PRACTICAL MEDICAL PHYSICS TU-D-202-3

Establishing an SBRT Program

Part III: Clinical and Radiobiological Considerations
3 of the AAPM SBRT sessions

• **HOW** do we and some others do SBRT?
  – Tuesday 730 am, “Physics and Dosimetry of SBRT”, moderator M Miften, Educational Session

• **WHY** did we reach this place?
  – Tuesday 130 pm, “Establishing an SBRT Program”, moderator S Benedict, Practical Medical Physics

• **WHAT** have we accomplished so far?
Revised title

100 years of Radiotherapy: Why did we arrive at SBRT?
100 years of Radiotherapy: 
So much Magical Realism

• Fantastical events mixed with everyday life
  – Has anyone ever seen a megavoltage x-ray?

• Non-linear time
  – You’ll see: we return to past ideas again and again…

• Sense of mystery
  – Tumors come and go…How? Why?

First edition of One Hundred Years of Solitude: Editorial Sudamericana, Buenos Aires, 1967
Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

Give many treatments!

Arguments to go slowly will be up here

Use only a few treatments!

Arguments to go quickly will be down here
Leopold Freund (1868-1943): first radiotherapy scientist

1896, pre- and post-RT
10 treatments to upper, 21 to lower

70 years later
First successful treatment of cancer with radiotherapy, 1899

Before and 30 years later

Tor Stenbeck (left)
Roentgen Institute, Stockholm
Gas tube device
For pt above, 99 treatments given
Austrian proponents of “expeditive” radiotherapy: Holznecht, Kienock
ON THE RADIO-THERAPEUTIC TREATMENT OF DISEASES OF THE HAIR.

By Professor Dr. ROBERT KIENBÖCK, Vienna.*

1, 2, 3, 4, Position of the normal ray in the various positions of the focus-tube; A, B, C, position of the leaden shield for irradiations 1, 3, and 4.
• The “Law of Bergonie and Tribondeau”:
  – “X-rays are more effective on cells which have a greater reproductive activity; the effectiveness is greater on those cells which have a longer dividing future ahead, on those cells the morphology and the function of which are least fixed. From this law it is easy to understand that roentgen radiation destroys tumors without destroying healthy tissues.”
The other thing Bergonie and Tribondeau said:

From the standpoint of the practice of radiotherapy, one must learn from these facts that one must avoid the production of atypical mitoses by radiotherapeutic treatments. It seems pretty clear that the practice of delivering small and repeated doses, in contradistinction to the technique of few and heavy doses, is more apt to produce these nondestructive irritations with resulting monster cells. Therefore, one should prefer the method of massive doses.

The ideal technique...would be to make this complex tissue absorb in one sitting the maximal dose of radiation compatible with the preservation of the other elements one wishes to preserve.
Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

- More is better!
- Go slow to monitor effect
- Hurry up!
- Don’t cause cancer!
- Do “expeditive” RT: and measure dose!
Dr. William D. Coolidge
and his NEW MAGIC RAY

Producing as Many ELECTRONS Every SECOND as a TON of RADIUM

What will it do for Humanity?

By Robert Merrill

Since recent activity, minium has been known to produce substance extraordinary phenomena which are now called magic rays and are now recognized as the work of science.

In the same forest that sheltered primitive people the ancient wonders called dimly with words and poetry at which man thought was magic. In the dimly lit home or thunder Powers of nature, the wonder people believed they knew no more of the reality of the universe.

In the picture shown the new type of vacuum tube, perfected by Dr. Coolidge, which projects the Magic cathode ray, the modern alchemist that changes solids into liquids and liquids into solids. Its possibilities in the medical world have not been explored. It is known to produce marvelous changes in living tissue.
1930s:
The normal tissue argument for multiple fractions

Claudius Regaud 1870-1940

Henri Coutard 1876-1950

Long duration treatment
Less acute toxicity

Short duration treatment
More acute toxicity

Coutard believes it is always necessary to treat patients until a marked radio-epithelitis has developed. If the tumor has entirely disappeared by that time, and if its histological appearance suggests that it is of a very anaplastic type, treatment is discontinued. If, on the other hand, it is of a highly differentiated type, treatment may be continued; the duration of further treatment and the extent of further dosage depends upon personal judgment and experience.

**TABLE 3.—Summary of Roentgen Therapy Results**

<table>
<thead>
<tr>
<th>Total number of cases treated</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically well (arrested?)</td>
<td>4</td>
</tr>
<tr>
<td>Improved (but died of subsequent bronchopneumonia)</td>
<td>3</td>
</tr>
<tr>
<td>Unchanged (no extension) of lesion for some months</td>
<td>1</td>
</tr>
<tr>
<td>No Improvement (died)</td>
<td>1</td>
</tr>
<tr>
<td>Total number living</td>
<td>5</td>
</tr>
<tr>
<td>Total number dead</td>
<td>4</td>
</tr>
</tbody>
</table>

**TABLE 6.—Summary of Surgical Results**

| Total number of cases operated | 8   |
| Clinically well (untraced but ? arrested) | 2   |
| Improved but developed recurrence | 3   |
| No Improvement (died postoperative) | 3   |
| Total number living unknown, but possibly | 3   |
| Total number dead              | 5   |
Lea DE, Catcheside DG. J Genetics 1942; 44:216-245, cf. p227
The 1942 Lea-Catcheside paper

- Concerned with the rate of chromatid interchanges as function of radiation dose

- The “D²” comes from the expectation of kinetics similar to a bimolecular reaction

- Here, the two components are essentially the same entity, namely a broken chromatid

\[
[A] + [B] \rightarrow [AB]
\]

\[
\frac{d[AB]}{dt} = k[A][B]
\]

\[
\frac{d[chromatid\_exchanges]}{dt} = k[chromatidbreaks]^2
\]

\[
\frac{d[chromatid\_exchanges]}{dt} = k'[dose]^2
\]
The 1942 Lea-Catcheside paper, continued

- There was also a factor proposed to modify the "$D^2$" term with the term $G$
- The $\alpha$ term counts double strand breaks as a function of dose.
- Purpose of $G$ was to account for exposures that took enough time for there to be decay of the chromatid breaks produced as the radiation exposure continues.

$$\alpha D + \beta D^2 G$$

$$G = \frac{2}{D^2} \int_{-\infty}^{\infty} \int_{-\infty}^{t} \dot{D}(t')dt' e^{-\lambda(t-t')} \dot{D}(t')dt'$$
1940s, 1950s….and continuing on for a while:
A resurrection of an old trick to give large doses—
"grid" or “sieve” radiotherapy

Zhang et al, DOSIMETRIC VALIDATION OF THE MCNPX MONTE CARLO SIMULATION FOR RADIOBIOLOGIC STUDIES OF MEGAVOLTAGE GRID RADIOTHERAPY, IJROBP 2006
Grid radiotherapy: theoretical advantages

- Some skin sparing achieved
- Mimics interstitial brachytherapy dose distribution to some extent
- Maybe even allow for normal tissue stem cell migration into high dose volumes
Lack of late skin necrosis in man after high-dose irradiation using small field sizes: experiences of grid therapy

By *H. Shirato, MD, *N. K. Gupta, FRCR, †T. J. Jordan, PhD and ‡J. H. Hendry, PhD

*Department of Radiotherapy, †Department of Medical Physics and ‡Cancer Research Campaign
Department of Radiobiology, Paterson Institute for Cancer Research, The Christie Hospital and Holt Radium Institute, Manchester M20 9BX, UK

- Patients treated with single dose of 45 Gy to surface for lung cancer
- No skin necrosis seen in long-term (2+ yr) survivors
- Proposed explanation:
  - volume effect, ie can do this with small grid holes that don’t cause necrosis
The arrival of high energy beams I: Cobalt-60

Dr. T.A. (Sandy) Watson, John MacKay of ACME Machine and Electric, and Prof. Harold Johns Saskatchewan

Table HCT-1. First cobalt-60 treatments in the world, 1951

<table>
<thead>
<tr>
<th></th>
<th>Saskatchewan</th>
<th>W. Ontario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalt-60 source delivered</td>
<td>July 30</td>
<td>October 16</td>
</tr>
<tr>
<td>Unit installed</td>
<td>August 17</td>
<td>October 23</td>
</tr>
<tr>
<td>Calibration</td>
<td>11 weeks</td>
<td>—</td>
</tr>
<tr>
<td>First patient treated</td>
<td>November 8</td>
<td>October 27</td>
</tr>
</tbody>
</table>

The arrival of high energy beams II: The betatron, 1950s

• First unit developed in 1940, U of Illinois (figure)
  – Electrons accelerated by magnetic fields and aimed at target to produce high energy x-rays

• First cancer treatment center with a betatron in Shorewood Hills, WI, ca. 1957
  – Higher energy beams mean good skin sparing for deep tumor treatment

Dr Donald Kerst
Professor of Physics, U of I
The arrival of high energy beams III:
The linear accelerator, 1950s
Christie Hospital, Newcastle Hospital, Stanford
The key advantage of high energy: skin sparing
High dose palliative RT with high energy beams, late 1950s

- 22.5 MeV Betatron
  - Less skin dose the kV
- Typical once per week fractions of 5-12.5 Gy
- Generally palliative intent

**Table I: Massive-Dose Rapid Palliative Radiotherapy**

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
<th>Subjective Improvement</th>
<th>Objective Improvement</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Breast</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>24</td>
<td>13</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Head and neck</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Esophagus and stomach</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Misc.</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>37</td>
<td>29</td>
<td>9</td>
</tr>
</tbody>
</table>

Columbia U series:
case III, prior grid RT for thymoma, later 2 x 12.5 Gy for recurrence

Fig. 5. Case III. Sixty-year-old white male had left forequarter amputation seventeen years before for fibrosarcoma. In 1954 a mediastinal thymoma was discovered at thymectomy and the patient received 9,000 r air dose (250 kv radiation) through a grid. Film one month prior to therapy, showing recurrent mass in left chest.

Fig. 6. Case III. Chest roentgenogram two weeks following completion of 2,500 r tumor dose in eight days (two fractions) through opposing 12 X 15-cm. portals. Reduction in size of mass.

Fig. 7. Case III. Roentgenogram of chest one year following completion of therapy, showing marked fibrosis in field of irradiation. Patient was asymptomatic at this time.
ACTION OF X-RAYS ON MAMMALIAN CELLS* †

BY THEODORE T. PUCK, PH.D., AND PHILIP I. MARCUS

(From the Department of Biophysics, Florence R. Sabin Laboratories, University of Colorado Medical Center, Denver)

(Received for publication, February 3, 1956)
Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

- Slow and steady wins the race!
- The race goes to the swift!
- Go slow to monitor effect
- Be careful with normal tissues
- Don’t cause cancer!
- Do “expeditive” RT: and measure dose!
- New technology can help us here!
1960s image guidance technology

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An Hilarious Optical Illusion

ONLY $1.00

Scientific optical principle really works. Imagine — you put on the "X-Ray" Specs and hold your hand in front of you. You seem to be able to look right through the flesh and see the bones underneath. Look at your friend. Is that really his body you "see" under his clothes? Loads of laughs and fun at parties. Send only $1 plus 25¢ shipping charges or order COD and pay postman on delivery $1 plus COD shipping charges. Money Back Guarantee either way.

HONOR HOUSE PRODUCTS CORP.
Lynbrook, N. Y., Dept. 68XR02
1970s: Dawn of the applied modeling era, featuring the LQ formulation

- Douglas & Fowler study was intended to determine means of adjusting RT schedules for same normal tissue effect

- 9000 mice irradiations!!!!
APPENDIX C

The quadratic form obtained here for the cell survival curve is consistent with the postulate that cell death results from lethal interaction of two primary lesions placed close together in the cell. From Neary (20), the probability that primary lesions will occur in each of two cylindrical targets in one site in a cell is

\[ 1 - \exp(-mk^2)[1 - [1 - \exp(-mk + mgk^2)^4]]. \]

Here \( k \) is the probability that one track through the target will produce a primary lesion, \( g \) is the probability that a track that traverses one target will pass through the second target in the same site, and \( m \) is the mean number of tracks through the mean projected area of a target in the site.

Multiplying by the mean number of sites per cell \( N \) yields the mean number of sites per cell that contain lesions in both targets,

\[ \lambda = N[1 - \exp(-mk^2)[1 - [1 - \exp(-mk + mgk^2)^4]]]. \]

The possibility of cell death from radiation in the range of doses considered is assumed to be present only in cells with sites containing lesions in both targets. It is assumed that correct repair may be prevented by the interaction of the two lesions.

If the probability that both lesions will not be repaired correctly is \( p \), then the probability of survival of a cell with \( \Theta \) sites containing lesions in both targets is \((1 - p)^\Theta\). It is assumed that the distribution with respect to \( \Theta \) is Poisson in form.

Summing over the Poisson distribution yields the surviving fraction \( s \):

\[ s = \sum_{\Theta=0}^{\infty} \frac{\lambda e^{-\lambda}}{\Theta!} (1 - p)^\Theta = e^{-\lambda p}. \]

Substituting for \( \lambda \),

\[ s = \exp(-pN[1 - \exp(-mk^2)[1 - [1 - \exp(-mk + mgk^2)^4]]]). \] (24)

If \( mk \ll 1 \), the above can be approximated by taking the lowest terms in the expansion of the exponentials and

\[ s = \exp(-pN[mk^2 + mk^2(1 - gk^2 - gk^2/2)]). \]

As \( m \) is proportional to \( D \), where \( D \) is the dose in rads and \( p, N, g, \) and \( k \) are constants for a given quality of radiation, this can be written as

\[ s = \exp[-(\alpha D + \beta D^2)], \]

where \( \alpha \) and \( \beta \) are constants. The full equation (24) has the form

\[ s = \exp(-\lambda_1[1 - e^{-\lambda_1 D}][1 - [1 - e^{-(\lambda_1 + \lambda_2)D^2}]]. \] [Eq. (14)],

where \( \lambda_1 \) and \( \lambda_1 \) are proportional to the inactivation constants for one and both members, respectively, of each pair of targets by a single photon, and \( \lambda_1 \) is \( pN \) above.
Building on the LQ formalism

\[ s = \exp[-(\alpha D + \beta D^2)] \]

**Figure 6** The difference in shape between the dose-response curves for early or late reactions, matched at 200 cGy per fraction. Smaller doses per fraction would require a larger increase of total dose for late than for early reactions.

Fowler, Br J Cancer 1984
RTOG 90-03

- Standard 2 Gy/d to 70 Gy versus 2 alternatives:
  - Hyperfractionated RT (1.2 Gy bid) to 81.6 Gy
  - Accelerated RT via concomitant boost (1.8/1.5) or 1.6 BID with split

Fu et al, 2000
Hypofractionation: lessons from complications

Gilbert H. Fletcher

Department of Clinical Radiotherapy, The University of Texas, M.D. Anderson Cancer Center, Houston, TX, U.S.A.

Late complications in patients with Stage III cancer of the cervix free of disease in the pelvis (from Singh [25]).

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 Gy whole pelvis in 20 daily fractions (TDF:66), then intracavitary</td>
<td>5 weekly doses of 5.8 Gy (TDF:66), then same intracavitary gamma-ray,</td>
</tr>
<tr>
<td></td>
<td>gamma-ray, then 10 Gy to pelvic walls in 5 daily fractions (minimum</td>
<td>then 1 fraction of 5.8 or 6.7 Gy depending on thickness of the patient</td>
</tr>
<tr>
<td></td>
<td>follow-up 24 months)</td>
<td>(minimum follow-up 12 months)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>No complications</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Proctitis lasting</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>over 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe bowel</td>
<td>0</td>
<td>10 (3 dead)</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectovaginal fistula</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Edema of vulva,</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>months, etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE I

Failures and severe complications in patients treated with protracted irradiation alone with $^{60}$Co (from Montague [21]).

<table>
<thead>
<tr>
<th></th>
<th>5 fractions/wk</th>
<th>3 fractions/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast: 60 Gy/8 wk +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–40 Gy boost over</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumor*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axilla: 50 Gy/5 wk +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–20 Gy boost over</td>
<td></td>
<td></td>
</tr>
<tr>
<td>palpable tumor through</td>
<td></td>
<td></td>
</tr>
<tr>
<td>small appositional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>portal*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 days per week: 88</td>
<td>2</td>
<td>11.5</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 days per week: 57</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The tangential portals for the breast were treated on alternate days. The AP and PA portals covering the shoulder and axilla were treated every day.

Radiotherapy and Oncology, 20 (1991) 10–15
…brevity is the soul of wit…

Polonius, in *Hamlet*, Act 2, Scene 2
W. Shakespeare

- Early interest in hypofractionated treatment regimens as long ago as the 1960s
  - Largely driven by resource limitation, not tumor biology

- Sir Laurence Olivier
  - Actor
  - *prostate cancer survivor*

- Treated in 1967 on an experimental protocol involving 6 fractions of 6 Gy
  - 22 yrs NED after that
Earliest “high dose” extracranial stereotactic treatment: Hamilton et al, Neurosurgery, 1995

Rigid clamps connected to vertebral bodies, a la rigid head frame
5 patients treated, modest dose by today’s standards
STEREOTACTIC HIGH DOSE FRACTION RADIATION THERAPY OF EXTRACRANIAL TUMORS USING AN ACCELERATOR

Clinical experience of the first thirty-one patients

HENRIC BLOMGREN, INGMAR LAX, INGEMAR NÄSLUND and RUT SVANSTRÖM

Blomgren et al, Acta Oncol 1995
SBRT: operational definition

- **Stereotactically** localized, ultra-high-dose radiotherapy
  - Given to discrete tumor nodules in *extracranial* locations
  - Within a *hypofractionated* regimen (1-5 treatments)
    - Unlike typical 6-7 week course of radiotherapy
  - Analogous to cranial stereotactic radiosurgery (SRS)
Early SBRT experience

Karolinska Institute

**TABLE 2** Anatomic Distribution of 1965 Tumors That Have Been Treated with Stereotactic Body Radiation Therapy at the Karolinska Hospital from 1991 to 2003.

<table>
<thead>
<tr>
<th>Organ</th>
<th>No. Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>997</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>78</td>
</tr>
<tr>
<td>Liver</td>
<td>484</td>
</tr>
<tr>
<td>Pancreas</td>
<td>149</td>
</tr>
<tr>
<td>Suprarenal glands</td>
<td>30</td>
</tr>
<tr>
<td>Abdomen(^a)</td>
<td>118</td>
</tr>
<tr>
<td>Skeleton</td>
<td>25</td>
</tr>
<tr>
<td>Miscellaneous(^b)</td>
<td>46</td>
</tr>
</tbody>
</table>

\(^a\)Mainly kidneys and para-aortic regions.

\(^b\)Pelvic area, muscles, and so forth.

**FIGURE 7.** Diagram shows the cumulative number of patients and tumors treated during the years 1991 to 2003.
1990’s: 
SBRT pioneers on 3 continents

Lax & Blomgren (Karolinska)  
Uematsu (Saitama), Nagata (Kyoto)  
Timmerman & Papiez (Indiana U)

Common denominators:
– Average equipment
– Clever low-tech solutions to allow high-tech treatments

Common goal:
– **Kill more cancer, more efficiently**
“Conformal radiotherapy now being investigated for the treatment of primary tumors may find the treatment of oligometastases its most important application…

This technique allows both an increase in the tumor dose and a reduction in normal tissue toxicity by restricting…the radiation to the…tumor while avoiding critical normal tissues…

It requires … precise reproducible … radiation delivery…”
Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

- Patience is a virtue!
- Go slow to monitor effect
- Be careful with normal tissues
- Don’t cause cancer!
- New technology can help us here!
- He who hesitates is lost!
- Do “expeditive” RT: and measure dose!
21st century radiobiology
Radiation as potent anti-angiogenic: Observations from the MSKCC spinal SBRT experience

- 93 patients, 103 lesions
  - No spinal cord compression
- Single fraction 18-24 Gy
  - Spinal cord max 12-14 Gy
- Better control at higher dose (24 Gy) than lower (above)


Metastatic colorectal ca example
MSKCC argument why SBRT works so well:
Tumor response to high dose radiotherapy is largely driven by endothelial cell apoptosis

- Fibrosarcoma and melanoma models
- Growth delay after RT influenced by apoptotic capacity
- Dose-dependence of percent apoptosis in endothelial cells

Garcia-Barros et al, Science, 2003
Sources of guidance for SBRT normal tissue dose constraints

• AAPM TG 101 report
  – Benedict et al, Med Phys, Aug 2010

• Selected RTOG SBRT studies

• QUANTEC papers
  – very limited SBRT, mostly conventional

  • Mostly unvalidated but well considered estimates for 1, 3, and 5 fractions
Timeline of Radiotherapy Philosophical Debate about how many treatments should be given: what really happened

Concurrent chemotherapy explodes everything and makes the nuances of conventional fractionation discussion almost completely disappear.

Like it or not, this is where radiation oncology has evolved, and there is no end insight to the use of large doses per treatment.

Don’t be a fool!

Don’t be a Luddite!
Thanks for your attention!