Stereotactic Ablative Radiotherapy (SAbR): Then, Now and in the Future

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Disclosures

- Research funding to UTSW
  - Varian Medical Systems
  - Elekta Oncology
  - Accuray, Inc.

- Scientific Advisory
  - D3 Corporation
SAbR is over 20!

- Hamilton spine treatment in Arizona using rigid immobilization
- Lax and Blomgren treating liver tumors at Karolinska (Sweden) in a stereotactic body frame
- Uematsu and Shirato in Japan understanding tumor motion in lung cancer
- All first presented in the 1990s

Our Early Beginnings

- 1994: Our first stereotactic treatments for lung cancer
- Joe Montebello (colleague at Indiana Univ) really championed brachytherapy
  - Would occasionally encounter an endobronchial obstruction by tumor
  - Would try to open the obstruction using early SAbR
- Not really an encompassing cancer treatment – more to facilitate brachytherapy
  - Brachy had a really good record for effective palliation
  - Mostly stage III patients (recurrent)
Tip of Bronchoscope is a “fiducial” defining a stereotactic Rx.
Parabolic Method Isodose Lines

1500 cGy  
1200 cGy (script)  
900 cGy  
600 cGy

More beams would make this better
Example of Karolinska input

Clever strategy to avoid normal tissue dose is to NOT TREAT IT (aka, conformal avoidance)
If several beams don’t treat it, then intermediate dose is improved

Conventional aperture

“Negative” margin

Strategies for Improving Intermediate Dose
Strategies for Improving Intermediate Dose

What dose should we use?

- Early on, it was a difficult question
  - No experience
  - Swedes were using different doses for different patients based on "judgement"

- ASTRO decided to define SAbR to be entire course of therapy in 5 or fewer fractions
  - Since we were from Indiana, we picked the middle – 3 fractions
  - All our initial studies stuck with 3 fractions

- Options
  - Phase I testing (evidence based medicine)
    - Independently assess a variety of dose levels and pick the best one
  - Expert consensus (eminence based medicine)
    - Perhaps converted from a biological model (e.g., LQ)
Approaches varied

- Most chose eminence based medicine
  - Karolinska picked 45 Gy in three (15 Gy) fractions
  - Kyoto picked 48 Gy in four (12 Gy) fractions
  - Several German groups picked 26-34 Gy in one fraction

- A few chose evidence based medicine
  - We designed a phase I study starting at 24 Gy in three fractions
  - Cleveland Clinic and Stanford jointly did a phase I study

- Our experience was simply terrifying!
  - Phase I study funded by a NIH R21 grant
  - Dose kept escalating without toxicity past 48 Gy in 3 fxs
  - We wanted to be quitters
  - NIH forced us to go on

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

Robert Traumann, MD; Leck Foyos, PhD; Ronald McGarry, MD; Laura Ikeda, RE; Colleen Balliro, MS; Stephanie Frost, MS; and Mark Williams, MD

*CHEST 2003; 124:1946–1953

- 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
Local Control

P = 0.01

Overall Survival

P = 0.93

Dose Levels
- 2400 to 3600
- 4200 to 5400
- 6000 to 7200

4-year Local Control

Approaching plateau of efficacy

Therapeutic Window

Dose Response

Total Dose in 3 Fractions
What to call it?

- Our first paper called it Extracranial Stereotactic Radioablation (ESR)
  - Good name, descriptive
  - Didn’t work out for political reasons

- ASTRO higher ups named it Stereotactic Body Radiation Therapy (SBRT)
  - This name really sucked
  - Not catchy, not descriptive,

- Billy Loo came up with Stereotactic Ablative Radiotherapy (SAbR)
  - This is a cool name, much better
  - “Can you SAbR the tumor?” … “Sure”

Mine’s bigger than yours…
Ablative Radiotherapy

- Surgical definition: a treatment that “destroys” or “burns”
- Radiotherapy definition: related originally to radioactive iodine treatments for thyroid cancer
  - Most cancer radiotherapy disrupts cellular division (clonogenicity)
  - Radioablative treatment ALSO disrupts cellular function
    - Stop production of thyroid hormone
    - Would have same effect on tumor hormone (e.g., PSA)
- Dose potency needed to disrupt cellular function is much higher than needed to stop mitosis

Do we need to ablate?

- Theoretically, NO, unless tumor function is problematic
  - e.g., hormonally active pituitary adenoma (acromegaly)
  - e.g., enlarging cystic masses
- But, likelihood of COMPLETE disruption of mitotic activity is more likely in the ablative dose range
- And, ablation is associated with “Threshold” effects
  - Tumor microenvironment effects
    - e.g., vascular effects
    - e.g., immune effects
- Importantly, there is ABSOLUTELY NO benefit to ablate functioning, surrounding normal tissue
Sigmoid Dose Response

- Plateau: Dose response minimal, Treatment Effect maximal
- Transition: Dose response maximal, Treatment Effect variable
- Threshold: Dose response minimal, Treatment Effect minimal

Deterministic Threshold Effects

- Effect #1 (DNA Damage)
- Effect #2 (?)

Probability of Response vs. DOSE PER FRACTION

- 0% to 100% Probability
- 2 Gy, 5 Gy, 10 Gy DOSE PER FRACTION
**A few (of many) threshold effects**

- Hallahan’s lab showed blood flow changes, decreased blood vessel density, and induction of endothelial apoptosis at 16 Gy

- Kolesnick/Fuks’ lab showed induction of ceramide related pathway resulting in tumor vascular injury at 10 Gy

- Fu/Weichselbaum’s lab showed induction of meaningful immune stimulation at 15 Gy

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**Ablative/Hypofractionated Radiotherapy 101**

- **Targets**
  - Abandon prophylactic treatment

- **High dose radiation must NOT treat (much) normal tissue**
  - Intermediate dose should be reduced, too

- **Beams**
  - Using MANY beams allows opportunities for conformal avoidance of high dose (3-D, IMRT)

- **Margins**
  - Small margins must be justified by image guidance, stereotaxy, and motion control
Conventionally Fractionated (2-D) Radiotherapy

- High dose is NOT conformal
- Intermediate and low dose are the same
- Margins can be fairly big
- Fractionation “forgives” the SLOPPINESS

Hypofractionated Radiotherapy

- High dose is conformal
- Intermediate dose is compact
- Low Dose is very large (low dose bath)
Rationale for Hypofractionated Dose Distribution

<table>
<thead>
<tr>
<th>Dose (cGy)</th>
<th>Normal Tissue Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>Low (&quot;safe&quot;)</td>
</tr>
<tr>
<td>3000</td>
<td>Intermediate (toxic)</td>
</tr>
<tr>
<td>6000</td>
<td>High (very toxic)</td>
</tr>
</tbody>
</table>

Proof of Concept – Brain SRS

- HYPO fx treatment in THE BRAIN (least tolerant tissue in body)
- 40 years of *positive* experience – the sky did *not* fall
More beams are better

Conformal arcs and multiple beams are generally more useful than IMRT

4-pi would even be better

Use “stereotactic” fields for ablative SAbR

• With modern equipment, adding more fields is NOT a significant burden
  – Not a burden for treatment planning or treatment

• Take advantage of the “stereotactic paradigm”
  – Trade larger low dose volumes for smaller high dose volumes
  – Toxicity primarily occurs in high dose regions

• Tissues respond according to a sigmoid dose/response relationship
  – Below a “threshold” dose, there is little or no toxicity
Low Dose Lung Toxicity

• Mary Graham showed V-20 associated with grade 2-5 pneumonitis
  – V-20 is the "threshold" dose

• 2006 MD Anderson showed V-5 > 42% had a 38% risk of pneumonitis for 3-D conformal therapy (mostly 4 fields)

• 2007 MD Anderson showed V-5 up to 70% had 2% risk of pneumonitis for IMRT (mostly 6 fields)

• RTOG 0617 settled this definitively… V5 (low dose) doesn’t matter
  – That’s good news since SAbR has lots of low dose

Conventionally Fractionated (2-D) Radiotherapy

• Intermediate and low dose are the same
Hypofractionated Radiotherapy

- Intermediate and low dose are NOT the same

Does this sound right? Planning Priorities

1. Respect the spinal cord constraint
   • Similar but negotiable priority for the brachial plexus

2. Cover the tumor conformally

3. Create "compactness" of dose

4. Respect other normal tissue constraints
Are these priorities sacrilegious (first, do no harm…)?

- We can never justify recklessness

- However, if you are in a position to control a deadly cancer with high probability…do it
  - Surgeons have been in this position
  - Historically, we have not been in this position

- Most normal tissue constraints, especially for SABR, are simply guesses

- Importantly, normal serial tissues can be injured (after exceeding “tolerance”), and still heal!
  - They were designed to do this
  - Surgeons are well aware of this fact

What if you exceed a Dose Constraint?

- What is the consequence?
  - Terrible Toxicity for the patient?
    - End of quality of life?

- What if you get caught?
  - Did you exceed Quantec, Enami, ?
  - Litigation, malpractice, loss of licensure, embarrassment, scandal, ruin

- Many have told me, “Maybe you can do these aggressive treatments at UTSW, but in the community there is no tolerance of toxicity.”

- BUT, in the community, lots of surgery gets done
  - Surgery injures serial tissue with every operation
Urethral Injury/Repair

- A TURP is effectively a near prostatectomy, retaining the capsule
  - Prostatic urethra is totally removed

- Yet, within a few months, the urethra grows back by second intention
  - Mucosa migrates down from the bladder
  - Up from the penile urethra

- Yet, within a few years, the prostate grows back by proliferation of residual remnants

Trans-anal Rectal CA Resection

- Occasionally used for smaller, more inferior early stage rectal cancers
  - Frail patients, etc
  - Full thickness excision

- Desirable to close horizontally, but open, full thickness defect will most commonly heal EVEN AROUND A FECAL STREAM
Medical Personalities

• Medical specialists attract, train, and foster their practitioners to create a “like-mindedness”
  – Solidifies a parochialism

• e.g., Surgeons MUST take risks
  – Not a field for wimps or the squeemish
  – To reach the full benefit, you must take and accept significant risks
  – “While the operation was a success, unfortunately, the patient died”

Medical Personalities

• Radiation oncologists are EXTREMELY risk adverse
  – It is atrocious for radiotherapy to cause a severe injury (likely a medical mistake)
  – The kind and gentle therapy for the medically frail

• This mind-set has STIFFLED progress as a curative therapy
  – Protons, IMRT, etc, were used for fractionated RT
  – True potential of radiotherapy only “scratched upon”
  – That is…until SAbR
A very unusual radiotherapy...

- Papillon technique for small, low rectal cancers
  - 50 KVP
    - 5mm dose is 60% of surface
    - Very little lateral penumbra
    - Direct visualization (optimal image guidance)
- Give 20-40 Gy per fraction q2 weeks for over 100 Gy
  - Likely left a defect in the rectal wall
- High control, little toxicity

Schema and Conduct

- Simulation
  - Implant fiducials
  - Gold/Calypso
  - Enema
  - Rectal balloon 60cc
  - Foley Cath.
  - +/- MRI

- Treatment
  - Daily image guidance
  - Daily enema
  - Daily rectal balloon
  - IMRT

Follow for toxicity and PSA control

CTV expanded 3mm to PTV
- Anterior rectal wall allowed 105% of prescription
- Strict dose limits to lateral and posterior rectal wall
- Urethra allowed 105% of prescription
Anoscope

Endoscopic View through Anoscope
Unexpected Realities

• At 45 Gy (hence also at >45 Gy), every patient had a demarcated “erosion” (ulcer) on the anterior rectal wall which healed in all cases in 3-6 months

• DVH constraints did not prevent the obvious injury
  – Compliance for dosimetry was 100%
  – Large majority were asymptomatic

• All patients were injured. Nonetheless, all patients at this dose level healed
  – This is sounding more like surgery than radiotherapy

Truth be told…

• Serial functioning tissue was DESIGNED to repair
  – This repair is aggressive and effective
  – BUT it can be overwhelmed

• Large volume high dose radiation bath has two problems:
  1. Large volumes are more likely to exceed radiation tolerance
  2. The resulting damage may not be repaired

• Small volume injuries are very different
  – Not much experience historically except with brachytherapy
  – Even extremely high doses can, indeed, HEAL!
Parallel functioning tissue

- Peripheral lung, liver, kidney
  - Tree analogy (leaves are the parallel functioning tissue)
- Each “functional unit” (leaf) is damaged at a relatively low dose
  - Damage is mostly all or none (functions or doesn’t function)
- Overall toxicity, however, is mostly volume dependant (number of leaves damaged rather than degree of damage to each leaf)

The Critical Volume

- The critical volume of organ parenchyma (parallel tissue) must be preserved
  - Avoid the toxic “threshold dose”
- Don’t forget, however, what every surgeon knows (surgery bubble)
  - THE CRITICAL VOLUME OF PARENCHYMA MUST MAINTAIN A CONNECTION TO THE BODY
    - tubes and wires – serial tissue
    - Serial tissue has a different tolerance and mode of repair than parallel
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

- Note: NO patient had massive hemoptysis
What was the mechanism of injury?

• Bronchial stenosis?
  − Unlikely, consequent lobar atelectasis was rare
    o Large airways are "propped open" by cartilage rings
  − We saw more sublobar atelectasis related to smaller airways in peripheral lung (no cartilage)

• SABR is ablative (disrupts function)
  − The function of the bronchial hilum
    o act as a conduit
    o carry out pulmonary toilet
  − Most likely, pulmonary toilet was impaired at the junction between sterile and non-sterile bronchi

60 Gy in 3 fractions

Pre-treatment Treatment planning One year post treatment

Post treatment bronchoscopy

Wedge-like collapse of segmental bronchus
No evidence of tumor recurrence on PET
No tumor cells on bronchial biopsy or brushings
Fly with Caution Zones

- Effectively, danger near any organ’s hilum

Abutting Targets/Serial Structures

Subvolume A: Try to strictly meet organ limits using IMRT
Subvolume B: Max dose no more than 90% of script dose

* Does NOT apply to spinal cord!
Re-alignment Maneuvers

• Initial acquisition

Re-alignment Maneuvers

• Final adjustment
Image guidance is useful only if acted upon

• Goal is to reduce margins
  – Targeting margins
  – Machine “slop”
  – Interfraction setup error
  – Intrafraction setup error

• Margins are not “bought” when purchasing the equipment
  – Based on performance in the hands of the user

• Collect data to assess performance
  – e.g., Van Herk, etc
  – If possible, reduce the margins

Primary sites for SAbR

▪ Lots of data for lung
  – Emphasis now is on an effective adjuvant
  – Maybe SAbR as a boost (billing code problem)

▪ Prostate
  – POTEN-C trial
  – Patients with intact prostates will vote with their feet

▪ Liver
  – Not radioresistant afterall

▪ Breast
  – CK and Gamma Pod

▪ Head and neck
  – Recurrence
  – Glottis

▪ GI
  – Pancreas
Primary Reason Therapy Fails

• METASTASES

• 20-30% of early stage lung cancer patients develop distant mets with follow-up
  – Even for T1 tumors
  – Occult at diagnosis- missed by staging exams including PET

• Crying need for an effective systemic therapy
  – Surgeons have collected tissue for predictive assays
  – Alas, medical oncologists have provided mostly impotent therapies

• A solution to this problem would be a GAME CHANGER!

Clinical Model: Metastatic Lung Cancer

• Newly diagnosed (1st Line)
  – Platinum doublet
  – Sometimes add anti-vascular or anti-EGFR

• Median progression free survival (when)
  – 3-4 months (Schiller, et al, NEJM 346, 92-8, 2002)

• Characterization of the progression
  – In addition to when, characterize where, why, and how
  – Perhaps find a rationale for SAbR
Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis

KYLE E. RUSTHOVEN¹, SUSAN F. HAMMERMAN², BRIAN D. KAVANAGH¹, MICHAEL J. BIRTWHISTLE², MARK STARES², & D. ROSS CAMIDGE²

Acta Oncologica, 2009; 48: 578-583

• Careful assessment of pattern of failure (POF)
  – E (existing sites) or N (new sites)
  – Brain mets scored separately

  91%

• E only failure in 64%, E+N in 27%, N only in 9%
  – 1st line therapy fails to control gross disease in 91%

• Over HALF of these E failures could be feasibly targeted with SAbR

Erlotinib in NSCLC

• EGFR Tyrosine kinase inhibitor

• FDA approved as 2nd line therapy for metastatic NSCLC (after platinum doublet)
  – Median PFS 2.3 months in patients unselected for mutation
  – Around 20% of patients have EGFR mutation

• Could these results be improved?

Shepherd et al, NEJM, 2005
UTSW/U Colo Erlotinib/SAbR Trial

**NSCLC**
1. Progressed after first line systemic therapy
2. ≤6 “sites”
3. eligible for erlotinib and SAbR to all lesions

**Week 1**
- begin erlotinib 150 mg/d

**Weeks 2-4**
- Continue erlotinib
- begin SAbR*

**Post-SAbR**
erlotinib until disease progression or unacceptable toxicity*

**VERY CONSERVATIVE SAbR DOSES:**
eg 1 x 19 Gy, 3 x 11 Gy, 5 x 8 Gy

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**Sites treated**

- 2 adrenal, 1 hilar
- 1 lung, 1 bone

**4 lung targets**

**24 patients treated to 44 lesions**

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>4</td>
</tr>
<tr>
<td>Adrenal</td>
<td>7</td>
</tr>
<tr>
<td>Lung</td>
<td>18</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
</tr>
<tr>
<td>Mediastinal or hilar lymph node</td>
<td>14</td>
</tr>
<tr>
<td>Non-mediastinal lymph node</td>
<td>3</td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
</tr>
</tbody>
</table>
Acceptable toxicity
- 2 grade 3 radiation toxicities (pneumonitis and vertebral compression)
- Most grade 3 toxicities were Erlotinib related
  - rash, diarrhea, and fatigue

First failure in new (untreated) sites is dominant pattern
- Only 3/44 sites with existing failure

Outcomes exceed historical controls
- Median PFS = 14.7 mos

Of 11 tested patients, none had EGFR mutation

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SAbR in 1st Line Metastatic NSCLC

**Study Schema**

Stage IV NSCLC Patients

<table>
<thead>
<tr>
<th>CR Progression</th>
<th>Partial Response</th>
<th>Stable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAbR to all sites of disease determined by CT or PET/CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary End Point – PFS

Secondary End Points – OS, Toxicity, Patterns of Failure

All metastatic sites were treated with SAbR. Primary disease was treated with either SAbR or hypofractionated radiation (45Gy in 15Fx).
## Radiation Schemas

<table>
<thead>
<tr>
<th>Prescription Dose</th>
<th>Total Cumulative Dose Encircling 95% of Planning Target Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Fractions</td>
<td>Protocol Compliant</td>
</tr>
<tr>
<td>1</td>
<td>21-27 Gy</td>
</tr>
<tr>
<td>3</td>
<td>26.5-33 Gy</td>
</tr>
<tr>
<td>5</td>
<td>30-37.5 Gy</td>
</tr>
</tbody>
</table>

15 45 Gy

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## Patterns of Failure

<table>
<thead>
<tr>
<th>Sites of Progression</th>
<th>SABR + Maintenance</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>In-field</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

5 sites in 4/14 patients  13 sites in 10/15 patients
Progression Free Survival

- SAIR + Maintenance
- Maintenance Only

HR 0.304, CI 0.113-0.815 p = 0.013

Time (Days)

SAIR: 14 12 6 3 1
Maint: 16 8 1 1 1

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Postow et al. NEJM March 8th, 2012
Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2—
Tumor and Immunological Responses
Steven K. Seung et al
Sci Transl Med 4, 13Tra74 (2012);
DOI: 10.1126/scitranslmed.3003649

8 (66.3%) patients had an overall response
60% of mRCC patients had a PR

What will our future look like?

• Current radiotherapy center
  – Most common treatments: breast and prostate
  – Hypofractionated radiation used for palliation
  – Average number of fractions per course of therapy: 28

• Centers are being trained to carry out new techniques
• Competition is fierce to show distinction, good outcomes, and value
• Prospective research on large scales are ongoing

• Future radiotherapy center
  – Most common treatments: metastases (not for palliation, for improved survival
  – Hypofractionated IGRT and SAbR will be mainstream
  – Average number of fractions per course of therapy: Currently 14 at UTSW
Conclusions

• We’ve learned a lot in the past 20 years about SAbR for lung and other primary cancers

• We’ve made many mistakes
  – Published them to avoid repeating mistakes

• Prospective testing (particularly phase I) has helped us:
  1. Reach potential of efficacy
  2. Minimize the number of patients treated imprudently

• SAbR is just scratching the surface of potential

Happy Trials!