What Can Anatomical Treatment Assessment Tell Us?

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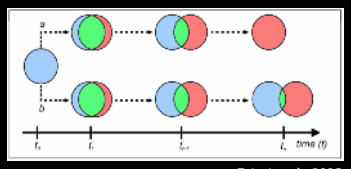
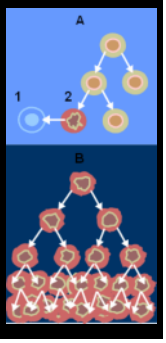
Cancer: Phenomenological View

- Cancer: An abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize.





Grizzi et al., 2006

Theoretical Biology and Medical Modelling

BioMed Central

Commentary

Open Access

Cancer initiation and progression: an unsimplifiable complexity

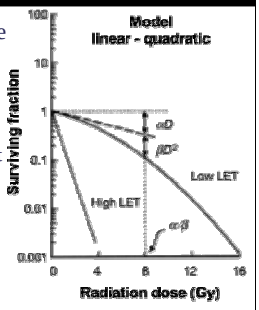
Fabio Grizzi*[1,5], Antonio Di Ieva[2], Carlo Russo[1], Eldo E Frezza[3,4], Everardo Cobos[4,5], Pier Carlo Muzzio[6,7] and Maurizio Chiriva-Internati[4,5]

- Expect *non-linear responses*
  - Phase dependence, unpredictable, dependence on initial conditions
- *Asynchrony* and *self-progression* of a cancer cell population suggest that the extent to which each neoplastic cell differ in *time* and in *space.*
  - Modulated by environment; heterogeneous
- The observed phenomenon at each scale has structural and behavioural properties that do not exist at lower or higher organizational levels.

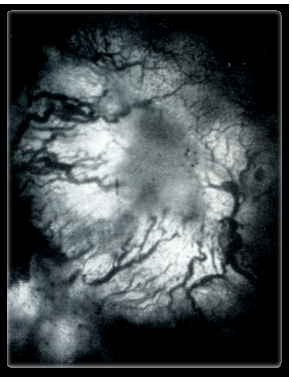
Grizzi et al., 2006

RT and Cell Death

- A/the model for describing the cell survival curve is the linear-quadratic model with constants α and β.
  - The ratio α/β gives the dose at which the linear and quadratic components of cell killing are equal.



More than a mass of cells.



In the late thirties *in vivo* images of tumour blood vessels began being published. Shown here is an image of a rabbit epithelioma obtained by **Gordon Ide** and collaborators at **Rochester University.** These dark streaks represent the tumour vasculature the Brown–Pearce rabbit epithelioma\ carcinoma (malignant tumor of the epithelial tissue) in a transparent chamber in the rabbit ear.

Ide et al 1939 *Am. J. Roentgenol.* **42**

Getting Beyond the Cell as a Target

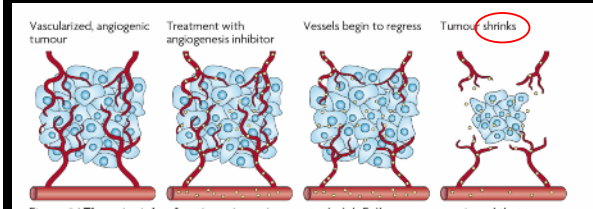
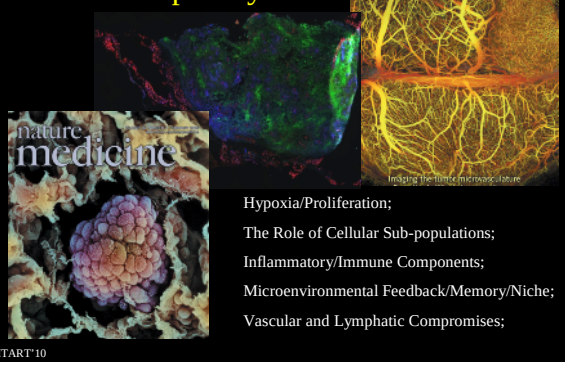


Figure 2 | **The principle of anti-angiogenic agents.** Judah Folkman was convinced that tumour angiogenesis was a necessary component of tumour growth and based on this was the premise that antagonism of the angiogenic process could constitute a new form of cancer therapy. He made this clear in the 1971 *New England Journal of Medicine* paper, which was the first to use the term "antiangiogenesis" to describe a potential therapeutic approach.

From: "Timeline: The scientific contributions of M. Judah Folkman to cancer research," Zetter et al. Nature Reviews Cancer 8, 647-654

Growing appreciation of the complexity.



Hypoxia/Proliferation;

The Role of Cellular Sub-populations;

Inflammatory/Immune Components;

Microenvironmental Feedback/Memory/Niche;

Vascular and Lymphatic Compromises;

What Can Anatomical Treatment Assessment Tell Us?

"The term molecular imaging can be broadly defined as the *in-vivo* characterization and measurement of biologic processes at the cellular and molecular level. In contradistinction to "classical" diagnostic imaging, it sets forth to probe the molecular abnormalities that are the basis of disease rather than to image the end effects of these molecular alterations."

Weissleder et al., Volume 219 (2), Molecular Imaging, 2001

Anatomical Imaging for Treatment Assessment:

Imaging the end of effect of molecular alterations induced by disease and therapy.

3D Anatomical Imaging

- Computed Tomography (CT)
  - Measures x-ray attenuation coefficient, density
- Magnetic Resonance Imaging (MRI)
  - Water proton relaxation
  - Proton Density, Spin-Spin (T_1), Spin-Lattice (T_2)
- Ultrasound (US)
- Exogenous Contrast Agents
  - Small molecule (Iodine-CT, Gadolinium-MR)
  - Macro-molecular agents (non-diffusing; bubbles)

COMPUTED MEDICAL IMAGING

Nobel Lecture, 8 December, 1979

BY
GODFREY N. HOUNSFIELD
The Medical Systems Department of Central Research Laboratories EMI, London, England

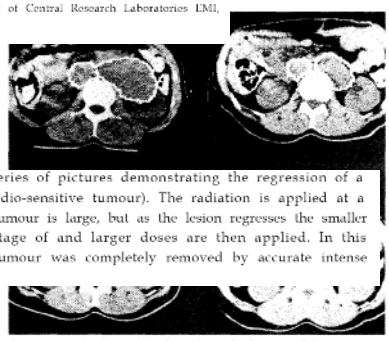


Fig. 13 shows a series of pictures demonstrating the regression of a seminoma (a very radio-sensitive tumour). The radiation is applied at a low level while the tumour is large, but as the lesion regresses the smaller area is taken advantage of and larger doses are then applied. In this particular case the tumour was completely removed by accurate intense radiation.

Fig. 13. Demonstrating the regression of a seminoma after four stages of therapy treatment.

Reprinted from
19 March 1971, Volume 171, pp. 1151-1153

SCIENCE

Tumor Detection by Nuclear Magnetic Resonance

Raymond Damadian

Table 2. Spin-lattice (T_1) and spin-spin (T_2) relaxation times (in seconds) in tumors.

Rat No.	Weight (g)	T_2	T_1
		Walker sarcoma	
6	156	0.700	0.100
7	150	.750	.100
8	495	.794 (0.794)*	.100
9	233	.688	
10	255	.750	
Mean and S.E.		0.736 ± 0.022	.100
P		<.01†	
		Novikoff hepatoma	
11	155	0.798	0.120
12	160	.852	.120
13	231	.827	.115
Mean and S.E.		0.826 ± 0.013	0.118 ±
P		<.01†	0.002
		Fibroadenoma (benign)	
14		0.448	
15		.537	
Mean		.492	
		Distilled water	
		2.691	
		2.690	
		2.640	
Mean and S.E.		2.677 ± 0.021	

It was also found that the differences between the relaxation rates of malignant tumors and normal liver could be used to distinguish the two malignancies from all of the normal tissues studied [*P* values less than .01 (Table 2)]. The values of T_1 in Walker sarcoma (0.736 second) and Novikoff hepatoma (0.826 second) were significantly greater than the values of T_1 in any of the normal tissues (0.293 to 0.595 second). The

Give us a 'water-weighted' assessment of the intra and extra-cellular organization in tissues.

Damadian, Science, 1971

Eur Radiol (2007) 17: 2441–2457
DOI 10.1007/s00330-007-0616-9

MOLECULAR IMAGING

Markus Rudin

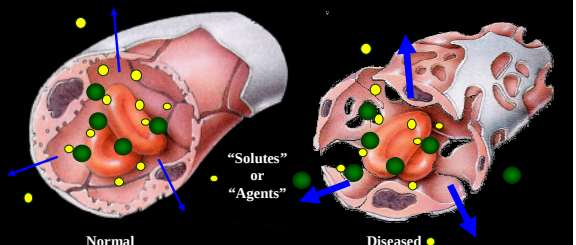
Imaging readouts as biomarkers or surrogate parameters for the assessment of therapeutic interventions

Rudin, Eur Radiol. (2007)

Table 1 Potential imaging biomarkers for oncology

Tumor hallmark	Mechanisms	Imaging biomarker	Development status
Angiogenesis/vascularity	Vascular permeability	Dynamic contrast-enhanced MRI (DCE-MRI) using low molecular weight contrast agents	Evaluation/deployment
	Vascular permeability/blood volume	DCE-MRI using macro-molecular contrast agents	Development/evaluation
Metabolism	Glucose utilization (glucose transporter and hexokinase activity)	[^{18}F]-2-fluoro-2-deoxyglucose PET (FDG-PET)	Deployment
Proliferation	Membrane turnover	MR spectroscopy (MRS): phosphorylcholine signal	Evaluation
		[18F]-fluorocholine PET (FCh-PET)	Development/evaluation
	DNA synthesis	[^{18}F]-fluoro-thymidine PET (FLT-PET)	Evaluation/deployment
Apoptosis	Apoptotic cell body formation	MRI: Apparent water diffusion coefficient	Evaluation
	Externalized phosphatidyl-serine	^{99m}Tc-Annexin-5A	Evaluation/development as diagnostic
Cell surface receptor over-expression	Somatostatin receptor (SSTR) binding	^{111}In-DTPA-D-Phe-octreotide	Deployment/diagnostic product (Octreoscan)
	Estrogen receptor binding	[^{18}F]-fluoro-estradiol	Identification/development

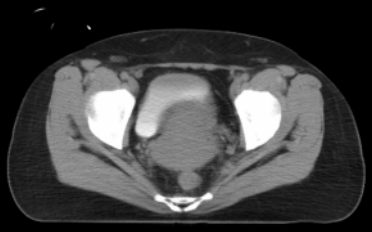
Vascular Permeability/Hydraulic Conductivity, Concentration, Pressure, and Flow >>> Oxygenation, Nutrient Support, pH, Drug Delivery.



Perfusion (fCT) or Dynamic Contrast Enhancement (DCE-MR) methods seek to characterize the vascular/intra-tumoral transport as a metric of the disease and its response to therapy.

Method Review - Leach et al. BJR (2005)

E.g: Perfusion CT - Cervix Cancer



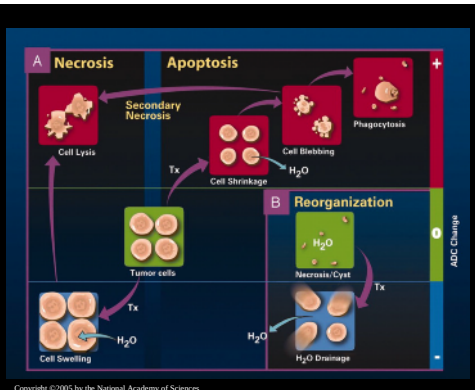
Low-molecular weight agent:
Omnipaque

Courtesy of I.Yeung, M.Milosevic and R.Hill

Diffusion Weighted MR

- Diffusion-weighted magnetic resonance imaging (DW-MRI) depends on the microscopic mobility of water.
- This mobility, classically called Brownian motion, is due to thermal agitation and is highly influenced by the cellular environment of water.
- Motion in gradients encodes for diffusion.
- Findings on DW-MRI could be an early harbinger of biologic abnormality or an early harbinger of therapeutic response.

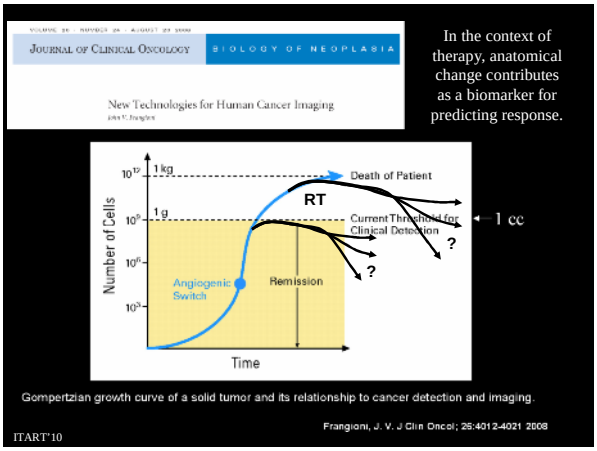
Padhani et al. Neoplasia (2009)



From Moffat et al. (2005) Proc. Natl. Acad. Sci. USA 102, 5524-5529

What Can Anatomical Treatment Assessment Tell Us?

- Gross Anatomical Change (CT/MR)
  - Cell death, inflammation, edema
- 'Meso'-scopic transport changes
  - Vascular structure, function
  - Permeability, intra-tumoral transport
- Cellular/Intra-cellular Structure (Water Diffusion)
- RT: Opportunity for Geometric Adaptation

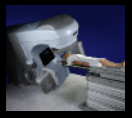


Does any of this happen quickly enough to detect during a course of radiation therapy?

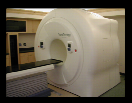
Yes.

IG Technologies for RT

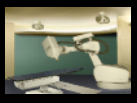
kV CBCT

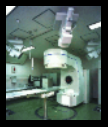


MV CT



kV Radiography



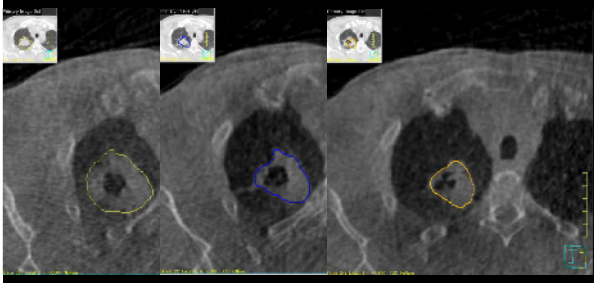


MV CBCT

IGRT Detected Changes in Lung Targets

- Siker ML et al. "Tumor volume changes on serial imaging with megavoltage CT for non-small-cell lung cancer during intensity-modulated radiotherapy: how reliable, consistent, and meaningful is the effect?
  - *Int J Radiat Oncol Biol Phys. 2006 1;66(1):135-41*
- Kupelian PA et al. "Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumor regression during treatment.
  - *Int J Radiat Oncol Biol Phys. 2005 Nov 15;63(4):1024-8*

IGRT Detected Changes in Lung Targets



Detectable Changes in Volume of 'Something'

NSCLC Courtesy of Lung Group, PMH

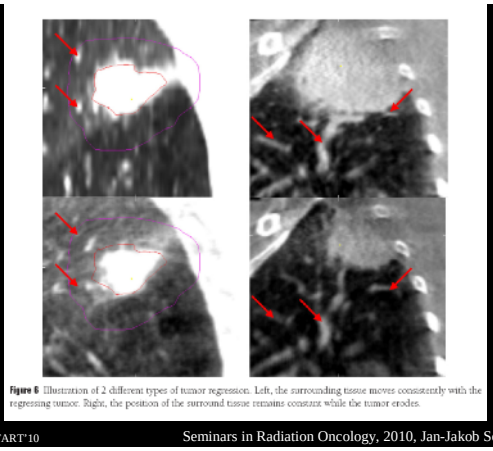


Figure 6 Illustration of 2 different types of tumor regression. Left, the surrounding tissue moves consistently with the regressing tumor. Right, the position of the surround tissue remains constant while the tumor erodes.

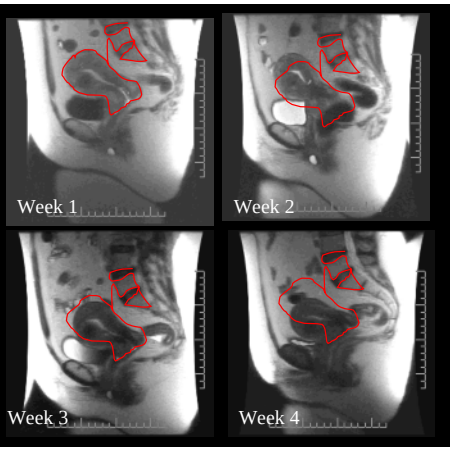
Seminars in Radiation Oncology, 2010, Jan-Jakob Sonke, NKI

Anatomical Treatment Assessment and the Domain of Adaptation in RT

- Concerns regarding the true extent of disease (in planning and during RT).
- Is there opportunity to reduce target volumes as therapy progresses?
  - Depends on what is changing – normal tissue vs target volumes (mass effect)
- Need to reflect on the definition of GTV and CTV
  - State-of-the-art IGRT imaging systems are not standard of care for use in target definition
  - Redefinition of target volumes is not standard of care in RT
- Greater value as a biomarker? To be determined.

Cancer of the Cervix: Therapy-induced Changes

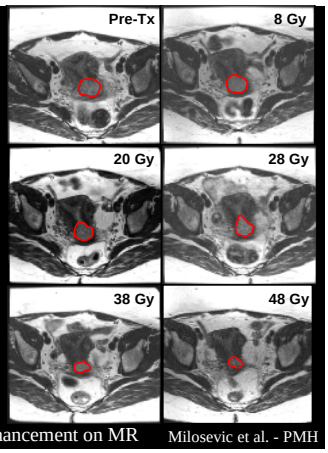
Sagittal Images



Milosevic et al., PMH

Ca Cervix: 'GTV' Reduction During EBRT

Patient #	Correlation Coefficient	Slope
1.	-0.986	-0.64
2.	-0.978	-1.16
3.	-0.963	-1.76
4.	-0.987	-0.60
5.	-0.987	-0.58
6.	-0.965	-0.37
7.	-0.976	-0.54
8.	-0.954	-0.65
9.	-0.986	-1.38
10.	-0.988	-1.62
11.	-0.981	-1.25
12.	-0.963	-1.77



ITART'10

GTV - T2 Enhancement on MR

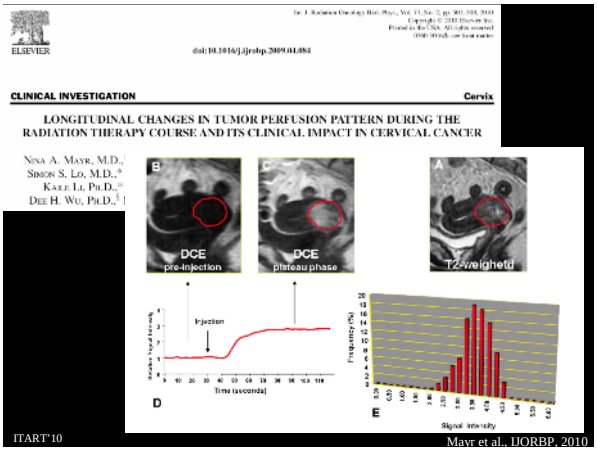
Milosevic et al. - PMH

Mayr et al: Translating Response During Therapy into Ultimate Treatment Outcome … in Cervical Cancer.

- Serial MRI in cervix cancer patients to define the regression parameters' prognostic value validated with local control and survival correlation.
  - 115 patients with Stage IB(2)-IVA cervical cancer treated with RT
  - Serial MRI before, during RT (2-2.5 wks and 4-5 wks), and after (80/115 - 2 months)
  - Mean follow-up was 5.3 years
- CONCLUSION:
  - Tumor response can now be directly translated into individual patients' outcome for clinical application.
  - In patients with >/=20% residual volume at 40-50 Gy and >/=10% post-RT, the risk for local failure and death are so high that aggressive intervention may be warranted.

ITART'10

Mayr et al. Int J Radiat Oncol Biol Phys. 2009



ELSEVIER

CLINICAL INVESTIGATION Cervix

LONGITUDINAL CHANGES IN TUMOR PERFUSION PATTERN DURING THE RADIATION THERAPY COURSE AND ITS CLINICAL IMPACT IN CERVICAL CANCER

ITART'10

Mayr et al., IJORBP, 2010

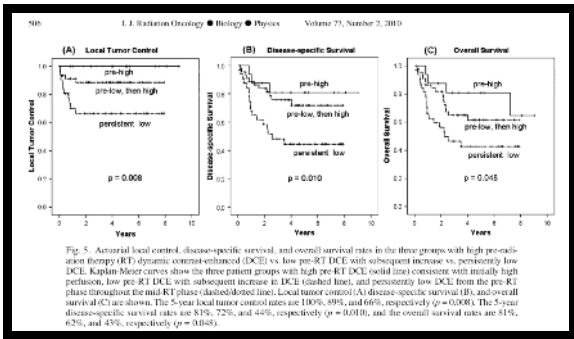


Fig. 5. Actuarial local control, disease-specific survival, and overall survival rates in the three groups with high pre-radiation therapy (RT) dynamic contrast-enhanced (DCE) vs. low pre-RT DCE with subsequent increase vs. persistently low DCE. Kaplan-Meier curves show the three patient groups with high pre-RT DCE (solid line) consistent with initially high perfusion, low pre-RT DCE with subsequent increase in DCE (dashed line), and persistently low DCE from the pre-RT phase throughout the mid-RT phase (dashed/dotted line). Local tumor control (A) disease-specific survival (B), and overall survival (C) are shown. The 5-year local tumor control rates are 100%, 89%, and 66%, respectively ($p = 0.008$). The 5-year disease-specific survival rates are 81%, 72%, and 44%, respectively ($p = 0.010$), and the overall survival rates are 81%, 62%, and 43%, respectively ($p = 0.048$).

Our data suggest that DCE-MRI is an effective noninvasive means to assess the longitudinal changes of tumor perfusion status during RT, which may play an essential role in assessing tumor reoxygenation and radiosensitivity and may be used as a predictive approach to optimize and therapy strategy for personalized radiation medicine.

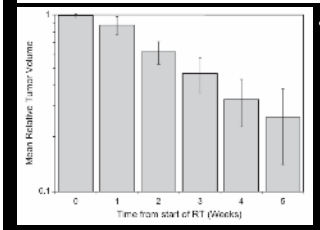
ITART'10

Mayr et al., IJORBP, 2010

CLINICAL INVESTIGATION — Cervix

CERVICAL CANCER REGRESSION MEASURED USING WEEKLY MAGNETIC RESONANCE IMAGING DURING FRACTIONATED RADIOTHERAPY: RADIOBIOLOGIC MODELING AND CORRELATION WITH TUMOR HYPOXIA

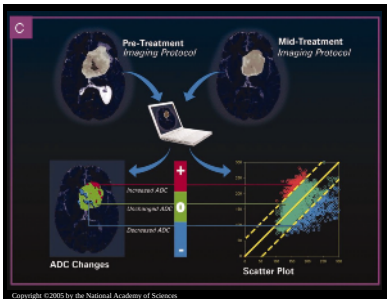
Karen Lim, M.B.B.S.,[a†] Philip Chan, M.B.B.S.,[a] Robert Dinniwell, M.D.,[a†] Anthony Fyles, M.D.,[a†] Masoom Haider, M.D.,[‡§] Young-Bin Cho, Ph.D.,[a‖] David Jaffray, Ph.D.,[a†] Lee Manchul, M.D.,[a†] Wilfred Levin, M.D.,[a†] Richard P. Hill, Ph.D.,[†¶] and Michael Milosevic, M.D.[a†]



- Radioresistant tumors with an SP_{2Gy} >0.71 were significantly more hypoxic (HP_{med}, Eppendorf) at the start of therapy than were radiosensitive (SP_2<=0.71) tumors.

ITART'10

Lim et al. IJORBP Jan 2008 70(1)



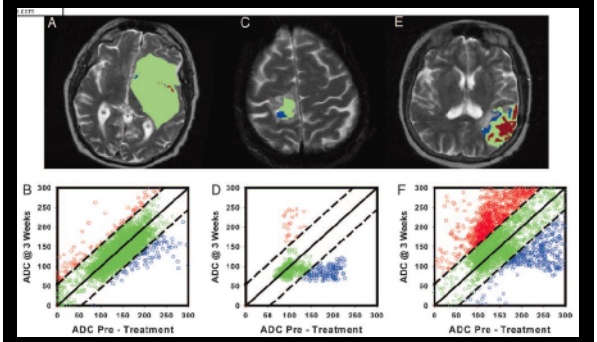
Cluster Analysis: 100% sensitivity and a specificity of 100% for distinguishing Partial Response patients from Stable or Progressive Disease patients

The predictive values and overall accuracy for discriminating PR, SD, and PD patients at 3 weeks post-treatment initiation were found to be 100% for all 20 patients.

20 Patients RT, Chemo or both

Pre-Tx and Intra-Tx Course MR Diffusion (Apparent Diffusion Coefficient, ADC)

Moffat, Bradford A. et al. (2005) Proc. Natl. Acad. Sci. USA 102, 5524-5529

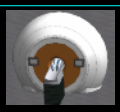


Progressive Disease | Stable Disease | Partial Response

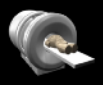
Moffat, Bradford A. et al. (2005) Proc. Natl. Acad. Sci. USA 102, 5524-5529

Next Generation IG Technologies for RT

Edmonton Solution



Utrecht Solution



Viewray Solution

MR-Guided RT

Summary

- Imaged 'anatomical' changes will play a role in predicting outcome in RT.
  - Image-guidance technologies will heighten our awareness of these changes.
- Can capitalize on changes in anatomical target to reduce normal tissue irradiation
  - Caution - Re: target delineation
- Given the 'biomarker' nature of the observations, it is unclear what the feedback to the intervention should be.
  - Within RT, outside RT.

ELSEVIER

Seminars in RADIATION ONCOLOGY

Adaptive Management of Cervical Cancer Radiotherapy

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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 decreased morbidity compared with the past are appearing. At the dawn of this new era, it is the aim of the present article to give an overview of the use of image-guided adaptive radiotherapy in the multimodal management of locally advanced cervical cancer.
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Rationale and Potential

Today, the standard treatment of locally advanced cervical cancer is external beam radiotherapy (EBRT), concomitant 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