Radiobiological knowledge is used to optimize treatment

In this lesson we consider some concepts associated with radiobiology and related to treatment optimization

1. Fractionation
2. The 4 R’s (5R’s) of radiobiology
3. Dose-volume histograms (DVH) and isodose curves
4. Equivalent Uniform Dose (EUD)
5. Optimization (basic concepts of treatment plans)
1. Fractionation

**Fractionation** of radiation treatment specifies how to split dose over a period of weeks rather than in a single session so that the treatment results in a better therapeutic ratio.

To achieve the desired level of biological damage the total dose in a fractionated treatment is much larger than that in a single treatment.
In a simple Poisson model of the surviving fraction, i.e., with an exponent that is proportional to the dose. Fractionation approaches this linear behavior.

\[ S(D) = e^{-D/D_0} = 10^{-D \log_{10} e / D_0} = 10^{-D / D_{10}} \]

\[ D_{10} = D_0 / \log_{10} e \approx 2.3D_0 \]
The algebra of fractionation, using the linear-quadratic law

Survival probability with $n$ doses $D$ 

$$[S(D)]^n$$

The corresponding **biological effect** is

$$E = - \ln[S(D)]^n = -n \ln S(D)$$
$$= n(\alpha D + \beta D^2)$$
$$= \alpha (nD) \left(1 + \frac{D}{\alpha/\beta}\right)$$

- total dose
- relative effectiveness
The relative effectiveness is always $> 1$, therefore the biologically effective dose is always greater than the total dose.
Response to fractionation varies with tissue, fractionation spares late responding tissues

When $\alpha/\beta$ is high (>6Gy) the survival curve is almost exponential, when $\alpha/\beta$ is low (1-4Gy) the shoulder is wide.
<table>
<thead>
<tr>
<th>Early-Responding Tissues</th>
<th>$\alpha/\beta$</th>
<th>Late-Responding Tissues</th>
<th>$\alpha/\beta^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunal mucosa</td>
<td>13</td>
<td>Spinal cord</td>
<td>1.6–5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(110, 166, 245, 284, 285, 322)</td>
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<tr>
<td>Colonic mucosa</td>
<td>7</td>
<td>Kidney (44, 127, 291, 305)</td>
<td>0.5–5</td>
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<tr>
<td>Skin epithelium</td>
<td>10</td>
<td>Lung</td>
<td>1.6–4.5</td>
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<td></td>
<td></td>
<td>(90, 211, 214, 275, 289, 295)</td>
<td></td>
</tr>
<tr>
<td>Spermatogenic cells</td>
<td>13</td>
<td>Liver (91)</td>
<td>1.4–3.5</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>9</td>
<td>Human skin</td>
<td>1.6–4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(32, 211, 279, 280)</td>
<td></td>
</tr>
<tr>
<td>Melanocytes (302)</td>
<td>6.5</td>
<td>Cartilage and submucosa</td>
<td>1.0–4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(171, 329)</td>
<td></td>
</tr>
<tr>
<td>Tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse fibrosarcoma metastases (173)</td>
<td>10</td>
<td>Dermis (106)</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>Human tumors (169, 171, 195, 258)</td>
<td>6–25</td>
<td>Bladder (252, 265)</td>
<td>5.0–10.0</td>
</tr>
<tr>
<td>Experimental tumors (306)</td>
<td>10–35</td>
<td>Bone (212)</td>
<td>1.8–2.5</td>
</tr>
</tbody>
</table>
An equation for BED that includes tumor repopulation

After a "kickoff time" \( T_k \), tumor cells start proliferating again, therefore the tumor population after treatment has changed by the total factor

\[
\frac{N(T)}{N_0} = \left[ S(D) \right]^n 2^{(T-T_k)/T_p}
\]

where \( T_p \) is the tumor cells’ duplication time. Taking logarithms, we find

\[
n \ln[S(D)] + \frac{T - T_k}{T_p/\ln 2} = -\alpha n D \left( 1 + \frac{D}{\alpha/\beta} \right) + \frac{T - T_k}{T_p/\ln 2}
\]
\[ n \ln[S(D)] + \frac{T - T_k}{T_p/\ln 2} = -\alpha n D \left(1 + \frac{D}{\alpha/\beta}\right) + \frac{T - T_k}{T_p/\ln 2} \]

BED\((D, n, T) = (nD) \left(1 + \frac{D}{\alpha/\beta}\right) - \frac{T - T_k}{\alpha T_p/\ln 2} \]

BED\((D, n) - \frac{T - T_k}{\alpha T_p/\ln 2} \]
Example, conventional treatment:

**30F x 2Gy/6 weeks**

\[\text{BED(early)} = (nD) \left( 1 + \frac{D}{\alpha/\beta} \right)\]

\[= (60 \text{ Gy}) \left( 1 + \frac{2}{10} \right)\]

\[= 72 \text{ Gy}_{10}\]

\[\text{BED(late)} = (60 \text{ Gy}) \left( 1 + \frac{2}{3} \right)\]

\[= 100 \text{ Gy}_3\]

39% difference between early- and late-responding
Example, hyperfractionation:

70F x 1.15 Gy twice daily/7 weeks

BED(early) = (nD) \left( 1 + \frac{D}{\alpha/\beta} \right)

= (80.5 \text{ Gy}) \left( 1 + \frac{1.15}{10} \right)

= 89.8 \text{ Gy}_{10}

BED(late) = (80.5 \text{ Gy}) \left( 1 + \frac{1.15}{3} \right)

= 111.4 \text{ Gy}_3

24\% \text{ difference between early- and late-responding}
The basic aim of hyperfractionation is to further separate early and late effects.

The overall treatment time remains conventional at 6 to 8 weeks, but because two fractions per day are used, the total number of fractions is 60 to 80.

The dose must be increased because the dose per fraction is decreased.

Early reactions may be increased slightly, tumor control improved, and late effects greatly reduced.

Hyperfractionation has been shown in randomized clinical trials of head and neck cancer to improve local tumor control and survival with no increase in acute or late effects.
CHART stands for continuous hyperfractionated accelerated radiation therapy.

The protocol consists of 36 fractions over 12 days (three fractions per day) to a total dose of 50.4 to 54 Gy.

Tumor control is maintained because of the extreme acceleration of treatment time; late effects are not increased and may even decrease because of the low dose; the acute effects are severe, but their peak occurs after completion of treatment, so patient compliance is not prejudiced.
Example, CHART:

36F x 1.5 Gy (3F/day)/12 days

BED(early) = \( (nD) \left( 1 + \frac{D}{\alpha/\beta} \right) \)

\[ = (54 \text{ Gy}) \left( 1 + \frac{1.5}{10} \right) \]

\[ = 62.1 \text{ Gy}_{10} \]

BED(late) = \( (54 \text{ Gy}) \left( 1 + \frac{1.5}{3} \right) \)

\[ = 81 \text{ Gy}_3 \]

30% difference between early- and late-responding
Isoeffect equation

when two fractionation strategies have the same BED we find

\[ D_1 \left[ 1 + \frac{d_1}{(\alpha/\beta)} \right] = D_2 \left[ 1 + \frac{d_2}{(\alpha/\beta)} \right] \]

For comparison purposes it is useful to define the Equivalent Dose at 2Gy:

\[ \text{EQD}_{2\text{Gy}} = D \frac{d + \alpha/\beta}{2\text{Gy} + \alpha/\beta} \]

- equivalent dose with 2Gy fractions
- actual dose delivered in \( d \) Gy fractions
The conventional wisdom

• The LQ model satisfactorily describes the relationship between total isoeffective dose and dose per fraction over the range of dose per fraction from 1 Gy up to 5–6 Gy. In contrast, power-law formulae can only be made to fit data over a limited range of dose per fraction.

• The α /β ratio describes the shape of the fractionation response: a low α /β (0.5–6 Gy) is usually characteristic of late-responding normal tissues and indicates a rapid increase of total dose, with decreasing dose per fraction and a survival curve for the putative target cells that is significantly curved.

• A higher α /β ratio (7–20 Gy) is usually characteristic of early-responding normal tissues and rapidly-proliferating carcinomas; it indicates a less significant increase in total dose with decreasing dose per fraction and a less curved cell-survival response for the putative target cells.
The conventional wisdom (ctd.)

- **The EQD$_2$ formulae provide a simple and convenient way of calculating isoeffective radiotherapy schedules, based on the LQ model.** Tolerance calculations always require an estimate of the $\alpha / \beta$ ratio to be included.

- For short interfraction intervals, a correction may be necessary for incomplete repair. When using the EQD$_2$ formulae to calculate schedules with multiple fractions per day or continuous low dose rate, an estimate of the repair halftime must also be included.

- The basic LQ model is appropriate for calculating the change in total dose for an altered dose per fraction, assuming the new and old treatments are given in the same overall time. For late reactions it is usually unnecessary to modify total dose in response to a change in overall time, but for early reactions (and for tumour response) a correction for overall treatment time should be included. Although the effect of time on biological effect is complex, simple linear corrections have been shown to be of some value.
QUANTEC guidelines

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines are a recent effort to review and summarize normal tissue toxicity, which may suggest dose-volume treatment planning guidelines and likely reduce the rates of side effects.

The primary goal is to provide a simple set of data to be used by the busy community of practitioners of radiation oncology, physicists and dosimetrists.

The second goal is to provide reliable predictive models of the relationships between dose-volume parameters and normal tissue complications to be used in the planning of radiation therapy.

The results of this large study can be found on this webpage

http://aapm.org/pubs/QUANTEC.asp

Note that these guidelines are not final and shall certainly be revised in the future as new data become available.
PUBLICATIONS

Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)

Acknowledgement:

The QUANTEC effort was made possible, in part, by generous financial support from the American Society for Radiation Oncology (ASTRO) and the American Association of Physicists in Medicine (AAPM). The results were published in March 2010 in a special issue of the International Journal of Radiation Oncology-Biology-Physics (the Red Journal). The work is the result of the diligent efforts of numerous investigators, authors, reviewers, and support personnel. These important papers have heretofore only been available to Red Journal subscribers but ASTRO has now made this important effort open to all AAPM members through the following link. To avoid future delays in access to important papers like these members are encouraged to recommend the Red Journal to their institution's librarian. More information on the journal can be found at www.redjournal.org

» Access QUANTEC Special Issue «
2. The 4 R’s (5 !!!) of radiotherapy: a radiobiological rationale for fractionated radiotherapy

Radiobiological mechanisms that impact on the efficacy of radiotherapy. A summary list of what is important in radiotherapy (introduced by Withers in 1975)

A. Repair
B. Redistribution of cells within the cell cycle
C. Repopulation
D. Reoxygenation

... and

E. Radiosensitivity (the new, 5th R)
A. Repair

The repair of sublethal damage must be taken into account

• because it affects the tolerance of healthy tissue to radiotherapy (allowing cells to repair we can continue a treatment that should otherwise be interrupted)

• because tumor cells often have a reduced ability to repair damage, e.g., when they have a mutated P53 gene

When considering repair one must keep into account the mean repair time – e.g., the spinal cord tissue has a slow mean repair time of about 4 hours, and this means that daily doses must have at least this separation to spare that tissue.

Dose rate must also be taken into account: too low a dose rate means that both healthy and tumor tissues can start repair during a session.
**Figure 8.8** Effect of interfraction interval on intestinal radiation damage in mice. The total dose required in five fractions for a given level of effect is less for short intervals, illustrating incomplete repair between fractions. From Thames et al. (1984), with permission.
B. Redistribution

Proliferating cells have different radiosensitivities. After a session more of the cells in the S phase survive, and waiting for a redistribution of cells in different phases helps in killing them.

A low dose rate means that redistribution can take place during a session, and this should be taken into account.
C. Repopulation

Repopulation takes place both in healthy and in diseased tissues.

Usually healthy early-responding tissues begin repopulation at about 4 weeks into treatment. Prolonging treatment over 4 weeks means a reduced early radiotoxicity for these tissues. This is not relevant for late-responding tissues.

At least some tumors display accelerated repopulation after 4-5 weeks into treatment. This means that this repopulation must be countered in long treatments.
RAT TUMOUR RESPONSE

A comparison of the growth rates of these two cell lines both in the animal and in culture is of interest. Although the R1/LBL line grows faster in vivo than the R2D2 line (TD ranging from 4-8-7 days over a 20 day period cf 5-8-10 days) the reverse is true in vitro where the cultured R2D2 cells have a shorter doubling time, 14 h cf 18 h for R1/LBL. Thus, there is no correlation between the two cell lines in their growth rates in vivo and in vitro.

Studies have recently been reported on the growth delay observed for tumours of the R1/LBL line after helium-ion and neon-ion irradiation (Curtis et al., 1978). Fig. 1 shows the volume response after various doses of 220-kV X-rays as an example of the type of data obtained. The radiation-induced growth delay is determined from the tumour volume response data by calculating the difference between the times for the irradiated and the control tumours to double in volume.

In Fig. 2 tumour growth delays are plotted as a function of dose for carbon-, neon- and argon-ion beams, and are compared with the growth delay curve obtained following exposure to X-rays. RBE's for different growth delays e.g. 50 days (RBE50 values) and their standard deviations are easily calculated from these

<table>
<thead>
<tr>
<th>TABLE I.-RBE's for growth delay and tumour cure</th>
</tr>
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<tbody>
<tr>
<td>Radiation modality</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>12C</td>
</tr>
<tr>
<td>20Ne</td>
</tr>
<tr>
<td>40Ar</td>
</tr>
<tr>
<td>12C</td>
</tr>
<tr>
<td>20Ne</td>
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<tr>
<td>15 MeV neutrons</td>
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</tbody>
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* Extrapolated value.
* RBE for TCD 90/120, calculated from extrapolation of cell survival data.

![Graph showing normalized tumour volume over time after irradiation.](image)

**Fig. 1.**—Volumes of R1/LBL tumours are plotted as a function of time for controls and for tumours receiving graded doses of 220-kV X-rays. The volumes have been normalized to unity on the day of irradiation. Numbers in parentheses represent the number of tumours exposed to each radiation dose. Error bars represent one standard error of the mean.
D. Reoxygenation

Many tumor tissues are hypoxic, and this protects tumor cells from radiation because of the Oxygen Effect. Therefore one useful strategy consists in helping oxygen diffuse through tissues.

Reoxygenation can be achieved by killing cells closer to blood vessels, so that oxygen penetrates more deeply into the tumor tissue, and also using growth factors that reestablish a healthier, more regular vascularization in the tumor tissue (e.g., VEGF).
FIG. 4.—Oxic survival curves are compared for R2D2 cells irradiated in vitro as a suspension and in vivo within a solid tumour. The survival curve for oxygenated cells in vivo was calculated from the measured survival curves for tumours irradiated in situ in air-breathing rats (data points shown) and in nitrogen-asphyxiated rats.
E. Radiosensitivity

Radiosensitivity differs in different cell types, and this factor must be included in the therapeutic strategy.

Radiosensitivity can be enhanced in tumor cells with proper sensitizing chemicals.
3. Isodose curves and dose-volume histograms (DVH)

Dose is distributed in space and both tumor tissue and normal tissue are affected.

For this reason it is important to characterize the dose received by both tumor tissue and normal tissue in a quantitative way.
Edoardo Milotti - Radiobiology

Example of two-dimensional isodose curves in the treatment of retroperitoneal liposarcoma, close to critical organs – kidneys and spinal cord.

PTV = Planned Target Volume
OAR = Organ At Risk
Dose deposited in patient is measured using a fine cubical grid, and the cubes are called **voxels**.
Dose-volume histograms are cumulative distributions of the voxels receiving at least the given dose.

Differential dose-volume histograms are also used (fraction of the voxels receiving exactly the given dose).
4. Equivalent Uniform Dose (EUD)

According to Niemierko (who introduced the concept in 1997),

“For any dose distribution, the corresponding Equivalent Uniform Dose EUD is the dose in Gy, which, when distributed uniformly across the target volume, causes the survival of the same number of clonogens.”

In the discussion of EUD, “it is assumed that an irradiated tumor is composed of a large number of independent clonogens, and that random killing of the clonogens is well described by Poisson statistics. The binary response – control or failure – of an irradiated tumor is assumed to be determined by the expected number of surviving clonogens. Therefore, two different target dose distributions are equivalent if the corresponding expected number of surviving clonogens are equal.”

from Niemierko, Med. Phys. 24 (1997) 103
Example with a Poisson cell kill model

\[ S(D) = \exp\left(-\frac{D}{D_0}\right) \]
\[ S(D_{\text{ref}}) = \exp\left(-\frac{D_{\text{ref}}}{D_0}\right) \]

Surviving fraction for a generic dose \( D \) and for a reference dose \( D_{\text{ref}} \)

The surviving fraction can be rewritten as an explicit function of the reference dose

\[ \ln S(D_{\text{ref}}) = -\frac{D_{\text{ref}}}{D_0} \quad \Rightarrow \quad D_0 = -\frac{D_{\text{ref}}}{\ln S(D_{\text{ref}})} \]

\[ \ln S(D) = -\frac{D}{D_0} = \frac{D \ln S(D_{\text{ref}})}{D_{\text{ref}}} \quad \Rightarrow \quad S(D) = \left(S(D_{\text{ref}})\right)^{D/D_{\text{ref}}} \]
Now assume that there are \( N \) cells uniformly scattered in a volume \( V \), which is subdivided in subvolumes \( V_i \) which receive each a dose \( D_i \). Then the number of cells that survive in the i-th volume is

\[
\sum_i n_i = \frac{N}{V} \sum_i V_i S(D_i) = \frac{N}{V} \sum_i V_i (S(D_{\text{ref}}))^{D_i/D_{\text{ref}}}
\]

Therefore the total surviving fraction is

\[
\frac{1}{N} \sum_i n_i = \sum_i \frac{V_i}{V} (S(D_{\text{ref}}))^{D_i/D_{\text{ref}}} = \sum_i v_i (S(D_{\text{ref}}))^{D_i/D_{\text{ref}}}
\]
We would obtain the same surviving fraction

\[ \bar{S} = \sum_i v_i \left( S(D_{\text{ref}}) \right)^{D_i/D_{\text{ref}}} \]

with an equivalent uniform dose EUD such that

\[ \bar{S} = \left( S(D_{\text{ref}}) \right)^{\text{EUD}/D_{\text{ref}}} \]

\[ \rightarrow \quad \text{EUD} = D_{\text{ref}} \frac{\ln \bar{S}}{\ln S(D_{\text{ref}})} = D_{\text{ref}} \frac{\ln \sum_i v_i S(D_{\text{ref}})^{D_i/D_{\text{ref}}}}{\ln S(D_{\text{ref}})} \]
This holds for the simple Poisson-model surviving fraction. More complex cases are treated in the paper by Niemierko:

- absolute volume effect
- nonuniform spatial distribution of clonogens
- dose-per-fraction effect (using the LQ model)
- proliferation effect
- inhomogenity of patient population
5. Optimization (basic concepts of treatment plans)

We optimize a treatment by

• maximizing damage to tumor tissue
• minimizing damage to normal tissue

This is a complex process that requires numerical solutions.

In the following slides we analyze a simple example that utilizes Monte Carlo simulation to analyze the effects of an IMRT (Intensity-Modulated Radiation Therapy) treatment (IMRT is an improved version of the 3D-treatment).
In this example the radiation is delivered by beams with the same Gaussian intensity modulation (this kind of intensity modulation is not realistic, it is just part of this specific example)

We also take simple sigmoid approximations of the NTPC and TCP curves
Example distribution with 6 beams

Each dot represents the position of one absorbed photon. About $10^5$ photons have been generated in this simulation run.

Red dots represent photons absorbed in the tumor.
Isodose curves

From voxels to isodose curves
6- and 8-beam comparison
Dose-volume histograms in the target volume with 6 and 8 beams
Distribution of TCP values in the voxels of the target volume
Dose-volume histograms outside the target volume with 6 and 8 beams

About 12% of all voxels outside the target region receive at least 10 Gy

About 5% of all voxels outside the target region receive at least 10 Gy
Distribution of NTCP values in the voxels outside the target volume
By carefully adjusting the beam parameters we can optimize the results of radiation therapy.

This simple example shows how to use the basic principles, however:

- example limited to 2D (real treatment plans must be 3D)
- no real physics (intensity does not change because of absorption, no Compton scattering of photons, etc.)
- quantification of damage with simplified TCP and NTCP curves
- simple structure with circular symmetry (real cases are much more complex)
- no organ-at-risk in the vicinity
- ...
Conclusions
Overview

Molecular Biology for the Radiation Oncologist: the 5Rs of Radiobiology meet the Hallmarks of Cancer

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ABSTRACT:
Recent advances in our understanding of the biology of cancer have provided enormous opportunities for the development of novel therapies against specific molecular targets. It is likely that most of these targeted therapies will have only modest single agent activities but may have the potential to accentuate the therapeutic effects of ionising radiation. In this introductory review, the 5Rs of classical radiobiology are interpreted in terms of their relationship to the hallmarks of cancer. Future articles will focus on the specific hallmarks of cancer and will highlight the opportunities that exist for designing new combination treatment regimens. Harrington, K. et al. (2007). Clinical Oncology 19, 561–571
After decades of stagnation, technological developments have brought three-dimensional conformal radiotherapy and intensity-modulated radiotherapy within the reach of most departments [1]. In fact, with a few exceptions, the pace of introduction of the new technologies has outstripped our ability (or willingness) to conduct carefully controlled randomised clinical trials comparing them with conventional radiotherapy. In addition, the use of particulate radiation (protons, carbon ions) is receiving renewed attention and large collaborative projects have been established in Europe and the USA [2,3]. The next 20 years will probably require significant research effort by clinical oncologists as they focus on implementing the new technologies for radiation delivery.

More recently, after much previous debate and controversy, meta-analyses have clearly shown the clinical benefit of adding concomitant cytotoxic chemotherapy to radiotherapy in a number of tumour types in both radical and adjuvant postoperative settings [4–9]. As a consequence, concomitant chemoradiotherapy has become the standard of care for many tumour types. This change in practice has brought with it new problems, including the selection of appropriate patients for chemoradiotherapy and the management of the increased acute (and possibly late) toxicity of chemoradiotherapy [10,11].

While these changes in clinical practice have been taking place, we have witnessed fundamental changes in our understanding of the biology of cancer and, as a consequence, we are just beginning to reap the rewards of this research in the form of novel targeted agents. For example, a recent phase III randomised study of radiation with or without a targeted monoclonal antibody (cetuximab) in patients with head and neck cancer showed a very significant advantage for the combined regimen [12] and this agent is now undergoing evaluation in randomised studies with chemoradiotherapy [13]. Undoubtedly, the next decade will see a wide range of new targeted drugs coming to the clinic for use alongside standard chemoradiotherapy regimens. Indeed, it is not inconceivable that in due course some of these agents may replace cytotoxic chemotherapy in combination strategies.
Receptor signaling can also be deregulated by elevating the levels of receptor proteins displayed at the cancer cell surface, rendering such cells hyperresponsive to otherwise-limiting amounts of growth factor ligands themselves, to which they can respond via the expression of their signaling powers; instead, the oncogenic mutations compromising Ras GTPase activity, which are thought to be transmitted in a temporally and spatially regulated fashion from one cell to its neighbors; such paracrine signaling of cognate receptors, resulting in autocrine proliferative stimulation. Alternatively, cancer cells may send signals to stimulate normal cells within the supporting tumor-associated microenvironment.

Remarkably, the precise identities and sources of the proliferative signals operating within normal tissues were poorly understood (Lemmon and Schlessinger, 2010; Witsch et al., 2002). Moreover, we still stand a decade ago and in general remain so. Attenuate Proliferative Signaling Disruptions of Negative-Feedback Mechanisms that are capable of enhancing proliferative signaling. The pathways radiating from growth factor receptors.

High-throughput DNA sequencing analyses of cancer cell genomes have revealed somatic mutations in certain human ras genes compromising Ras GTPase activity, which affect the levels of receptor proteins displayed at the cancer cell surface. Evolving signaling and thereby ensure homeostatic regulation of the flux of signals coursing through the intracellular circuitry (Wertz et al., 2002).

The past decade has witnessed remarkable progress toward understanding the mechanisms that regulate progression through the cell cycle as well as cell growth (that is, increases in cell number and thus maintenance of normal tissue architecture and function). The latter proceed to emit signals via branched intra-cellular signaling pathways, including its Akt/PKB signaling circuitry, including its key Akt/PKB signal transducer (Jiang and Liu, 2009; Yuan and Cantley, 2008). The outcome can result from structural alterations in the receptor molecules that derive from the constitutive activation of the kinase signaling pathways, including the activation of Akt/PKB kinases (see, for example, Schlessinger, 2000).

Weinberg [14] provided a useful framework for thinking about the potential relationships between the 5Rs of radiobiology (repair, repopulation, redistribution, reoxygenation, and radiosensitivity) and the hallmarks of cancer. This illustration encompasses the six hallmark capabilities originally proposed in our 2000 perspective. The past decade has witnessed remarkable progress toward understanding the mechanistic underpinnings of each hallmark.

**Figure 1. The Hallmarks of Cancer**
This illustration encompasses the six hallmark capabilities originally proposed in our 2000 perspective. The past decade has witnessed remarkable progress toward understanding the mechanistic underpinnings of each hallmark.


**Fig. 2 – Potential relationships between the 5Rs of radiobiology and the hallmarks of cancer.**

A picture of a future trial design that aims to hit the various targets on offer at a biologically optimal time in the case of Head and Neck cancer.
Therefore, in addition to possessing expertise with the new technologies, clinical oncologists will be expected to conduct and assess trials of novel targeted agents in combination with (chemo)radiotherapy. It is of paramount importance that the specialty embraces this challenge in order to ensure that the direction of clinical studies is informed by sound radiobiological principles, such that the focus is on maximising the effect of the most important component of the treatment (i.e. radiation). Failure to rise to this challenge means that clinical oncologists will take a passive role in the development of new strategies and will run the risk of being relegated to the role of radiation technicians.