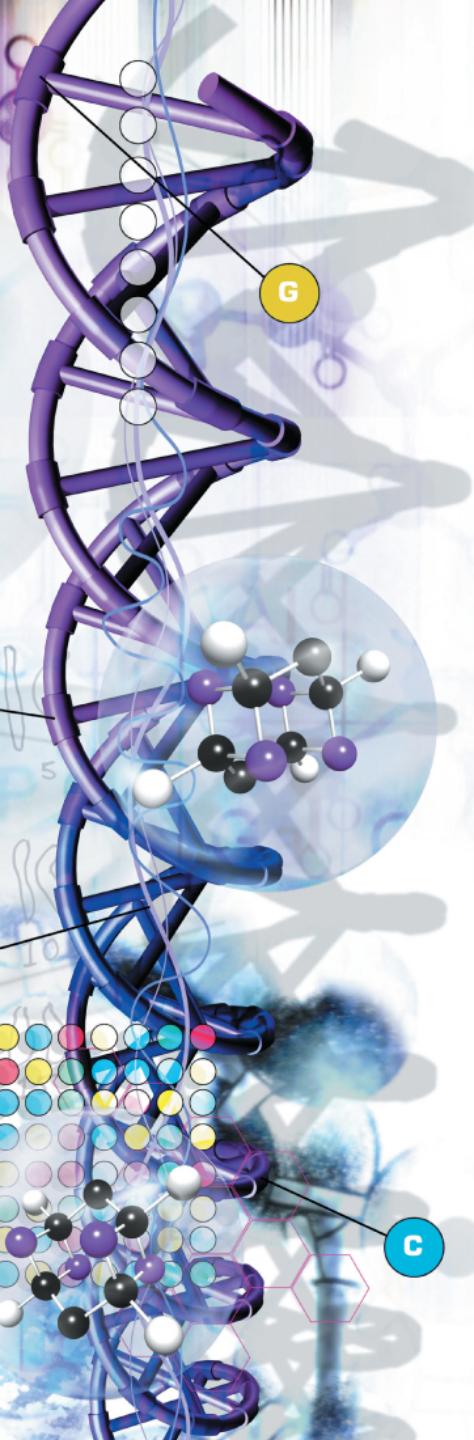


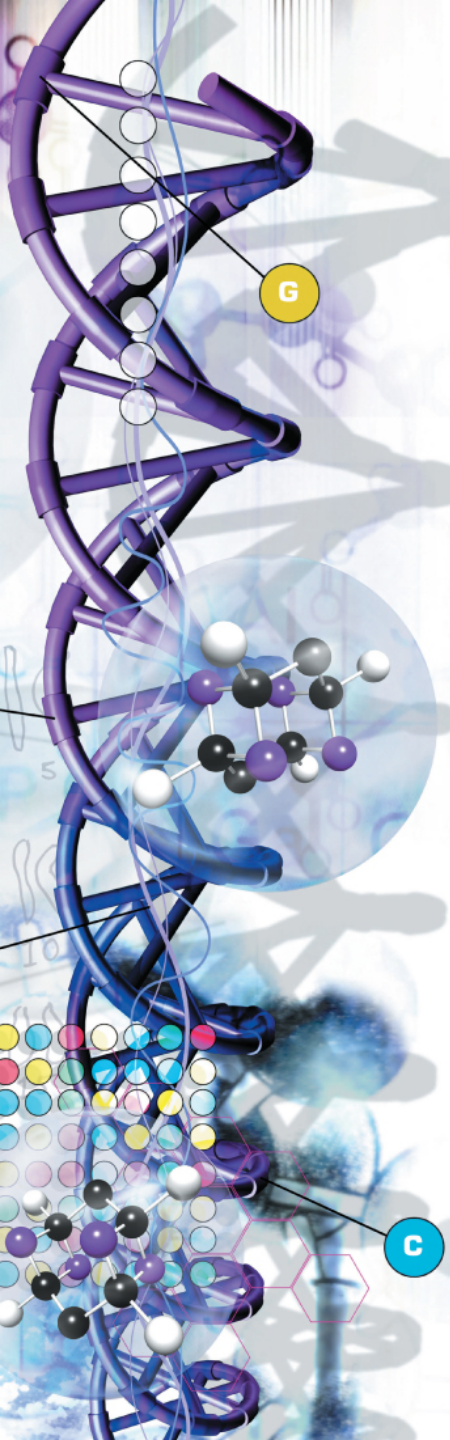
L'imaging molecolare e i modificatori epigenetici di radioresistenza

Giovanni Luca Gravina, MD

University of L'Aquila

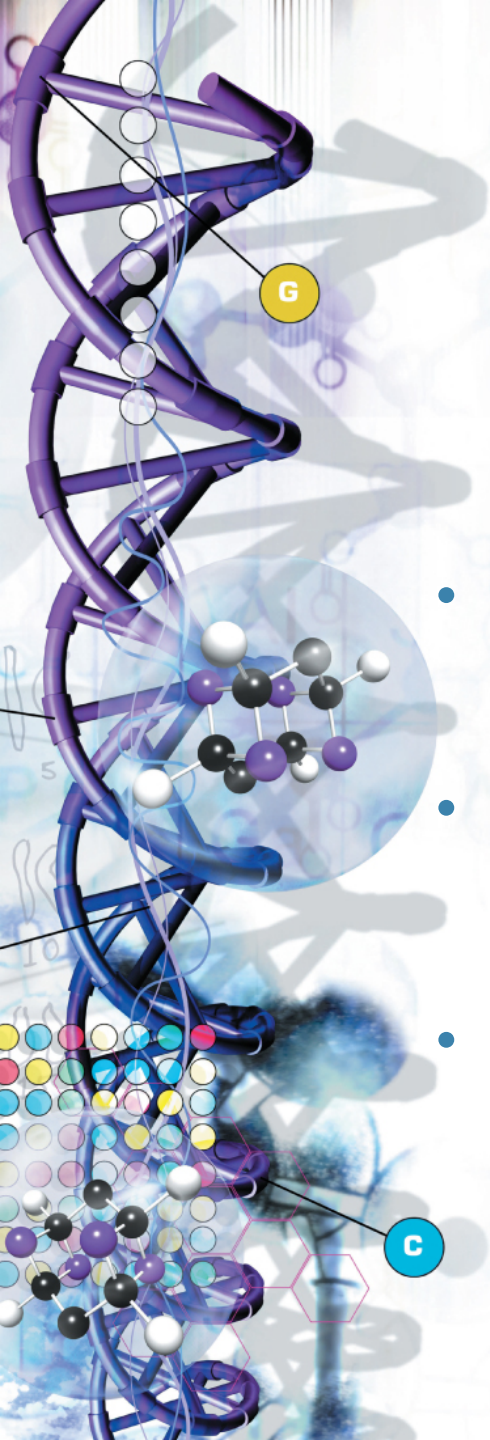
Division of Radiotherapy and Radiobiology

L'Aquila



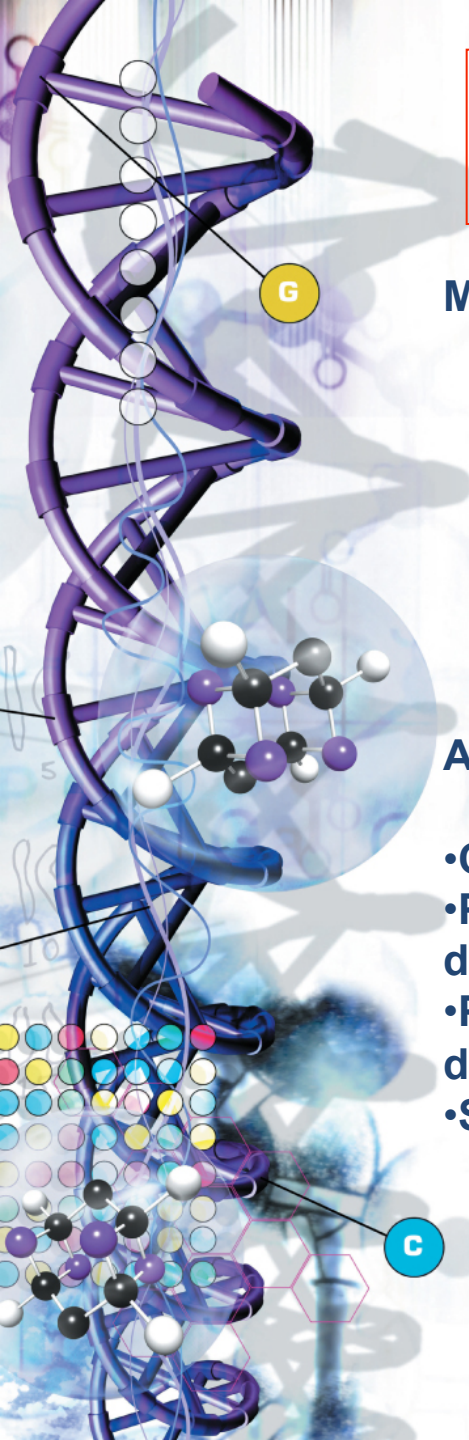
Imaging and Cancer Therapy: Outline

- What is functional/molecular imaging?
- Imaging as a cancer biomarker
  - Goals and imaging targets
  - Prognosis
  - Prediction
  - Response



Cautions

- Focus on cancer and nuclear medicine imaging
- Many of the imaging methods presented are considered investigational
- Discussion of results and possible applications is not a claim of clinical efficacy



Response Evaluation Criteria in Solid Tumors (RECIST)

Methodologies:

- WHO: largest diameter and its perpendicular
- RECIST: Largest Diameter (LD) only

Assessment criteria:

•CR (complete response) = disappearance of all target lesions
•PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions
•PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions
•SD (stable disease) = small changes that do not meet above criteria

Tumor Shrinkage as a Criterion for Response

Original Article

Cancer

Early Changes in Tumor Size in Patients Treated for Advanced Stage Nonsmall Cell Lung Cancer Do Not Correlate With Survival

REPORT

Annals of Oncology **9**: 1079–1084, 1998.

Original article

Response rate as an endpoint for evaluating new cytotoxic agents in phase II trials of non-small-cell lung cancer

I. Sekine,[1] K. Kubota,[1] Y. Nishiwaki,[2] Y. Sasaki,[3] T. Tamura[1] & N. Saijo[1]

[1]*Internal Medicine and Thoracic Oncology Division, National Cancer Center Hospital, Tokyo;* [2]*Thoracic Oncology,* [3]*Oncology and Hematology Divisions, National Cancer Center Hospital East, Kashiwa, Japan*

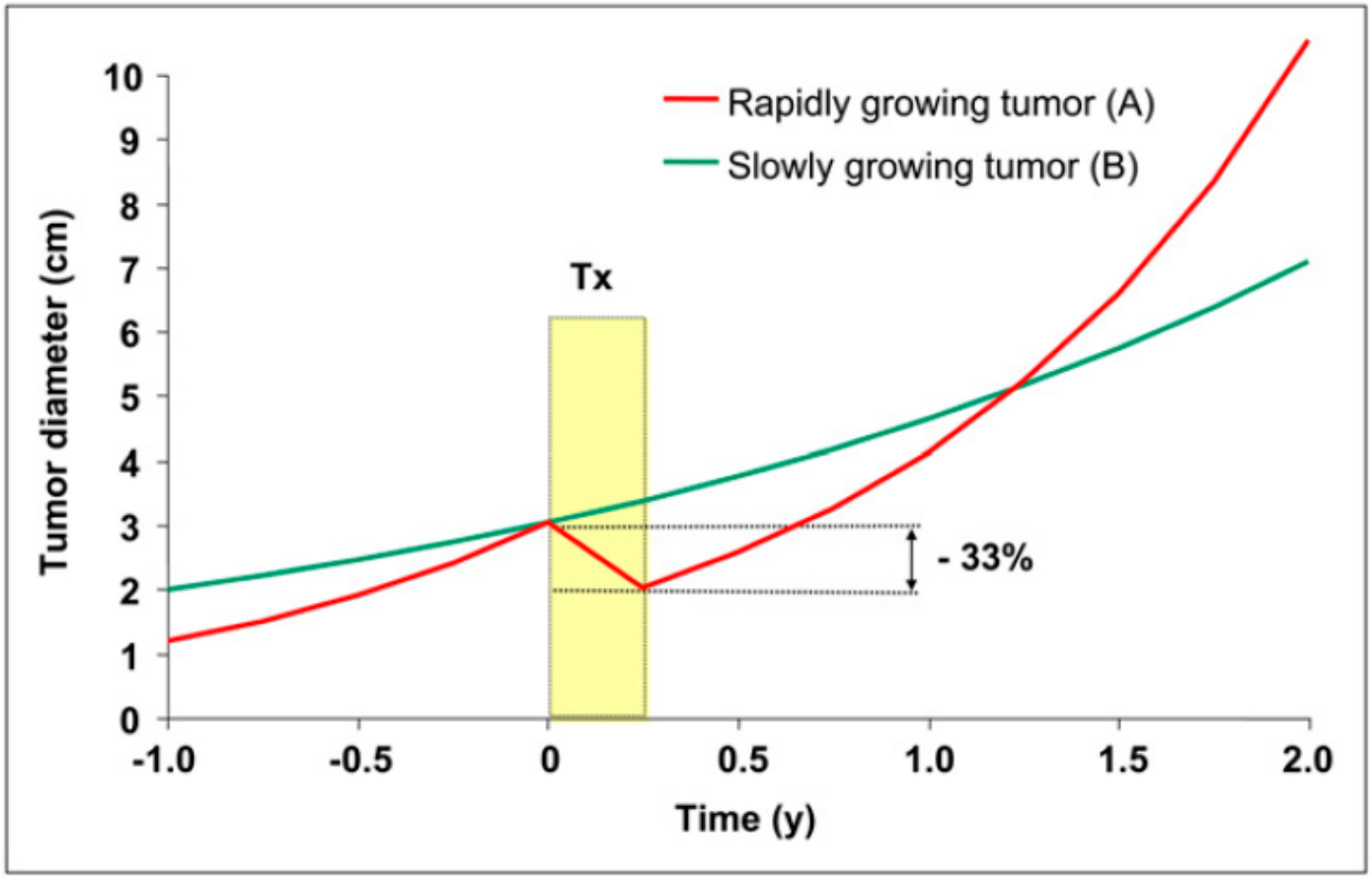
Summary

Background: Response rate (RR) has been used as a defining endpoint of new-agent phase II trials for non-small-cell lung cancer (NSCLC). However, tumor responses to chemotherapy do not always result in prolonged survival of patients with this disease.

Design: Single-agent phase II trials were identified by a MEDLINE search of the period from 1976 to 1995. Associations between RR, median survival time (MST) and character-

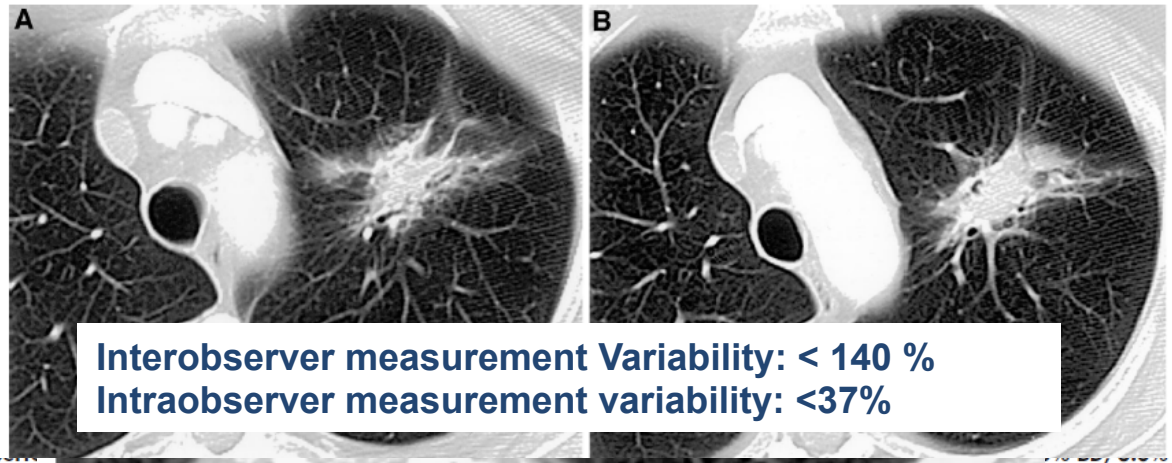
epirubicin, ifosfamide, edatrexate, irinotecan, vinorelbine, docetaxel, paclitaxel, etoposide, vindesine, and 254-S, produced a RR of more than 20%. An MST of eight months or longer was obtained with 12 drugs, but there were cases in which no objective responses were produced by these drugs. MST was correlated with RR ($r = 0.504$, $P < 0.0001$), but ranged broadly at a given level of RR. Multiple linear regression analysis showed a significant correlation between RR and MST (regression coefficient = 0.60, $P = 0.00003$) after adjustment for other variables

Tumor Shrinkage as a Criterion for Response



Tumor Shrinkage as a Criterion for Response

Interobserver measurement Variability: < 7.1%
Intraobserver measurement variability: <4.8%



Interobserver measurement Variability: < 140 %
Intraobserver measurement variability: <37%

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dently by five thoracic radiologists using printed film and were repeated after 5 to 7 days. Inter- and intraobserver measurement variations were estimated through statistical modeling.

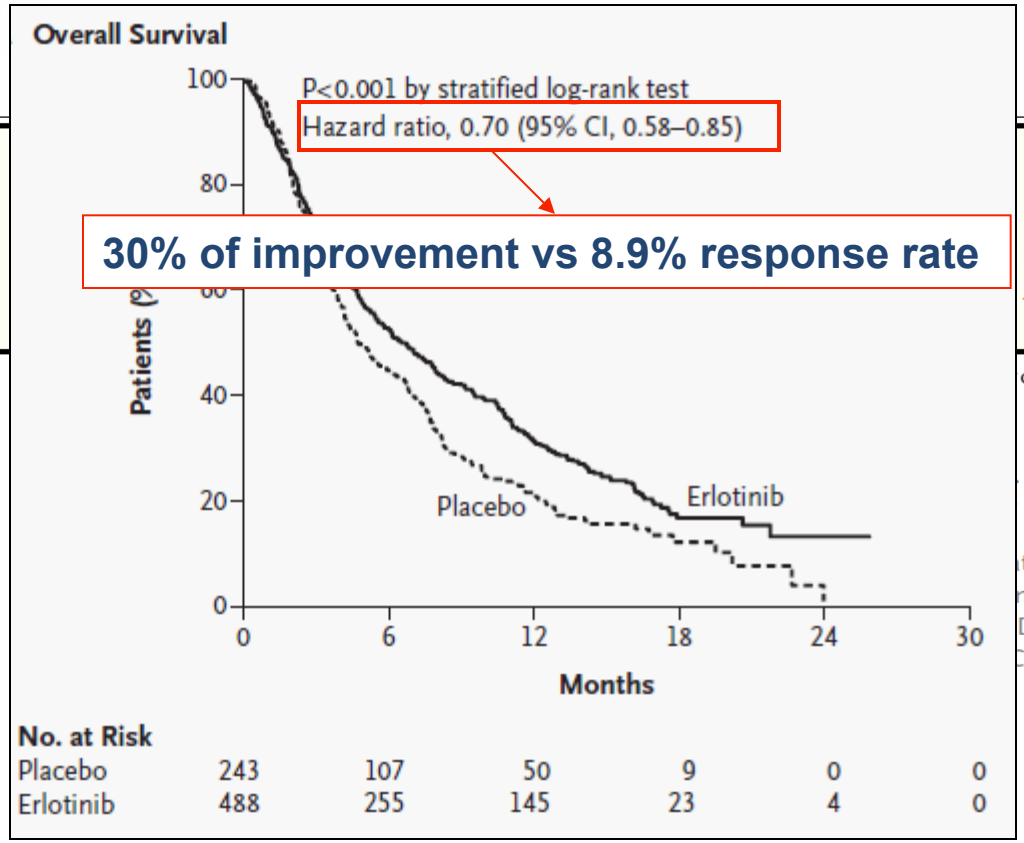
Results: There were 40 tumors with an average size of 1.8 to 8.0 cm (mean, 4.1 cm). Analysis of variance showed a significant difference ($P < .05$) among readers and among

Conclusion: Measurements of lung tumor size on CT scans are often inconsistent and can lead to an incorrect interpretation of tumor response. Consistency can be improved if the same reader performs serial measurements for any one patient.

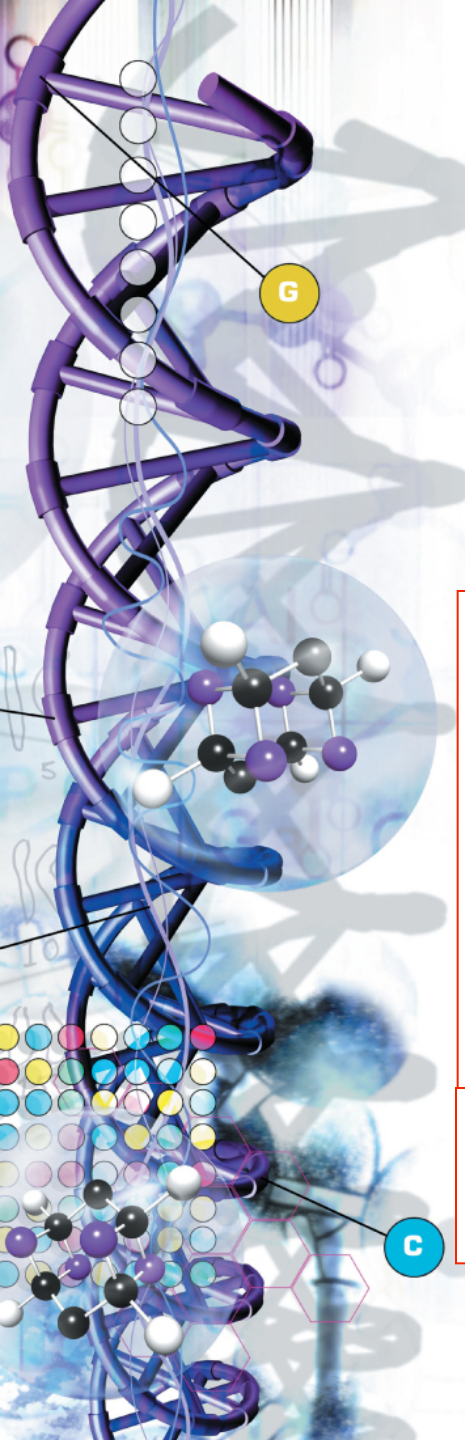
J Clin Oncol 21:2574-2582. © *2003 by American Society of Clinical Oncology.*

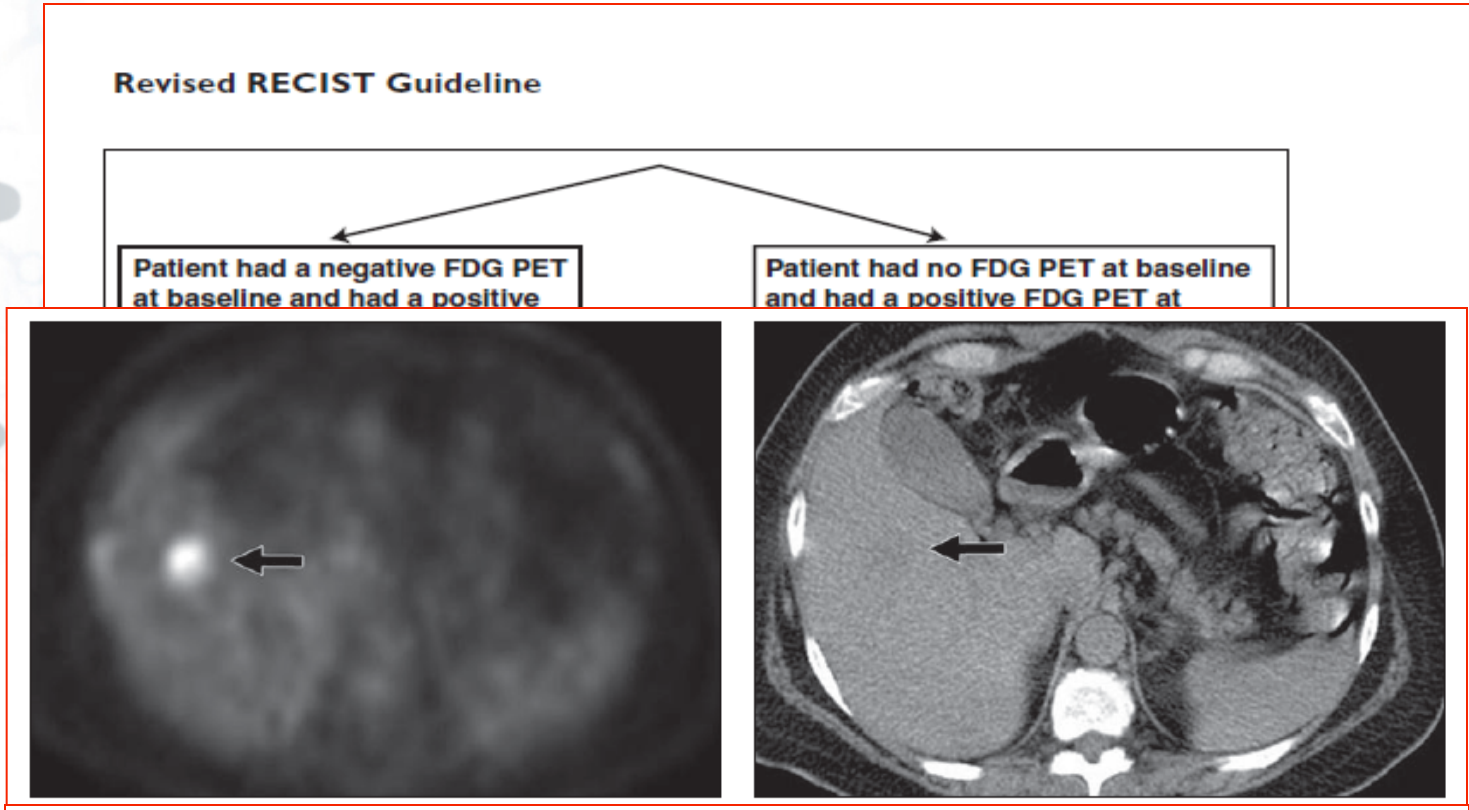
ICGC

Tumor Shrinkage as a Criterion for Response

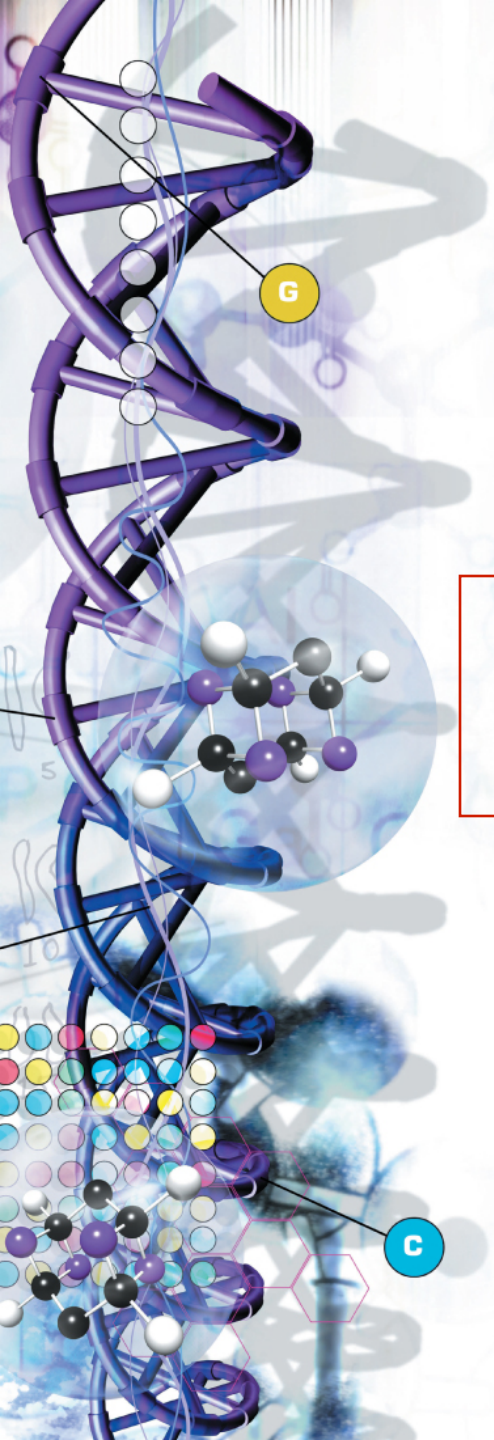


Revised RECIST guideline

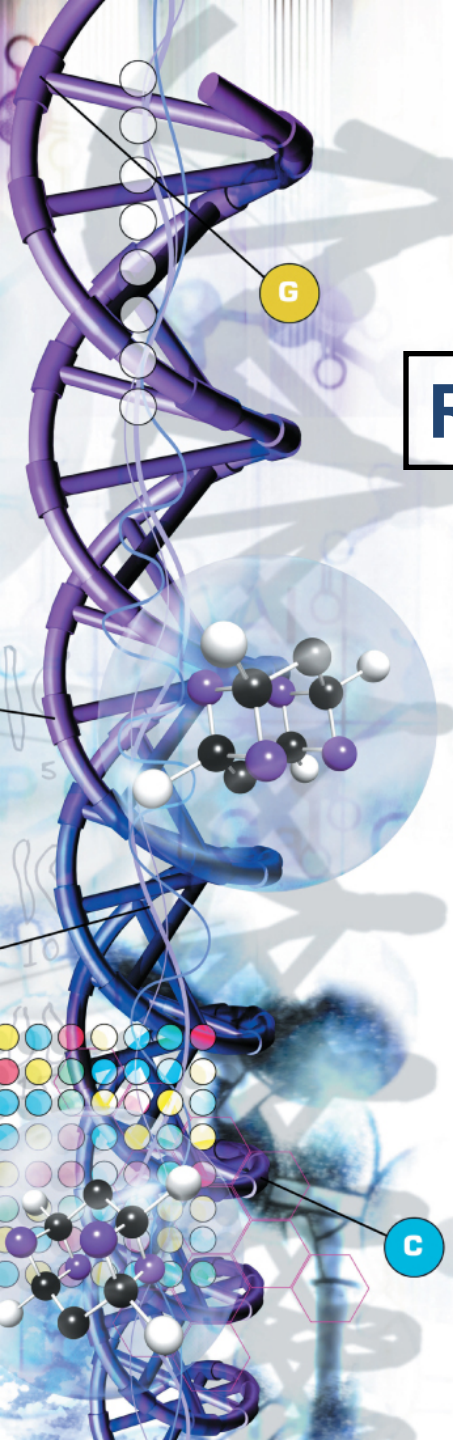




Finding meets criteria for progressive disease using Response Evaluation Criteria in Solid Tumors 1.1 because new lesion has been detected on FDG PET



What is Functional/Molecular Imaging?



Biologic Events in Response to Successful Cancer Therapy

Rationale for Measuring Early Response by Functional/molecular Imaging

Rx

↓ **Cellular Proliferation**

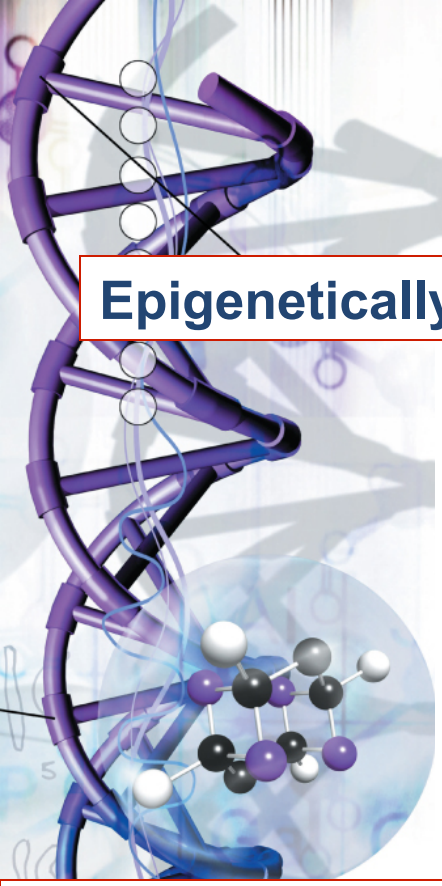
or

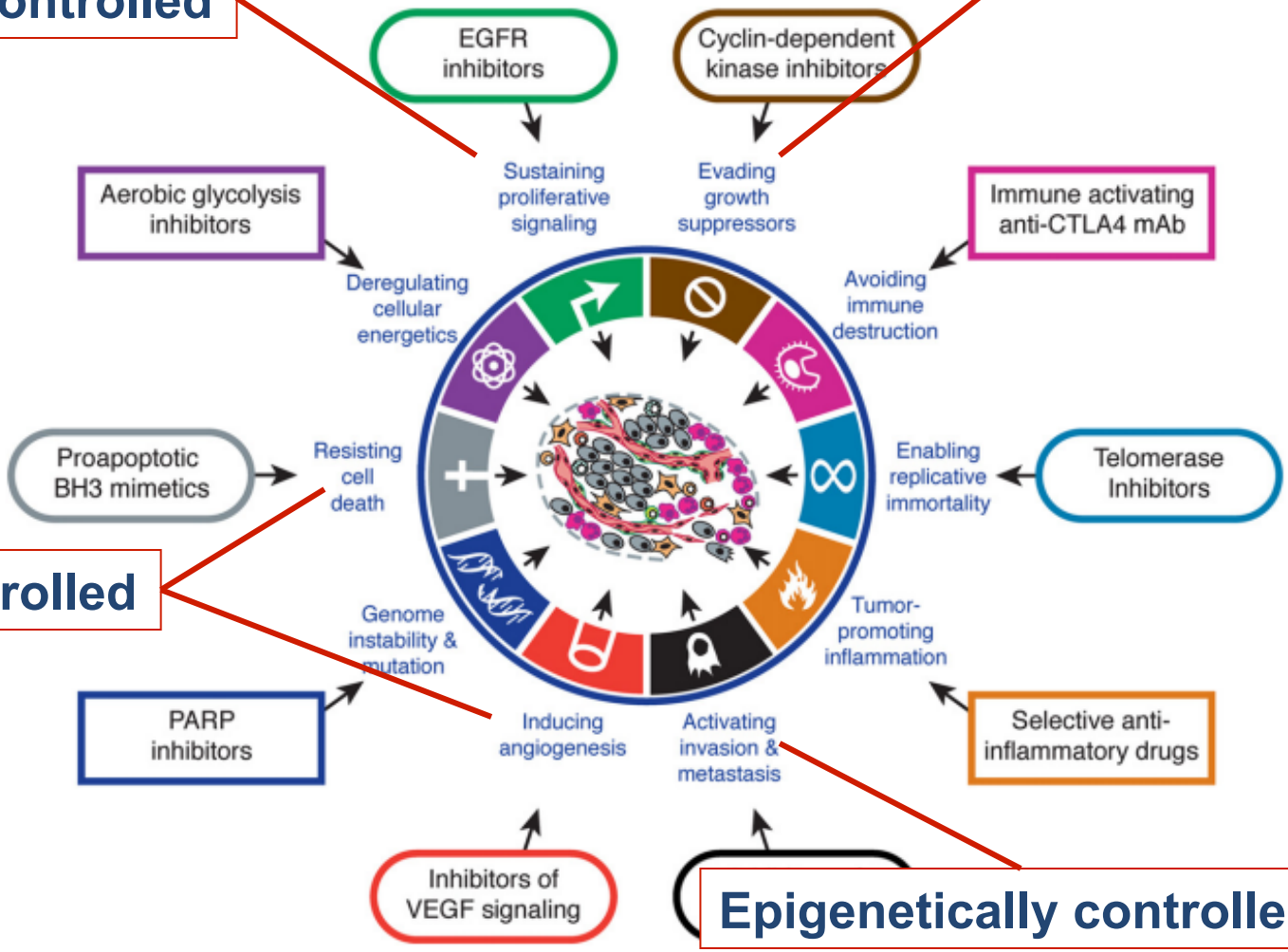
↑ **Cell Death**

↓ **Viable Cell Number**

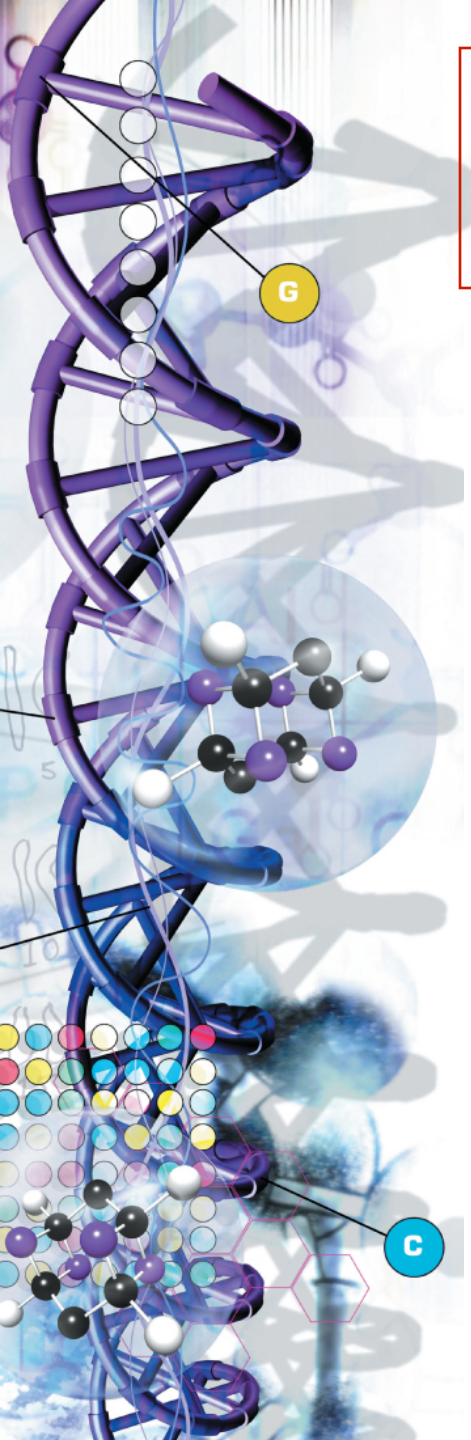
↓ **Tumor size**

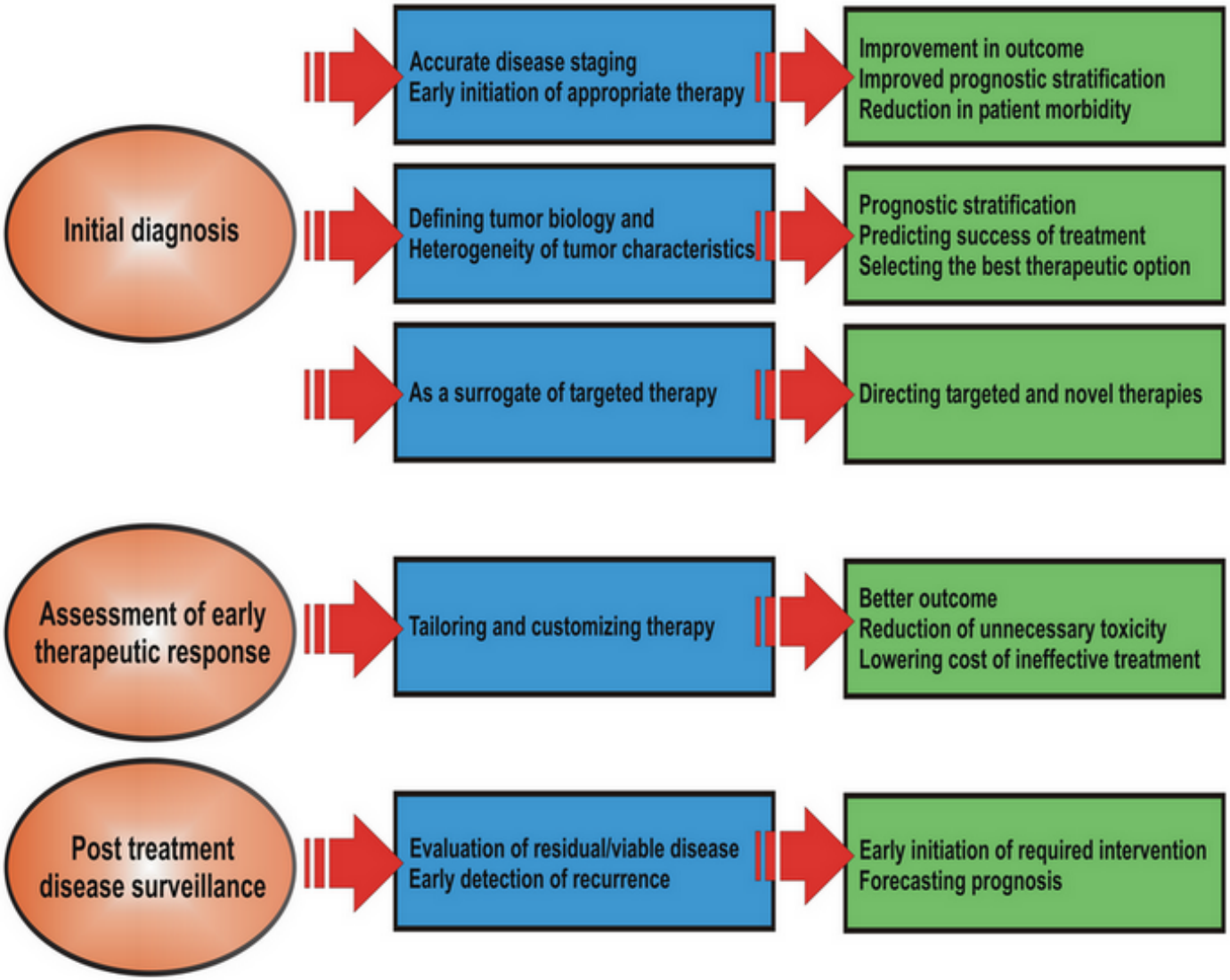
Hallmarks of Cancer



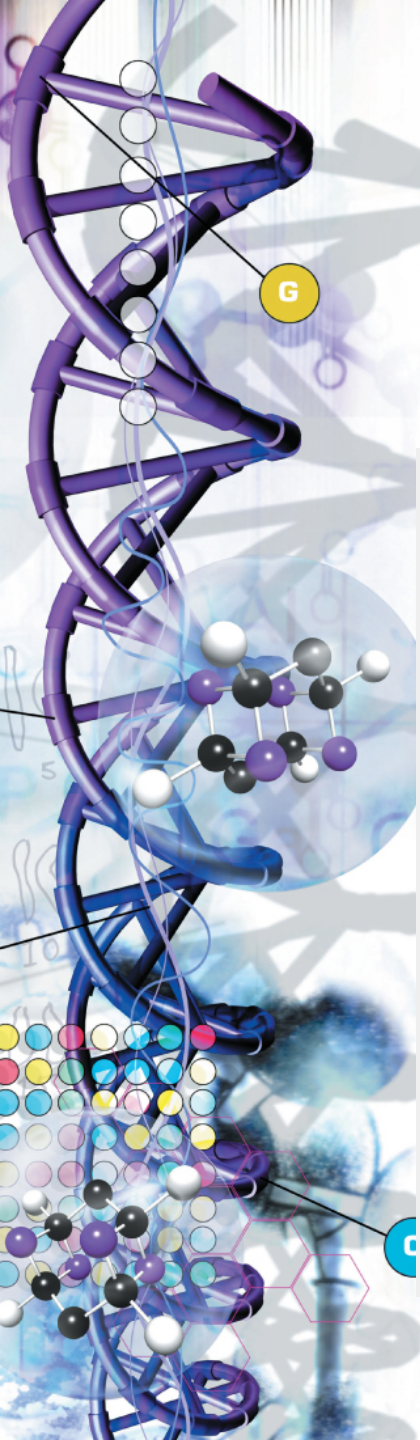


Clinical application of Molecular Imaging.





Modalities for molecular imaging.



Sensitivity

pM

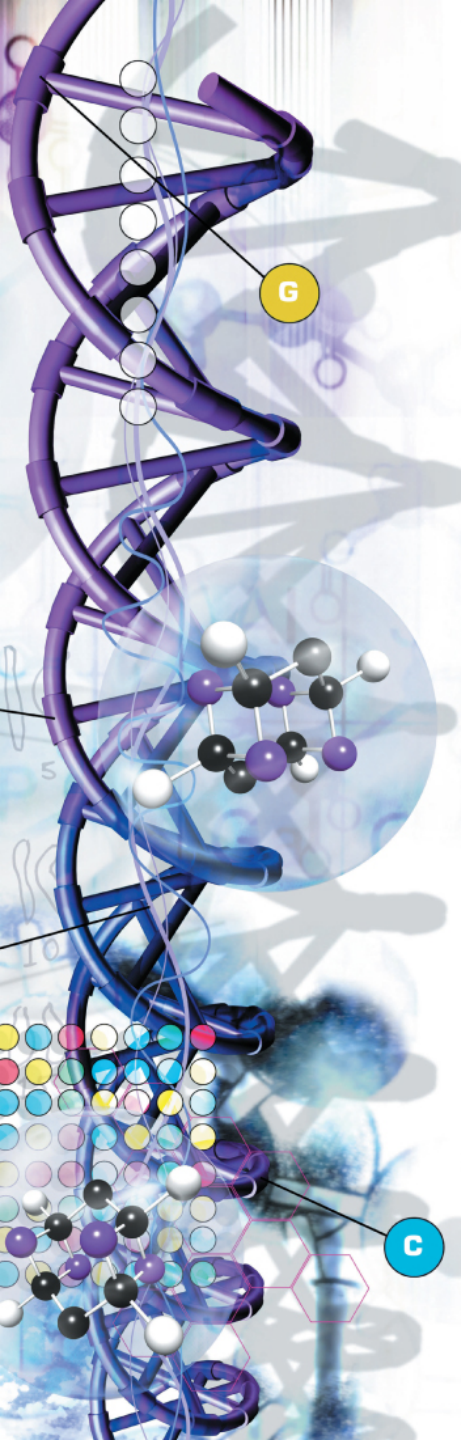
nM

μM

(10 μm)

Modality	Agents	H	R	Primary uses	Examples
• *Optical*					
FMT	fluorescent proteins		X	gene expression, tagging superficial structures	GFP, RFP, NIRF probes
BLI	luciferin		X	gene expression, therapeutic monitoring	fLuc rLuc
• *Nuclear*					
SPECT	^{99m}Tc, $^{123/5}$I, ^{111}In	X	X	site-selectivity, protein labeling	^{99m}Tc-annex in V, ^{123}I-A85380
PET	^{11}C, ^{18}F, ^{124}I, $^{64/62/60}$Cu	X	X	site-selectivity, gene expression, drug development	^{11}C-RAC, ^{124}I-FIAU, ^{64}Cu-ATSM
• *MRI*					
spectro-scopy	endogenous metabolites	X	X	CNS, prostate , heart , breast	NAA, Cr, Cho, Glx, ml, ^{31}P
contrast agents	Gd, Mn, FeO		X	cell trafficking, enzymatic activation	poly-L-lysine, dendrimers, MION
• *Ultrasound*					
contrast agents	perfluorinated microbubbles		X	drug-delivery, gene transfection	human albumin (Optison)

H=human, R=rodent



PET Tracers for Imaging Cancer Biology

Tracer	What is Measured
[^{18}F]-FDG	Glucose metabolism
[^{15}O]-Water	Blood flow
[^{18}F]-FES	ER expression
[^{18}F]-FDHT	AR expression
[^{18}F]-FLT	Tumor proliferation
[^{18}F]-FMISO	Hypoxia
[^{18}F]-F-RGD peptides	Angiogensis
[^{18}F]-F-annexin	Cell death

Under epigenetic control

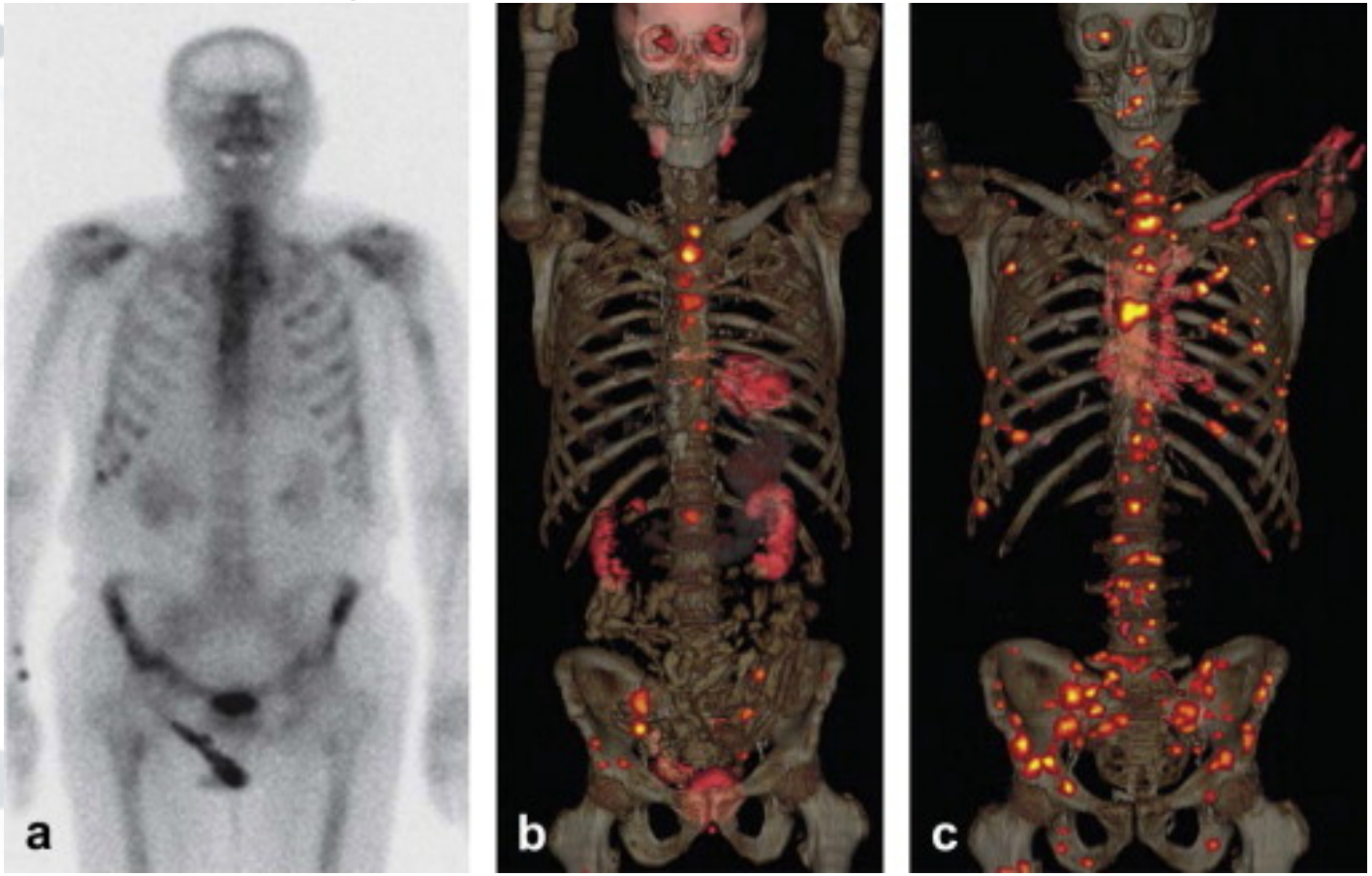
Androgen receptor based molecular imaging

Performed the Same week

Technetium-99 m bone scanning

FDG-PET/CT

FDHT-PET/CT



Radiology. 2011 Jun; 259(3):633–640

Androgen receptor based molecular imaging

FDHT-PET/CT

Baseline

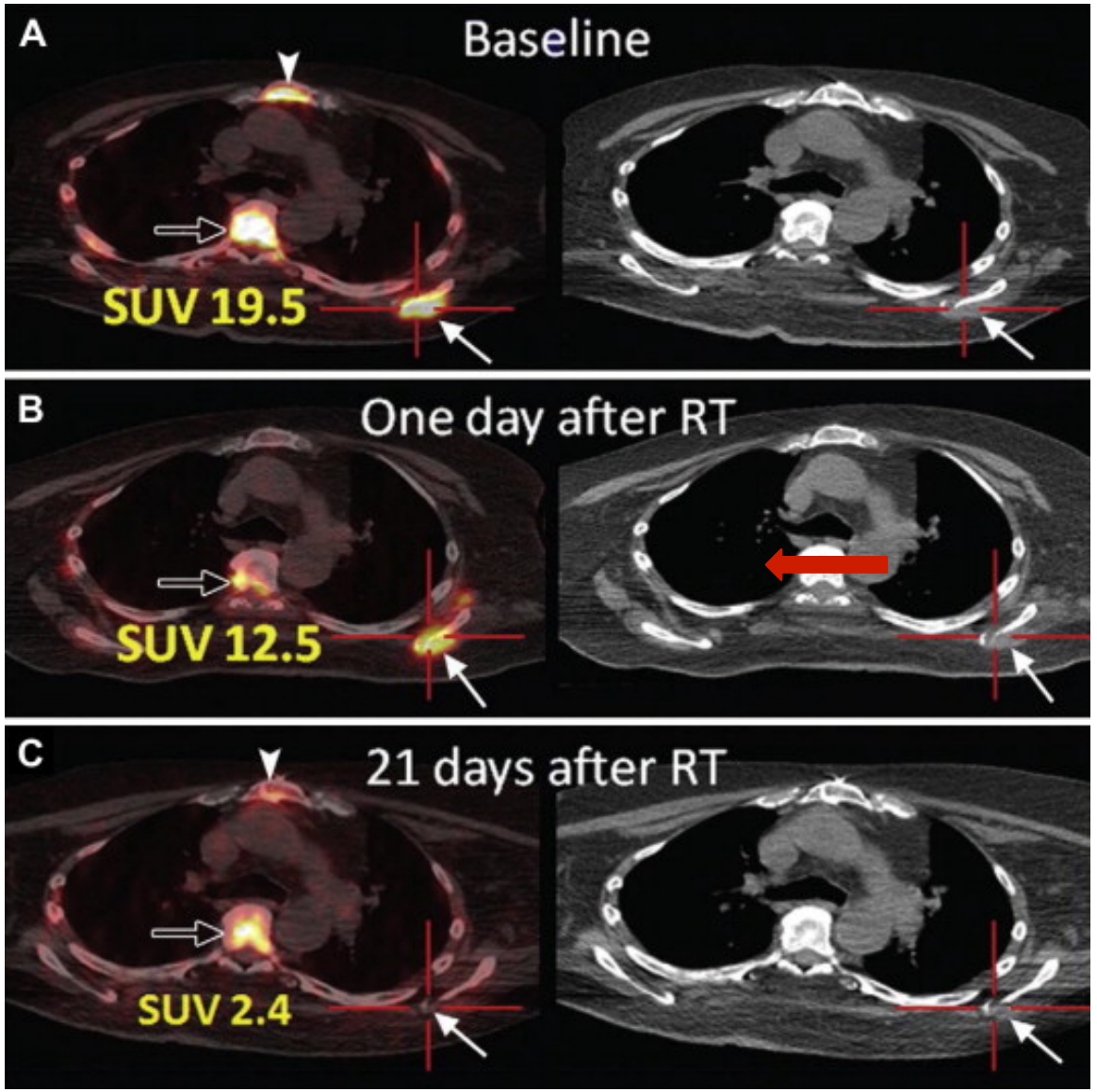
FDHT-PET/CT

4 weeks after

Successful targeting of the androgen receptor by MDV3100

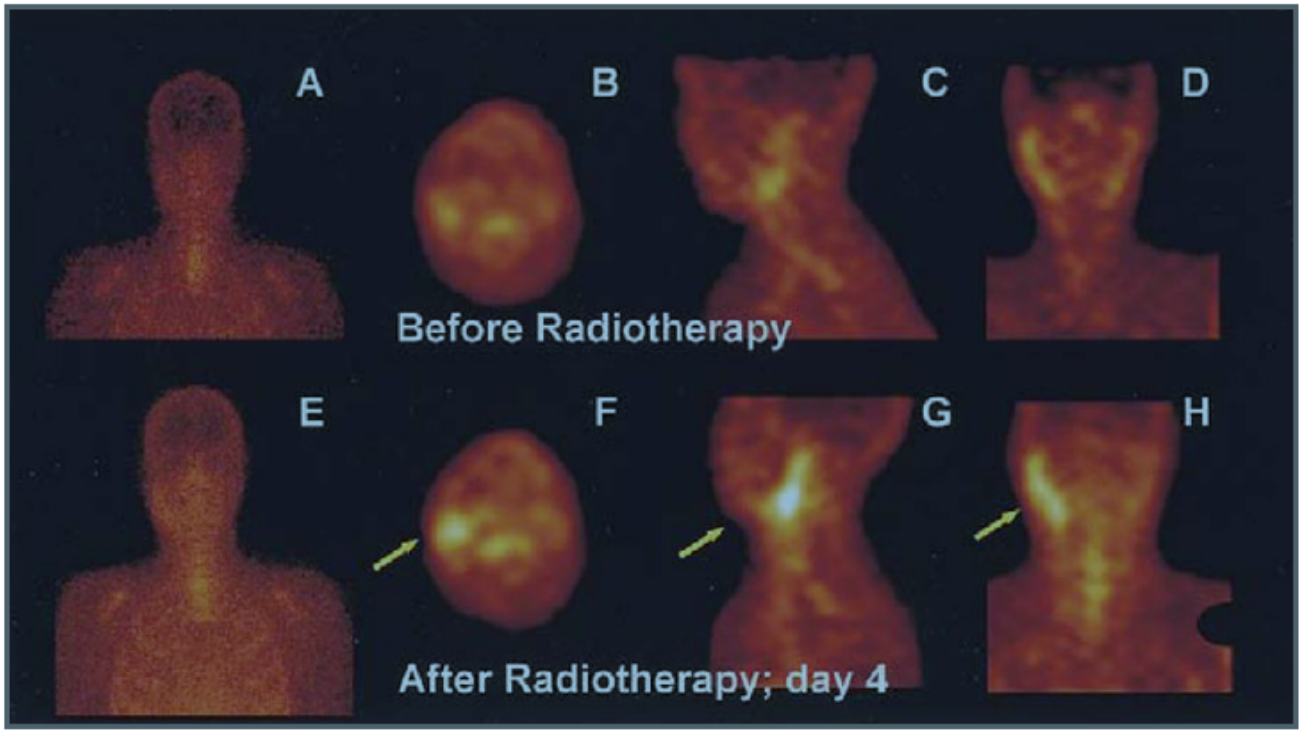
Radiology. 2011 Jun; 259(3):633–640

18 F L-thymidine (FLT) based molecular imaging



Annexin-V based molecular imaging

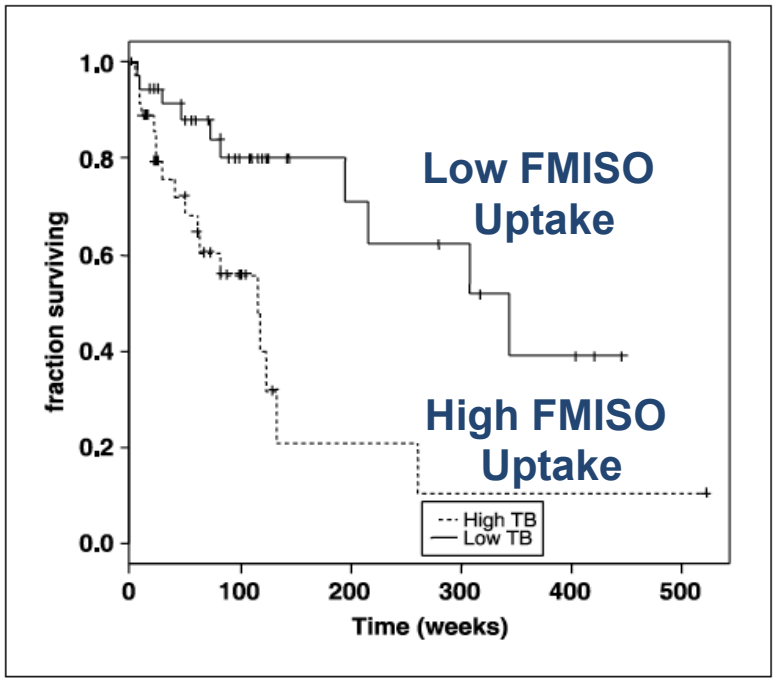
Patient with follicular lymphoma



High uptake in tumor-bearing lymph nodes after radiation therapy

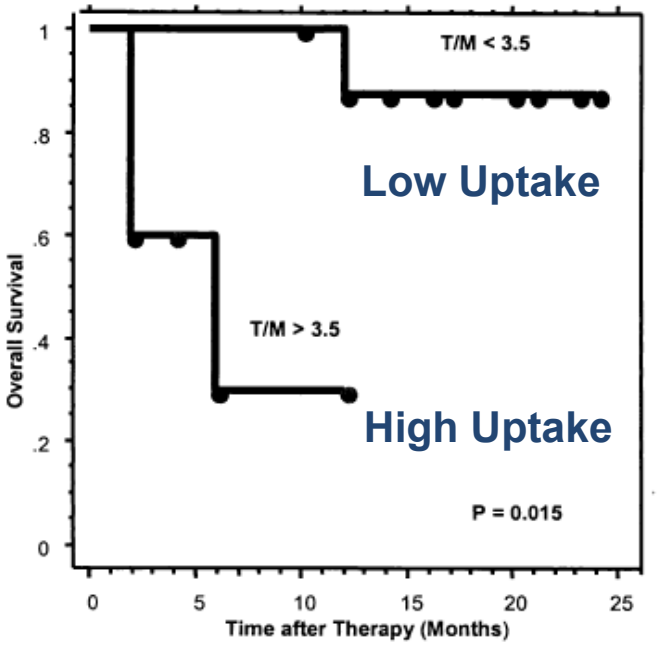
Tumor Hypoxia Quantified by PET Predicts Survival after radiotherapy

FMISO PET H & N Cancer



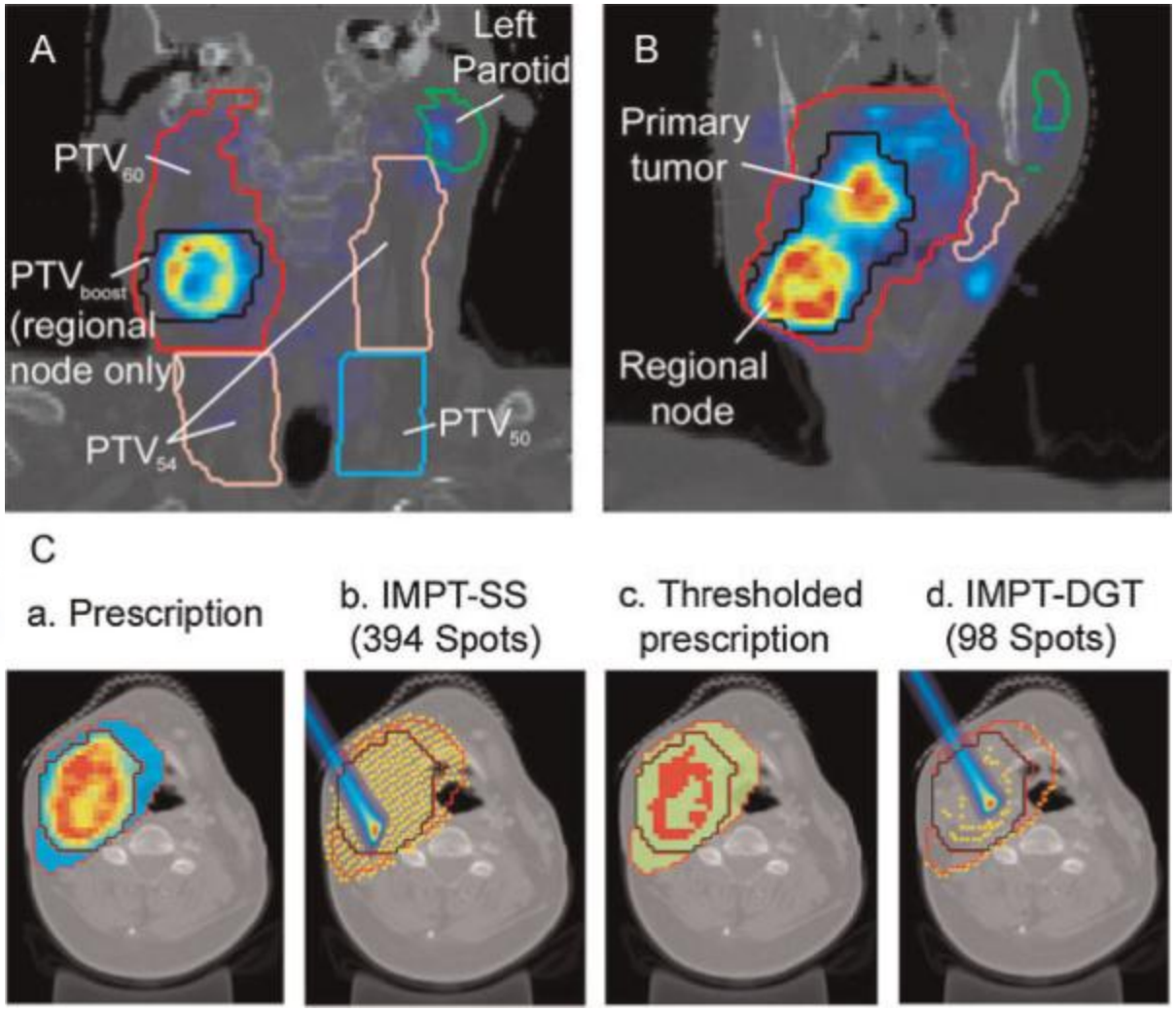
(Rajendran, Clin Can Res, 2007)

Cu-ATSM PET Cervical Cancer

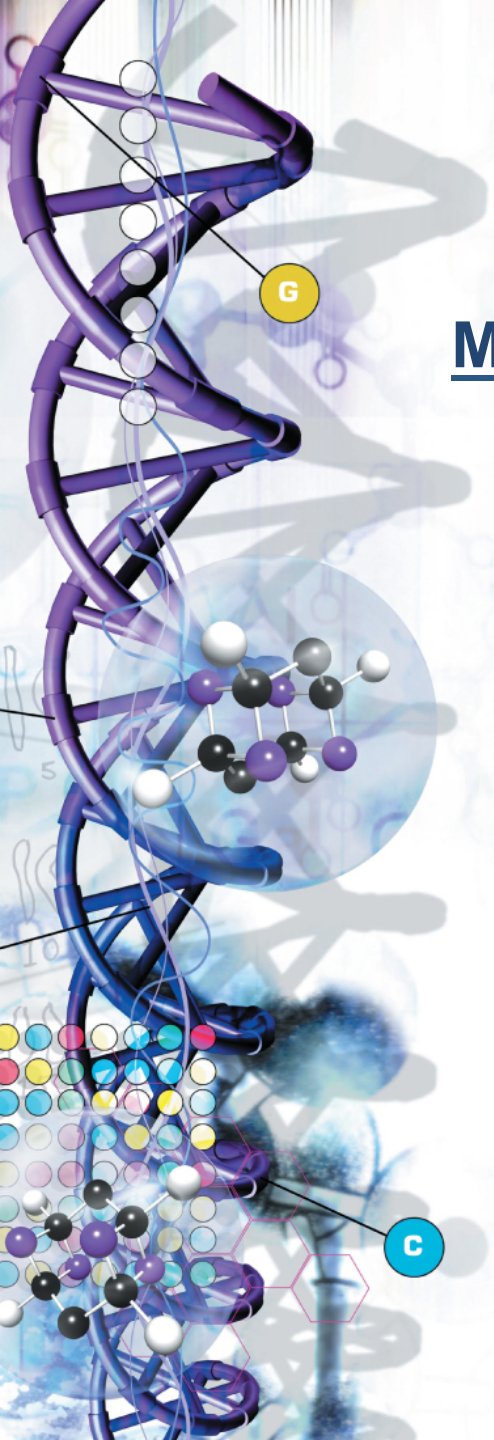


(Dehdashti, Int J Radiat Oncol Biol Phys, 2003)

Hypoxia-based theranostic imaging



Flynn RT, et al Phys. Med. Biol. 2008; 53:4153–4167.



Summary

Major role in three areas of oncology

1. As a basis for choosing what treatment is right for an individual patient

2. As tool for guiding target therapies

3. As part of the “tool kit” that will be used to Develop and optimize new therapeutics