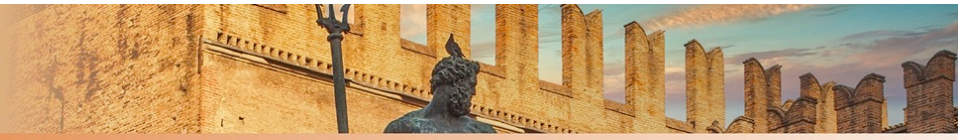
Biomarkers

Andrea R. Filippi

Università di Pavia e Fondazione IRCCS Policlinico San Matteo

Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia



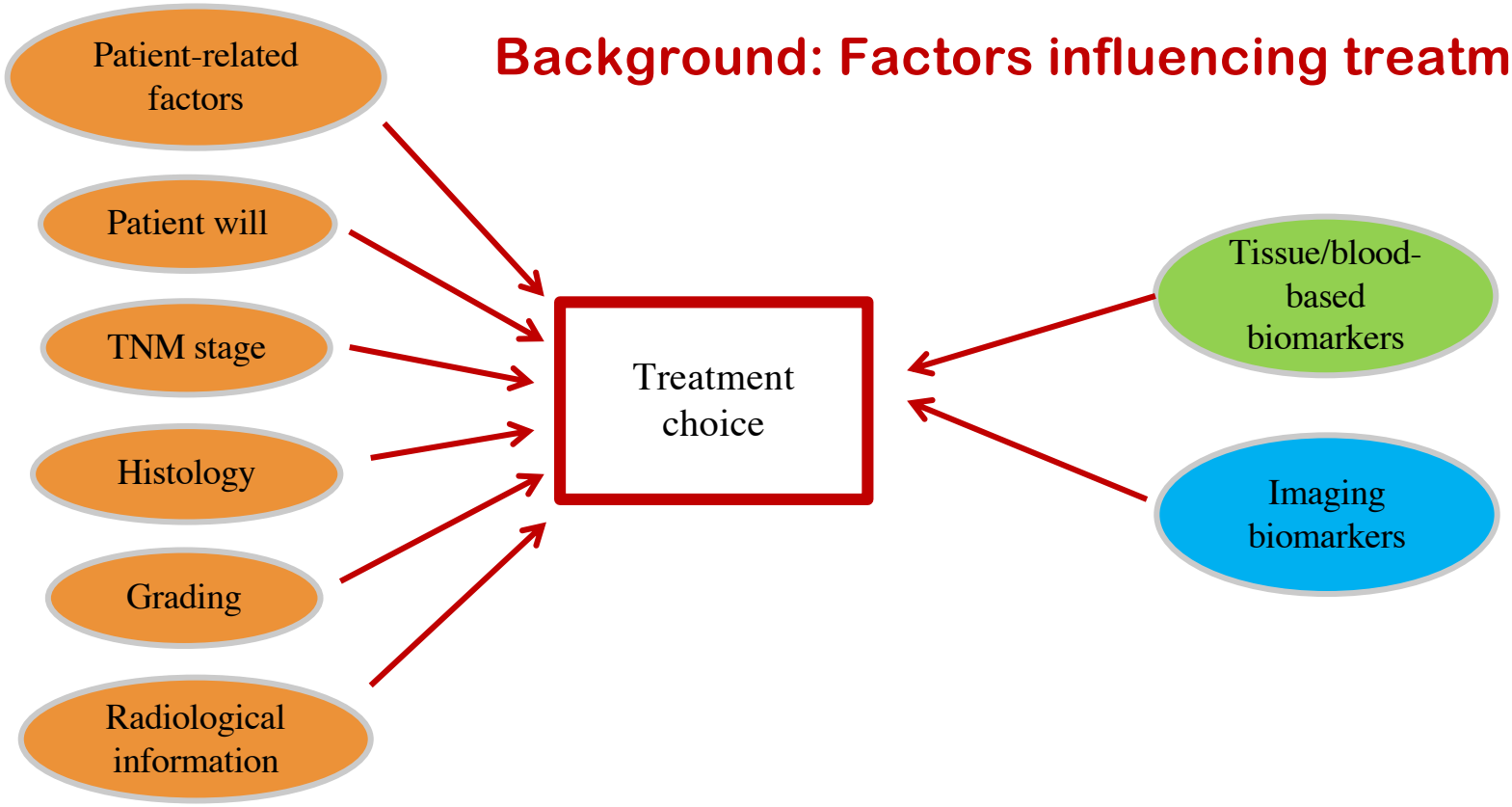
DICHIARAZIONE

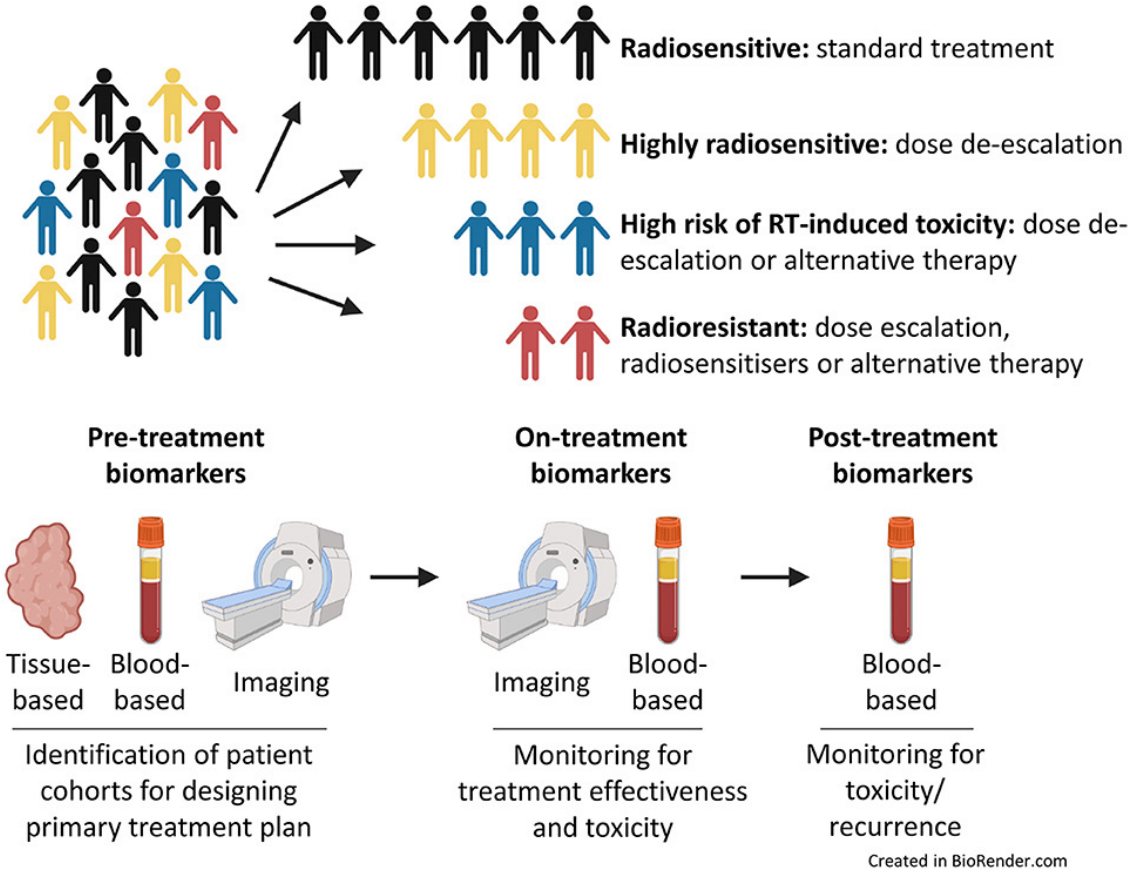
Relatore: Andrea R. Filippi

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **ASTRA ZENECA, ROCHE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **ASTRA ZENECA, ROCHE, MSD (istituzionali)**
- Partecipazione ad Advisory Board **ASTRA ZENECA, ROCHE**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**

Background: Factors influencing treatment choice

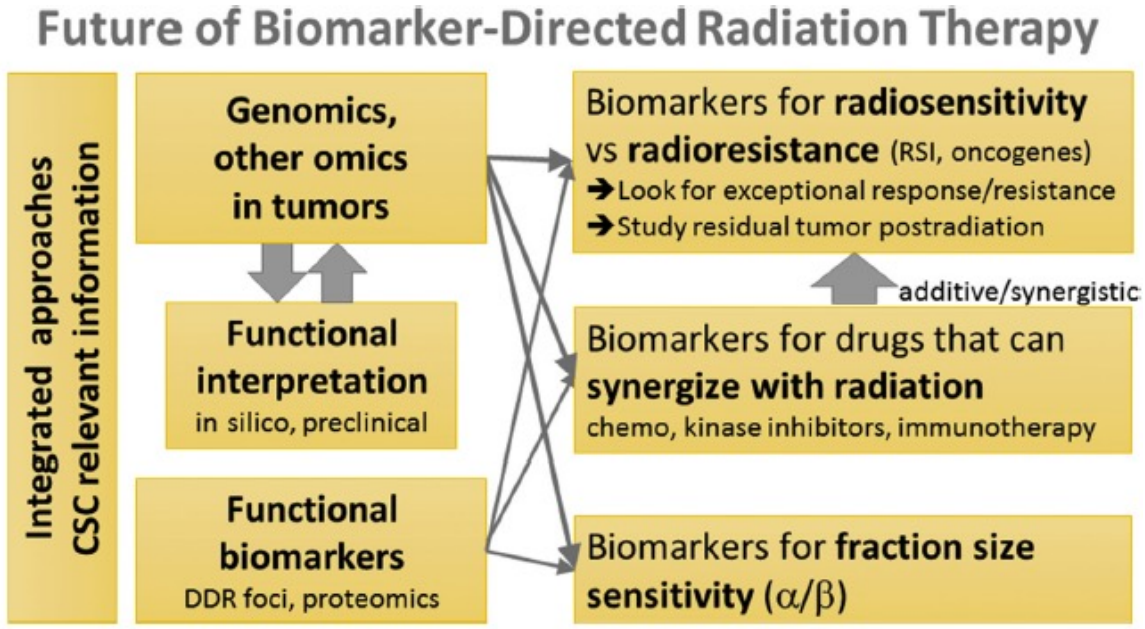




Meehan et al. Front. Oncol., 24 April 2020

Toward a New Framework for Clinical Radiation Biology

Henning Willers, MD , Florence K. Keane, MD Sophia C. Kamran, MD

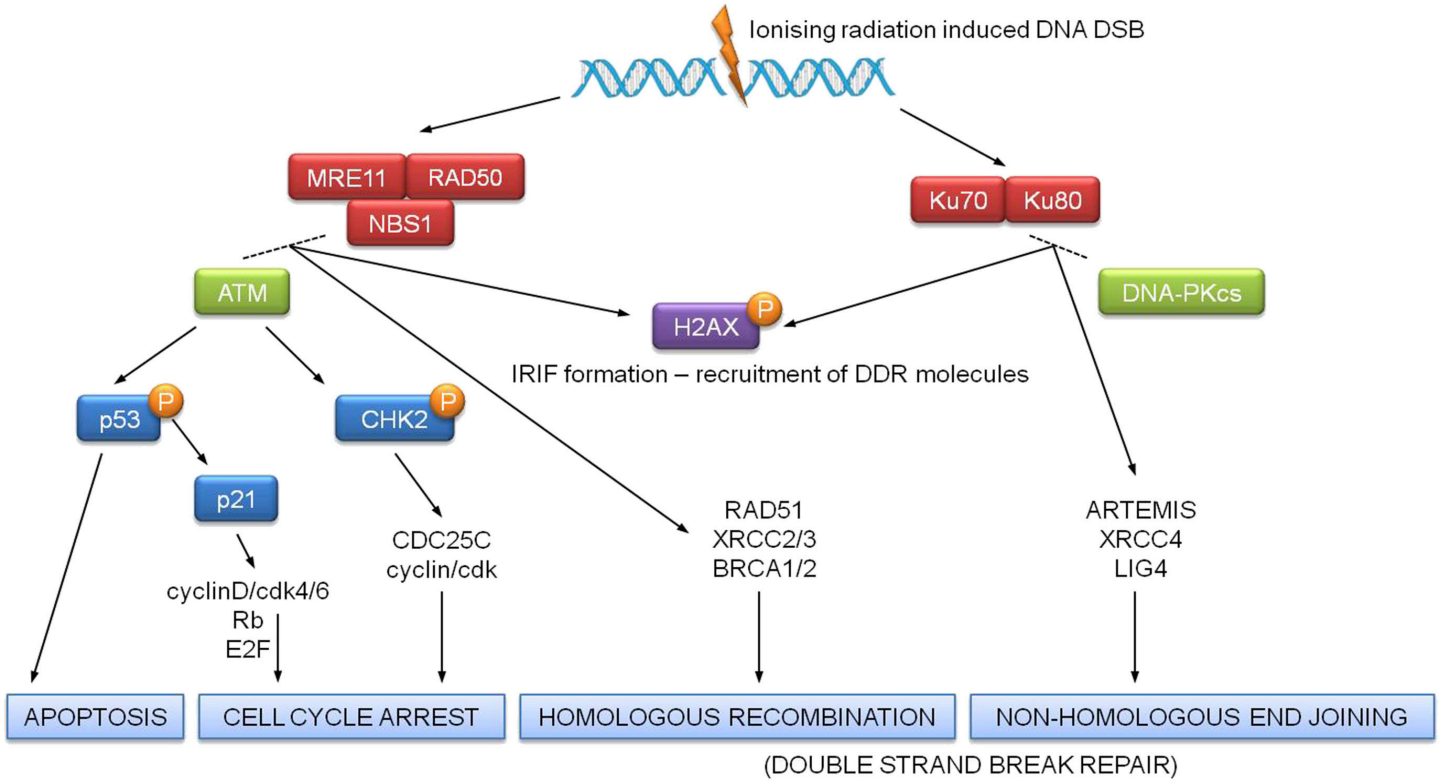


Hematology/Oncology Clinics 2019

Static, tissue-based biomarkers

4 main types of "biomarkers have been studied; so far, no-one has been validated in a RCT:

1. DDR-related biomarkers (MRE11, etc.)
2. Genetic signatures (RSI)
3. Epigenetic signatures (microRNA)
4. Microenvironmental biomarkers (immune-related biomarkers)



Clinical Oncology 2015 27561-569DOI: (10.1016/j.clon.2015.06.002)

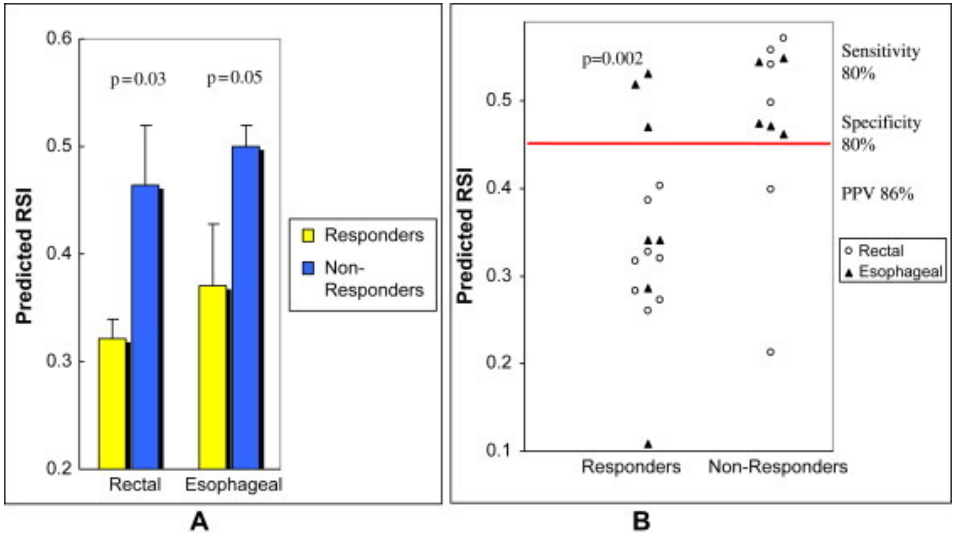
A Gene Expression Model of Intrinsic Tumor Radiosensitivity: Prediction of Response and Prognosis After Chemoradiation

Table 3. Radiation network hub genes

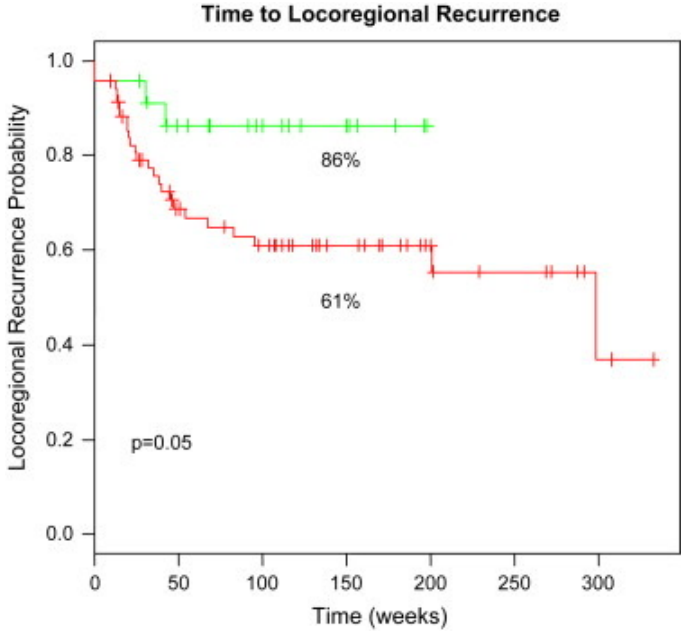
Gene name	HU6800 Probeset	U133Plus Probeset	NKI reporter
Androgen receptor	M23263_at	211110_s_at	324293
c-Jun	J04111_at	201466_s_at	329987
STAT1	AFFX-HUMISGF3A/ M97935_MA_at	AFFX-HUMISGF3A/ M97935_MA_at	308421
PKC	X06318_at	207957_s_at	322907
RelA (p65)	U33838_at	201783_s_at	326475
c-Abl	X16416_at	202123_s_at	304192
SUMO-1	U83117_at	208762_at	308596
CDK1 (p34)	U24153_at	205962_at	332859
HDAC1	D50405_at	201209_at	308690
IRF1	L05072_s_at	202531_at	310653

Eschrich S et al, IJROBP 2009

A Gene Expression Model of Intrinsic Tumor Radiosensitivity: Prediction of Response and Prognosis After Chemoradiation



RSI correlates to response for rectal and esophageal cancer patients



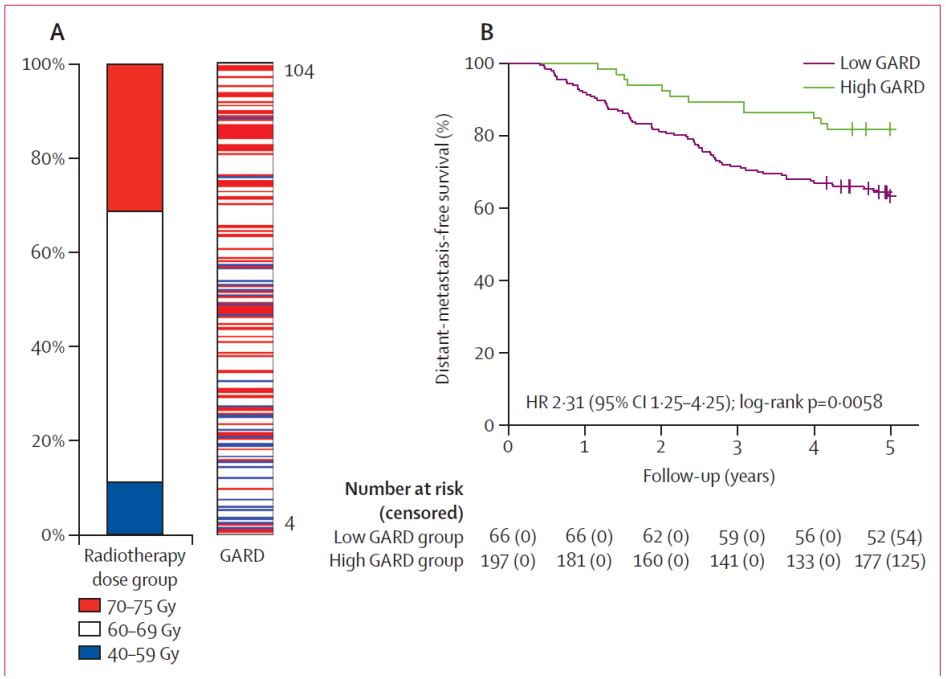
RSI correlates with LC in the H&N cancer cohort, n=92

Eschrich S et al, IJROBP 2009

A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study.

Genomic-Adjusted Radiation Dose (GARD): a novel model that integrates RSI and physical dose of radiation to quantify the biological effect ofa given dose in an individual patient.

GARD is a pre-clinically and clinically validated combination of a genomic profile, which assumes pan-tissue biological networks of radiosensitivity, with LQ model.

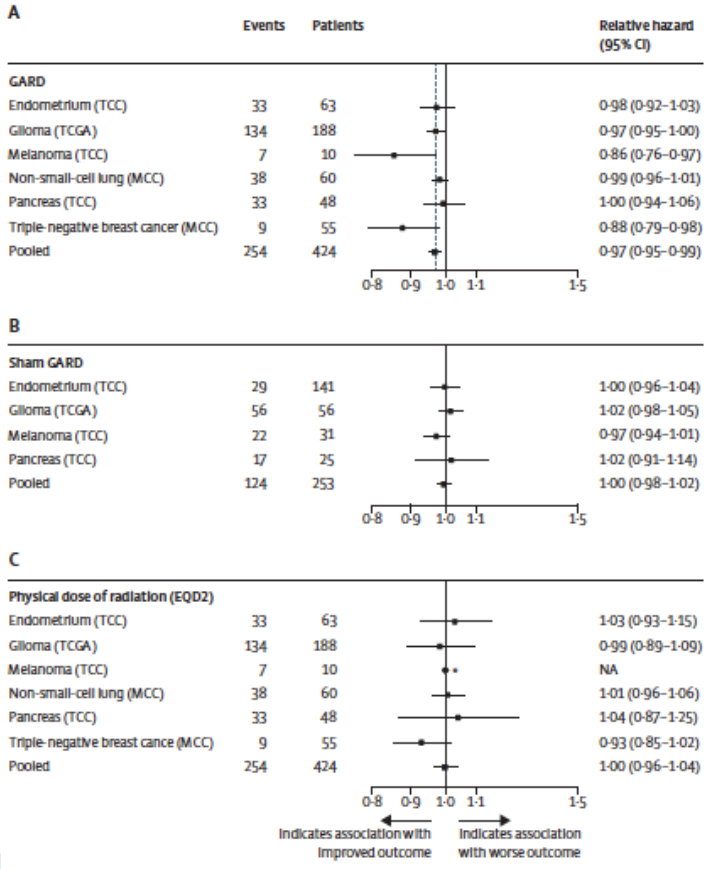


Erasmus breast cancer cohort distant-metastatis free survival

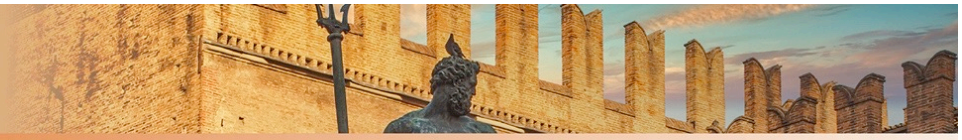
Scott et al., Lancet Oncol 2017

Pan-cancer prediction of radiotherapy benefit using genomic-adjusted radiation dose (GARD): a cohort-based pooled analysis.

GARD is associated with time to first recurrence and overall survival for different cancer types, overperforming physical radiation dose (EQD2)



Scott et al., Lancet Oncol 2021



npj | Genomic Medicine
www.nature.com/npjgenmed

ARTICLE OPEN

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Radiosensitivity index emerges as a potential biomarker for combined radiotherapy and immunotherapy

Yang-Hong Dai[1], Ying-Fu Wang[1], Po-Chien Shen[1], Cheng-Hsiang Lo[1], Jen-Fu Yang[1], Chun-Shu Lin[1], Hsing-Lung Chao[1,2] and Wen-Yen Huang[1,3]✉

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY · BIOLOGY · PHYSICS
www.redjournal.org

BIOLOGY CONTRIBUTION

The Radiosensitivity Index Gene Signature Identifies Distinct Tumor Immune Microenvironment Characteristics Associated With Susceptibility to Radiation Therapy

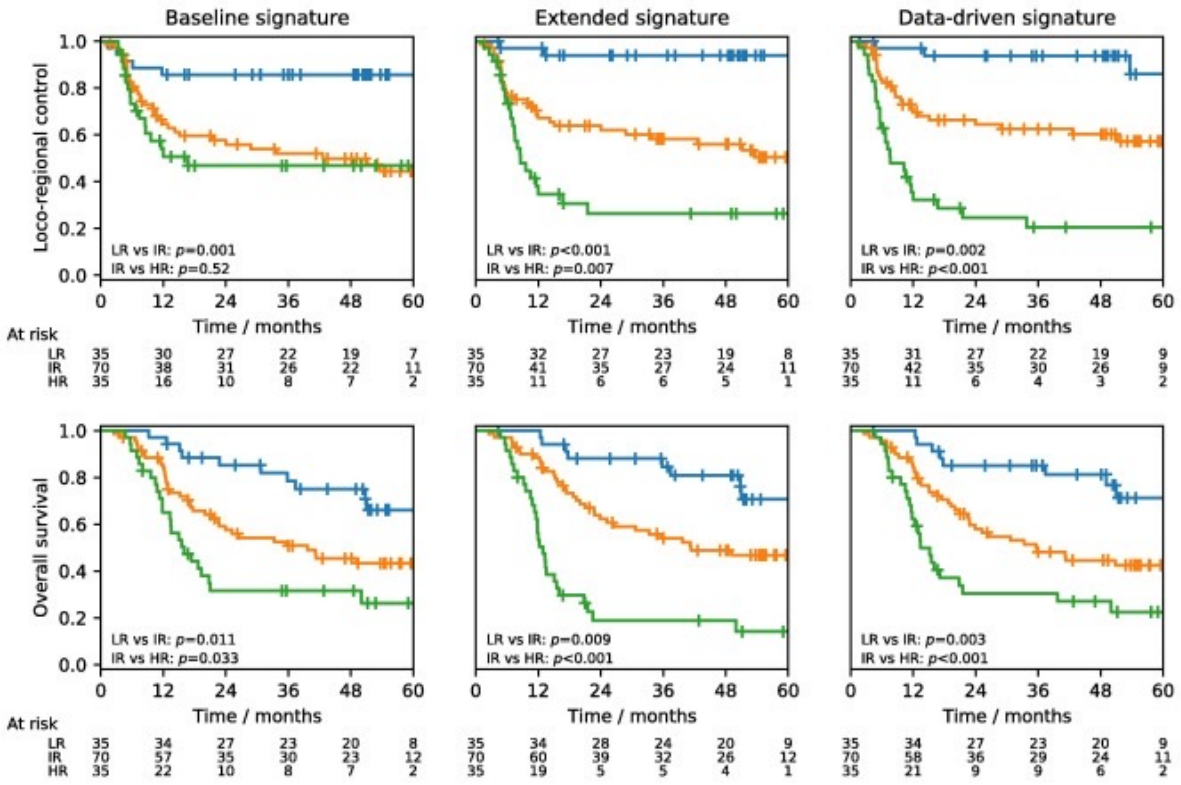
G. Daniel Grass, MD, PhD,* Juan C.L. Alfonso, PhD,† Eric Welsh, PhD,† Kamran A. Ahmed, MD,* Jamie K. Teer, PhD,‡ Shari Pilon-Thomas, PhD,§ Louis B. Harrison, MD,* John L. Cleveland, PhD,‖ James J. Mulé, PhD,§ Steven A. Eschrich, PhD,† Heiko Enderling, PhD,*,¶ and Javier F. Torres-Roca, MD*

Tumors with an estimated high sensitivity to RT demonstrated distinct enrichment of interferon-associated signaling pathways and immune cell infiltrates (eg, $CD8^+$ T cells, activated natural killer cells, M1-macrophages; $q < 0.05$), which was in the context of diverse expression patterns of various immunoregulatory molecules.

npj Genomic Medicine 2021 and IJROBP 2022

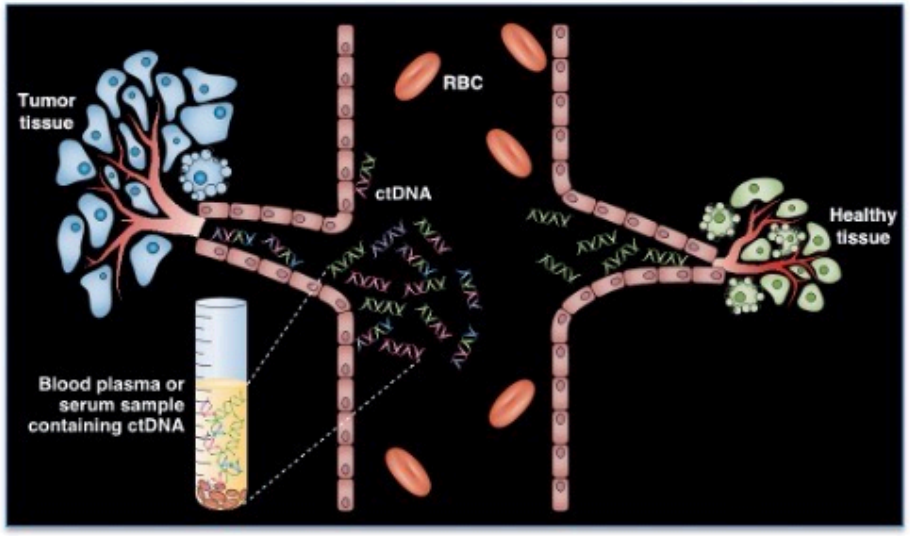
Biomarker signatures for primary radiochemotherapy of locally advanced HNSCC. Hypothesis generation on a multicentre cohort of the DKTK-ROG

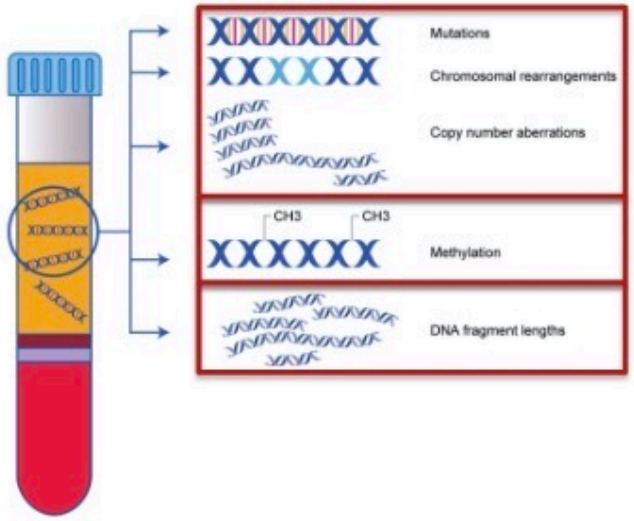
Variable		Median (range)
GTV (cm^3)		26.8 (4.40 – 175.8), Missing: 1
SLC3A2		−2.60 (−4.37 – −0.72), Missing: 20
		Number of 158 (%)
p16	Negative	125 (79.1)
	Positive	24 (15.2)
	Missing	9 (5.7)
CD44 protein	Negative	28 (17.7)
	Positive	108 (68.4)
	Missing	22 (13.9)
15-gene hypoxia classifier	Less hypoxic	55 (34.8)
	More hypoxic	83 (52.5)
	Missing	20 (12.7)
Tumour mutational burden classifier	Low	69 (43.7)
	High	32 (20.3)
	Missing	57 (36.1)
rs1799793/ERCC2	GG	48 (30.4)
	GA + AA	84 (53.2)
	Missing	26 (16.5)
rs13181/ERCC2	AA + CA	109 (69.0)
	CC	23 (14.6)
	Missing	26 (16.5)
rs17655/ERCC5	GG	80 (50.6)
	CG + CC	52 (32.9)
	Missing	26 (16.5)
icCXCR4	Negative	16 (10.1)
	Positive	124 (78.5)
	Missing	18 (11.4)
mCXCR4	Negative	103 (65.2)
	Positive	37 (23.4)
	Missing	18 (11.4)
icSDF-1	Negative	38 (24.1)
	Positive	102 (64.6)
	Missing	18 (11.4)
mSDF-1	Negative	80 (50.6)
	Positive	60 (38.0)
	Missing	18 (11.4)
CD8	Sum score ≤ 6	123 (77.8)
	Sum score > 6	24 (15.2)
	Missing	11 (7.0)



Lock et al, Radiother Oncol 2022

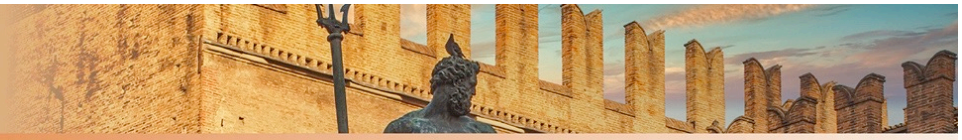
Dynamic biomarkers: ctDNA





Modified from Crowley et al. (2013) *Nat Rev Clin Oncol*

Keller et al. (2020) *Br J Cancer*



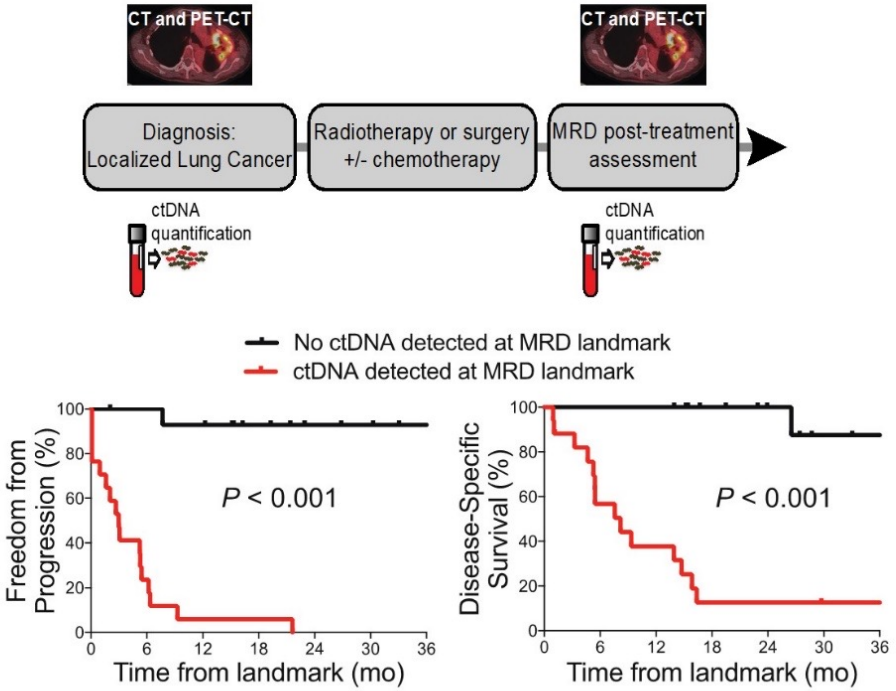
Retrospective ctDNA MRD Data From >240 NSCLC Patients

	N	Stage	Treatment(s)	ctDNA assay
Abbosh 2017	24	IA-IIIB	Surgery +/- chemo	Natera
Chaudhuri 2017	37	IB-IIIB	RT and/or surgery +/- chemo	CAPP-Seq
Chen 2019	25	I-III	Surgery +/- chemo	cSMART
Moding 2020	48	IIB-IIIB	chemoRT +/- immunotherapy	CAPP-Seq
Abbosh 2020	88	I-III	Surgery +/- chemo	ArcherDx
Zviran 2020	22	I-III	Surgery +/- chemo	MRDetect

All demonstrate strong prognostic power of ctDNA MRD in localized NSCLC

Abbosh et al. *Nature* 2017
Chaudhuri et al. *Cancer Discov* 2017
Chen et al. *Clin Cancer Res* 2019
Moding et al. *Nat Cancer* 2020
Abbosh et al. *AACR Annual Mtg* 2020
Zviran et al. *Nat Med.* 2020

ctDNA MRD Detection in Localized NSCLC

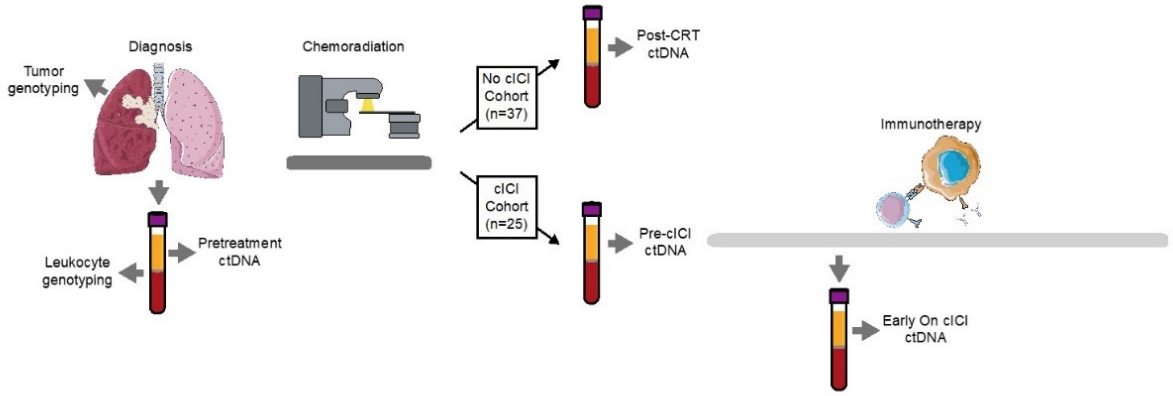


Chaudhuri et al *Cancer Discovery* 2017

Stanford MEDICINE

"*In silico*" Clinical Trial to Test Effect of Consolidation Immunotherapy in ctDNA MRD+ NSCLC

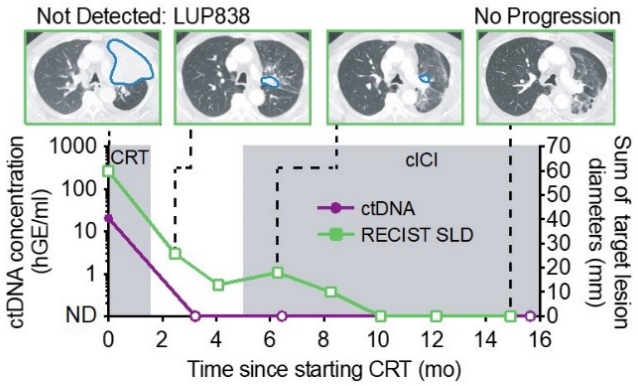
- Retrospective study of 62 patients with Stage III NSCLC
- *In silico* model of ctDNA-guided trial
- No differences in baseline characteristics between cohorts

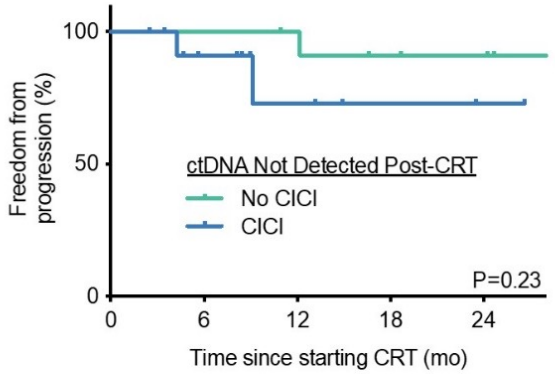


Collaborators: Steven Lin (MD Anderson), Heather Wakelee/Joel Neal (Stanford)

Stanford MEDICINE

Outcomes in Patients with Undetectable ctDNA After CRT

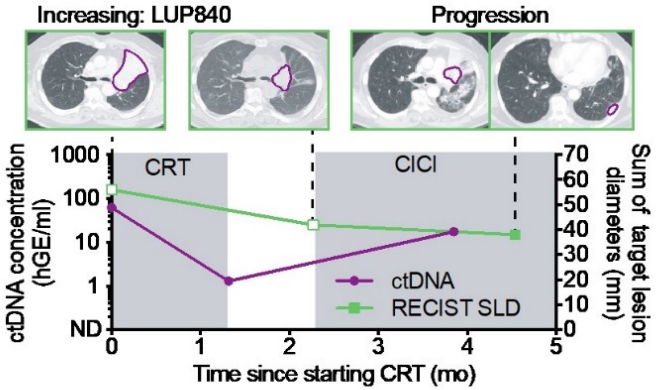


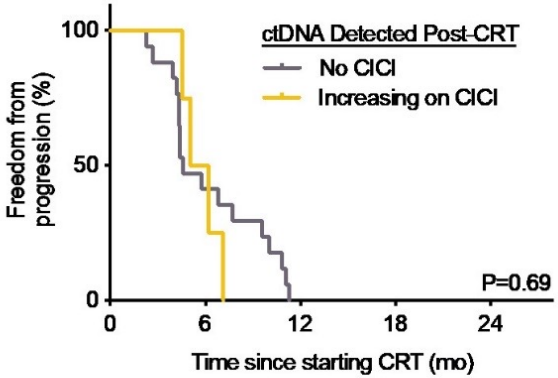


Assuming ~10% OS benefit for consolidation I/O, number needed to treat to benefit one ctDNA MRD-negative patient is >100

E. Moding et al. *Nature Cancer* 2020

Outcomes in Patients Without ctDNA Response During Consolidation ICI

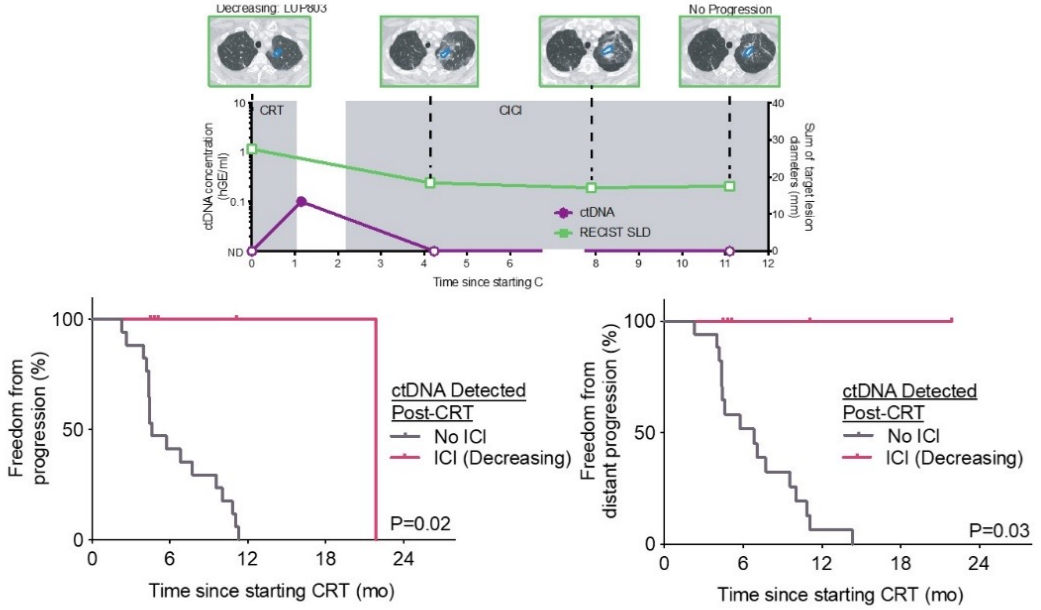




Lack of ctDNA response early during consolidation immunotherapy is associated with poor outcomes

E. Moding et al. *Nature Cancer* 2020

ctDNA Clearance During Consolidation ICI is Associated With Improved Outcomes



E. Moding et al. *Nature Cancer* 2020

Stanford MEDICINE

Dynamic Imaging Biomarkers

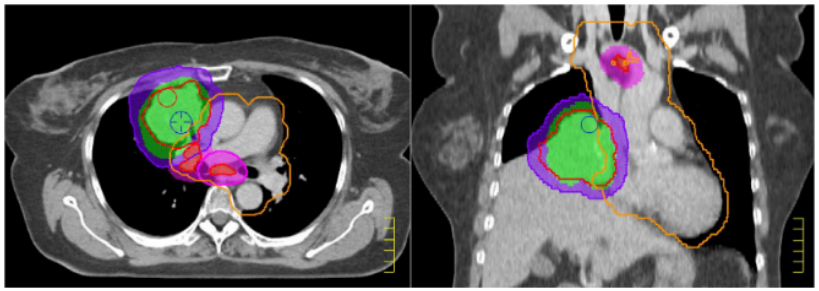
Imaging tumour metabolism and dose painting

Dose painting: selectively deliver dose to different parts of a tumour, i.e. higher doses to treatment-resistant areas, rather than escalating the dose to the whole tumour ("biologic target volume").

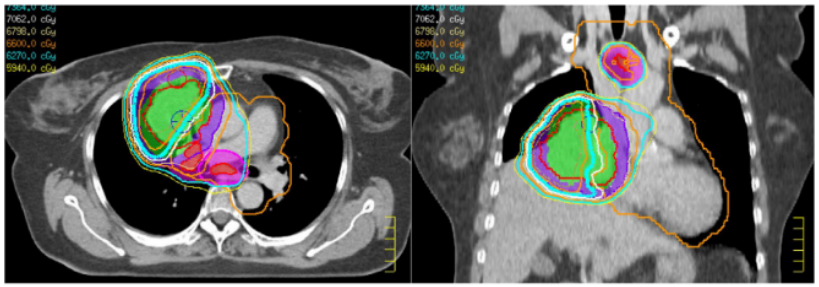
Areas of high pre-treatment 2-[$_{18}$F]FDG uptake within the primary tumour are considered to be more aggressive. Therefore, these areas may be considered the target for dose-escalation.

PET-boost trial (Netherlands, NCT01024829) showed the feasibility of dose-escalation using an integrated boost to the primary tumour or high FDG uptake regions (>50% SUVmax) whilst keeping the pre-defined dose constraints. The dose could be escalated to at least 72 Gy in 75% of patients, without increasing the dose to the OAR.

Van Diessen et al, 2018



A – Red=gross tumor volume; orange=PRV (mediastinal envelope + 5 mm margin); pink=planning target volume (PTV) of involved lymph nodes; green=PTV of FDG-avid regions (>50% SUV_{max}); purple=PTV of primary tumor.



B – Typical dose distribution of a patient treated with a high radiation dose to the whole primary tumor (homogeneous boost). The thick blue line represents the 95% isodose of the boost dose to the primary tumor; the thin blue line depicts the 95% isodose of 66 Gy to the involved lymph nodes. This example shows that a part of the PTV of the primary tumor overlaps with the mediastinal envelope. This part of the PTV is not escalated and receives the conventional dose of the mediastinal envelope.

Fig. 1. Example of treatment planning taking into account the mediastinal envelope.

Dynamic Imaging Biomarkers

Intermediate/mid-treatment 2-[18F]FDG PET/CT and adaptive RT: RTOG1106

Prospective phase 2 RTOG1106 trial:
LA NSCLC, dose escalation to persistent FDG avid tumour on mid-treatment FDG PET/CT (after 40 Gy)
Boost as SIB with daily-fraction size 2.2 to 3.8 Gy up to 80.4 Gy/30 fractions (median 71 Gy).

	R0617 Control Arm	R0617 High-dose Arm	R1106 Control Arm	R1106 Adaptive Arm
3-yr OS	44.5%	31.1%	49.1%	47.5%
3-yr Local-regional failure (institution reported)	47.1%	50.9%	30.0%	30.2%
2-yr In-field primary tumor local control (institution reported)	NS	NS	58.5%	75.6%
2-yr In-field local-regional control (institution reported)	NS	NS	55.6%	66.3%
Cardiac event Grade 3+ (crude %)	17.9%	19.8%	2.6%	1.3%
Pulmonary toxicity Grade 3+ (crude %)	20.6%	19.3%	14.3%	23.8%
Esophagitis Grade 3+ (crude %)	5.0%	17.4%	7.9%	3.8%

Kong et al, ASCO 2021

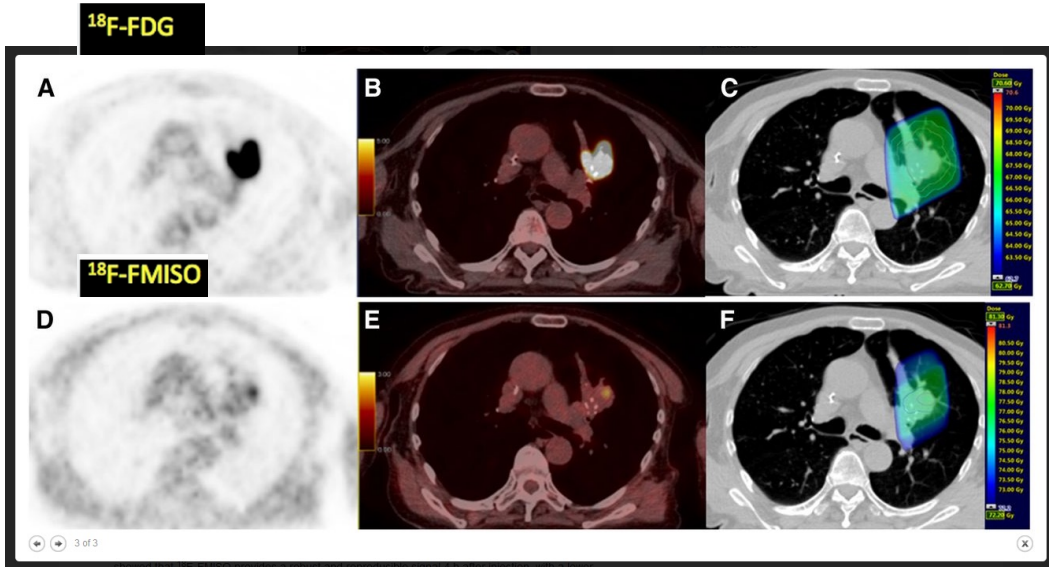
Dynamic Imaging Biomarkers

Other non-2-[18F]FDG radiopharmaceuticals

PET tracers other than 2-[18F]FDG have a potential role in imaging tumour biology and heterogeneity, through the evaluation of hypoxia, proliferation, and vascularization ([18F]FMISO, [18F]HX4 and [18F]FAZA).

A prospective phase II multicenter dose escalation study applying [18F]FMISO in NSCLC in hypoxic sub-volumes (RTEP5), showed the feasibility of escalating dose up to 86 Gy, without significant toxicity.

After 3 years of follow-up, the RT boost increased median OS by 11.2 months in [18F]FMISO-positive patients.



Vera et al, RTEP5 Study, 2017

Dose escalation to hypoxic subvolumes in head and neck cancer: A randomized phase II study using dynamic [18F]FMISO PET/CT

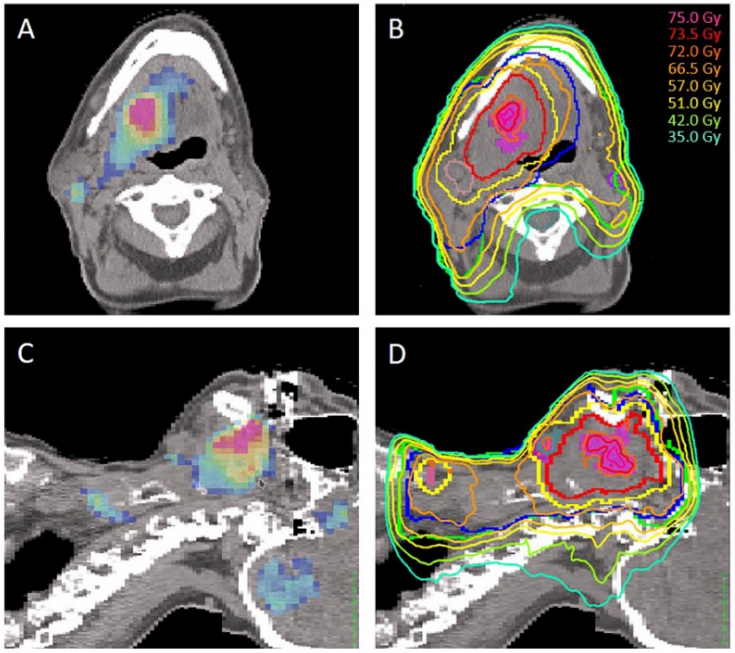


Fig. 2. Example patient (#041) in study arm C with dynFMISO based DE: (A, C) planning CT with FMISO PET (2 h pi). (B, D) planning CT with contours (GTV, red; lymph nodes, pink, skin, grey; PTV_{70Gy}, yellow; PTV_{60Gy}, blue; PTV_{54Gy}, light green; spinal cord, dark green; parotid gland left, purple) with HV overlaid in pink and isodose distribution of radiotherapy plan with dose escalation.

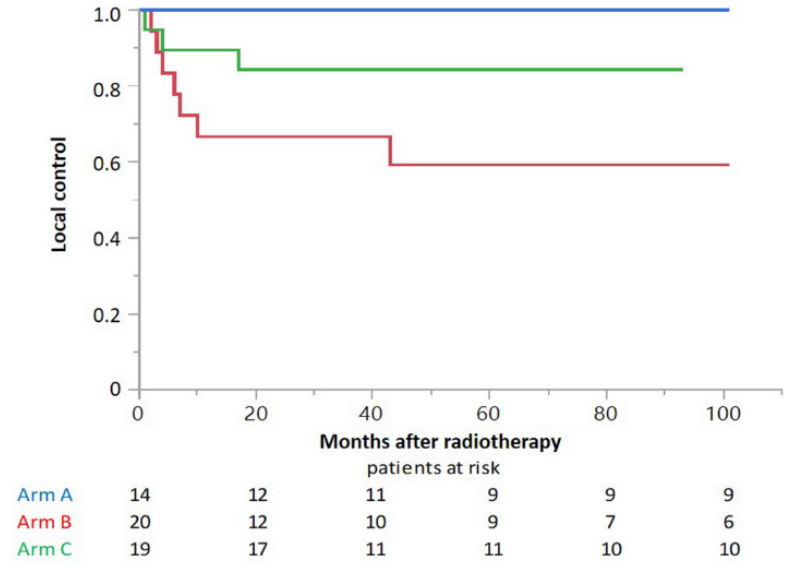
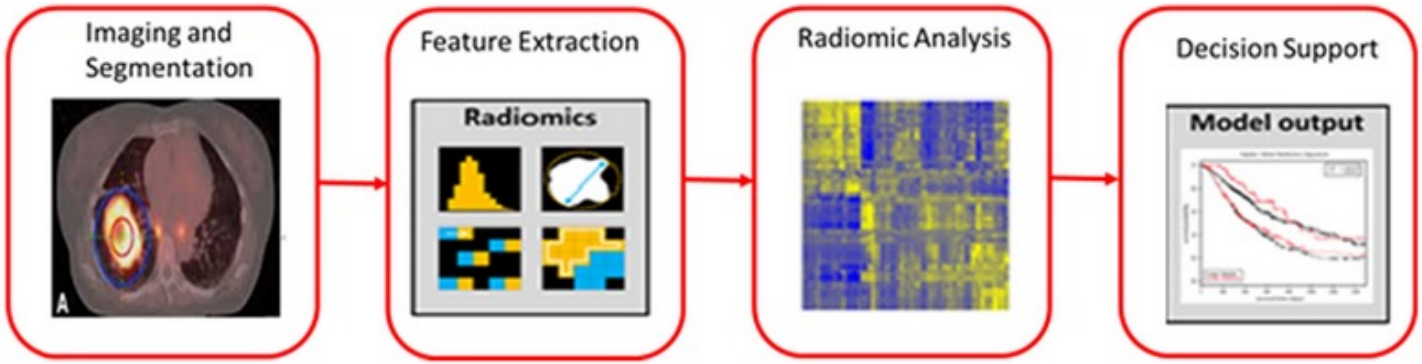


Fig. 3. Local control of the three study groups. Arm A: non-hypoxic (blue); arm B: hypoxic, ST (red); arm C: hypoxic, DE (green). Log-rank test for non-hypoxic (arm A) vs. hypoxic (arms B + C): p = 0.039. Log-rank test for study arms B (ST) vs. C (DE): p = 0.150.

Welz et al, Radiother Oncol 2022

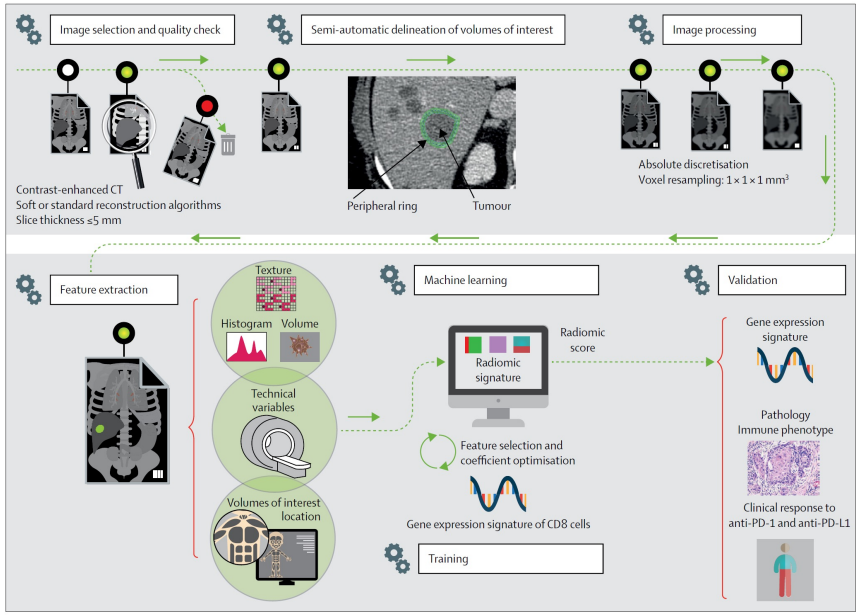
Radiomics/Radiogenomics Biomarkers

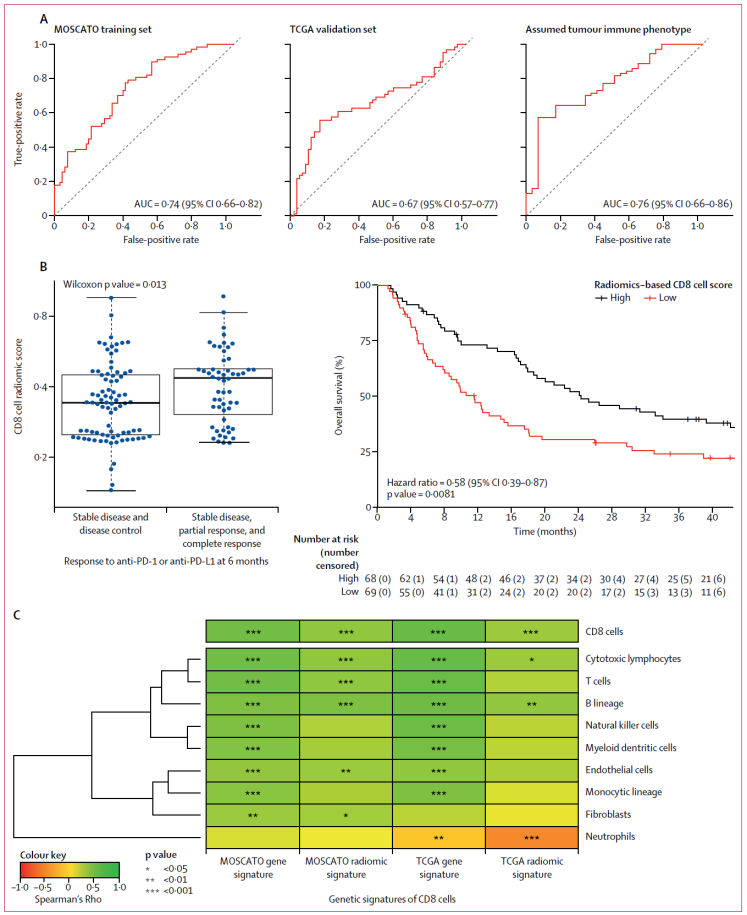


Extraction of a large number of quantitative features from medical images using advanced imaging processing and analysis tools.

PET and CT features were found predictive of local control in retrospective analyses for many tumour entities, e.g. lung and rectal cancer.

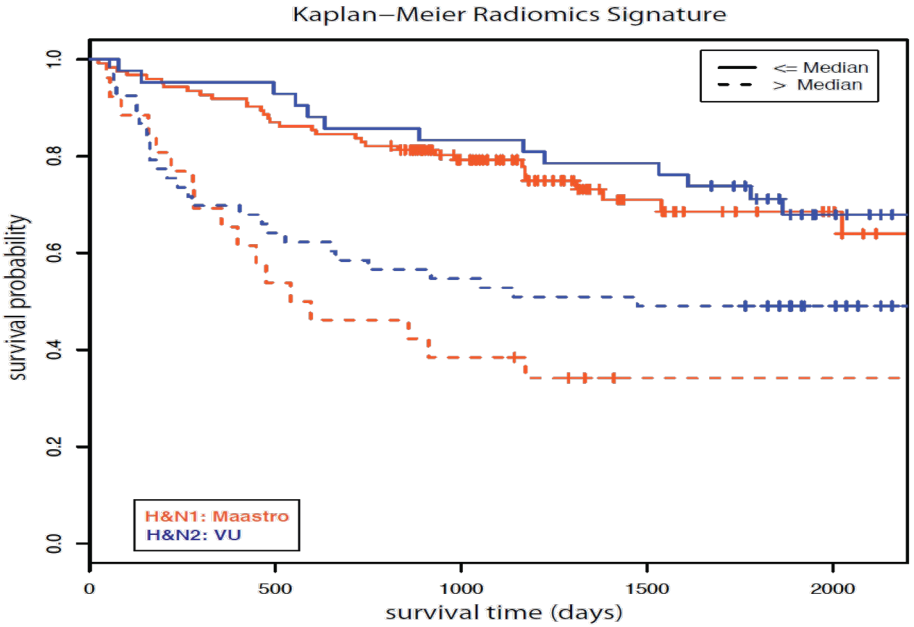
A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study





Sun et al. Lancet Oncol 2018

The exact same CT-based signature, trained in lung cancer, works in head & neck cancer



H&N1
Maastro HNSCC
n=136

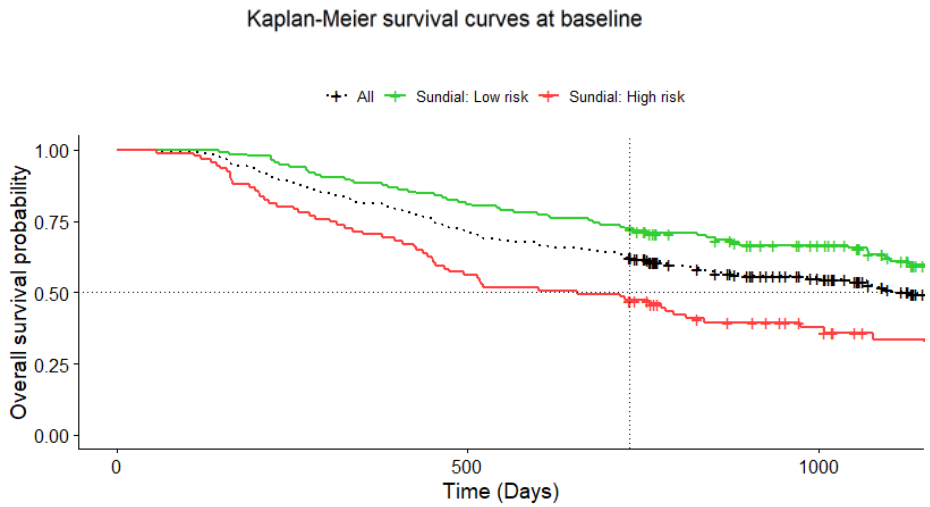
c-index = 0.69
(p-value= 7.99×10^{-07})

H&N2
VU Amsterdam
OPSCC
n=95

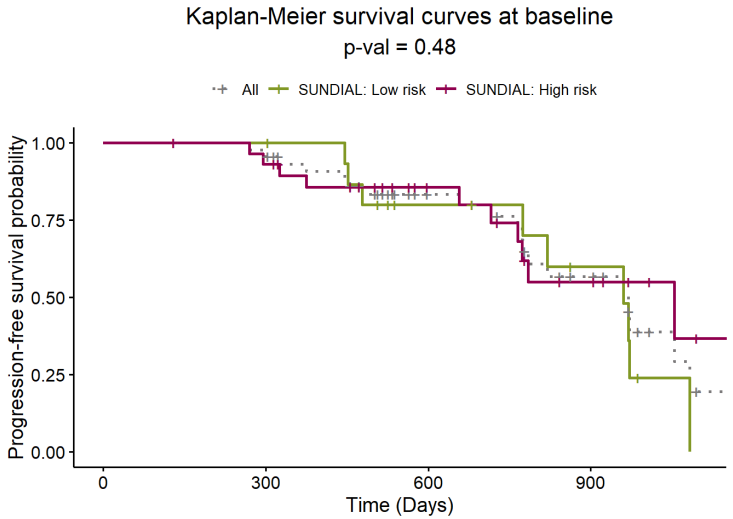
c-index = 0.69
(p-value= 3.53×10^{-06})

Aerts, Lambin et al. Nat. Commun. 2014; Leijenaar et al, Acta Oncologica 2015

Results of applying SUNDIAL in the BlueSky Radiomic Study



SUNDIAL cohort



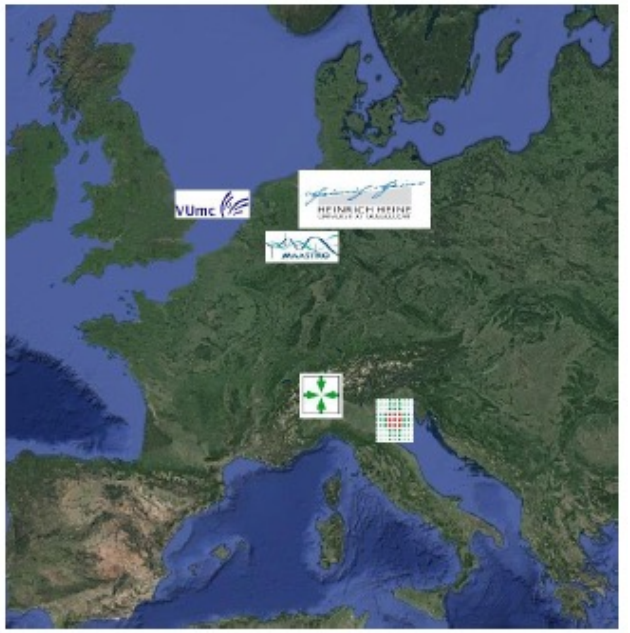
BlueSky cohort

The application of the SUNDIAL radiomics signature in the BlueSky cohort did not statistically significantly separate patients classified with different prognosis (unresectable stage 3 receiving CRT plus durvalumab)

Filippi et al, poster@ELCC22

H&N: BD2Decide study

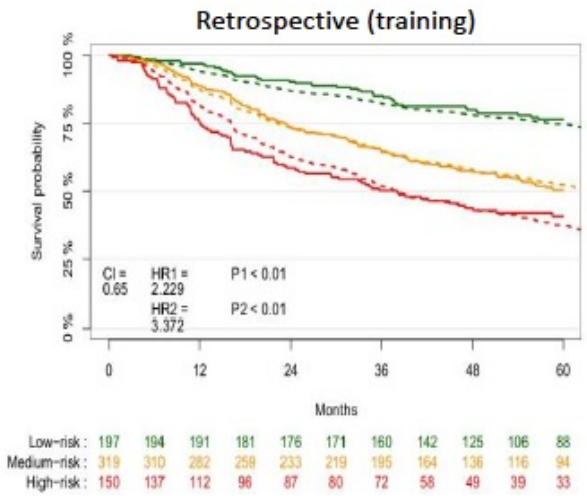
- Multicentric European clinical trial
- Advanced HN cancer patients (Stage III-IVB HPV- and +)
- Includes CT imaging, Clinical, and biological data
- Multiple outcomes (OS, PFS, DM)
- Retrospective + prospective cohort

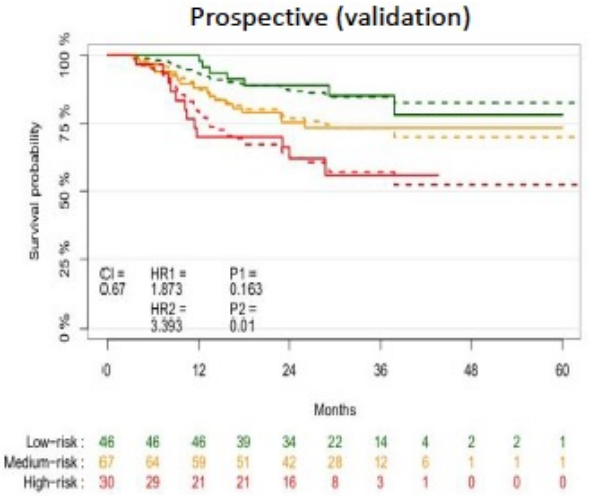


BD2DECIDE

Keek *et al* Cancers 2021 doi: 10.3390/cancers13133271.

Radiomics result

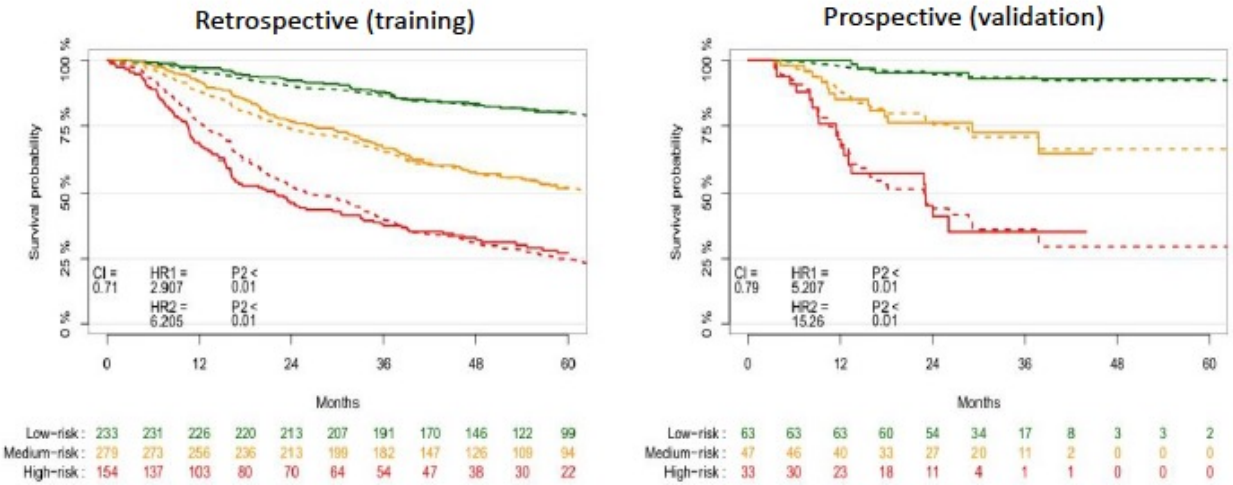




Radiomics feature
log.sigma.5.0.mm.3D_glszm_GrayLevelNonUniformity
wavelet.HLH_glszm_ZoneEntropy
wavelet.HLL_glszm_ZoneEntropy
wavelet.LLH_glszm_ZoneEntropy
original_shape_Sphericity
log.sigma.4.0.mm.3D_gldm_DependenceEntropy
wavelet.HHH_glrlm_LowGrayLevelRunEmphasis
wavelet.HHL_glszm_ZoneEntropy
log.sigma.5.0.mm.3D_gldm_LowGrayLevelEmphasis
original_firstorder_Kurtosis
log.sigma.2.0.mm.3D_glrlm_RunEntropy

Keek *et al* Cancers 2021 doi: 10.3390/cancers13133271.

Multiomics result



Radiomics feature
log.sigma.5.0.mm.3D_glszm_GrayLevelNonUniformity
wavelet.HLH_glszm_ZoneEntropy
wavelet.HLL_glszm_ZoneEntropy
wavelet.LLH_glszm_ZoneEntropy
original_shape_Sphericity
log.sigma.4.0.mm.3D_gldm_DependenceEntropy
wavelet.HHH_girlm_LowGrayLevelRunEmphasis
wavelet.HHL_glszm_ZoneEntropy
log.sigma.5.0.mm.3D_gldm_LowGrayLevelEmphasis
original_firstorder_Kurtosis
log.sigma.2.0.mm.3D_girlm_RunEntropy

Clinical/Biological features
TNM8
Age
ACE-27 comorbidity score
Pack years
Alcohol at diagnosis
P16-status
Haemoglobin level

Keek *et al* Cancers 2021 doi: 10.3390/cancers13133271.

Final remarks

- Currently, there are no biomarkers predictive of radiosensitivity or radiotherapy benefit used as standard of care.
- A few on the horizon show promise, especially when different approaches are combined.
- We need prospective to validate biomarkers-based strategies: GARD is one of the most advanced in application, as researchers at Lee Moffitt are starting a GARD-based study for deintensification in HPV-pos H&N and a second for guiding the use of RT boost in TNBC.
- Most of the radiomics studies are prognostic, and not prospectively validated; however, high-quality efforts are ongoing in the field.
- As RT is such a commonly utilized form of cancer therapy, identifying and validating biomarkers would have the potential to improve outcomes for a very large number of patients across different cancer types, with a huge effect on oncology practice.