Clinical Applications of Brachytherapy Radiobiology

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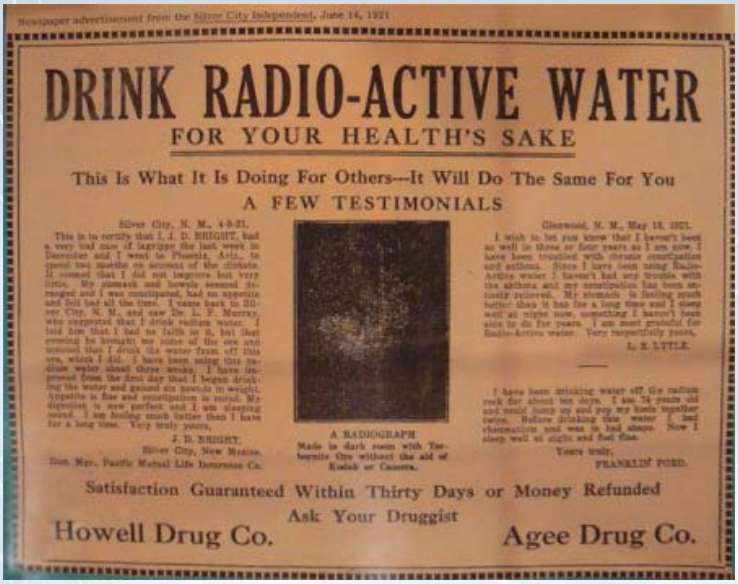
Radiobiology is Essential

- Knowledge of radiobiological principles is essential to the brachytherapist
- Empirical prescription replaced by modelling
- Radiobiology no substitute for a badly placed implant-good geometry is still key


Newspaper advertisement from the Silver City Independent, June 14, 1921

DRINK RADIO-ACTIVE WATER

FOR YOUR HEALTH'S SAKE

This Is What It Is Doing For Others---It Will Do The Same For You

A FEW TESTIMONIALS

Silver City, N. M., 4-8-21.

This is to certify that I, J. D. BRIGHT, had a very bad case of lagrippe the last week in December and I went to Phoenix, Ariz., to spend two months on account of the climate. It seemed that I did not improve but very little. My stomach and bowels seemed deranged and I was constipated, had no appetite and fell bad all the time. I came back to Silver City, N. M., and saw Dr. L. F. Murray, who suggested that I drink radium water. I told him that I had no faith in it, but that evening he brought me some of the ore and showed that I drink the water from off this ore, which I did. I have been using the radium water about three weeks. I have improved from the first day that I began drinking the water and gained six pounds in weight. Appetite is fine and constipation is cured. My digestion is now perfect and I am sleeping sound. I am feeling much better than I have for a long time. Very truly yours,

J. D. BRIGHT,
Silver City, New Mexico.
Dist. Mgr., Pacific Mutual Life Insurance Co.

A RADIOGRAPH
Made in dark room with Terrestrio Ore without the aid of Kodak or Camera.

Glenwood, N. M., May 18, 1921.

I wish to let you know that I haven't been as well in three or four years as I am now. I have been troubled with chronic constipation and asthma. Since I have been using Radio-Active water I haven't had any trouble with the asthma and my constipation has been entirely relieved. My stomach is feeling much better than it has for a long time and I sleep well at night now, something I haven't been able to do for years. I am most grateful for Radio-Active water. Very respectfully yours,

L. E. LITTLE.

I have been drinking water off the radium rock for about ten days. I am 74 years old and could jump up and pop my heels together twice. Before drinking this water I had rheumatism and was in bad shape. Now I sleep well at night and feel fine.

Yours truly,
FRANKLIN FORD.

Satisfaction Guaranteed Within Thirty Days or Money Refunded

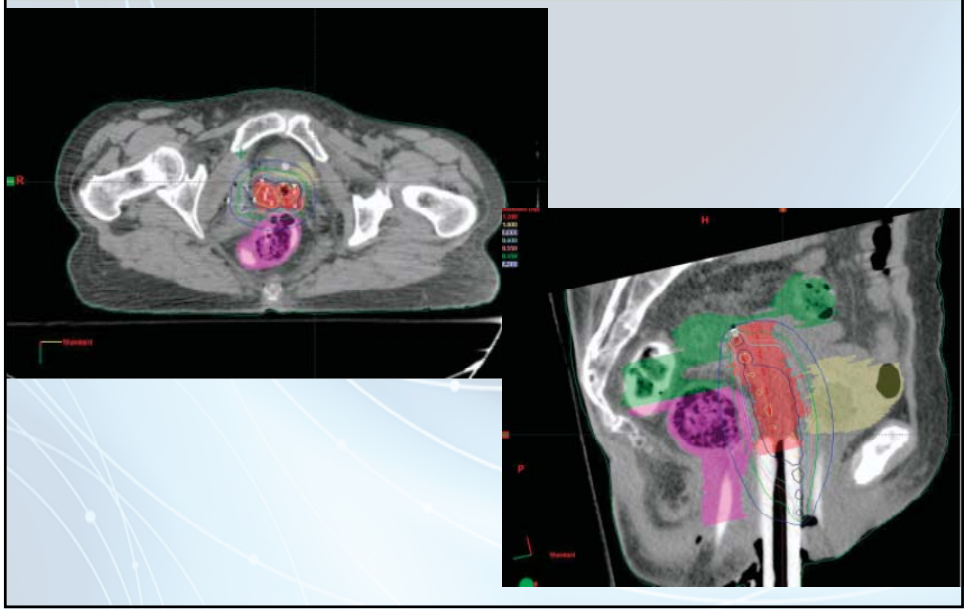
Ask Your Druggist

Howell Drug Co. Agee Drug Co.

Dose volume differences

EBRT	BT
Volume treated is usually quite large.	Treated Volume is rather small
Variation in dose is kept minimal	Minimum dose is prescribed to an isodose encompassing the PTV
Homogeneous dose distribution with < 5% lower doses and < 7% higher doses	Very inhomogeneous dose distribution within the treated volume

Gynaecologic Brachytherapy



Repair

- The lower the dose rate of radiation, the more likely that repair will occur.
- PDR-allows time for sublethal damage repair during treatment.
- HDR-full normal tissue repair occurs if more than 6-24 hrs between fractions.

Repopulation

- Clear evidence of improved tumour control and survival if RT is given in shorter overall time (Perez 1995, Petereit 1995).
- Okkan et al 2003-average time to complete RT with HDR=70 days, with LDR=57 days.
- Chen et al 2003-DFS drops from 83% to 65% if overall RT time over 63 days (HDR).

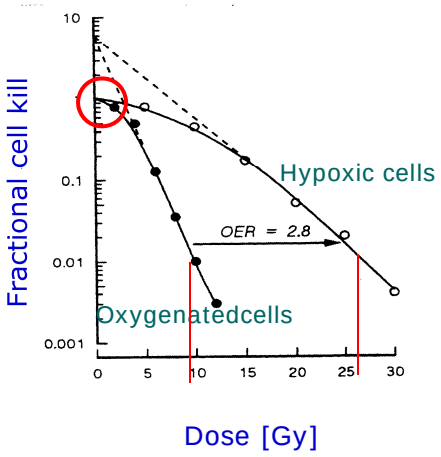
Reoxygenation

- Clear evidence of decreased survival in cervix Ca with a low initial Hb/decreased Hb during treatment
- PDR-allows for acute hypoxia to correct during treatment.
- HDR-allows for tumor shrinkage and reoxygenation of chronically hypoxic areas.

Effect of Hypoxia on Radiosensitivity

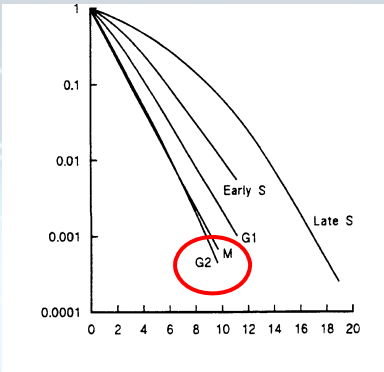
OER = Oxygen Enhancement Ratio:

$$\frac{\text{radiation dose in hypoxia}}{\text{radiation dose in air}}$$



Reassortment

Cells can pass out of radioresistant late S and early G_2 into more radiosensitive G_2 and M during treatment.



Steel, 2002

Dose-fractionation

- How best to convert HDR to LDR?
- For cervix recommend HDR<7 Gy per fraction to achieve excellent cure with low late toxicity
- But in India 20 Gy in 2 fractions used with good effect
  - Av BED doses in US
    - IB & IIB-96 Gy_{10}
    - IIIB-100 Gy_{10}
  - Av BED doses in UK (historic)
    - 83.3 Gy_{10}
  - Av BED doses in Vienna
    - 100.7 Gy_{10}

Correlated with control!

HDR BT Cervix Ca

Importance of fraction size (to point A)

Complications:	< 7 Gy	> 7Gy
G 2 - 4	7.6%	11.2%
G 3 - 4	1.3%	3.4%

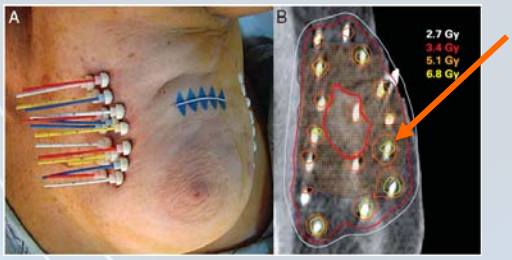
Orton, 1991

Accelerated Partial Breast Irradiation

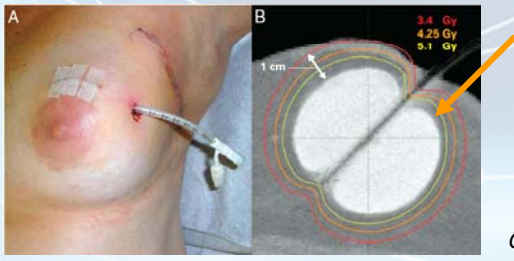
- The variety of techniques used can demonstrate the importance of radiobiological principles
  - Intraoperative photons
  - Interstitial HDR
  - Single catheter HDR

The importance of radiobiology for dose

- START A trial was used to determine α/β ratio of breast tumour
  - Approx 3.4 Gy
- Thus small changes in fraction size can produce large changes in effect of treatment
- Change from multi-catheter interstitial to single channel MammoSite had radiobiologic implications



Lots of little hotspots!



One big hotspot!

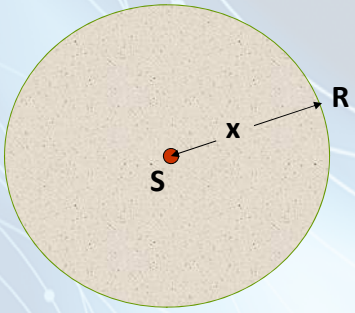
Courtesy David Wazer

Interstitial Brachytherapy

- Long history of use
- LDR doses converted to HDR using LQ equation
- Dose homogeneity important
- DHI = V100-V150/V100
  - Should be over 75 (over 85 ideal)
- Size of V150 and V200 also important

BEDs and dose gradients.

- Dose/BED is specified at a location (reference point R) which is distant from the sources/dwell positions (S). Doses at points within the prescription isodose will therefore be higher; BEDs higher still.



Between R and S, dose increases according to $1/x^2$. BEDs increase at an even higher rate – very close to the source/dwell position BED increases according to $1/x^4$. Therefore, the effective BED associated with single catheter brachytherapy applications is *always* higher than that determined at the dose reference point.

Slide Roger Dale

Single catheter HDR balloon device

- Inhomogeneous distribution
- EUD concept applies
  - In our series mean EUD 3.5Gy higher than prescribed dose
  - Increased EUD correlated with toxicity
  - EUD decreases with multiple dwell positions and larger balloon sizes
- DHI-only favorable with very large balloons

Effect of diameter and dwell positions on RB

Balloon diameter (cm)	Single dwell position			Multiple dwell positions		
	BED ($Gy_{3.6}$)	EQD2 (Gy)	EUD (Gy)	BED ($Gy_{3.6}$)	EQD2 (Gy)	EUD (Gy)
4.0	77.9	50.1	37.9	75.4	48.5	37.1
4.5	77.7	49.9	37.9	75.1	48.3	37.0
5.0	77.4	49.8	37.8	74.8	48.1	36.9
5.5	77.2	49.6	37.7	74.5	47.9	36.8
6.0	76.9	49.5	37.6	74.2	47.7	36.7

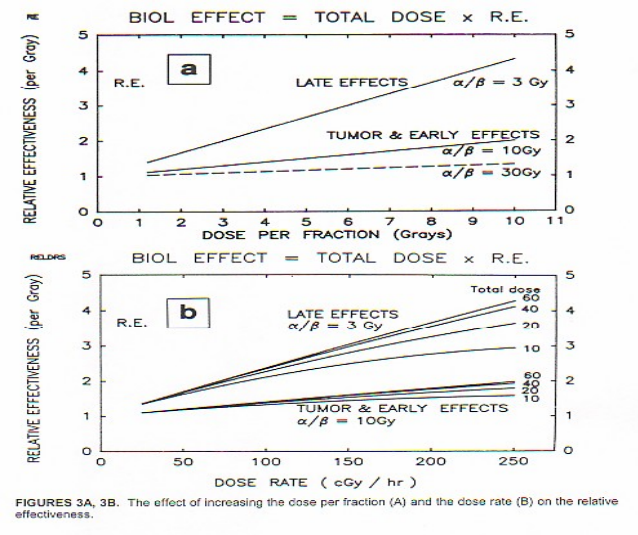
Our series results for RB comparisons

	BED		EQD2		EUD	
	Mean	**Range**	**Mean**	**Range**	**Mean**	**Range**
Tumour ($Gy_{3.6}$)	76.6	65.1-77.8	49.2	41.8-50.1	37.5	33.6-37.9
Acute toxicity (Gy_{10})	54.0	46.9-55.0	45.0	39.1-39.4	38.9	34.8-39.4
Late toxicity (Gy_{3})	83.6	70.6-84.8	50.2	42.3-50.9	37.3	33.4-37.6

Intra-Operative Brachytherapy

- LQ equation less accurate predictor at large fraction sizes
- When considering prescribed dose remember Single fraction has similar cell kill to 1/3-1/2 total dose of fractionated RT
- Increased RBE with photons as energy decreases

Relative Effectiveness



FIGURES 3A, 3B. The effect of increasing the dose per fraction (A) and the dose rate (B) on the relative effectiveness.

Possible Radiobiological Benefits

- Negates risk of accelerated repopulation
- No time for hypoxia to set in
- Geographical accuracy optimal
- Normal tissue protection using lead shields
- Possible favourable alteration of wound environment

Electronic Brachytherapy

Electronic brachytherapy

- Hotter doses within treatment volume
- Higher V150 and V200s
- Spherical dose, no optimization
- Higher RBE at 1 cm with 50 kV x-rays
- Lower doses beyond PTV volume
- 3.4 Gy x 10 fractions?
- More data needed

Conclusions

- Radiobiology is becoming increasingly important in all aspects of radiotherapy
- More accurate applicators and imaging gives ability for dose escalation-but with due care
- Translational research will be important to identify who may benefit from different techniques
- Long term follow up is essential to determine response and toxicity