Modern Radiation Oncology

Jamie Cesaretti, M.D., M.S.
Terk Oncology
7017 AC Skinner Parkway
Jacksonville, FL
### The Number and Type of Ionizing Radiation Induced Lesions in DNA – per Gray/per Cell!

<table>
<thead>
<tr>
<th>TYPE OF LESION</th>
<th>NUMBER /Gy /diploid cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>double strand break</td>
<td>40</td>
</tr>
<tr>
<td>single strand break</td>
<td>500-1000</td>
</tr>
<tr>
<td>base damage</td>
<td>1000-2000</td>
</tr>
<tr>
<td>sugar damage</td>
<td>800-1600</td>
</tr>
<tr>
<td>DNA-DNA crosslinks</td>
<td>30</td>
</tr>
<tr>
<td>DNA-protein crosslinks</td>
<td>150</td>
</tr>
</tbody>
</table>
How Did RT Technology Evolve?

- Brachytherapy (1910 to today)
- 2D RT (2 Dimensional RT 1970s)
- Proton therapy (1980s)
- 3D RT (3 Dimensional RT 1990s)
- IMRT (Intensity Modulated RT 2000s)
- SBRT/SRS (1990s brain, 2000s body)
- IGRT (2005)
- VMAT (2010s)
2D RT With Customized Blocks
Multileaf Collimator
3D-CRT vs IMRT
VMAT for Prostate Cancer
VMAT

- X-ray film exposed using IGRT radiation therapy
- Demonstrates the precision and accuracy with which radiation dose can be delivered
Applications in Brain
SRS Planning for Brain Lesion

MRI/CT scan fusion

SRS planning
Brain mets response after SRS

(a) lung cancer mets in pons

(b) 2 months post VMAT
Application in Lung Cancer
SBRT for Medically Inoperable Early Stage NSCLC

Pre-treatment CT scan  Two months after VMAT/SBRT
Outcomes of SBRT for Medically Inoperable Early Stage NSCLC

One hundred eighty-six pts (NSCLC) with 204 lesions

Pts were typically treated to 50 Gy in 4 (peripheral) or 5 (central) fractions

At 2 years, LC was 97%.

Operable pts refusing surgery had similar LC (100% vs 96%, $P=.28$), CSS (96% vs 96%, $P=.86$), although they trended to better 2-year (85% vs 69%, $P=.09$) and median and OS than inoperable pts.

Grade 2 rib fracture occurred in 1%, pneumonitis 3%. No grade >2 acute or late toxicity was observed.
s/p sublobar resection and seed mesh placement
Density correction causes dose to go further.

Ribs and chest bone cause strong local energy deposition.

The dose perturbation is complicate and strongly depends on the anatomy.

Comparison of TG-43 (Variseed) and MC (density correction only)

40 yo female s/p thymoma resection (s/p radiation to 50 Gy), 12 months later gross recurrence and re-resection (mesh placement).
Liver Cancer and Metastasis
SBRT for Liver Metastasis

• 63 yo male with colon adenocarcinoma, diagnosed in 03/2014. s/p hemicolecctomy and liver metasteceomy for solitary mass.

• Adjuvant chemotherapy

• 07/2014, PET: 2 liver lesions, one recurrence, the second one was new lesion

• 07/2014: SBRT for both lesions
PET prior to vs 3 months after SBRT
SBRT outcomes for Liver Mets
JCO Vol 27, 10, April 1, 2009

• Pts with 1-3 hepatic lesions, maximum tumor< 6 cm
• 36 to 60 Gy in 3 fractions
• 47 pts with 63 lesions, 69% had received at least one prior chemotherapy, 45% had extrahepatic mets
• Only one pt (2%) experience grade 3 or higher toxicity
Various Metastasis
Note: complete replacement of L5 vertebral body

Tumor mass in L5 vertebral body
Beam configuration

Isodose distribution
PET comparison prior to vs 3 months after SBRT for adrenal metastasis from NSCLC
SBRT for recurrent retroperitoneal LNs in patient with endometrial Ca

PET/CT: hypermetabolic RP LNs

SBRT using VMAT to avoid normal tissue
50 year old male s/p surgery and radiation with paraspinal recurrence.
S/P Prior resection (followed by chemo-xrt) and subtotal resection of a gross recurrence
Brachytherapy for Gynecological and Prostate Cancers
Temporary Brachytherapy for GYN malignancy
Permanent Radioactive seeds implantation for prostate cancer
General Concepts

- Dose
- Imaging
- Accuracy
- Experience
- Biology
CURE RATE = DOSE

- There is a significant difference between less than 70.2 Gy (2.5D) and the higher doses.

- At elevated doses there is still a significant “persistent cancer at biopsy” (risk versus benefit)
  - 14% 81 Gy
  - 20% 75.6 Gy
  - 22% 70.2 Gy
  - 58% <70.2 Gy

ASTRO 2004
CURE RATE = DOSE

70 GY VERSUS 80 GY IN LOCALIZED PROSTATE CANCER: 5-YEAR RESULTS OF GETUG 06 RANDOMIZED TRIAL

Véronique Beckendorf, M.D.,* Stéphane Guerif, M.D.,† Elisabeth Le Prisé, M.D.,‡
Jean-Marc Cosset, M.D., Ph.D.,§ Agnes Bougnoux, M.D.,¶ Bruno Chauvet, M.D.,‖
Naji Salem, M.D.,# Olivier Chapet, M.D., Ph.D.,** Sylvain Bourdain, M.D.,††
Jean-Marc Bachaud, M.D.,‡‡ Philippe Maingon, M.D., Ph.D.,§§
Jean-Michel Hannoun-Levi, M.D., Ph.D.,¶¶ Luc Malissard, M.D.,‖‖
Jean-Marc Simon, M.D., Ph.D.,## Pascal Pommier, M.D., Ph.D.,***
Men Hay, M.D., ††† Bernard Dubray, M.D., Ph.D., ††‡
Jean-Léon Lagrange, M.D., Ph.D., §§§ Elisabeth Luporsi, M.D.,*
and Pierre Bey, M.D.§

*Centre Alexis Vautrin, Vandoeuvre les Nancy, France; †Centre Hospitalier Universitaire, Poitiers, France; ‡Centre Eugène Marquis, Rennes, France; §Institut Curie, Paris, France; ¶Hôpital Bretonneau Tours, France; ‌Institut Sainte-Catherine, Avignon, France; ‡Institut Paoli-Calmette, Marseille, France; **Centre Hospitalier Lyon-Sud, Pierre-Bénite, France; ††Centre René Gauducheau, Saint Herblain, France; ‡‡Centre Claudius Regaud, Toulouse, France; §§Centre George-François Leclerc, Dijon, France; ‌Centre Antoine Lacassagne, Nice, France; ¶¶La Chaussée Saint Victor, France; §§§Hôpital de la Pitié-Salpêtrière, Paris, France; ‌‌Centre Léon Bérard, Lyon, France; †††Centre Val D’Aurelle, Montpellier, France; ††‡Centre Henri Becquerel, Rouen, France; §§§Hôpital Henri-Mondor, Creteil, France
CURE RATE = DOSE
Toxicity = Technique
Toxicity = Technique
Long term outcomes of Brachytherapy
FROG Long-Term Outcomes: Low Risk
Cesaretti, Terk, Kasraeian, Swartz, Vashi et al, 2012

- First 355 consecutive patients treated 1997-2001
- **MINIMUM** follow-up 10 years (10-14 years)
- No failures occurred after 5.5 years

**Outcomes:**
- **Low Risk:** 98% success rate
- Intermediate Risk: 94% success rate
- High Risk: ~80% success rate (88% if 1 risk factor)
Fig. 4. Distribution of prostate-specific antigen (PSA) levels at last follow-up in patients free from biochemical failure.
Fig. 2. Correlation of Gleason score and prostate-specific antigen (PSA) failure rate.
Why is brachytherapy effective?

What is happening to the prostate gland?
Brachytherapy is causing metabolic atrophy.
Fig. 2. Fraction of all patient scans in each follow-up interval having >90% (dotted bars) and 95% (lined bars) of prostate spectroscopic voxels indicating metabolic atrophy. Trend lines added for guidance.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean time to PSA nadir (mo)</th>
<th>Mean time to T &gt; 95% MA (mo)</th>
<th>PSA nadir – T &gt; 95% MA (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI alone</td>
<td>42.5</td>
<td>28.9</td>
<td>13.6</td>
</tr>
<tr>
<td>EBRT + PPI</td>
<td>32.8</td>
<td>25.6</td>
<td>7.2</td>
</tr>
<tr>
<td>EBRT + HT + PPI</td>
<td>25.3</td>
<td>28.0</td>
<td>-2.6 (PSA nadir before MRSI)</td>
</tr>
<tr>
<td>EBRT + HT + PPI (excluding patients with one long time point)</td>
<td>25.3</td>
<td>20.6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

*Abbreviations: PSA = prostate-specific antigen; T > 95% MA = time to >95% metabolic atrophy.*
High Risk

> 40 mo Med F/U or < 50 pts

- Prostate Cancer Results Study Group 3/31/15
- Numbers within symbols refer to references
Radiotherapy done by a low volume inexperienced practitioner.

*What went wrong at the Philadelphia V.A.*

These computer-generated images, part of a presentation produced by the Nuclear Regulatory Commission, show two specific patients who received the treatment. The images show the major organs, with the surrounding tissue rendered as white. Seeds that are implanted in or near the bladder or rectum can cause undue damage to otherwise healthy organs.

Here some of the radioactive seeds were implanted near the patient’s rectum, potentially causing damage to that organ. In addition, the patient’s prostate received only 40 gray of the 100 prescribed by the doctor.

In this case, nearly all of the seeds have been placed outside of the prostate in the perineum. Of the prescribed dose of 100 gray the prostate received only 24. This means that the patient’s prostate cancer was only minimally treated by the procedure.
Target Delineation

MRI Treatment Planning
T2 axial image with surface coil, Left SV dark on T2 (and dark on T1).
Optimal Target Identification

Fused CT/MRI showing Seminal Vesicle invasion on MRI: This justifies including gross seminal vesicle disease to 81 Gy PTV

Fused CT image  Fused MRI image
Toxicity = Technique

LIFESTYLE MODIFICATION!
Toxicity = Technique

Soy Isoflavones in Conjunction With Radiation Therapy in Patients With Prostate Cancer

Iftekhar U. Ahmad, Jeffrey D. Forman, Fazlul H. Sarkar, Gilda G. Hillman, Elisabeth Heath, Ulka Vaishampayan, and Michael L. Cher
Karmanos Cancer Institute, Wayne State University, Detroit, Michigan, USA

Fundagul Andic
Department of Radiation Oncology, Cukurova University School of Medicine, Adana, Turkey

Peter J. Rossi and Omer Kucuk
Winship Cancer Institute, Emory University, Atlanta, Georgia, USA
Toxicity = Technique

**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Soy Isoflavone)</th>
<th>Group 2 (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Disease stage (TNM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>T2a</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>T2b</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pre-PSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Post-RT PSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median: 4–6 mo</td>
<td>0.9</td>
<td>2</td>
</tr>
<tr>
<td>PSA reduction</td>
<td>Pre-vs. post-RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75.70%</td>
<td>59.20%</td>
</tr>
</tbody>
</table>

*Abbreviations are as follows: TNM, tumor, node, metastasis staging classification; T, tumor; PSA, prostate specific antigen; RT, radiation therapy.*
Toxicity = Technique

**TABLE 2**

Decreased adverse effects of radiation therapy by soy isoflavones

<table>
<thead>
<tr>
<th>Variable</th>
<th>3 Mo</th>
<th>6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Soy (n = 13)</td>
<td>Placebo (n = 13)</td>
</tr>
<tr>
<td>Genitourinary effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leakage or dripping of urine</td>
<td>15.4%(2)</td>
<td>23.1%(3)</td>
</tr>
<tr>
<td>Big/medium problem with frequency</td>
<td>38.5%(5)</td>
<td>38.5%(5)</td>
</tr>
<tr>
<td>Big/medium problem with urgency</td>
<td>0%</td>
<td>30.8%(4)</td>
</tr>
<tr>
<td>Function same as before RT or better</td>
<td>92.3%(12)</td>
<td>92.3%(12)</td>
</tr>
<tr>
<td>Gastrointestinal effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cramping or diarrhea</td>
<td>15.4%(2)</td>
<td>7.7%(1)</td>
</tr>
<tr>
<td>Big/medium pain with bowel movements</td>
<td>7.1%(1)</td>
<td>0%</td>
</tr>
<tr>
<td>Erectile function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to have full erections</td>
<td>69.2%(9)</td>
<td>61.5%(8)</td>
</tr>
<tr>
<td>Reduction in ability to have erections</td>
<td>15.4%(2)</td>
<td>46.2%(6)</td>
</tr>
<tr>
<td>Function same as before RT or better</td>
<td>84.6%(11)</td>
<td>61.5%(8)</td>
</tr>
</tbody>
</table>

*Abbreviation is as follows: RT, radiation therapy.*
The One Thing You Cannot Change – Yet!
Results: Rectal Bleeding Grade 1 and 2

% Incidence

0 0.7 1.4 2.1 3.6

ATM Alteration
Entire Group
No ATM Alteration

Fisher’s Exact Test

<table>
<thead>
<tr>
<th></th>
<th>ATM Alteration</th>
<th>Entire Group</th>
<th>No ATM Alteration</th>
<th>Fisher’s Exact Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>36</td>
<td>32</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>ATM Alteration</td>
<td>4 / 13</td>
<td>4 / 11</td>
<td>6 / 17</td>
<td>2 / 7</td>
</tr>
<tr>
<td>No ATM Alteration</td>
<td>1 / 23</td>
<td>1 / 21</td>
<td>3 / 11</td>
<td>3 / 5</td>
</tr>
<tr>
<td>Fisher’s Exact Test</td>
<td>p=0.05</td>
<td>p=0.04</td>
<td>p=1</td>
<td>p=0.56</td>
</tr>
</tbody>
</table>

Cesaretti et al.
Summary

1. Image Guidance is Essential.
2. VMAT is the latest development in radiation technology.
3. Radiation works well for many body sites.
4. Experience Matters Especially with Brachytherapy (there is a risk it is becoming a lost art).
5. Increased dose = increased local control
6. Cancer identification is very important
7. Lifestyle Modification matters for symptom management.
8. Decision Points around whether to use radiation may become genetically determined in the near term.
Comment on Proton Therapy
Intensity-Modulated Radiation Therapy, Proton Therapy, or Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer

Nathan C. Sheets, MD
Gregg H. Goldin, MD
Anne-Marie Meyer, PhD
Yang Wu, PhD
YunKyung Chang, PhD
Til Stürmer, MD, PhD
Jordan A. Holmes, BS
Bryce B. Reeve, PhD
Paul A. Godley, MD, PhD
William B. Carpenter, PhD
Ronald C. Chen, MD, MPH

**Context** There has been rapid adoption of newer radiation treatments such as intensity-modulated radiation therapy (IMRT) and proton therapy despite greater cost and limited demonstrated benefit compared with previous technologies.

**Objective** To determine the comparative morbidity and disease control of IMRT, proton therapy, and conformal radiation therapy for primary prostate cancer treatment.


**Main Outcome Measures** Rates of gastrointestinal and urinary morbidity, erectile dysfunction, hip fractures, and additional cancer therapy.

**Results** Use of IMRT vs conformal radiation therapy increased from 0.15% in 2000 to 95.9% in 2008. In propensity score--adjusted analyses (N=12,976), men who received IMRT vs conformal radiation therapy were less likely to receive a diagnosis of gastrointestinal morbidities (absolute risk, 13.4 vs 14.7 per 100 person-years; relative risk [RR], 0.91; 95% CI, 0.86-0.96) and hip fractures (absolute risk, 0.8 vs 1.0 per 100 person-years; RR, 0.78; 95% CI, 0.65-0.93) but more likely to receive a diagnosis of erectile dysfunction (absolute risk, 5.9 vs 5.3 per 100 person-years; RR, 1.12; 95% CI, 1.03-1.20). Intensity-modulated radiation therapy patients were less likely to receive additional cancer therapy (absolute risk, 2.5 vs 3.1 per 100 person-years; RR, 0.81; 95% CI, 0.73-0.89). In a propensity score--matched comparison between IMRT and proton therapy (n=13,682), IMRT patients had a lower rate of gastrointestinal morbidity (absolute risk, 12.2 vs 17.8 per 100 person-years; RR, 0.66; 95% CI, 0.55-0.79). There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy.

**Conclusions** Among patients with nonmetastatic prostate cancer, the use of IMRT compared with conformal radiation therapy was associated with less gastrointestinal morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy was associated with less gastrointestinal morbidity.
IMRT, protons or conformal radiation therapy: morbidity and disease control in prostate cancer
Sheets et al. *JAMA* April 2012

- Largest proton study to date
- Reviewed SEER Medicare database of 12,000 pts
- Proton therapy patients had significantly higher GI complications than IMRT
- Proton therapy had NO improvement in success rates compared to IMRT
The End.

Jamie Cesaretti, M.D., M.S.
Terk Oncology
7017 AC Skinner Parkway
Jacksonville, FL
904-520-6800