New Cancer Treatments:
The last 100 Years

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A Brief History of Radiation

• Wilhelm Roentgen discovered X-rays on November 8, 1895, while experimenting with a gas-filled cathode tube
  - He noted an image of the bones of his hand projected on a screen when placed between the tube and the fluorescent screen

• He called this X-ray

Early radiograph taken by Roentgen, January, 1896.
Brief History of Radiation Therapy

• The first patient was treated with radiation in 1896, two months after the discovery of the X-ray.

• Rapid technology advances began in the early 1950s with cobalt units followed by linear accelerators a few years later.

• Recent technology advances have made radiation more effective and precise.
Process of Care: Delivery of Radiation Therapy

Radiation therapy can be delivered two ways:

- **External beam** radiation therapy typically delivers radiation using a linear accelerator.
- **Internal radiation** therapy, called *brachytherapy*, involves placing radioactive sources into or near the tumor.
How Is Radiation Therapy Used?

Radiation therapy is used two different ways.

• **To cure cancer:**
  - Destroy tumors that have not spread to other body parts.
  - Reduce the risk that cancer will return after surgery or chemotherapy.

• **To reduce symptoms:**
  - Shrink tumors affecting quality of life, like a lung tumor that is causing shortness of breath.
  - Alleviate pain by reducing the size of a tumor.
Head and Neck Cancer
Xerostomia

- Xerostomia is the prominent long term RT side effect in the H&N ca pts

- Permanent xerostomia affects QOL, causing
  - dental caries, difficulty chewing, swallowing, speaking, increased incidence of oral candidiasis and reflux esophagitis
Xerostomia

• Treatments
  - siologogues - pilocarpine
  - radioprotectant - WR 2721
  - parotid sparing radiation - IMRT technique
  - Others - surgery, acupuncture
Teh et al., 1999

- IMRT is a new technology in RT that delivers radiation precisely to the tumor while relatively sparing the surrounding normal tissues.
H&N IMRT

- 9 beam angles
Compare conventional vs IMRT

- Case 1
- conventional plan
- IMRT plan
WR 2721 (Amifostine/Ethyol)

- US army synthesized 4000 compounds to identify a drug that would give protection to the infantry in the event of a nuclear conflict.

- Randomized study by Brizel D et al J Clin Oncol 2000

<table>
<thead>
<tr>
<th></th>
<th>acute dry</th>
<th>chronic dry</th>
<th>DFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>RT</td>
<td>78</td>
<td>57</td>
<td>53</td>
<td>71</td>
</tr>
<tr>
<td>RT+WR2721</td>
<td>51</td>
<td>34</td>
<td>57</td>
<td>66</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0001</td>
<td>0.002</td>
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<td>NS</td>
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</table>
Conclusion

- Xerostomia is a significant problem for HN cancer pts receiving radiation therapy

- IMRT and WR 2721 significantly spares the parotid gland and avoids xerostomia for HN cancer pts
Breast Cancer
The Operation.—Though the area of disease extend from cranium to knee, breast cancer in the broad sense is a local affection, and there comes to the surgeon an encouragement to greater endeavor with the cognition that the metastases to bone, to pleura, to liver, are probably parts of the whole, and that the involvements are almost invariably by process of lymphatic permeation and not embolic by way of the blood. Extension,
Bernard Fisher 1981/ NSABP 4

- 1971-1974, 1655 pts, operable breast ca
- RM vs SM+RT vs SM(+LND)

10 yrs result

<table>
<thead>
<tr>
<th></th>
<th>LF/ N0 (%)</th>
<th>OS/ N0 (%)</th>
<th>LF/ N1 (%)</th>
<th>OS/ N1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RM</td>
<td>2</td>
<td>57</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>SM + RT</td>
<td>2</td>
<td>57</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>SM (+LND)</td>
<td>18</td>
<td>57</td>
<td>not ran</td>
<td>not ran</td>
</tr>
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</table>

Concl

No difference in OS in any groups
Bernard Fisher 1995/ NSABP 6

- 1843 pts, stage I, II, randomized
- MRM vs lumpectomy+ALND vs Lumpectomy +ALND+RT

12 yrs result

<table>
<thead>
<tr>
<th></th>
<th>LF (%)</th>
<th>LF/ N0 (%)</th>
<th>LF/ N1 (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRM</td>
<td>59</td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Lump + LND</td>
<td>35</td>
<td>32</td>
<td>41</td>
<td>60</td>
</tr>
<tr>
<td>Lump + LND + RT</td>
<td>10</td>
<td>12</td>
<td>5</td>
<td>62</td>
</tr>
</tbody>
</table>

Concl
- OS is independent of mastectomy vs lumpectomy
- RT reduces local failures and is crucial for BCT
Over the last 100 yrs

- Halstedian concept of RM does not improve OS

- Breast cancer is a systemic dz and systemic therapy was introduced to cure pts

- RT is essential for LC and is a critical part of multimodality management for breast cancer pts
Case presentation/ Breast Tx 2007

3D CRT

Breast

Tumor bed

Contralat breast

IMRT
Brachytherapy for Breast Ca

• Mammosite
  - **BID radiation over 1 week**

• High-Dose-Rate (HDR)
  - High energy source delivers the dose in a matter of minutes rather than days
    > Gynecologic, breast and some prostate implants may use high-dose-rate brachytherapy

HDR brachytherapy for breast cancer using MammoSite catheter (B) with an Iridium-192 source (A) and a high-dose-rate afterloader (C). This is an example of a temporary high-dose-rate implant.
**BID RT over 1 week for Breast Cancer**

- There have been several clinical studies since the MammoSite® Radiation Therapy System received FDA clearance in 2002.

- **5-year results from the initial 43-patient MammoSite clinical trial show:** No local recurrences and 82% of patients had good/excellent cosmetic results.

- Five hundred and eighty patients have been enrolled in a manufacturer-sponsored registry trial designed to determine the technical reproducibility and acute toxicity involved in the large scale use of the device. This registry is now managed by the American Society of Breast Surgeons. The registry contains 81 sites (36 sites are enrolling patients) and 94 surgeons.

Ongoing Clinical Trial

NSABP PROTOCOL B-39
RTOG PROTOCOL 0413

A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer

National Surgical Adjuvant Breast and Bowel Project (NSABP) Radiation Therapy Oncology Group (RTOG)
RTOG PROTOCOL 0413/
BID RT over 1 week

RANDOMIZATION

GROUP 1*
Whole Breast Irradiation (WBI)
50 Gy (2.0 Gy/fraction) or
50.4 Gy (1.8 Gy/fraction)
to whole breast,
followed by optional boost**
to 60.0 Gy-66.6 Gy

GROUP 2*
Partial Breast Irradiation (PBI)***
34 Gy in 3.4 Gy fractions using
multi-catheter brachytherapy

or

34 Gy in 3.4 Gy fractions using
MammoSite® balloon catheter

or

38.5 Gy in 3.85 Gy fractions using
3D conformal external beam radiation

For all PBI techniques: RT given to tissue
surrounding lumpectomy cavity only, BID
(with a fraction separation of at least
6 hours), for a total of 10 treatments given on
5 days over a period of 5 to 10 days.
RTOG PROTOCOL 0413/
BID RT over 1 week
Lung Cancer
Statement of Problem

- Correlation between dose and LC for NSCLC from published data.

- Increasing RT dose improves LC.

Statement of Problem

• **Results:** in multivariate only V20 significant.

<table>
<thead>
<tr>
<th>Pneumonitis</th>
<th>V20 (%)</th>
<th>gr 2 (%)</th>
<th>gr 3-5 (%)</th>
<th>fatal (total pt)</th>
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<tbody>
<tr>
<td>&lt; 22</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22-31</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>32-40</td>
<td>13</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt; 40</td>
<td>19</td>
<td>23</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

• **Concl:**
  - Strong correlation between V20 and severity of pneumonitis.
  - V20 is a useful parameter to evaluate pneumonitis.
Cyber Knife

- Cameras on the ceiling act as eyes - Map out movement caused by pts breathing
- Accuracy humans cannot achieve - sub millimeter
- The design came from the automotive industry
Conclusions

• New robotic radiation treatment significantly improved target coverage

• Reduced the volume of normal lung irradiated

• Reduced the volume of critical structures
Chemotherapy for Lung Cancer

- Targeted drug therapy
  - Avastine

Tumor vasculature before VEGF inhibition.  Tumor vasculature after VEGF inhibition. Basement membrane ghosts (arrows) may serve as scaffolding for rapid regrowth if VEGF inhibition is not sustained. Adapted from Baluk 2005.1 Reproduced with permission from Current Opinion in Genetics & Development.
Chemotherapy for Lung Cancer

Targeted therapy
Tarceva

HER1/EGFR functions inappropriately  EGFR receptor overexpression

Cell proliferation and inhibit apoptosis  Blocks EGFR mediated downstream signals
Gene therapy for Lung Cancer

- Human Genome Study giving doctors new tools to fight lung cancer.

**Gene therapy** – healthy genetic materials are introduced into the cancer cells via artificially created viruses, causing cancer cell death.
Immunotherapy for Lung Cancer

- Human Genome Study giving doctors new tools to fight lung cancer.

**Immunotherapy** – immune hormones alert the immune system of the body to create immune cells to kill cancer cells.
Prostate Cancer
Prostate Cancer

- Prostate is surrounded - by the bladder, rectum, and urethra. The prostate is encircled by tissues and nerves - easily damaged during treatments - damage that can lead to cystitis, proctitis, impotence and incontinence.
Pollack et al 2002/ 3DCRT

- FFF/OS results at 6 yrs

<table>
<thead>
<tr>
<th>Doses</th>
<th>PSA &lt; 10</th>
<th>PSA &gt; 10</th>
<th>all pt</th>
<th>all OS</th>
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</thead>
<tbody>
<tr>
<td>70 Gy</td>
<td>75</td>
<td>43</td>
<td>64</td>
<td>87</td>
</tr>
<tr>
<td>78 Gy</td>
<td>75</td>
<td>62</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>p value</td>
<td>ns</td>
<td>0.01</td>
<td>0.03</td>
<td>0.67</td>
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p value ns 0.01 0.03 0.67
Pollack et al 2002/ 3DCRT

- Late toxicity results at 6 yrs

<table>
<thead>
<tr>
<th>Doses</th>
<th>Rectal gr ≥ 2 (%)</th>
<th>Bladder gr ≥ 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 Gy</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>78 Gy</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>p value</td>
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Zelefsky et al 2002/ IMRT

Seminars in Radiation Oncology:12(3), 229, 2002
Zelefsky et al 2002/ IMRT

- Results: actuarial PSA free survival
- Median f/u 24 m (6 - 60 m)

<table>
<thead>
<tr>
<th>Risk</th>
<th>3D CRT</th>
<th>3DCRT</th>
<th>IMRT</th>
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<tr>
<td>group</td>
<td>at 5 yrs (%)</td>
<td>at 5 yrs (%)</td>
<td>at 3 yrs (%)</td>
</tr>
<tr>
<td>fav</td>
<td>64.8-70.2 Gy</td>
<td>75.6-86.4 Gy</td>
<td>81-86.4 Gy</td>
</tr>
<tr>
<td>int</td>
<td>50</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>unfav</td>
<td>21</td>
<td>47</td>
<td>81</td>
</tr>
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</table>
Zelefsky et al 2002/ IMRT

- Results: acute and late toxicity
- Median f/u 24 m (6 - 60 m)

<table>
<thead>
<tr>
<th>Tox grade</th>
<th>acute GI (%)</th>
<th>late GI (%)</th>
<th>acute GU (%)</th>
<th>late GU (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>74</td>
<td>89</td>
<td>33</td>
<td>74</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>9</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1.5</td>
<td>28</td>
<td>9.5</td>
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<tr>
<td>3</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
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</table>

Conclusions/ Prostate

- IMRT can improve Prostate Cancer outcome.
- IMRT reduced GI toxicity in prostate cancer pts
High Dose Rate/ Prostate Cancer

- Temporary High Dose Rate (HDR) brachytherapy technique, commonly dubbed as ‘smart bomb’ is being popularized.
Cyber Knife/ Prostate Cancer
Gene therapy / Prostate Cancer

- Replacement of mutated tumor-suppressor gene
- Introduction of effector gene stimulating body’s immune response
- Suicide gene activating pro drug into toxic chemotherapy
- Gene injected before surgery
- Combination treatment involving the gene therapy with IMRT to see which treatment is most effective.

Fig 1. — Transverse section of a prostate showing the positions of 2 anterior and 3 posterior needles for p53 injection (N = needle for p53 injection, NVB = neurovascular bundle, U = urethra, UC = urethral catheter).

Fig 2. — The p53 gene in adenoviral vector is being injected into the prostate. During the injection, the needle is withdrawn from the base to the apex of the prostate to facilitate as extensive a distribution of vector as possible.
Robotic Prostatectomy

- The latest advancements in robotic-assisted technology and allows a surgeon greater visualization, enhanced dexterity, precision, control and superior ergonomics.

- Shorter hospital stay
  - Less pain
  - Less risk of infection
  - Less blood loss and transfusions
  - Less scarring
  - Faster recovery
  - Quicker return to normal activities
Robotic Prostatectomy

The Robot is In

The da Vinci Surgical System is being used in 38 hospitals across the country, including Memorial Hospital—Coventina University Medical Center. During an operation the surgeon works inside a two-level control tower—one for each arm—that magnifies the field 10 times. Though the surgeon is 10 feet away, he is actually inside the patient.

Remote Control

The surgeon manipulates the instruments with two hands, his arm movements translated into corresponding movements of the instruments. The robot is computer controlled and is typically used for more delicate surgery.

Stereoscope

In the stereoscope, the surgeon has a 3D view of the patient. This allows for precise targeting and minimizes the risk of injury to surrounding organs.

Pedal to the Metal

With his feet, the surgeon controls the camera at the front of the robot. The surgeon controls the robot at the front using a control panel and a joystick that mimics the movements of the instruments.

Caught out Camera

Two cameras are selected in the end of each robotic arm and inserted into the patient. These provide a magnified view of the surgical field during operation.

Arms’ Length

During the procedure, a surgical assistant adjusts the robotic arms. Attached to the arms are 10-inch surgical instruments. The assistant makes sure each instrument is accurately inserted into the patient.

Arms

Robotic arms are used to perform the surgery. They are designed to move with precision and provide a better view of the surgical area.

Tools of the Trade

Each robotic arm contains a variety of instruments, such as scissors, forceps, and electrocautery, enabling the surgeon to perform a wide range of procedures.

Surgical Instrument

This instrument is used to cut or dissect tissue during the surgery.

Light

A light is attached to the robotic arm to provide illumination of the surgical site.

Scoping It Out

The scope has two lenses, one for each arm, and two lights, so surgeons get a clear, 3-D view. Most of the systems used in conventional surgery provide 2-D images.

Camera arms

Two cameras are selected in the end of each robotic arm and inserted into the patient. These provide a magnified view of the surgical field during operation.

Operating table

The patient is securely fixed to the operating table to ensure stability and prevent movement during the procedure.
Cancer death rates 1930-2003


- Lung & bronchus
- Stomach
- Colon & rectum
- Prostate
- Pancreas
- Liver
- Leukemia

*Age-adjusted to the 2000 US standard population.
Cancer death rates 1930-2003


*Age-adjusted to the 2000 US standard population.
Conclusions

- Cancer treatments require a multi-modality management including surgery, chemotherapy and radiation.

- Each cancer pt should be consulted by all specialty, including a radiation oncologist.
Conclusions

• IMRT is the latest radiation therapy technique.
  
  - Preventing dry mouth for H&N cancer pts
  
  - Less skin dose for breast cancer pts
  
  - Higher cure rate/lower side effects for prostate cancer pt
Conclusions

• Newest cancer therapy
  – IMRT for Head & Neck cancer pts
  – Mammosite for breast cancer pts
  – Gene and immunotherapy for lung cancer pts
  – Robotic Cyber Knife for lung and prostate cancer pts
  – HDR radiation therapy for prostate cancer pts
  – Gene therapy for prostate cancer pts
  – Robotic surgery for prostate cancer pts
Conclusions

• Cancer treatments have come a long way in last 100 yrs, now actively contributing to cure of cancers.
Conclusions

- Still many treatments are on the horizon and will continue to be developed until cancer, like polio and smallpox, one day is a distant memory.