Robert A. Weinberg

The Biology of Cancer
First Edition

Chapter 17:
The Irrational Treatment of Cancer

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Oncology 520
RADIOThERAPY (XRT)

Lecturer: Dr. David Murray
March 20th, 2012
Role of XRT in the management of cancer

- **XRT** is one of the most effective treatments for cancer.

- **Surgery** is usually the primary form of treatment: it leads to good therapeutic results in a range of early non-metastatic tumors.

- **XRT** has replaced surgery for many tumors of the head and neck, cervix, bladder, prostate and skin, where it gives a reasonable probability of tumor control with good cosmetic result.

- In addition to its curative role, XRT is a valuable means of palliation for many patients with a variety of types of cancer.

- **Chemotherapy (CT)** is currently the third most important modality. Many patients receive CT at some point in their management. Useful symptom relief and disease arrest is often obtained.

- CT is being increasingly used in an adjuvant setting.
“Radiotherapy remains a mainstay in the treatment of cancer. Comparison of the contribution towards cure by the major cancer treatment modalities shows that of those cured, 49% are cured by surgery, 40% by radiotherapy and 11% by chemotherapy”

**Therapeutic Index (TI)**

- **TI** is the most important factor in XRT.
- The dose that can be delivered to a tumor is limited by damage to surrounding normal tissue and the consequent risk of complications.
- As radiation dose is increased, tumor response generally increases, but the same is true of normal tissue injury.
TCP and NTCP

–XRT treatments are designed on the basis of the upper limit of tolerance of the dose-limiting normal tissue.

• Optimization of XRT treatment plans involves the computation of two factors:
  
  **Tumor Control Probability (TCP); and**
  
  **Normal Tissue Complication Probability (NTCP).**

• **TI** depends on maximizing TCP for a given clinically acceptable level of NTCP (usually 5%).
Hypothetical dose responses for TCP (−) and NTCP (−−), illustrating the concept of TI for XRT.

A greater TI based on the same level of 5% NTCP would be achieved if the differential response between tumor tissue and critical normal tissue elements could be increased through the appropriate use of modifying agents, as shown in the right hand panel.
Unfortunately, malignant tumors tend to infiltrate surrounding normal tissue, so the treatment field must encompass a margin of normal tissue around the known extent of a tumor.

- Clinical target volume [CTV] = GTV + 0.5 cm margin.
- Internal target volume [ITV] = CTV + patient specific margin for tumor motion.
- Planning target volume [PTV] = CTV/ITV + 0.5 cm margin.
- CTV2 = involved or at-risk lymph nodes.
- PTV2 = CTV2 + 1 cm margin.

{OAR = organ at risk}. 
The major TI in XRT derives from **dosimetric** factors (contrast with CT in the next lecture).

To obtain the maximum dose to a tumor while minimizing dose to surrounding normal tissue, the oncologist will often use a number of overlapping external radiation beams.

The dose at any given location is calculated by summing the doses given by the various individual beams.

The dose distribution is represented by a series of iso-dose curves (like contours on a map).
XRT delivery:
“Physical” therapeutic index
A second major contribution to TI derives from "dose-fractionation".

XRT usually involves giving 25-35 individual dose fractions of about 2 Gy* given 5 or 6 days/week over a period of 5-7 weeks.

Why is this? Tumors do continue to grow during treatment!

*Gy (Gray): The SI unit of absorbed radiation dose. 1 Gy = 1 J/kg.
Clonogenic cell survival curves: the basis for experimental XRT

• Tumor control by XRT depends on preventing the continued proliferation of clonogenic tumor (stem?) cells.

• The effects of radiation on normal tissues are also believed to be mediated in part by the death of stem cells within those tissues.

• Evaluation of the survival of clonogenic cells following treatment is thus an important tool in experimental cancer therapy.
Cell survival curves

- Cell killing is usually described by a "survival curve".

- The fraction of cells surviving after a given dose (plotted on a log scale) is graphed versus radiation dose in Gy (plotted on a linear scale).

Survival curve (solid line) as defined by the linear-quadratic (LQ) model of cell killing. The curves defined by the two components of the equation are shown separately as the dashed lines.

The Linear-Quadratic (LQ) model

- Survival curves for human tumor cells are well fitted by the LQ equation.

\[ SF = e^{-(\alpha D + \beta D^2)} \quad \text{or} \quad -\ln[SF] = \alpha D + \beta D^2 \]

- Survival at doses < 2 Gy is dominated by the linear (\( \alpha \)) term.
- As will be seen later, the quadratic/2-hit (\( \beta \)) term is important because it represents the fraction of killing caused by damage that can be repaired by fractionation of the radiation dose over time, i.e., the impact of \( \beta \)-type damage is time-dependent.
- In contrast, \( \alpha \)-type/1-hit damage is independent of time.
- The \( \alpha/\beta \) ratio is the dose where the \( \alpha \) and \( \beta \) contributions to cell killing are equal.
- There are no systematic differences between the survival curves for normal and malignant cells.
The 5 Rs of XRT

- The biological factors that influence the response of normal and neoplastic tissues to fractionated XRT have been summarized as the 5 Rs of XRT:

  R1. Repair
  R2. Redistribution (of cells within the cell cycle)
  R3. Repopulation
  R4. Reoxygenation
  R5. Radiosensitivity

- Repair and repopulation tend to make the tissue more resistant to a second dose of radiation, i.e., to increase the total dose required to achieve a given level of biological damage (an iso-effect) when XRT is fractionated.

- Redistribution and reoxygenation tend to make tissues more sensitive, i.e., to reduce the required total dose for an iso-effect.

- Redistribution and repopulation are important only in rapidly proliferating cell populations.
In the first half of the 20th century, it became evident that the biological effect of XRT given as fractionated daily doses was less than the effect of the same total dose given as a single treatment.

A major development in the 1980s was the realization that early and late normal-tissue complications are differently modified by a change in dose fractionation.

**Late**: injury manifests months to years post-XRT. Can be life threatening!

**Early**: injury manifests within days to weeks post-XRT. Generally manageable.
Repair: Split-dose recovery/repair

• Split-dose recovery/repair is the major mechanism underlying the clinical observation that a larger total dose can be tolerated when an XRT dose is fractionated.

• The repair capacity of cells can be related to the parameter $\beta$ in the LQ equation. Larger values of $\beta$ imply a greater split-dose recovery capacity.

• Single-hit ($\alpha$) damage, in contrast, is not spared by dose fractionation.

• Recovery occurs during the first few hours after exposure.

• Human tissues typically require $\sim 4$-12 h for complete split-dose repair.

Influence of dose fractionation on the shape of cell-survival curves. When complete repair occurs between the fractions, the shoulder of the survival curve is repeated for every fraction (after Elkind and Sutton, 1960).
The LQ model and fractionation for normal tissues

- The LQ model nicely describes the relationship between total iso-effective dose and the dose per fraction in fractionated XRT.

- If iso-effective total dose (or tolerance dose) is measured as a function of decreasing dose per fraction (or increasing number of fractions), it becomes apparent that late-responding tissues are spared by dose fractionation much more (steeper curve!) than early-responding tissues.

Relationship between total iso-effective dose and dose per fraction for a variety of normal tissues in experimental animals. The curves for late-responding tissues (full lines) are steeper than those for early-responding tissues (broken lines).

Why the difference between the fractionation response of early and late-responding tissues

**EARLY**  
High $\alpha/\beta$ ratio (7-20 Gy)  
Flatter survival curve  
Low repair capacity

**LATE**  
Low $\alpha/\beta$ ratio (0.5-6 Gy)  
Bendier survival curve  
High repair capacity


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Hypothetical survival curves for target cells in early- and late-responding tissues

- **Tumors** are typically (but not always) like **early** responding normal tissues, sometimes with an even higher $\alpha/\beta$ ratio, i.e., show little repair.
"Redistribution" results from cell-cycle progression effects occurring during a fractionated treatment.

Following the first fraction of XRT, a certain proportion of tumor cells will be killed.

Cells that survive a first dose of XRT will tend to be in a resistant phase of the cell cycle (e.g., late-S).

Within a few hours, they may progress to a more sensitive phase and be killed more efficiently by the next XRT fraction.

Applies to both tumors and proliferating normal tissues.

Radiosensitivity of cells in the different phases of the cell cycle


Cyc = cyclin; cdk = cyclin-dependent kinase, M = mitosis, S = DNA synthesis, G = “gap”.

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• During a 5-7 week course of XRT, cells that survive irradiation may proliferate and thus increase the number of cells that must be killed.

• **Repopulation** applies to both tumors and proliferating normal tissues.

• Tumor-cell proliferation during treatment may thus reduce the effectiveness of XRT.

• Withers *et al* (1988) drew attention to this phenomenon; re-analysis of their data by Bentzen and Thames (1991) plots the dose to achieve tumor control in 50% of cases (i.e., TCD$_{50}$) versus overall treatment time for squamous cell carcinomas of the head and neck.

R4: Reoxygenation

- Hypoxic cells are more resistant to X rays than well-oxygenated cells.
- The **oxygen-enhancement ratio (OER)** for cell killing is ~2.5-3 for many mammalian cell types.
- Most tumors contain a significant proportion of hypoxic cells and hence are more resistant to radiation.
- In contrast, most normal tissues are well oxygenated and are fully sensitive to radiation.
- Hypoxia (and thus reoxygenation) effects thus apply mostly to tumors.

Survival of human cells exposed to X rays in the presence or absence of oxygen.

Two general models have been proposed to explain the existence of hypoxic cells in tumors.

The tumor cord model suggests that hypoxic cells exist at the limits of the diffusion range of oxygen away from the blood vessels (~150 µm). This is referred to as "chronic" hypoxia.

Hypoxia development, 2

- A second model proposes that flow in tumor blood vessels fluctuates such that regions of tumors supplied by one or more blood vessels may become hypoxic for short periods of time as a result of intermittent interruptions in blood flow.

- This results in "transient" or "acute" hypoxia.

Principal differences between the vasculature of normal and malignant tissues.

- Normal tissues have relatively uniform blood vessels that are sufficiently close together to oxygenate all of the tissue.
- Tumor blood vessels are tortuous and have sluggish irregular blood flow.
- Consequently, tumors have regions of hypoxia between the vessels (chronic hypoxia) and areas of acute or “transient” hypoxia adjacent to temporarily closed vessels.

Reoxygenation

- **Reoxygenation**: the process by which tumor cells that were hypoxic at the time of irradiation become oxygenated afterwards.

- Because of the OER effect, more cells will be killed in the well-oxygenated regions of the tumor than in the hypoxic region.

- The cells that survive the first dose of XRT will tend to be hypoxic, but thereafter their oxygen and nutrient supply may improve, leading to an increase in their radiosensitivity.

The time course of changes in the hypoxic fraction during the life history and response to XRT of a tumor.
If reoxygenation is rapid and complete, hypoxic cells should have little influence on the outcome of a course of fractionated XRT (e.g., 30 x 2-Gy fractions).

Recent studies using an Eppendorf electrode/oxygen sensor indicate that:
- tumors do contain areas of hypoxia ....

**PURPOSE:** To investigate changes in tumor oxygenation ($pO_2$) by polarographic needle electrode measurements, following fractionated external beam XRT in carcinoma of the cervix.

**METHODS:** Normal and tumor tissue oxygenation measured in 19 patients prior to and after 40-45 Gy of XRT delivered in 20 fractions over 4 weeks.

**RESULTS:** Tumor oxygenation increased in the majority of patients (15/19) following 40-45 Gy of XRT. No significant difference in normal tissue oxygenation pre- and post-XRT.


... and reoxygenation does indeed occur in human tumors during fractionated XRT.
Despite fractionation and reoxygenation, hypoxia is predictive for clinical response (TCP) in:

- Head and neck cancer (M Nordsmark et al., 1996; D Brizel et al., 1999).

TCP is predicted by pre-treatment hypoxia in carcinomas of the head and neck. 

\[ pO_2 \text{ was measured using an Eppendorf electrode.} \]
• The Eppendorf electrode is invasive and limited to accessible tumors.

• Non-invasive imaging techniques are an attractive alternative but need to be validated.
Non-invasive hypoxia positron emission tomography (PET)-imaging probes?

• These are typically based on the 2-nitroimidazole CORE containing the positron-emitting isotope $^{18}\text{F}$.

- $[^{18}\text{F}]$ penta-F-etanidazole (EF5)
- 1-$\alpha$-D-(5-deoxy-5-$[^{18}\text{F}]$-fluoroarabinofuranosyl)-2-nitroimidazole ($^{18}\text{F}$-FAZA)
- $[^{18}\text{F}]$ F-misonidazole (FMISO)
Non-invasive hypoxia PET imaging with $^{18}$F-EF5 and $^{18}$F-FMISO: Pre-clinical

$^{18}$F-EF5 and $^{18}$F-FMISO uptake in mice bearing subcutaneous B16 murine melanoma tumors.

SM Ametamey et al., 2004.
Non-invasive hypoxia PET imaging with $^{18}$F-FMISO: Clinical

$[^{18}F]$-FMISO selectively binds in hypoxic areas of head-and-neck tumors. Scans are of the same patient. Left, $^{18}$F-FMISO; Right $^{18}$F-FDG

PET ($^{18}$F-FMISO) and Eppendorf electrode measurements correlate fairly well.


[$^{18}$F]-FMISO versus Eppendorf electrode assessments of tumor hypoxia in 16 head-and-neck cancer patients.
And finally, hypoxia has major non-radiobiological effects

- Chronically hypoxic tumors are also more clinically aggressive and metastatic (Bristow RG, Hill RP. Hypoxia, DNA repair and genetic instability. Nat Rev Cancer 8, 180-192, 2008.)

- The chronically hypoxic tumor environment may promote and/or select for genomic instability and genetic heterogeneity, and thus for more malignant cellular phenotypes.

- Hypoxia may also influence tumor response to therapy by altering gene expression. E.g., activation of the transcription factors HIF-1 and NF-κB by hypoxia may contribute to malignant progression by promoting cell proliferation and survival and/or up-regulating genes that control angiogenesis and cell adhesion.
R5: Radiosensitivity

- Human tumors differ in their curability by XRT.
- A range of radiosensitivity is also found among human tumor cell lines.

(a) Survival curves for a number of different human melanoma cell lines.
(b) The low dose region of these curves.

Radiosensitivity, contd.

- That the cellular radiosensitivity of human tumors could be an important determinant of clinical radioresponsiveness was demonstrated by Fertil and Malaise (1981) and by Deacon et al (1984).

- These studies determined parameters such as surviving fraction at 2 Gy (SF2).

- Within each category of clinical radioresponsiveness there was a significant trend in the data towards Group A having lower and Group E having higher SF2 values.

SF2 values for 51 human tumor cell lines classified according to clinical tumor radioresponsiveness

A Neuroblastoma, lymphoma, myeloma
B Medulloblastoma, small-cell lung carcinoma
C Breast, bladder, and cervix carcinoma
D Pancreas, colorectal, squamous lung carcinoma
E Melanoma, osteosarcoma, glioblastoma, renal carcinoma

J Deacon et al. Radiother Oncol. 2:317-323;1984
Radiosensitivity, contd.

● Radiosensitivity is predictive for clinical response in some tumor sites, notably:
  
  Cervical carcinoma (West et al 1997)*
  Head and neck cancer (Girinsky et al 1992)
  as well as in late-reacting normal tissues (Burnet et al 1994; Geara et al 1993).

TCP data for cervical cancer patients stratified by *in vitro* SF2 values.
Tumor size

- The dose of XRT required to control a tumor depends on the number of stem cells.

- Large tumors are more difficult to cure because more clonogenic cells have to be killed.

- A course of XRT that can achieve a surviving fraction of $10^{-9}$ could be curative in a tumor that has less than $10^9$ clonogenic cells, but probably not in one that has $10^{12}$.

Recent advances in XRT

Most improvements have come in 3 areas:

- Better fractionation.
- Better dose distribution.
- Individualization of treatment.
Hyperfractionation

- Most tumors behave like early-responding normal tissues (high $\alpha/\beta$ ratio, low repair capacity); because late reactions are usually dose-limiting, small doses per fraction should give the best therapeutic index (TI).

- **Hyperfractionation** using a larger number of dose fractions below 2 Gy is predicted to give a therapeutic gain.

- There is no change in overall treatment time. Because of the reduced fraction size and increased total dose, more fractions are required and these must be given more than once per day. The fraction interval is maintained at ~6 h to ensure sufficient time for repair.
Hyperfractionation

- Tested in a randomized clinical trial of oropharyngeal cancer.

- The larger total dose in the hyperfractionated treatment produced an increase of ~19% in TCP.

EORTC (22791) trial of hyper-fxn.
Local tumor control; Patients free of late effects, grade 2+.

Hyper-fxn: 70 x 1.15 Gy (2 fxn/day, 4-6 h interval); total dose 80.5 Gy.

Conventional: 35 x 2 Gy; total dose 70 Gy.
Overall time 7 weeks in both arms.

[2] Accelerated fractionation

• Use of a reduced overall treatment time with a conventional dose per fraction, achieved using multiple fractions per day.

• Aim is to reduce the adverse impact of tumor-cell repopulation during XRT, thereby increasing TCP.
Accelerated fractionation

• H&N patients with slowly proliferating tumors responded significantly better than patients with rapidly proliferating tumors.

• When patients were stratified into those receiving conventional (7.5 weeks) or accelerated (5 weeks) XRT, patients with rapidly proliferating tumors responded better to accelerated treatment.

• For patients with slowly proliferating tumors, it made no difference.

Results of the EORTC 22851 cooperative trial of accelerated XRT in advanced head and neck (H&N) cancer, analyzed at 3 years. A: Survival. B: local tumor control. Conventional: 72 Gy, 2 Gy per fraction, 1 fraction per day, no split, ~7 weeks overall time. Accelerated: 72 Gy, 1.6 Gy per fraction, 3 fractions per day, 1 week XRT - 2 weeks gap - 2 weeks XRT, 5 weeks overall time.

Continuous Hyperfractionated Accelerated XRT (CHART) is a combination of hyperfractionation and accelerated fractionation.

Early results of a phase II CHART trial in head and neck and bronchial cancer. There was a significant difference in local control: head and neck, $p = 0.005$; bronchus, $p < 0.001$.

[4] Sealed-source brachytherapy
Low dose-rate “unsealed source” therapies: Radioisotope Therapy (RIT)

- Low dose-rate XRT represents the ultimate hyper-fractionation and presumably sparing of late effects.
- **RIT** can be defined as the:

  “Systemic administration of a targeted radionuclide utilizing short range $\beta$ particle or electron emissions to achieve a clinically important outcome for a patient with primary or metastatic cancer”

RIT targeting strategies

- Monoclonal antibodies (MAbs)
- Antibody constructs/fragments
- Peptides
- Small molecules
- Metabolic precursors
- Biologicals
- Physiological processes (e.g., hypoxia)
Principles of Radioimmunotherapy

- Targeted delivery of radiation to tumor cell antigens.
- Greater exposure of tumor vs. surrounding normal tissues by virtue of limited path length of particle emissions and selectivity of the carrier antibody.
- Crossfire of particle emissions.
- Continuous low dose rate exposure.

<table>
<thead>
<tr>
<th>MAbs</th>
<th>Peptides</th>
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<tr>
<td>$^{90}$Y Zevalin - Lymphoma</td>
<td>$^{131}$I Lymphorad - Lymphoma</td>
</tr>
<tr>
<td>$^{131}$I Bexxar - Lymphoma</td>
<td>$^{111}$InOctreotide</td>
</tr>
<tr>
<td>$^{90}$Y HMFG 1 - Ovarian</td>
<td>$^{90}$Y Octreotide</td>
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<td>$^{90}$Y Lanreotide</td>
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<td>$^{177}$Lu Octreotate - Neuroendocrine tumors</td>
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Zevalin targets bind to the CD20 antigen found on the surface of normal and malignant B cells (but not B cell precursors).

\(^{18}\text{F-Fluorodeoxyglucose (FDG) PET scans:}\)
FDG is a marker for metabolic activity/glycolysis

Source: Dr. Sandy McEwan
Use of sophisticated computerized treatment planning and delivery, e.g., Tomotherapy

- Use of increasingly sophisticated imaging-based 3-dimensional dose-delivery techniques such as image-guided adaptive radiotherapy (IGAR) or intensity-modulated radiotherapy (IMRT).

- **Tomotherapy** is a current extension of this approach.

- Involves complex computer-controlled beam delivery using multi-leaf collimators.
Helical Tomotherapy unit
Helical Tomotherapy

Multi-leaf collimator (modulates fan beam)

MV CT Scan

Megavoltage Detector: provides delivery verification and dose reconstruction.

Helical scanning
**Mesothelioma**

Mesothelioma: a form of cancer almost always caused by asbestos. Malignant cells develop in the mesothelium, a protective lining that covers most of the body's internal organs. The most common site is the **pleura** (outer lining of the lungs and internal chest wall).

**Malignant Mesothelioma, coronal CT scan.** The mesothelioma is indicated by yellow arrows; the central pleural effusion is marked with a yellow star. (1) right lung, (2) spine, (3) left lung, (4) ribs, (5) aorta, (6) spleen, (7) left kidney, (8) right kidney, (9) liver.
Tomotherapy for the treatment of mesothelioma
Tomotherapy-IMRT as an option for patients with hypoxic tumors identified by PET/MRI?

If PET or MRI imaging can reliably define hypoxic zones in tumors, then what are the possibilities?

- Other modalities, such as charged particle beams.
- Hypoxic-cell radiosensitizers, cytotoxins and chemosensitizers such as Tirapazamine [next time].
- **Tomotherapy**: image guided dose-escalation to hypoxic zones ("dose painting").


http://www.medizin.uni-tuebingen.de/medphys/research.html
Optimizing TI by screening for XRT-hypersensitive patients

• XRT is generally given to some "acceptable" level (5%) of complications based on the dose-limiting normal tissue for that field/tumor.

• If one could identify genetically predisposed individuals (for complications) that might contribute to this 5% and remove them from the curve, then a higher dose could be given to the remainder, leading to increased tumor cure probability.


NTCP curves for stratified vs. heterogeneous patient populations

Courtesy of Dr. R Gatti, UCLA
Predictive assays of individual radiosensitivity: where to?

- Gene expression using microarrays, polymorphisms in key radiosensitivity genes
- Applicable to both normal tissue and tumor responses.

*Cancer Therapy: Clinical*

Association of DNA Repair and Steroid Metabolism Gene Polymorphisms with Clinical Late Toxicity in Patients Treated with Conformal Radiotherapy for Prostate Cancer

Sambasivarao Damaraju,1,2,3 David Murray,1,3 Jennifer Dufour,2 Diana Carandang,2 Sten Myrehaug,1,3 Gino Fallone,1,3 Colin Field,1,2 Russell Greiner,2,4 John Hanson,1 Carol E. Cass,1,2,3 and Matthew Parlament1,3