Personalized Cancer Medicine: Precision Therapy Redux

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Disclosure

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Over Three Decades of Personalizing Cancer Treatment

Conformal Radiation Therapy (CRT)

Intensity Modulation Radiation Therapy (IMRT)
In a period of 10 years, Radiation Therapy has evolved from employing:

10 Mb to 1000 Mb of Data (100X)

10 to 1000 Digital Treatment Parameters (Robotic Control)

Supervised, Image-guided Operation
Accommodating the 4D nature of the lung and tailoring dose patterns to anatomy.

At 24 months, no significant differences were seen between randomised groups in non-xerostomia late toxicities, locoregional control, or overall survival.

47 patients were assigned to each treatment arm. Median follow-up was 44.0 months (IQR 30.0–59.7). At 12 months xerostomia side-effects were reported in 73 of 82 alive patients; grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group than in the conventional radiotherapy group.
Adoption of daily IGRT with same PTV margins. Retrospective analysis of toxicity and biochemical control (N=186 vs N=190)
Next Gen RT Technologies: Better dose control through physics, imaging, computation, and robotics.

- PET-guided RT
- MR-Guided RT
- Edmonton Solution
- Utrecht Solution
- Viewray Solution
- Adjacent Solutions
- Protons+
Next Generation of Personalization

- Adaptive Radiation Therapy – geometric and functional
- Image-based Biological Targets - targets and normal tissues
- Patient-specific Radiation Sensitivity – decision-making and dose prescription.
Database of Dose Targets and Tolerances

Capacity to Integrate Molecular/Functional Imaging in RT

Specific Patient

CT

CT/PET

MR

Contouring

Optimization

Geometry Change

Calc’n

IMRT Beam Patterns

Biology Change

IGRT Adjustments

\[ \sum ; \Delta \]
From the ‘3D Hypothesis’ to the ‘4D Hypothesis’

- **4D Hypothesis**: Adapting to imaged changes in geometry or function during RT will improve the therapeutic ratio.
  - A.k.a. ‘Adaptive Radiation Therapy’
Fig. 13 shows a series of pictures demonstrating the regression of a seminoma (a very radio-sensitive tumour). The radiation is applied at a low level while the tumour is large, but as the lesion regresses the smaller area is taken advantage of and larger doses are then applied. In this particular case the tumour was completely removed by accurate intense radiation.
Complex Machinery of Adaptive Radiation Therapy

Temporal Scales of Adaptive Radiation Therapy

Off-line
Auto-segmentation, deformation, inverse planning, dose accumulation, response assessment, PET/MR/CT

On-line
MV/kV CT, online planning, dose accumulation, rapid QA, monitoring, deformation, seed detection

Real-time
kV Fluoro, MR-RT, ultrasound, robotic needles/couches, motion tracking, gating, control, prediction

Intent

Therapeutic Intent
(Prescribed Dose and Constraints)

Image-based Information To Inform Adaptation
(Geometry, Biology)

Adaptive Intervention
(External Beam, Brachytherapy)
“Adaptive radiotherapy has been introduced as a feedback control strategy to include patient-specific treatment variation explicitly in the control of treatment planning and delivering during the treatment course.” D. Yan
Adaptive Radiation Therapy for Prostate Cancer

Michel Ghilezan, MD, PhD, Di Yan, DSc, and Alvaro Martinez, MD

Figure 1 Flow chart depicting the off-line image guided adaptive radiation therapy process.

Table 3 Toxicty in 728 Patients Treated With Adaptive CRT/IMRT

<table>
<thead>
<tr>
<th></th>
<th>Adaptive CRT</th>
<th>Adaptive IMRT</th>
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<tr>
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<td>Chronic</td>
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<tr>
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<tr>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Rectal bleeding</td>
<td>16%</td>
<td>4%</td>
<td>&lt;.01</td>
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</table>
Adaptive Management of Cervical Cancer Radiotherapy

Kari Tanderup, PhD, * Dietmar Georg, DSc, † Richard Pötter, MD, † Christian Kirisits, DSc, † Cai Grau, DMSoc, MD, * and Jacob C. Lindegaard, DMSoc, MD *

Since the breakthrough 10 years ago with concomitant radio-chemotherapy, substantial progress in the treatment of locally advanced cervical cancer has been lacking. Radiotherapy continues to be the cornerstone in the treatment of this disease and now shows much potential for progress, as image guidance of both external beam radiation therapy and brachytherapy, linked with strong tools for treatment planning and dose delivery, is becoming available. With these new techniques, it again seems possible to improve the therapeutic ratio as we begin to understand how the treatment for each patient can be individualized, not only in terms of volume (3-dimensional), but also during treatment (4-dimensional), as the tumor regresses and the topography of the target and organs at risk change significantly. New promising data with increased loco-regional control and de-radiation in the multimodal management of locally advanced cervical cancer.

Semin Radiat Oncol 20:121-129 © 2010 Elsevier Inc. All rights reserved.

Rationale and Potential

Today, the standard treatment of locally advanced cervical cancer is external beam radiotherapy (EBRT), concomitant chemoradiotherapy (CCRT) and salvage SBRT and/or IMRT. The use of concomitant chemotherapy, using different chemotherapeutic drugs (such as cisplatin or carboplatin) or continuous hyperfractionated accelerated radiotherapy (CHART) has been shown to increase local control, while large randomized trials show the potential for improved survival [9,25,26]. The use of intensity modulated radiation therapy (IMRT) has also been shown to be beneficial in the setting of locally advanced disease with improved local control and decreased normal tissue toxicity. However, the local

aging and point-based BT dose prescription. High rates of local control in the range 80%-95% can be achieved in small tumors, such as International Federation of Gynecology and Obstetrics stage IB1 and small stage IIB. However, the local

aging and point-based BT dose prescription. High rates of local control in the range 80%-95% can be achieved in small tumors, such as International Federation of Gynecology and Obstetrics stage IB1 and small stage IIB. However, the local
Ca Cervix: “Tumour” Shrinkage & Deformation During RT

GTV - T2 Enhancement on MR

Pre-Tx 8 Gy

20 Gy

28 Gy

38 Gy

48 Gy

Gyne Site Group - PMH
Ca Cervix – Interfraction Motion

Planning

ORBIT Workstation

Rectum-Sigmoid

Cervix

Uterus

Tumour

Bladder
Ca Cervix – Interfraction Motion

Week 1
Ca Cervix – Interfraction Motion

Week 2
Ca Cervix – Interfraction Motion
Ca Cervix – Interfraction Motion

ORBIT Workstation

Week 4
Ca Cervix – Interfraction Motion

ORBIT Workstation

- Rectum-Sigmoid
- Cervix
- Uterus
- Tumour
- Bladder

Week 5
Methods

- 33 patients with stage IB-IVA cervix cancer
- Target volumes (GTV and CTV) and OARs (rectum, sigmoid, bladder, and bowel) contoured on fused MR-CT baseline image and subsequent weekly MR scans
- Primary CTV defined as union of:
  - GTV
  - Cervix
  - Parametria
  - 2 cm of uterus superior to GTV
  - 2 cm of upper vagina inferior to GTV
Methods – Dose Accumulation / ORBIT

Planned Dose

Apply planned dose at each fraction

Deform each fraction to planning geometry

Accumulate across all fractions

Accumulated Dose
Results – Target Coverage

Message: A large fraction of patients would maintain coverage with a 3mm margin!
Computational Advances Needed for Testing the ‘4D’ Hypothesis

Auto-segmentation

Dose Tracking

Deformable Registration

Re-planning
From the ‘3D Hypothesis’ to the ‘BTV Hypothesis’

- **BTV Hypothesis**: Patterning radiation dose according to imaged functional or molecular distributions of the individual will increase the therapeutic ratio.
  - A.K.A. ‘Biologically Targeted Radiation Therapy’
“Incremental to the concept of gross, clinical, and planning target volumes (GTV, CTV, and PTV), we propose the concept of “biological target volume” (BTV) and hypothesize that BTV can be derived from biological images and that their use may incrementally improve target delineation and dose delivery.” - Ling et al.
Functional and Molecular Imaging for RT

- Tumour burden, altered metabolism, and clonogen density (e.g. FDG, MRS)
- Tumour hypoxia (e.g. F-MISO, I/FAZA, CAIX, MR-BOLD, HX4)
- Tumour proliferation (e.g. FLT)
- New imaging targets (e.g. FACBC amino acid, EGFR for re-population)
- Functional imaging of crucial healthy tissues (e.g. SPECT/CT/MR derived lung perfusion)
- Vascular and physiological measures (DCE-MR/CT, MR DWI/ADC)

Impact of Specific and Sensitive Imaging of Disease on Radiation Therapy

1. Reduce observer-dependent variation in the extent of gross and clinical targets.

2. Enable biologically-modulated targeting of the radiation dose.

3. Enable prediction of response based upon pre- or intra-treatment changes in the image-based biomarkers.

See Steenbakers 2006, Bentzen 2005, Mayr 2010
Magnetic Resonance Imaging: Burden of Disease in the Prostate

- ↓ T2
- Fast T1 contrast enhancement & washout
- ↓ Water diffusivity
- ↑ Choline/Citrate

Courtesy of C. Menard
Boost – Either HDR Brachytherapy or VMAT

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<th>IB-VMAT</th>
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<table>
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<table>
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<td>110</td>
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<td>120</td>
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<tr>
<td>130</td>
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NCIC Funded Project - Menard/Craig - PMH
Lung Cancer - Survival of Metabolic Responders vs Non-responders

L: Mac Manus (Melbourne), JCO 2003;21(7):1285
M: van Baardwijk (MAASTRO), Radiother Oncol 2007;82(2):145
RT: Eschmann (Tuebingen), Lung Cancer 2006;55:165
Residual Response Correlates with Site of Recurrence

Can we spend our IGRT-enable normal tissue dose savings on a well-placed concurrent boost?

A. Dekker - Maastricht
Lung cancer

Individualised iso-toxic accelerated radiotherapy and chemotherapy are associated with improved long-term survival of patients with stage III NSCLC: A prospective population-based study

Dirk De Ruyscher\textsuperscript{a,*}, Angela van Baardwijk\textsuperscript{a}, Jessie Steevens\textsuperscript{b}, Anita Botterweck\textsuperscript{a}, Geert Bosmans\textsuperscript{a}, Bart Reymen\textsuperscript{a}, Rinus Wanders\textsuperscript{a}, Jacques Borger\textsuperscript{a}, Anne-Marie C. Dingemans\textsuperscript{c}, Gerben Bootsma\textsuperscript{d}, Cordula Pitz\textsuperscript{e}, Ragnar Lunde\textsuperscript{f}, Wiel Geraedts\textsuperscript{g}, Michel Oellers\textsuperscript{a}, Andre Dekker\textsuperscript{a}, Philippe Lambin\textsuperscript{a}

\textsuperscript{a} Department of Radiation Oncology, Maastricht University Medical Centre; \textsuperscript{b} Comprehensive Cancer Centre The Netherlands, Maastricht, The Netherlands; \textsuperscript{c} Department of Pulmonology, Maastricht University Medical Centre; \textsuperscript{d} Department of Pulmonology, Atrium Medical Centre, Heerlen; \textsuperscript{e} Department of Pulmonology, Laurentius Hospital, Roermond; \textsuperscript{f} Department of Pulmonology, St. Jansgaasthuis, Weert; \textsuperscript{g} Department of Pulmonology, Orbis Medical Centre, Sittard, The Netherlands

“INDAR” - Individualised iso-toxic accelerated radiotherapy (INDAR) to the primary tumour and the pre-Tx involved lymph nodes on FDG-PET-CT scan.

D. De Ruyscher et al. / Radiotherapy and Oncology 102 (2012) 228–233

\*64.8 Gy given in 36 bi-daily fractions of 1.8 Gy
The ESTRO Regaud Lecture*

Inherent radiosensitivity of tumor and normal tissue cells as a predictor of human tumor response

Lester J. Peters

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

(Received 23 July 1989, revision received 23 August 1989, accepted 23 August 1989)

Key words: Tumor c

In his introduction to this lecture, Dr. Fletcher characterizes prediction of the radiocurability of individual tumors as the “Holy Grail of Radiotherapy”.

Radiotherapy and Oncology, 17 (1990) 177–190
Elsevier
The normalized dose-response gradient

\[ \gamma_n = D \cdot \frac{dP}{dD} \approx D \cdot \frac{\Delta P}{\Delta D} = \frac{\Delta P}{\Delta D / D} \]

- Response probability
- Dose (Gy)
- D\(_{50}\)

Courtesy of S. Bentzen
Steepness of DR curves for HNSCC

- Larynx
- Head & Neck
- Supraglottic
- Pharynx
- Neck nodes

Courtesy of S. Bentzen
HNC – Oropharynx: Two Populations?

• Traditional risk factors for head & neck cancers (HNC) are cigarette smoking, and EtOH consumption
• Epidemiology has changed in recent decades
• HPV-related Disease versus Classical Disease
Separation of Patients by p16 Expression

**OS**
- p16 positive, n=72, 3y Survival=88%
- p16 negative, n=39, 3y Survival=68%
- p16 positive vs. p16 negative, HR=0.3, 95% CI:0.13-0.73
- Log-rank p-value=0.0046

**DFS**
- p16 positive, n=72, 3y DFS=77%
- p16 negative, n=39, 3y DFS=46%
- p16 positive vs. p16 negative, HR=0.32, 95% CI:0.17-0.61
- Log-rank p-value=0.00027

Shi et al; JCO 27:6213, 2009
The ESTRO Regaud Lecture*

Inherent radiosensitivity of tumor and normal tissue cells as a predictor of human tumor response

Lester J. Peters

Division of Radiotherapy, Thu
(Received 23 July 1

Key words: Tumor cell radiosens

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<tr>
<th></th>
<th>Empiric</th>
<th>Radiobiologic</th>
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<tr>
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<td>Site of origin</td>
<td>Clonogen number</td>
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<tr>
<td></td>
<td>Histology</td>
<td>Radiosensitivity intrinsic</td>
</tr>
<tr>
<td></td>
<td>Size (stage)</td>
<td>environmental</td>
</tr>
<tr>
<td></td>
<td>Morphology</td>
<td>Proliferation kinetics</td>
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<td><strong>Patient</strong></td>
<td>Performance status</td>
<td>Genetic determinants</td>
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<tr>
<td></td>
<td>Age, sex</td>
<td>of radiosensitivity</td>
</tr>
<tr>
<td></td>
<td>Host-response parameters</td>
<td></td>
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</table>
Median number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies.
Genetic heterogeneity in tumors – illustrated by a primary pancreatic tumor and its metastatic lesions.
A molecular assay of tumor radiosensitivity: a roadmap towards biology-based personalized radiation therapy

\[
SF_{2x} = k_0 + k_1(y_x) + k_2(TO) + k_3(\text{ras status}) + k_4(p53 \text{ status}) \\
+ k_5(y_x)(TO) + k_6(y_x)(\text{ras status}) + k_7(TO)(\text{ras status}) \\
+ k_8(y_x)(p53 \text{ status}) + k_9(TO)(p53 \text{ status}) \\
+ k_{10}(\text{ras status})(p53 \text{ status}) + k_{11}(y_x)(TO)(\text{ras status}) \\
+ k_{12}(y_x)(\text{ras status})(p53 \text{ status}) \\
+ k_{13}(TO)(\text{ras status})(p53 \text{ status}) \\
+ k_{14}(y_x)(TO)(\text{ras status})(p53 \text{ status}) \\
+ \ldots
\]

Data taken from [44].

Classifier. A leave-one-out cross-validation approach was utilized to develop and test the assay for radiation-specific biomarkers to build the classifier. The classifier was based on a linear regression model for the selected genes and \( k_i \) are coefficients generated during the training process. Variable prediction (not binary; \( p = 0.002 \)).

A molecular assay of tumor radiosensitivity: a roadmap towards biology-based personalized radiation therapy

**Figure 5.** Radiosensitivity index distinguishes clinical populations with different disease-related outcomes in head and neck cancer. Radiosensitivity predictions were generated with the gene-expression model as described in 92 patients treated with definitive concurrent radiotherapy at The Netherlands Cancer Institute (Amsterdam, The Netherlands). Using the 25th percentile as the cutoff point, there is a superior 2-year locoregional control in the predicted radiosensitive group (green vs red, 86 vs 61%; \( p = 0.05 \)).


Reproduced with permission from [64] © Elsevier (2009).
Overview

Biomarkers of Radiation Exposure: Can They Predict Normal Tissue Radiosensitivity?

M.L.K. Chua*†, K. Rothkamm †

*University College London Cancer Institute, London, UK
†Public Health England, Centre for Radiation, Chemical and Environmental Hazards.

Received 28 February 2013; received in revised form 23 April 2013; accepted 26 June 2013

Radiogenomics and biomarkers:

– SNPs, CNV, GWAS Studies
– Radiogenomics Consortium – 2009
– What dose was actually delivered?
The ultimate goal of radiogenomics is to add an additional element of personalised medicine to the radiotherapy planning and prescription, to improve the outcome for the patient. Such individualisation, combined with the very best radiotherapy treatment planning and delivery techniques, will also allow for more imaginative combination with pharmaceutical agents and should achieve both lower toxicity and higher cure rates.
Identification of noninvasive imaging surrogates for brain tumor gene-expression modules

Maximilian Diehn*,†, Christine Nardini*, David S. Wang*, Susan McGovern‡, Mahesh Jayaraman§, Yu Liang¶, Kenneth Aldape‡, Soonmee Cha‖, and Michael D. Kuo*,**,††

*Department of Radiology and **Center for Translational Medical Systems, University of California San Diego Medical Center, San Diego, CA 92103; †Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305; §Department of Neuropathology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; ¶Department of Radiology, Brown University, Providence, RI 02912; ‡Department of Neurological Surgery, Brain Tumor Research Center, University of California San Francisco Medical Center, San Francisco, CA 94143; and ‖Department of Radiology, University of California San Francisco Medical Center, San Francisco, CA 94143

Communicated by Helen M. Ranney, University of California at San Diego, La Jolla, CA, February 9, 2008 (received for review October 16, 2007)

Fig. 4. The infiltrative/edematous radiophenotype predicts survival of GBM patients. (A) Expression of the infiltrative radiophenotype-associated genes in the initial set of GBMs. Data are displayed as in Fig. 1. (B) Kaplan–Meier analysis based on the infiltrative/edematous radiophenotype for the initial set of GBMs. (C) Kaplan–Meier analysis based on the infiltrative/edematous radiophenotype for an independent cohort of 110 GBM patients. Median overall survival was 390 days for edematous tumors and 216 days for infiltrative tumors ($P < 3.1 \times 10^{-7}$).
We now realize that most examples of pharmacogenomic traits (adverse drug reactions, as well as drug efficacy) resemble complex diseases and other multi-factorial traits such as height or body mass index. These traits reflect contributions from innumerable low-effect genes.

D. W. NEBERT1,2* AND G. ZHANG1

1Division of Human Genetics, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH 45229–2899, USA.
2Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH 45267–0056, USA.
The failure to give suitable weight to clinical variation is not the fault of the statistical paradigm any more than it is the fault of the molecular orientation of contemporary medicine. The problem lies with the atrophy of clinical science. Physician investigators whose clinical knowledge equips them to create the needed clinical taxonomies have been distracted by quantitative models or reductionist science. What is needed to complement the power of genomics is an emphasis on personal attributes of patients and their environments, and to incorporate these features into an enriched approach to personalized medicine.
Is it possible for us to integrate these rich and varied data sources?

Can we draw this information together to assure precision and accuracy in treatment?
What else affects our Kaplan-Meier curves?

Methods:

• 127 patients with definitive 3D-CRT for prostate cancer (78 Gy)
• Rectal distension assessed by calculation of the average cross-sectional rectal area (CSA; defined as the rectal volume divided by length) and measuring three rectal diameters on the planning CT.
• Test the impact of rectal distension on biochemical control, 2-year prostate biopsy results, and incidence of Grade 2 or greater late rectal bleeding was assessed.

The quality of the intervention is important for each patient, but also for advancing PCM.

Median Cross-sectional Area (CSA) = 11.2 cm²

TROG Trial #02.02 was designed to test the benefit of using a new drug (tirapazamine) in combination with chemo+RT. The outcomes were negative. Why?

Peters et al. JCO 2010
"If it were not for the great variability among individuals, medicine might as well be a science, not an art."

Sir William Osler, 1892
Understanding cancer, developing personalized cancer medicine strategies, and delivering high performance cancer therapy are highly dependent activities.

Paradoxically, Getting Personal Requires Getting Industrial
Medical Physicists have become very good at managing complexity.

- Over the past 20 years medical physicists have brought one of the most complex technology in healthcare (IG-IMRT) alive with a remarkable track record.
- This is a powerful skill.
- Where do we go next?
Converting on the Promise of Personalized Cancer Medicine

- From delivering ‘state-of-the-art’ care to driving the next generation of care.
  - Medical physicists have always innovated practice, but this needs to be industrialized to accommodate the complexity of data collection, decision making, and delivery.
- Maximizing intervention performance (quality) to detect sub-populations and evaluate the value of new, more personalized therapies
- Building cancer informatics tools to enable analysis, exploration, and rapid evaluation of novel therapies or stratification.
RT: A Highly Personalized Cancer Medicine

Summary

• Medical physicists have always been at the forefront in bringing greater precision to cancer treatment.

• We have established skills in the domains of computing, informatics, quality management, and clinical interaction that are of extreme relevance to the future of personalized medicine.

• The opportunity for further engagement in the domains of technology and processes, informatics and modeling, and from basic to clinical science are greater than ever.

• Few medical professions are better equipped to contribute.
More Complete H&N cancer BN

[Diagram of the More Complete H&N cancer BN network]

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Mark Phillips  Organism-level models:  When mechanisms and statistics fail