Stereotactic Body Radiation Therapy: Updates on Clinical, Biological, and Physics/QA

Part One: Biological and Clinical Updates

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Disclosures:

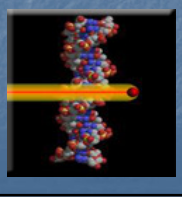
Current Federal Funding:
2012 CMS Innovation Challenge
Award to Develop STAT RAD

Discussion Topics

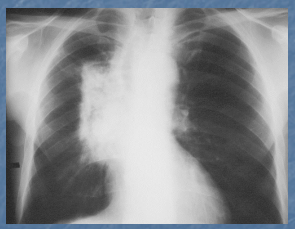
- SBRT Radiobiology and Normal Tissue Constraints
- SBRT Institutional and Cooperative Group Trials
- STAT RAD: Possible future direction for rapid pain palliation of osseous metastases

Radiobiology

- Classical Fractionated Radiobiology
- SBRT Radiobiology: variations of the LQ model
- Normal Tissue Constraints for SBRT

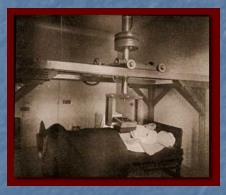


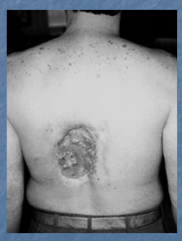
Radiobiology: How does radiation interact and effect living cells and organisms ?



Physics to Chemistry to Biology

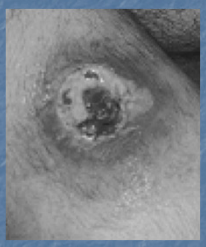
Curie's discoveries lead to "Curie Therapy" (Beginning of "*Radiation Oncology*")





Radium was shown to be a useful tool for destroying cancer cells and normal tissues

Late Radiation Toxicity



Occurs 90 days or longer after completing radiation.

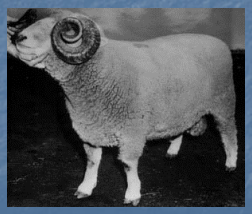
Mainly due to a combination of:

1) vascular effects (obliteration of the microvasculature and development of telangiectasias leading to bleeding,

2) chronic stem cell depletion, leading to poor mucosalization, fibrosis, and ulceration.

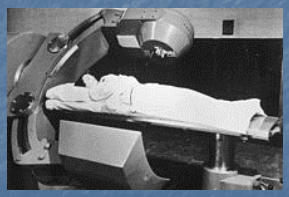
Late Toxicity is Related to: Total Dose, Dose per fraction, Radiation Dose Rate, Volume of Tissue Treated, Type of Tissues Treated, Patient specific factors

Animal Model for fractionated radiation therapy: Ram Sterilization Model



Using Sterilization of the Ram as a model system (spermatogonia modeled tumor and the scrotum modeled normal tissues), early radiation researchers realized that they could sterilize the ram with less scrotal irritation if they delivered multiple smaller radiation doses rather than one large dose.

Conventionally fractionated radiation becomes standard of care to minimize normal tissue toxicity

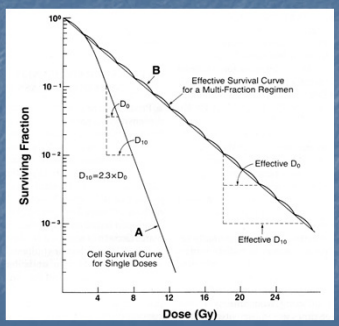


The Four R's of Radiobiology:

1. Repair of sublethal damage
2. Reassortment of cells into radiosensitive phases of the cell cycle (G_2/M)
3. Repopulation of cells due to cell doubling / proliferation
4. Reoxygenation of hypoxic cells in a tumor core

Withers HR. The four R's of radiotherapy. Adv Radiat Biol. 1975;5:241–247.

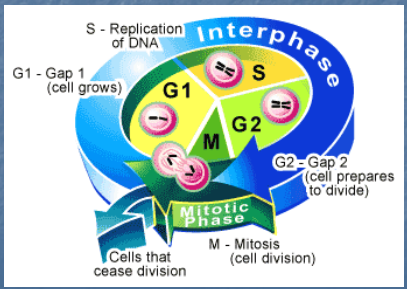
Single and Multiple Fractionated Radiation Therapy Survival Curves



Shoulder of curve: sublethal repair

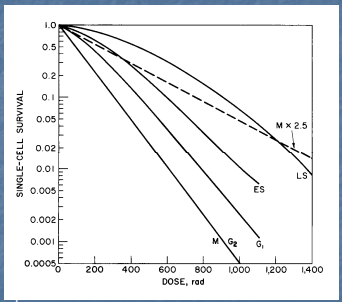
(E.J.H., Fig.3.10, p.46)

Cells have differential radiation sensitivity depending on their cell cycle status



Cell cycle dependency of radiosensitivity

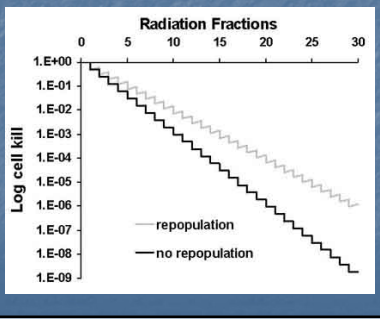
General age response pattern for x or γ-rays – synchronized cells



Hall Radiobiology Textbook

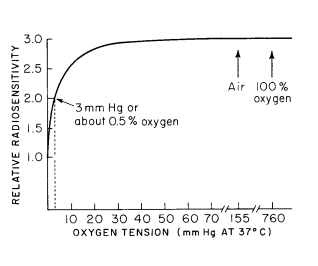
Most sensitive $G_2/M > G_1 >$ early S > late S Most resistant

Effect of tumor repopulation during fractionated therapy



Hall Radiobiology Textbook

Dependence of radiosensitivity on oxygen concentration (idealized)



Hall Radiobiology Textbook

Only a small quantity of oxygen is required for radiosensitization (0.5% oxygen increases R.R to 2.0)

Linear-quadratic model:

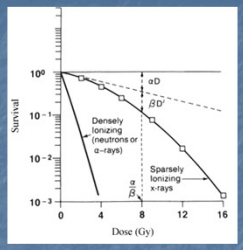
S = fraction of cells surviving a dose D

$S = e^{-(\alpha D + \beta D^2)}$

Linear and quadratic components equal at:

$D = \alpha/\beta$

The model provides the mechanistic biologic rationale related to single- and double-strand DNA breaks.



$$BED = D \cdot \left(1 + \frac{d}{\alpha/\beta}\right)$$

Fowler JF. The linear quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679–694.

Multi-target Model for Cell Kill

Multi-target model assumes an alternative description of clonogenic survival as a function of dose with n targets that need to be hit to disrupt clonogenicity

$$S = e^{-d/d_1} \cdot \left\{1 - \left(1 - e^{-d/D_0}\right)^{\bar{n}}\right\} \quad [3]$$

where d_1 and D_0 are the parameters that determine the initial (first log kill) and final "slopes" of the survival curve. In the high-dose range, where $d >> D_0$, the multitarget model survival curve approaches an asymptote.

$$\ln S \approx -\frac{1}{D_0} d + \ln(\bar{n}) = -\frac{1}{D_0} d + \frac{D_q}{D_0} \quad [4]$$

Elkind MM, Whitmore GF. The radiobiology of cultured mammalian cells. New York: Gordon & Breach; 1967.

Rationale for a universal survival curve and single fraction equivalent dose

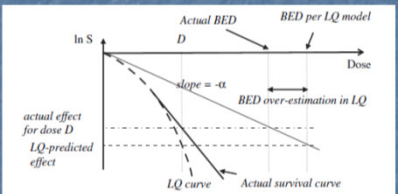


Fig. 1. Biologically effective dose (BED) when expressed through linear quadratic (LQ) model parameters overestimates actual biologically effective dose as determined through empirical survival curve.

Park et al. IJRBP 2008;70(3):847-852.

Universal Survival Curve

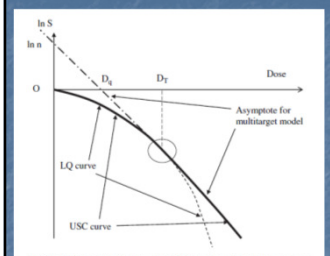


Fig. 2. Universal survival curve (USC) and transition between dose range at which linear quadratic (LQ) model is valid and dose range at which multitarget model is valid. Below transition dose D_T, USC curve is identical with LQ model curve and above D_T, USC curve is identical with terminal linear portion of multitarget model curve.

$$\ln S = \begin{cases} -(\alpha \cdot d + \beta \cdot d^2) & \text{if } d \le D_T \\ \frac{1}{D_0} d + \frac{D_q}{D_0} & \text{if } d \ge D_T \end{cases}$$

$$BED = \begin{cases} D\left(1 + \frac{d}{\alpha/\beta}\right) & \text{if } d \le D_T \\ \frac{1}{\alpha \cdot D_0}(D - n \cdot D_q) & \text{if } d \ge D_T \end{cases}$$

$$SFED = \begin{cases} \alpha D_0 D\left(1 + \frac{d}{\alpha/\beta}\right) + D_q & \text{if } d \le D_T \\ D - (n-1) \cdot D_q & \text{if } d \ge D_T \end{cases}$$

$$D_T = \frac{2 \cdot D_q}{1 - \alpha \cdot D_0}$$

Park et al. IJROBP 2008;70(3):847-852.

Other Novel SBRT Radiobiologic Considerations

- Endothelial Apoptosis: mediated via acid sphingomyelinase pathway at high dose per fraction.
  Garcia-Barros M, et al. Science 2003;300:1155-1159.
- T-cell priming in draining lymphoid tissue resulting in distant tumor reduction/ eradication via CD8+ T-cell dependent fashion.
  Lee Y, et al. Blood. 2009;114:589-595.

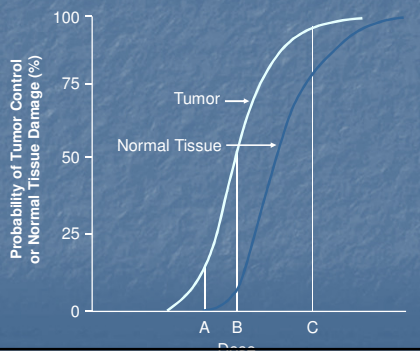
Emami normal tissue dose constraints for fractionated therapy

EMAMI CONSTRAINTS 1991 - Literature Review and Consensus Clinical Experience

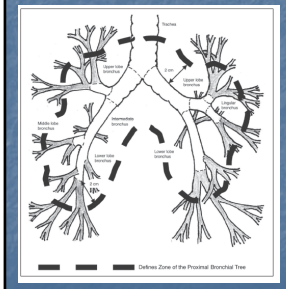
Organ	TD5/5 Volume 1/3rd	TD5/5 Volume 2/3rd	TD5/5 Volume 3/3rd	TD50/5 Volume 1/3rd	TD50/5 Volume 2/3rd	TD50/5 Volume 3/3rd	Most Important Adult Clinical Effect; Standard Fractionation 5x a week, 180-200 cGy/fraction
Eye lens			1000			1800	Cataract requiring intervention
Larynx**		4500	4500			6000	Laryngeal edema
Eye retina I and II			4500			6500	Blindness
Parotid ** (TD 100/5 is 50000cGy)		3200	3200		4600	4620	Xerostomia
Lung	4500	3000	1750	6000	4000	2450	Pneumonitis, Pulmonary Fibrosis
Small intestine	5000		4500	6000		5500	Obstruction, perforation / fistula
Ear midexternal**	3000	3000	3000	4000	4000	4000	Acute serous otitis
Liver	5000	3500	3000	6500	4500	4000	Liver failure
Brain	6000	5000	4500	7500	6500	6000	Necrosis, infarction
Rectum			6000			8000	Severe proctitis/ necrosis/fistula, stenosis
Skin (100 cm^2)			5000			6500	Telangiectasia
Brain stem	6000	5300	5000			6500	Necrosis infarction
Optic nerve I & II			5000			6500	Blindness
Chiasma			6000			6500	Blindness
Stomach	6000	5500	5000	7000	6700	6500	Ulceration, perforation
Skin	7000	6000	5500			7000	Necrosis, Ulceration
Heart	6000	4800	4500	7000	5600	5500	Pericarditis
Femoral Head			5200			6500	Necrosis
Cauda equina			6000			7500	Clinically apparent nerve damage
Brachial plexus	6200	6100	6000	7000	7630	7500	Clinically apparent nerve damage
Esophagus	6000	5400	5500	7200		6800	Clinical stricture/ perforation
Bladder			6500		6500	6500	Symptomatic bladder contracture and volume loss
Colon	6500		4800	6500		5500	Obstruction, perforation / fistula
Kidney**	6000	3000	2300		4000	2800	Clinical nephritis
T-M joint mandible Rib cage Skin	6500	6000	6000	7700	7200	7200	Marked limitation of joint function
Ear midexternal**	6500	5500	5500	6500	6500	6500	Chronic serous otitis
Ear, inner			6000			7000	Sensoneural hearing loss
Larynx**	7500	7000	7000	9000	8000	8000	Cartilage necrosis
Spinal Cord (5, 10, 20 cm respectively)	6000	5000	4750	7000	7000		Myelitis necrosis
Rib Cage	6000			6500			Pathologic fracture

Emami B et al, IJROBP.1991;21(1):109-122

How do we determine the dose? Tumor/Normal Tissue Response Curves



Parallel vs. Serial Organ Structure



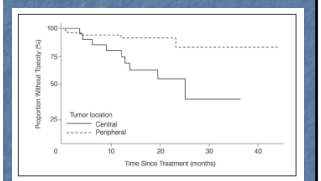


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

SBRT: Normal Tissue Dose Constraints

- Constraints are confusing as these have been reported by multiple institutions with little followup toxicity data.
- Parameters used include max point doses, absolute volume constraint, percentage volume constraint, critical volume spared

Timmerman RD. Semin Radiat Oncol. 2008;18(4)215-222

Grimm et al. J Applied Clin Med Phys 2011;12(2)267-292

Summary of Table 2 "Mostly Unvalidated Normal Tissue Dose Constraints for SBRT"

From Timmerman 2008 "Overview of Hypofractionation" in Seminars in Radiation Oncology (Vol. 18, Num. 4)

Patient Name:	Smith, John	
MRN:		
Rx # and name:	1a - liver SBRT	
Total Rx Dose:	45	Gy
Dose / fx:	15	Gy / fx
# fractions:	3	-

3 Fraction Treatment

Parallel Tissue Constraints			User Input							
Organ	Critical Vol (cc)	Critical Vol Dose Max (Gy)	Total OAR volume		DVH volumes			OAR Vol < Dose Max		Met Requirement?
Total Liver	700	17.1	900.00	cc	V17.1 Gy	150.00	cc	750.00	cc	Yes
Total Kidneys	200	14.4	350.00	cc	V14.4 Gy	145.00	cc	205.00	cc	Yes
Total Lung	1,500	10.5	4000.00	cc	V10.5 Gy	2600.00	cc	1400.00	cc	NO
	1,000	11.4			V11.4 Gy	2200.00	cc	1800.00	cc	Yes

Organ	Max Point Dose (Gy)	Max Dose Limit (Gy)	Met Requirement?	DVH Input			Volume Limit (cc)		Met Requirement?
Spinal Cord	13.00	22.0	Yes	V18.0 Gy	0.20	cc	0.25	cc	Yes
Spinal Cord	-	-	-	V11.1 Gy	1.10	cc	1.20	cc	Yes
Skin	na	24.0	na	V22.5 Gy	na	cc	10.00	cc	na
Heart	21.00	30.0	Yes	V24.0 Gy	14.00	cc	15.00	cc	Yes
Esophagus	27.00	27.0	NO	V21.0 Gy	6.50	cc	5.00	cc	NO
Stomach	15.00	24.0	Yes	V21.0 Gy	9.00	cc	10.00	cc	Yes
Duodenum	na	24.0	na	V15.0 Gy	na	cc	5.00	cc	na
Jejunum / Ileum	na	27.0	na	V16.2 Gy	na	cc	5.00	cc	na
Chestwall	-	-		V30.0 Gy	21.00	cc	30.00	cc	Yes

Major SBRT Institutional and Cooperative Group Clinical Trials

- Lung
- Liver
- Spine
- Prostate

Key Retrospective Japanese Lung SBRT experience

- Uematsu reported a 94% 3-year local control rate for patients treated with 50-60 Gy in 5-6 fractions.
- Nagata reported a 98% local control rate at 30 months for patients treated with 48 Gy in 4 fractions.
- Onishi reported a retrospective study involving 245 patients treated at 13 institutions with a 92% 2-year median local control rate for patients treated to a biologic effective dose BED of at least 100 Gy.

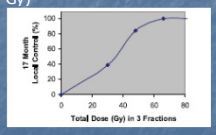
•Uematsu M, Shioda A, Tahara K, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: 5-year experience. Int J Radiat Oncol Biol Phys 2001;51:666–670.

•Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 4 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427–1431.

•Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623–1631

Phase I dose escalation trial by Timmerman at University of Indiana

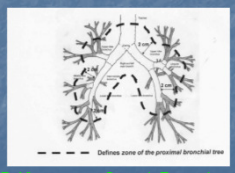
- 47 patients were stratified into 3 groups based on tumor size (<3 cm, 3-5 cm, 5-7 cm)
- Dose escalation in cohorts of 3 patients with all patients receiving 3 fractions of 3D conformal radiation starting at 8 Gy per fraction.
- The maximal tolerated dose was not reached for the 2 smaller tumor subgroups despite treating to 60-66 Gy and was 66 Gy for the largest tumor subgroup.
- 2-year local control rate for patients treated with 18-24 Gy x 3 fractions was 90%. (BED = 100 Gy)



Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946–1955.

Phase II dose escalation trial by Timmerman at University of Indiana

- 70 patients: patients stratified for tumor size
- 35 patients with smaller tumors (5 cm or less) treated with 60 Gy/ 3 fractions
- 35 patients with larger tumors treated with 66 Gy/3 fractions
- The actuarial 2-year local control rate was 95% with a 56% overall survival with death mostly from co-morbid illness.
- Dose limiting toxicity (grade 3-5) was reported to be 11 times higher for patients treated with central tumors compared to peripheral tumors.



Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833–4839.

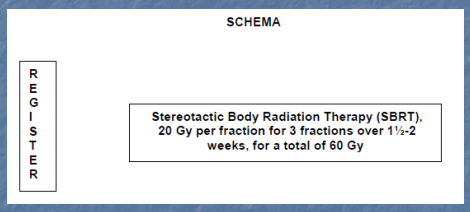
JCOG 0403

- Single arm phase II study for patients with stage 1A lung cancer based on excellent local control rates reported from Kyoto University Hospital
- Study stratifies patients based on medically operable and medically inoperable
- Treatment is 48 Gy/ 4 fractions prescribed to the isocenter.
- Primary endpoint was 3-year overall survival (OS)
- 64 evaluable patients: the 3-yr OS =76% and local PFS=68.5% with only 6.2% grade 3 toxicity no grade 4 or 5 toxicity
- Concluded that dose escalation is feasible based on toxicity and may improve PFS.

RTOG Lung SBRT Trials

- RTOG 0236 phase II closed n = 59 3D
- RTOG 0618 phase II closed n = 33 3D and IMRT
- RTOG 0813 phase I/II open n = 97 3D and IMRT
- RTOG 0915 Phase II closed n= 94 3D and IMRT
- RTOG 1021 Phase III open target n= 420

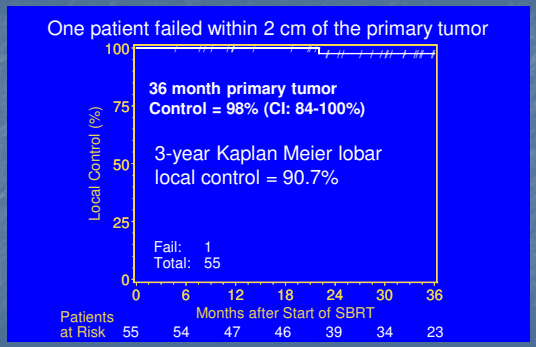
RADIATION THERAPY ONCOLOGY GROUP RTOG 0236
A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer



Patients with T1, T2 (<= 5 cm), T3 (<= 5 cm), N0, M0 medically inoperable non-small cell lung cancer; patients with T3 tumors chest wall primary tumors only; no patients with tumors of any T-stage in the zone of the proximal bronchial tree*. Patients with T3 tumors based on mediastinal invasion or < 2 cm toward carina invasion are not eligible.

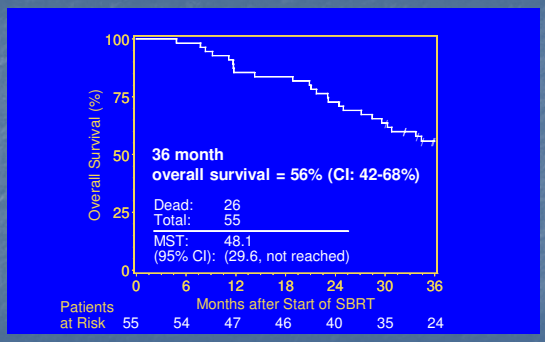
Primary Tumor Control:RTOG 0236

One patient failed within 2 cm of the primary tumor



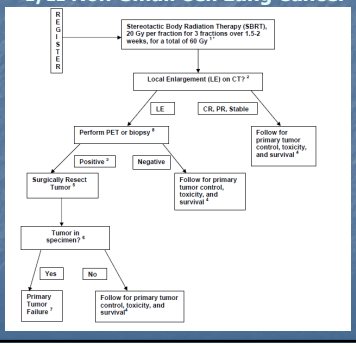
Slide courtesy of Dr. Timmerman

Overall Survival RTOG 0236



Slide courtesy of Dr. Timmerman

RADIATION THERAPY ONCOLOGY GROUP RTOG 0618
A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT)in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer



RADIATION THERAPY ONCOLOGY GROUP: RTOG 0813
SEAMLESS PHASE I/II STUDY OF STEREOTACTIC LUNG RADIOTHERAPY (SBRT) FOR EARLY STAGE, CENTRALLY LOCATED,NON-SMALL CELL LUNG CANCER (NSCLC) IN MEDICALLY INOPERABLE PATIENTS

SCHEMA

Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks

Dose Level	Level 1	Level 2	Level 3	Level 4	†Level 5	Level 6	Level 7	Level 8	Level 9
Dose per Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	**10 Gy**	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40 Gy	42.5 Gy	45 Gy	47.5 Gy	**50 Gy**	52.5 Gy	55 Gy	57.5 Gy	60 Gy

†Protocol treatment begins at Level 5. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) starting dose.

Patients with stage T1-2, N0, M0, non-small cell lung cancer, tumor size ≤ 5 cm, who are not candidates for a complete surgical resection in the opinion of a thoracic surgeon; **only patients with tumors within or touching the zone of the proximal bronchial tree or adjacent to mediastinal or pericardial pleura** (see Section 3.1.5 for details).

RADIATION THERAPY ONCOLOGY GROUP RTOG 0915 (NCCTG N0927) A RANDOMIZED PHASE II STUDY COMPARING 2 STEREOTACTIC BODY RADIATIONTHERAPY (SBRT) SCHEDULES FOR MEDICALLY INOPERABLE PATIENTS WITHSTAGE I PERIPHERAL NON-SMALL CELL LUNG CANCER

SCHEMA

S		**R**	**Stereotactic Body Radiation Therapy (SBRT)**
T	**Zubrod Performance Status**	**A**	
R	1. 0	**N**	**Arm 1**: 34 Gy in 1 fraction
A	2. 1	**D**	
T	3. 2	**O**	
I		**M**	**Arm 2**: 48 Gy in 4 once-daily consecutive fractions
F	**T Stage**	**I**	
Y	1. T1	**Z**	
	2. T2	**E**	

See Section 5.0 for site credentialing required prior to patient registration. See Section 6.0 for details of SBRT.

Medically inoperable, biopsy proven early stage T1, T2 (< 5 cm) NSCLC patients; clinically node negative by PET, with peripherally located tumors (> 2 cm in all directions around the proximal bronchial tree; see figure below)

Phase III trials randomizing operable candidates with early NSCLC to SBRT vs Surgery

RTOG 1021
A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

STARS TRIAL
A Randomized Phase III study of Cyberknife (60 Gy in 3-4 fractions) versus VATS or Open Thoracotomy in operable patients with T1N0 or T2N0 (<4 cm) NSCLC

ROSEL Trial
A Randomized Phase III study of SBRT (60 Gy in 3-5 fractions) vs. Surgical Resection in operable Stage IA patients with NCSLC

Table 2 | Outcomes of SBRT for lung metastases from selected studies

Study	Trial type	Number of patients	Number of targets	Radiation dose	Median follow-up (months)	Outcomes
Uematsu et al. (1998)[7]	Retrospective	22	43	30–75 Gy in 5–15 fractions prescribed to 80%	9	LC: 98% (crude) No or minimal adverse effects
Hara et al. (2002)[28]	Retrospective	14	18	20–30 Gy in one fraction prescribed to periphery of PTV	12	LC: 78% at 13 months. No grade 3 or higher toxic effects
Lee et al. (2003)[30]	Retrospective	19	26	30–40 Gy in 3–4 fractions (10 Gy per dose) prescribed to periphery of PTV	18	LC: 88% at 2 years OS: 88% at 2 years No symptomatic or late serious complications
Hof et al. (2007)[31]	Retrospective	61	71	12–30 Gy in one fraction prescribed to isocenter	14	LPF: 88.6%, 73.7% and 63.1% at 1, 2 and 3 years, respectively OS: 78.1%, 65.1% and 47.8% at 1, 2 and 3 years, respectively No clinically significant toxic effects
Okunieff et al. (2006)[32]	Retrospective	42	125	50 Gy in 10 fractions (5 Gy per dose) prescribed to 80%	18.7	LC: 94% (crude), 91% at 3 years PFS: 25% and 16% at 1 and 2 years, respectively Grade 3 toxic effects: 4%
Norihisa et al. (2008)[33]	Retrospective	34	43	48 Gy or 60 Gy in 4–5 fractions (12 Gy per dose) prescribed to isocenter	27	LRF: 90% at 2 years OS: 84.3% at 2 years PF: 34.9% at 2 years Grade 2 and 3 toxic effects: 12% and 3%, respectively
Guckenberger et al. (2009)[34]	Retrospective	84	118	4–8 fractions of 6–7 Gy, 3 fractions of 10–12.5 Gy or one fraction of 26 Gy, prescribed to 65%	14	LC: 82% at 3 years OS: 16% at 3 year Grade 3 or higher toxic effects: 1.2%
Ernst-Stecken et al. (2006)[35]	Prospective (phase I–II)	18	36	35 Gy in 5 fractions of 7 Gy each or 40 Gy in 5 fractions of 8 Gy each (coverage of 90% of PTV required)	NA	CR: 51% PR: 33% SD: 3% (whole group)* No grade 4 or higher toxic effects
Ruisthoven et al. (2009)[12]	Prospective (phase I–II)	38	63	48–60 Gy in 3 fractions prescribed to isodose line covering PTV	15.4 for assessable lesions	LC: 100% and 96% at 1 and 2 years, respectively OS: 39% at 2 years No grade 4 or higher toxic effects

*Including three patients with primary lung tumors. Abbreviations: CR, complete response; LC, local control; LPF, local progression free; LRF, local relapse free; NA, not available; OS, overall survival; PF, progression free; PR, partial response; PTV, planning treatment volume; SBRT, stereotactic body radiation therapy; SD, stable disease.

SBRT FOR LUNG METASTASES

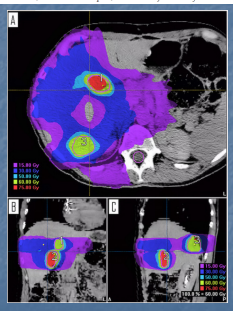
Local control rates of 78-100%

Lo SS, Fakiris AJ, Chang EL, et al. Nature reviews.Clin. Onc. 2010; 7:44-54.

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter

- Eligibility
  - 1-3 liver metastases
  - Solid tumors
  - No tumor diameter >6cm
  - Liver and kidney function OK
  - No systemic therapy within 14 days pre- or post-SBRT
- SBRT Dose
  - Phase I escalation to 20 Gy x 3
  - 20 Gy x 3 fractions for Phase II



Rusthoven KE, Kavanagh BD, Cardenes et al. J Clin Oncol. 2009; 27:1572-1578 (Slide courtesy of Dr. Kavanagh)

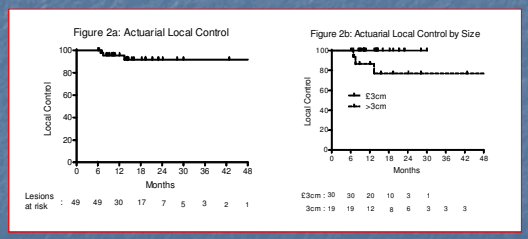
Liver and Non-liver Protocol Dose Volume Constraints

- Non-liver:
  - Total kidney volume > 15 Gy to be < 35%
  - Max spinal cord dose 18 Gy
  - Max dose to stomach or intestine 30 Gy
  - Later, max point to skin <21 Gy
- Modified critical volume method for liver:
  - At least 700 cc had to receive < 15 Gy

Rusthoven KE, Kavanagh BD, Cardenes et al. J Clin Oncol. 2009; 27:1572-1578 (Slide courtesy of Dr. Kavanagh)

Results: (1) no severe liver toxicity (2) tumor volume effect

1 grade 3 skin toxicity due to inadvertent subcutaneous hotspot



Rusthoven KE, Kavanagh BD, Cardenes et al. J Clin Oncol. 2009; 27:1572-1578 (Slide courtesy of Dr. Kavanagh)

Table 3 | Outcomes of SBRT for liver metastases from selected studies

Study	Type	Number of patients	Number of targets	Radiation dose	Median follow-up (months)	Outcomes
Katz *et al.* (2007)[28]	Retrospective	69	174	30–56 Gy in fractions of 2–6 Gy prescribed to 80%	14.5	LC: 76% and 57% at 10 and 20 months, respectively OS: 46% and 24% at 6 and 12 months, respectively Grade 3 or higher toxic effects: 0%
Wulf *et al.* (2001)[47]	Retrospective	23	23	30 Gy in 3 fractions of 10 Gy prescribed to 65%	9.0	LC: 76% and 61% at 1 and 2 years, respectively* OS: 71% and 43% after 1 and 2 years, respectively* Grade 3–5 toxic effects (acute): 0%
Gumén *et al.* (2006)[30]	Retrospective	7	9	20–40 Gy in 2–4 fractions, 30–45 Gy in 2–3 fractions, or 40 Gy in 2 fractions prescribed to 65%	117.0	LC: 100% (crude) OS: 100% (crude)
Herfarth *et al.* (2001)[45]	Prospective (phase I–II)	33	56	14–26 Gy in 1 fraction prescribed to 80%	5.7.0	LC: 78% (crude); 75%, 71% and 67% at 6, 12 and 18 months, respectively* OS: 72% at 1 year* RILD: 0%
Mendez Romero *et al.* (2006)[48]	Prospective (phase I–II)	14	34	37.5 Gy in 3 fractions prescribed to 65%	12.9	LC: 94% (crude); 100% and 86% at 1 and 2 years, respectively OS: 85% and 62% at 1 and 2 years, respectively Grade 3 toxic effects: acute (*n* = 3); late (*n* = 1) Grade 4 or higher toxic effects: 0%
Rusthoven *et al.* (2009)[33]	Prospective (phase I–II)	47	63	12–20 Gy in 3 fractions prescribed to isodose line covering PTV	16.0 for assessable lesions	LC: 95% and 92% at 1 and 2 years, respectively‡ OS: 30% at 2 years Grade 4 toxic effects: 0%
Lee *et al.* (2009)[42]	Prospective (phase I)	70	143	27.7–60.0 Gy in 6 fractions prescribed to isodose line covering PTV (median 41.4 Gy)	10.8 for 68 assessable patients	LC: 71% at 1 year OS: 47% at 18 months PFS: median 3.7 months Acute grade 3 toxic effects: 10% Late grade 4 and 5 toxic effects: 2.9% and 1.5%, respectively

*Analysis includes one patient with primary liver tumor. ‡Analysis includes four patients with primary liver tumors. §With follow-up times 6 months or longer. Abbreviations: LC, local control; OS, overall survival; PFS, progression-free survival; PTV, planning treatment volume; RILD, radiation-induced liver disease; SBRT, stereotactic body radiation therapy.

SBRT FOR LIVER METASTASES

Local control rates of 71-100%

Lo SS, Fakiris AJ, Chang EL, et al. Nature reviews: Clin Onc. 2010; 7,44-54.

Table 4 | Outcomes of SBRT for spinal metastases from selected studies

Study	Trial type, population of patients	Number of patients (number of tumors)	Radiation dose	Follow up (months)	Outcomes
Ryu *et al.* (2004)[66]	Retrospective, unirradiated	49 (61)	10–16 Gy in 1 fraction	6–24	LC: 93% (crude) Late neurologic complications: 0%
Rock *et al.* (2006)[67]	Retrospective, postoperative	18 (18)	10–16 Gy in 1 fraction (median 14 Gy) or 25 Gy in 10 fractions (EBRT) plus 6–8 Gy in 1 fraction	4–36, median 7	LC: 94% (crude) Late neurologic complications: 0%
Gerszten *et al.* (2005)[3]	Retrospective, postoperative	26 (26)	16–20 Gy in 1 fraction (mean 18 Gy)	11–24, median 16	LC: 92% (crude) Late neurologic complications: 0%
Sahgal *et al.* (2007)[5]	Retrospective, mixed	26 (37)	9–30 Gy in 1–5 fractions (median 24 Gy in 3 fractions)	0.5–48.0, median 8.5	LC: 87% (crude) FFP: 85% at 1 year Late neurologic complications: 0%
Gerszten *et al.* (2007)[68]	Retrospective, mixed	393 (500)	12.5–25.0 Gy in 1 fraction (mean 20 Gy) or EBRT plus SBRT boost (dose not specified)	3–53, median 21	LC: 88% (crude) Late neurologic complications: 0%
Yamada *et al.* (2005)[9]	Retrospective, mixed	21 (21)	20–30 Gy in 5 fractions (median 20 Gy)	1–24, median 7	LC: 90% (crude); 81% (actuarial) Late neurologic complications: 0%
Chang *et al.* (2007)[69]	Prospective, phase I/II	63 (74)	30 Gy in 5 fractions or 27 Gy in 3 fractions	1–50, median 21.3	LC: 77% (crude) FFP: 84% at 1 year Late neurologic complications: 0%

Abbreviations: EBRT, external beam radiation therapy; FFP, free from progression; LC, local control; SBRT, stereotactic body radiation therapy.

SBRT FOR SPINAL METASTASES

Local control rates of 77-94%

Lo SS, Fakiris AJ, Chang EL, et al. Nature reviews: Clin Onc. 2010; 7,44-54.

RADIATION THERAPY ONCOLOGY GROUP: RTOG 0631 PHASE II/III STUDY OF IMAGE-GUIDED RADIOSURGERY/SBRT FOR LOCALIZED SPINE METASTASIS

PHASE II COMPONENT	
R	
E	
G	**Radiosurgery/SBRT**:
I	Single fraction dose of 16 Gy
S	
T	
E	
R	

PHASE III COMPONENT			
S		R	
T	**Number of Spine Metastases**	A	**Arm 1: Radiosurgery/SBRT**:
R	1) 1	N	Single fraction dose of 16 or 18 Gy**
A	2) 2-3	D	
T		O	**Arm 2: External Beam Radiation Therapy**:
I	**Type of Tumor**	M	Single fraction dose of 8 Gy
F	1) Radioresistant tumor*	I	
Y	2) Other	Z	Randomization ratio (Arm 1: Arm 2) = 2:1
		E	
	Intended Radiosurgery/SBRT Single Fraction Dose**		
	1) 16 Gy		
	2) 18 Gy		

*Radioresistant tumors include soft tissue sarcomas, melanomas, and renal cell carcinomas.

**Patients randomized to Arm 1 (experimental arm) will be stratified according to the single fraction dose for image-guided radiosurgery/SBRT, using either 16 or 18 Gy as preferred by the treating physician.

RADIATION THERAPY ONCOLOGY GROUP: RTOG 0631 PHASE II/III STUDY OF IMAGE-GUIDED RADIOSURGERY/SBRT FOR LOCALIZED SPINE METASTASIS

Phase II Component: Determine the feasibility of successfully delivering image-guided radiosurgery/SBRT for spine metastases in a cooperative group setting.

Phase III Component: Determine whether image-guided radiosurgery/SBRT (single dose of 16 Gy) improves pain control (as measured by the 11 point NRPS) as compared to conventional external beam radiotherapy (single dose of 8 Gy).

Patients with localized spine metastasis from the C1 to L5 levels (a solitary spine metastasis; 2 separate spine levels; or up to 3 separate sites); each of the separate sites must have a maximal involvement of 2 contiguous vertebral bodies.

SBRT for Localized Prostate Cancer

Overview of SBRT schedules and biochemical outcomes for localized prostate cancer.

Reference	No of patients	No of fractions	Fraction size (Gy)	Total dose (Gy)	NTD_2 for α/β estimate 1.5 Gy	3Gy	Median Follow up (months)	Biochemical control rate
Collins 1991	232	6	6	36.0	77.1	64.8	≥24	–
Choi 2007	44	4	9	36	108	86.4	13	78% at 3-years
Madsen 2007	40	5	6.7	33.5	78	57.8	41	90% at 48-months
Tang 2008	30	7	5	35	85	70	6	–
Friedland 2009	112	7	5	35	85	70	24	98%
Bolzicco 2010	45	5	7	35	85	70	20	100%
Katz 2010	50	5	7	35	85	70	36	100%
Katz 2010	254	5	7.25	36.25	96	78	17	98%
King 2011	41	5	7.25	36.25	96	78	33	94% at 4-years
Freeman 2011	41	5	7.25	36.25	96	78	60	93%

Arcangeli S, Scorsetti M, Alongi F. Critical Reviews in Oncology/Hematology. 2012 epub

RADIATION THERAPY ONCOLOGY GROUP: RTOG 0938 A RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED RADIOTHERAPY FOR FAVORABLE RISK PROSTATE CANCER

SCHEMA

STRATIFY		RANDOMIZE	
	Treatment techniques/machine 1. All linear accelerator based treatment (excluding Cyberknife) 2. Cyberknife 3. Protons		**Arm 1** 36.25 Gy in 5 fractions of 7.25 Gy over two and a half weeks (in 15-17 days)* **Arm 2** 51.6 Gy in 12 daily fractions of 4.3 Gy over two and a half weeks (in 16-18 days)*

*For proton doses, see Section 6.1.4.

Histologically confirmed diagnosis of adenocarcinoma of the prostate within 180 days of randomization; Gleason scores 2-6; Clinical stage T1-2a; PSA < 10 ng/mL (PSA should not be obtained within 10 days after prostate biopsy).

A Real Time TomoTherapy-based Scan-Plan-QA-Treat STAT RAD treatment procedure in 30 minutes is possible

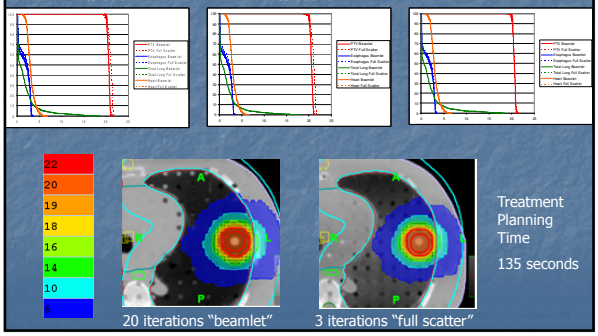
TomoTherapy to Introduce StatRT at AAPM

MADISON, Wis., July 8, 2007 - TomoTherapy Incorporated (NASDAQ: TTPY) today announced that it will introduce StatRT™ at the annual American Association of Physicists in Medicine (AAPM) meeting in Minneapolis, July 22-26, 2007.

Lung SBRT Dosimetric Comparison of "beamlet" algorithm and "full scatter" STAT RT algorithm

20 Gy prescribed to cover 95% of the PTV

1 iteration | 2 iterations | 3 iterations



20 iterations "beamlet" | 3 iterations "full scatter"

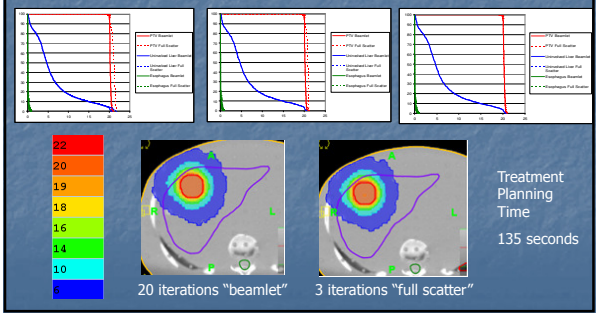
Treatment Planning Time

135 seconds

Liver SBRT Dosimetric Comparison of "beamlet" algorithm and "full scatter" STAT RT algorithm

20 Gy prescribed to cover 95% of the PTV

1 iteration | 2 iterations | 3 iterations



20 iterations "beamlet" | 3 iterations "full scatter"

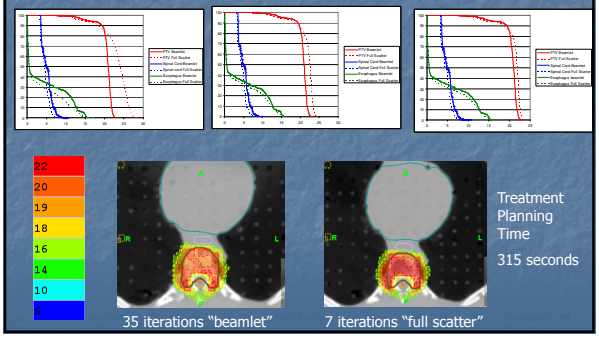
Treatment Planning Time

135 seconds

Spine SBRT Dosimetric Comparison of "beamlet" algorithm and "full scatter" STAT RT algorithm

20 Gy prescribed to cover 85% of the PTV

3 iterations | 5 iterations | 7 iterations



35 iterations "beamlet" | 7 iterations "full scatter"

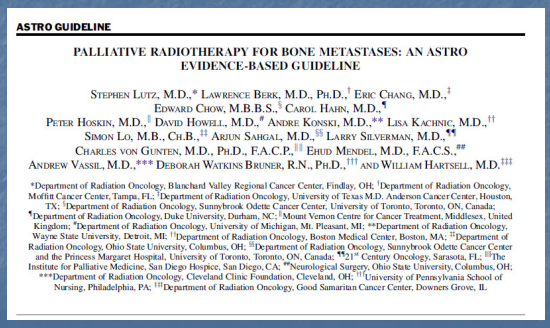
Treatment Planning Time

315 seconds

2007 STAT RT Clinical Problems

- No good contouring tools
- No QA methods

2011 ASTRO Consensus Guidelines on Bone Metastases



ASTRO GUIDELINE

PALLIATIVE RADIOTHERAPY FOR BONE METASTASES: AN ASTRO EVIDENCE-BASED GUIDELINE

Stephen Lutz, M.D.,* Lawrence Berk, M.D., Ph.D.,† Eric Chang, M.D.,‡ Edward Chow, M.B.B.S.,§ Carol Hahn, M.D.,¶ Peter Hoskin, M.D.,‖ David Howell, M.D.,# Andre Konski, M.D.,** Lisa Kachnic, M.D.,†† Simon Lo, M.B., Ch.B.,‡‡ Arjun Sahgal, M.D.,§§ Larry Silverman, M.D.,¶¶ Charles von Gunten, M.D., Ph.D., F.A.C.P.,‖‖ Ehud Mendel, M.D., F.A.C.S.,## Andrew Vassil, M.D.,*** Deborah Watkins Bruner, R.N., Ph.D.,††† and William Hartsell, M.D.‡‡‡

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Lutz et al. Int J Rad Oncol Biol Phys. 2011;79(4):965-76.

2012 ACR Appropriateness Criteria Non-spine Bone Metastases

JOURNAL OF PALLIATIVE MEDICINE
Volume 15, Number 5, 2012
Mary Ann Liebert, Inc.
DOI: 10.1089/jpm.2011.0512

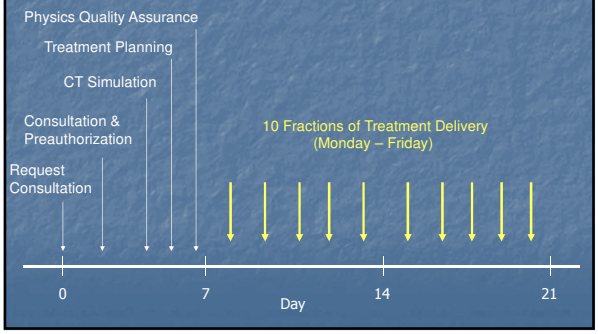
Special Report

ACR Appropriateness Criteria® Non-Spine Bone Metastases

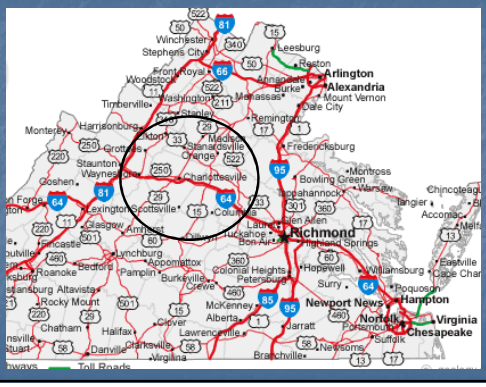
Expert Panel on Radiation Oncology–Bone Metastases: Stephen T. Lutz, M.D., M.S.,[1] Simon Shek-Man Lo, M.B., Ch.B.,[2] Eric L. Chang, M.D.,[3] Nicholas Galanopoulos, M.D.,[4] David D. Howell, M.D.,[5] Edward Y. Kim, M.D.,[6] Andre A. Konski, M.D.,[7] Neeta D. Pandit-Taskar, M.D.,[8] Samuel Ryu, M.D.,[9] Larry N. Silverman, M.D.,[10] Catherine Van Poznak, M.D.,[11] and Kristy L. Weber, M.D.[12]

Lutz et al. J Pal Med. 2012;15(5):521-526.

Radiation Oncology Patient Workflow: Major Barrier to Patient Access



50 mile radius around Charlottesville



1200 miles is approximately the distance from New York to Omaha, Dallas or Miami

Clinical Investigation

A One-Step Cone-Beam CT-Enabled Planning-to-Treatment Model for Palliative Radiotherapy-From Development to Implementation

Rebecca K.S. Wong, M.B.Ch.B., M.Sc., F.R.C.P., Daniel Letourneau, Ph.D., Anita Varma, B.Sc., M.R.T., Jean Pierre Bissonnette, Ph.D., David Fitzpatrick, M.B.Ch.B., F.R.C.P., Daniel Grabarz, M.D., Christine Elder, M.B.Ch.B., F.R.A.N.Z.C.R., Melanie Martin, B.Sc.(Med.Rad.Sci.), M.R.T.(T.), Andrea Bezjak, M.D., M.Sc., F.R.C.P., Tony Panzarella, M.Sc., Mary Gospodarowicz, M.D., F.R.C.P.C., F.R.C.R., and David A. Jaffray, Ph.D.

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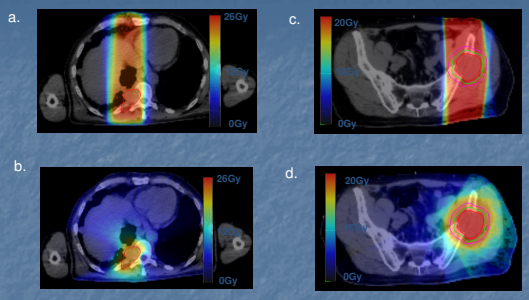
Summary

Palliative radiotherapy should be delivered as soon as is reasonable. The goal of our project was to convert a multistep, multisystem radiotherapy planning-to-treatment process into a one-step integrated process using a cone-beam computed tomography–enabled treatment unit. Our study showed that the process can be executed with a mean duration of 35 minutes while preserving the quality of the treatment plan and is

Wong et al. Int J Rad Oncol Biol Phys. 2012; May 15th epub.

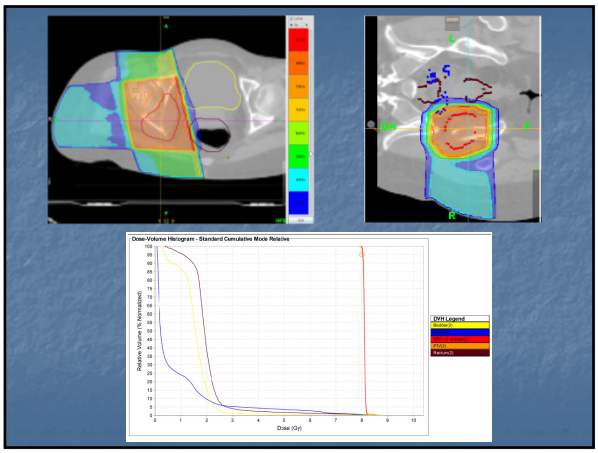


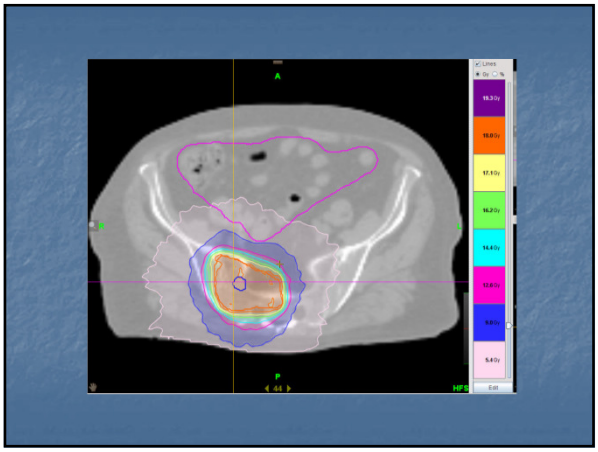
Adoption of SBRT treatment concepts for spinal irradiation to non-spinal bone metastases.

Proposed SCAN PLAN QA TREAT WORKFLOW

Pre-contour Diagnostic Image Set → Immobilization and MVCT simulation → Image Co-registration Velocity ® →

VoLO GPU-based Treatment Planning → QA: Monte Carlo Second Dose Check → Dose Delivery with second QA: CT Detector Dose Check





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Josh Evans

Thanks for your attention !!

Questions ? Email: pwr3u@virginia.edu

CLINICAL INVESTIGATION Palliation

INTERNATIONAL PATTERNS OF PRACTICE IN PALLIATIVE RADIOTHERAPY FOR PAINFUL BONE METASTASES: EVIDENCE-BASED PRACTICE?

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Purpose: Multiple randomized controlled trials have demonstrated the equivalence of multifraction and single-fraction (SF) radiotherapy for the palliation of painful bone metastases (BM). However, according to previous surveys, SF schedules remain underused. The objectives of this study were to determine the current patterns of practice internationally and to investigate the factors influencing this practice.

Methods and Materials: The members of three global radiation oncology professional organizations (American Society for Radiology Oncology [ASTRO], Canadian Association of Radiation Oncology [CARO], Royal Australian and New Zealand College of Radiologists) completed an Internet-based survey. The respondents described what radiotherapy dose fractionation they would recommend for 5 hypothetical cases describing patients with single or multiple painful BMs from breast, lung, or prostate cancer. Radiation oncologists rated the importance of patient, tumor, institution, and treatment factors, and descriptive statistics were compiled. The chi-square test was used for categorical variables and the Student *t* test for continuous variables. Logistic regression analysis identified predictors of the use of SF radiotherapy.

Results: A total of 962 respondents, three-quarters ASTRO members, described 101 different dose schedules in common use (range, 3 Gy/1 fraction to 60 Gy/20 fractions). The median dose overall was 30 Gy/10 fractions. SF schedules were used the least often by ASTRO members practicing in the United States and most often by CARO members. Case, membership affiliation, country of training, location of practice, and practice type were independently predictive of the use of SF. The principal factors considered when prescribing were prognosis, risk of spinal cord compression, and performance status.

Conclusion: Despite abundant evidence, most radiation oncologists continue to prescribe multifraction schedules for patients who fit the eligibility criteria of previous randomized controlled trials. Our results have confirmed a delay in the incorporation of evidence into practice for palliative radiotherapy for painful bone metastases. © 2009 Elsevier Inc.

Survey, bone metastases, palliation, radiotherapy, patterns of practice.

Fairchild et al, Int J Rad Onc Biol Phys 75(5) 1501-10

US: prefers 30 Gy/10 fractions

Case 1, breast cancer with thoracic spine metastases

Case 2A, prostate cancer with shoulder metastasis

Case 2B, prostate cancer with femur metastasis

Case 3, NSCLC with spine metastasis

Case 4, NSCLC with neuropathic pain, spine BM

Case 5A, prostate cancer with spine retreatment

Case 5B, prostate cancer with hip retreatment

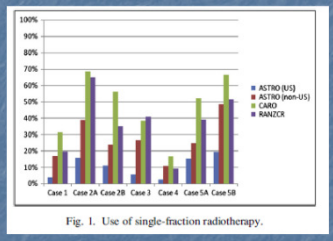
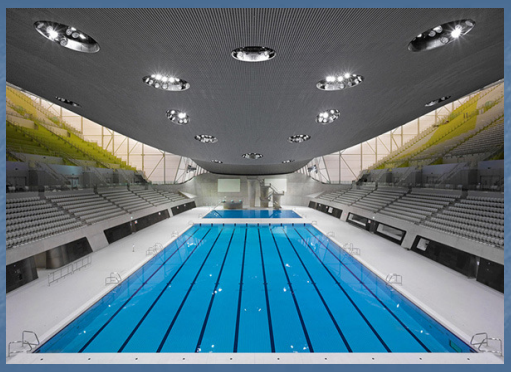
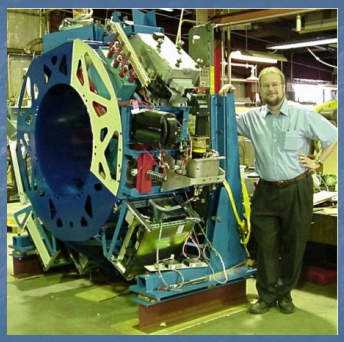


Fig. 1. Use of single-fraction radiotherapy.

Fairchild et al, Int J Rad Onc Biol Phys 75(5) 1501-10

At least tumor motion management is not this complex !!!





Wenlock (above), the mascot of the Olympic Games, is named after the English town of Much Wenlock, which inspired Baron Pierre de Coubertin to found the modern Olympic movement.

Mandeville (a[illegible] Paralympics, is named after the town of Stoke Mandeville, the birthplace of the Paralympic Games.