Molecular & Biological Imaging
Present Status & Future Directions

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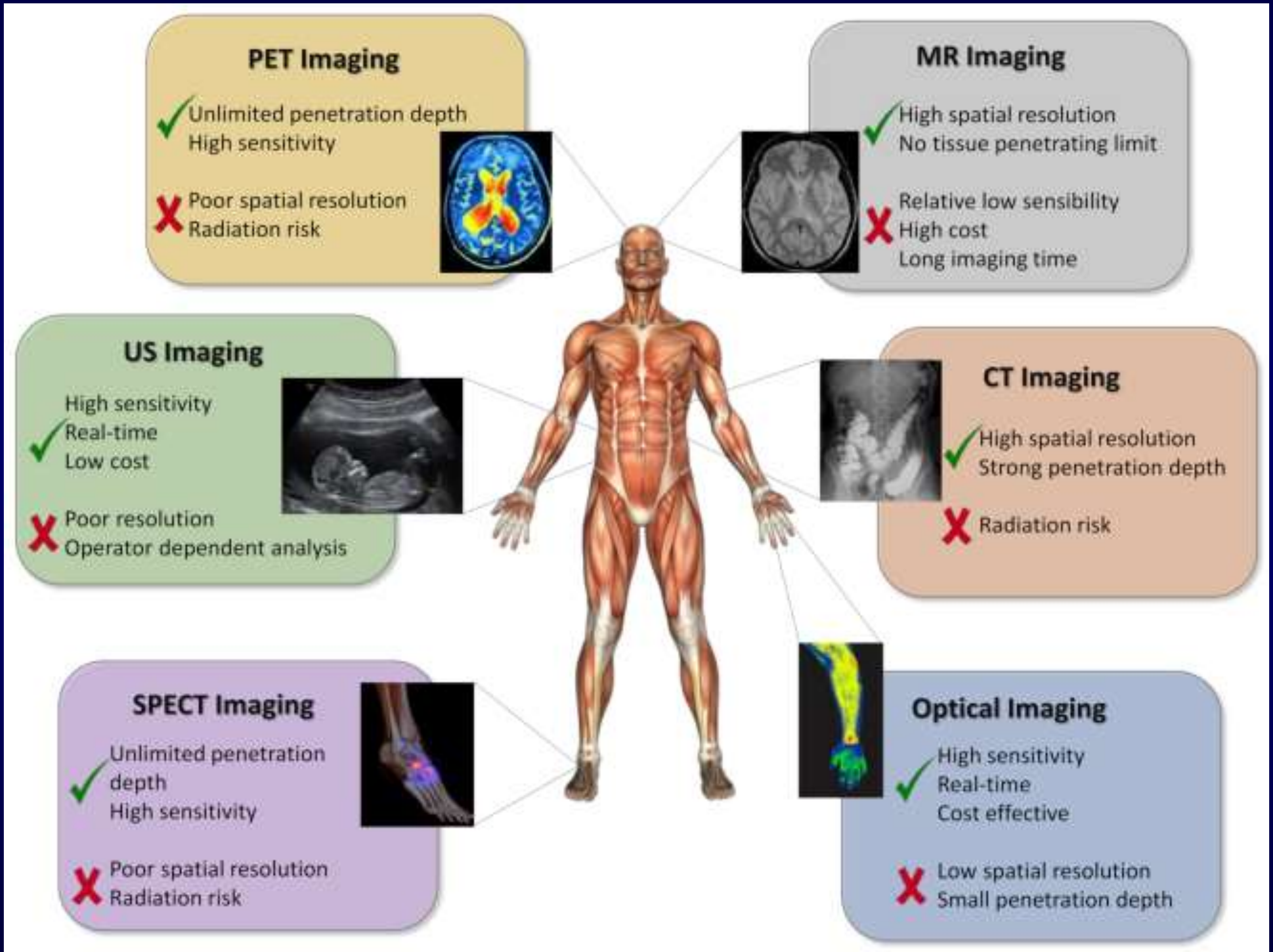
Imaging in oncology



Luengo Morato Y et al. Magnetic Nanoparticle-Based Hybrid Materials. Fundamentals and Applications. Cap 14: Hybrid Magnetic Nanoparticles for Multimodal Molecular Imaging of Cancer.

What do we want from imaging ?

- Good anatomical data
- Good resolution
- More specificity
- More sensitivity
- Reproducibility
- Cost effectiveness

- **More than anatomical & structural data -** Functional, genotypic, phenotypic - biological data\
- Guiding and decision making for treatment

Molecular Imaging – definition

Molecular Biology + **In Vivo Imaging**

" Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems "

Society of Nuclear Medicine's Molecular Imaging Center of Excellence (MICoE)
effective Oct. 1, 2010 to the Center for Molecular Imaging Innovation and Translation (CMIIT)

Mankoff DA. A definition of molecular imaging. J Nucl Med. 2007 Jun;48(6):18N, 21N.

Molecular imaging agents

" Probes used to visualize, characterize, and measure biological processes in living systems. Both endogenous molecules and exogenous probes can be molecular imaging agents "

Society of Nuclear Medicine's Molecular Imaging Center of Excellence (MICoE)
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Molecular Imaging

- In vivo imaging
- Molecular biology aiming at identifying or describing living biological process
- Cellular and molecular level using noninvasive procedures
- Reveal abnormalities in cells and molecules

Biological Imaging

- Final anatomical and structural abnormality caused by cellular or molecular changes
- Images of the human body or parts of it to diagnose or examine disease, and microscopy, which creates images of objects that are too small to see with the naked eye

Weissleder R, Mahmood U. Molecular imaging. Radiology. 2001 May;219(2):316-33. doi: 10.1148/radiology.219.2.r01ma19316.

Molecular + Biological imaging

- Complement traditional imaging techniques by providing additional information about the underlying biological processes that may be causing disease
    - PET – Glucose metabolism, Hypoxia
    - MRI – MRS, BOLD, oxygenation
    - SPECT – Pharmaceutical distribution in body
- Biomarkers - interact chemically with their surroundings and in turn alter the image according to molecular changes occurring within the area of interest

Biological + Molecular Imaging

- Biological images broadly include
  - Metabolic
  - Biochemical
  - Physiological
  - Functional
- Should also encompass
  - Molecular
  - Genotypic
  - Phenotypic images

Ling CC et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys. 2000 Jun 1;47(3):551-60.

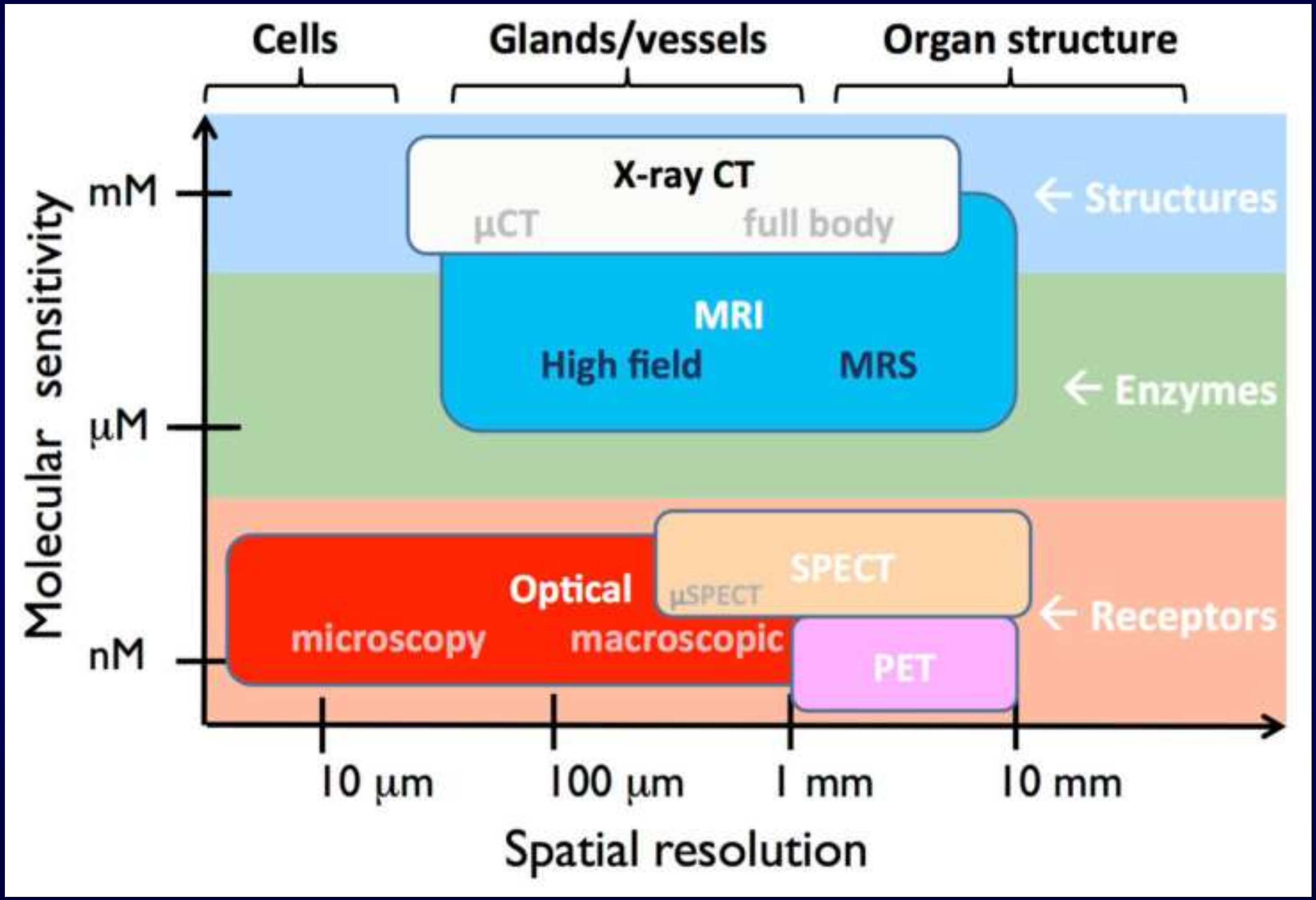
Biological imaging

From Wikipedia, the free encyclopedia

Biological imaging may refer to any imaging technique used in biology. Typical examples include:

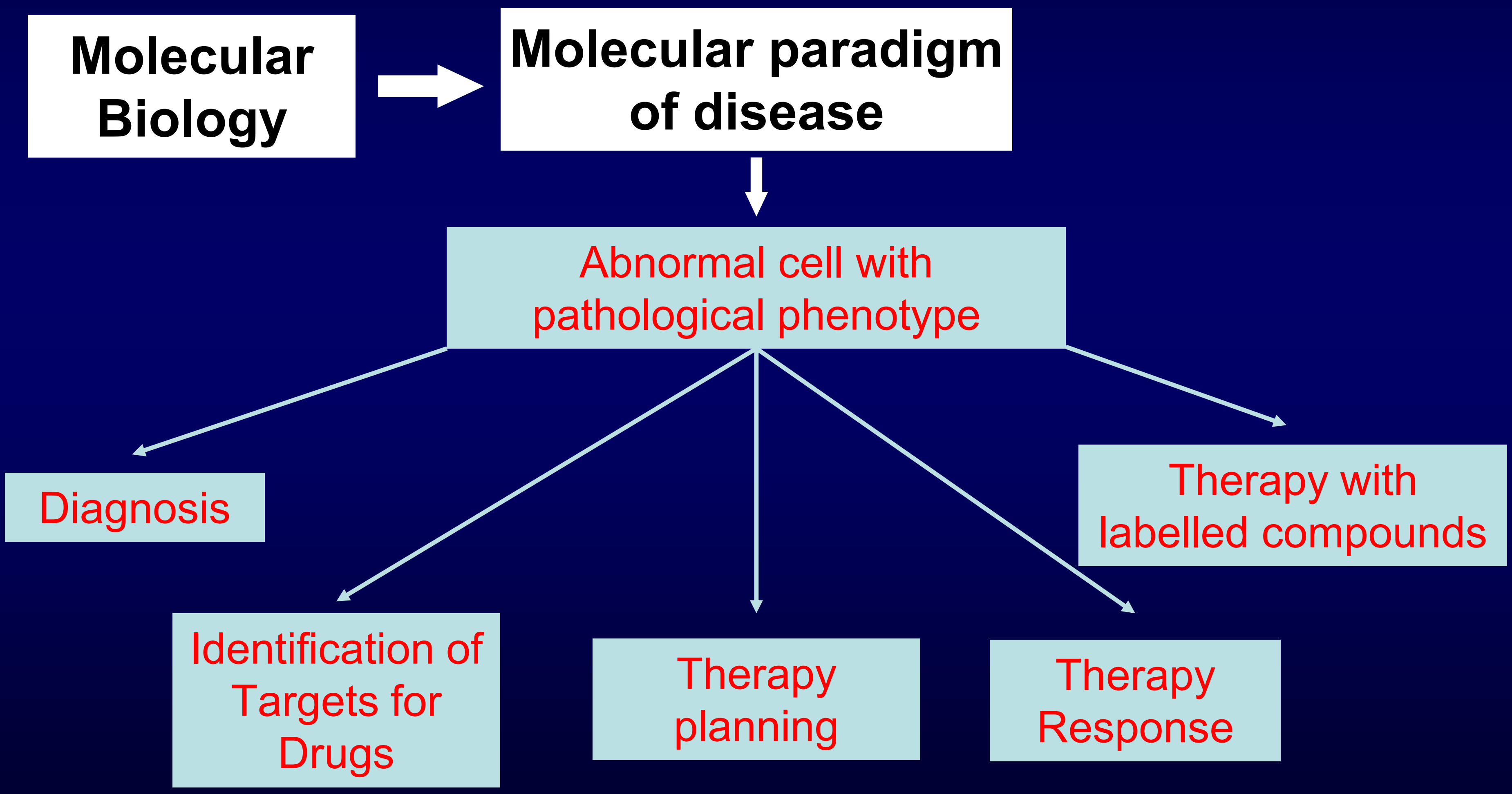
- Bioluminescence imaging, a technique for studying laboratory animals using luminescent protein
- Calcium imaging, determining the calcium status of a tissue using fluorescent light
- Diffuse optical imaging, using near-infrared light to generate images of the body
- Diffusion-weighted imaging, a type of MRI that uses water diffusion
- Fluorescence lifetime imaging, using the decay rate of a fluorescent sample
- Gallium imaging, a nuclear medicine method for the detection of infections and cancers
- Imaging agent, a chemical designed to allow clinicians to determine whether a mass is benign or malignant
- Imaging studies, which includes many medical imaging techniques
- Magnetic resonance imaging (MRI), a non-invasive method to render images of living tissues
- Magneto-acousto-electrical tomography (MAET), is an imaging modality to image the electrical conductivity of biological tissues[1]
- Medical imaging, creating images of the human body or parts of it, to diagnose or examine disease
- Microscopy, creating images of objects or features too small to be detectable by the naked human eye
- Molecular imaging, used to study molecular pathways inside organisms
- Non-contact thermography, is the field of thermography that derives diagnostic indications from infrared images of the human body.
- Nuclear medicine, uses administered radioactive substances to create images of internal organs and their function.
- Optical imaging, using light as an investigational tool for biological research and medical diagnosis
- Optoacoustic imaging, using the photothermal effect, for the accuracy of spectroscopy with the depth resolution of ultrasound
- Photoacoustic Imaging, a technique to detect vascular disease and cancer using non-ionizing laser pulses
- Ultrasound imaging, using very high frequency sound to visualize muscles and internal organs

Current Imaging



Tichauer KM et al. Quantitative in vivo cell-surface receptor imaging in oncology: kinetic modeling and paired-agent principles from nuclear medicine and optical imaging. Phys Med Biol. 2015 Jul 21;60(14):R239-69.

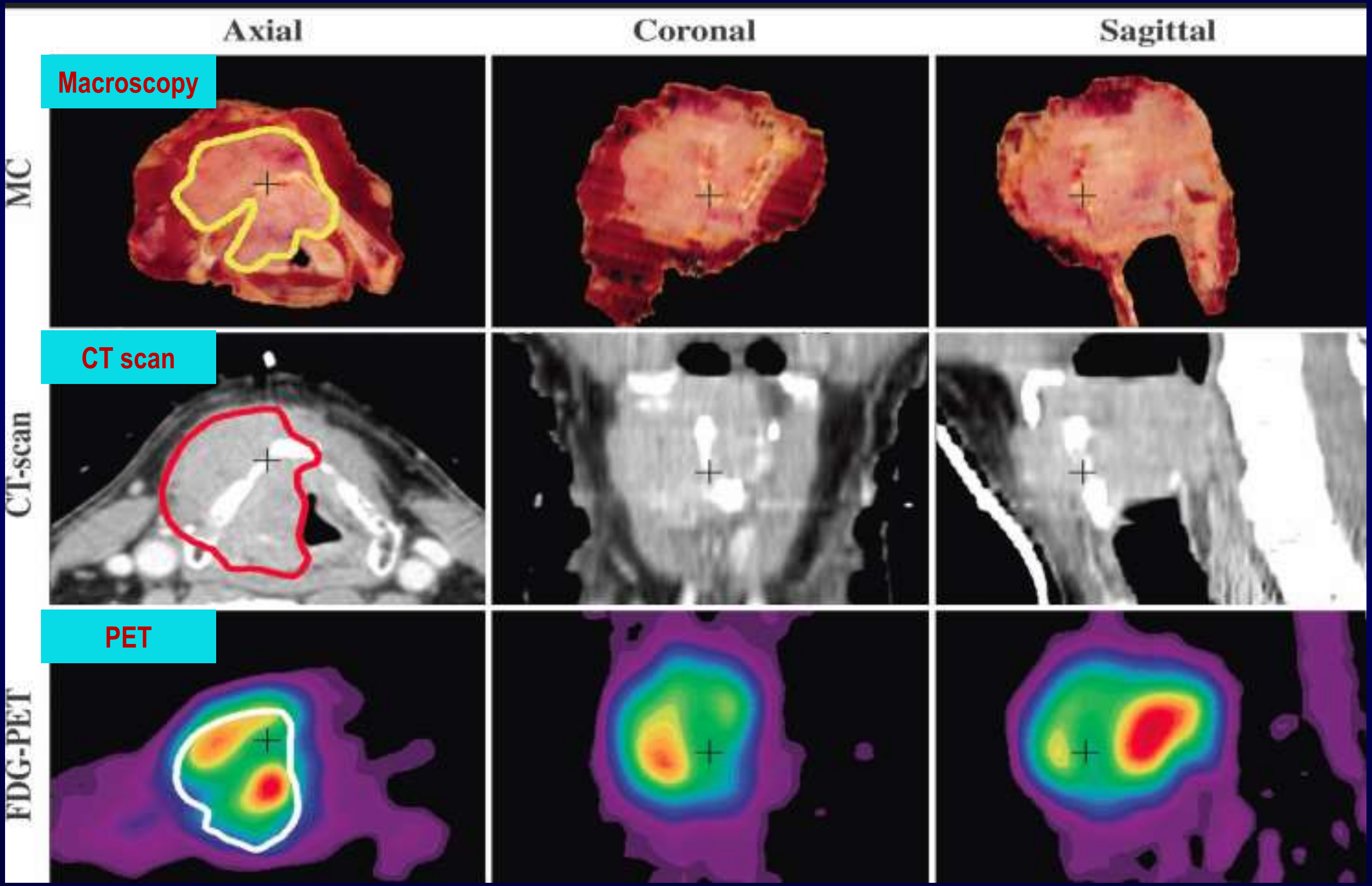
Imaging & Clinical application



Imaging & Radiotherapy

- Diagnosis
- Staging
- Treatment
    - Dose planning – Dose painting
    - Boost
        - High EFGR expression areas in tumor in Head & neck cancers
        - High dose in PET avid region
        - Hypoxic areas – dose escalation
    - Treatment planning – GTV delineation - PET/ MRI etc.
        - Treatment planning – SEPCT perfusion studies in lung cancer
- Response assessment
- Follow up

Is one imaging sufficient ?



Daisne JF et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology. 2004 Oct;233(1):93-100.

Is one imaging sufficient ?

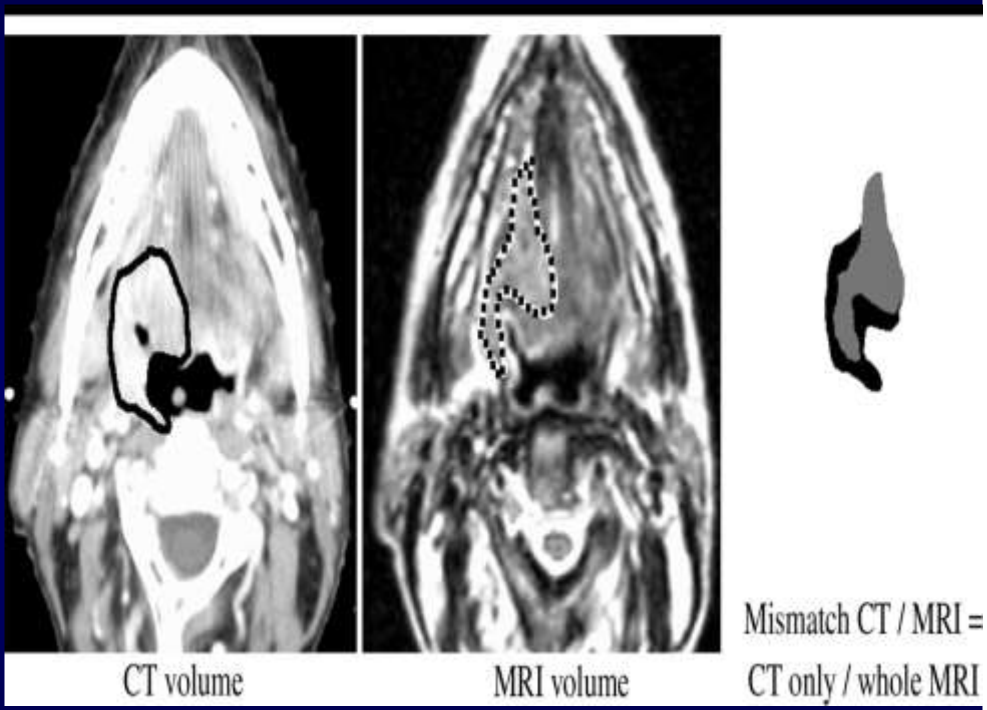


TABLE 5
Average Mismatch of Laryngeal GTVs between Imaging Modalities and the Surgical Specimen

Pair	Mismatched Volume (%)
CT	
To MR imaging	26 (6.2/23.8)
To FDG PET	48 (7.8/16.3)
To specimen	81 (10.2/12.6)
MR imaging	
To CT	45 (9.3/20.8)
To FDG PET	67 (11.0/16.3)
To specimen	107 (13.4/12.6)
FDG PET	
To CT	17 (3.5/20.8)
To MR imaging	15 (3.6/23.8)
To specimen	46 (5.8/12.6)
Specimen	
To CT	10 (2.0/20.8)
To MR imaging	9 (2.2/23.8)
To FDG PET	13 (2.1/16.3)

Note.—Data in parentheses are the average mismatched volumes in cubic centimeters.

No modality adequately depicted superficial tumor extension this was due to limitations in spatial resolution

false-positive results were seen for cartilage, extralaryngeal, and preepiglottic extensions

Daisne JF et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology. 2004 Oct;233(1):93-100.

GTV variation CT PET MRI

TABLE 1. Patient and Tumor Chara

					^{18}F-FDG-1		^{18}F-fluoromisonidazole-1		^{18}F-fluoromisonidazole-2	
Patient no.	Primary tumor site	cT	cN	GTV_{CT} (mL)	GTV_{FDG} (mL)	SUV_{max}	Hypoxic volume (mL)	T/B_{max}	Hypoxic volume (mL)	T/B_{max}
1	Hypopharynx	4a	1	46.38	25.74	8.00	6.4	1.59	0.09	1.42
2	Hypopharynx	1	2b	17.82	6.07	9.41	0.9	1.38	0.03	1.24
3	Larynx	3	0	23.06	8.13	17.46	—	—	0	0.96
4	Oropharynx	3	2b	19.08	9.29	10.85	6.74	1.80	0	1.23
5	Oropharynx	2	2c	16.96	10.09	8.25	0.02	1.25	0	1.00
6	Oropharynx	2	2c	19.9	11.07	13.17	9.32	2.09	0	1.17
7	Oropharynx	4a	1	42.3	22.21	14.84	—	—	0	1.09
8	Oropharynx	4a	1	28.01	23.42	6.98	6.1	1.51	3.23	1.61
9	Oropharynx	2	2b	14.53	15.01	9.53	0	1.17	0.85	1.38
10	Larynx	3	2b	68.34	25.39	11.80	0	1.23	0	1.03
11	Larynx	4a	2c	20.47	15.1	8.25	3.74	1.51	0.03	1.28
12	Hypopharynx	4a	1	19.37	5.24	8.22	—	—	0	0.96
13	Larynx	4a	2c	33.82	16.7	6.80	0	1.13	0	1.00
14	Larynx	1	2c	84.97	81.14	7.00	16.56	1.53	0	1.17
15	Oral cavity	4a	2c	48.51	6.33	6.59	0	1.16	0	1.08

Dirix P, et al, Dose painting in radiotherapy for head and neck squamous cell carcinoma: value of repeated functional imaging with (18)F-FDG PET, (18)F-fluoromisonidazole PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI. J Nucl Med. 2009 Jul;50(7):1020-7.

GTV variation CT PET MRI

CT – MRI – Good correlation

CT – PET – Significantly higher volume in CT

9 recurrences - in-field - within the GTVCT and thus the high-dose region.

Similarly, all recurrences were within the initial GTVT1 and GTVT2 and within the pre treatment GTVFDG on baseline 18F-FDG PET

These results confirm the added value of 18F-FDG PET and 18F-fluoromisonidazole PET for planning radiotherapy of HNSCC, and they suggest the potential of DW and dynamic enhanced MRI for dose painting and early response assessment.

Dirix P, et al, Dose painting in radiotherapy for head and neck squamous cell carcinoma: value of repeated functional imaging with (18)F-FDG PET, (18)F-fluoromisonidazole PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI. J Nucl Med. 2009 Jul;50(7):1020-7.

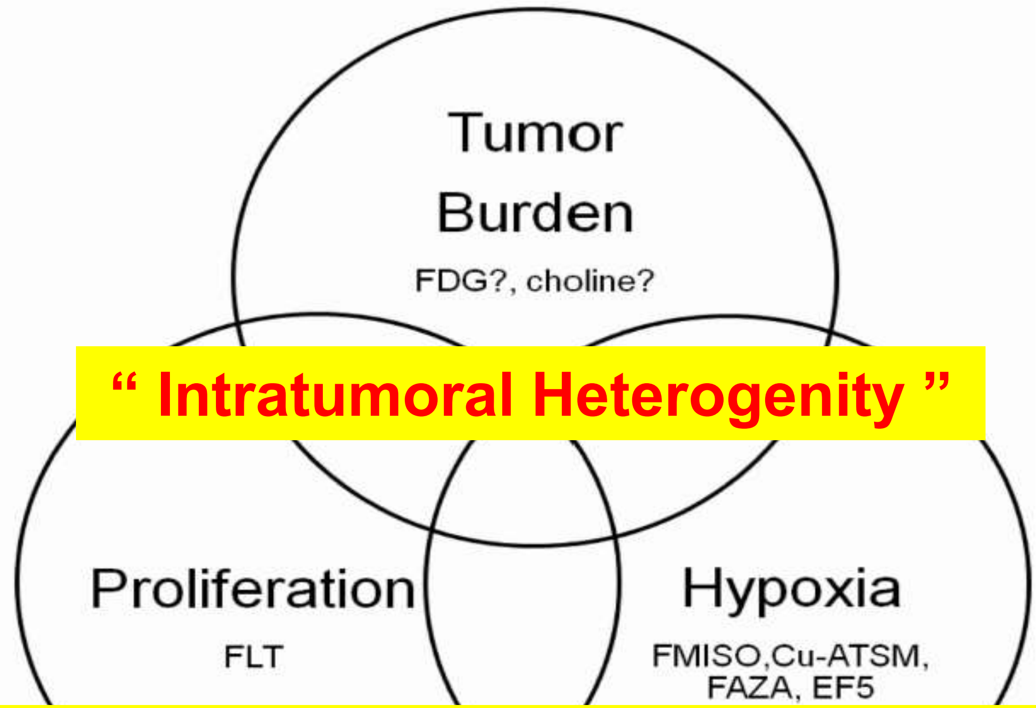
Biological Imaging & Radiotherapy

- CT scan – GTV delineation, Perfusion studies – response
- MRI – GTV delineation – Nasopharynx , DWI
    - MR Spectroscopy – Prostate brachytherapy I-125 therapy
- PET – GTV delineation, Response assessment
- Hypoxia – Hypoxic volume assessment, resistance, Response correlation

Molecular & functional data

Complimentary to anatomical imaging

Targets



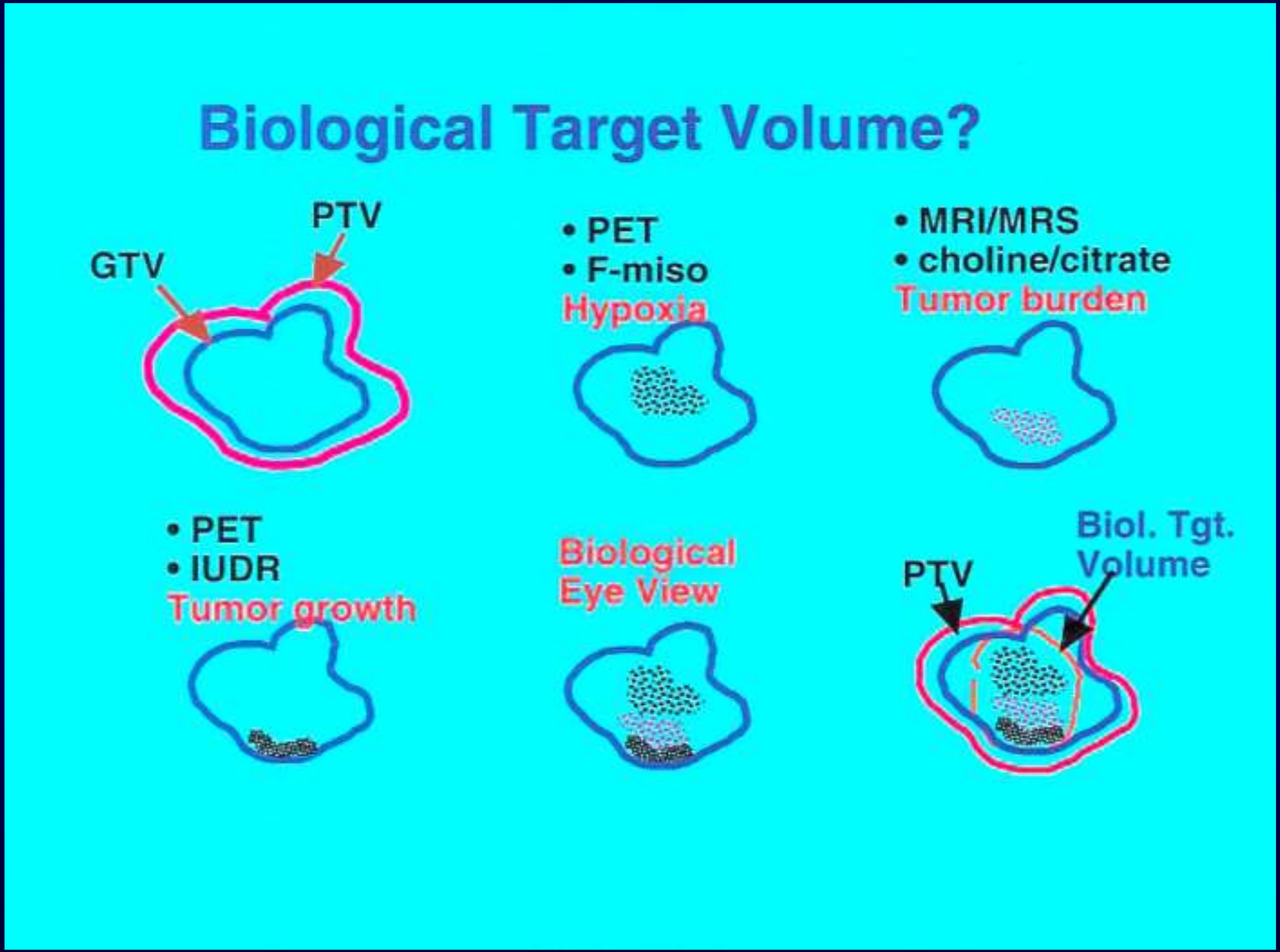
" Intratumoral Heterogenity "

Functional imaging of critical healthy tissue

Figure 1.
Established clinical causes of local treatment failure after fractionated radiation therapy and selected PET tracers of interest as surrogates for these phenotypes.

Bentzen SM, Gregoire V. Molecular imaging-based dose painting: a novel paradigm for radiation therapy prescription.
Semin Radiat Oncol. 2011 Apr;21(2):101-10.

Biological Target Volume



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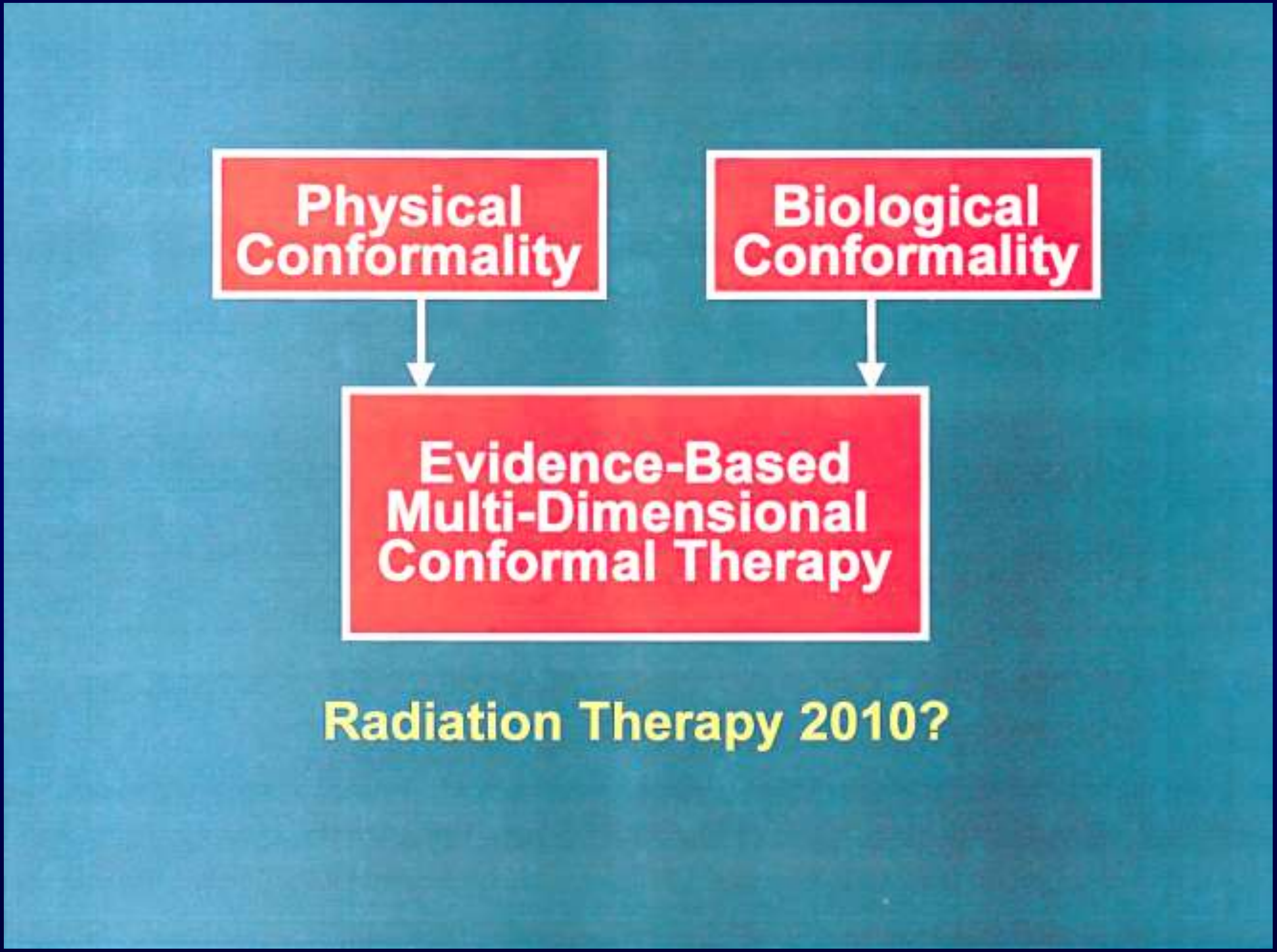
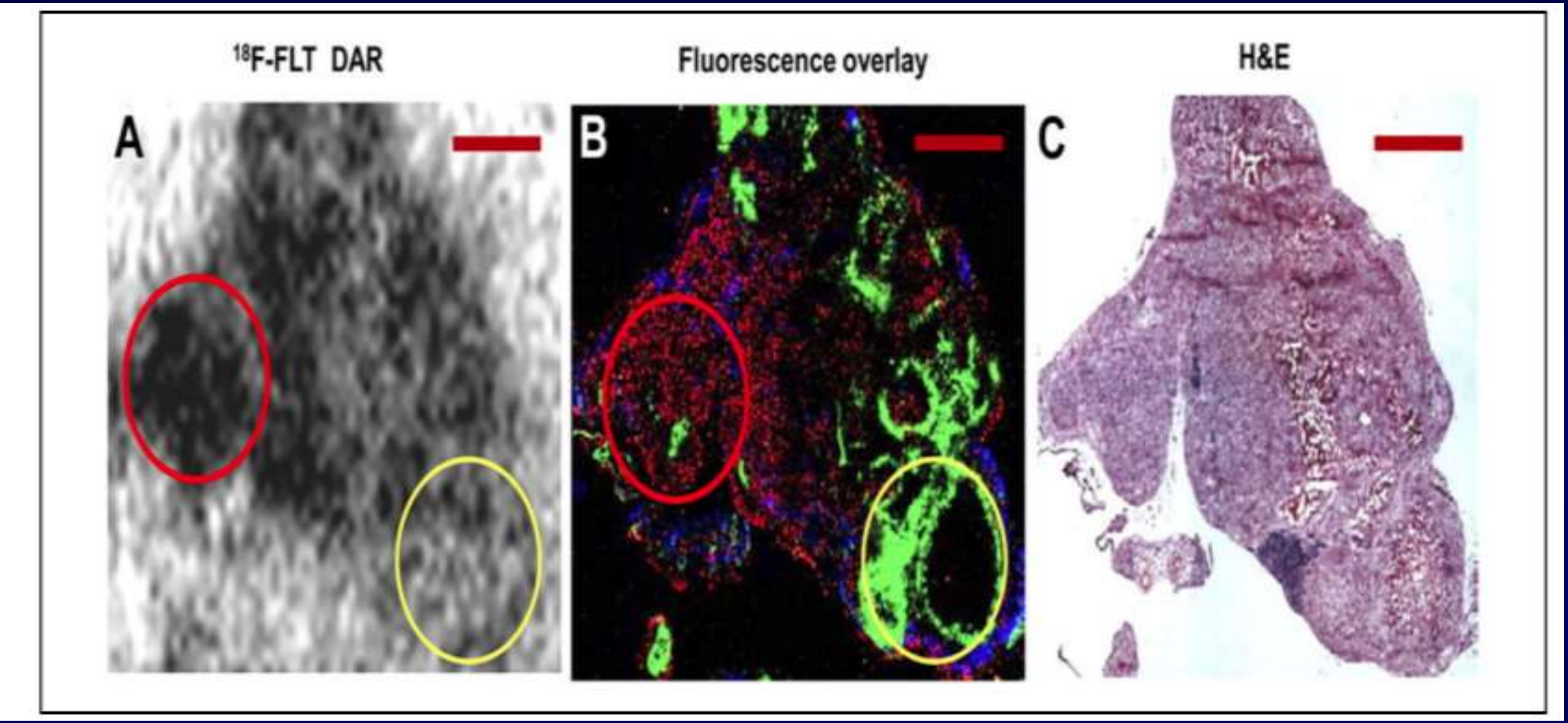
Int J Radiat Oncol Biol Phys. 2000 Jun 1;47(3):551-60.

Biological Target Volume



Ling CC et al.Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality.
Int J Radiat Oncol Biol Phys. 2000 Jun 1;47(3):551-60.

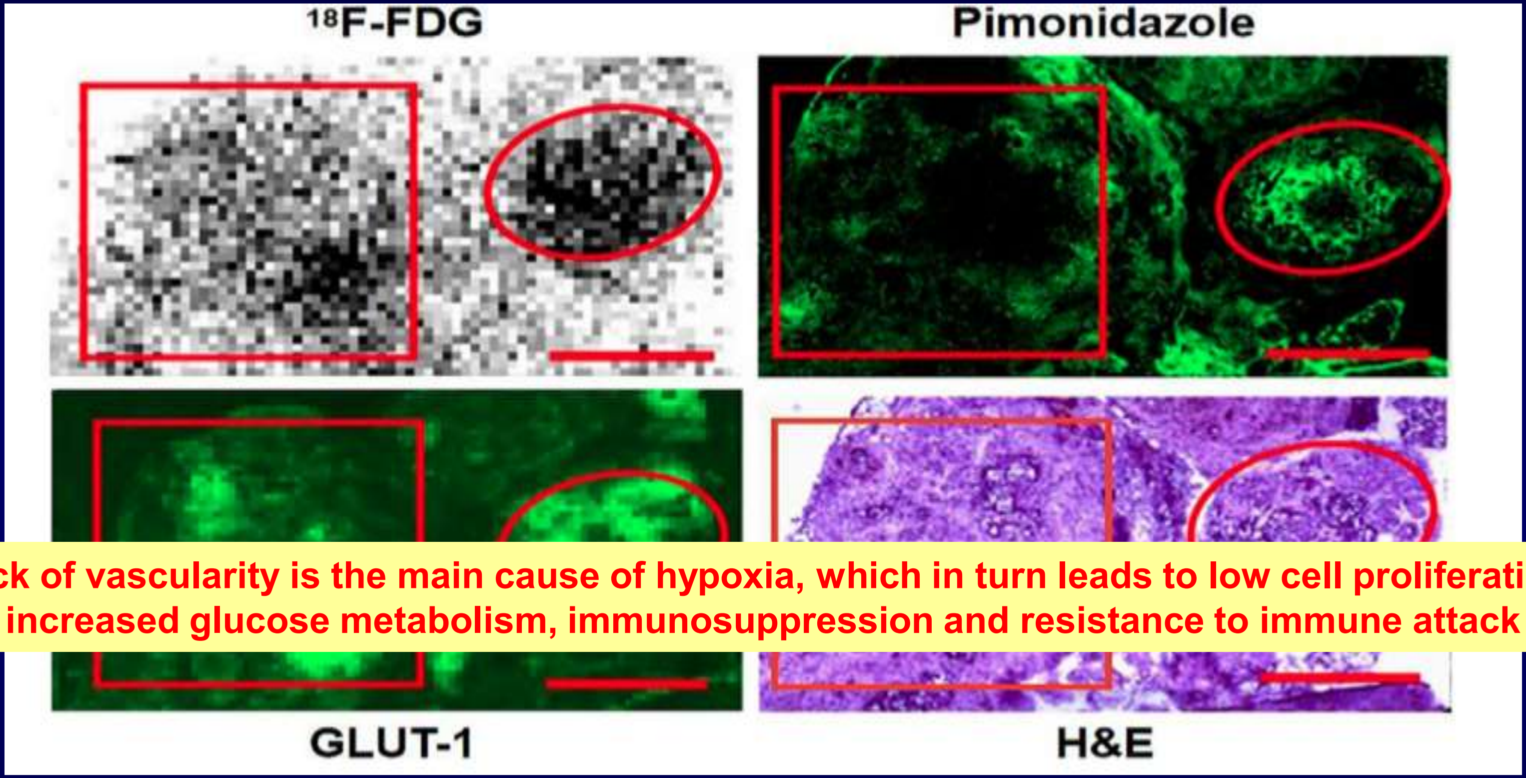
Proliferation & Hypoxia



- 18F-FLT – Proliferation
- Pimonidazole – Hypoxia marker - Green
- Bromodeoxyuridine – Proliferation marker - Red
- Hoechst 33342 - Blood perfusion marker – Blue
- GLUT 1 -

Li Y, Zhao L, Li XF. Hypoxia and the Tumor Microenvironment. Technol Cancer Res Treat. 2021 Jan-Dec;20:15330338211036304..

Tumor Hypoxia and FDG uptake



Lack of vascularity is the main cause of hypoxia, which in turn leads to low cell proliferation, increased glucose metabolism, immunosuppression and resistance to immune attack

- 18F - FDG – glucose uptake – not oxidative metabolism
- Pimonidazole – Hypoxia marker - Green
- Bromodeoxyuridine – Proliferation marker - Red
- Hoechst 33342 - Blood perfusion marker – Blue
- GLUT 1 –Glucose transporter -1

Li Y, Zhao L, Li XF. Hypoxia and the Tumor Microenvironment. Technol Cancer Res Treat. 2021 Jan-Dec;20:15330338211036304..

Theragnostic imaging

- Use of information from medical images to determine how to treat individual patients – term coined by Ling and colleagues
- Application of the quantitative information in biomedical images to produce a prescribed dose map – DPBN
- Not just a map of where to treat but ideally also of the local dose fractionation that will optimize tumor control under specified normal tissue constraints
- e.g. Rationale for theragnostic imaging of tumour-cell proliferation - rapid tumour-cell proliferation during radiotherapy as a resistance mechanism in fractionated radiotherapy -
  - Radiolabelled deoxyuridines
  - FLT PET
  - Ki-68

Bentzen SM, Gregoire V. Molecular imaging-based dose painting: a novel paradigm for radiation therapy prescription. Semin Radiat Oncol. 2011 Apr;21(2):101-10.

Theragnostic imaging

- Tumour Burden & clonogenic density – FDG PET
- Hypoxia – hypoxia markers
  - 2-nitroimidazole group (eg, fluoride-18- misonidazole, iodide-123-iodoazomycin arabinoside
  - D-125I-iodoazomycin galactopyranoside
  - copper-62-labelled diacetylbis (N(4)-methylthiosemicarba-zone)
  - Technetium-99m-labelled 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime
  - HIF1α imaging
- Tumour Proliferation – FLT scans
- Functional imaging of crucial healthy tissue

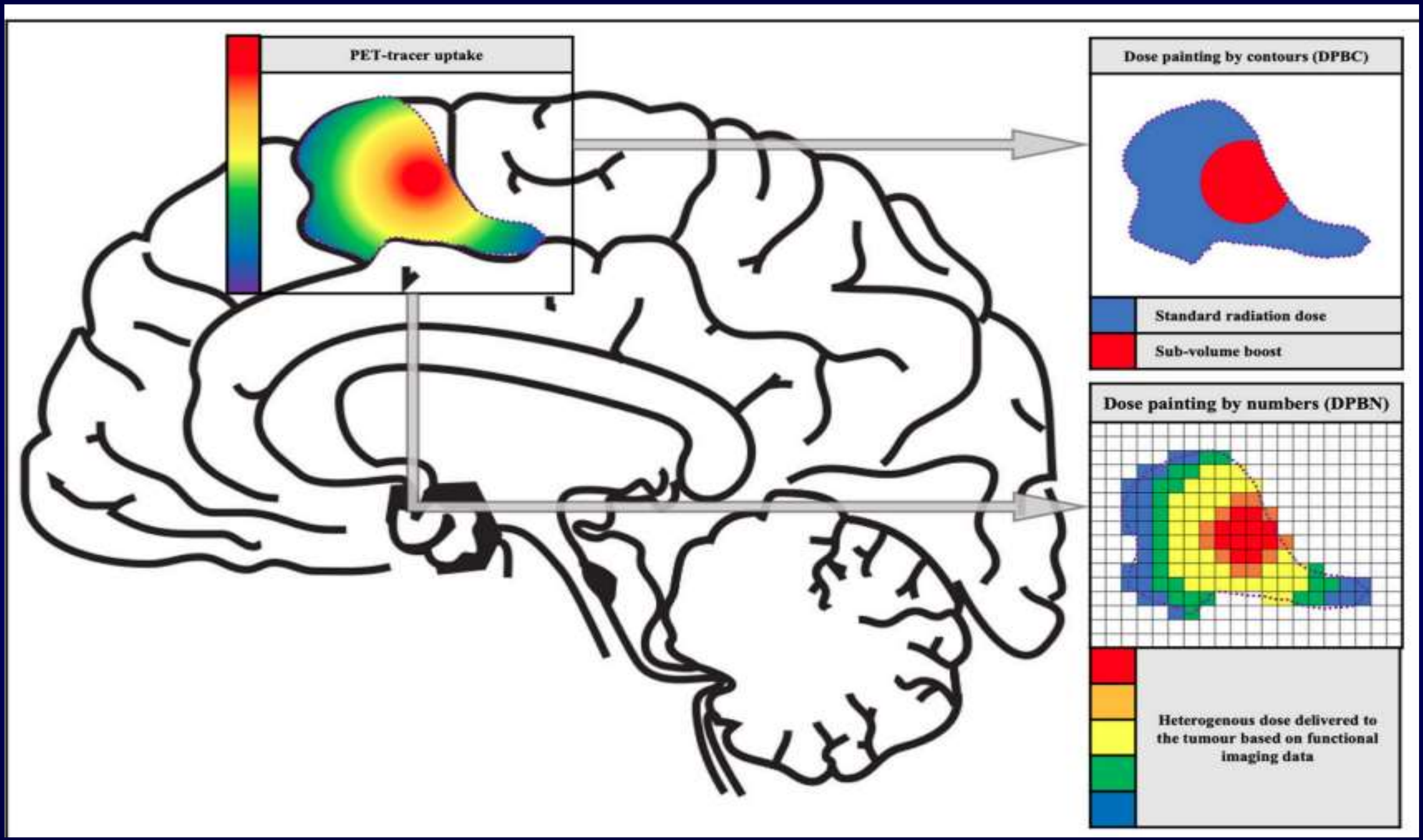
Bentzen SM, Theragnostic imaging for radiation oncology: dose-painting by numbers. Lancet Oncol 2005; 6: 112–17.

Dose Painting

- To replace, completely or in part, the morphologically or anatomically defined target volume with a map of the spatial distribution of a specific tumor phenotype that is hypothesized or has been shown to be related to local tumor control after radiotherapy
- Local recurrences - cellular or micro-environmental niches - (relatively) resistant at the radiation dose level that can safely be routinely delivered using a uniform dose distribution
- Molecular and functional imaging - spatiotemporal mapping regions of relative radioresistance
- Advances in radiation therapy planning and delivery technologies - delivery of a graded boost to such regions - improved local tumor control with acceptable side effects

Bentzen SM, Gregoire V. Molecular imaging-based dose painting: a novel paradigm for radiation therapy prescription. Semin Radiat Oncol. 2011 Apr;21(2):101-10.
Mankoff DA. A definition of molecular imaging. J Nucl Med. 2007 Jun;48(6):18N, 21N.

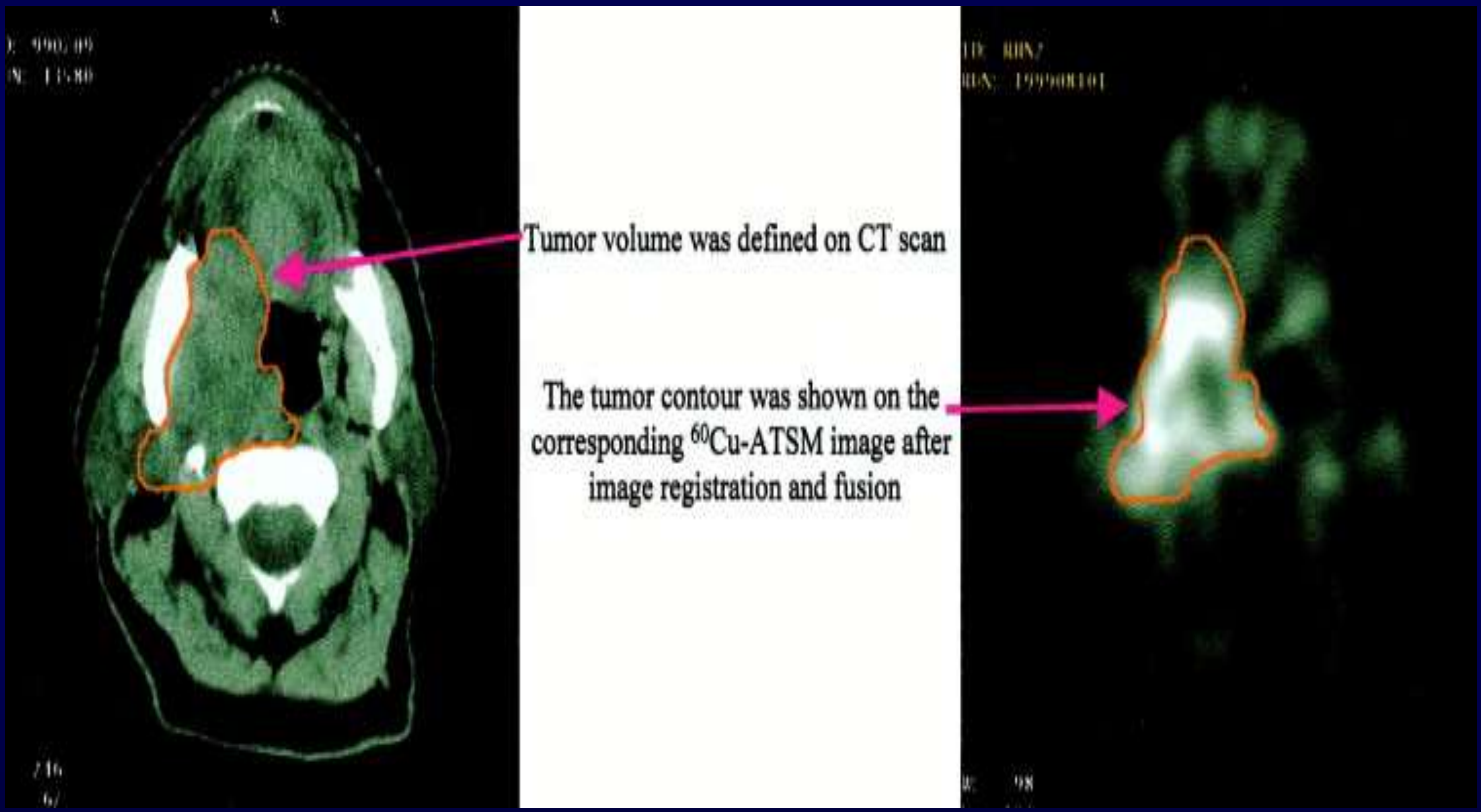
Dose Painting



1. DPBC (Sub Volume Boosting), 2. DPBN

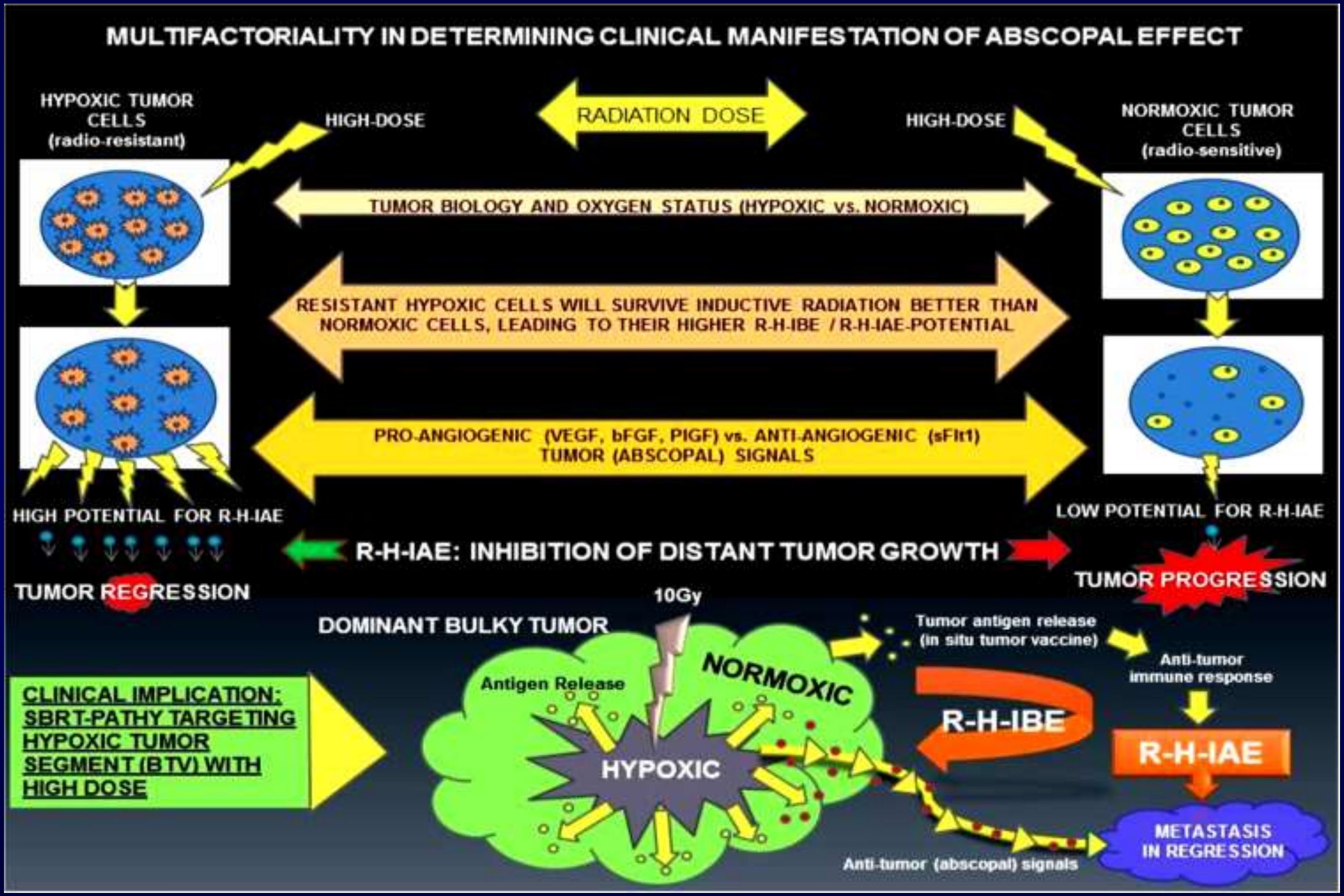
Donche S et al. The Path Toward PET-Guided Radiation Therapy for Glioblastoma in Laboratory Animals: A Mini Review. Front Med (Lausanne). 2019 Jan 29;6:5.
Bao S et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006 Dec 7;444(7120):756-60..

Hypoxia directed RT



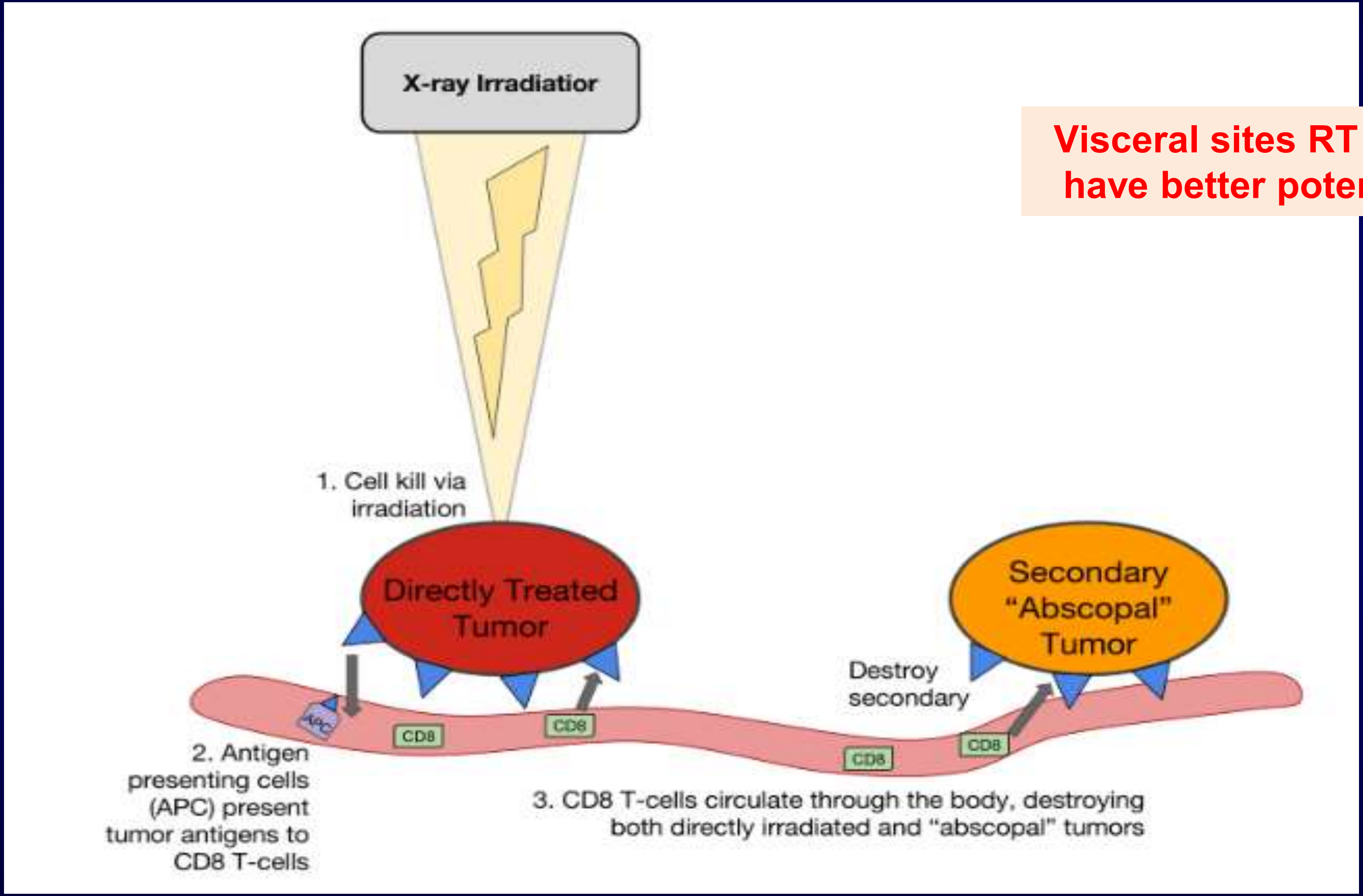
Chao KS et al. A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2001 Mar 15;49(4):1171-82.

Exploiting - Bystander & Abscopal effects



Tubin S et al . Novel stereotactic body radiation therapy (SBRT)-based partial tumor irradiation targeting hypoxic segment of bulky tumors (SBRT-PATHY): improvement of the radiotherapy outcome by exploiting the bystander and abscopal effects. Radiat Oncol. 2019 Jan 29;14(1):21.

RT as abscopal effect



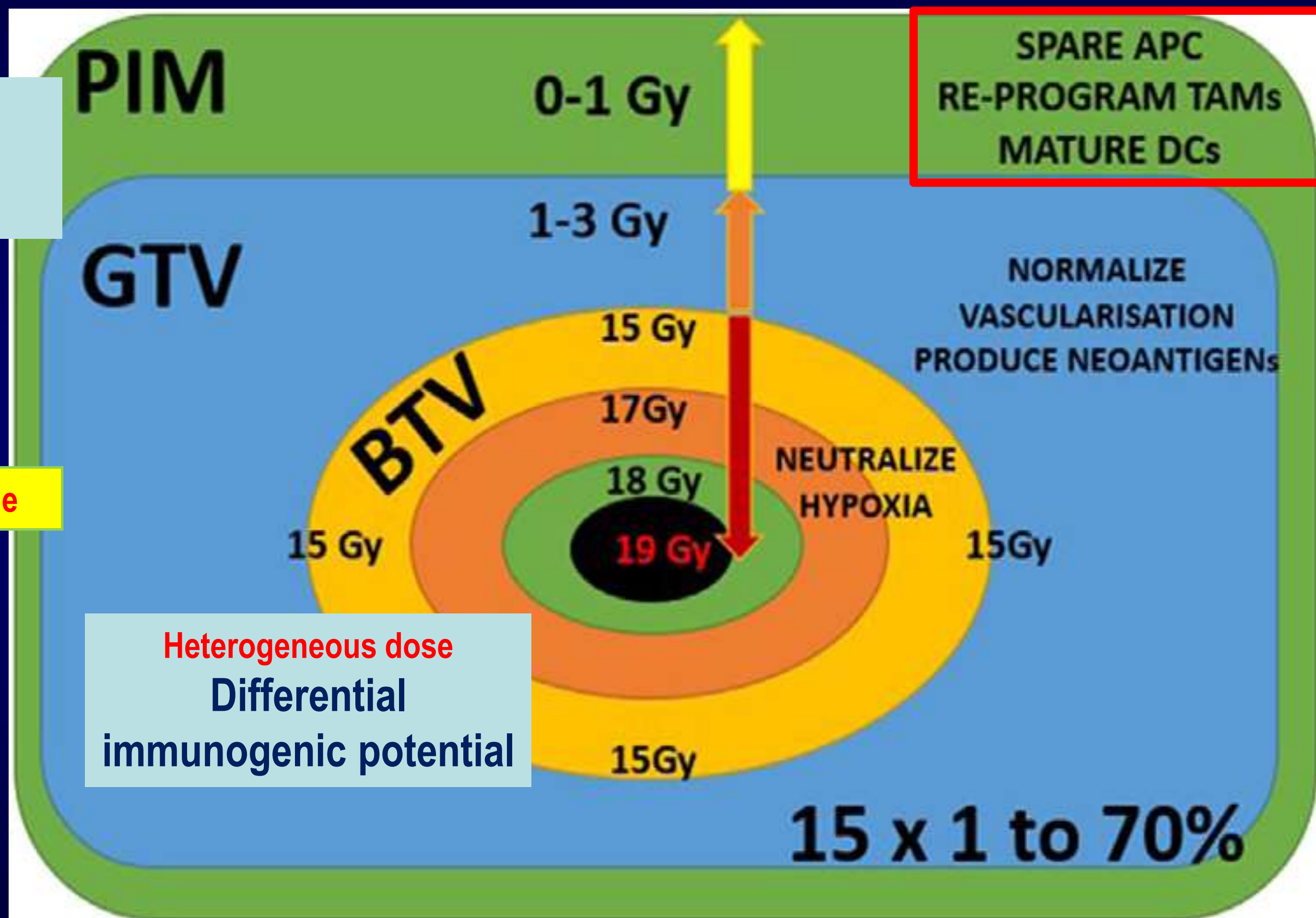
Visceral sites RT may have better potential

Nora Sundahl et al. Piet Ost, Randomized Phase 1 Trial of Pembrolizumab with Sequential Versus Concomitant Stereotactic Body Radiotherapy in Metastatic Urothelial Carcinoma, European Urology, Volume 75, Issue 5, 2019, Pages 707-711

Bystander Tumor Volume - BTV

Peritumoral Immune Microenvironment
OAR

Bystander Tumor Volume



Heterogeneous dose
Differential immunogenic potential

Tubin S. A Partial Tumor Irradiation Approach for Complex Bulky Disease. Semin Radiat Oncol. 2024 Jul;34(3):323-336.

How to contour

- Contrast-enhanced (vascularized) peripheral tumor segment
- Contrast-unenhanced (necrotic) central tumor segment,
- Contrast-hypoenhanced (hypovascularized) tumor segment as an up to a maximum of 5mm junctional zone between the central-necrotic and the remaining peripheral-vascularized tumor segments
- PET was used for definition of a hypometabolic junctional zone between the necrotic and the peripheral hypermetabolic tumor segment. A SUV of 3 defined the boundary
- No additional margins (neither CTV nor PTV) were applied to the BTV. The pathologic lymph nodes and metastases were not irradiated.

How to contour

- Delineating tumour necrosis region on contrast-enhanced CT and then expanding it for 5mm)
- Approximately one third of the central tumor volume - contracting the GTV by 1cm from the surface
- Hypoxia imaging – Cu - 64 ATSM PET
- PIM Peritumoral Immune Microenvironment –
    - Tumor-associated immune cells like TAMs, DC, TILs etc.
    - Contoured as the 1cm-large ring at the tumor surface
    - Expanding the GTV for 1cm and then subtracting the GTV from that“GTV+1cm”-structure

Exploiting - Bystander & Abscopal effects

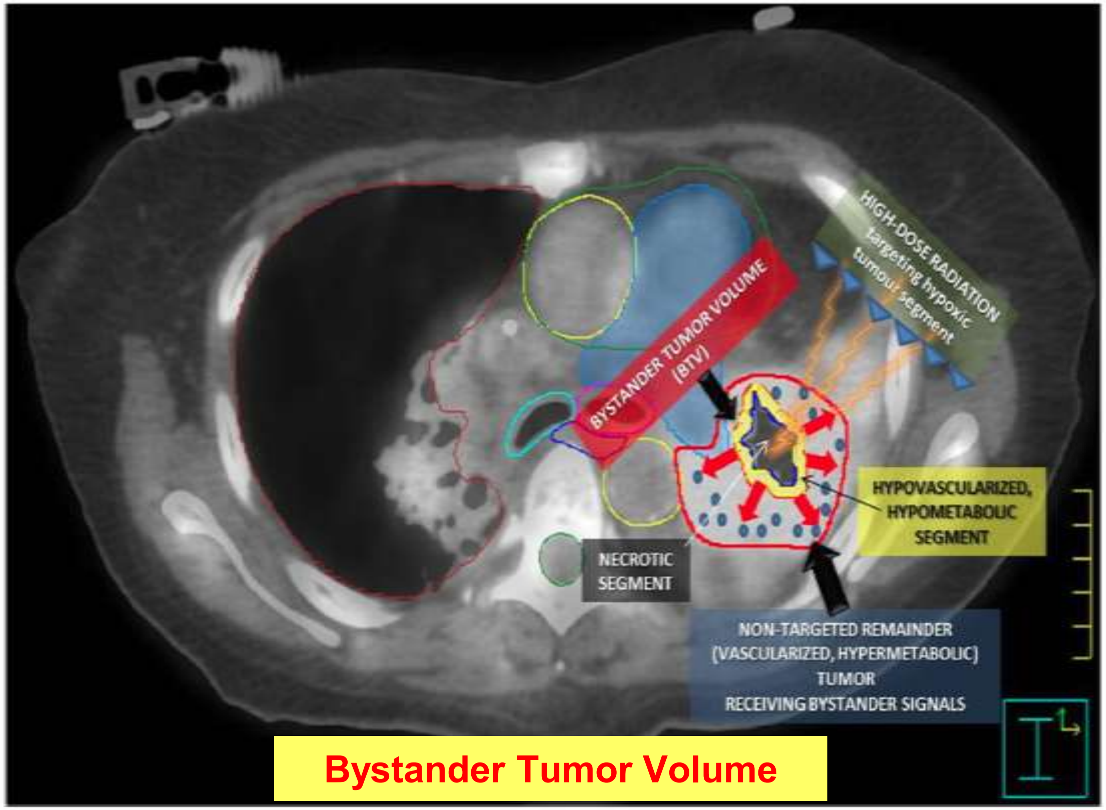
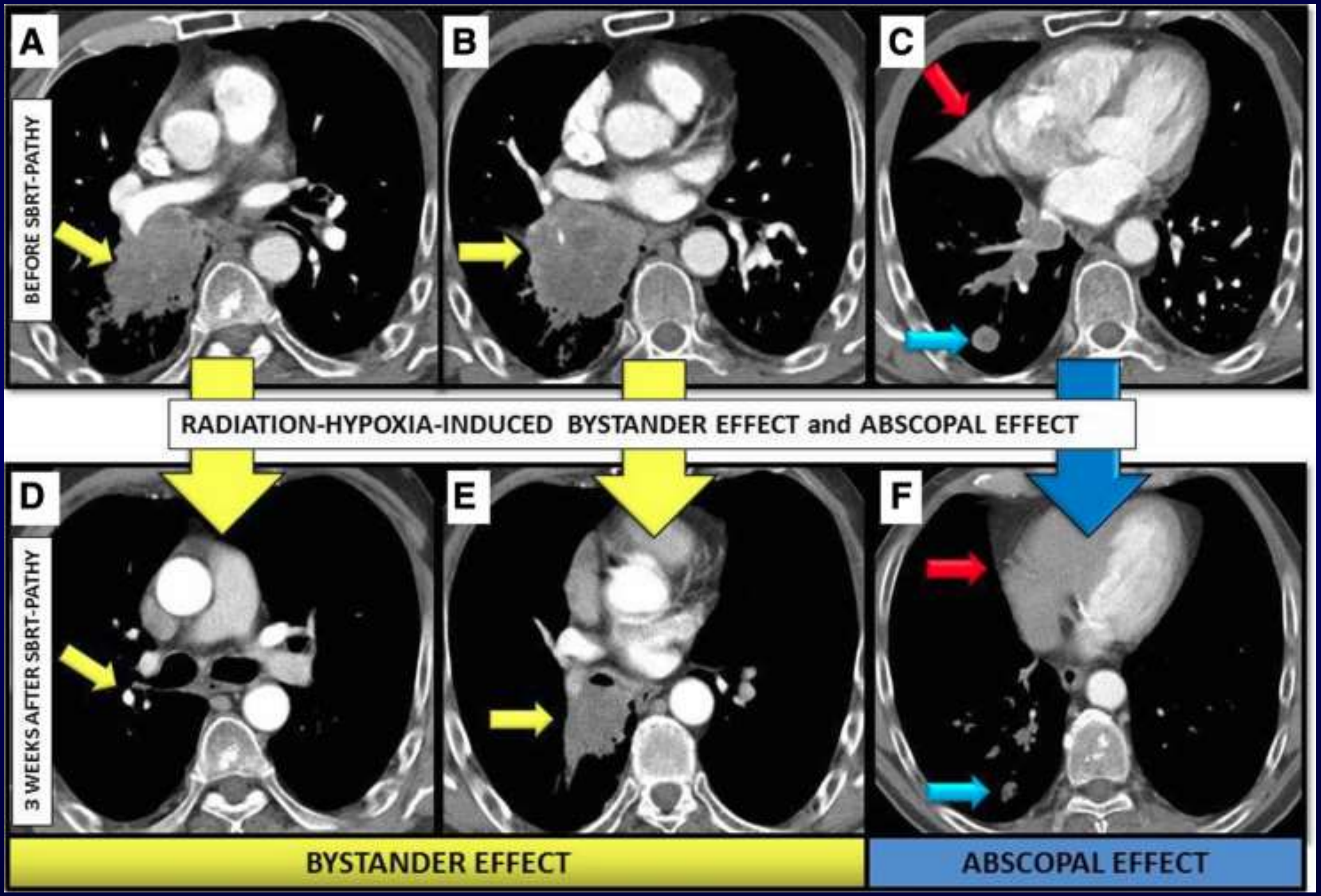


Fig. 2 DEFINITION OF THE BYSTANDER TUMOR VOLUME (BTV): The figure summarizes the radiobiology of the bystander effect-induction by SBRT-PATHY. An 18F-FDG PET combined with a contrast-enhanced CT was used for the definition of BTV (smaller yellow contour), which corresponds to the junctional region between the central necrotic segment (black region) and the contrast-enhanced, hypermetabolic peripheral tumor (red contour, not targeted for irradiation). The red arrows represent "anti-angiogenic bystander signal" (blue pellets) released by the irradiated hypoxic tumor, inducing the regression of the non-targeted tumor

Tubin S et al . Novel stereotactic body radiation therapy (SBRT)-based partial tumor irradiation targeting hypoxic segment of bulky tumors (SBRT-PATHY): improvement of the radiotherapy outcome by exploiting the bystander and abscopal effects. Radiat Oncol. 2019 Jan 29;14(1):21.

Bystander & Abscopal effects



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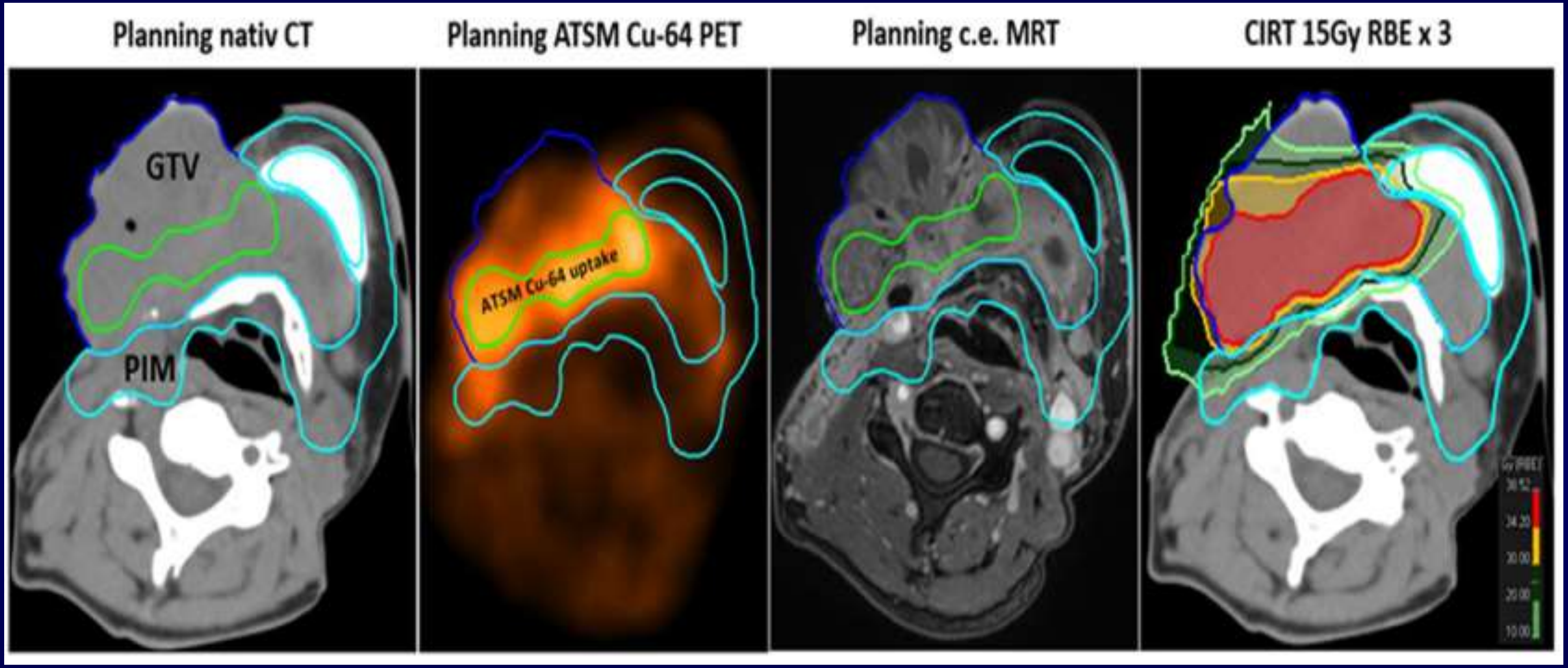
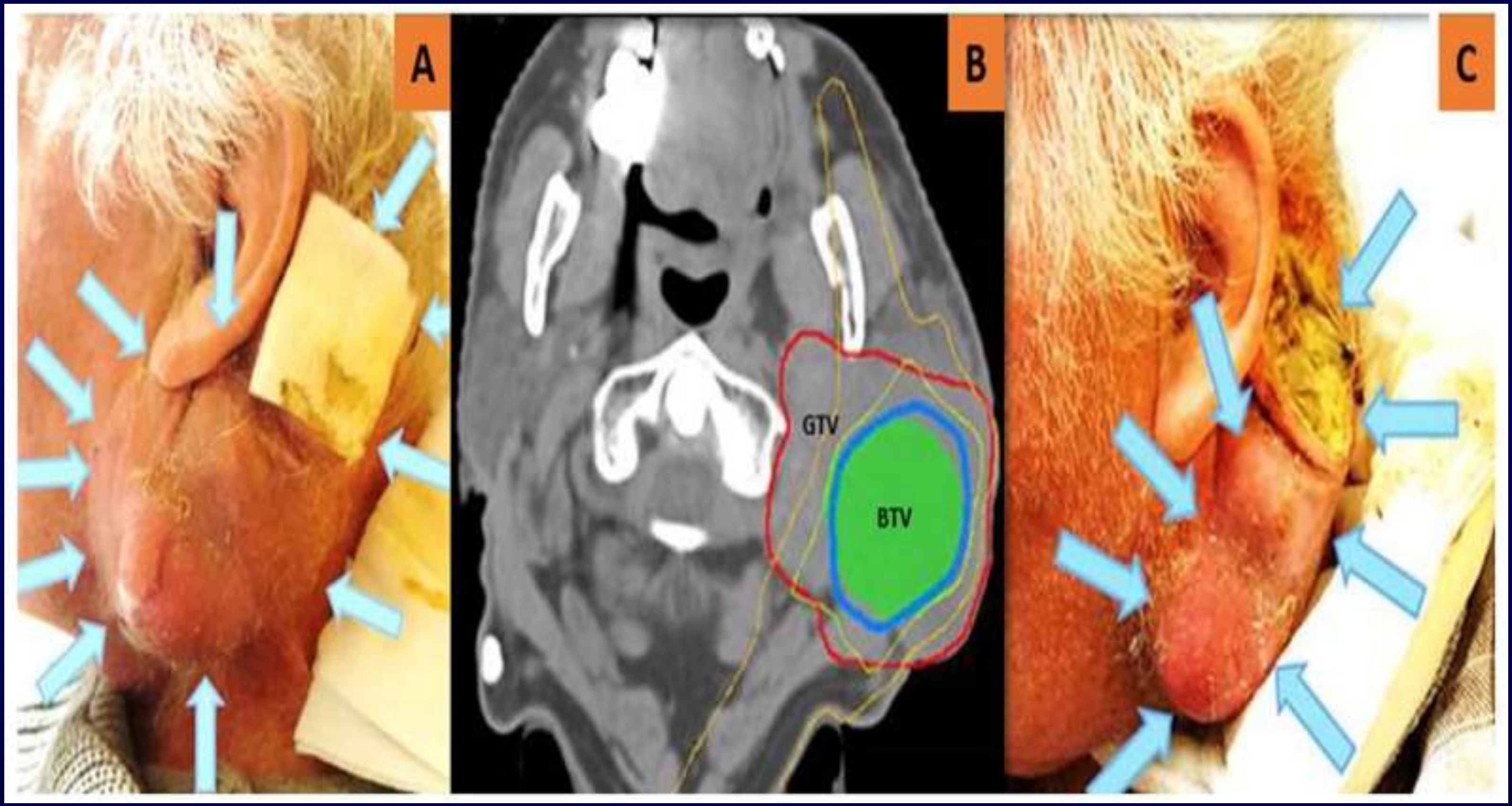
PArtial Tumor Irradiation Targeting HYpoxic Segment (PATHY)



Direct radiation induced tumor cells killing
+
Radiation-induced immune-mediated tumor cell killing

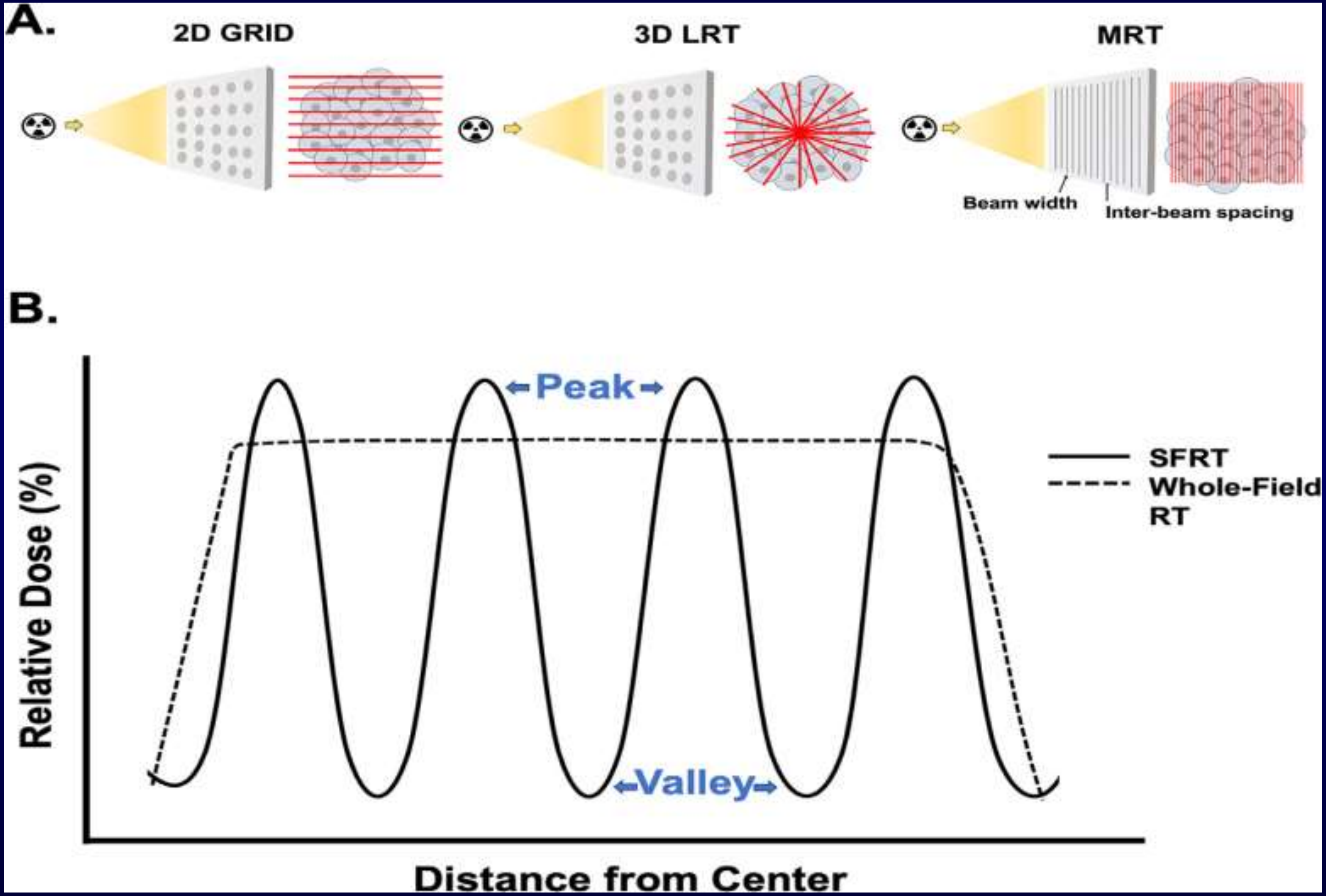
Tubin S. A Partial Tumor Irradiation Approach for Complex Bulky Disease. Semin Radiat Oncol. 2024 Jul;34(3):323-336.

PArtial Tumor Irradiation Targeting HYpoxic Segment (PATHY)



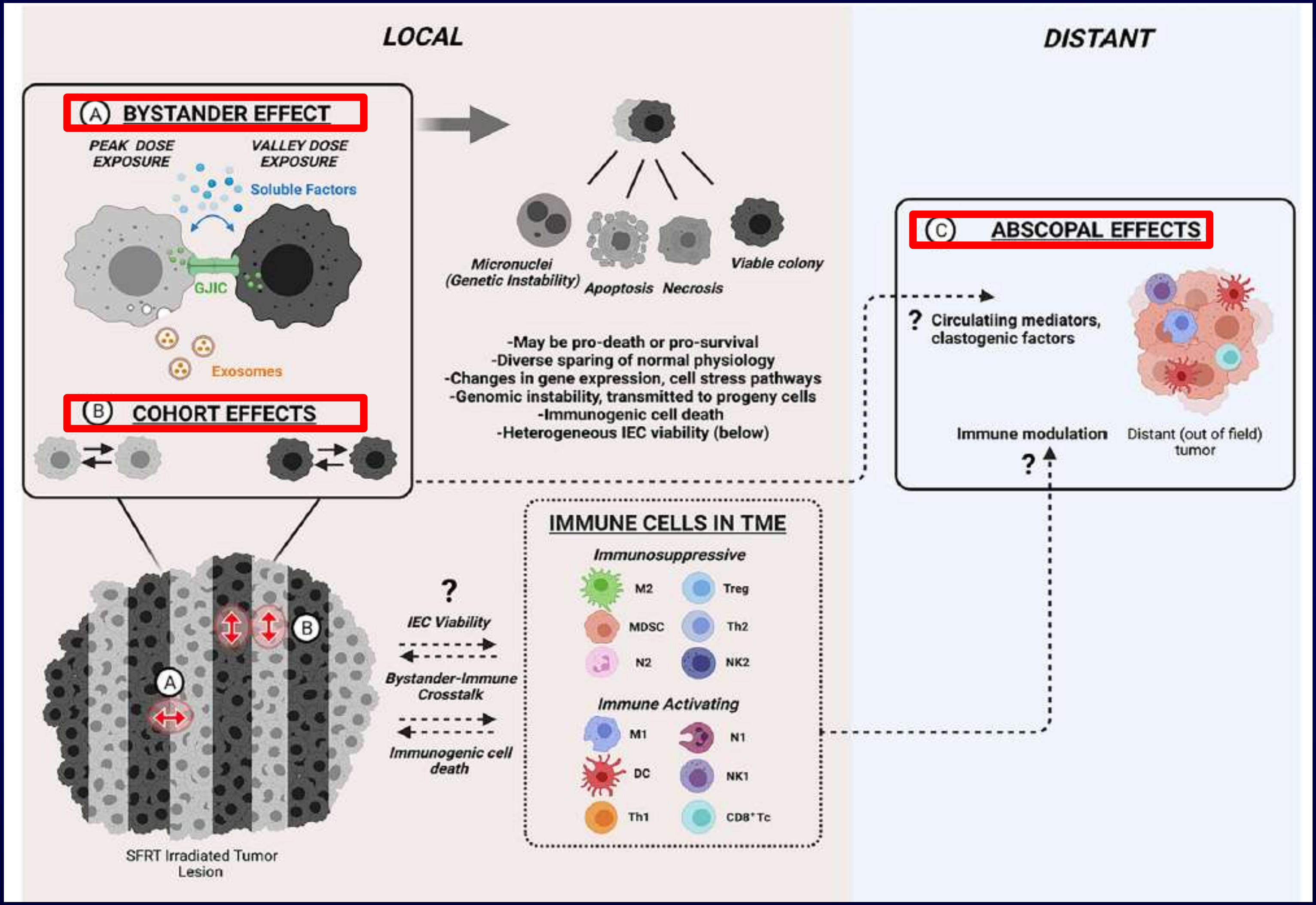
Tubin S. A Partial Tumor Irradiation Approach for Complex Bulky Disease. Semin Radiat Oncol. 2024 Jul;34(3):323-336.

SFRT or GRID therapy



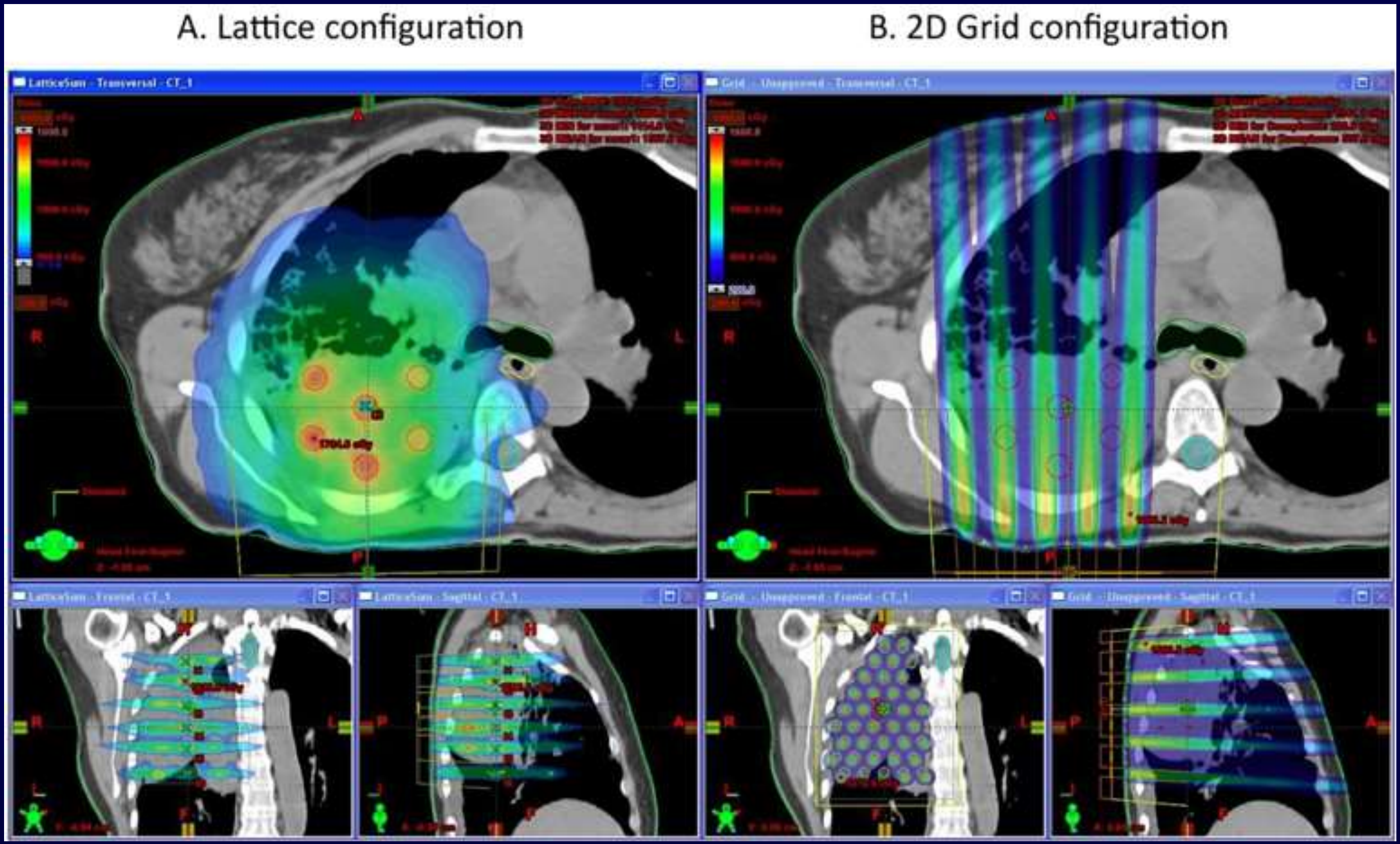
S.V. Jenkins et al. Bystander Effects in Spatially Fractionated Radiation Therapy, Semin Radiat Oncol. 2024 34:284−291.

SFRT or GRID therapy



S.V. Jenkins et al. Bystander Effects in Spatially Fractionated Radiation Therapy, Semin Radiat Oncol. 2024 34:284−291.

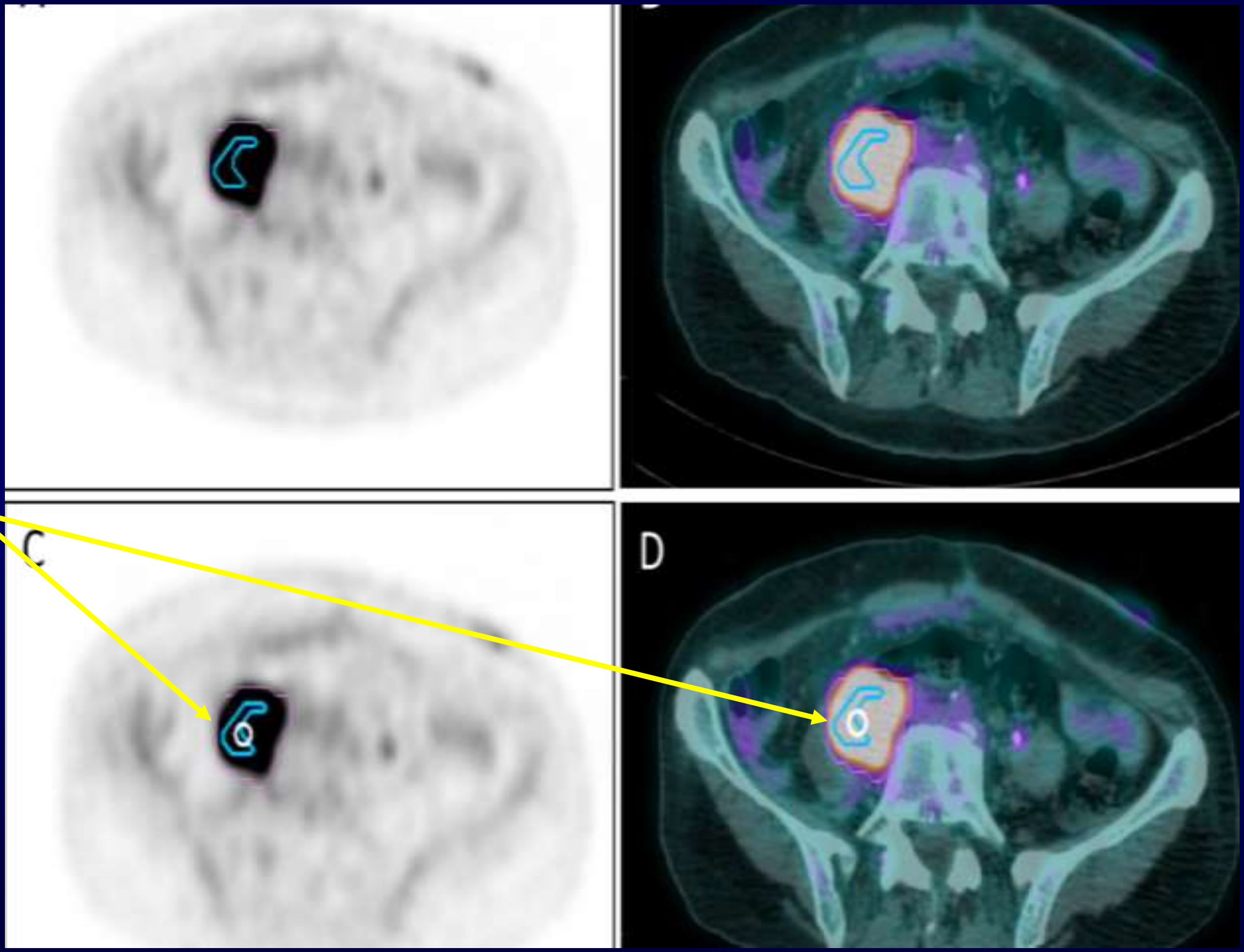
SFRT or GRID therapy



Yan W et al. Spatially fractionated radiation therapy: History, present and the future.
Clin Transl Radiat Oncol. 2019 Oct 22;20:30-38.

Metabolism Guided Lattice RT

1 cm-diameter sphere called "Vertex" between Super Avid PET Area (SAPA) and and the remaining part of the Avid PET Area (APA)



Ferini G et al. Impressive Results after "Metabolism-Guided" Lattice Irradiation in Patients Submitted to Palliative Radiation Therapy: Preliminary Results of LATTICE_01 Multicenter Study. Cancers (Basel). 2022 Aug 12;14(16):3909.

Radiomics

- Extraction of quantitative parameters from routinely acquired medical imaging data, thereby allowing additional data analysis at low cost - underlying image (tumor) heterogeneity

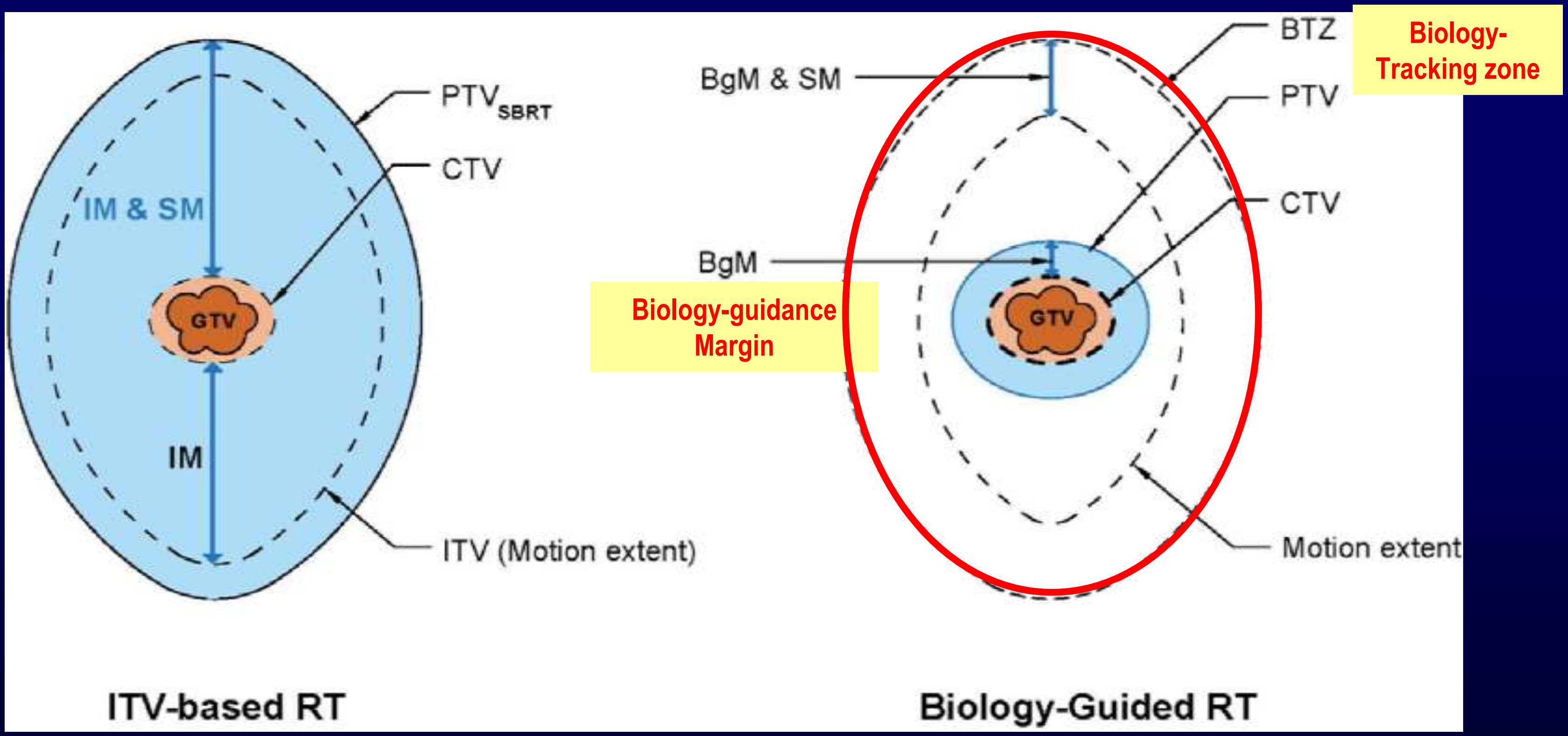
- Feature-based radiomics - radiomics features to be extracted are predefined and calculated from a manually or semi-automatically segmented image
- Deep learning-based radiomics - radiomics features are not predefined, but identified and generated from the underlying data by computational models

Lohmann P et al. Radiomics in radiation oncology-basics, methods, and limitations.
Strahlenther Onkol. 2020 Oct;196(10):848-855.

BgRT – Biology Guided RT

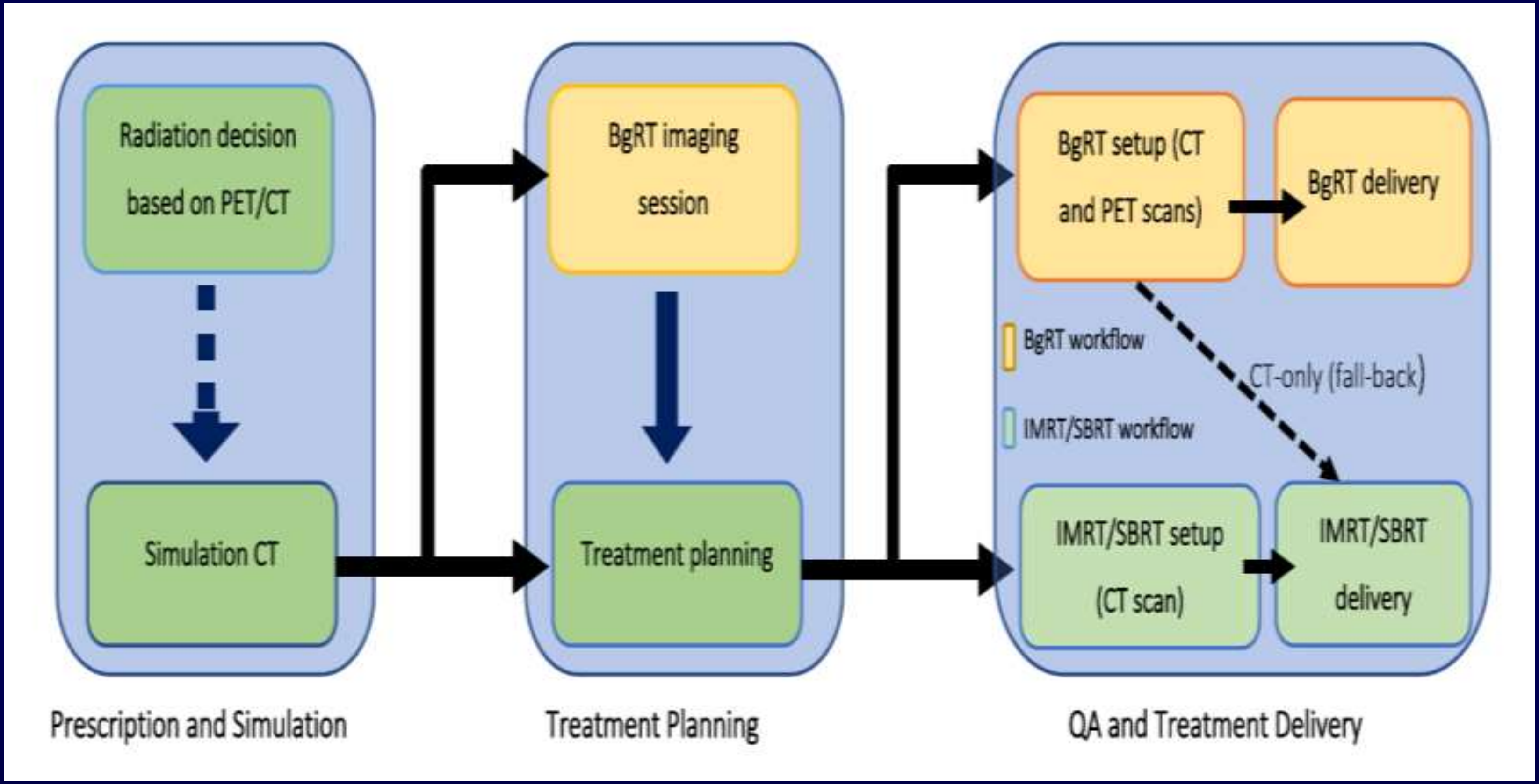
- RefleXion X1, a system for biology-guided radiotherapy (BgRT). This system is a multi-modal tomography (PET, fan-beam kVCT, and MVD)

Biological fiducial
Enabling a tumor to communicate its present position directly to a linear accelerator

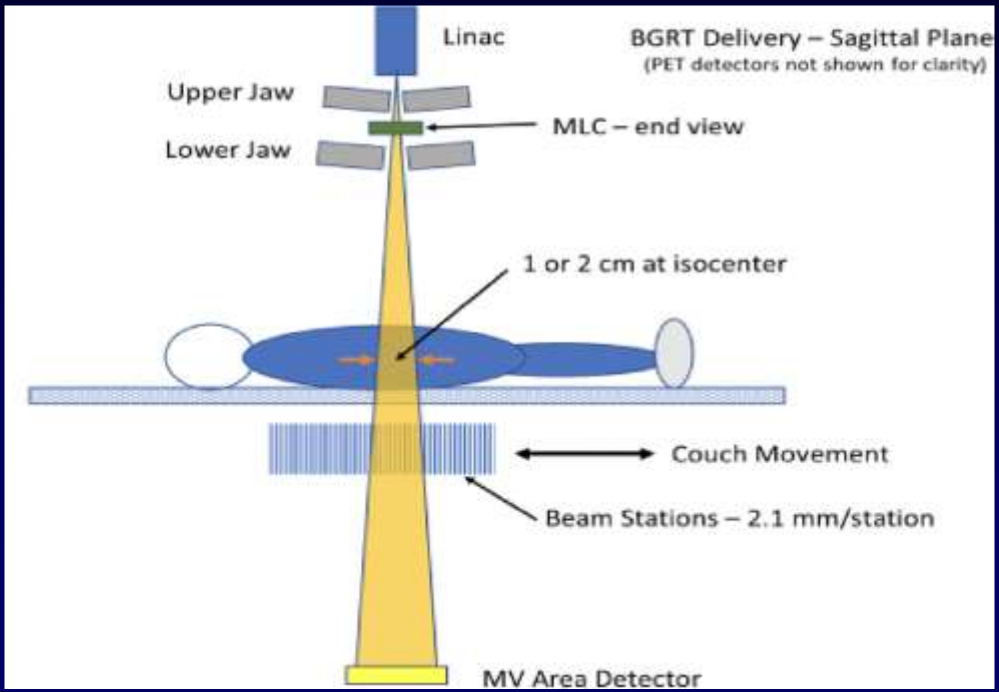


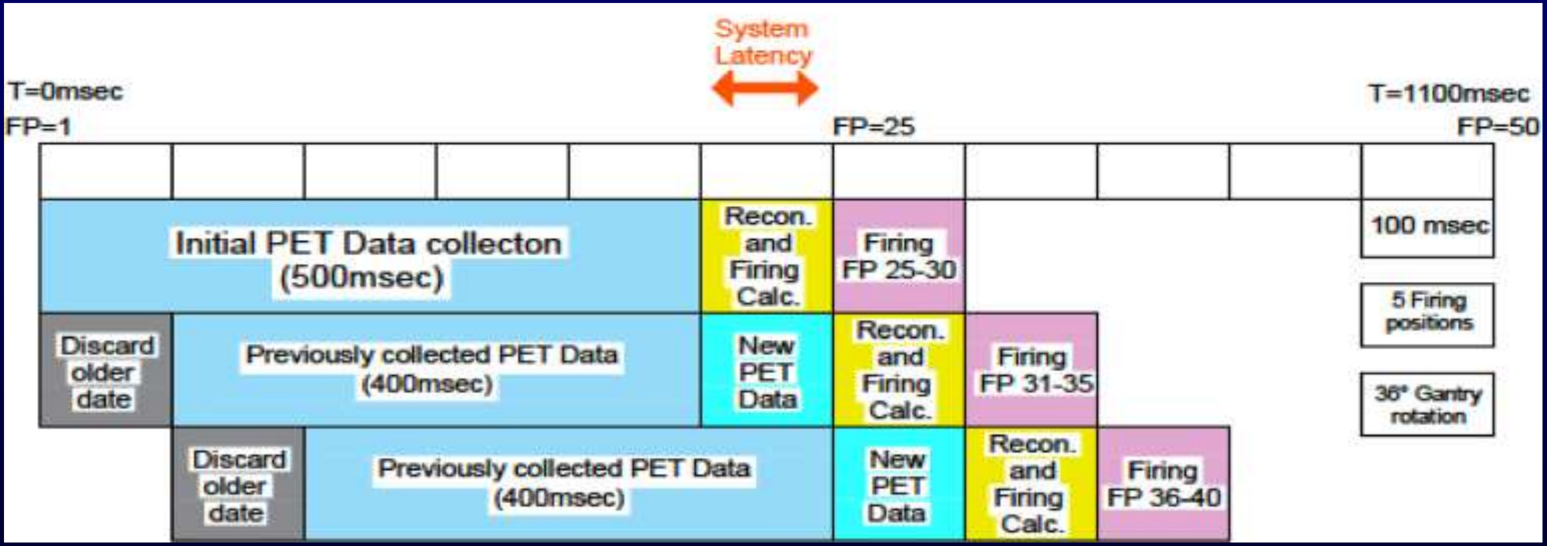
Oderinde OM et al. The technical design and concept of a PET/CT linac for biology-guided radiotherapy. Clin Transl Radiat Oncol. 2021 Apr 17;29:106-112.

BgRT – Biology Guided RT



Oderinde OM et al. The technical design and concept of a PET/CT linac for biology-guided radiotherapy.
Clin Transl Radiat Oncol. 2021 Apr 17;29:106-112.


Linac
BGRT Delivery – Sagittal Plane
(PET detectors not shown for clarity)
Upper Jaw
MLC – end view
Lower Jaw
1 or 2 cm at isocenter
Couch Movement
Beam Stations – 2.1 mm/station
MV Area Detector


System Latency
T=0msec
FP=1
FP=25
T=1100msec
FP=50
Initial PET Data collecton (500msec)
Recon. and Firing Calc.
Firing FP 25-30
100 msec
5 Firing positions
36° Gantry rotation
Discard older date
Previously collected PET Data (400msec)
New PET Data
Recon. and Firing Calc.
Firing FP 31-35
Discard older date
Previously collected PET Data (400msec)
New PET Data
Recon. and Firing Calc.
Firing FP 36-40

Lung Perfusion Guided RT

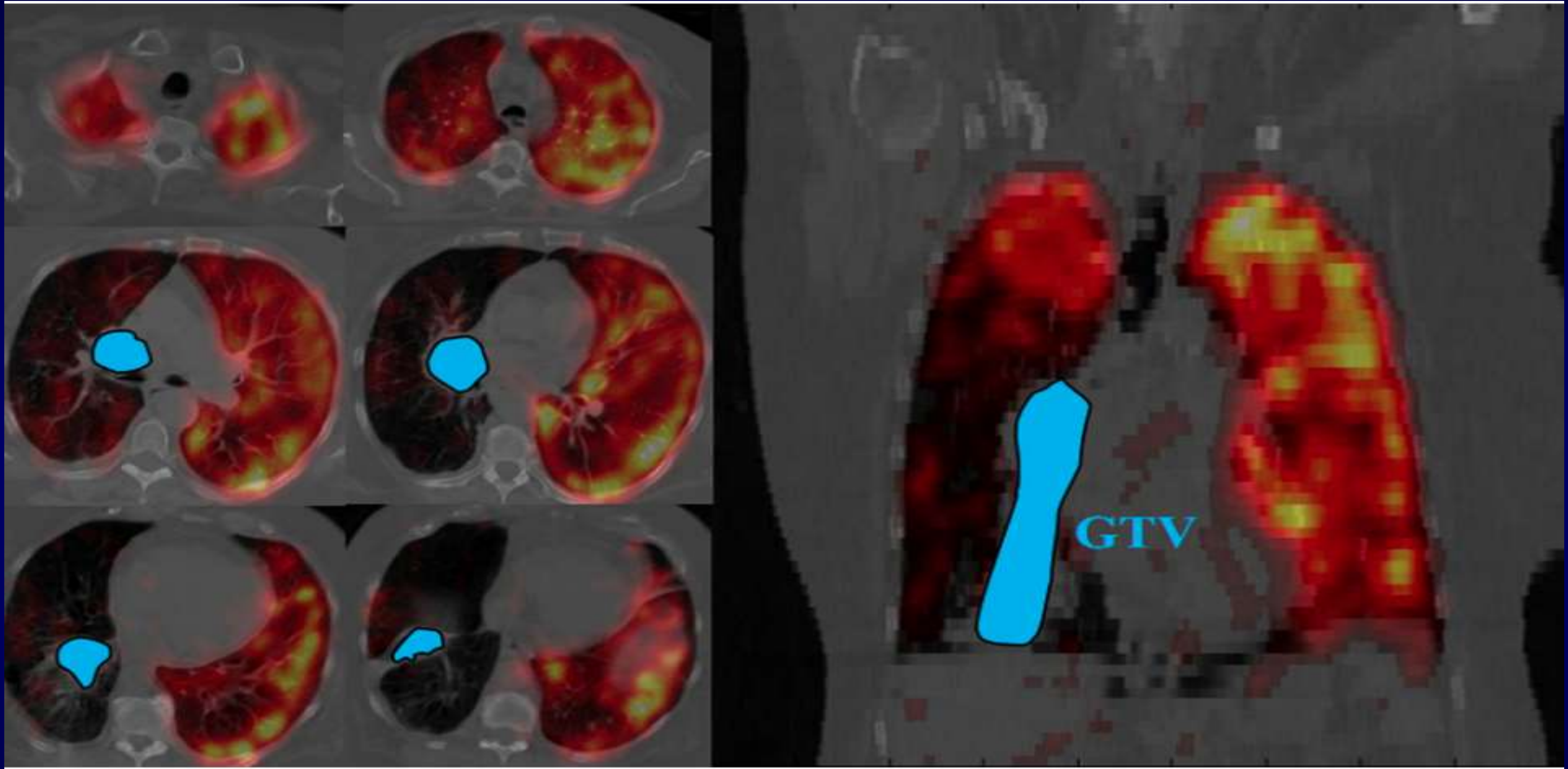


Figure 1.9: Transaxial(left) and coronal(right) views of lung perfusion overlaid with CT images. Color index from red to yellow corrsponding to low and high lung perfusion

Liu Yin. Perfusion SPECT guided dose escalation in radiation therapy for lung cancer patients, 2012, https://api.semanticscholar.org/CorpusID:74525237

Lung Perfusion Guided RT

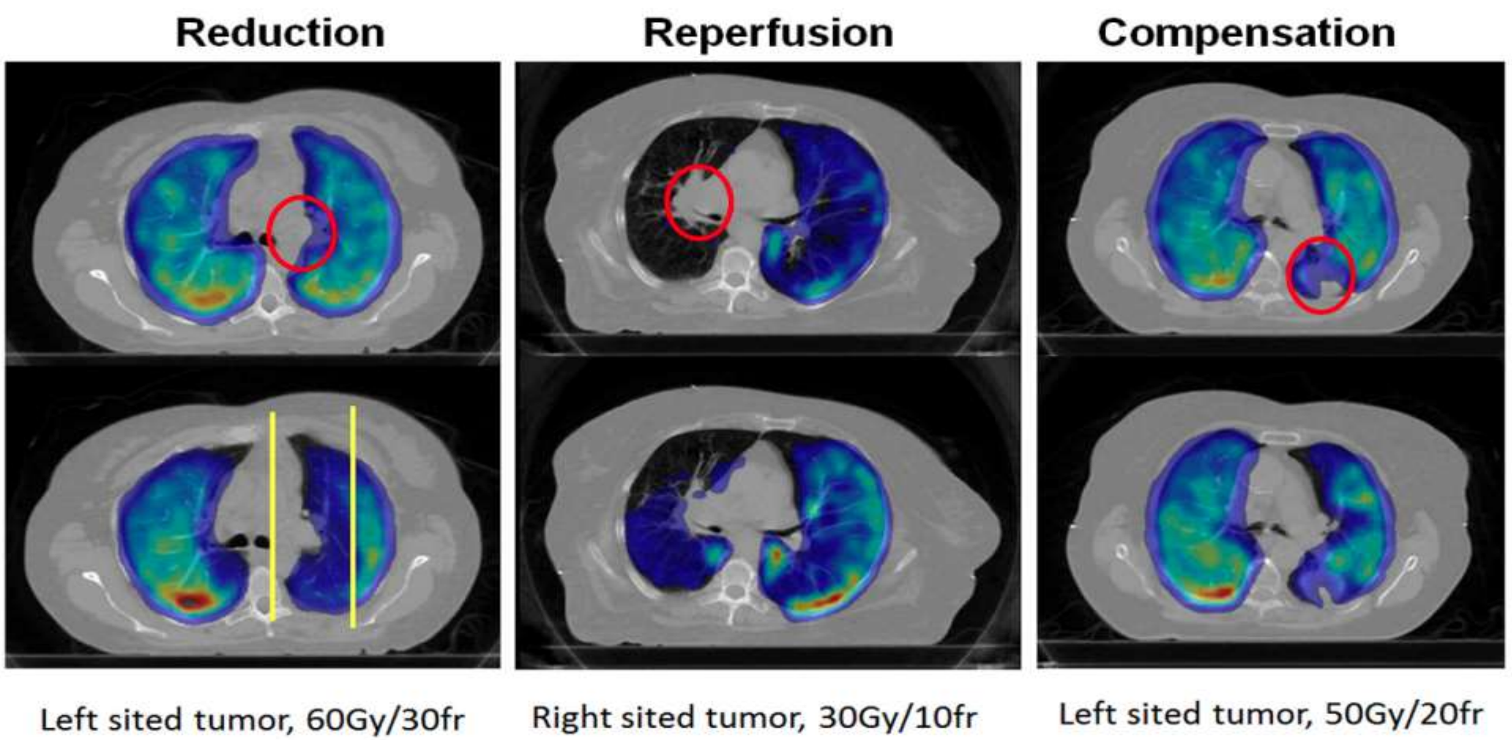
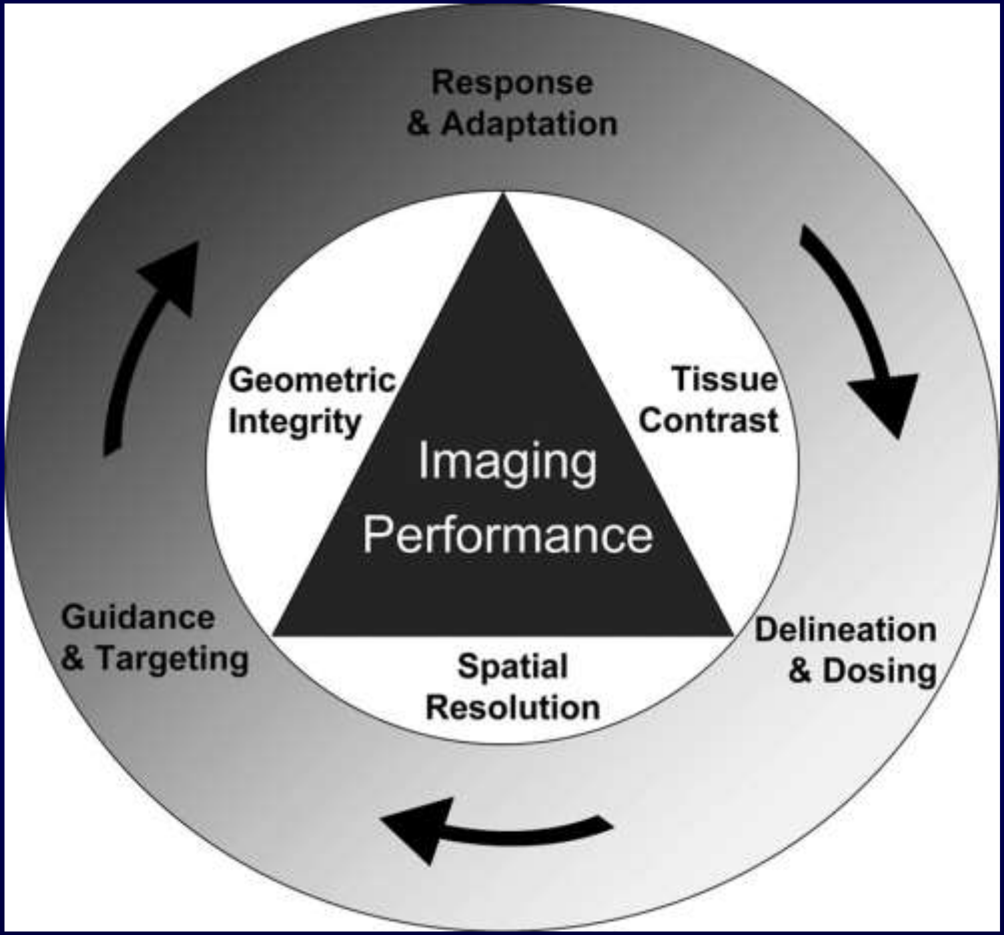


Figure 5.1: Pre-RT (upper row) and post-RT (bottom) SPECT scans demonstrating reduction, reperfusion and compensation of perfusion respectively. Red contours indicate the position of tumor. Yellow contours shows a rough estimate of high dose (>20Gy) region.

Liu Yin. Perfusion SPECT guided dose escalation in radiation therapy for lung cancer patients, 2012, https://api.semanticscholar.org/CorpusID:74525237

Issues



Dawson LA et al. Imaging in radiation oncology: a perspective. Oncologist. 2010;15(4):338-49.

Imaging immune system

Table 1 SPECT and PET Radiopharmaceuticals for Imaging Immune Cells

Target	Probe	Immune Cell Population	Imaging Modality	Isotope	Applications	References
CD2	Anti-CD2	T-cells	SPECT	^{111}In	Preclinical	10, 14, 15
CD7	Anti-CD7	NK	PET	^{89}Zr ^{11}C ^{18}F	Preclinical	8, 12, 13
CD56	Anti-CD56	NK	SPECT	^{99m}Tc	Preclinical	9, 16
CD3	Anti-CD3 (Muromonab, Visilizumab)	T-cells	SPECT	^{99m}Tc	Preclinical Clinical	17-21
			PET	^{89}Zr	Preclinical	22-27
CD4	Anti-CD4	T-cells	SPECT	^{111}In	Preclinical	33
			PET	^{89}Zr	Preclinical	34
CD8	Anti-CD8	T-cells	PET	^{89}Zr ^{64}Cu	Preclinical	36, 37
CTLA-4	Anti- CTLA-4	T-cells	SPECT	^{111}In	Preclinical	39-41
PD-1/PD-L1	PD-1/PD-L1		PET	^{64}Cu ^{68}Ga ^{89}Zr	Preclinical	43, 45-49
CD25	IL2	T-cells	SPECT	^{123}I ^{99m}Tc	Preclinical Clinical	50-50, 62-69
			PET	^{18}F ^{68}Ga	Preclinical	70-73
CD20 CD19	Anti-CD20 (Rituximab, Ibritumomab)	B-cells	SPECT	^{111}In ^{99m}Tc	Clinical	76-80
	Anti-CD19		PET	^{124}I ^{89}Zr ^{64}Cu	Preclinical Clinical	81, 82-88
TNF-α	Anti-TNF-α (Infliximab)	B-cells	SPECT	^{99m}Tc	Clinical	89, 90
SDF1-α	CXCR4	T-cells B-cells Tumoral cells	SPECT PET	^{111}In ^{124}I ^{18}F ^{68}Ga	Preclinical Preclinical Clinical	99 100-104

Lauri C et al. Present status and future trends in molecular imaging of lymphocytes. Semin Nucl Med. 2023 Jan;53(1):125-134.

Imaging immune system

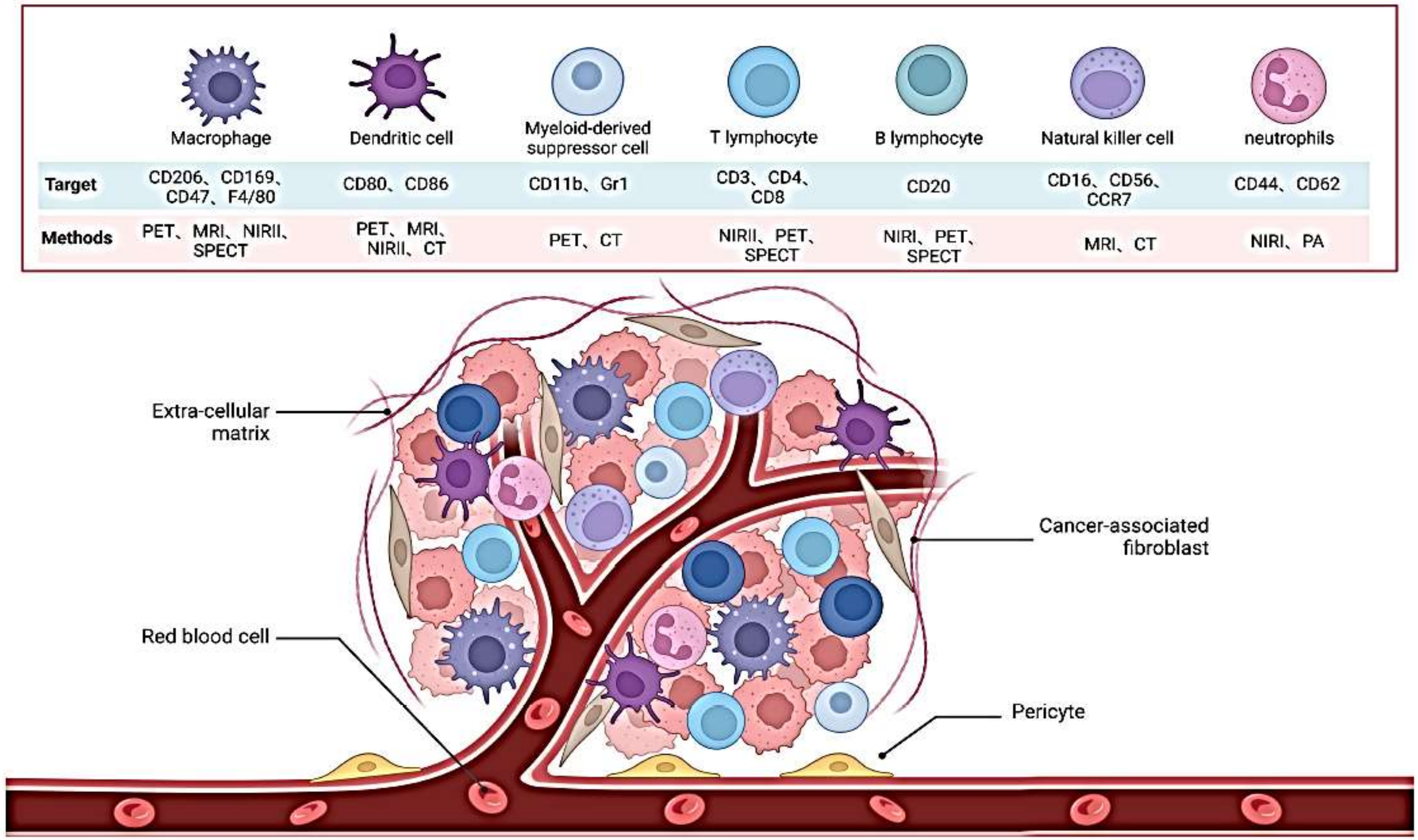


FIGURE 2
Schematic of the molecular images used to target immune cells, which include B cells, MDSC, NK cells, T cells, neutrophils, DCs and macrophages in TME.

Wang X, et al. Current status and future prospects of molecular imaging in targeting the tumor immune microenvironment. Front Immunol. 2025 Jan 22;16:1518555.

Imaging immune system

TABLE 1 Imaging of immune cells.

Imaging modalities	Cell type	Tracer	Purpose	Ref
PET	T cell	^{18}F-AraG	Study T cell distribution and activation in healthy individuals and cancer patients undergoing immunotherapy	(60)
PET	T cell	^{124}I-Basiliximab	Promise results in distinguishing activated from non-activated human peripheral blood mononuclear cells	(10, 54)
PET	B cell	[^{89}Zr]-DFO-H1.2F3	Detect CD69 expression on B cells	(68)
NIR	B cell	Miltuximab®-IRDye800	Promise in targeting and visualizing B cells in tumors	(69)
MRI	Macrophages	SPIO	Visualization of TAMs in breast cancer	(74)
PET	Macrophages	^{68}Ga-labeled M2pep peptide	Focus on the rapid and targeted accumulation of macrophages in tumors	(76)
PET	NK cell	^{18}F-FDG	Track CAR NK-92 cells localization to HER2/neu-positive tumors	(88)
MRI	NK cell	^{19}F	Monitor NK cell migration in neuroblastoma and lymphoma xenografts	(93)
MRI	DC	SPIO	Track dendritic cells and response to DC vaccine in melanoma patients	(101)
PET	DC	^{124}I	Monitor bone marrow-derived dendritic cell migration and antitumor effects	(105)
MRI	Neutrophils	SPIO	Provide a safe and effective way to monitor neutrophil dynamics	(115)
PET	Neutrophils	^{18}F-CXCR2	Demonstrate specificity and diagnostic potential in neutrophil imaging	(116)
PET	MDSCs	^{18}F-DPA-714	Characterize the heterogeneity of myeloid cell infiltration at different disease stages	(121)
MRI	MDSCs	-	Utilize a manganese dioxide coating and MDSC cell membrane camouflage to target the tumor microenvironment	(122)

Wang X, et al. Current status and future prospects of molecular imaging in targeting the tumor immune microenvironment. Front Immunol. 2025 Jan 22;16:1518555.

Imaging immune system

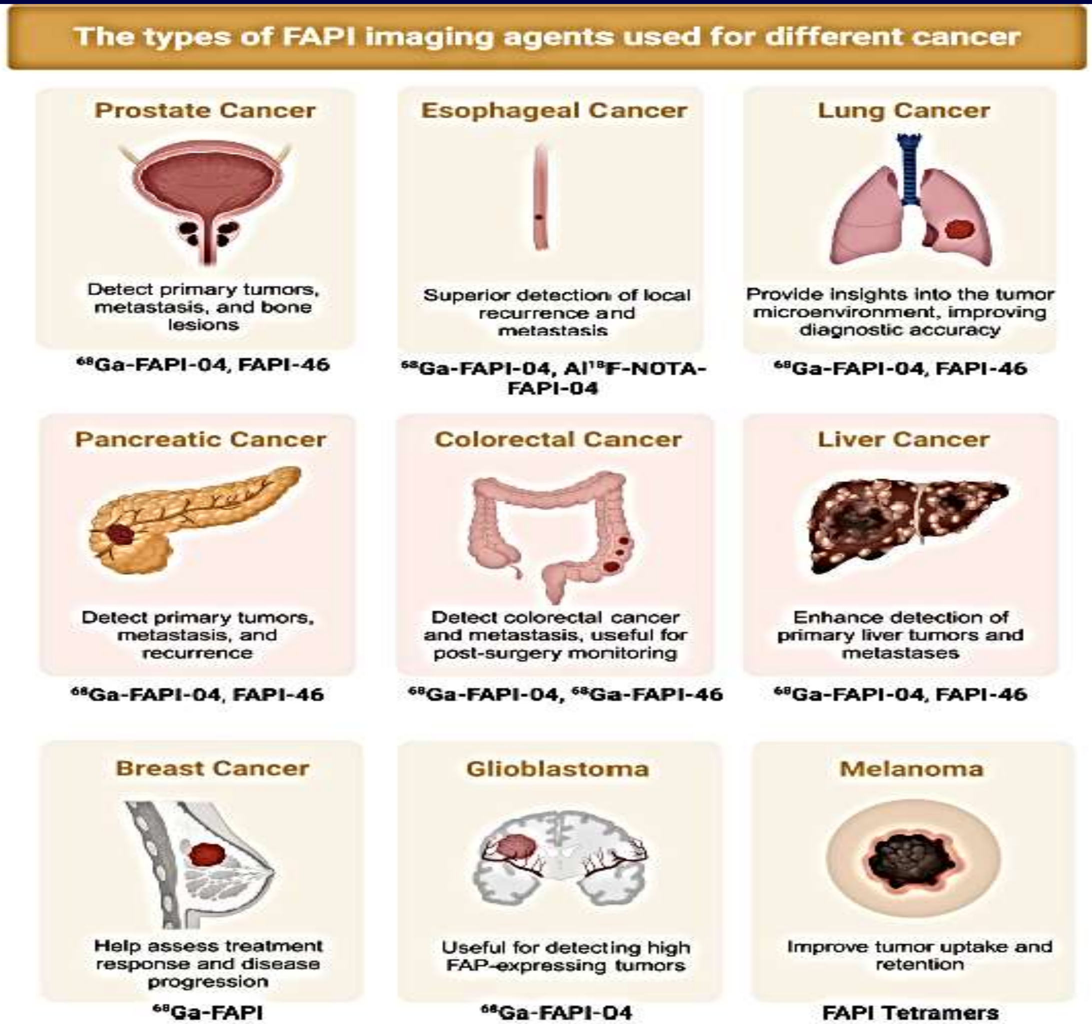


FIGURE 3
Published studies of fibroblast activating protein inhibitor positron emission tomography (FAPI) in the diagnosis of various types of cancer.

Wang X, et al. Current status and future prospects of molecular imaging in targeting the tumor immune microenvironment. Front Immunol. 2025 Jan 22;16:1518555.

PET GTV issue

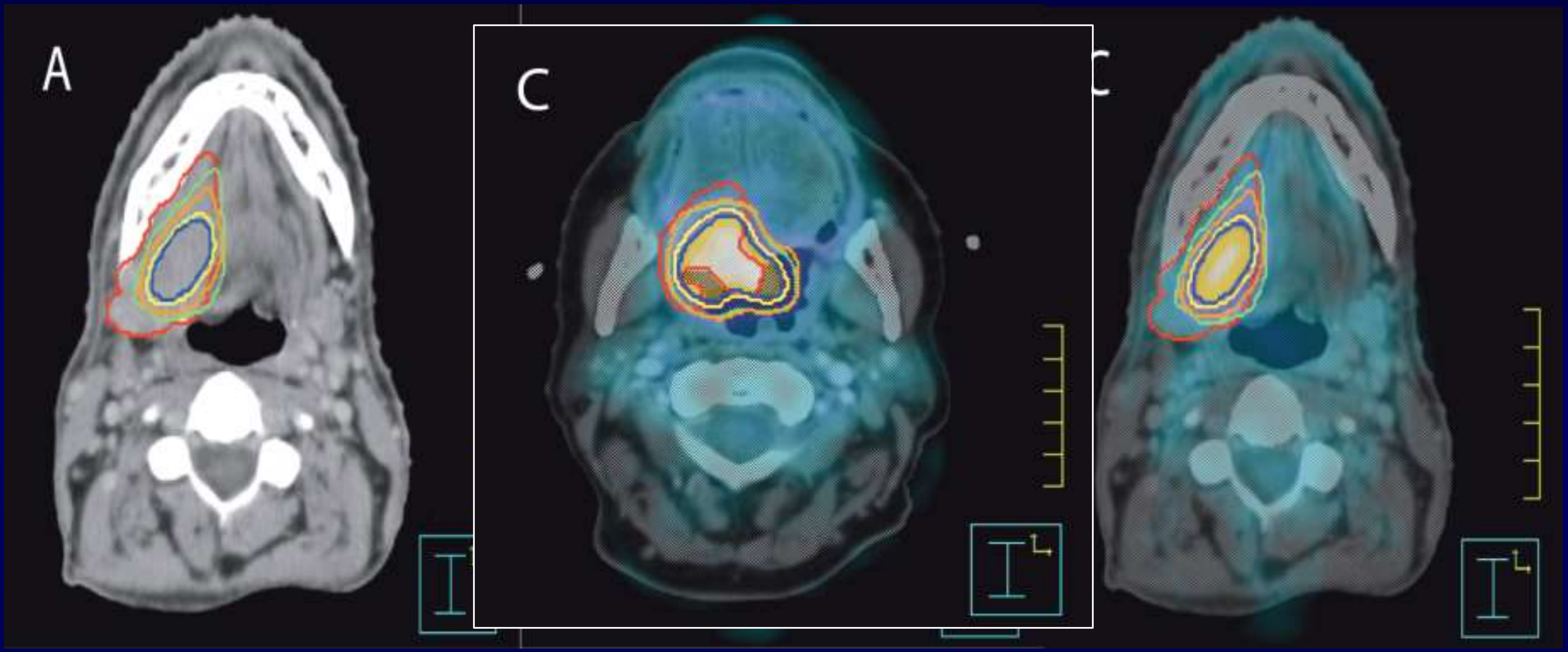


Figure 1 **Planning CT scan (A), corresponding FDG-PET scan (B) and fusion image (C) show differences in target volume definition. Volume GTV CT (red) = 47.5 cm^3, GTV VIS (green) = 43.8 cm^3, GTV 40% (yellow) = 20.1 cm^3, GTV 2.5 (orange) = 32.6 cm^3, GTV UCL (blue) = 15.7 cm^3. Note that GTV UCL is significantly smaller than GTV CT and GTV VIS.**

Schinagl DA et al. From anatomical to biological target volumes: the role of PET in radiation treatment planning. Cancer Imaging. 2006 Oct 31;6(Spec No A):S107-16.

Issues

- Validation of the imaging target
  - Imaging variable correlates with a local biological property
  - Clinical importance of the validation marker for the radiobiological characteristic in question e.g if Ki-67 labelling index actually selects for a benefit from accelerated radiotherapy

- Temporal stability
  - Hypoxia/proliferation area – Spatial short-term and long-term stability of the three-dimensional map of density of specific cellular phenotypes or micro environmental variables e.g Reoxygenation issue

Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. Lancet Oncol. 2005 Feb;6(2):112-7.

Issues

- Image Quality
  - Spatial resolution
  - Partial volume artefacts

- Prescription function
  - Mathematical link between a specific value of an imaging variable and the optimum clinical dose to be prescribed to the corresponding voxel
  - Unlikely to be defined from radiobiological measurements made in vitro but will have to be derived from outcome data in human beings or in animals

Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. Lancet Oncol. 2005 Feb;6(2):112-7.

Conclusion

- Addition to the oncology information
  - Diagnosis
  - Therapy planning
  - Reponses
- Radiation
  - Guidance for RT planning
  - Defining Dose
- Issue to address
  - Validation
  - Quality
  - Stability
  - Prescription

Lohmann P et al. Radiomics in radiation oncology-basics, methods, and limitations.
Strahlenther Onkol. 2020 Oct;196(10):848-855.

Thank You