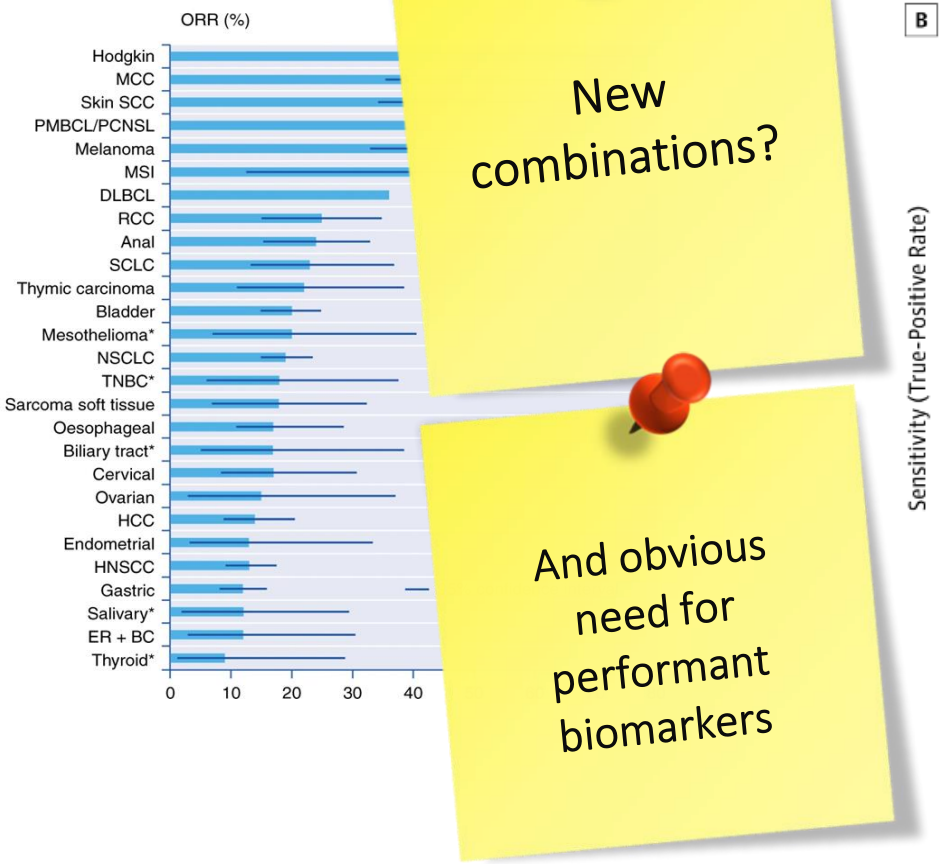
Radiomics for Immunotherapy and radio-immunotherapy combinations: towards ultraprecision medecine?

Roger Sun, MD PhD

Gustave Roussy, Radiotherapy, INSERM U1030

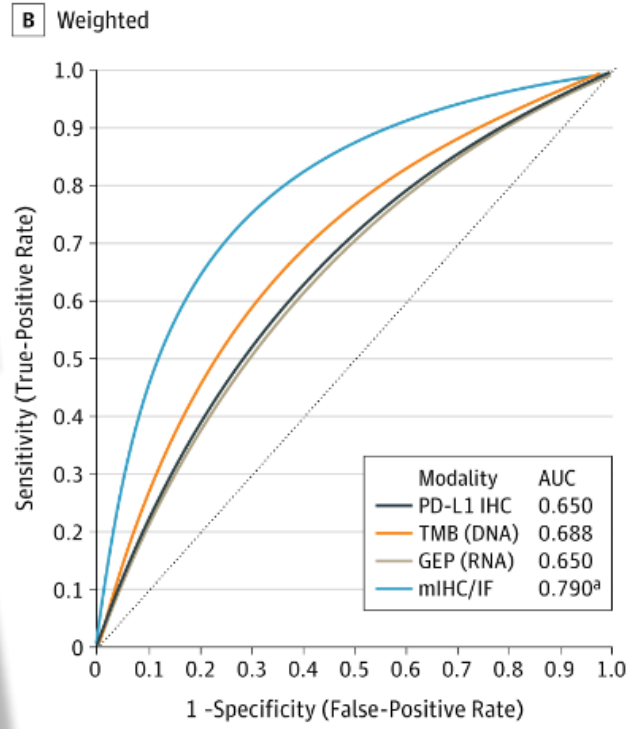
Immunotherapy for oncology: a revolution

Hirsch L *et al.* BJC 2019



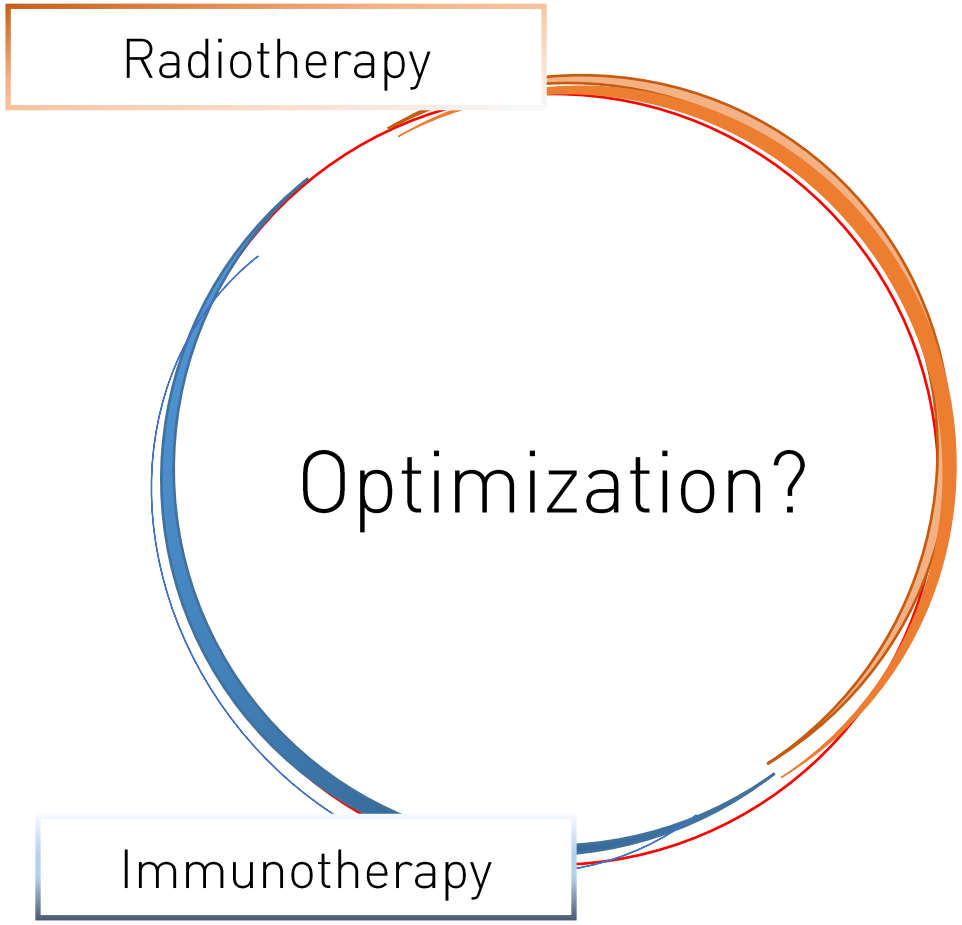
New combinations?

And obvious need for performant biomarkers

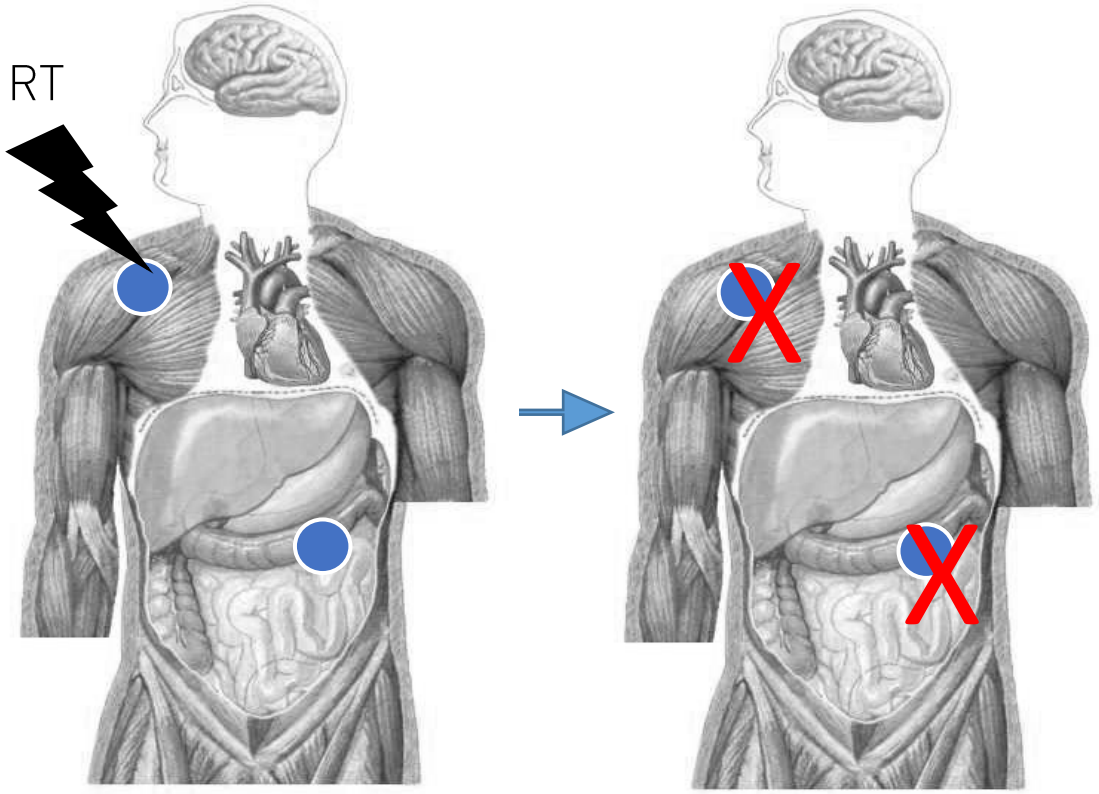


Lu S et al. *JAMA Oncol.* 2019

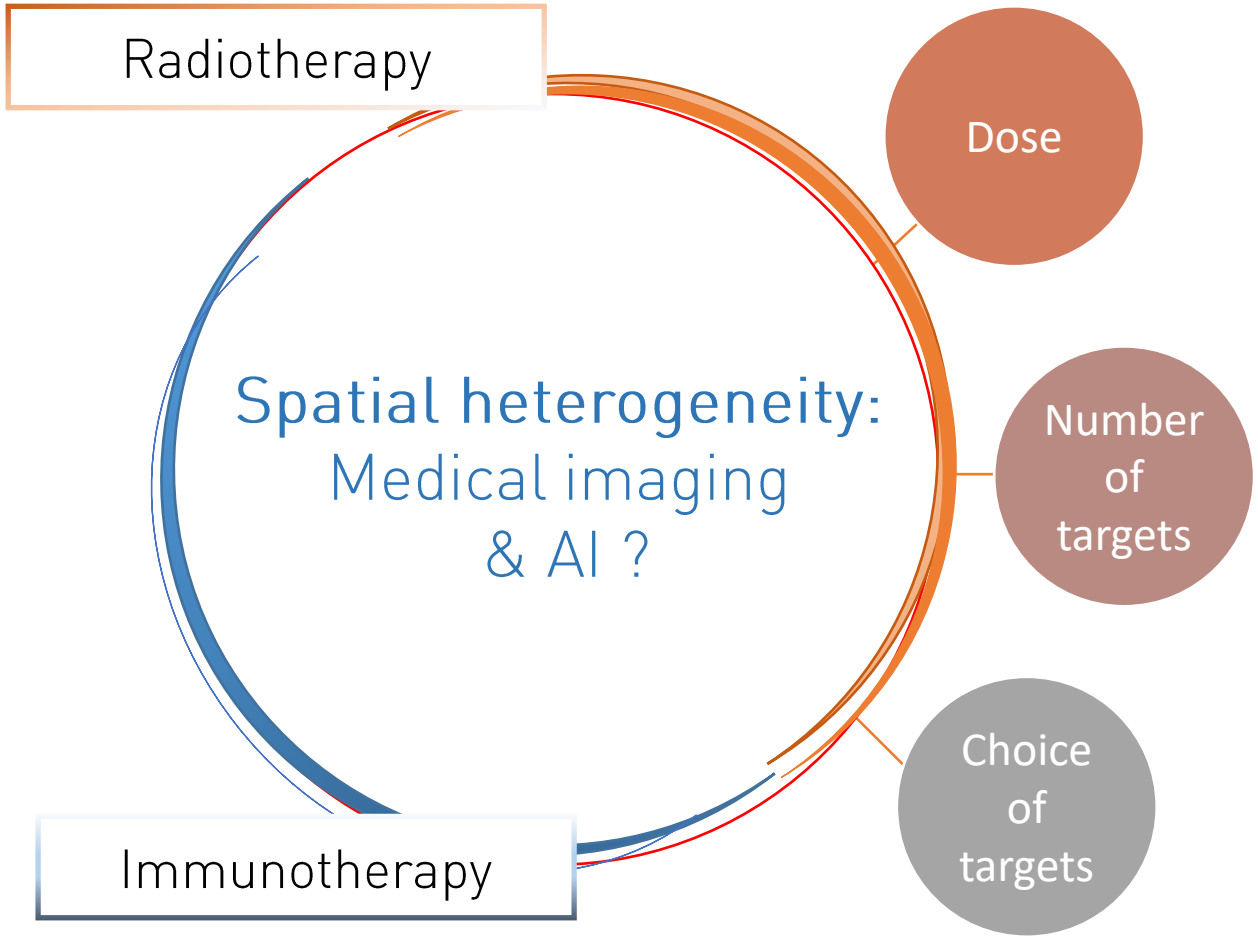
Radioimmunotherapy

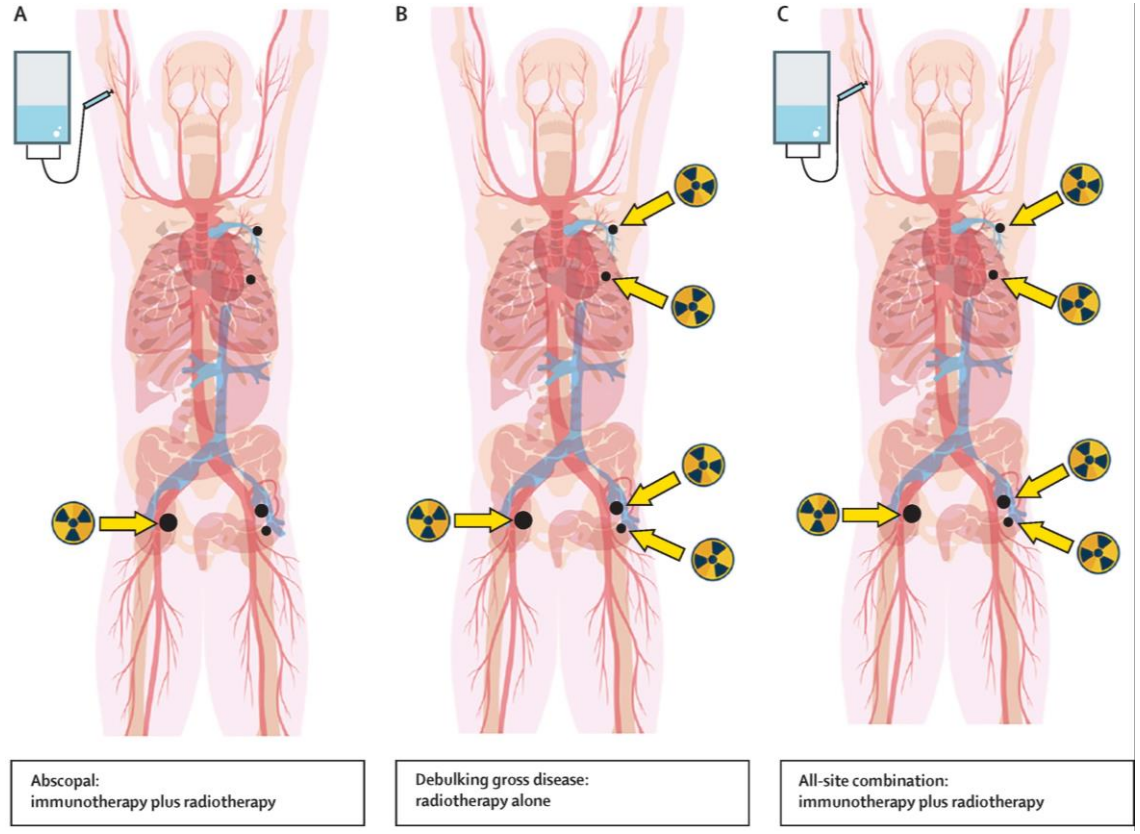


« Abscopal » effect



Radioimmunotherapy

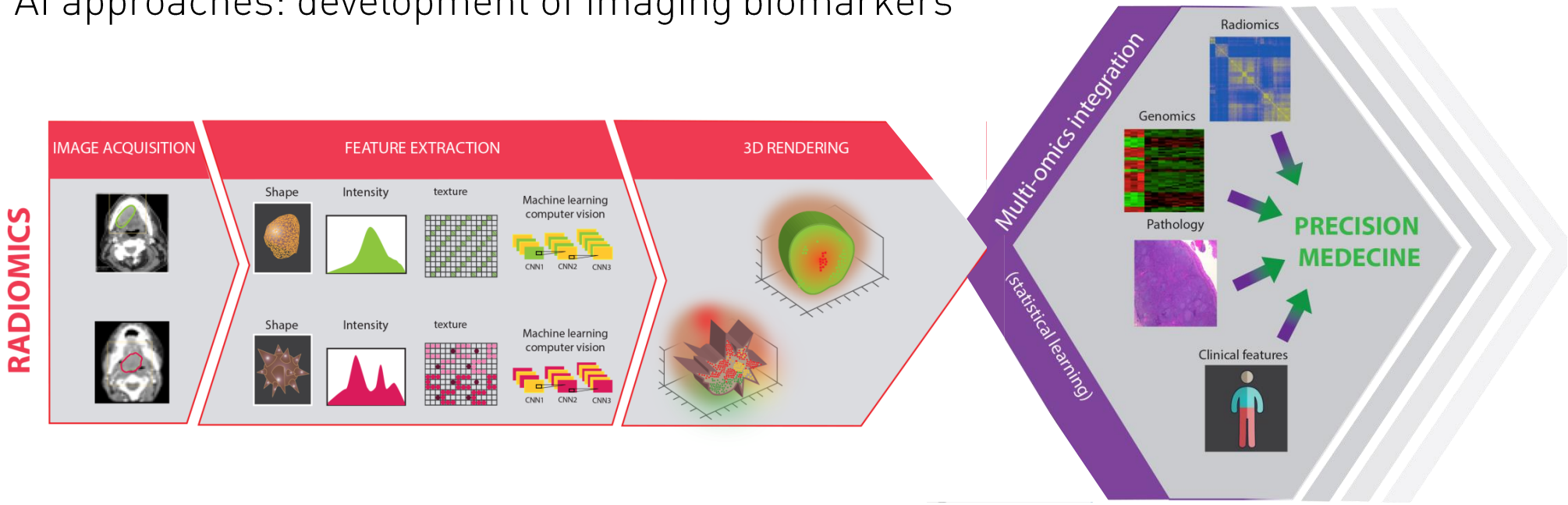




Deutsch *et al.* Lancet Oncol 2019

Radiomics

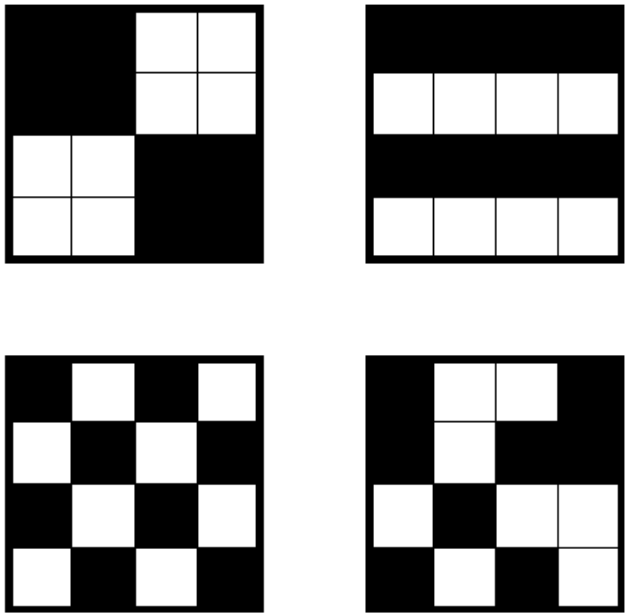
- Translates medical imaging into quantitative data
- Reflects the tumor phenotype (cellular and molecular properties)
- AI approaches: development of imaging biomarkers



Limkin E, Sun R *et al.* Ann Oncol 2017

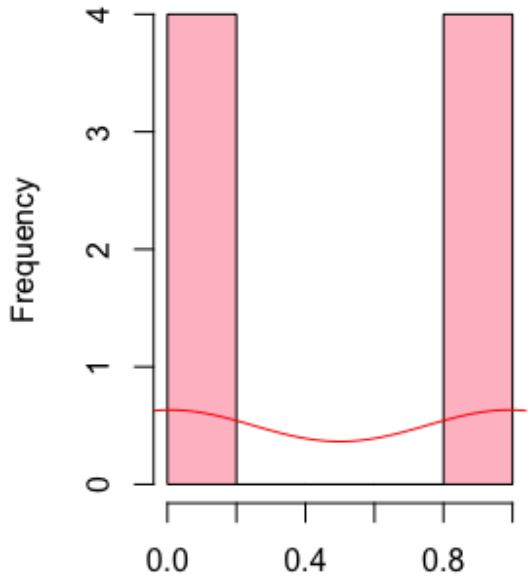
Radiomics pipeline: feature extraction

Histogram or 1st-order features



Histogram features
Skewness
Kurtosis
Entropy
Energy

But no spatial information



4 different patterns:
- 8 black voxels
- 8 white voxels

→ Same histogram

S. Reuzé et al, IJROBP 2018

Radiomics pipeline: feature extraction

Texture or 2nd order Features

1	1	1	3
0	2	1	3
3	0	3	3
1	0	1	0

GLCM : Gray Level Co-occurrence Matrix

Neighbor Pixel Value

Reference Pixel Value	0	1	2	3
0	0	1	1	1
1	2	2	0	2
2	0	1	0	0
3	1	0	0	1

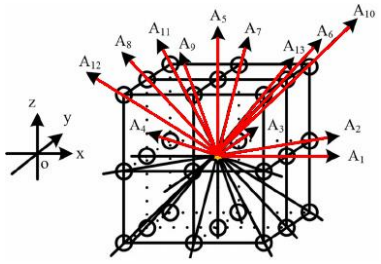
GLRLM : Gray Level Run-Length Matrix

Length = 3 voxels

Length

Gray level	1	2	3	4
0	4	0	0	0
1	3	0	1	0
2	1	0	0	0
3	3	1	0	0

13 directions are needed to connect a voxel with its 26 neighbors in 3D



Reuzé S *et al.* IJROBP 2018

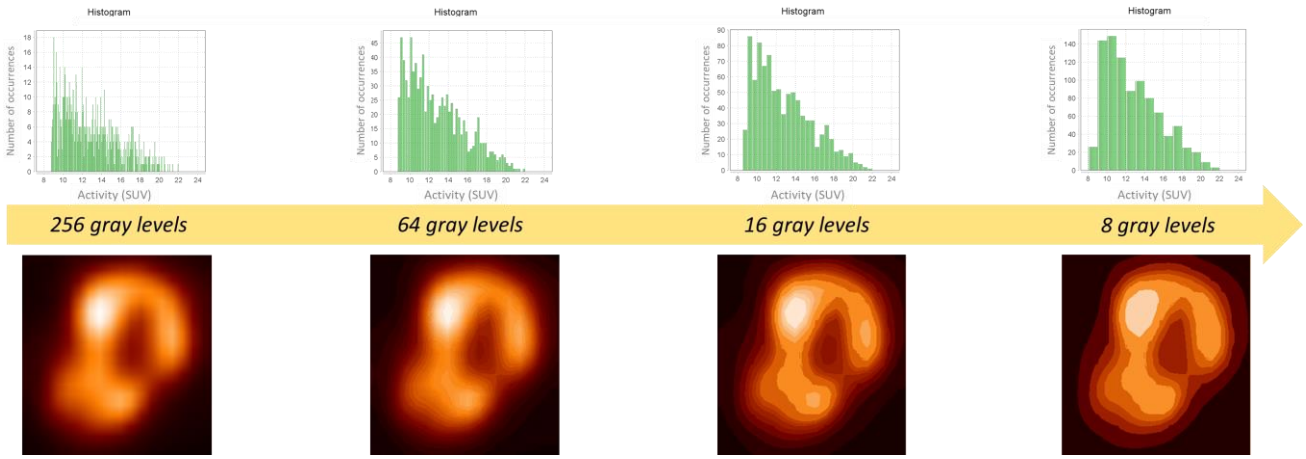
Radiomics pipeline: feature extraction

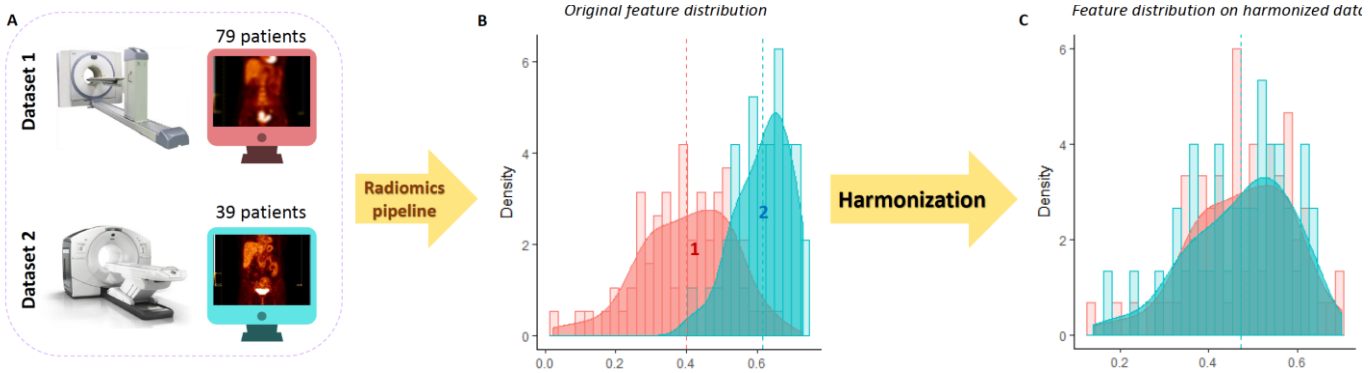
Imaging preprocessing

Voxel resampling

Intensity (SUV) Discretization

Radiomics features standardization



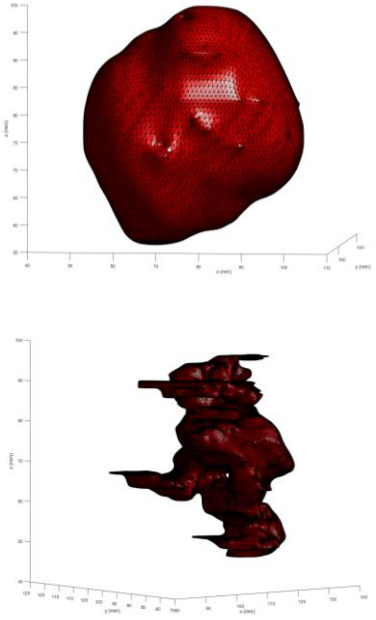


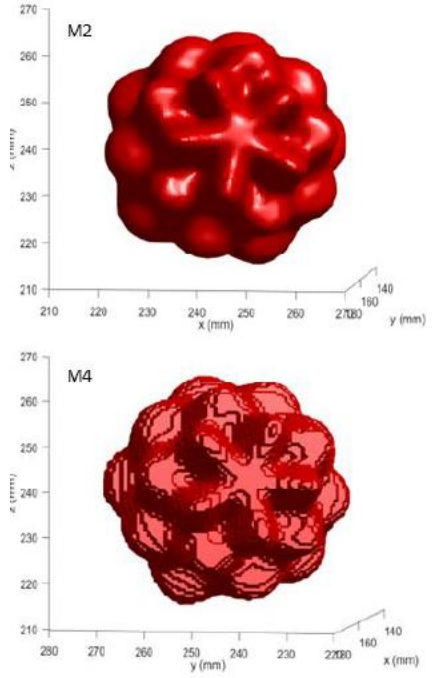
Reuzé S *et al.* Oncotarget 2017
Reuzé S *et al.* IJROBP 2018

Radiomics pipeline: feature extraction

Shape features

FEATURE	DESCRIPTION	FORMULA
Volume [23]	Determined by counting the number of pixels in the tumor region and multiplying this value by the voxel volume.	$Number\ of\ pixels * voxel\ volume$
Surface area [23]	Surface area, calculated by triangulation (i.e. dividing the surface into connected triangles)	$A = \sum_{i=1}^{N} \frac{1}{2} \lvert a_i b_i \times a_i c_i \rvert$
Surface to Volume ratio [23]	Ratio of surface area to volume	$surface\ to\ volume\ ratio = \frac{A}{V}$
Compactness 1 [23]	describes how much the shape of a tumor resembles that of a sphere/ can be encompassed by a sphere compactness of a sphere = 1	$compactness\ 1 = \frac{V}{\sqrt{\pi} A^{\frac{2}{3}}}$
Compactness 2 [23]		$compactness\ 2 = 36\pi \frac{V^2}{A^3}$
Compactness 3 [18]		$compactness\ 3 = 1 - \frac{4\pi A}{P^2}$
Spherical disproportion [23]	The ratio of the surface area of the tumor to the surface area of a sphere with the same volume as the tumor	$spherical\ disproportion = \frac{A}{4\pi R^2}$
Sphericity [23]	measure of the roundness or spherical nature of the tumor, where the sphericity of a sphere is the maximum value of 1	$sphericity = \frac{\pi^{\frac{1}{3}} (6V)^{\frac{2}{3}}}{A}$
Fractional concavity	the cumulative length of the concave segments in the tumor divided by the total length of the tumor contour	$Fcc\_3D = \frac{surface\ area\ conv}{surface\ area}$



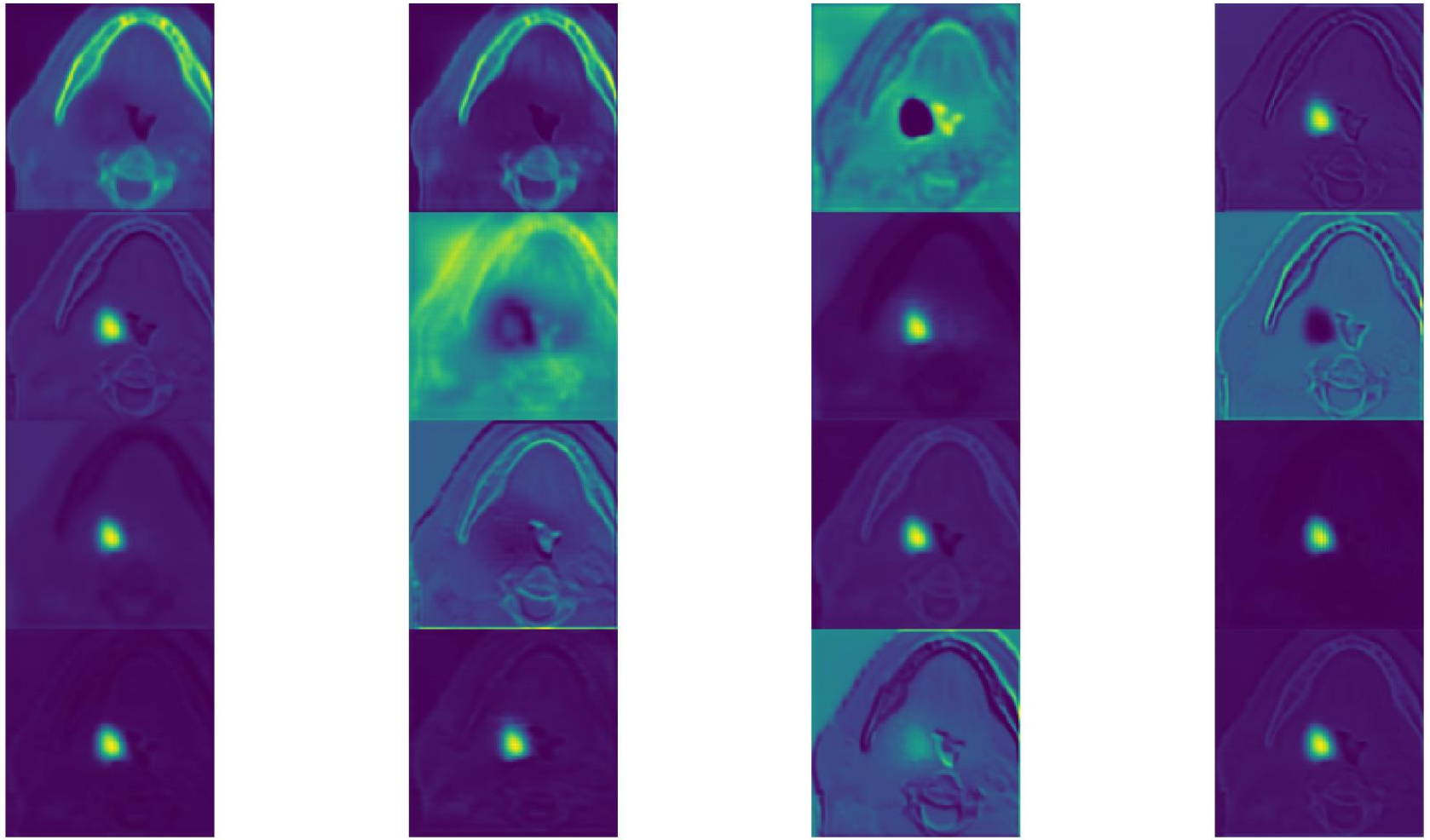


Volume dependency

Limkin et al, Scientific Reports 2019

Radiomics pipeline: feature extraction

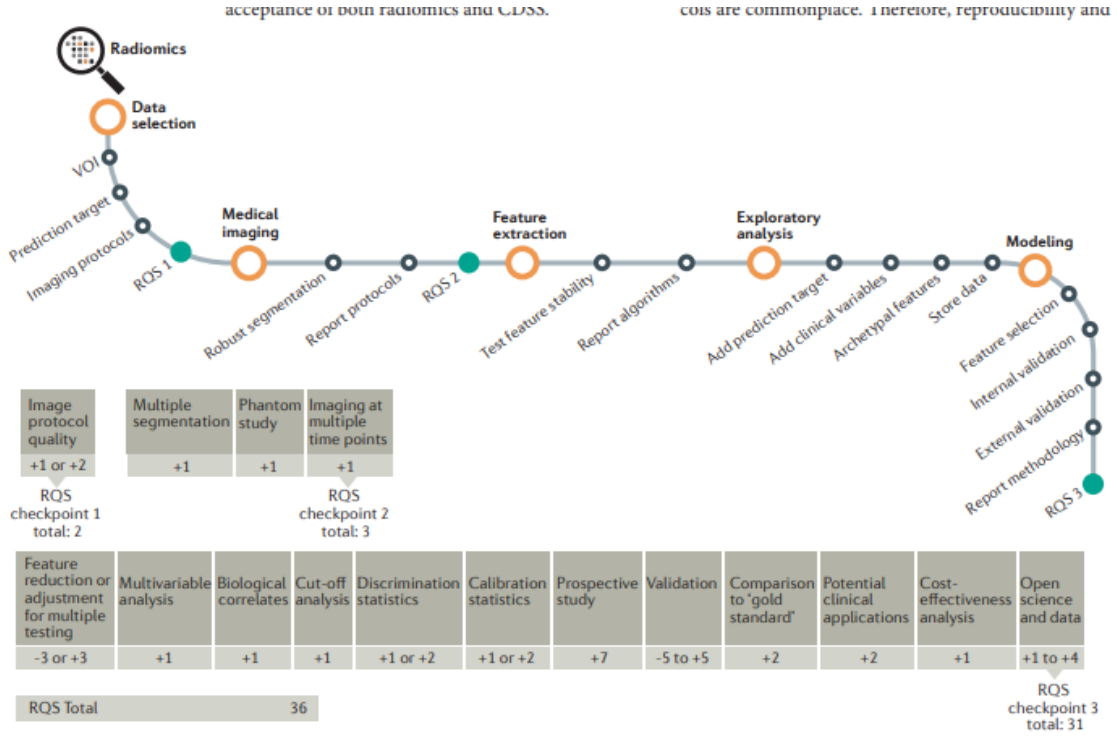
Deep Learning and deep features



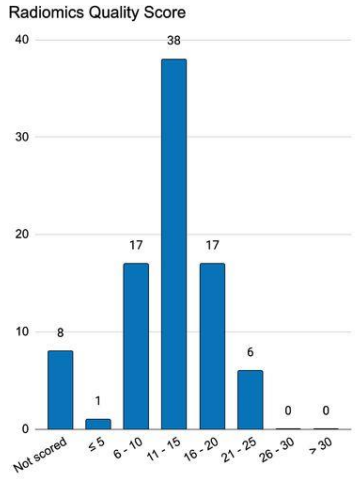
Courtesy T. Estienne

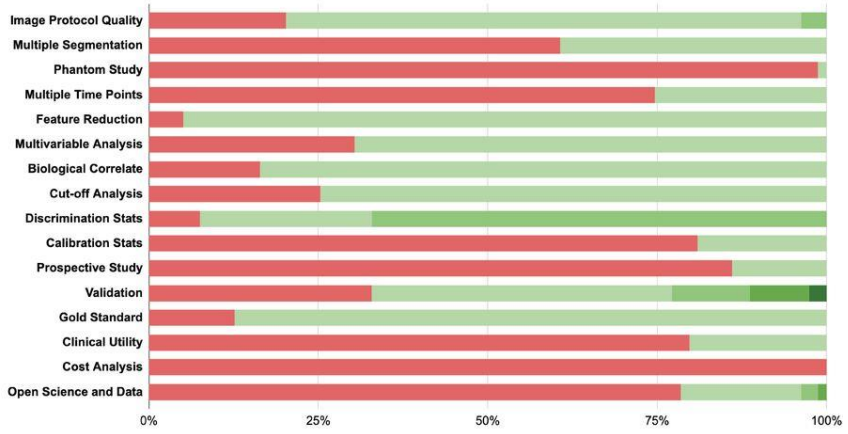
Validity of radiomics studies

Radiomics Quality Score



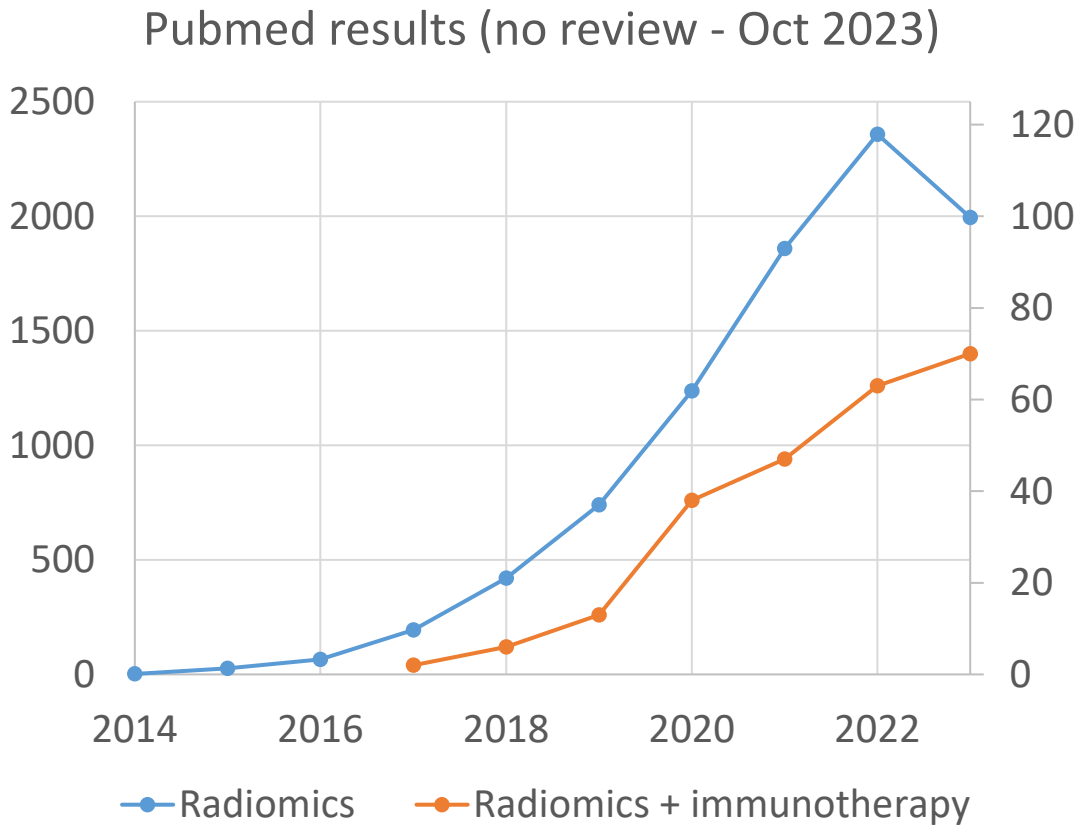
Lambin et al, NRCO 2017





Dercle et al, JITC 2022

Radiomics for immunotherapy?



Molecular pathways of immune response, inflammation, TILS, PD-L1

Grossman et al. eLife 2017
Tang et al. Sci Rep 2018
Chen et al. Eur Radiol 2019
MSI: Golia Pernicka et al. Abdom Radiol 2019

Microenvironment > IO response

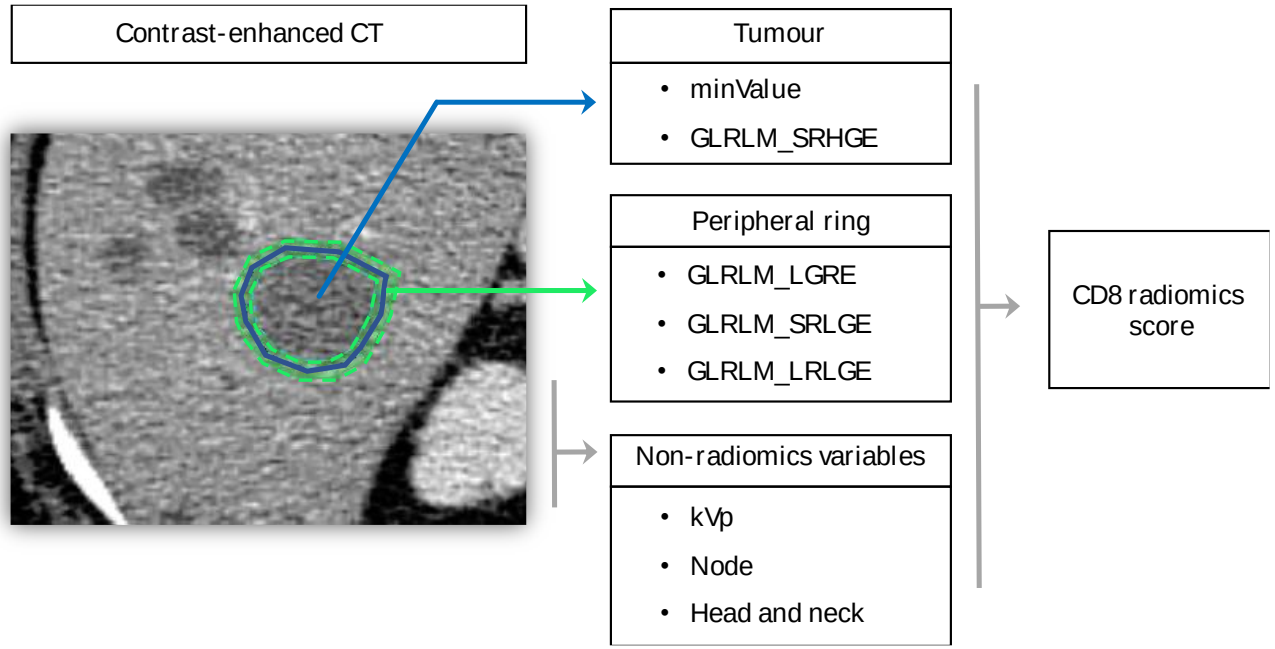
CD8: Sun et al. Lancet oncol 2018
TMB: He et al. J Immunother Cancer. 2020
PDL1: Mu et al. J Immunother Cancer. 2021
Hypoxia: Tunali et al. JNCI Cancer Spectr. 2021

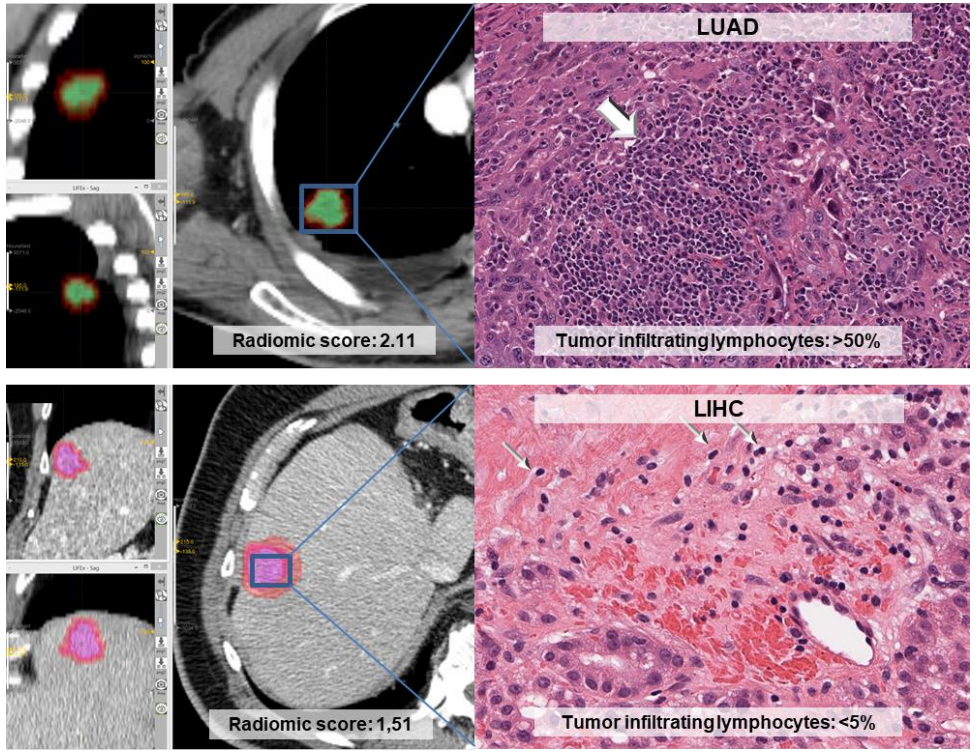
Response to IO directly

Tunali et al. Lung Cancer 2019
Trebeshi et al. Ann oncol 2019
Khorrami et al. Cancer Immunol Res 2019
Mu et al. EJNMMI 2020
Liu et al. Front Oncol 2021
MDSC-targeting immunotherapy : Devkota Sci Adv. 2020 (mice)

CD8 Radiomics signature

Prediction of CD8 T cells using radiomics on contrast enhanced CTs

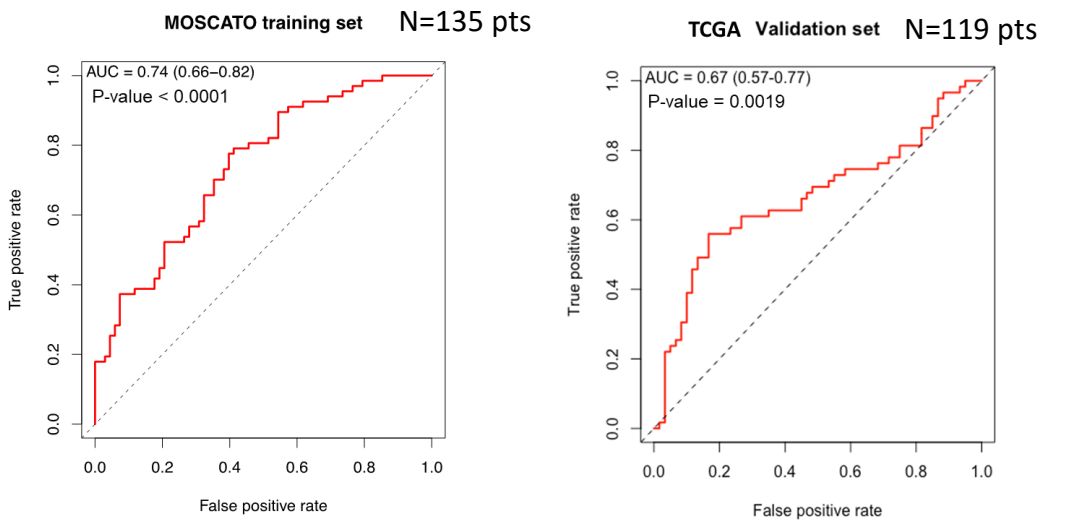


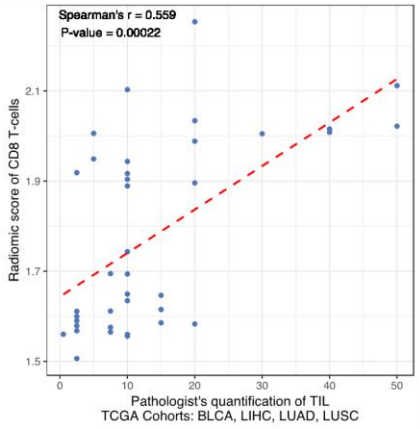


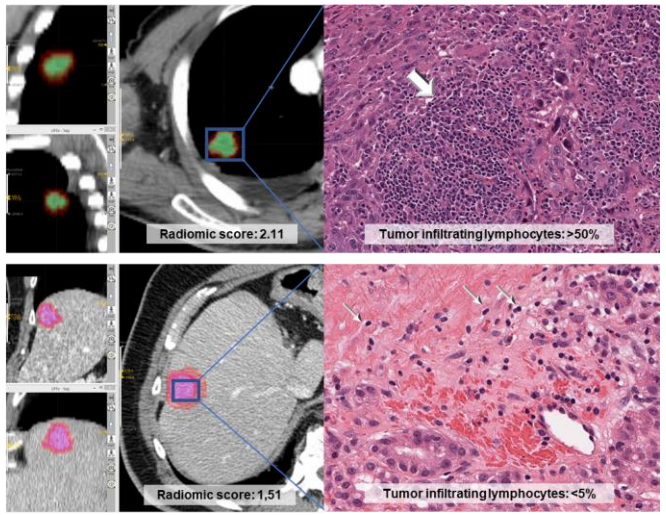
Sun R, et al – Lancet Oncol 2018

CD8 Radiomics signature

The radiomic signature could discriminate high vs low genomic score of CD8 T-cells infiltration

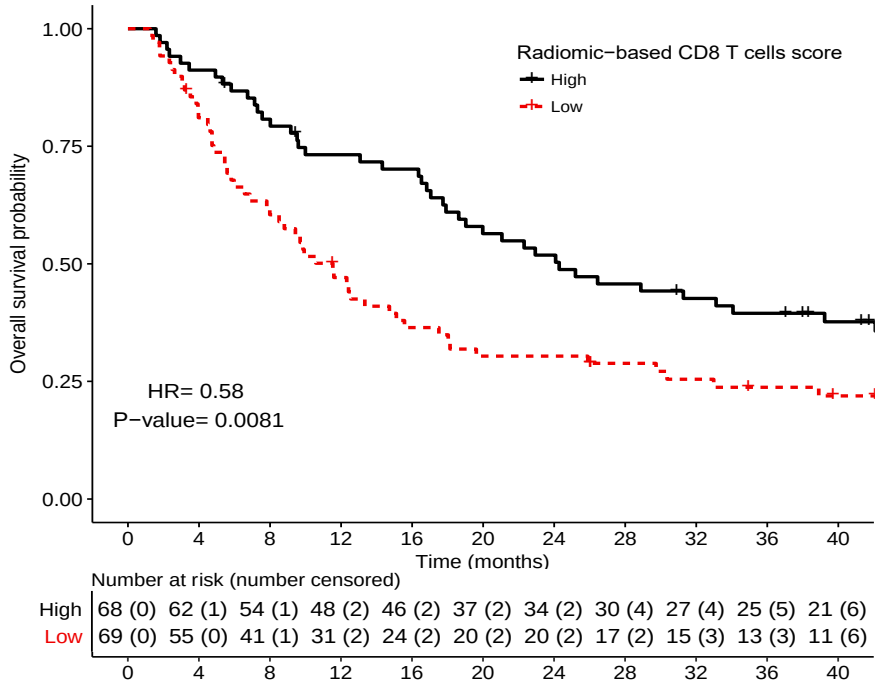






And was associated with OS in patients treated with anti-PD-1/PD-L1

N=137 pts



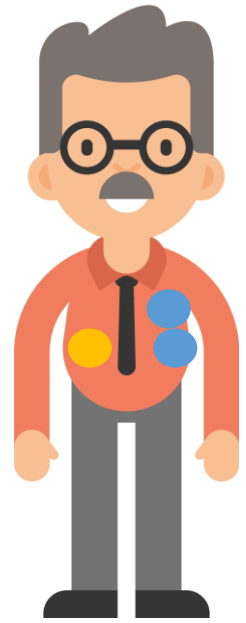
Sun R et al. Lancet Oncol 2018

Useful for radioimmunotherapy?

Patients

Gustave Roussy	SABR	Phase II **CRC, melanoma, lung** stage IV	Stereotactic RT (SBRT) : 3 x 15 Gy	Atezolizumab
	Mel-Ipi-Rx	Phase I **Melanoma** Stage III-IV	Hypofractionated 3 x 3 / 5 / 6 Gy	Ipilimumab
Gent	SBRT Ipilimumab	Phase I **Melanoma** Stage IV	SBRT : 3 x 8 / 10 / 12 Gy	Ipilimumab
	SBRT Nivolumab	Phase II **Melanoma** Stage III-IV	SBRT : 3 x 8 Gy	Nivolumab
	SBRT Pembrolizumab	Phase I **Urothelial** Stage IV	SBRT : 3 x 8 Gy	Pembrolizumab
Erlangen	ST-ICI	Observational **H&N, lung** Stage III-IV	Palliative and/or curative RT	Nivolumab Pembrolizumab

94 patients

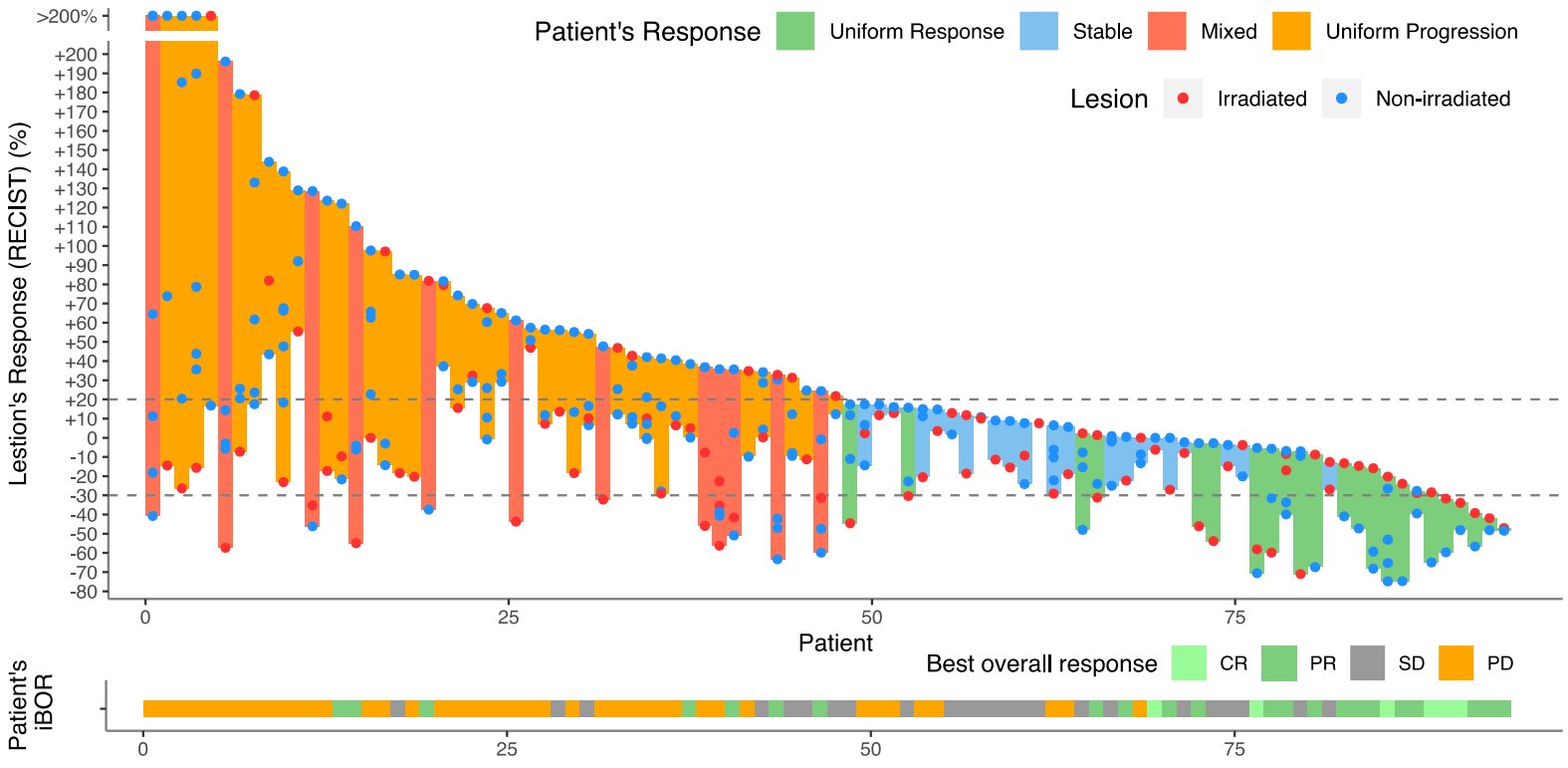


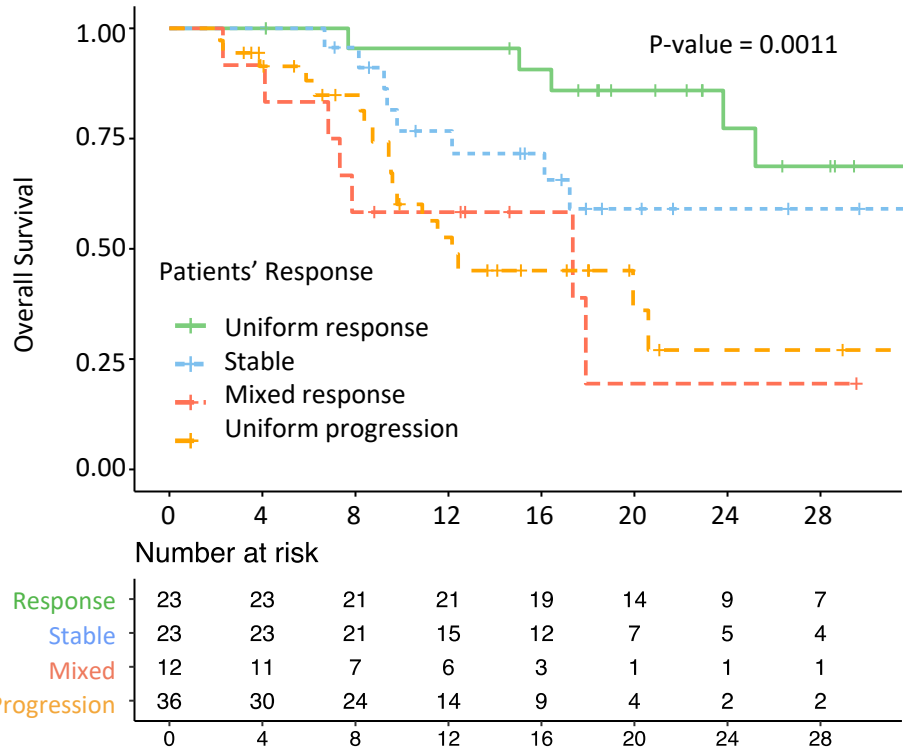
100 irradiated lesions
189 non-irradiated lesions

Sun et al. JITC 2020

RTIO cohort

Patient patterns of response

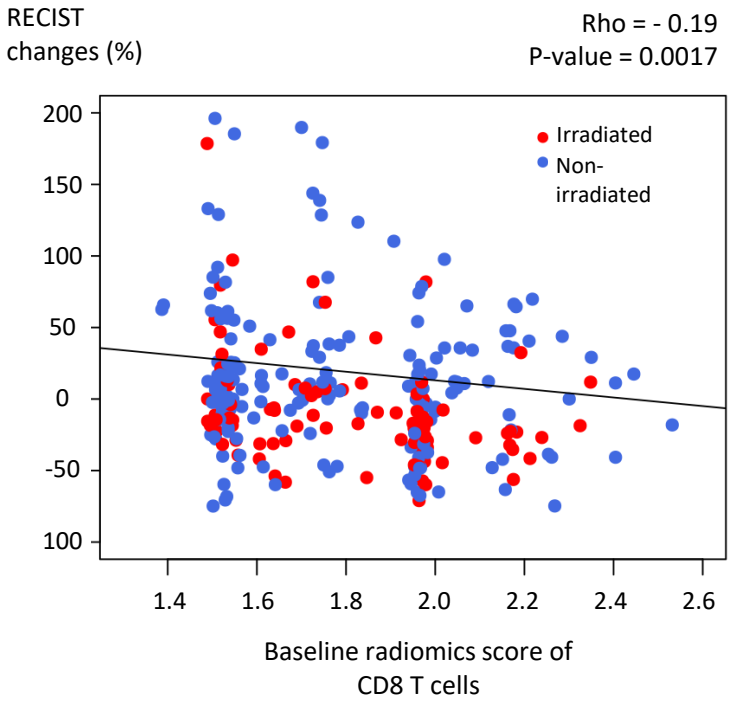




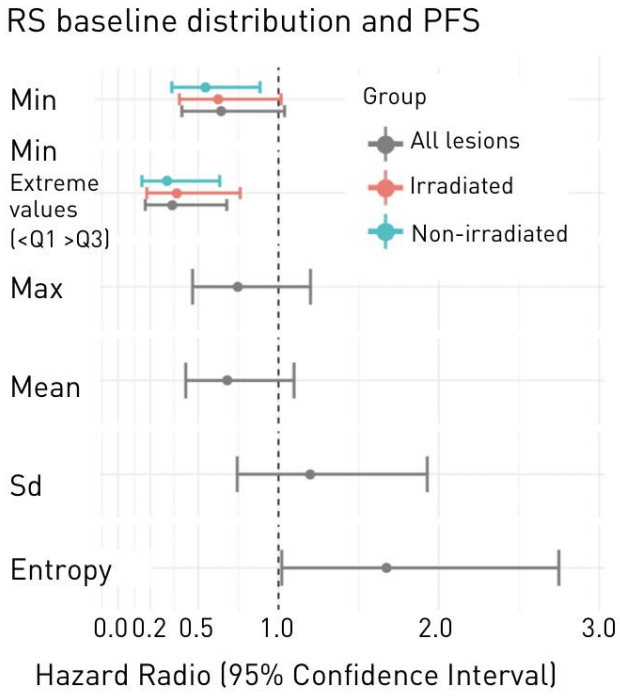
RTIO cohort

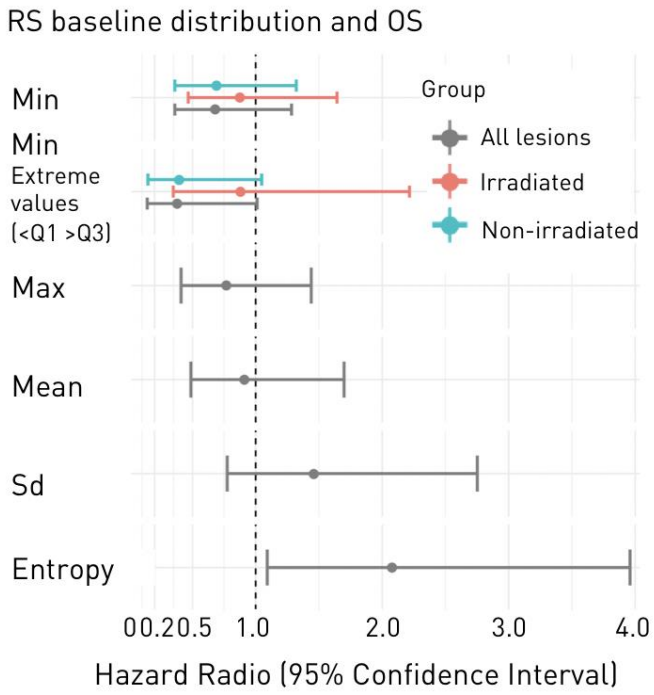
CD8 radiomic score distribution

Lesion response



Patient response



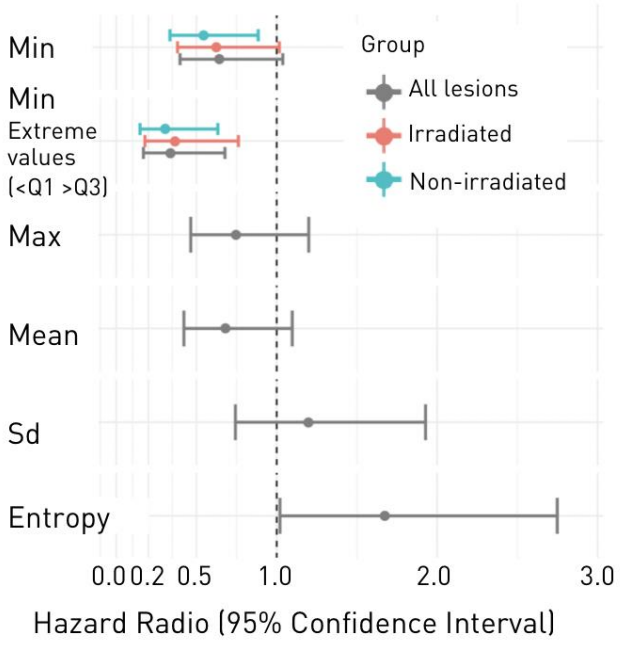


Sun et al. JITC 2020

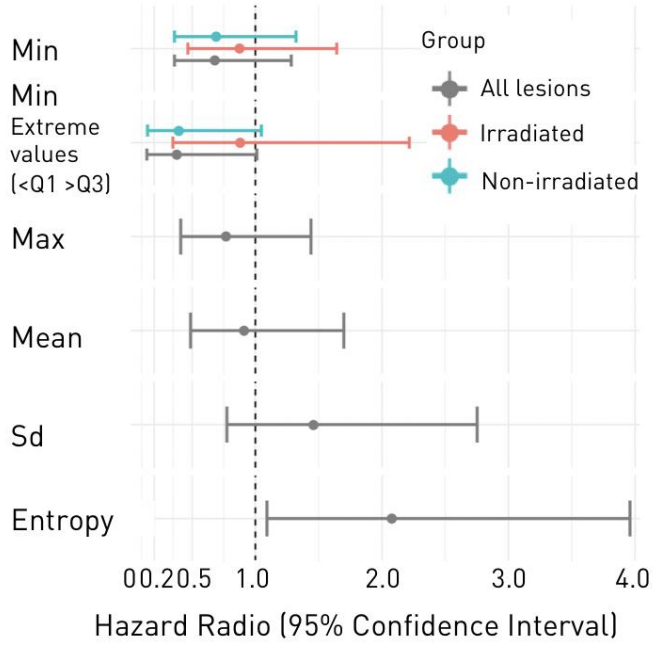
CD8 radiomic score distribution

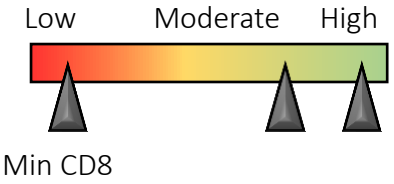
Patient response

RS baseline distribution and PFS



RS baseline distribution and OS





Min CD8 RScore

Predictive value of
the **least immune-infiltrated**
and **non-irradiated**
metastasis

May help to guide radiotherapy

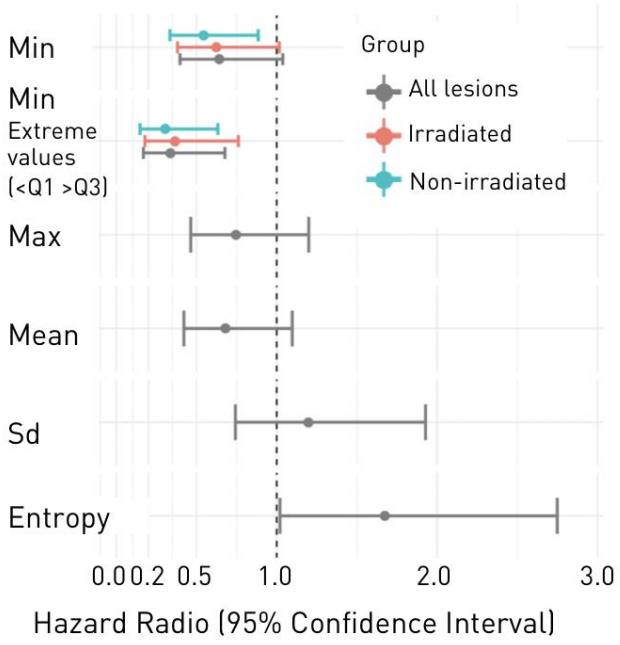
Sun et al. JITC 2020

RTIO cohort

CD8 radiomic score distribution

Patient response

RS baseline distribution and PFS



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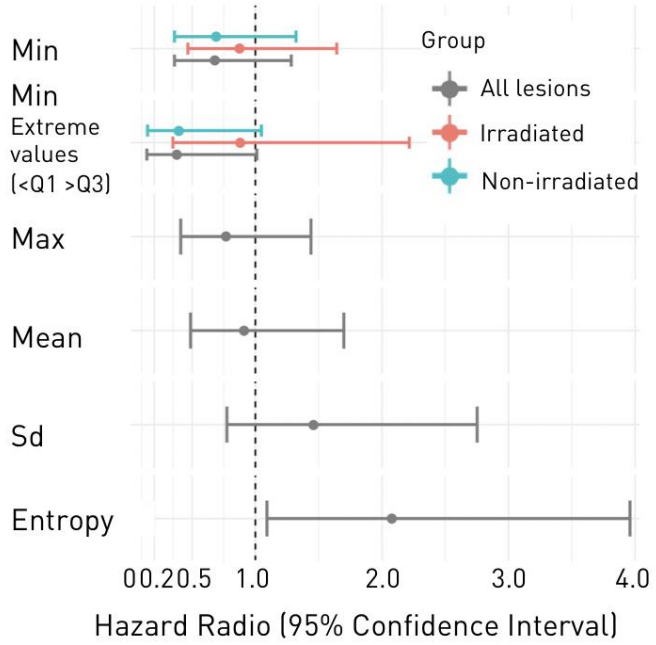
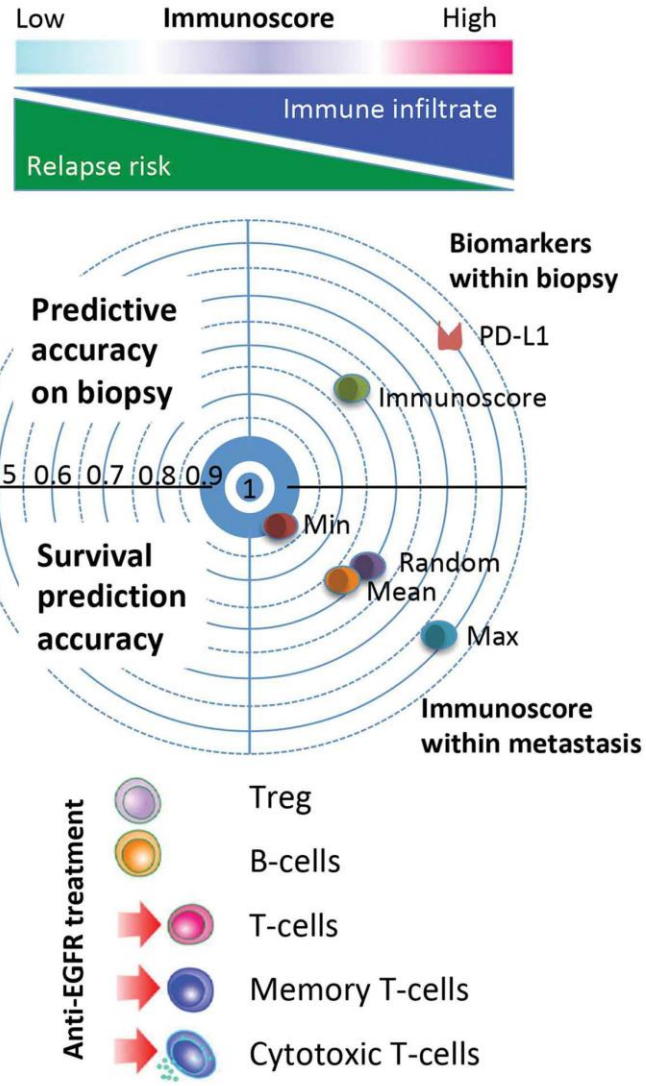




Van den Eynde et al. Oncoimmunology 2020

CD8 signature: validated for melanoma

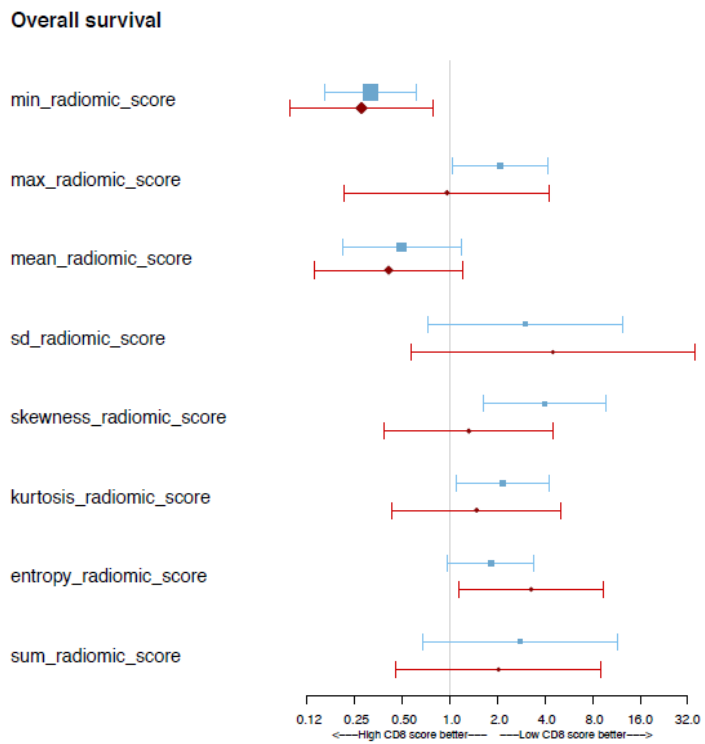
CD8 radiomics score

Melanoma patients

Immunotherapy: anti-PD1 (mono or bitherapy)

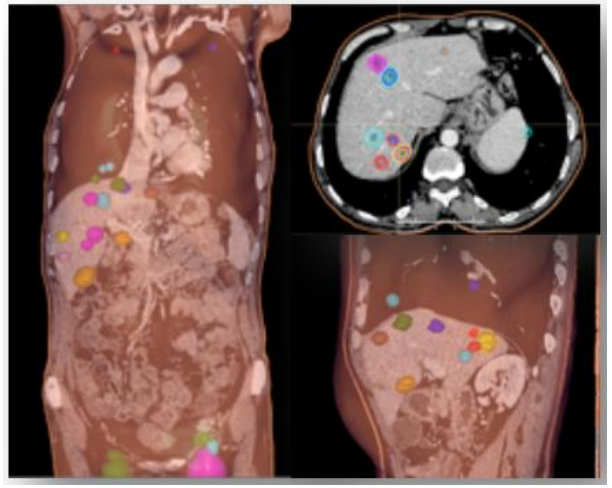
Baseline CT available:
N= 136 patients
1120 lesions delineated at baseline

Baseline and E1 CTs available:
N= 127 patients
1052 lesions delineated at both times



Min CD8 RScore

Predictive value of the **least immune-infiltrated** metastasis



Sun et al. JITC 2022

Radiomics CD8 score and liver mets?

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Article | Published: 04 January 2021

Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination

Jiali Yu, Michael D. Green , Shasha Li, Yilun Sun, Sara N. Journey, Jae Eun Choi, Syed Monem Rizvi, Angel Qin, Jessica J. Waninger, Xueting Lang, Zoey Chopra, Issam El Naqa, Jiajia Zhou, Yingjie Bian, Long Jiang, Alangoya Tezel, Jeremy Skvarce, Rohan K. Achar, Merna Sitto, Benjamin S. Rosen, Fengyun Su, Sathiya P. Narayanan, Xuhong Cao, Shuang Wei, ... Weiping Zou Show authors

Nature Medicine **27**, 152–164 (2021) | Cite this article

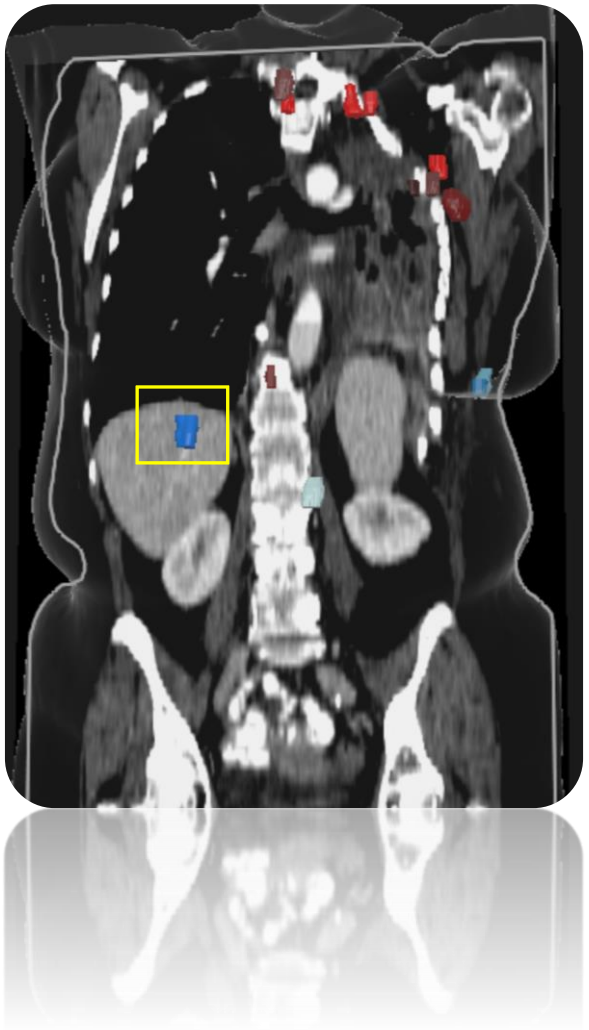
Radiomics CD8 score and liver mets?

2024 ASCO ANNUAL MEETING

NSCLC cohort

Stratification of patients:
- with liver mets: cold vs hot liver lesions
- without liver mets: cold vs hot non-liver lesions

Cold liver lesion



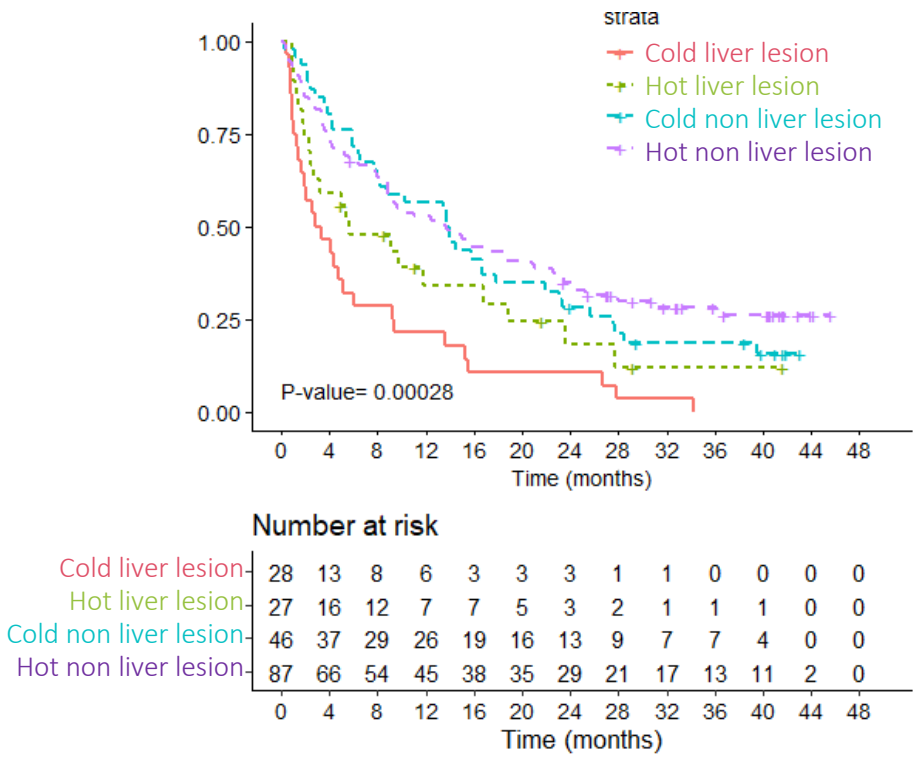
Hot liver lesion

2024 ASCO ANNUAL MEETING

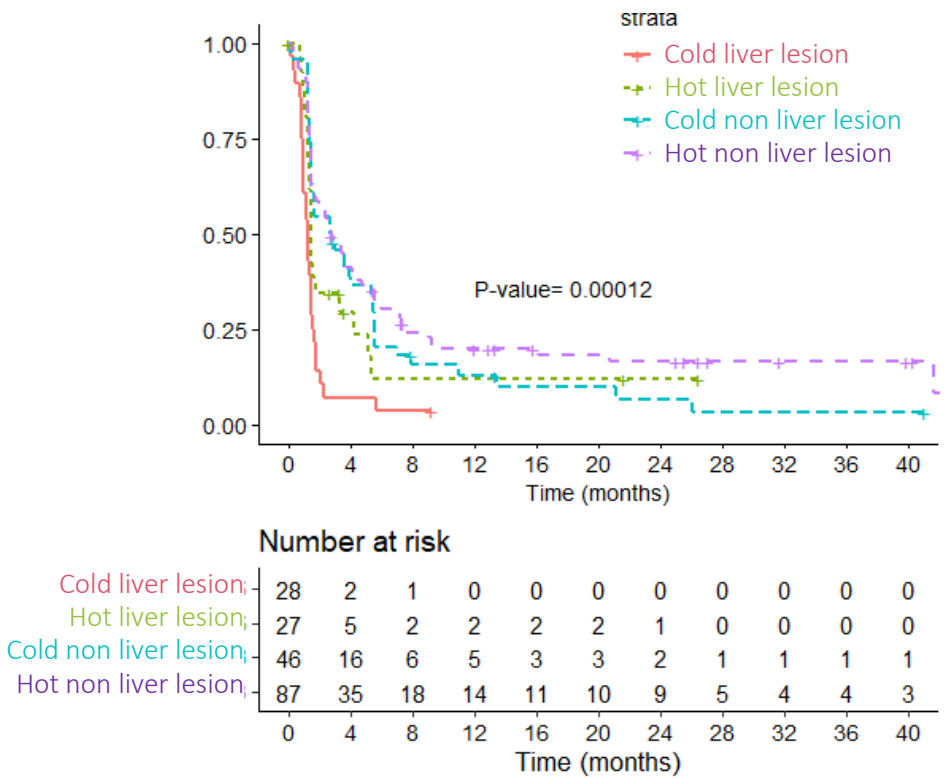
NSCLC cohort

Stratification of patients:
- with liver mets: cold vs hot liver lesions
- without liver mets: cold vs hot non-liver lesions

Overall survival



Progression free survival



Liver lesion irradiation and outcomes

Patients

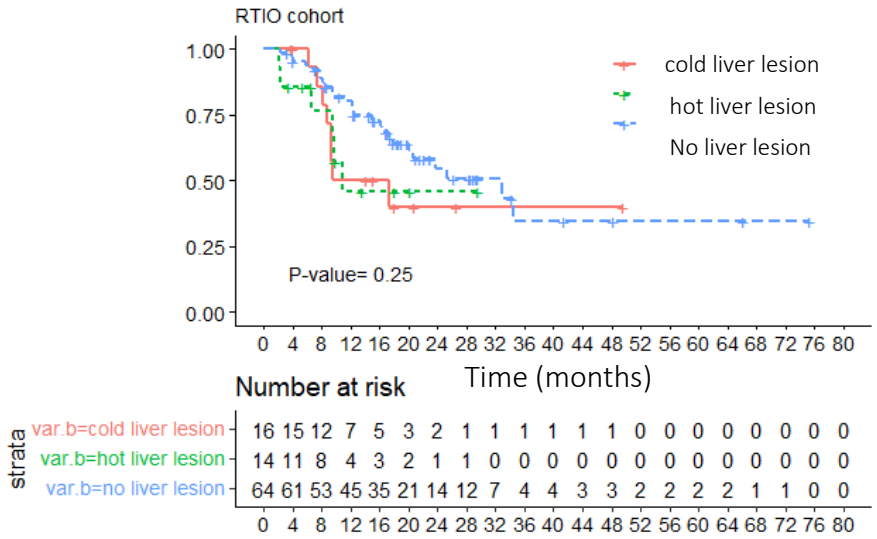
N=94 pts treated with ICI + RT (mostly 3 x 8 Gy)

- 30 patients with liver lesions (32%)
- Cold liver lesions: according to the median value
- Median OS : 13 mo vs 10 mo vs 33 mo (NS)

SBRT of liver lesion according to CD8 Radiomics score

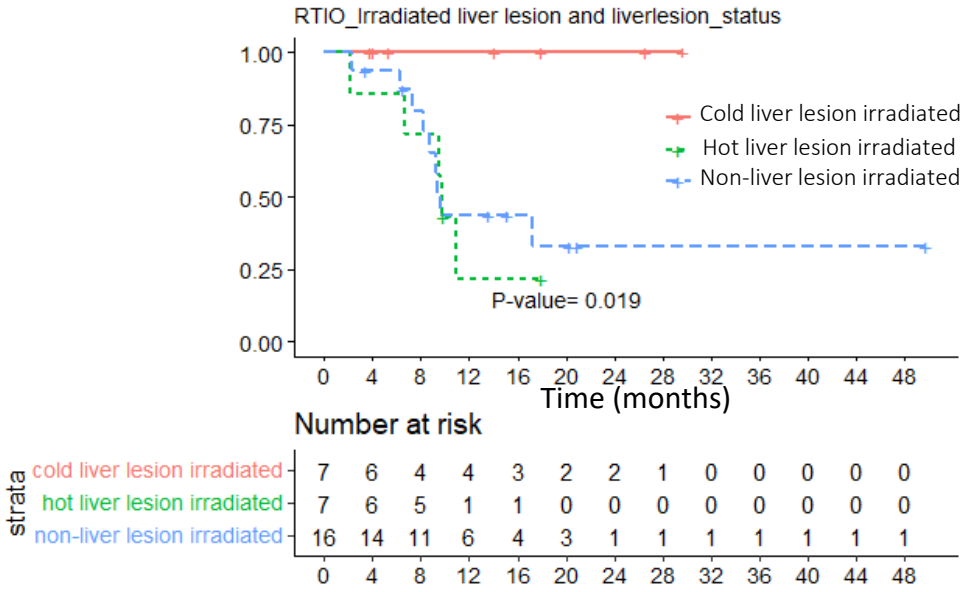
- SBRT to cold Liver lesions improved OS
  (according to the median Value of irradiated live lesions)
- Median OS:
  Not reached vs 9.8 mo.

Overall Survival



100 irradiated lesions
189 non-irradiated lesions

Overall Survival



Independent external validation

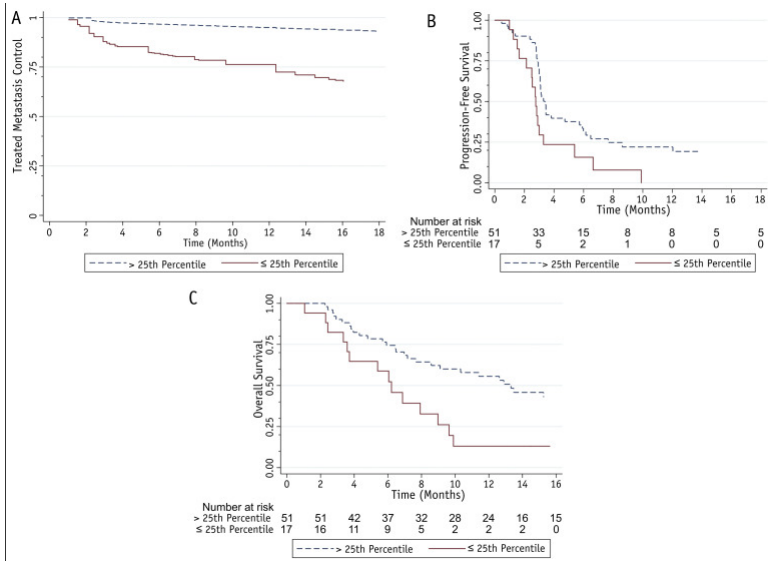
CLINICAL RESULTS OF IMMUNE THERAPY AND RADIATION | VOLUME 108, ISSUE 1, P189-195, SEPTEMBER 01, 2020

A Validated T Cell Radiomics Score Is Associated With Clinical Outcomes Following Multisite SBRT and Pembrolizumab

Mark C. Korpics, MD • Mei-Yin Polley, PhD • Sandeep R. Bhave, MD • ... Sean P. Pitroda, MD • Jason J. Luke, MD • Steven J. Chmura, MD, PhD • Show all authors

Published: June 19, 2020 • DOI: https://doi.org/10.1016/j.ijrobp.2020.06.026 • Check for updates

68 pts : 17 low-RS+51 high-RS pts



Association of radiomics score with clinical outcomes after stereotactic body radiation therapy and immune checkpoint blockade.

The Journal of Clinical Investigation CLINICAL MEDICINE

Partial tumor irradiation plus pembrolizumab in treating large advanced solid tumor metastases

Mark C. Korpics,[1] Benjamin E. Onderdonk,[1] Rebekah E. Dadey,[2] Jared H. Hara,[1] Lilit Karapetyan,[3] Yuanyuan Zha,[4] Theodore G. Karrison,[5] Adam C. Olson,[2] Gini F. Fleming,[6] Ralph R. Weichselbaum,[1,7] Riyue Bao,[2] Steven J. Chmura,[1] and Jason J. Luke[2]

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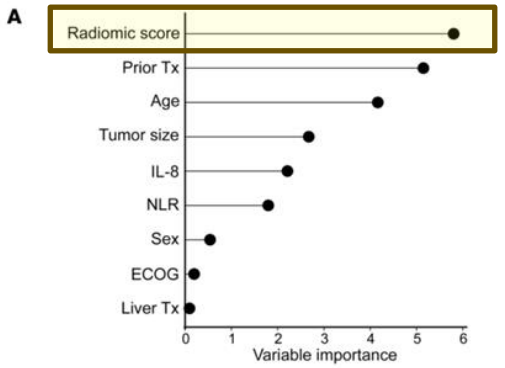
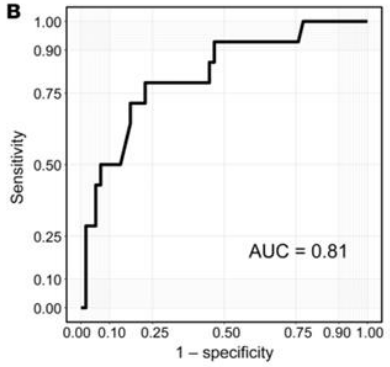
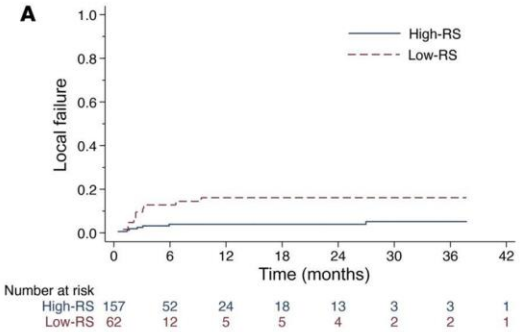
J Clin Invest. 2023;133(10):e162260. https://doi.org/10.1172/JCI162260.

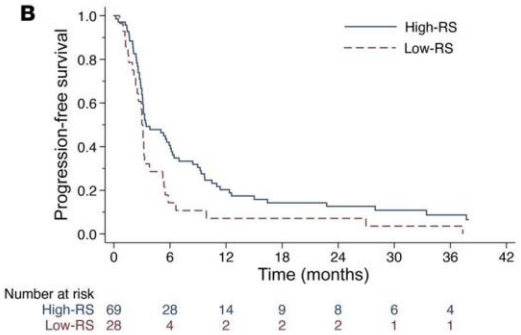
97 patients 219 irradiated lesions, 145 unirradiated lesions

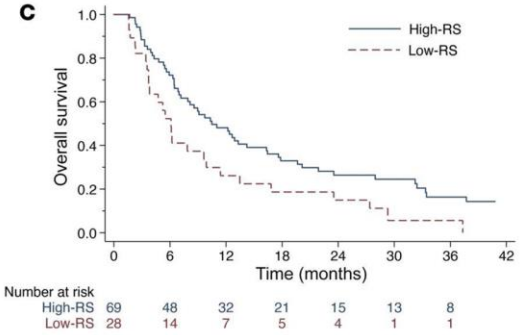




Modelling of responders/non-responders



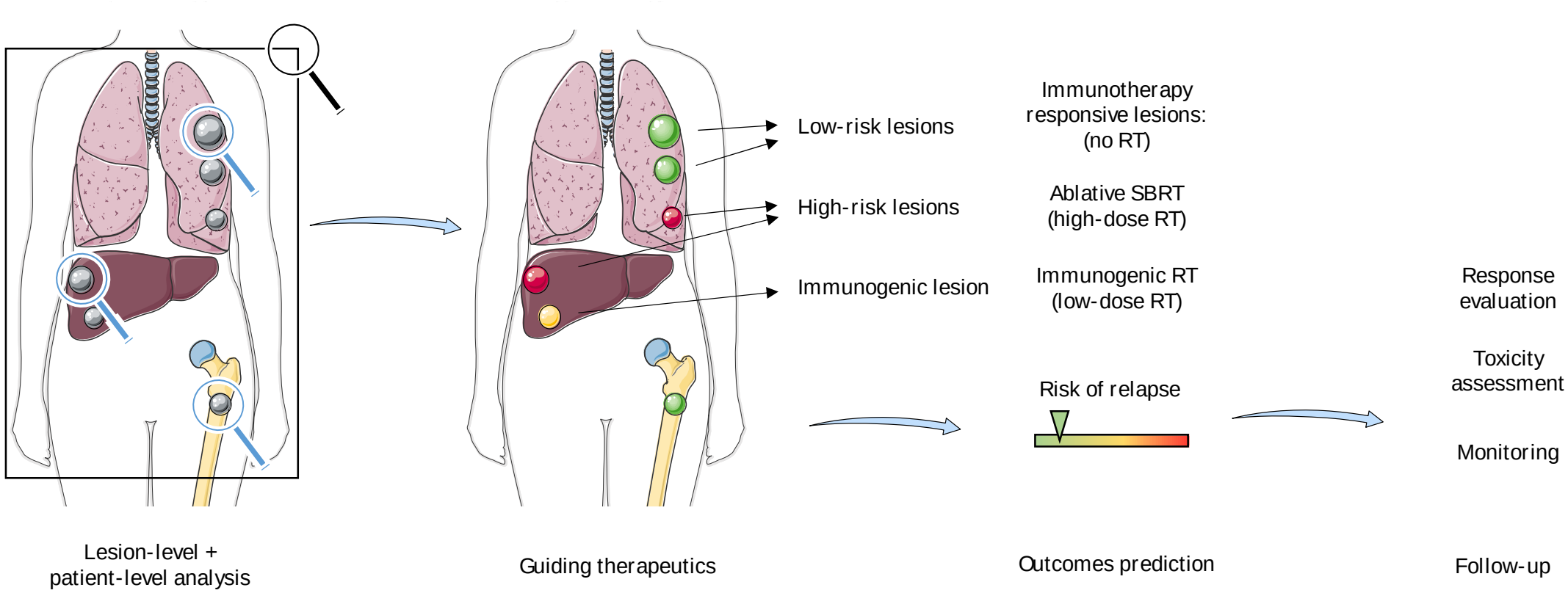




Korpics et al. IJROBP 2020, JCI 2023

Toward ultra-precision radioimmunotherapy ?

Imaging-biomarkers guided radiotherapy

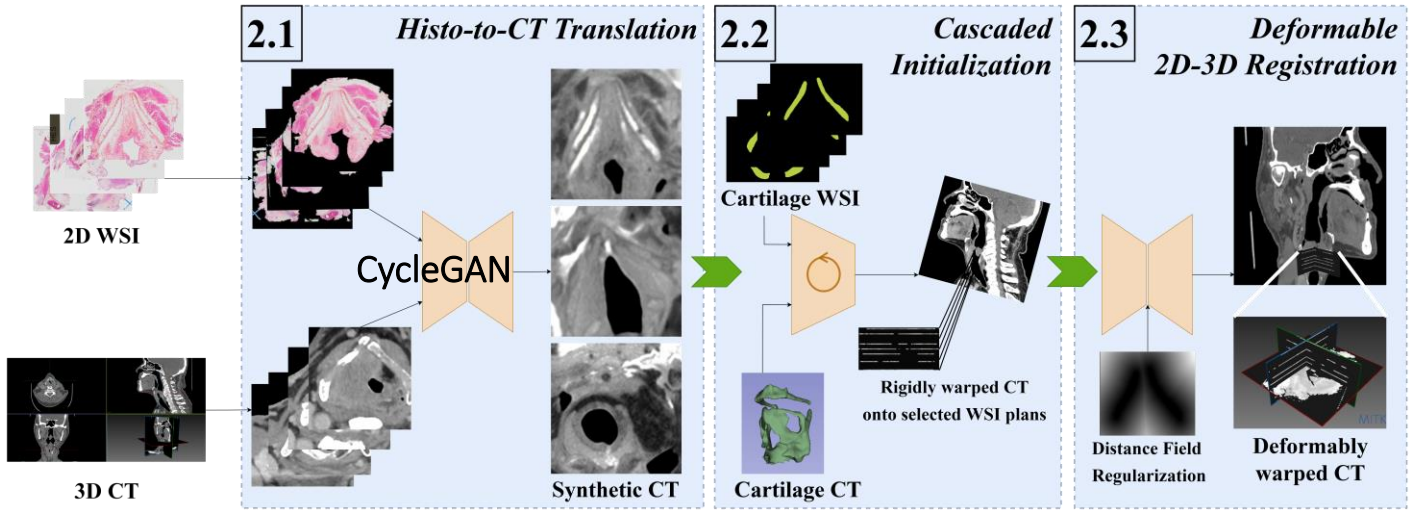


Sun R et al JITC 2022

Amaury Leroy

From pathology to CT :

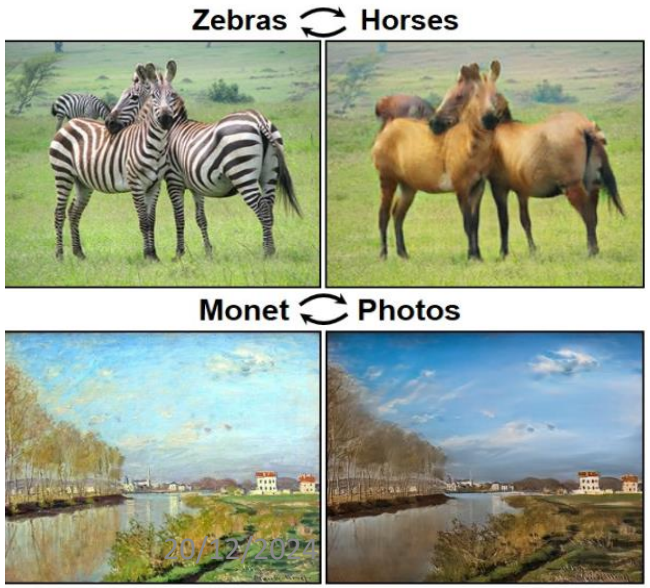
- Very different types of imaging:
  - Multimodal (colors, resolution)
  - 2D/3D

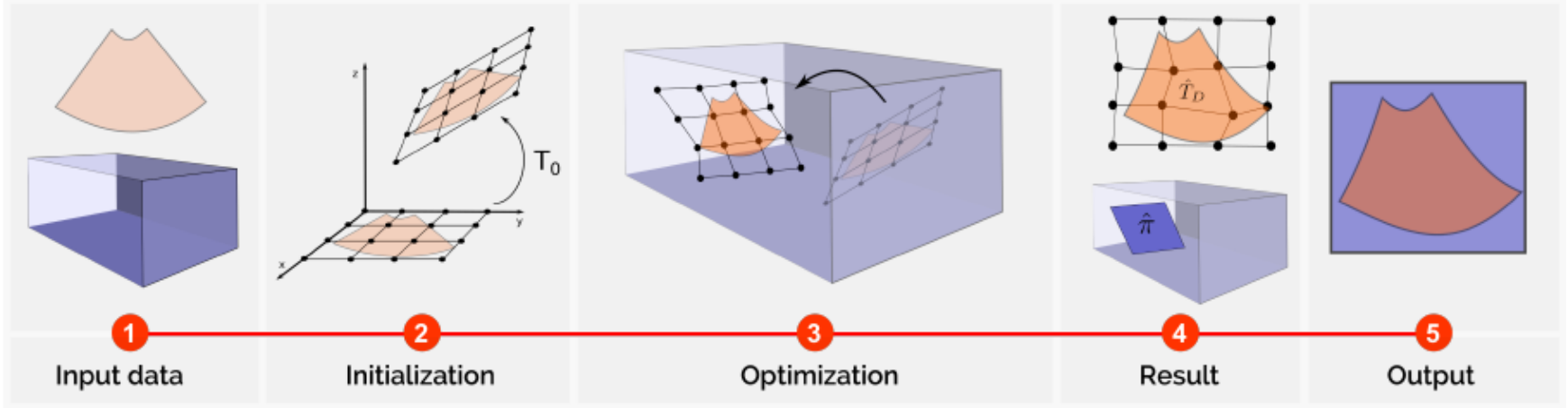


Modality Translation

Plane Selection

Refined deformation



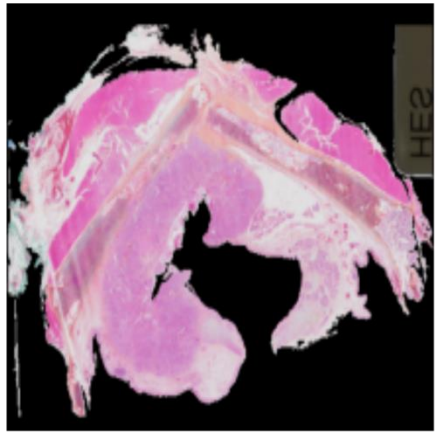


Leroy et al, Estro 2023

A Leroy

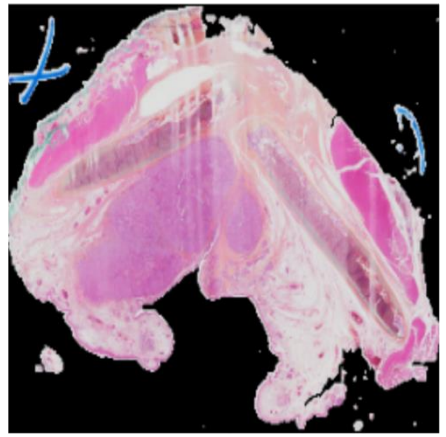
Micron level tumor infiltration characterisation

Moving CT



Fixed Histology

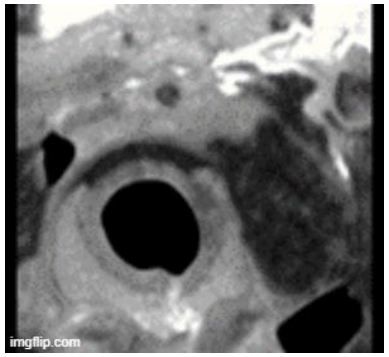
Moving CT



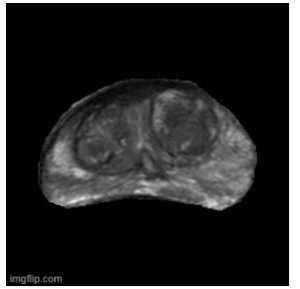
Fixed Histology

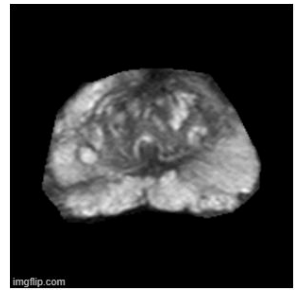
Virtual Histology Synthesis

CT/MRI to the microscope into 1 click !



CT to Histology





MR to Histology (prostate)

Leroy et al, Estro 2023

Conclusions

- Hétérogénéité inter-lésionnelle: un challenge majeur pour la radiomics
- Amélioration des connaissances tumor biology & radioimmunotherapy
- Guider un des traitements locaux (RT?)
- Importance d'un design d'étude adapté.

Merci pour votre attention !

U1030 et collaborations