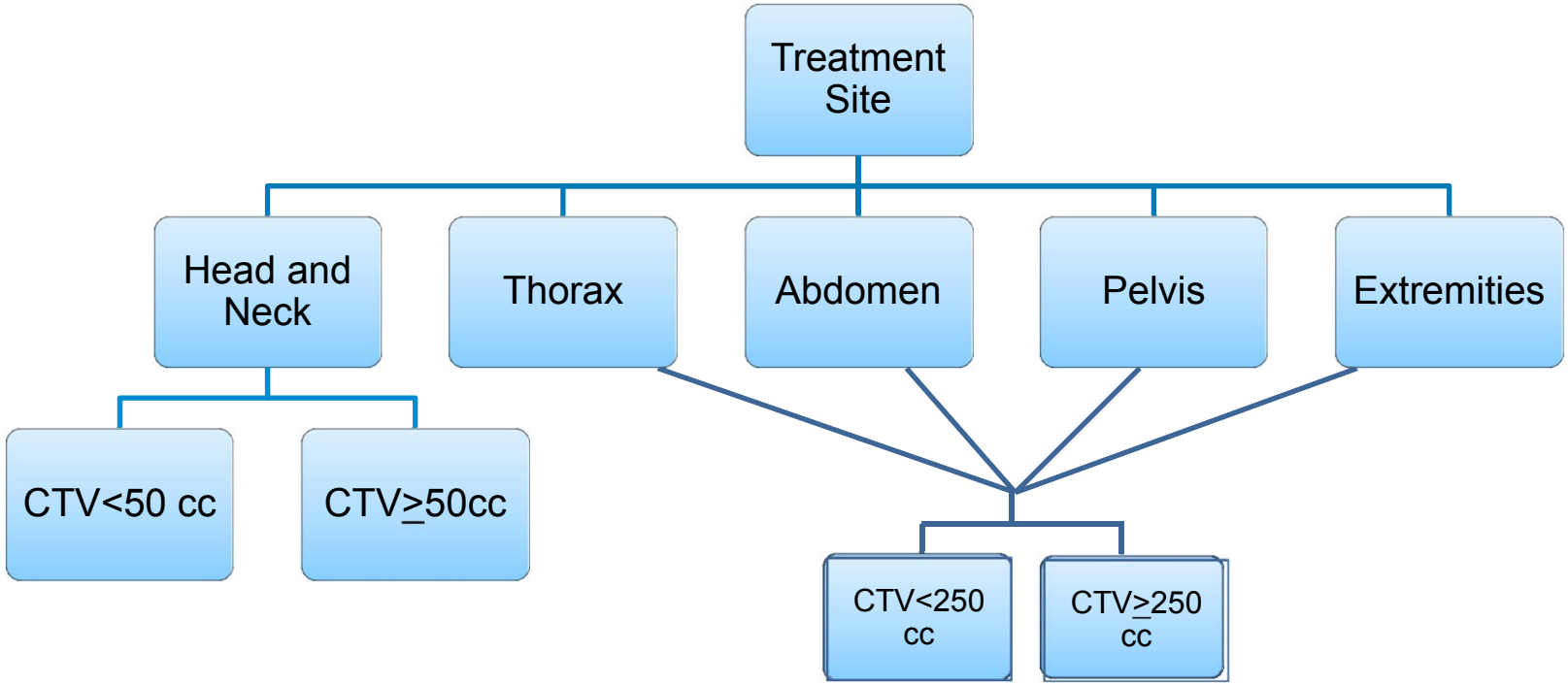
Primary and Secondary Objectives

- Primary Objectives:
  - Establish feasibility and acute toxicity of proton reirradiation
  - Toxicity: occurring within 90 days from reirradiation start
    - Unlikely, possibly, probably, or definitely related to RT
  - Feasibility: infeasible if >10% of patients are unable to:
    - Have a dosimetrically satisfactory treatment plan devised to have 95% of the target volume covered by 95% of the prescribed dose
    - Tolerate 15% of treatments using proton radiotherapy
    - Complete all treatments within 10 days of estimated date of treatment completion or treatment break > 5 days
- Secondary Objectives:
  - Assess late complications
  - Compare the dose distribution of proton plans and photon plans generated for comparison
  - Monitor rates of local control, overall and disease specific survival

Methods

- Inclusion Criteria
  - Histologically-confirmed malignancy
  - Previously radiated with a tumor recurrence *in* or *near* prior radiation fields
  - KPS $\geq$ 60, life expectancy $\geq$ 3 months
  - Age $\geq$ 18
- Exclusion Criteria
  - Prior radiation treatment < 3 months
- Toxicity scored according to CTCAE v4

Stratification: Ten Cohorts



- Feasibility Phase
  - First 12 patients in each cohort
  - Waiting period to assess for feasibility/acute toxicity
- Registration Phase

Prospective Study Stratification

- 90 patients with toxicity information at PTCOG 2014
- Treatment site of the first 195 patients enrolled (through May 2015)
  - Thoracic
    - n=106: NSCLC > esophagus > SCLC/sarcoma/breast/Hodgkin's
  - Abdomen
    - n=32: pancreas > sarcoma > HCC
  - Pelvis
    - n=27: rectal > sarcoma > anal/prostate/cervical/bladder
  - Head and neck
    - n=24: HNSCC > sarcoma > cordoma
  - Extremity
    - n=6: sarcoma
- Tumor volume stratification
  - Low: n=134
  - High: n=61

Acute Toxicity – First 161 Patients

- 161 patients enrolled from 3/2010 to 7/2014
  - 74 of 161 pts (46%) had grade 3 AEs
  - 18 of 161 pts (11%) had grade 4 AEs
  - 31 of 161 pts (19%) had grade 5 AEs
    - 26 deaths expected and related to cancer progression
    - 5 deaths deemed possibly or probably related to proton treatment
      - Neutropenic fever
      - Hemoptysis
      - Anorexia
      - Small bowel perforation
      - Esophageal ulceration

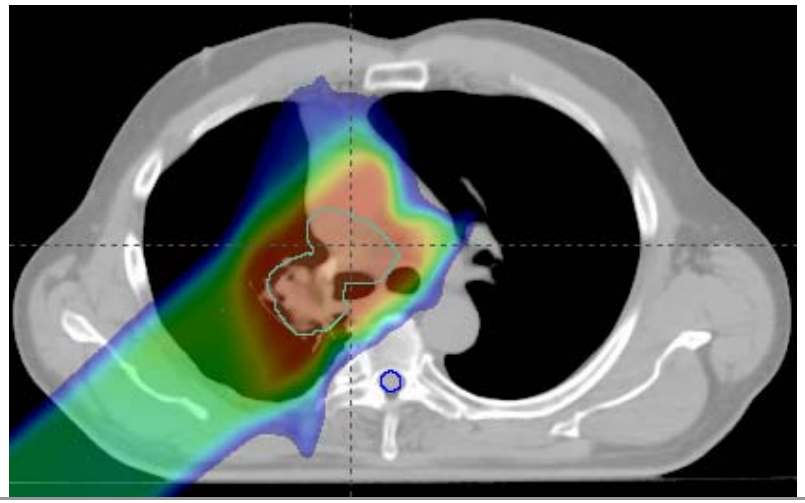
NON-SMALL CELL LUNG CANCER AND THORACIC REIRRADIATION

Rationale for Thoracic Reirradiation and Protons

- Local failures occur in 30-50% of patients with locally advanced NSCLC
  - Isolated first failures occurs locoregionally in 20-30% patients after chemoradiation and are potentially curable with additional local therapy but are traditionally treated with chemotherapy alone due to excessive toxicities associated with photon reirradiaiton
    - Chemotherapy: 4-6 month progression free survival
- Protons provide opportunity for reirradiation in the thorax when there would otherwise be few radiotherapy options
  - Allows for escalation of reirradiation dose
  - Lack of exit dose significantly decreases cord and contralateral lung doses, as well as heart, esophagus, ipsilateral lung doses
  - May also be critical for distal wall of mainstem bronchus/carina

Thoracic Reirradiation – Example Case

- Surgery for pT2N2M0 NSCLC (right paratracheal node) → adjuvant chemotherapy
- Reimaging before planned adjuvant RT = right paratracheal recurrence
- Treated to the right paratracheal node and mediastinum to 66.6 Gy
  - Spinal cord received >44 Gy from this first course
- First surveillance scan 3 months after RT = response
- 6 months after RT = progression in the right paratracheal node
- Second line chemotherapy → isolated right paratracheal progression
- Proton reirradiation to 66.6/1.8 Gy → alive, without recurrence ~3.5 yrs after reirradiation



Prior Thoracic Reirradiation Studies

Study	No. of Patients	Histology	Median Interval to reRT (mo)	Initial RT Dose Gy (median)	Re-RT dose Gy (median)	Median OS mo (range)
Green & Melbye 1982	29	NSCLC & SCLC (6%)	10	53	35	5 (1-54)
Jackson & Ball 1987	22	NSCLC & Other (14%)	15	55	30	5.4 (NS)
Montebello et al. 1992	30	NSCLC & Other (10%)	12	60	30	5 (NS)
Gressen et al. 2000	23	NSCLC & Other (27%)	15	59	30	4.9 (NS)
Okamoto et al. 2002	34	NSCLC & Other (24%)	23	66	50	8 (NS)
Wu et al. 2003	23	NSCLC & SCLC (30%)	13	66	51	14 (2-37)
Kramer et al. 2003	28	NSCLC	17	40-60	16	5.6 (NS)
Tada et al. 2005	19	NSCLC	16	50-70	50	7.1 (NS)
Ebara et al. 2007	44	NSCLC & SCLC (20%) & Other (10%)	12.6	30	40	6.5 (NS)
Centingoz et al. 2009	38	NSCLC & Other (26%)	9	30	25	3 (NS)

MDACC Retrospective Study

- 102 pts with locally recurrent NSCLC
  - Median age 67.5 yrs, 44% adenocarcinoma, 81% ECOG PS 0-1
  - Initial RT: median 70 EQD2 Gy (33–276 EQD2 Gy)
  - Time to recurrence 11 months, time to reirradiation 17 months
  - Reirradiation (protons or photons): median 60.5 EQD2 Gy (25.2–155 EQD2 Gy)
- Grade ≥3 toxicity: esophageal 7%, pulmonary 10%
- Factors affecting risk of grade ≥2
  - Esophageal increased toxicity with concurrent chemo ($p=0.029$), high max point dose ($p=0.001$), increased V_{60} ($p<0.001$)
  - Pulmonary increased toxicity with higher V_{10} ($p=0.025$), V_{20} ($p=0.025$), MLD ($p=0.032$), composite MLD ($p=0.024$)

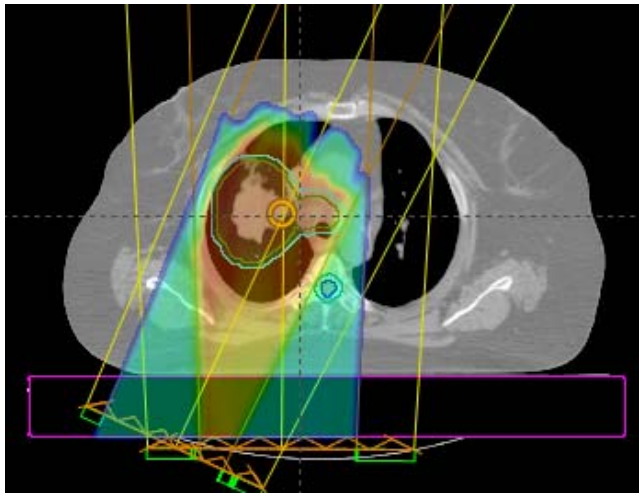
McAvoy S, et al. *IJROBP*. 2014;90(4):879-27.

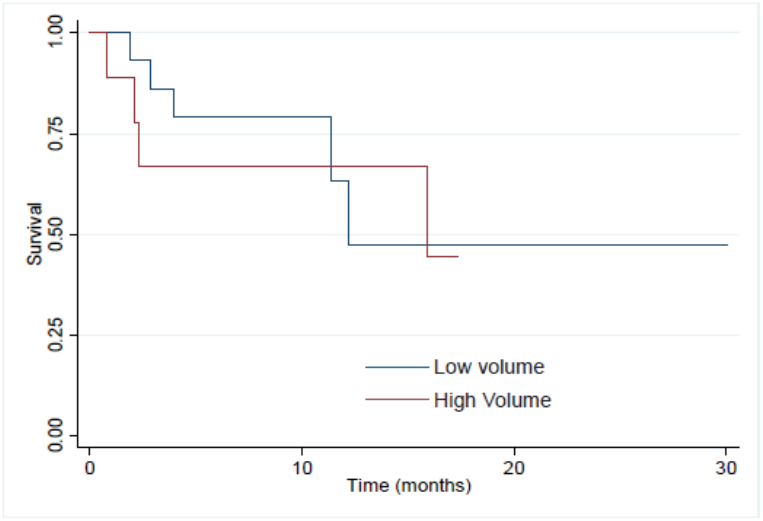
Outcomes and Multivariate Analysis

- Outcomes
  - OS: median 14.7 months
  - DMFS: median 11.4 months
  - Local failure free survival: median 11.4 months
- Multivariate for local control
  - Time to reirradiation > 6mo (HR=0.374, p=0.012)
  - Combined modality treatment (HR=0.154, p=0.0004)
  - iGTV <27cm^3 (HR=0.457, p=0.022)
- Multivariate for overall survival
  - Adenocarcinoma (HR=0.383, p=0.004)
  - Concurrent chemotherapy (HR=0.383, p=0.0045)
  - Higher EQD2 at reirradiation (HR=0.246, p=0.021)
  - Improved performance status (HR=0.327-0.395, p=0.02-0.028)
  - iGTV <27cm^3 (HR=0.366, p=0.0003)

Multi-center Thoracic Proton Reirradiation

- Presentation at ASCO 2013
  - 24 pts retreated from 10/2010-11/2012 using thoracic proton therapy reirradiation
  - Median prior dose 62.4 Gy, median retreatment dose 66.6 CGE, median plan sum dose 123 CGE
  - Only 1 in-field recurrence at median 7 month follow-up
  - Treatment well tolerated, particularly for patients with low volume disease (<250 cm^3 CTVs)





NSCLC: Dosimetric Outcomes

- Low volume cohort
  - Feasible in 15/16 patients
  - Mean reirradiation / plan sum OAR doses in low volume cohort
    - Lung: 6.4 Gy / 22.4 Gy
    - Heart: 5.6 Gy / 18.9 Gy
    - Proximal bronchial tree: 62.6 Gy / 123.8 Gy
    - Esophagus: 15.9 Gy / 48.2 Gy
- High volume cohort
  - Feasible in 4/6
  - 2 deaths possibly related to reirradiation
    - Hemoptysis at 32.4 Gy in a pt with an endobronchial tumor who presented with hemoptysis prior to starting reirradiation
    - Neutropenic fever the week after reirradiation completion

Revised High Volume Thoracic Protocol

- Inclusion Criteria
  - KPS of $\geq$ 60 → $\geq$ 70
  - Life expectancy $\geq$ 3 months → $\geq$ 6 months
- Exclusion Criteria
  - ANC< 1500/mm^3 or platelet count < 100,000/mm^3 if receiving concurrent chemotherapy
  - Pleural effusions > 5mm
  - Active pneumonia within 1 month
  - History of grade $\geq$ 3 radiation pneumonitis (severe, limiting self care ADL, requiring oxygen)
  - Weight loss > 10% within 6 months directly related to tumor

2015 PTCOG Update

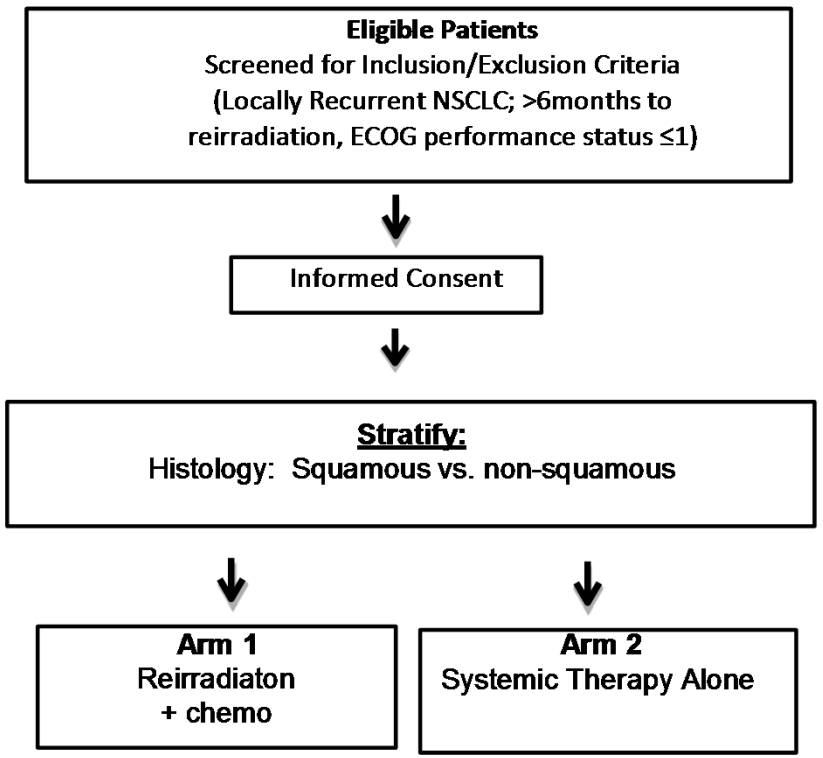
- 49 pts with recurrent NSCLC in or near their prior thoracic irradiation portal treated at 3 proton therapy centers:
  - University of Pennsylvania: n=37
  - CDH Proton Center, Warrenville, IL: n=10
  - Procure Proton Therapy Center, Oklahoma City: n=2
- Tumor volume
  - Low volume (CTV $\leq$250 cc; n=42), high volume (CTV >250 cc; n=7)
- Disease status
  - Alive without recurrence n=7 (14%)
  - Alive with locoregional recurrence n=14 (29%)
  - Alive with distant metastasis n=3 (6%)
  - Deceased n=25 (51%)
  - ***Only 1/49 (2%) with an in-field recurrence***

Typical Reirradiation Proton Beam Arrangement

- Essential to limit dose to cord, previously untreated normal lung tissue, trachea/proximal bronchus during reirradiation course
- We have used scattered beams for most reirradiation cases due to difficulties in accounting for motion with pencil beam scanning
- Typical field arrangements use 2-3 beams
  - 2 fields: posterior and posterior oblique or anterior or anterior and anterior oblique
    - The angle between the anterior and anterior oblique or posterior or posterior and posterior oblique beams must balance skin overlap (at small angles of separation) with increased lung dose (at large angles of separation)
  - 3 fields: posterior or anterior, lateral, and oblique
  - Beam angles are robust with respect to target coverage and there is minimal uncertainty in cord dose
  - Oblique angle should be chosen to block the cord with the aperture
  - Oblique angle must avoid the corner of the treatment table

Potential Future Reirradiation Trials

MDACC Plans



Primary Endpoint: Progression Free Survival

UPenn Plans

- Phase II trial of consolidation Pembrolizumab after concurrent chemotherapy and proton reirradiation for thoracic recurrences of non-small cell lung cancer
  - Merck sponsored
  - 35 patients, PD-1 unscreened
  - Primary Endpoint: Progression Free Survival
    - 80% power to detect improvement in PFS from 6 months (historical) to 10 months

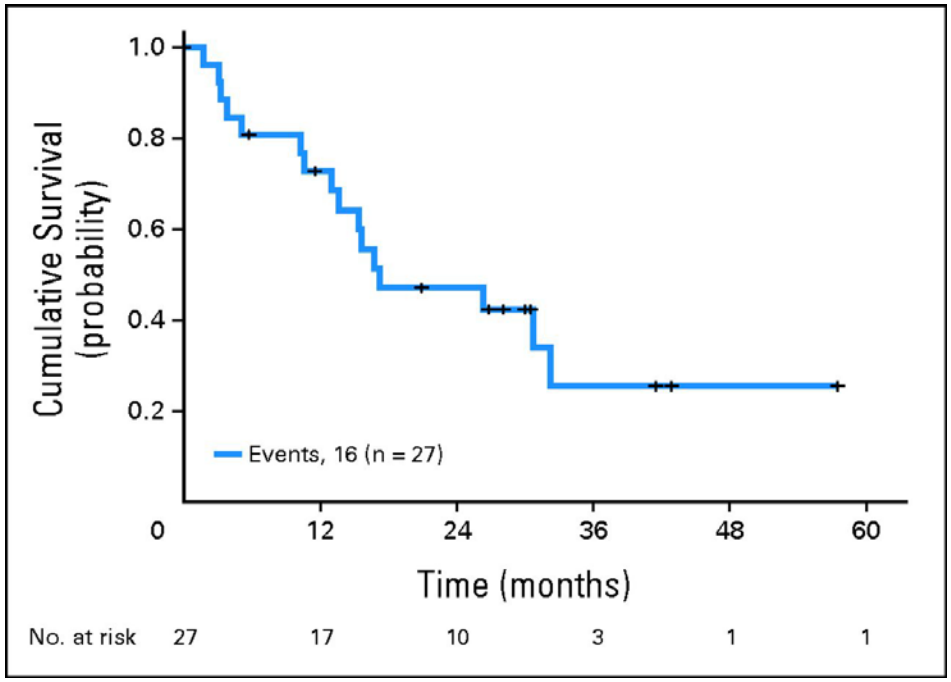
ESOPHAGEAL REIRRADIATION

Rationale for Reirradiation for Esophageal Cancer

- Locoregional recurrence of esophageal cancer occurs in 5-23% of patients after definitive therapy
  - Local recurrence can cause significant morbidity
- Limited salvage options
  - Surgery, brachytherapy, and endoscopic procedures are considered only in well selected patients and can have considerable morbidity
  - Chemotherapy generally is ineffective in controlling disease

Locoregional Recurrence After Esophageal CMT

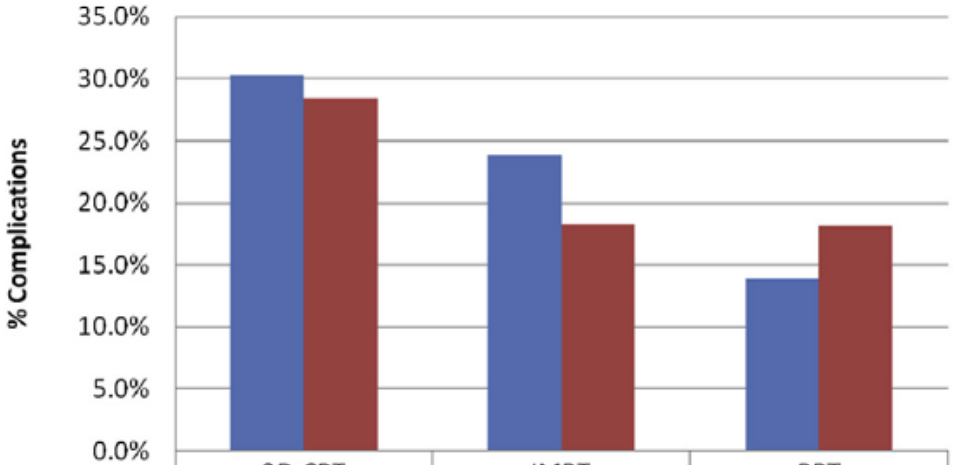
- Among 27 patients with isolated locoregional failure after trimodality therapy for esophageal adenocarcinoma
  - Median overall survival 17 months
  - 11 patients received salvage chemotherapy/supportive care alone → median OS 5 months, 1 survived >2 years
  - 12 had salvage chemoradiation → 5 survived >2 years
  - 4 had salvage surgery → 3 survived >2 years



Sudo K, et al. *J Clin Oncol*. 2013;31(34):4306-10.

Proton Therapy for Esophageal Cancer

- Proton therapy allows safer implementation of trimodality therapy: 444 patients treated with surgery after chemoradiation for esophageal cancer from 1998-2011

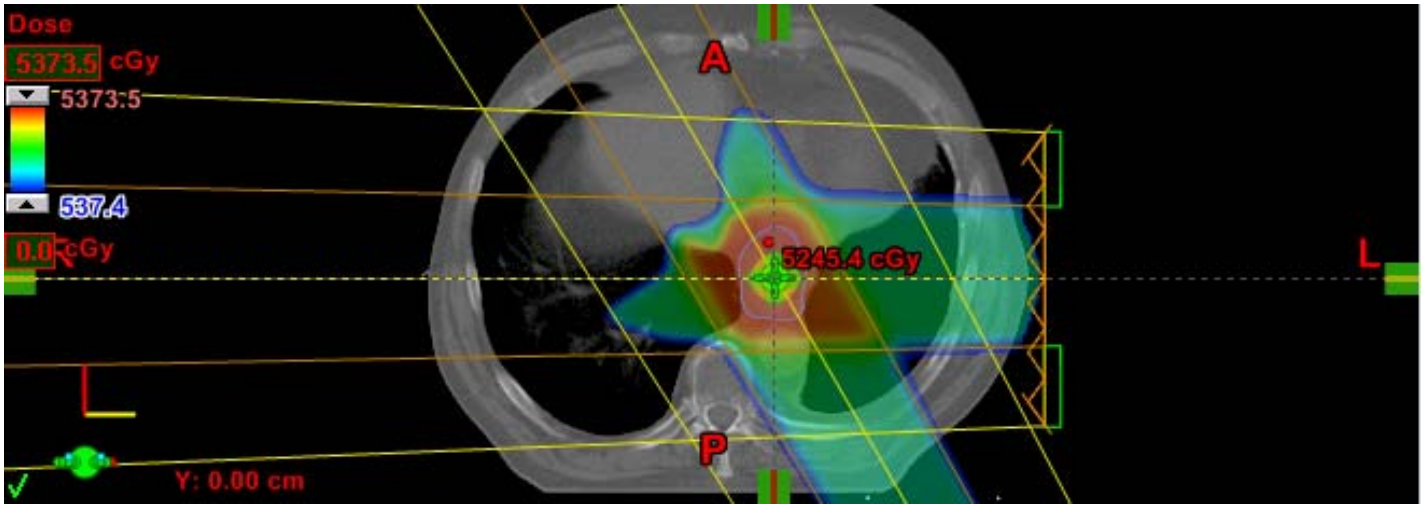


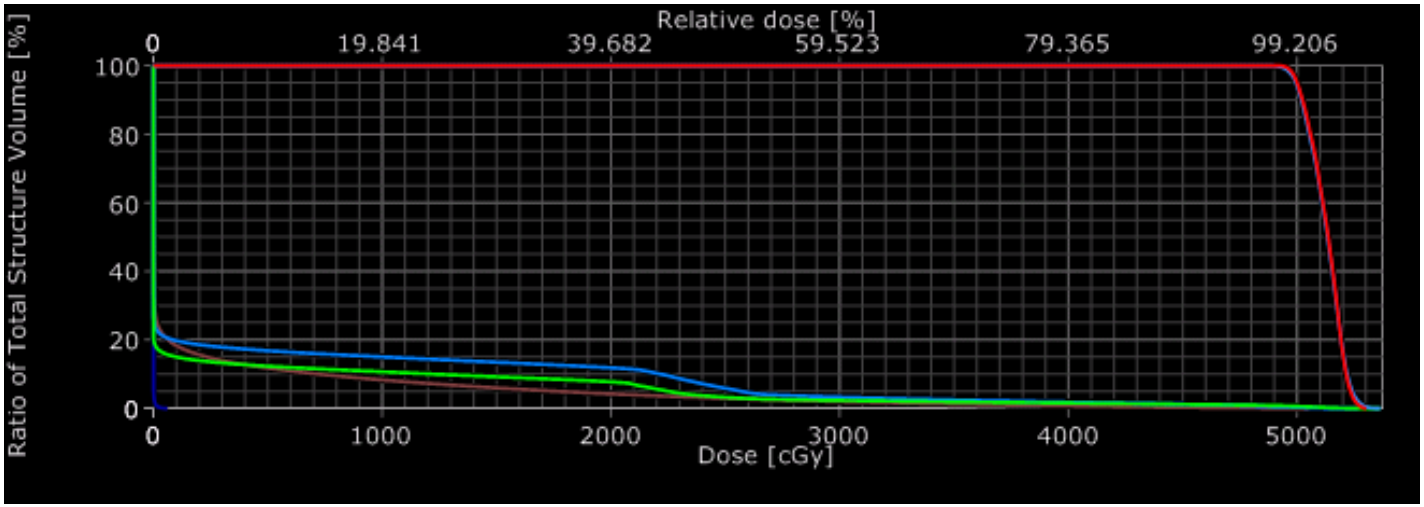
	3D-CRT	IMRT	PBT
Pulmonary	30.3%	23.8%	13.9%
GI	28.4%	18.3%	18.1%

- Proton therapy may offer an advantage in the re-irradiation setting due to the lack of exit dose and potential sparing of normal tissues

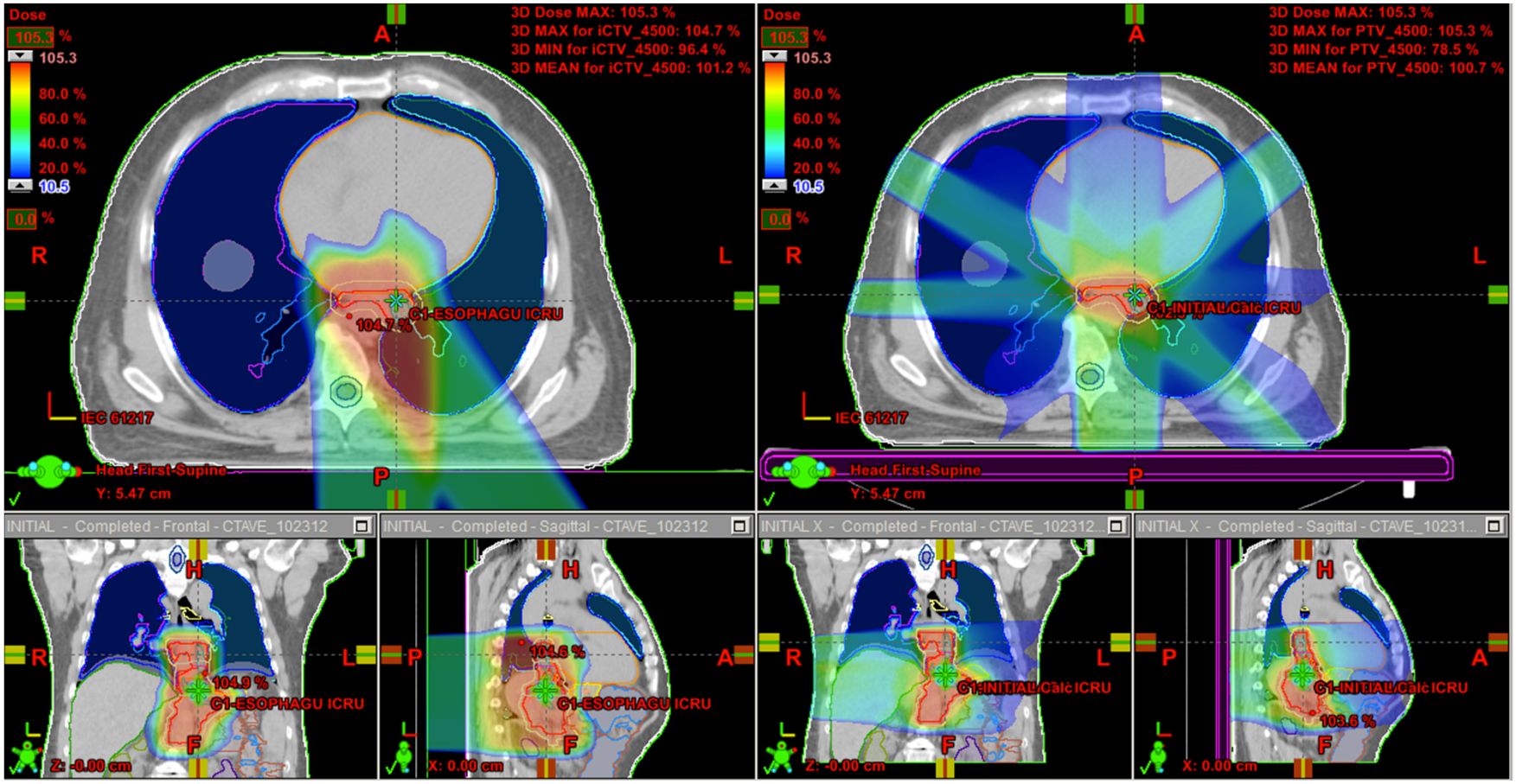
Wang J, et al. *IJROBP*. 2013;86(5):885-91.

Proton Reirradiation for Esophageal Cancer





Proton Reirradiation for Esophageal Cancer



2 Field Proton Therapy Plan

5 Field IMRT Plan

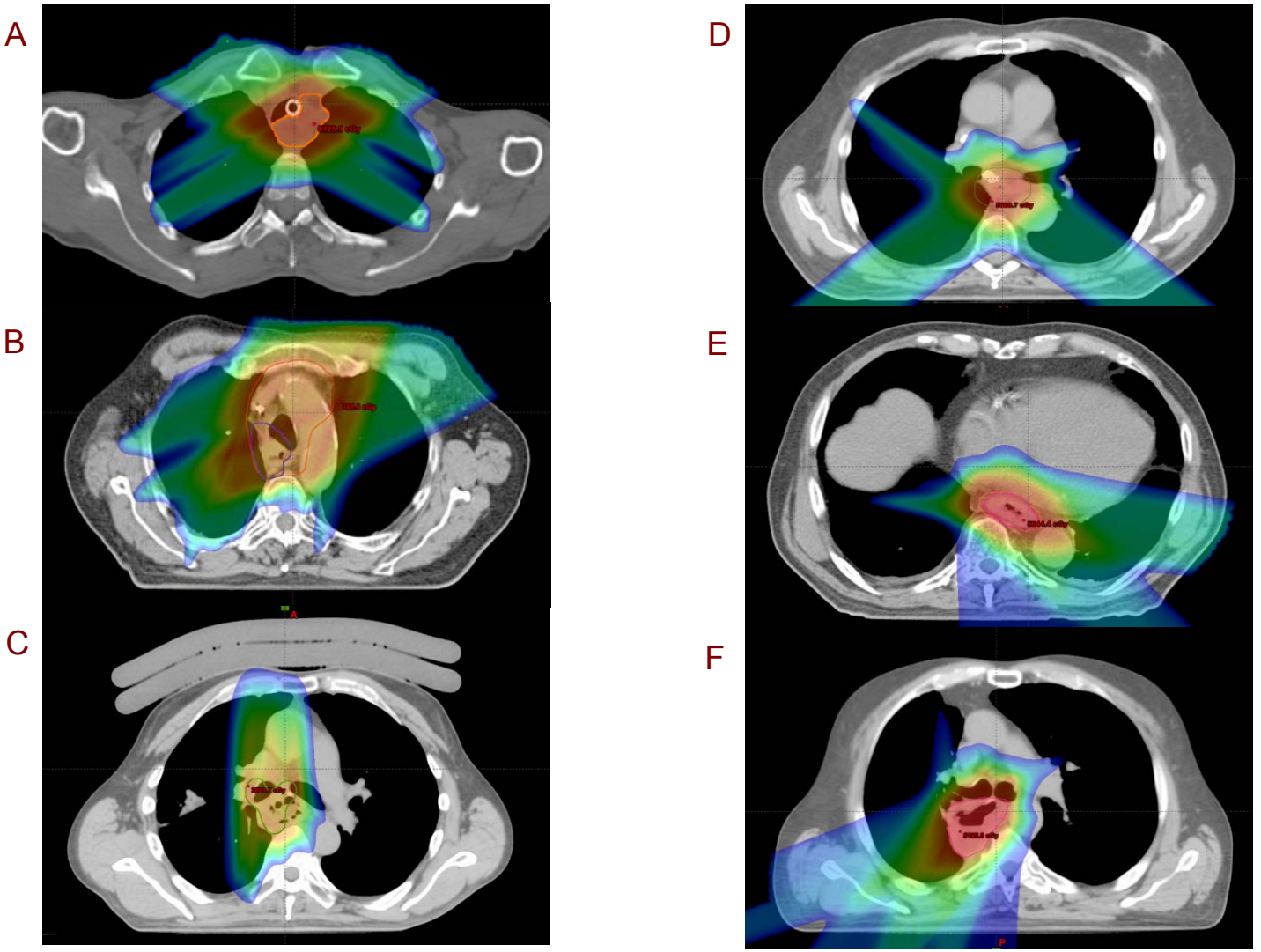
Results

- 14 patients retreated from 6/2010 to 2/2014
  - Mean age 68 years (53-91 years), ECOG PS 0 (n=6), 1 (n=5), 2 (n=3)
  - Histology: adenocarcinoma (n=10), squamous cell carcinoma (n=4)
  - 10 pts received re-irradiation for esophageal cancer recurrence
  - 4 patients developed esophageal cancer as a new primary after prior thoracic RT for a different primary cancer
  - The median interval between RT courses 32 months (10-307 months)
- Treatment
  - 11 pts received concurrent chemotherapy
  - Median reirradiation dose 54.0 Gy (RBE) (50.4-61.2)
    - 2-3 beams used with double scattering (1 of 14 had PBS)
    - Median cumulative dose 109.8 Gy (76-129.4 Gy)
  - To spare spinal cord → anterior/anterior oblique fields generally used
  - To spare the heart, lung, or liver → posterior/posterior oblique fields

Proton Beam Arrangements

Cord Sparing

Heart/Lung Sparing



Fernandes AT, et al. 2015; in press.

Toxicity

- Maximum acute non-hematologic toxicities possibly to definitely related to reiradiation was grade 2 (64%), 3 (29%), 4 (0%), 5 (7%)

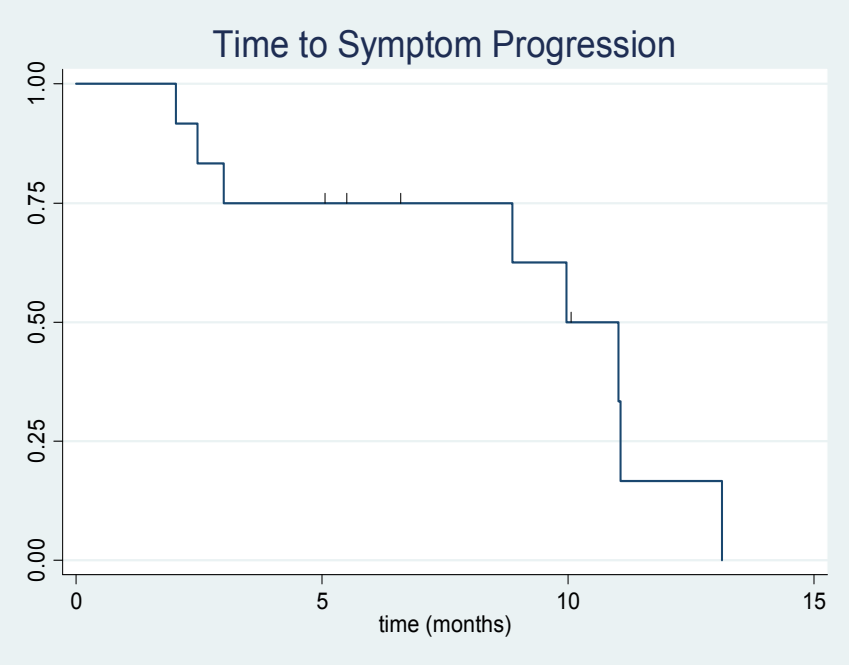
Acute Toxicity				
Category	Toxicity	Grade (n)		
		3	4	5
Hematologic	Anemia	2		
	Lymphopenia	1	4	
	Neutropenia	1	1	
Gastrointestinal	Dysphagia	2		
	GI Fistula			1
	GI Bleed	1		
Systemic	Anorexia/ Weight Loss	1		
Metabolic	Dehydration	2		
	Hyponatremia	1		
Respiratory	Infection	1		
Late toxicity				
Category	Toxicity	Grade (n)		
		3	4	5
Cardiovascular	Heart Failure	1		
Gastrointestinal	Esophageal Stenosis	1		
	Esophageal Ulcer	1		1
	Dysphagia	1		

Died <2 months after start of RT, fistula thought to be from tumor progression

Died 5 months after start of RT, ulcer thought to be from recurrence with biopsy revealing viable tumor (scored "possibly" related)

Results

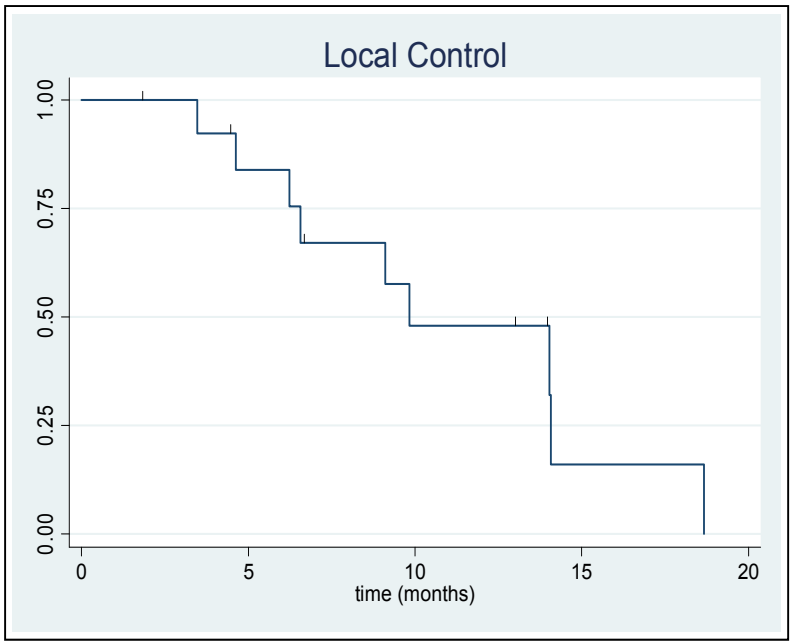
- 10 of 14 patients presented with symptomatic recurrence
  - 4 had complete resolution of symptoms
  - 3 had reduced symptoms
  - 1 had stable symptoms
  - 2 had progressive symptoms

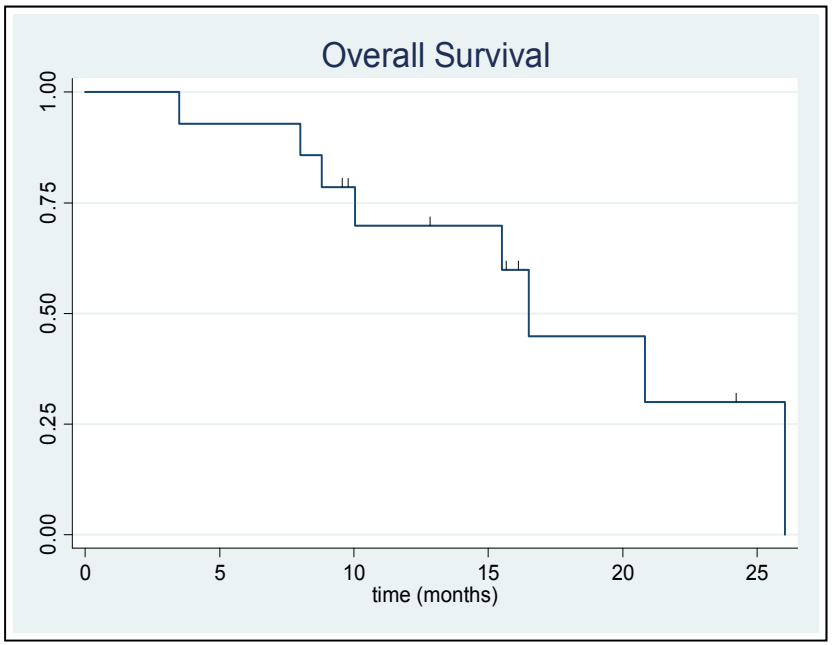


- Excluding the 2 patients with progressive symptoms during RT, the median time to symptom progression in the remaining 12 patients was 10 months

Results

- 6/14 pts developed metastatic disease
  - Median time to distant failure was 18 months after reirradiation
- 9/14 pts developed in-field locoregional recurrence
  - Median time to locoregional failure was 10 months
- Median overall survival was 16.5 months





Esophageal Reirradiation Conclusions

- Reirradiation of esophageal cancer using proton beam radiotherapy is feasible and associated with modest toxicity
- Reirradiation can improve symptom scores and provide durable locoregional control to a portion of patients presenting with isolated locoregional recurrence after prior combined modality therapy

RECTAL REIRRADIATION

Rational and Precedent for Rectal Reirradiation

- Rationale
  - 10-25% of patients with rectal carcinoma locally recur within or near a previously irradiated field
- 50 pts with prior pelvic radiotherapy and primary (n=2) or recurrent (n=48) rectal adenocarcinoma treated from 2/2001 to 2/2005 at MDACC with hyperfractionated accelerated RT (1.5 Gy BID)
  - 39 Gy if treatment interval ≥1 year, 30 Gy if <1 year
  - 96% received concurrent chemotherapy
  - 36% underwent surgical resection after reirradiation
- Toxicity
  - Acute toxicity: 2 pts with grade 3
  - Late toxicity: 13 pts with grade 3-4

MDACC Reirradiation Experience

- Better survival if the retreatment interval was >2 years (53% vs. 21%, p=0.001)
- 3-year rate of freedom from local progression 33%
  - 47% with surgery vs. 21% without, p=0.057
- 3-year overall survival 39%
  - 66% with surgery vs. 27% without, p=0.003

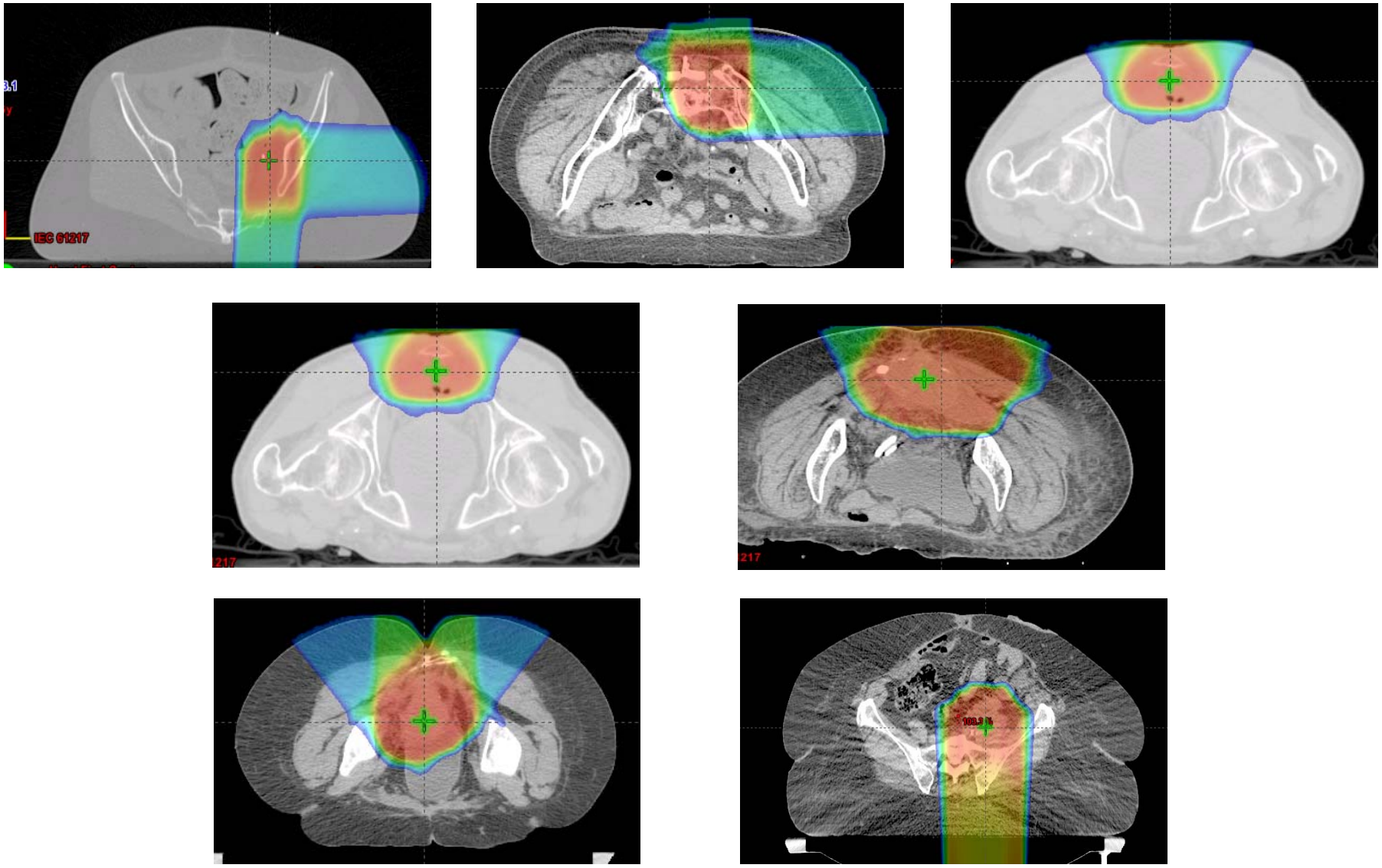
Table 4. Rates of grade 3 to 4 late toxicity

Treatment	3-y rate (%)	*p* value
Surgical resection	53	0.052
No surgical resection	15	
Retreatment ≤ 2 yr	18	0.535
Retreatment > 2 yr	39	
Prior radiation dose < 54 Gy	18	0.033*
Prior radiation dose ≥ 54 Gy	54	

Rectal Cancer Reirradiation Experience

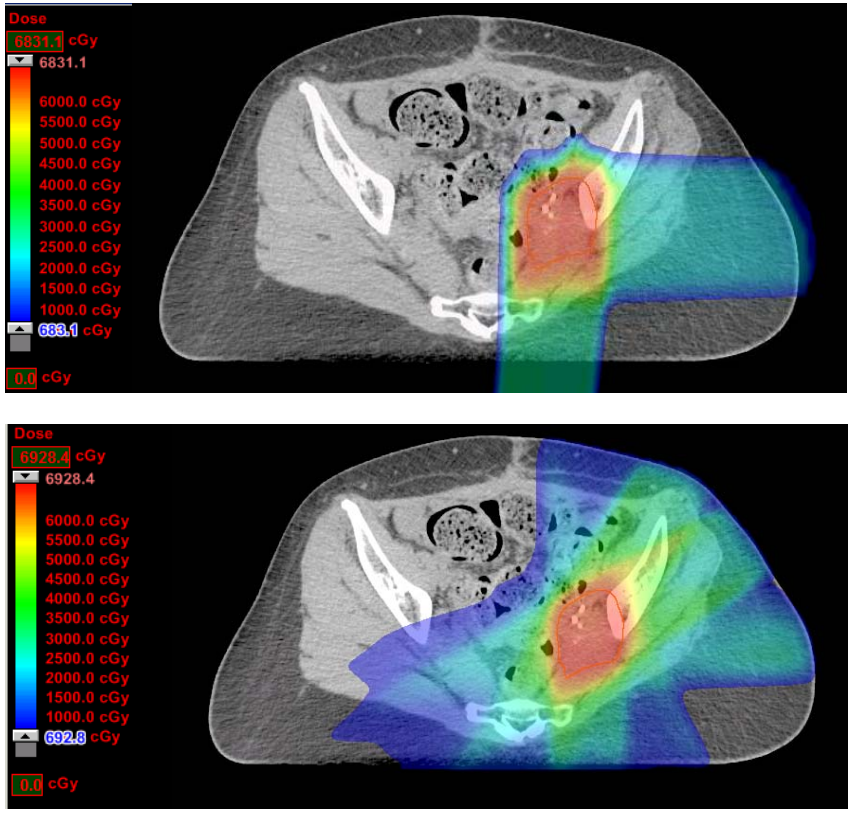
- Can protons more safely allow for retreatment, dose escalation, and combined administration of reirradiation and surgery?
- Patients
  - 7 patients with locally recurrent rectal carcinoma were prospectively enrolled from 3/2010 to 2/2011
  - Median follow-up 14 months (4.9–22.6)
  - Median dose of prior RT 50.4 cGy
  - Median proton reirradiation dose 61.2 cGy (RBE) (45.0–64.8 cGy)
  - Median plan sum 109.8 Gy (range, 95.4–151.2)
  - Six patients received concurrent 5-fluorouracil-based chemotherapy

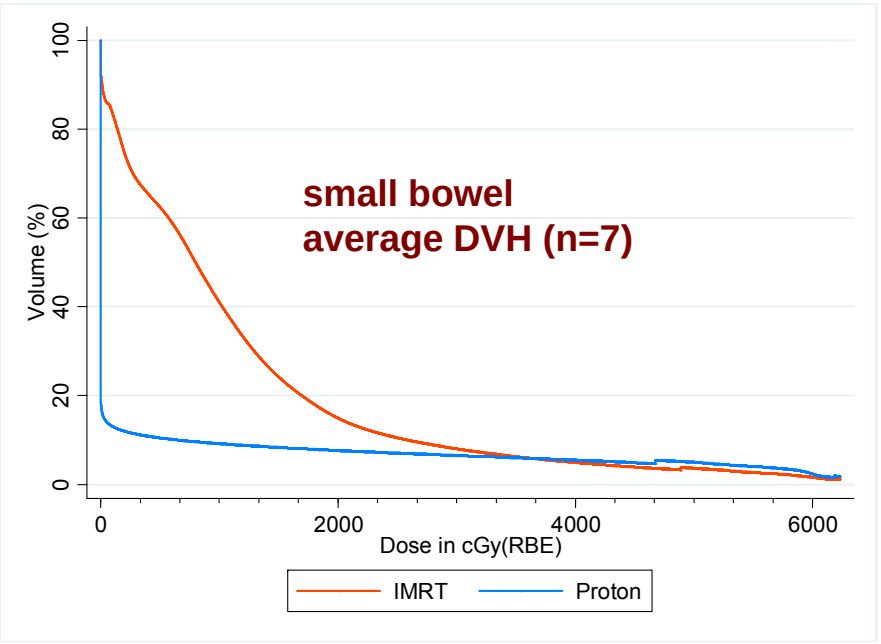
Rectal Cancer Reirradiation Experience



Rectal Cancer Reirradiation Experience

- Comparison IMRT plans were generated
  - Bowel volume receiving 10 and 20 Gy and dose to 200 and 150 cm^3 of bowel were significantly reduced with protons



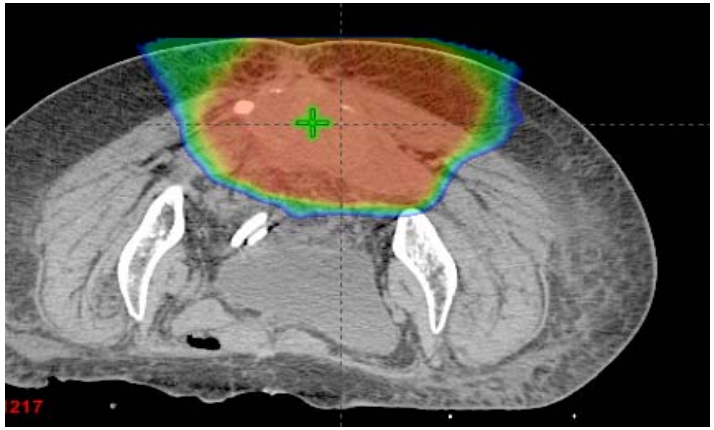


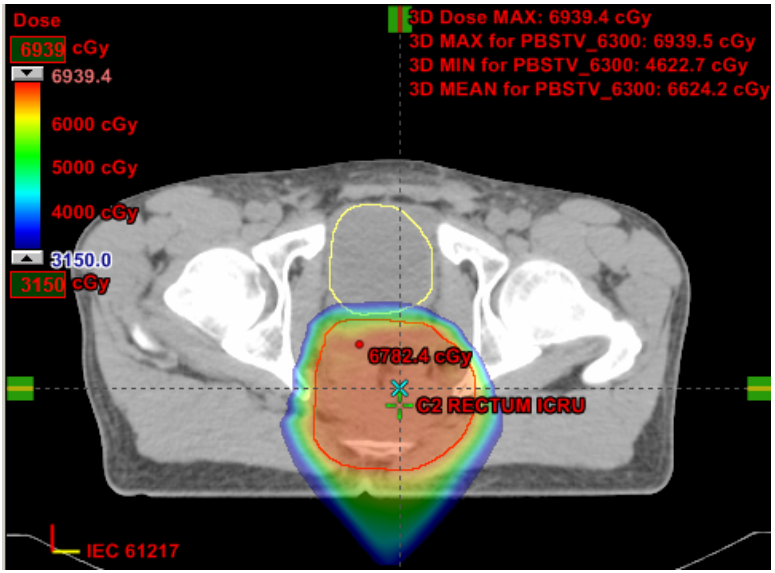
Rectal Cancer Reirradiation Experience

- Toxicity
  - Acute toxicity: 3 pts with grade 3 toxicity (1 abdominal pain, 3 diarrhea), all of which resolved; no grade 4-5 events
  - Late toxicity: 2 pts developed a small bowel obstruction both occurring 5 months after the start of reirradiation (one was postsurgical from attempted resection of post-reirradiation residual tumor); 1 pt developed an enterovaginal fistula at 10 months thought to be due to recurrent tumor invasion
- Clinical outcomes
  - 6 of 7 pts were symptomatic at the time of reirradiation, with 3 achieving complete pain resolution and 3 partial pain response
  - PERCIST responses: 1/7 complete metabolic response, 5/7 PR, 1/7 progression
  - Median survival not yet reached, 3/7 died [2 from local progression, 1 from brain metastasis]

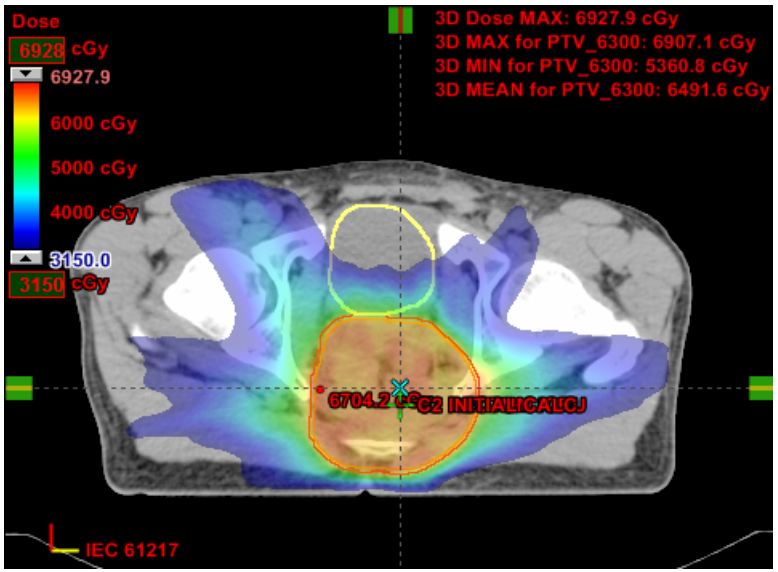
Skin Dose in Recurrent Rectal Cancer

DS





PBS



IMRT

PANCREATIC REIRRADIATION

Pancreatic Cancer Proton Reirradiation

- Rationale
  - Although most patients fail distantly, locoregional recurrence following definitive pancreatic adenocarcinoma treatment occurs in up to 25% of pts
  - Locoregional recurrence can be associated significant morbidity
  - Re-resection of local recurrences is difficult since additional margins cannot be achieved
  - Protons may allow for safer retreatment by limiting small bowel dose (and kidney, liver, cord)

Pancreatic Reirradiation - Results

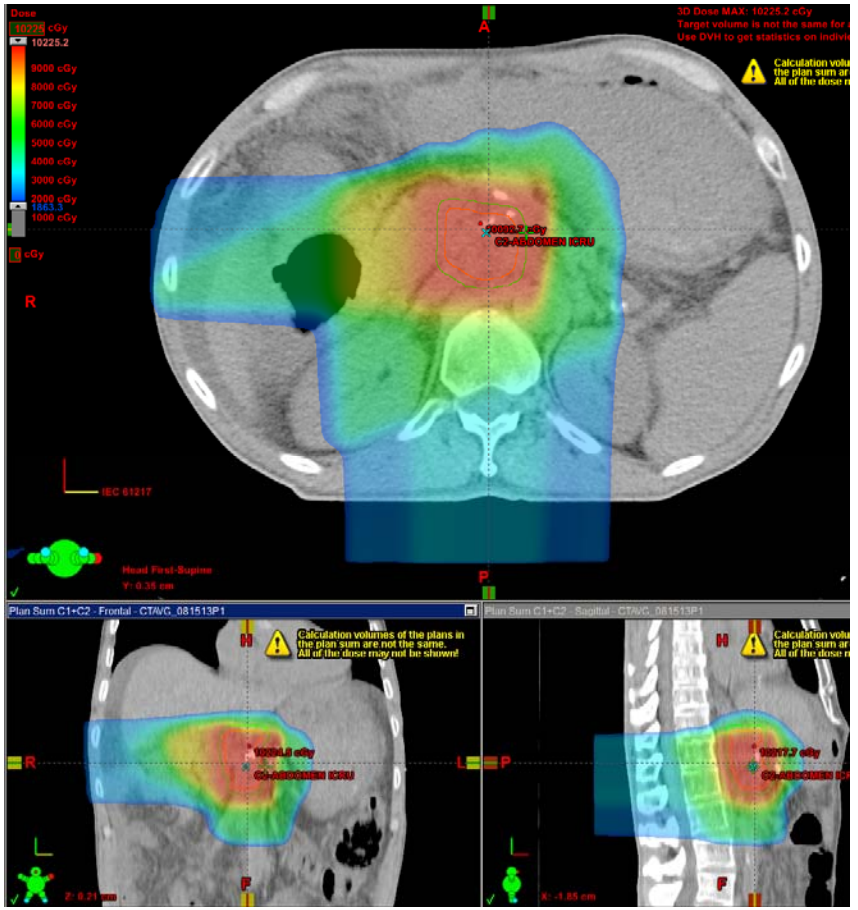
- From 8/2010 to 11/2014, 15 patients (median age 66 yrs) with locally recurrent pancreatic adenocarcinoma were treated with proton reirradiation
  - 11 of 15 received concurrent chemotherapy
  - Median prior RT dose 50.4 Gy (30.0-59.4 Gy)
  - Median time from end of prior RT course to start of proton reirradiation 26.7 months (7.0-461.3 months)
  - Median proton reirradiation dose 59.4 Gy (RBE) (37.50-59.4 Gy)
  - Median CTV size 75 cc (15-236 cc)
- Median survival 13.5 months (2.4-39.8 months)
  - 1-year OS 71.5%, local progression free survival 78%, distant metastasis free survival 52%

Pancreatic Reirradiation - Toxicity

- 2 of 15 pts had stents placed:
  - 1 was a biliary stent in the treatment field → developed grade 4 duodenal ulceration 1 month after reirradiation completion
  - 1 was an enteral stent placed 3 days after reirradiation completion for obstructive symptoms → died from grade 5 small bowel perforation following stent placement
- Of the other 13 patients:
  - 2 patients had acute grade 3 anorexia and fatigue (transient)
  - No grade ≥2 late RT-related toxicities
- Conclusion: in carefully selected patients, proton reirradiation is well-tolerated and results in prolonged overall survival and local control compared to historical controls of locally recurrent pancreatic cancer (OS <1 yr from diagnosis); caution combining reirradiation with stents

Grade 5 Toxicity: Bowel Perforation

- 59 M with pancreatic head adeno s/p Whipple in 7/2012 (pT3N1, PNI/LVI, invasion of lesser omentum) → 3 cycles of gemcitabine → chemoradiation to 50.4/1.8 Gy (EOT 2/2013) → adjuvant gemcitabine
- Local recurrence → FOLFOX → local progression (CA19-9 = 878) → proton reirradiation to 50/2.5 Gy (EOT 10/2013)
- Worsened ascites during RT (CA19-9 = 928) → metallic stent placed across gastrojejunostomy
- MRI abdomen showed thickened omentum c/w carcinomatosis (CA19-9 = 2062) → worsened abdominal pain, free air, died 1 month after reirradiation



Reirradiation Conclusions and Future Directions

- As systemic therapy has improved, local control is increasingly important
- Isolated local or regional recurrences can be treated with reirradiation to palliative symptoms, provide durable local control, and improve survival
  - Potentially the only chance of cure
- Toxicity from cumulative doses remains the greatest obstacle in reirradiation
- Re-irradiation with proton therapy can potentially reduce side effects and allow for more widespread use of reirradiation
  - PBS may be even more helpful in select cases
- Feasibility for individual disease site cohorts is being determined in a multicenter prospective study to help guide future selection criteria
- Critical to recognize and track late toxicities
  - May be tough to manage but can serve to guide future OAR constraints
- Future directions
  - Disease-specific protocols, refined selection criteria
  - Generate DVH models and cumulative constraints for OARs
  - Biomarkers to predict reirradiation tumor response and normal tissue sensitivity