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?

1. Impaired spirometry (24%)
2. Peripheral lung location (14%)
3. Impaired DLCO (16%)
4. Advanced age (16%)

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

---

Dose Response

- Effect
- Probability
- DOSE OF RADIATION

- Minimal response
- Dramatic effect
- Threshold
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

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

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
Clonagenic Survival

High Risk Hypothesis
LATE radiation toxicity: ulceration, denervation, devascularization, stenosis, fibrosis, devitalization

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)
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

Medically Inoperable Lung Cancer

- Generally, frail patients

<table>
<thead>
<tr>
<th>3-5 Year Outcome in Early Stage Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx Modality</td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage I*</td>
</tr>
</tbody>
</table>

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

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

Extracranial Stereotactic Radioablation

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

Robert Stovner, MD, Joel S. Reznick, MD, Donald McCarty, MD

(CHEST 2003, 124:1506-1513)

- 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

Indiana Univ. Phase I Trial

Pre-Treatment
12 Gy X 3 = 36 Gy

22 mo. Post-Treatment
T2 Tumor, 72 Gy

Dose Response

- IU 70 patient phase II study
- 20 Gy X 3 for T1
- 22 Gy X 3 for T2
- NO restriction on tumor location
Zone of the Proximal Bronchial Tree

- 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

RTOG 0236
- Non-small cell lung cancer - biopsy proven
- 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

Primary Tumor Control
- One patient failed within 2 cm of the primary tumor
- 36 month primary tumor control = 98% (CI: 84-100%)
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%

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%

Overall Survival

- 36 month overall survival = 56% (CI: 42-68%)
- Dead: 26
  - Total: 55
  - MST: 48.1 (95% CI): (29.6, not reached)
  - 36 month overall survival = 56% (CI: 42-68%)
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

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)

Stereotactic Body Radiation Therapy (SABR) is a protocol of radiation therapy that 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

SABR has become a standard of care for medically inoperable patients: Early Stage Lung Cancer

Multicenter Phase II Trials Medically Inoperable

- Dutch Investigators
  - 208 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%

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

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
DEPT OF RADIATION ONCOLOGY

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)

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

“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 …”)
ACOSOG Z4099 / RTOG 1021

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

Sequence:
- Histological confirmation
- NSCLC and confirmation technical negative lymph nodes
- Registration and randomization
- Arm 1: Autologous Radiation Therapy (ART)
- Arm 2: Observation, Body Radiation Therapy (SBRT)

Patients randomized to SABR will receive 18Gy in three fractions, for a total dose of 54Gy. Brachytherapy is allowed with SBRT. 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.

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

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
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”

Liver Metastases

- Similar story to SABR lung

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

Tracy E. Schiffer, M.D.,* Brian D. Kavanagh, M.D., M.P.H.,† Robert D. Thompson, M.D.,‡ Roberta R. Carlini, M.D.,§ Anna Burton, Ph.D.,□ and Larue F. George, M.D., M.B.A.*†


- 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)
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)

Multi-Institutional Phase II Trial
Median tumor dimension = 2.7 cm.
Favorable: breast, renal, colorectal, carcinoid, and sarcoma
One patient with grade ≥3 toxicity

UTSW 5-fraction Trial Schema

<table>
<thead>
<tr>
<th>Dose Levels</th>
<th>Total Dose / Dose per Fraction</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>30 GY / 10 GY*</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>50 GY / 10 GY</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>60 GY / 12 GY</td>
<td>9</td>
</tr>
</tbody>
</table>
**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%

**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

**UTSW Single Fraction Trial**

<table>
<thead>
<tr>
<th>No. Fractions</th>
<th>Dose per fraction (Gy)</th>
<th>Total Dose (Gy)</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>35</td>
<td>7-15</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>40</td>
<td>7-15</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
<td>7-15</td>
</tr>
</tbody>
</table>
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

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
**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

**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

**Partial Breast**

- Non-randomized
- NSABP/RTOG trial underway

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Fractionation</th>
<th>Median</th>
<th>Local</th>
<th>Distant (Brain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vran et al.</td>
<td>90</td>
<td>18 x 5 Gy 30%</td>
<td>30</td>
<td>14%</td>
<td>80%</td>
</tr>
<tr>
<td>Meyer et al.</td>
<td>70</td>
<td>30 x 1.5 Gy 30%</td>
<td>30</td>
<td>14%</td>
<td>80%</td>
</tr>
<tr>
<td>Langer et al.</td>
<td>90</td>
<td>30 x 1.6 Gy 30%</td>
<td>30</td>
<td>14%</td>
<td>80%</td>
</tr>
<tr>
<td>Kaur et al.</td>
<td>30</td>
<td>15 x 2 Gy 30%</td>
<td>10</td>
<td>10%</td>
<td>100%</td>
</tr>
<tr>
<td>Groome et al.</td>
<td>60</td>
<td>20 x 2.5 Gy 30%</td>
<td>10</td>
<td>10%</td>
<td>100%</td>
</tr>
</tbody>
</table>

CIG = critical organ sparing, NS = not reported.
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

Breast: Problems with Hypofractionation

Also Oncology, 2009, 40, 322-333
Hypofractionation in radiotherapy: An investigation of injured Swedish women, treated for cancer of the breast

For many of the women in our report, hypofractionation turned their lives into a disaster. They have been physically severely handicapped, some have had their union raised, their social relations diminished, some have had their marriages destroyed, and their economy devastated. Most of them had developed excruciating and dispro-

tant 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)
Prostate

- Hypofractionation has equivalent results to CFRT

<table>
<thead>
<tr>
<th>Reference</th>
<th>α</th>
<th>β</th>
<th>Shoulder Width</th>
<th>D0</th>
<th>D1</th>
<th>D2</th>
<th>D1/D0</th>
<th>Shoulder Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritter et al.</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>1.2</td>
<td>Small lobe</td>
</tr>
<tr>
<td>許 &amp; 鄭</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>1.2</td>
<td>Large lobe</td>
</tr>
<tr>
<td>姚 &amp; 蔡</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>1.2</td>
<td>Large lobe</td>
</tr>
<tr>
<td>謝 &amp; 蘇</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>1.2</td>
<td>Large lobe</td>
</tr>
<tr>
<td>王 &amp; 鄭</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>1.2</td>
<td>Large lobe</td>
</tr>
</tbody>
</table>


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 D0

Treatment Near or Beyond “Shoulder”

- Multi-target model
  - Dq (x-intercept – shoulder width)
  - D0 (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

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>$D_1$ (Gy)</th>
<th>$D_2$ (Gy)</th>
<th>$D_0$ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H460 (NSCLC)</td>
<td>1.6</td>
<td>6.13</td>
<td>1.25</td>
</tr>
<tr>
<td>DU-145 (Prostate CA)</td>
<td>1.91</td>
<td>3.55</td>
<td>1.91</td>
</tr>
<tr>
<td>PC-3 (Prostate CA)</td>
<td>1.02</td>
<td>4.22</td>
<td>1.06</td>
</tr>
<tr>
<td>Squamous CA (oxic)</td>
<td>4.89</td>
<td>16.01</td>
<td>1.06</td>
</tr>
<tr>
<td>Squamous CA (hypoxic)</td>
<td>2.82</td>
<td>84.98</td>
<td>1.58</td>
</tr>
<tr>
<td>Brain</td>
<td>10.23</td>
<td>22.56</td>
<td>1.2</td>
</tr>
<tr>
<td>Bone</td>
<td>8.4</td>
<td>18.96</td>
<td>1.67</td>
</tr>
<tr>
<td>Gut</td>
<td>7.61</td>
<td>21.54</td>
<td>1.64</td>
</tr>
<tr>
<td>Skin</td>
<td>2.7</td>
<td>6.84</td>
<td>1.11</td>
</tr>
<tr>
<td>Connective Tissue</td>
<td>4.24</td>
<td>9.74</td>
<td>1.49</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.46</td>
<td>1.8</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Shoulder Broadness

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

From Ritter et al. Semin Radiat Oncol. 18:240-256 © 2008

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

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

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

<table>
<thead>
<tr>
<th>RTOG Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative</td>
<td>20%</td>
<td>15%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Rectal</td>
<td>15%</td>
<td>10%</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

From Ritter et al. Semin Radiat Oncol. 18:240-256 © 2008
Phase I Dose-Escalation Study of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer

- 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

SABR Prostate Dosimetry

Hypofractionation: Then and Now
Conventional Radiation vs. SBRT Dosimetry

Postage Stamp  SBRT
A paradigm changing difference!

Tumor Burden In Oncology

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

Definitive Surgery

T
N
M
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
Acknowledgements

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  - Hak Choy, M.D.
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  - Michael Dimiao, M.D.
- UTSW Med Onc.
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  - David Gerber, M.D.
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  - Rebecca Paulus, Ph.D.
  - Linda Walters, M.S.
- RTOG Collaborators
  - Jeff Bradley, M.D.
  - Harvey Pass, M.D.
- RPC
  - Geoff Ibbott, Ph.D.
  - David Followill, Ph.D.
- ATC/ITC
  - Jeff Michalski, M.D.
  - Walter Bosch, Ph.D.
  - Bill Straube, Ph.D.

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.
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?

- 33% impaired spirometry
- 3% peripheral lung location
- 80% impaired DLCO
- 6% advanced age
impaired DLCO

- Published reports indicate that DLCO is compromised more than spirometry after SBRT (slide 21). The opposite is true for surgical resections.

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.

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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.

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Happy Trials!