Radiation Dose-Volume Effects for Liver SBRT

Moyed Miften, Ph.D.

Department of Radiation Oncology
University of Colorado School of Medicine

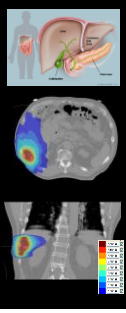
University of Colorado
Denver | Anschutz Medical Campus

AAPM Working Group on Biological Effects: SBRT Normal Tissue Complication Probability Abdominal Team

- Yevgeniy Vinogradskiy, Ph.D., University of Colorado Denver
- Vitali Moiseenko, Ph.D., University of California San Diego
- Jimm Grimm, Ph.D., Holy Redeemer, Meadowbrook
- Ellen Yorke, Ph.D., Memorial Sloan-Kettering Cancer Center
- Andrew Jackson, Ph.D., Memorial Sloan-Kettering Cancer Center
- Wolfgang A Tomé, Ph.D., Montefiore Medical Center and Institute for Onco-Physics
- Randall Ten Haken, Ph.D., University of Michigan
- Nitin Ohri, M.D., Montefiore Medical Center
- Alejandra Méndez Romero, M.D., Erasmus MC Cancer Institute
- Karyn A. Goodman, M.D., University of Colorado Denver
- Lawrence B. Marks, M.D., University of North Carolina
- Brian Kavanagh, M.D., University of Colorado Denver
- Laura A. Dawson, M.D., Princess Margaret Cancer Centre

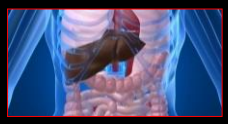
Introduction

- Stereotactic Body Radiation Therapy for liver cancer
  - highly effective in providing LC in selected patients with small hepatic malignancies
  - dose response with increasing doses yielding higher LC rates
  - risk to the adjacent OARs and, when selecting doses, there are trade-offs between LC and OARs complications
  - Various dosing and fractionation schemes with a wide range of toxicity end-points have been reported



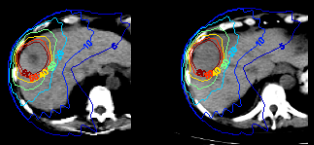
Objective

- Review/analyze the data reported in the literature for normal tissue dose-volume effects in liver SBRT
- Derive normal tissue complication probability models
- Recommend dose/volume limits



Radiological Changes Post SBRT

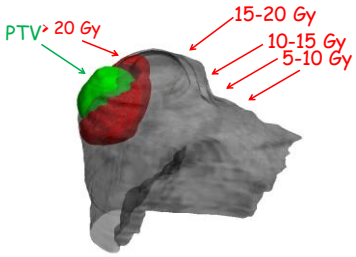
plan CT



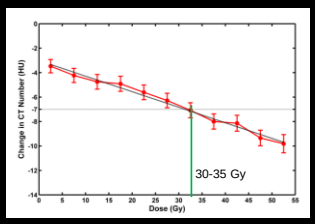
follow-up CT

=

- 34 patients with mets; 96 follow-up non-contrast CTs
- Presc. dose 52 Gy [39 – 60] in 3-5 fractions
- 1-8 follow-up CTs [median, 2 per patient] [range, 0.7-36 mos., median, 8 mos.]
- Dose mapped to follow-up using rigid registration
- In each time bin and in each 5 Gy dose region, mean HU change was computed

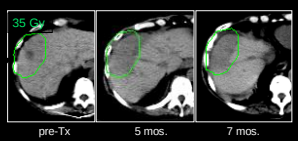


Liver Normal Tissue Dose-Response Curve



Howells et al, IJROBP (2012)

Liver Radiological Changes



- Hypodense radiation reaction is the result of acute changes: edema and variable amounts of fatty infiltration
- Chronic changes may appear iso- or hyperdense, the result of the *lack* of fatty replacement

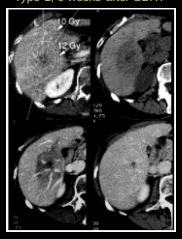
Herfarth Classification of Liver Reactions on CT after SBRT

	Portal venous phase	Late contrast phase
Type I	Hypodensity	Isodensity
Type II	Hypodensity	Hyperdensity
Type III	Iso/hyperdensity	hyperdensity

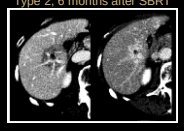
Herfarth KK et al. IJROBP, 2003.

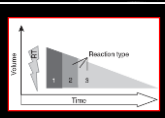
Liver Normal Tissue Reaction after SBRT

Type 1, 6 weeks after SBRT



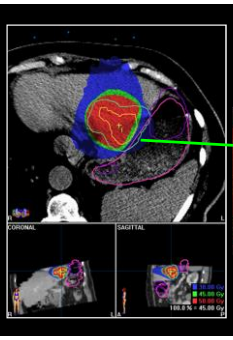
Type 2, 6 months after SBRT



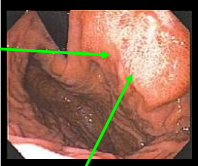


Wulf J, Herfarth KK. Normal Tissue Dose Constraints in SBRT for Liver Tumors. In *Stereotactic Body Radiation Therapy*, Kavanagh BD and Timmerman RD, eds. Lippincott Williams & Wilkins, 2005.

Courtesy of T. Schefter



Tolerance of adjacent intestinal mucosa is an important dose-limiting issue



30 Gy in 3 fractions given here; progressed to ulceration but eventually healed in approx 3 mos

Courtesy of B. Kavanagh

Literature Review

- 12 studies contained both dose/volume and toxicity data from 541 patients with HCC, IHC, and/or liver mets
- Median dose: 40 Gy (range, 18-60 Gy) in 1-6 fractions
- 3 end-points chosen for pooled dose-response analysis
  - G3+ liver enzyme elevation as a function of MLD
  - G2+ general GI toxicity as a function of RX or PTV dose
  - G3+ general GI toxicity as a function of RX or PTV dose
- RX/PTV doses were selected because doses to specific OARs were not available in many instances.

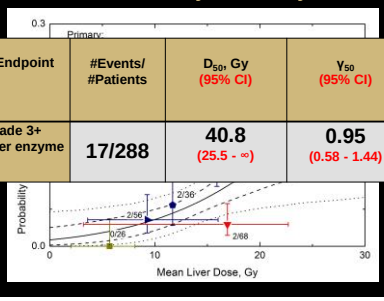
Paper	Diagnosis	Patients #	Fractions #	Total dose range (Gy)	All toxicities reported	Grade 3+ Liver Enzyme Toxicity Rate	Grade 2+ and 3+ General GI Toxicity Rate
Barney 2012	IHC	9	3, 5	45-60	Liver failure, General GI	NA	Grade 2+ 6/9 (67%)
Tse 2008	HCC or IHC	41	6	24-54	RILD, Liver enzymes, General GI, Biochemical changes	10/41 (24%)	Grade 2+ 18/41 (44%) Grade 3+ 4/41 (10%)
Vautravers-Dewas 2011	mets	42	3 , 4	40, 45	General GI	NA	Grade 2+ 19/42 (45%) Grade 3+ 0/42 (0%)
Huang 2012	recurrent HCC	36	4, 5	25-48	General GI	NA	Grade 2+ 10/36 (28%) Grade 3+ 1/36 (3%)
Kang 2012	HCC	47	3	42-60	Biochemical, General GI, CP progression	NA	Grade 2+ NA Grade 3+ 5/47 (11%)
Goodman 2010	HCC, IHC, mets	26	1	18-30	General GI	0/26 (0%)	Grade 2+ 3/26 (12%) Grade 3+ 0/26 (0%)
Lee 2009	mets	68	6	27.7-60	Liver enzymes, Biochemical, RILD, General GI	2/68 (3%)	Grade 2+ 30/68 (44%) Grade 3+ 5/68 (7%)
Andolino 2011	primary HCC	56	3, 5	40, 48	Liver enzymes, General GI, Biochemical, CP progression	2/56 (4%)	Grade 2+ 13/56 (23%) Grade 3+: NA
Bujold 2013	HCC	102	6	30-54	Liver enzymes, Biochemical, General GI, CP progression	11/102 (11%)	Grade 2+: NA Grade 3+ 4/102 (4%)
Son 2010	primary HCC	36	3	30-39	Liver enzymes, CP progression	2/36 (6%)	NA
Barney 2013	HCC, mets	43	1,3,5	28-60	General GI	NA	Grade 2: NA Grade 3 5/43 (12%)
Bae 2013	HCC	35	3,4,5	30-60	Liver enzymes, General GI	3/35 (9%)	Grade 2: NA Grade 3: 5/35 (14%)

Dose-Response Modeling

- Modeling was performed using a probit model with maximum likelihood (ML) parameter fitting.
- The ML method determined the probit model parameters that best fit the binomial (toxicity/no-toxicity) data.
- The input data were the reported toxicity rates and corresponding dose metrics reported in each study.
- The average toxicity rate was then binned into binary outcomes to facilitate probit model estimation with ML parameter fitting.

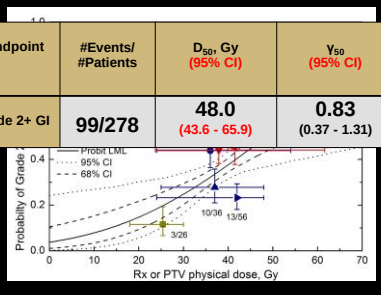
Grade 3+ liver enzyme toxicity vs. MLD

Endpoint	#Events/ #Patients	D_{50}, Gy (95% CI)	γ_{50} (95% CI)
Grade 3+ liver enzyme	17/288	40.8 (25.5 - ∞)	0.95 (0.58 - 1.44)



Grade 2+ general GI toxicity vs. RX/PTV dose

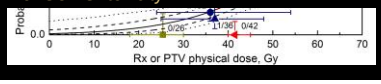
Endpoint	#Events/ #Patients	D_{50}, Gy (95% CI)	γ_{50} (95% CI)
Grade 2+ GI	99/278	48.0 (43.6 - 65.9)	0.83 (0.37 - 1.31)



Grade 3+ general GI toxicity vs. RX/PTV dose

Endpoint	#Events/ #Patients	D_{50}, Gy (95% CI)	γ_{50} (95% CI)
Grade 3+ GI	25/399	87.1 (61.1 - 194.4)	1.22 (0.78 - 1.68)

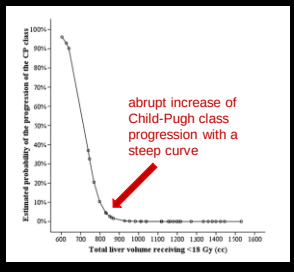
- ✓ D10 & D20 values were 50.6 Gy & 63.1 Gy
- ✓ D50 of 87.1 Gy can be attributed to low rates of G3+ GI toxicity



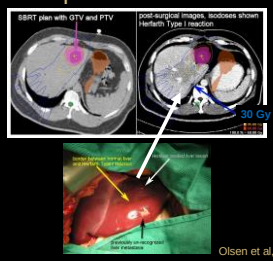
Recommended Dose Limits

- QUANTEC recommendations remain reasonable
  - Primary: MLD 13 Gy (3 fxs) & 18 Gy (6 fxs)
  - Mets: MLD 15 Gy (3 fx) & 20 Gy (6 fxs)
- Why
  - acceptable grade 3 liver enzyme toxicity risk → < 20%
- Liver planning objective ≥ 700cc to ≤ 15Gy
  → low G3+ GI toxicity: 7.6% (9/118)

HCC data from Son et al (IJROBP) suggest sparing ≥ 800cc to ≤ 18Gy in 3 fractions



RILD CT/Pathology correlation: evidence that partial volumes can be treated safely

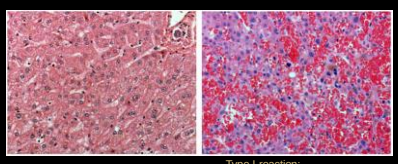


- **No** cases of classic or non classic RILD (clinical)
- We evaluated several cases who underwent surgery after SBRT in order to evaluate pathology associated with imaging changes
- CT obtained preoperatively 6 weeks after SBRT
- The treated area shows underlying pathologic findings c/w veno occlusive disease

Olsen et al, IJROBP 73(5) 2009

Courtesy of T. Schefter

SBRT results in focal classic RILD that <u>isn't clinically</u> manifest (c/w critical volume model)



Normal liver, same patient, outside zone of reaction

Type I reaction: lobular disarray, sinusoidal congestion, pigment accumulation in hepatocytes, some macrophages

Courtesy of T. Schefter

Special Situations

- Toxicity profile of patients with metastatic disease is different from patients with primary tumors.
- Patients with metastatic liver disease tolerate RT more than patients with primary liver tumors.
  - Not enough data to model each patient cohort separately.
- GI toxicity should be a function of the dose delivered to the individual GI organs.
  - In the absence of dosimetric data for each GI organ, RX or PTV doses were used.

Factors Beyond Dose/Volume Affecting Liver and GI Toxicities

- Pre-treatment Child-Pugh status
- Pre-existing GI conditions
- Increasing tumor size and pre-treatment systemic therapies
- Patients with primary tumors are more likely to develop RT-induced liver injury than patients with metastatic lesions

Future Studies

- Explicit studies of the toxicity differences between patients with liver mets, HCC, and IHC.
- Dose-response analysis could be improved if studies report on the achieved dose-volume metrics utilized for treatment planning.
- Minimum standards for reporting treatment outcomes should include relevant clinical and dosimetric data.
- Many journals allow for the inclusion of supplemental data that can be used to include detailed DVH data and additional dosimetric details.

Conclusions

- Not all publications reported on the “actual” delivered doses.
- HCC data suggest the total liver volume receiving <18 Gy should be > 800 cc to spare hepatic function.
- QUANTEC recommendations for MLD should be followed.
- Many studies that used ≥700cc ≤ 15 Gy in planning reported < 8% G3+ GI toxicity risk.
- RX or PTV mean dose of 50 Gy in 3-6 fractions would result in G3+ general GI toxicity risk of < 10%.

Thank You