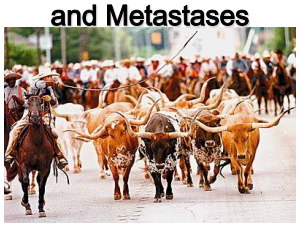
Stereotactic Ablative Radiotherapy (SABR) for Treatment of Primary Cancer and Metastases



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Disclosures

- I have research grants/funding with:
  - Accuray, Inc.
  - Elekta Oncology
  - Varian Medical Systems
  - US NIH
  - US DOD
  - Cancer Prevention Research Institute of Texas
- I am on the scientific advisory board for:
  - D3 Corporation

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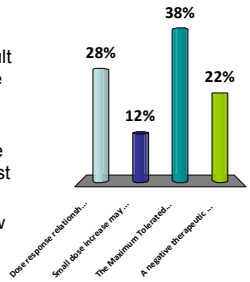
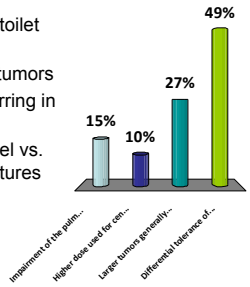
Which of the following statements regarding dose response relationships for ablative radiotherapy delivery is FALSE

1. Dose response relationships are best determined by phase I clinical trials
2. Small dose increase may result in large toxicity increase in the transition range of the dose response curve.
3. The Maximum Tolerated Dose (MTD) corresponds to the most ideal therapeutic ratio.
4. A negative therapeutic window results when efficacy is less likely than harm.



Early stage lung cancer was the most common clinical model studied in clinical trials testing SABR at centers across the world. The Indiana University trials demonstrated that treatments in the central chest were problematic for patients to tolerate likely related to:

1. Impairment of the pulmonary toilet function of the central chest.
2. Higher dose used for central tumors
3. Larger tumors generally occurring in the central chest
4. Differential tolerance of parallel vs. secular defined thoracic structures

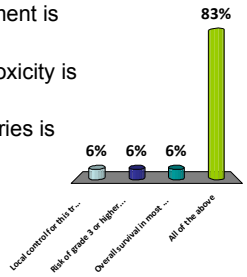


Based on published reports, what factors would be most concerning for increased risk of toxicity after SABR?

24% 1. impaired spirometry
14% 2. peripheral lung location
45% 3. impaired DLCO
16% 4. advanced age

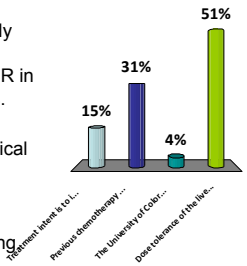
The following are true statements about the outcome of patients with early stage lung cancer treated with SBRT?

1. Local control for this treatment is predicted to be >80%.
2. Risk of grade 3 or higher toxicity is around 20% at 3 years.
3. Overall survival in most series is 60-75% at 2 years.
4. All of the above



The rationale and conduct for SABR treatment in metastatic cancer to the liver includes all of the following except:

1. Treatment intent is to improve survival, even cure.
2. Previous chemotherapy clearly limits tolerance and is a contraindication to using SABR in patients with liver metastases.
3. The University of Colorado multicenter trials used the critical volume methodology to avoid liver toxicity
4. Dose tolerance of the liver is similar to treatments in the lung.



New Cancer Therapy Assessments

- Eventually measure survival and quality of life
- Along the way:
  - Formulate (how should it be prescribed)
  - Optimize (maximize the therapeutic window)
- In therapies with variable potency, need to characterize dose response

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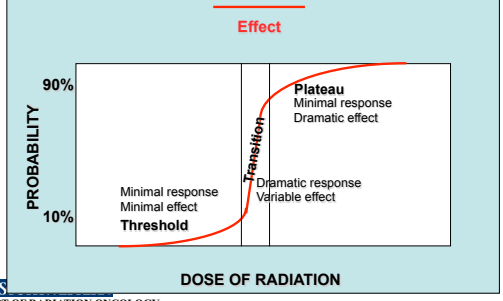
Dose Response



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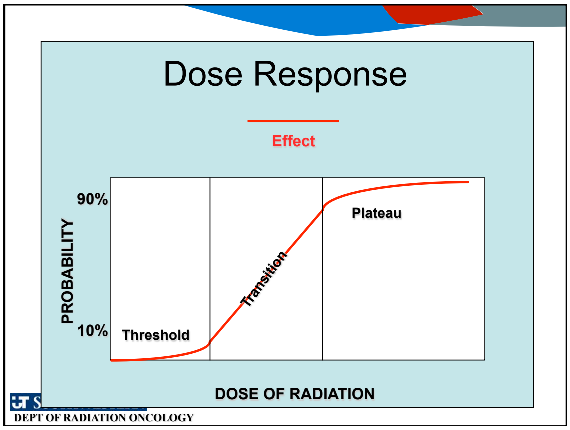
Dose Response
Effect
90%
10%
PROBABILITY
Threshold
Transition
Plateau
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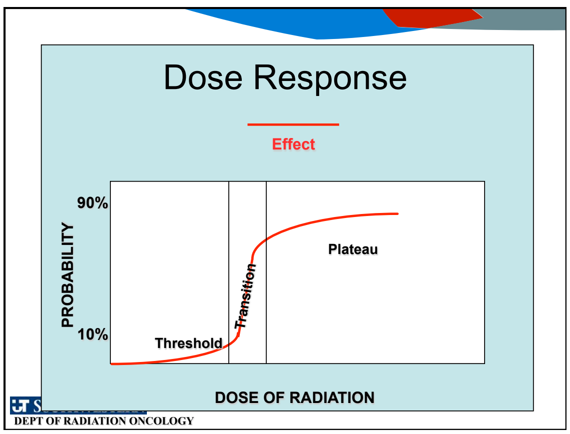
Dose Response
Effect
90%
10%
PROBABILITY
Threshold
Transition
Plateau
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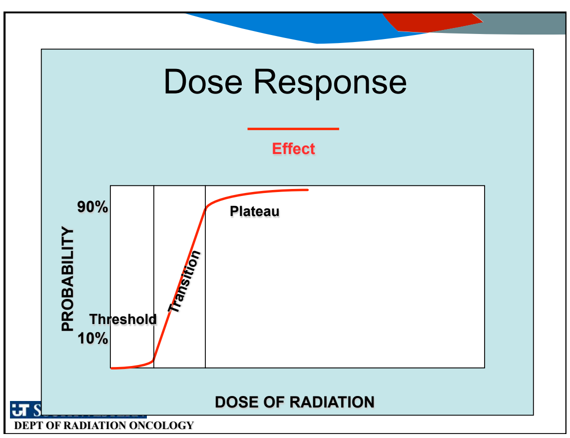
Dose Response
Effect
90%
10%
PROBABILITY
Threshold
Transition
Plateau
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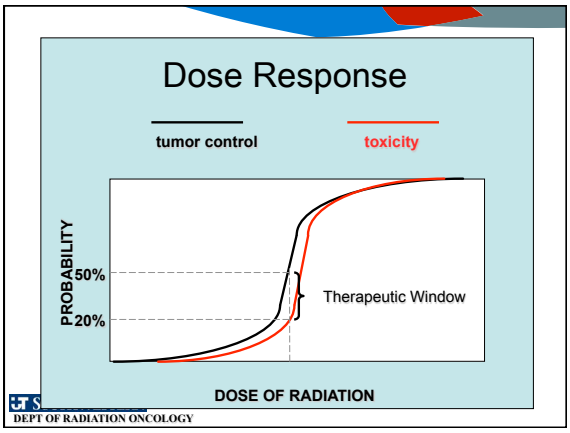
Dose Response
tumor control
toxicity
PROBABILITY
50%
20%
Therapeutic Window
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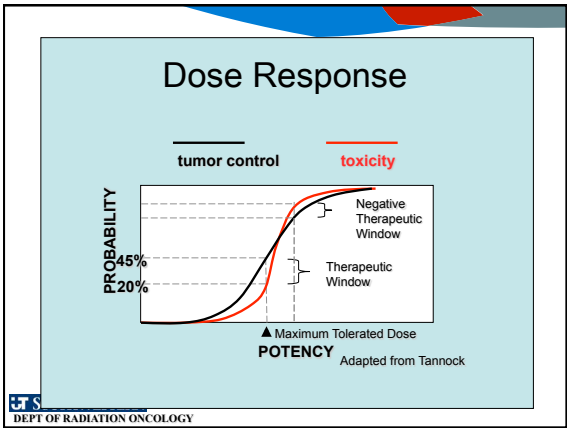
Dose Response
tumor control
toxicity
PROBABILITY
45%
20%
Negative Therapeutic Window
Therapeutic Window
Maximum Tolerated Dose
POTENCY
Adapted from Tannock
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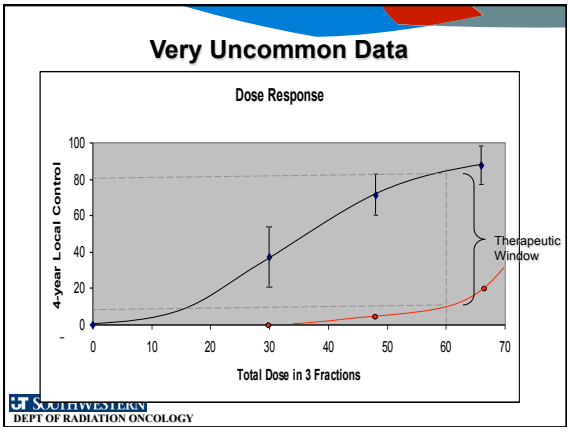
Very Uncommon Data
Dose Response
4-year Local Control
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Total Dose in 3 Fractions
Therapeutic Window
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Stereotactic Ablative Radiotherapy

- aka, extracranial stereotactic radioablation (ESR), stereotactic body radiation therapy (SBRT), etc
- SABR
  - Fitting
  - Descriptive
- Includes a "potpourri" of technologies to allow optimal immobilization, motion control, targeting, dose deposition, and accuracy to deliver oligofractionated radiotherapy

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Original Experience with SABR

- Innovations from US (Hamilton), Sweden (Lax and Blomgren) and Japan (Uematsu) in 1990s
- Treatment effect impressive
  - >10 Gy per fraction
  - Amazing tumor regression
- Needed systematic approach to find proper place

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Evaluating Technology

- In the case SABR, many technologies (all evolving)
- Characterized the treatment effect (physically and biologically) and created guidelines
- Formed hypotheses:
  - SABR technologies MIGHT enable delivery of ablative oligofractionated radiotherapy
  - Ablative radiotherapy will control tumors better than conventional radiotherapy or chemoradiotherapy
  - Toxicity will be increased, particularly in the late timeframe, but generally tolerable and offset by benefits

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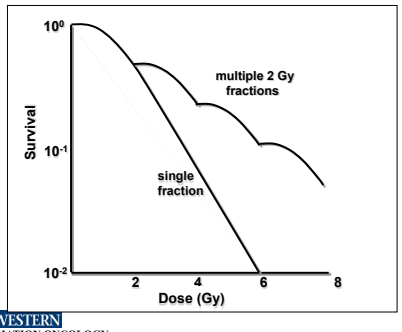
Clonagenic Survival



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High Risk Hypothesis

LATE radiation toxicity: ulceration, denervation, devasculization, stenosis, fibrosis, devitalization

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Best Data Collection Approach

- Valid, prospective, clinical scientific investigation
  - Hypothesis testing within a defined "clinical model"
  - Adult supervision (e.g., statistician, research manager, etc)
  - Independent scrutiny (IRB, data safety monitoring committee, other specialty input, etc)
  - Complete record-keeping (research staff, audits, etc.)
  - Phase I, II, II randomized, and III randomized
- Next best is population cohort and prospective registry
- Much further below is retrospective registries and chart reviews (non-conclusive, only hypothesis generating)

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Clinical Model: Early Stage Lung CA

- Risk groups based on surgery
- 3 broad groups:
  - Average Risk
    Generally can tolerate removal of an entire lobe
  - High Risk
    Can tolerate partial removal of a lobe
  - Medically Inoperable
    Cannot tolerate surgery for lung cancer

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Medically Inoperable Lung Cancer

- **Generally, frail patients**

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3-5 Year Outcome in Early Stage Lung Cancer

	Rx Modality	% alive
• Stage I	Surgery	60-80%
Stage I*	Conventional XRT	15-45%

	Rx Modality	% LC
• Stage I	Surgery	60-90%
Stage I	Conventional XRT	15-45%

*clinically staged and mostly medically inoperable
(significantly confounded by those who refused surgery)

Conventional RT generally 60-66 Gy delivered in 6-7 weeks

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SABR in Early Stage NSCLC

- First prospective trials were in medically inoperable patients with stage I NSCLC
- Intent, originally, was to improve tumor control
  - probably at the expense of increased toxicity
- Experience has been that tumor control is improved and treatment is surprisingly well tolerated

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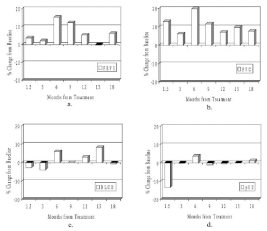
Extracranial Stereotactic Radioablation*

Results of a Phase I Study in Medically Inoperable Stage I Non-small Cell Lung Cancer

Robert Timmerman, MD; Lech Papiez, PhD; Ronald McGarry, MD; Laura Likes, RT; Colleen DesRosiers, MS; Stephanie Frost, MS; and Mark Williams, MD

(CHEST 2003; 124:1946–1955)

- **Classic phase I design**
- **Low starting dose 8 Gy X 3 = 24 Gy**
- **3 separate tumor size categories**
- **Dose escalation to very high doses 20-24 Gy X 3 = 60-72 Gy**



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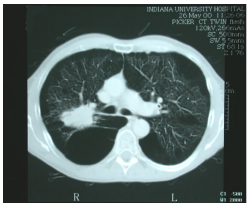
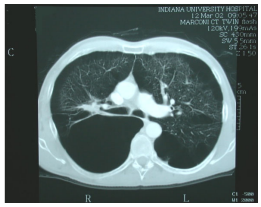
Indiana Univ. Phase I Trial





Pre-Treatment

22 mo. Post-Treatment

12 Gy X 3 = 36 Gy

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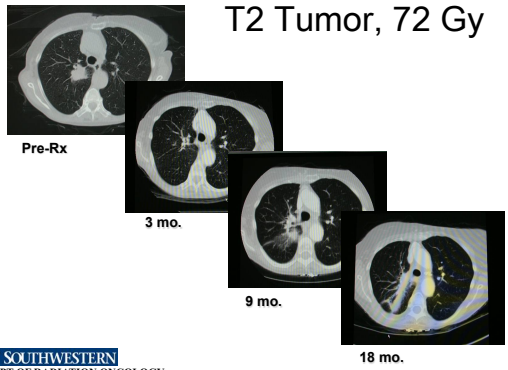
T2 Tumor, 72 Gy



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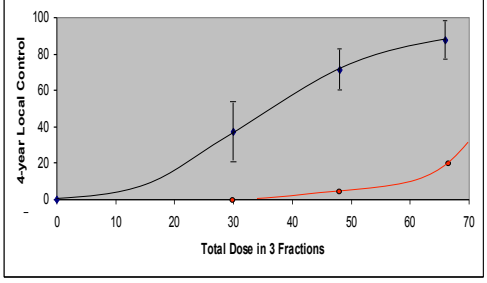
Dose Response



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VOLUME 24 · NUMBER 30 · OCTOBER 20 2006
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Conssentin Yiannoutsos, Lech Papiez, Kayley Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

- IU 70 patient phase II study
- 20 Gy X 3 for T1
  22 Gy X 3 for T2
- NO restriction on tumor location

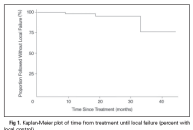

Fig 1. Kaplan-Meier plot of time from treatment until local failure (percent with local control).

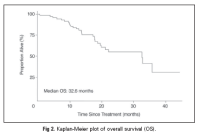

Fig 2. Kaplan-Meier plot of overall survival (OS).

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Zone of the Proximal Bronchial Tree

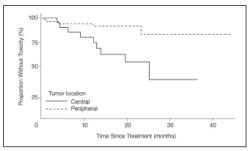
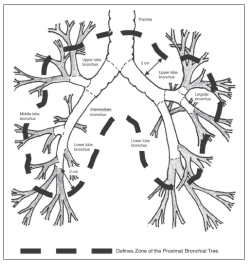


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

- Increased pneumonia, hypoxia, decline in PFT, and even death
- Likely related to impairment of pulmonary toilet at the junction between sterile and non-sterile bronchi



Defines Zone of the Proximal Bronchial Tree

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RTOG 0236

- Non-small cell lung cancer - biopsy proven

Only invasive step

- T1, T2 (≤ 5 cm) and T3 (chest wall only, ≤ 5 cm), N0, M0 Staging was non-invasive (PET/CT)
- Medical problems preclude surgery (e.g. emphysema, heart disease, diabetes)
- No other planned therapy

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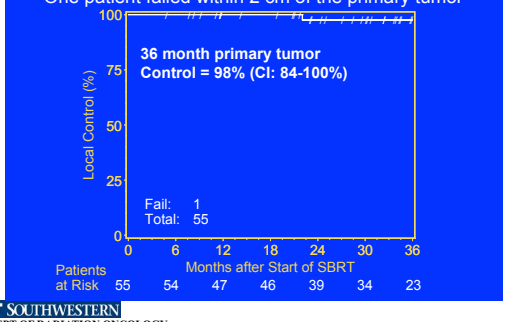
Primary Tumor Control

One patient failed within 2 cm of the primary tumor



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Local Control

- Local recurrence is primary tumor failure and/or failure within the involved lobe of the lung
- 1 patient had primary tumor failure
  +
  3 patients had failure within the involved lobe
- 3-year Kaplan Meier local control = 90.7%

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Regional Recurrence

- 2 patients have reported a regional failure, both after 2 years (2.8 and 3.0 years)
- Patients avoiding both local and regional recurrence (loco-regional control) is 87.2%

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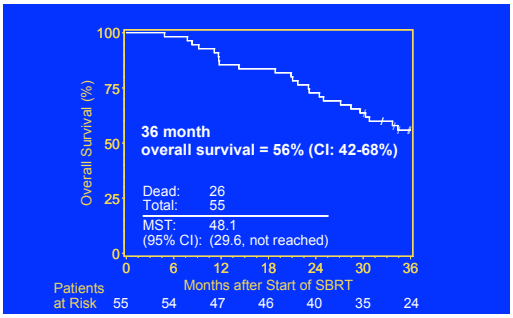
Overall Survival



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Severe Toxicity

- No grade 5 toxicities (treatment deaths)
- Two (4%) grade 4 protocol specified toxicity (decline in PFTs to <25% predicted & hypocalcemia)
- Seven (13%) grade 3 protocol specified toxicities

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Protocol Specified Grade 3 Toxicities

- 1 patient: low oxygen in blood (O_2 required)
- 2 patient: radiation inflammation of lung (O_2 required)
- 3 patients: decline in pulmonary function, (25-50% of predicted value)
- 1 patient: decline in pulmonary function and cough

= 7 patients (all pulmonary toxicity)

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JAMA

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

Robert Timmerman; Rebecca Paulus; James Galvin; et al.

JAMA. 2010;303(11):1070-1076 (doi:10.1001/jama.2010.261)

- SABR has become a standard of care for medically inoperable patients
  - Up to 10,000 patients per year in US
- Successful clinical model using hypofractionated radiotherapy:
  - Rigorously conducted, highly scrutinized
  - Multicenter QA
  - Rapid acceptance

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Multicenter Phase II Trials Medically Inoperable

- Dutch Investigators
  - 206 patients with Stage I
  - Risk adapted approach well tolerated
  - Primary tumor recurrence 3%, regional failure 9%, 2 year OS 64%

- JCOG 0403
  - Peripheral T1a, N0, M0
  - 100 patients – still enrolling

- Nordic Study Group
  - peripheral T1-T2, N0, M0
  - completed accrual of 57 patients 9/2005
  - Primary tumor recurrence 7%, 2 year OS 65%

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VOLUME 28 · NUMBER 35 · DECEMBER 10 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Impact of Introducing Stereotactic Lung Radiotherapy for Elderly Patients With Stage I Non–Small-Cell Lung Cancer: A Population-Based Time-Trend Analysis

David Palma, Otto Visser, Frank J. Lagerwaard, Jose Belderbos, Ben J. Slotman, and Suresh Senan

- Next best thing to a phase III randomized trial
  - Included all patients > 75 years old diagnosed with stage I lung cancer in Amsterdam
- 875 patients analyzed in 3 eras
  - 1999-2001 (pre SABR), 2002-2004 (some SABR), 2005-2007 (full SABR access)
- 299 patients got surgery, 299 RT (conventional or SABR), 277 neither

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Dutch Population Study

- From 1999 to 2007, utilization of RT increased significantly, 26% to 42%
  - No change in surgery, corresponding change in those untreated
- Those getting SABR as a form of RT increased from 23% to 55%
- Median overall survival for all patients increased from 16 to 21 months
  - All of the improvement came from the RT treated group

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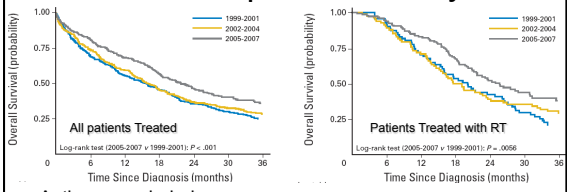
Dutch Population Study



- Authors concluded:
  - SABR increased utilization of RT in early stage lung cancer in elderly by 16%
  - Corresponding decrease in patients left untreated (reversal of nihilism)
  - SABR increased survival significantly (most plausible explanation)

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RTOG Strategies

- Refine SABR for medically inoperable patients
  - RTOG 0813 (Central Tumors – Bezjak, PI)
  - RTOG 0915 (Peripheral Tumors – Videtic/Chang, PIs)
    Completed accrual
- Explore use of SABR in "high risk" operable patient subset
  - RTOG 0618 (Peripheral Tumors – Timmerman, PI)
    Completed accrual
  - ACOSOG Z4099 / RTOG 1021
    Opened May 2, 2011

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"High Risk" Operable AKA "Marginally" Operable

Who are they?

- Poor cardiopulmonary (CP) reserve
- Will have difficulty during and after a lobectomy or pneumonectomy
  Getting off ventilator
  Getting out of hospital
  Readmissions
  Decreased vitality/quality of life post-resection ("Grandpa was never the same …")

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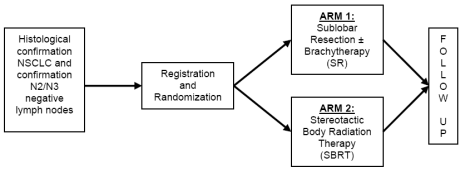
ACOSOG Z4099 / RTOG 1021

PIs: Hiran C. Fernando, MD (ACOSOG); Robert Timmerman, MD (RTOG)

Schema



Patients randomized to SABR will receive 18Gy in three fractions, for a total dose of 54Gy.
Brachytherapy is allowed with SR.
All registered patients will be followed for study endpoints, regardless of the status of their treatment. That includes patients receiving adjuvant therapy for any reason.

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Challenges

- Historical bias
  - Stage I NSCLC has been a "surgical disease"
- Disparate therapies
  - Incisions vs. non-invasive
  - Inpatient vs. outpatient
- Technically rigorous
  - Need established and effective QA for both Rx's

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Expanding SABR beyond the lung

- Lung cancer was the original clinical model
  - Established a new standard of care in medically inoperable population
- Could this approach be duplicated for other cancers in need of higher cure rates?
  - Metastases to the liver and lung
  - Pancreas
  - Etc.
- What about palliation?
  - Spine

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Curative Treatment of Metastases: A new (huge) indication for radiotherapy?

- Not talking about palliation at end of life
- Conventional fractionated radiotherapy has little role
  - Field size and volumes much too large (too toxic)
  - Attempts to use CFRT in liver mets (Hopkins, Univ of Michigan were unimpressive)
- Focused, ablative treatments using oligofractionation have promise
  - Basis in surgical resection
  - Some patients are clearly "cured"

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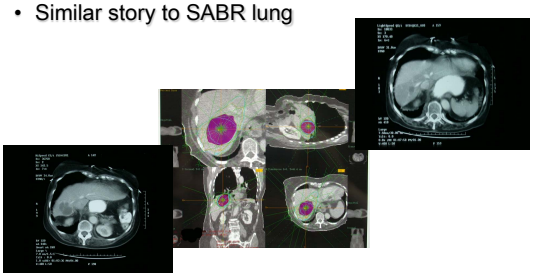
Liver Metastases

- Similar story to SABR lung



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A PHASE I TRIAL OF STEREOTACTIC BODY RADIATION THERAPY (SBRT) FOR LIVER METASTASES

Tracey E. Schefter, M.D.,* Brian D. Kavanagh, M.D., M.P.H.,* Robert D. Timmerman, M.D.,† Higinia R. Cardenes, M.D.,‡ Anna Baron, Ph.D.,§ and Laurie E. Gaspar, M.D., M.B.A.*

Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 5, pp. 1371–1378, 2005

- Multicenter prospective dose finding study
- Opened late 2001
- 3 fractions starting at 36 Gy
  - Waiting periods for toxicity
  - Introduced 'critical volume' liver constraint
- Variety of tumor histologies (mostly CRC)
- 18 patients enrolled to 5 levels up to 60 Gy (20 Gy per fraction)
  - No dose limiting toxicity (MTD not reached)

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

- 63 lesions in 47 patients
- 3 fraction regimen
- Poor risk group at entry:
  - 40% multiple
  - Most on 2nd and 3rd line systemic therapy
  - 45% had extrahepatic disease at study entry
- Median follow-up 16 months (6-54 months)

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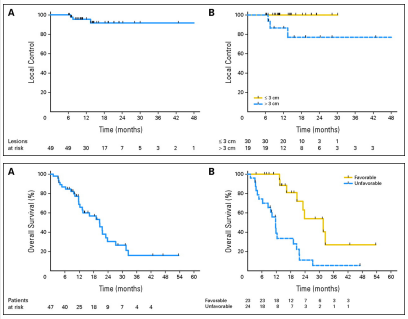
Multi-Institutional Phase II Trial



- Median tumor dimension = 2.7 cm
- Favorable: breast, renal, colorectal, carcinoid, and sarcoma
- One patient with grade ≥3 toxicity

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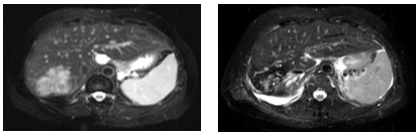
Rusthoven, K. E. et al. J Clin Oncol; 27:1572-1578 2009

UTSW 5-fraction Trial Schema



Dose Levels	Total Dose / Dose per Fraction	Number of Patients
I	30 GY / 10 GY*	9
II	50 GY / 10 GY	9
III	60 GY / 12 GY	9

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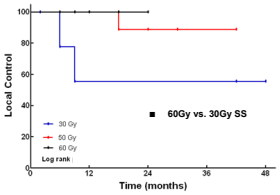
UTSW Results – Local Control

- Median Follow-Up: 20 Months (Range: 6-53 Months)



- 12 Month & 24 Month local control
  - 30Gy → 56% & 56%
  - 50Gy → 100% & 89%
  - 60Gy → 100% & 100%

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Stanford Experience

- Koong, et al, have published several reports using single fraction in pancreatic cancer
- Also have 18 month median follow-up on a phase II study in mostly CRC liver metastases with 30 Gy single fraction
- Recently published communication that 2 year local control is 80+% with no dose limiting toxicity

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UTSW Single Fraction Trial

Eligible patient → CT +/- MRI Simulation: -Treatment Planning → SABR 1 Fraction → Follow for toxicity and efficacy.

No. Fractions	Dose per fraction (Gy)	Total Dose (Gy)	No. Patients
1	35	35	7-15
1	40	40	7-15
1	45	45	7-15
1	50	50	7-15

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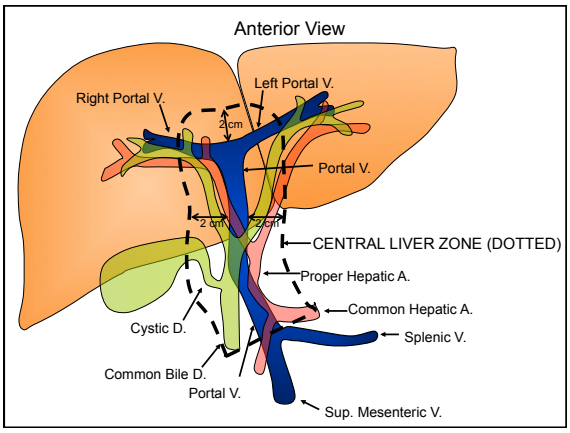

Lung Metastases

- Same story as in liver metastases
- Lung metastases are likely more radioresistant than primary lung cancer
- Lung metastases patients have healthier lungs than primary lung cancer
- University of Colorado consortium published phase I and II data

Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol* 2009;27:1579–1584.

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Spine Metastases

- Potential benefits
  - High and more durable local control
  - Faster pain relief
  - Potential for retreatment
  - Possibly reverse effects of cord compression
- Difficulties
  - Logistically difficult as an emergency therapy
  - Expensive compared to simple beams

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RTOG 0631 (Ryu, PI)

- Phase II/III trial in spinal metastases
  - Primary endpoint early complete pain relief (90 days)
- Phase II completed with good compliance
- Phase III just starting
  - Compares SABR (16-20 Gy in single fraction) to RTOG standard 8 Gy in one
  - Strict cord constraints

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SABR as an alternative

- Some cancers already have good treatments (good control, good toxicity)
  - More difficult to show improvement
  - Can always be worse
- Breast cancer
  - SABR is convenient and may offer better cosmesis
- Prostate cancer
  - SABR is convenient and perhaps less costly

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Partial Breast

- Non-randomized
- NSABP/RTOG trial underway

Table 3 Cohort Studies Evaluating Hypofractionation for Partial Breast Irradiation

Study	Patients	Fractionation Schedule	Median Follow-up (mo)	Local Recurrence (%)	Cosmetic Outcome (% excellent/good)
Vicini et al, 2007[39]	91	34 to 38.5 Gy/10 fractions/5 days	24	0	90
Wernicki et al, 2006[40]	78	30 Gy/5 fractions/10 days	28	0	92
Leonard et al, 2007[41]	55	34.–38.5 Gy/10 fractions/ 5 days	10	0	98
Kozak et al, 2006[42]	20	32 CGE/8 fractions (protons)	12	0	100
Vicini et al, 2005[43]	51	38.5 Gy/10 fractions/5 days	NR	NR	NR
Olivotto et al, 2006[44]	93	35 to 38.5 Gy/10 fractions/5 to 8 days	6	NR	NR

CGE = cobalt gray equivalent; NR = not reported.

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UTSW SABR Partial Breast Trial

- Phase I dose optimization
  - 5 fraction regimen starting at 6 Gy per fraction
- Uses a robotic linac
  - Favorable beam trajectories for anterior target
  - Fiducial tracking
- Surgically cavity with 1.5 cm expansion in most directions
- Careful evaluation of cosmetic results

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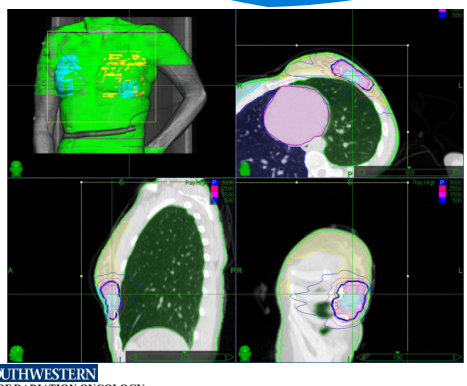

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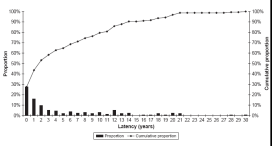
Breast: ? Problems with Hypofractionation

Acta Oncologica, 2009; 48: 822–831

Hypofractionation in radiotherapy. An investigation of injured Swedish women, treated for cancer of the breast

STEN FRIBERG[1] & BENGT-INGE RUDÉN[2]

For many of the women in our report, hypofractionated radiotherapy turned their lives into a disaster. They have been physically severely handicapped, some have had their careers ruined, their social relations diminished, some have had their marriages destroyed, and their economy devastated. Most of them have developed excruciating and drug-resistant pain.



- Most treated before 1980 (prior to CT planning)
- Mostly related to brachial plexopathy
  - 2 Gy equivalent dose exceeded 146 Gy per LQ model (e.g., 6 Gy X 13)
  - 6 Gy X 13 has a SFED of 20-28 Gy (for SABR, we limit SFED to 16-18)

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Prostate

- Hypofractionation has equivalent results to CFRT

TABLE 1. Hypofractionation Trials: Schedules and Equivalent Doses in 2 Gy Fractions

References	No. Pts	Dose/Fx Size/No. Fxs	Total Equivalent Dose in 2 Gy Fractions (EQD$_2$) α/β = 1.5 (Tumor)	α/β = 3 (Late Effects)	Med. F/U (mo)	Intermed. Risk % bDFS	≥Grade 2 Late Toxicity (%) GI	GU
Livsey et al[43] Manchester	705	50 Gy/3.13 Gy/16 fx	66 Gy	61.3 Gy	60	56 (5 yr)	5	9
Akimoto et al[44] Gamma	52	69 Gy/3 Gy/23 fx	88.7 Gy	82.8 Gy	33	—	25	—
Tsuji et al[45] Chiba	201	66 Gy/4 F/2.5 Gy/E/20 fx (carbon ions)	90.5 Gy	83.1 Gy	10	97	2	6
Higgins et al[46] Edinburgh	300	52.5 Gy/2.625 Gy/20 fx	61.9 Gy	59.1 Gy	12	55	—	—
Soete et al[47] Jette, Belgium	36	56 Gy/3.5 Gy/16	80 Gy	72.8 Gy	—	—	—	—
Martin et al[48] Princess Margaret	92	60 Gy/3 Gy/20 fx	77.2 Gy	72 Gy	36	85	4	3
Kupelian et al[49,50] Cleveland Clinic	770	70 Gy/2.5 Gy/28 fx	80 Gy	77 Gy	45	85	4.5	5.3
Ritter et al[51] Wisconsin	100	64.7 Gy/2.94 Gy/22 fx	82.6 Gy	77 Gy	38	95	8.5	1
	100	58.1 Gy/3.63 Gy/16 fx	85.1 Gy	77 Gy	24			
	80 (active)	51.6 Gy/4.3 Gy/12 fx	85.3 Gy	75 Gy	14			
Lukka et al[52] NCIC	466	52.5/2.625 Gy/20 fx	61.9 Gy	59.1 Gy	68	40	1.3	1.9
	470	66 Gy/2 Gy/33 fx	66 Gy	66 Gy				
Yeoh et al[54] Adelaid	108	55 Gy/2.75 Gy/20 fx	66.8 Gy	63.2 Gy	48	57.4	Alternate scoring	Alternate scoring
	109	64 Gy/2 Gy/32 fx	64 Gy	64 Gy		55.5		
Pollack et al[56] Fox Chase	150	70.2 Gy/2.7 Gy/26 fx	84.2 Gy	80 Gy	—	—	—	—
	150	76 Gy/2 Gy/38 fx	76 Gy	76 Gy				
RTOG www.rtog.org/members/protocols/0415/0415.pdf	Ongoing (to 1067 pts)	70 Gy/2.5 Gy/28 fx	80 Gy	77 Gy	—	—	—	—
		73.8 Gy/1.8 Gy/41 fx	69.6 Gy	70.8 Gy				
Khoo et al[58] MRC	Ongoing (to 2100 pts)	57 Gy/3 Gy/19 fx	73.3 Gy	68.4 Gy	—	—	—	—
		60 Gy/3 Gy/20 fx	77.2 Gy	72 Gy				

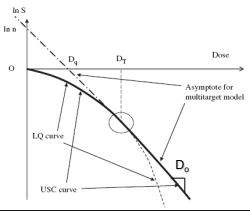
From Ritter et al Semin Radiat Oncol 18:249-256 © 2008

What is the α/β for prostate cancer?

- Some have made a career addressing this question
- Alpha and beta describe the radiation survival curve specifically within the shoulder region
- Hypofractionation is a treatment delivered near or beyond the shoulder region
  - Alpha and beta affect treatments near BUT not beyond the shoulder
- If SABR is delivered past the shoulder, then α/β is IRRELEVANT
  - All that matters beyond the shoulder is D_o

Treatment Near or Beyond "Shoulder"

- Multi-target model
  - D_q (x-intercept – shoulder width)
  - D_0 (slope – sensitivity beyond shoulder)
- Even more precisely, per Park, et al., (Universal Survival Model)
  - The "Transition Dose" between LQ (realm of repair) and pure target theory
  - $D_T = \frac{2 \cdot D_q}{1 - \alpha \cdot D_0}$



"Hypofractionation" Varies

Shoulder Broadness

Tissue Type	D_q (Gy)	D_T (Gy)	D_0 (Gy)
H460 (NSCLC)	1.8	6.13	1.25
DU-145 (Prostate CA)	1.91	3.55	1.91
PC-3 (Prostate CA)	1.02	4.22	1.06
Squamous CA (oxic)	4.89	16.01	1.06
Squamous CA (hypoxic)	22.82	84.98	1.58
Brain	10.23	22.39	1.2
Bone	8.4	18.96	1.67
Gut	7.61	21.54	1.64
Skin	2.7	6.84	1.11
Connective Tissue	4.24	9.74	1.49
Kidney	0.46	1.8	1.46

Ease of kill beyond shoulder

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SABR in Prostate Cancer

- Mix of low and intermediate risk
- Madsen dose seems too low
- Perhaps highest UTSW dose is too high
- ? What is just right

References	No. Pts	Dose/Fx Size/No. Fxs	Total Equivalent Dose in 2 Gy Fractions (EQD_2) $\alpha/\beta = 1.5$ (Tumor)	$\alpha/\beta = 3$ (Late Effects)	Med. F/U (mo)	≥Grade 2 Late Toxicity (%) GI	GU
Madsen et al[39] Virginia Mason	40	33.5 Gy/6.7 Gy/5 fx	78 Gy	64.9 Gy	41	7.5	20
King et al[41] Stanford	41	36.25 Gy/7.25 Gy/5 fx	90.6 Gy	74.3 Gy	33	15	29
Widmark (personal communication, 2008) Umea	105	42.7 Gy/6.1 Gy/7 fx	92.7 Gy	77.7 Gy	—	—	—
Tang et al[33] Univ. Toronto	30	35 Gy/7 Gy/5 fx	85.1 Gy	70 Gy	12	13	13
Timmerman (personal communication, 2008) UTSW, Dallas	15	47.5 Gy/9.5 Gy/5 fx	149 Gy*	118 Gy	—		—
	10 (ongoing)	50 Gy/10 Gy/5 fx	164 Gy	130 Gy			
	—	52.5 Gy/10.5 Gy/5 fx	180 Gy	142 Gy			

*The EQD_2 doses based on linear quadratic modeling may overpredict the biologically equivalent dose for large fractions, as in the University of Texas Southwestern trial.

From Ritter et al Semin Radiat Oncol 18:249-256 © 2008

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Freeman and King Radiation Oncology 2011, 6:3
http://www.ro-journal.com/content/6/1/3

RADIATION ONCOLOGY

Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes

Debra E Freeman[1*], Christopher R King[2]

- 2 centers pooled data
  - Low risk patients
  - 35-36.25 Gy in 5 fractions using Cyberknife

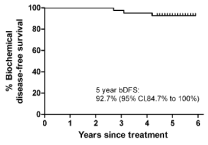

Figure 1 Kaplan-Meier biochemical disease-free survival curve after SBRT for prostate cancer. Median follow-up is 5-years. Three of the 41 patients recurred, at 33, 37 and 42 months post-treatment. Tick marks indicate censored patients.

Table 1 Late urinary and rectal toxicity on the RTOG scale for prostate cancer patients after SBRT

RTOG Grade	I	II	III	IV
Urinary	25% (10/41)	7% (3/41)	2.5% (1/41)	0%
Rectal	13% (6/41)	2.5% (1/41)	0%	0%

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.31.4377

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Dose-Escalation Study of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer

Thomas P. Boike, Yair Lotan, L. Chinsoo Cho, Jeffrey Brindle, Paul DeRose, Xian-Jin Xie, Jingsheng Yan, Ryan Foster, David Pistenmaa, Alida Perkins, Susan Cooley, and Robert Timmerman

- Dose escalation in the higher ranges
  - Low and intermediate risk
  - Used daily enema and daily rectal balloon
  - Safely escalated to 45, 47.5, and 50 Gy in 5 fractions using linac
- Currently enrolling to Phase II trial
  - Margins are down to 2 mm per image guidance

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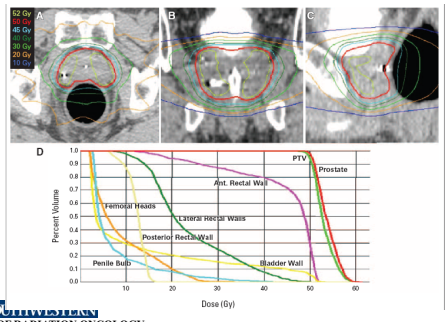
SABR Prostate Dosimetry



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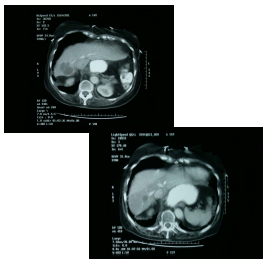
Hypofractionation: Then and Now



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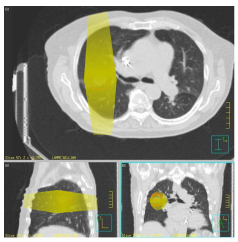
Conventional Radiation vs. SBRT Dosimetry



Targets (blue - GTV, red -PTV)

Postage Stamp

6000 cGy (script dose)

SBRT

A paradigm changing difference!

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Tumor Burden In Oncology

- Piles of bricks
  - Microscopic disease (1-8 logs)
  - Small volume gross disease (8-9 logs)
  - Bulky gross disease (>9 logs)

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Definitive Surgery

T

N

M

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Definitive Radiotherapy

T -

N -

M

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Definitive Systemic Therapy

T

N

M -

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Future Definitive Surgery

T -

N -

M

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Future Definitive Radiotherapy

T -

N -

M -

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Future Definitive Systemic Therapy

T -

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Conclusions

- SABR for primary lung cancer is effective and tolerable
  - Prospectively studied by hypothesis driven clinical trials
  - Encouraging and reproducible results
- Building on the primary lung experience, primary and metastatic tumors of the liver and metastatic tumors of the lung constitute a new indication for radiotherapy
- Spine metastases are being evaluated in a phase III trial
- Bread and butter indications (prostate and breast) need to show lack of downsides (since upsides are less likely) prior to general acceptance

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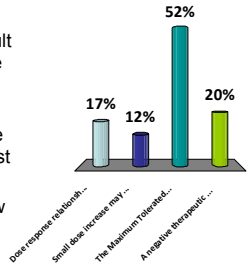
Which of the following statements regarding dose response relationships for ablative radiotherapy delivery is FALSE

1. Dose response relationships are best determined by phase I clinical trials
2. Small dose increase may result in large toxicity increase in the transition range of the dose response curve.
3. The Maximum Tolerated Dose (MTD) corresponds to the most ideal therapeutic ratio.
4. A negative therapeutic window results when efficacy is less likely than harm.

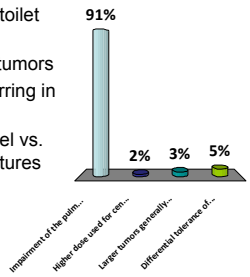


The Maximum Tolerated Dose (MTD) corresponds to the most ideal therapeutic ratio

- The only variable in a phase I trial is dose making it an ideal platform for studying dose response effects. The slope of the dose response curve is greatest in the transition region. In contrast to most chemotherapy regimens, the widest therapeutic window for SABR in lung cancer occurred at a dose considerably lower than the MTD (slide 10). If response curves for efficacy and toxicity cross (e.g., at higher dose levels), the therapeutic window will be negative.
- Ref: Timmerman RD, Park C, Kavanagh BD. The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. J Thorac Oncol 2007;2:S101-12

Early stage lung cancer was the most common clinical model studied in clinical trials testing SABR at centers across the world. The Indiana University trials demonstrated that treatments in the central chest were problematic for patients to tolerate likely related to:

1. Impairment of the pulmonary toilet function of the central chest.
2. Higher dose used for central tumors
3. Larger tumors generally occurring in the central chest
4. Differential tolerance of parallel vs. secular defined thoracic structures



Impairment of the pulmonary toilet function of the central chest

- Proximal airways facilitate the clearing of secretions within the lung by their expectorant and ciliary functions (slide 26). The Indiana University phase II trial used a narrow range of highly potent 3 fraction dose levels. Toxicity was observed both for T1 and T2 tumors. Ablative dose treatment shows distinct response between parallel and serial (not secular) structures.
-
- Ref: Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer

Based on published reports, what factors would be most concerning for increased risk of toxicity after SABR?

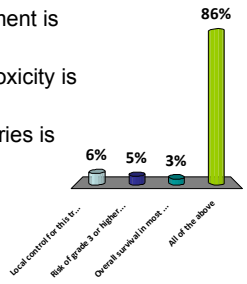
13% 1. impaired spirometry
2% 2. peripheral lung location
80% 3. impaired DLCO
6% 4. advanced age

impaired DLCO

- Published reports indicate that DLCO is compromised more than spirometry after SBRT[2] (slide 21). The opposite is true for surgical resections.
- Ref: 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;124:1946-55.

The following are true statements about the outcome of patients with early stage lung cancer treated with SBRT?

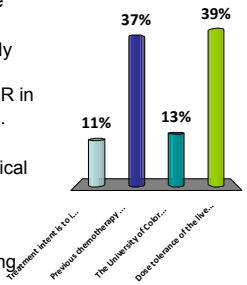
1. Local control for this treatment is predicted to be >80%.
2. Risk of grade 3 or higher toxicity is around 20% at 3 years.
3. Overall survival in most series is 60-75% at 2 years.
4. All of the above



All of the above

The rationale and conduct for SABR treatment in metastatic cancer to the liver includes all of the following except:

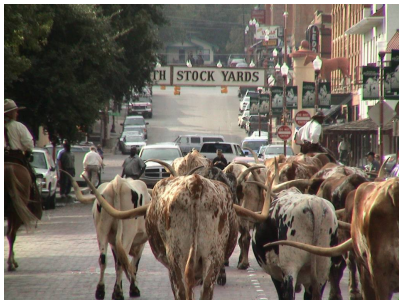
1. Treatment intent is to improve survival, even cure.
2. Previous chemotherapy clearly limits tolerance and is a contraindication to using SABR in patients with liver metastases.
3. The University of Colorado multicenter trials used the critical volume methodology to avoid liver toxicity
4. Dose tolerance of the liver is similar to treatments in the lung.



Previous chemotherapy clearly limits tolerance and is a contraindication to using SABR in patients with liver metastases.

- Patients with oligometastases from metastatic cancers (e.g., colorectal cancer) can be cured with metastectomy. Most patients treated in clinical trials testing SABR had already progressed after 1st and 2nd line (even 3rd line) chemotherapy (slide 47). The critical volume is the volume of organ necessary to avoid a defined clinical insufficiency. The critical volume must be spared (ie, not exceed) a threshold dose. The University of Colorado studies used this model allowing dose escalation to potent tumorcidal dose, similar to the Indiana University phase I/II studies in lung cancer.

Happy Trials!



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