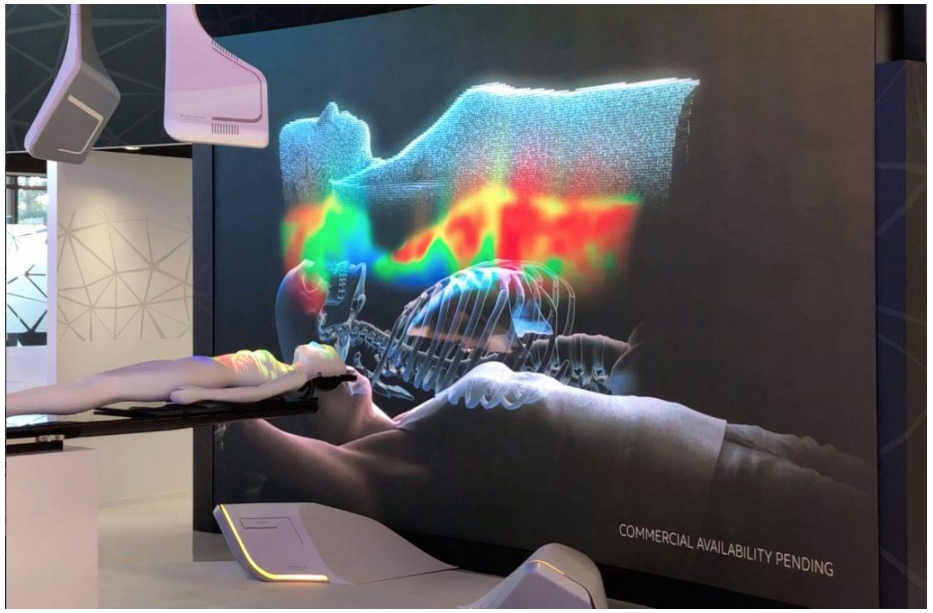


Kasvajate kiiritusravi

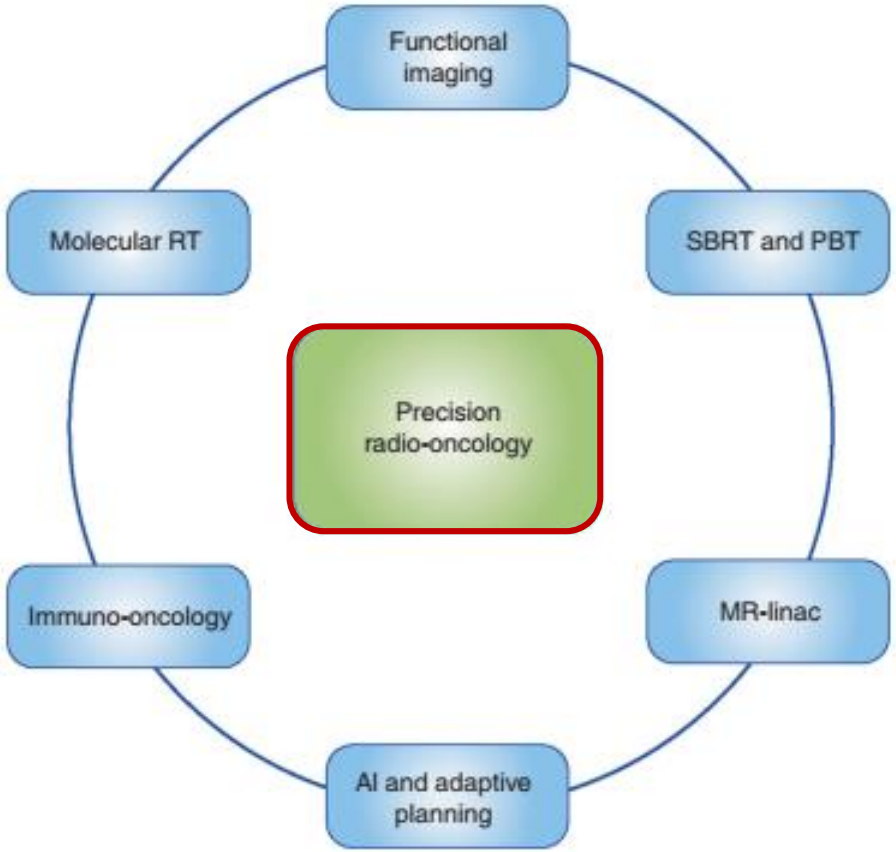
Maire Kuddu; SA PERH kiiritusravi keskus

13.09.2019

sissejuhatus

- Kiiritusravi on edukas vähiravi meetod olnud enam kui 100 aastat
- 50-60 % vähihaigetest saab kiiritusravi (RT) kas ainsa ravimeetodina või kombineerituna kirurgilise ja/või süsteem-ja immuunraviga
- Kirurgilise ravi kõrval teine oluline tervistav raviviis onkoloogias
- Näidustatud praktiliselt kõigi (sh enamlevinud) vähipaikmete ravis (k.a. healoomulised kasvajad, mittekasvajalised haigused)
- Kuratiivne ehk tervistav, (neo)adjuvantne ja palliatiivne näidustus
- Kulutõhusaim vähiravi meetod

Täppiskiiritusravi olevik/tulevik



- Füüsikal ja kuvastusel põhinev
- Bioloogiliselt/panoomiliselt suunatud

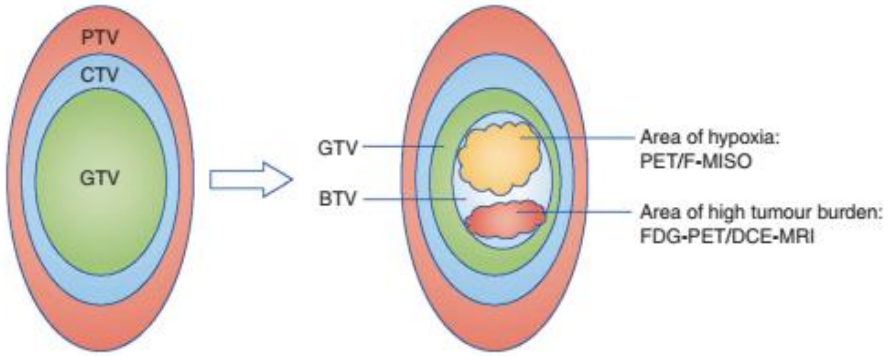
- Kaasaegne tehnoloogia
- Funktsionaalne kuvamine – **BTV***
- Bioloogiline RT doosi optimeerimine
- TI* assisteeritud adaptiivne RT planeerimine
- Immuunmodulaatorid + RT
- Bioloogiliselt sihtmärgistatud radiofarmatseutikumid

British Journal of Cancer (2019) 120:779–790;

BTV- *Biological Target Volume*
TI- tehisintellekt

Kuvamine kiiritusravis

- Sihtmahu määratlemine
- Organite ja sihtmahu liikumine
- Liikumise kontroll
- Sihtmahu ja organite mahuline muutumine RT ajal
- Sihtmahu kohaldamine RT ajal
- Adaptiivne raviplaan
- Ravivastuse hindamine



REVIEW ARTICLE

How rapid advances in imaging are defining the future of precision radiation oncology

Laura Beaton[1], Steve Bandula[1,2], Mark N. Gaze[2] and Ricky A. Sharma[1,2]

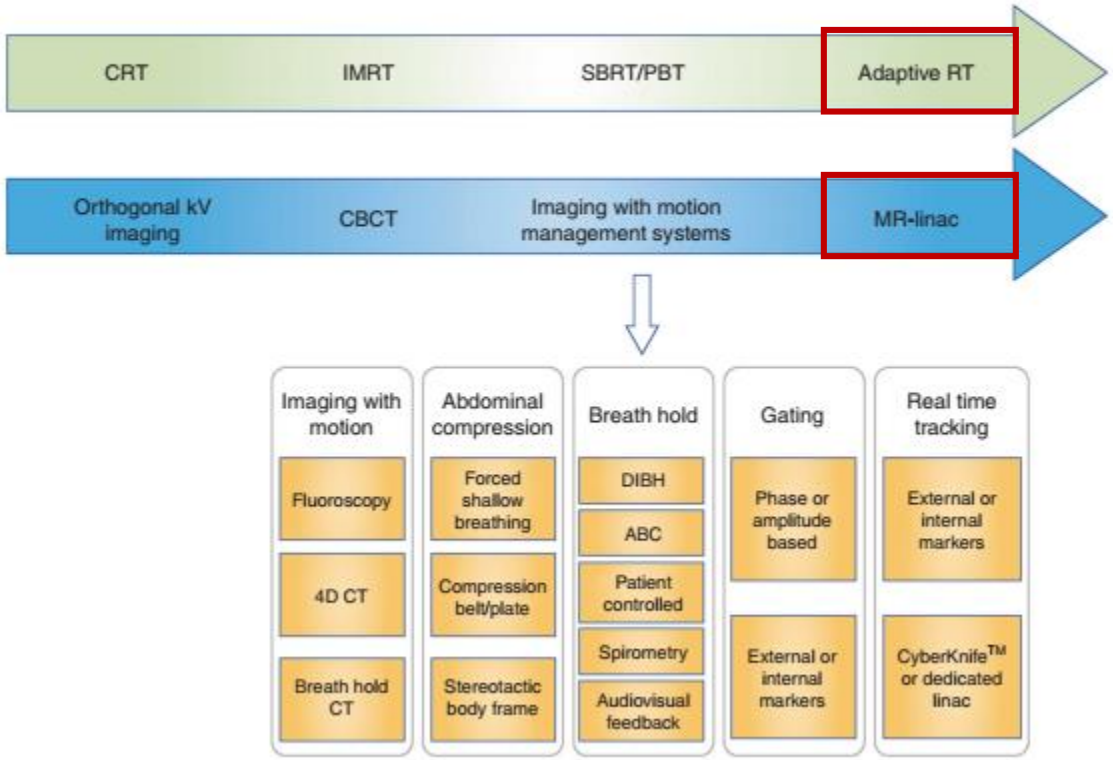
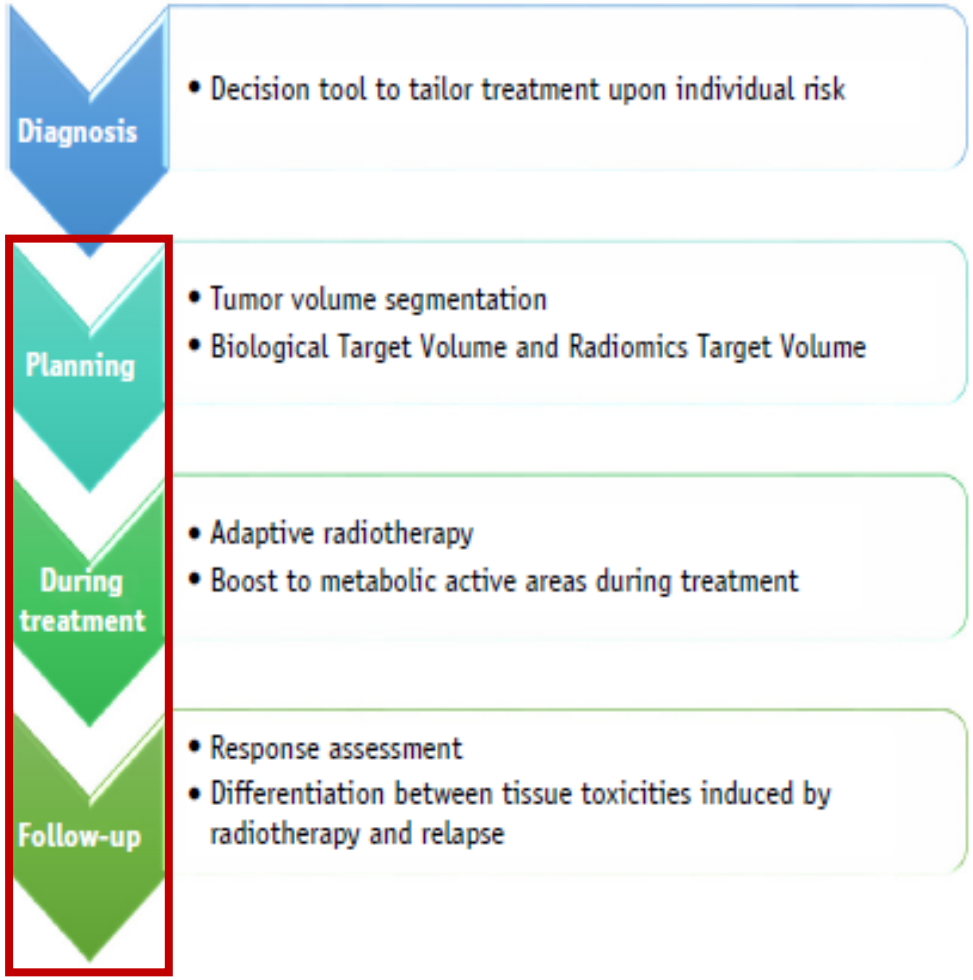


Fig. 3 Overview of advances in radiotherapy techniques and image-guided radiotherapy (IGRT) over time. Recent advances in imaging

British Journal of Cancer (2019) 120:779–790;

Applications of PET-based Radiomics in Radiation Oncology



Radiomics is a promising research area based on mapping multimodal imaging onto quantitative data and subsequent predictive model building to personalize decision making

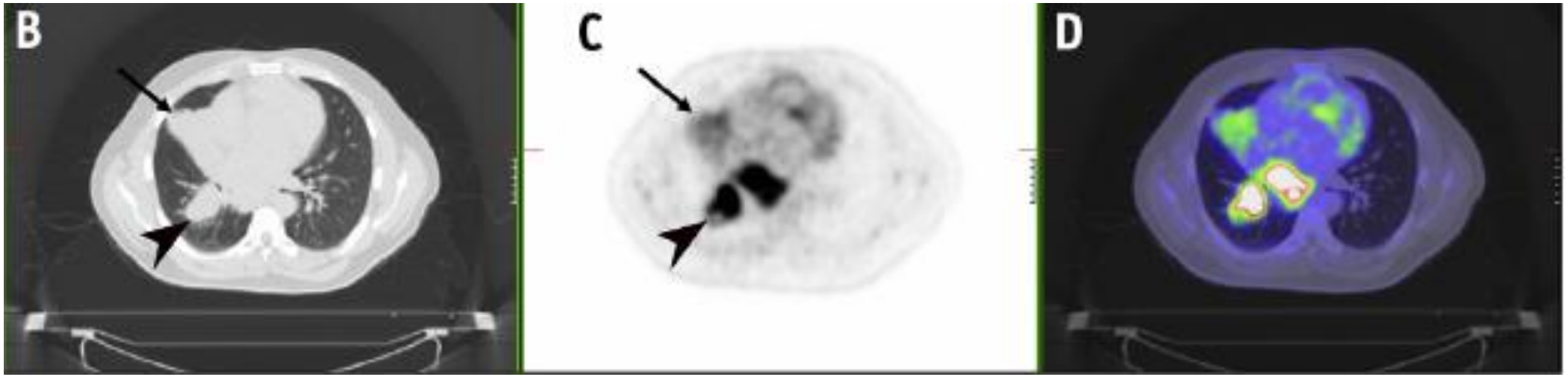
Fig. 1. Main applications of radiomics in the context of radiation oncology.

Reuzé et al. Int J Radiation Oncol Biol Phys, Vol. 102, No. 4, pp. 1117–1142, 2018

PET kiiritusravi planeerimisel

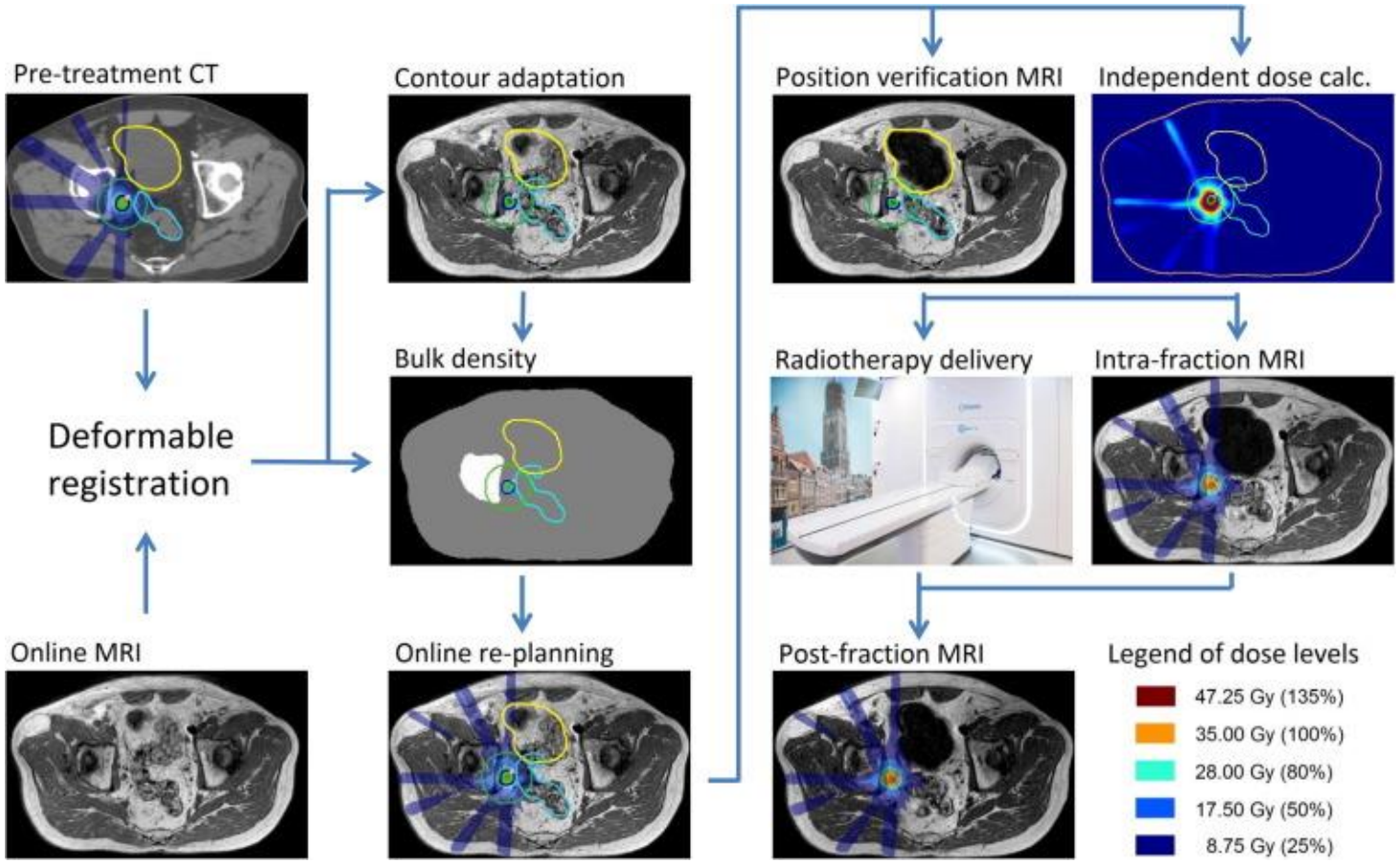
Table 1 Non-FDG PET radiopharmaceuticals used in oncology

Tracer	Radiopharmaceutical	Tumor biology detected	Clinical cancer application
FDG	^{18}F	Glucose metabolism	All tumor types; RT planning
PMSA	^{68}G	Prostate cell membranes	Prostate cancer; RT planning
DCFPyl	^{18}F	Prostate cell membranes	Prostate cancer; RT planning
FAZA	^{18}F	Hypoxia	HN cancer, lung cancer, RT planning
FMISO	^{18}F	Hypoxia	HN cancer, lung cancer, RT planning
Cu-ATSM	^{64}Cu	Hypoxia	HN cancer, lung cancer, RT planning



McKay et al. Int J Radiation Oncol Biol Phys, Vol. 102, No. 4, pp. 783–791, 2018

MRT kiirendi

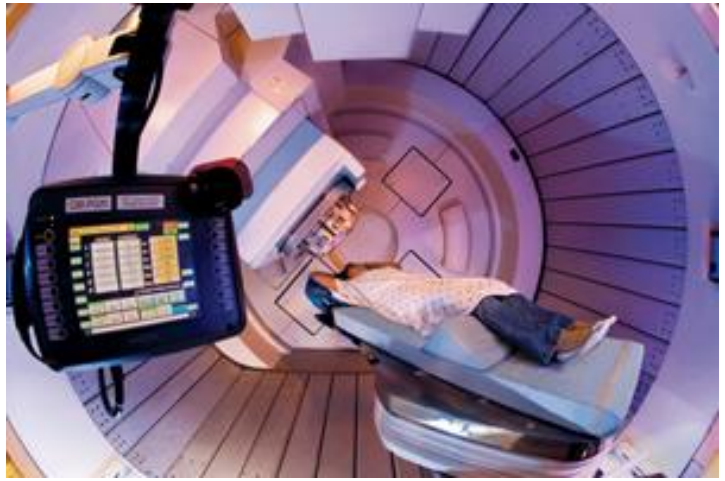


D. Winkel et al./Clinical and Translational Radiation Oncology 18 (2019)

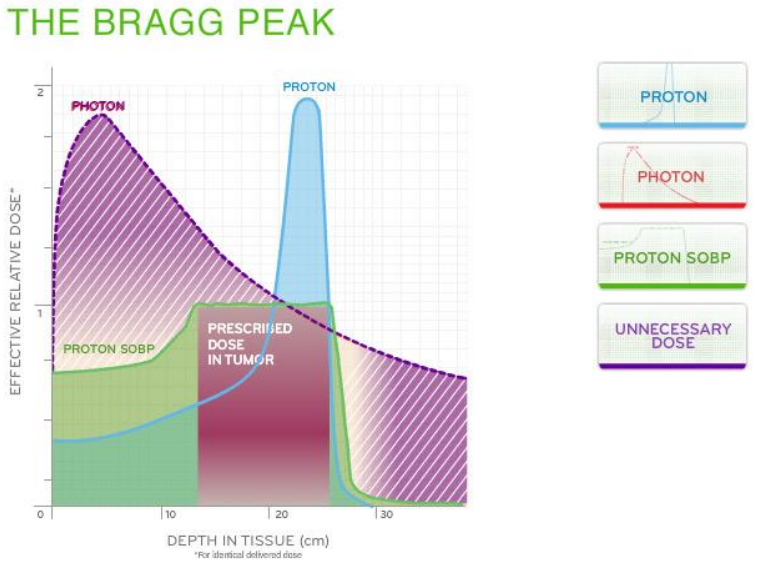
Kliiniline kasu:

- Kudede eristavus, **täpsem sihtmaht**
- **hüpoFx*** suurema doosiga RT (LC, OS)
- vähendada **TV (sihtmaht) piire**
- kontrollida liikumist reaalajas
- ohutum korduv kiiritusravi
- ***on-board* funktsionaalne kuvamine**
- **lokaalne *boost*** resistentsetele aladele
- personaliseeritud **inhomogeenne doosijaotus**
- **Reaalajas adaptiivne RT**

*hüpoFx- hüpofraktsioneeritud; vähem raviseansse
Boost- täiendav ravidoos



PROOTONRAVI



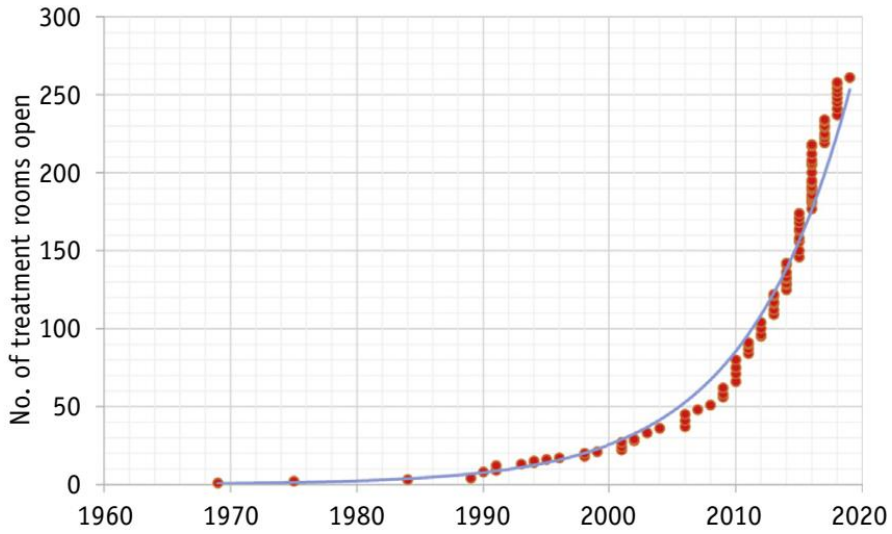
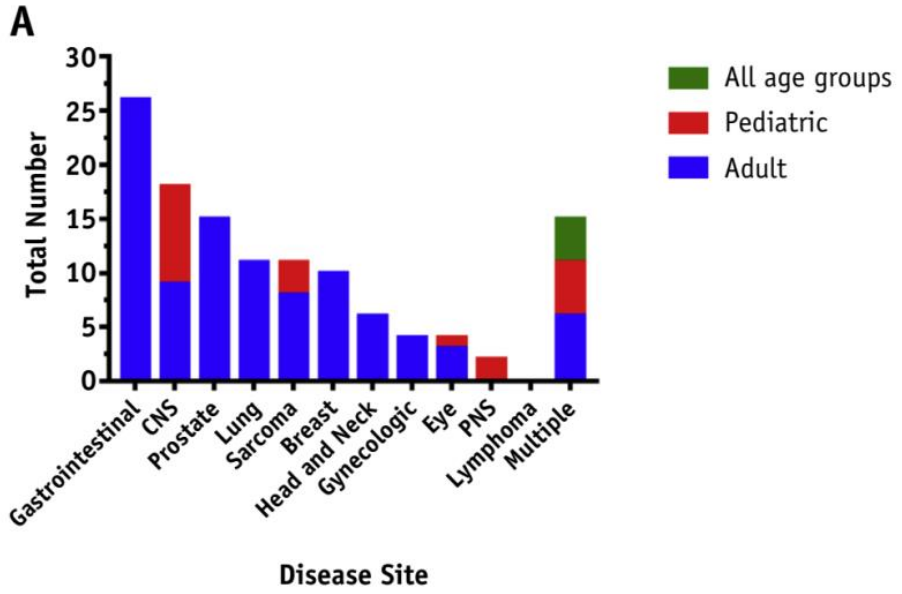


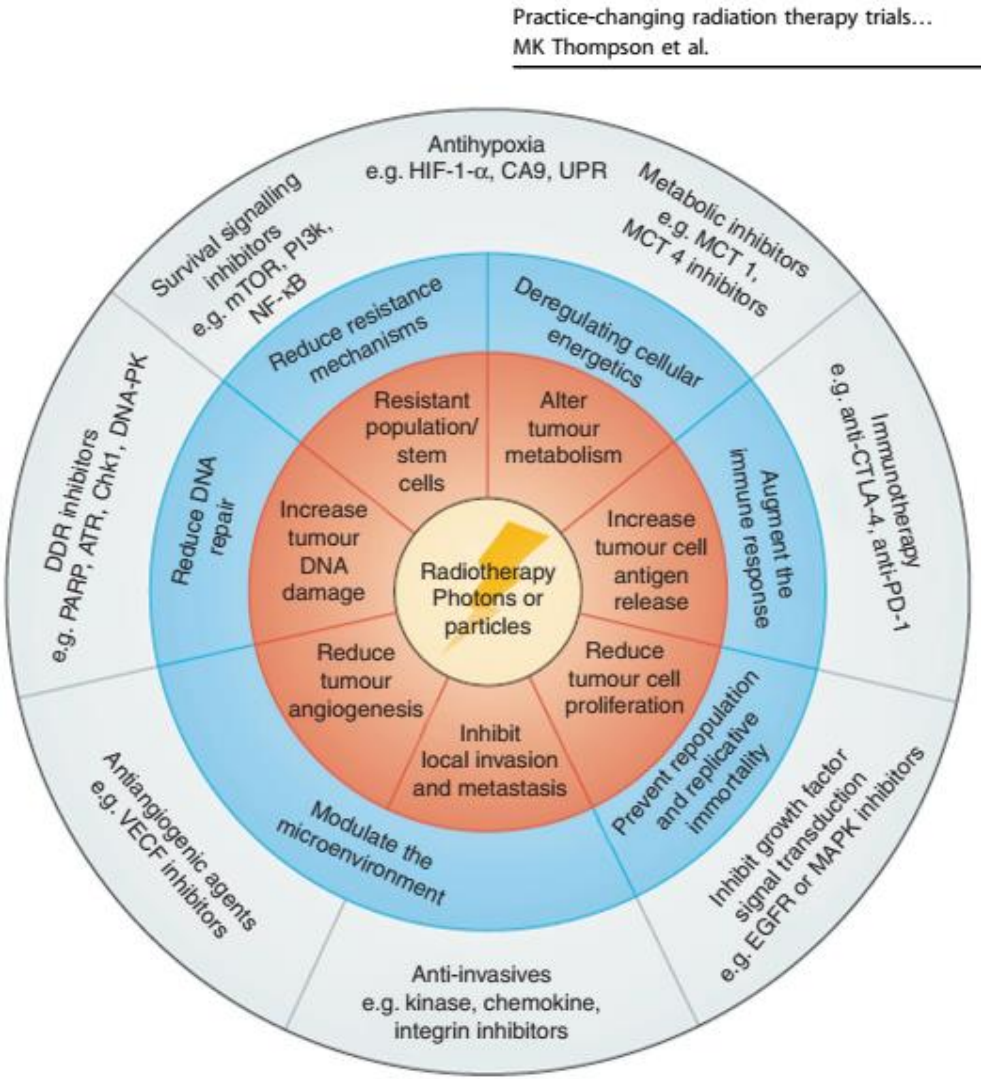
Fig. 5. Number of operating proton beam therapy rooms worldwide, 1970–present.

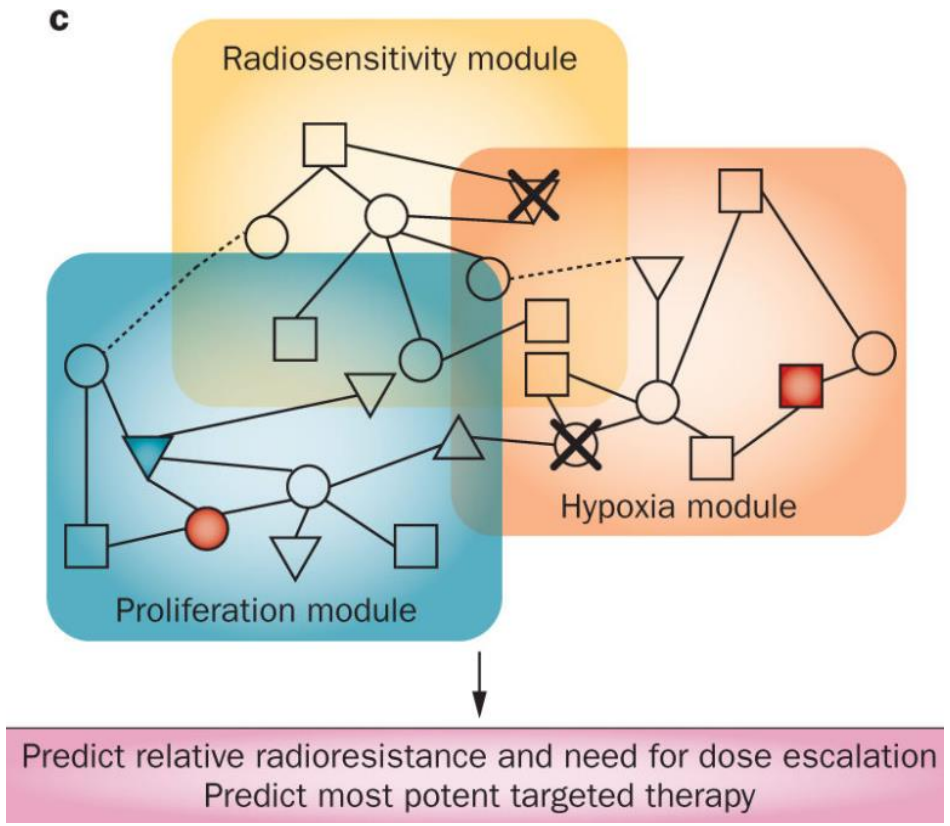


Proton beam therapy clinical trials

Mishra et al. International Journal of Radiation Oncology 2017

Genoomiliselt/panoomiliselt juhitud RT





Lambin et al.

Table 1 Existing data for personalization of radiation therapy treatment recommendations

Metric	Summary of applicability to personalized radiation therapy	Reference(s)
Genomically guided personalization methods		
Radiation Sensitivity Index	Multigene expression model based on the expression of 10 genes identified by the systems biology model of radiation sensitivity.	(16-19)
DCIS score	Association of 7 cancer-related genes and 5 reference genes with the risk of developing an ipsilateral breast event, found to complement existing clinical metrics prognostic for ipsilateral breast event.	(21)
Prolaris	Measurement of gene expression involved with cell cycle progression; score has been shown to be prognostic of death from prostate cancer and biochemical recurrence after treatment with radiation therapy.	(22, 23)
RadiotypeDX	Gene expression across radiation-resistant and -sensitive cell lines was identified to generate a radiation sensitivity signature.	(48)
Decipher	RNA biomarkers can help to identify patients at higher risk for distant metastatic disease.	(24)
PORTOS	RNA signature that predicts benefit from postprostatectomy radiation therapy.	(25)
GARD score	Genomically adjusted radiation dose, provides the ability to genomically adjust dose of radiation according to intrinsic susceptiabilty to radiation therapy-induced damage.	(20)
Single-nucleotide polymorphisms (SNPs)	Candidate SNPs have been identified that may be helpful in predicting radiosensitivity.	(31-33)
Genomic alterations in individual tumor genes	Mutations in genes such as *KRAS*, *NRF2*, and *KEAP1* may predict resistance to radiation therapy.	(26-28)
Tumor radiologic and pathologic metrics to personalize radiation therapy		
Tumor hypoxia	The presence of hypoxia in tumors is well known to correlate with poor response to radiation therapy. There are 15-gene and 26-gene hypoxia signatures being tested in clinical trials.	(36-40, 49, 50)
Human papillomavirus (HPV) positivity	HPV positivity has been shown to correlate with improved response to radiation therapy.	(47, 51)
Normal tissue metrics enabling radiation therapy response prediction		
Radiogenomics	Field identifying genetic variants predominantly associated with normal tissue responses to radiation therapy with possibility to enable radiation oncologists to predict which patients may develop normal tissue toxicity, but the field is also applicable to tumor outcomes.	(52-57)

Abbreviation: DCIS = ductal carcinoma in situ.

The future of personalised radiotherapy for head and neck cancer

Jimmy J Caudell, Javier F Torres-Roca, Robert J Gillies, Heiko Enderling, Sungjune Kim, Anupam Rishi, Eduardo G Moros, Louis B Harrison

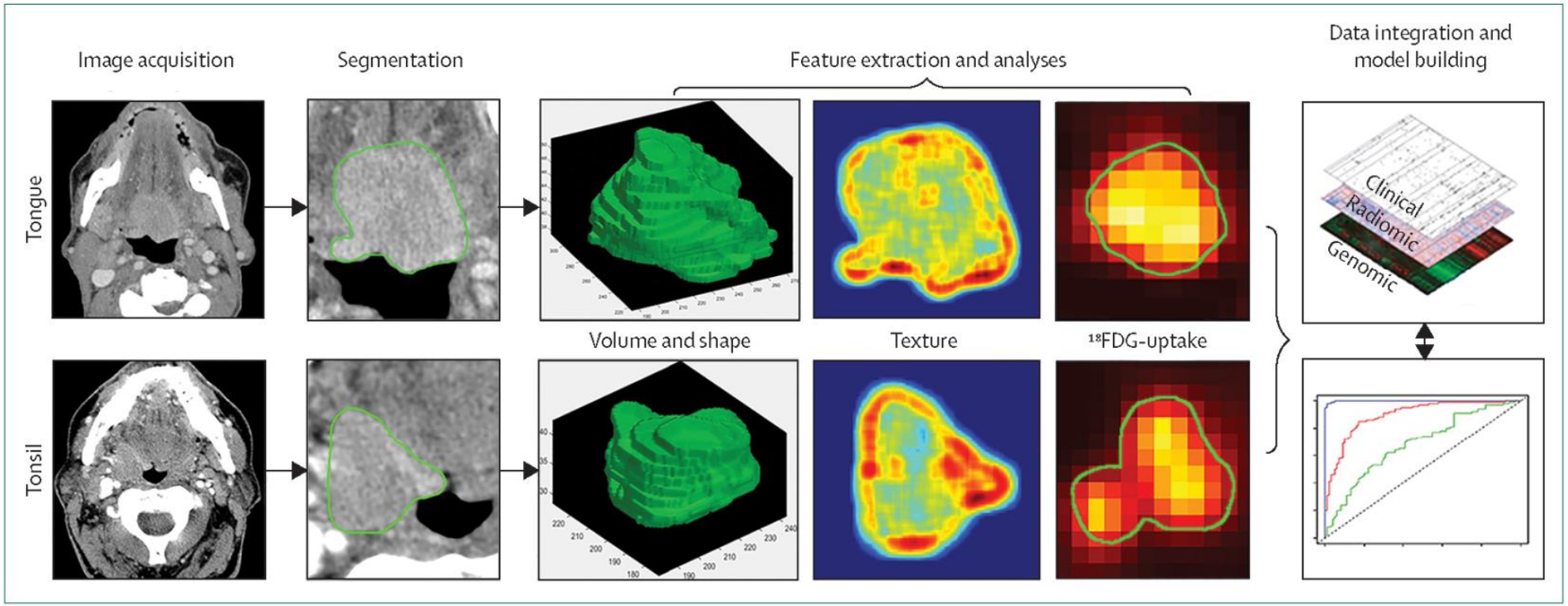
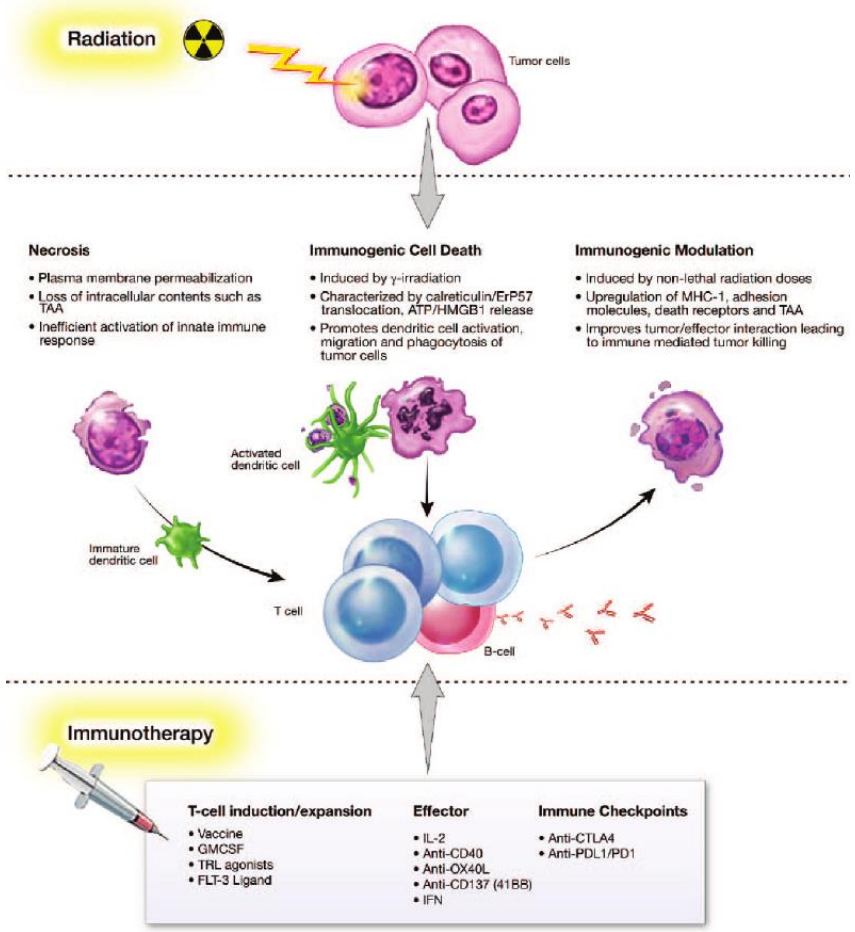


***Figure 2*: Radiomic process in two patients with squamous cell carcinoma of the base of tongue and tonsil treated with definitive radiotherapy**
Standard of care images are used for tumour delineation (segmentation) creating a volume of interest (third column). Quantitative features are then extracted from the volume of interest. The fourth column shows Hounsfield units heterogeneity and the fifth column shows standard uptake values, revealing significant intratumoural heterogeneity. These features can later be combined with clinical and genomic data to generate a predictive model (or decision support system) to guide therapy personalisation.

Lancet Oncol 2017; 18: e266–73

IMMUNO(RADIO)ONKOLOOGIA



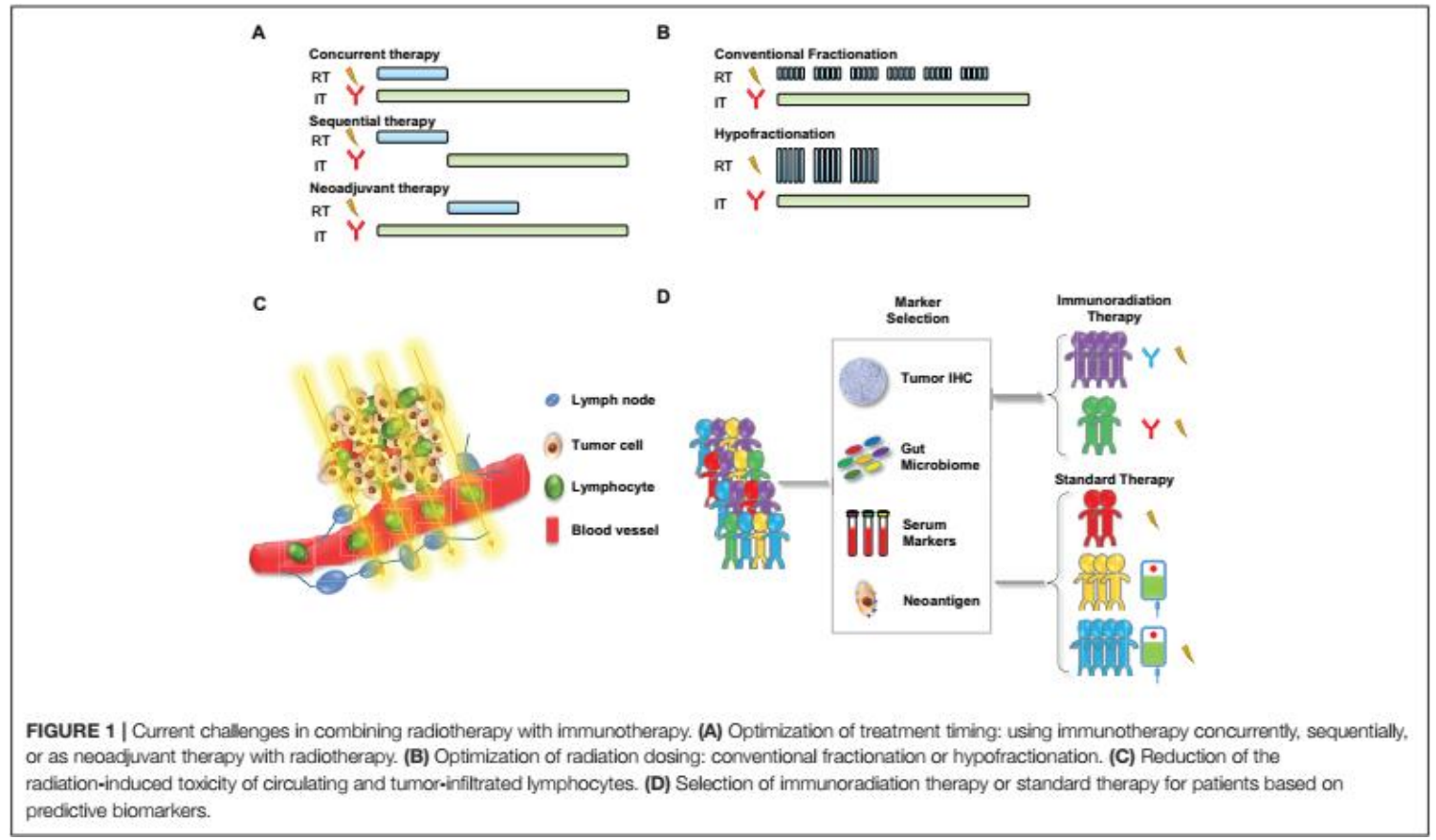


FIGURE 1 | Current challenges in combining radiotherapy with immunotherapy. **(A)** Optimization of treatment timing: using immunotherapy concurrently, sequentially, or as neoadjuvant therapy with radiotherapy. **(B)** Optimization of radiation dosing: conventional fractionation or hypofractionation. **(C)** Reduction of the radiation-induced toxicity of circulating and tumor-infiltrated lymphocytes. **(D)** Selection of immunoradiation therapy or standard therapy for patients based on predictive biomarkers.

SBRT (stereotaktiline keha kiiritusravi) oligometastaatilistele kasvajatele

- Oligomts- 1-3; 1-5
- Eesmärk parandada LC; PFS ja OS, QoL
- Kõrvaltoimeid vähe
- Mitteinvasiivne alternatiiv operatsioonile

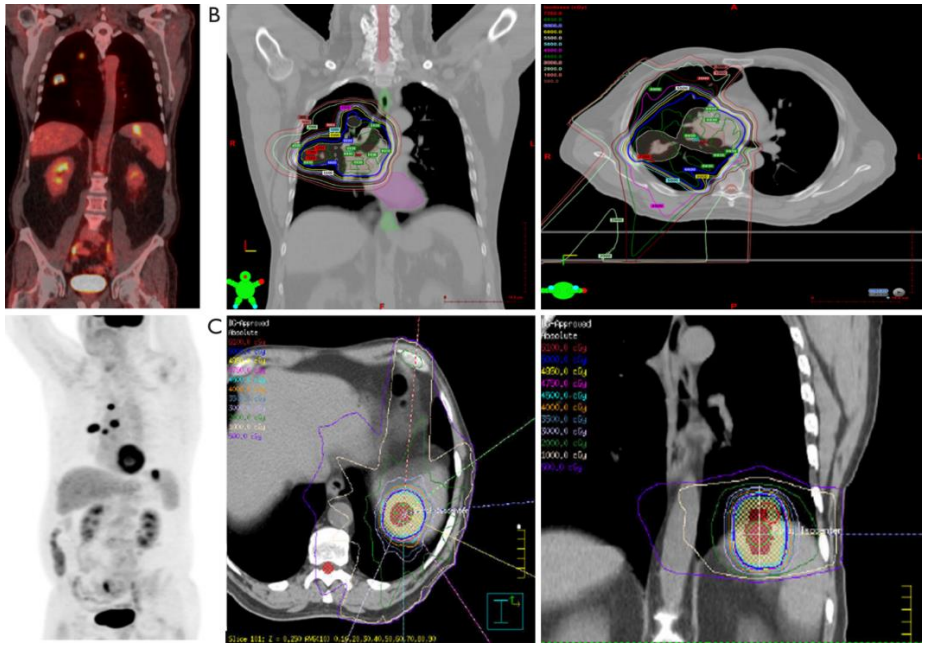


Table 1 Selected open trials of SABR for oligometastasis.

Name	Primary	No. of Mets	Treatments	Prior Treatment	Endpoint
SABR-COMET	NSCLC	≤5	SABR to all sites of disease vs. SOC	CT ≥ 4 weeks prior	OS
SARON-trial	NSCLC	≤3	SOC + conventional RT + SABR vs. Chemo	None	OS
STOMP	Prostate	≤3	Metastasis-directed therapy (surgery/SABR) vs. active surveillance	Surgery/RT or both	ADT-free survival
CORE	NSCLC, breast, prostate	≤3	SOC + SABR vs. SOC	CT ≥ 4–6 months prior	PFS
NRG BR002	Breast	≤2	SOC + SABR or surgery vs. SOC	≤6 months first-line CT	PFS, OS
NRG-LU002	NSCLC	≤3	Local consolidative therapy (SABR) + MT vs. MT alone	CT (at least 4 cycles)	PFS, OS

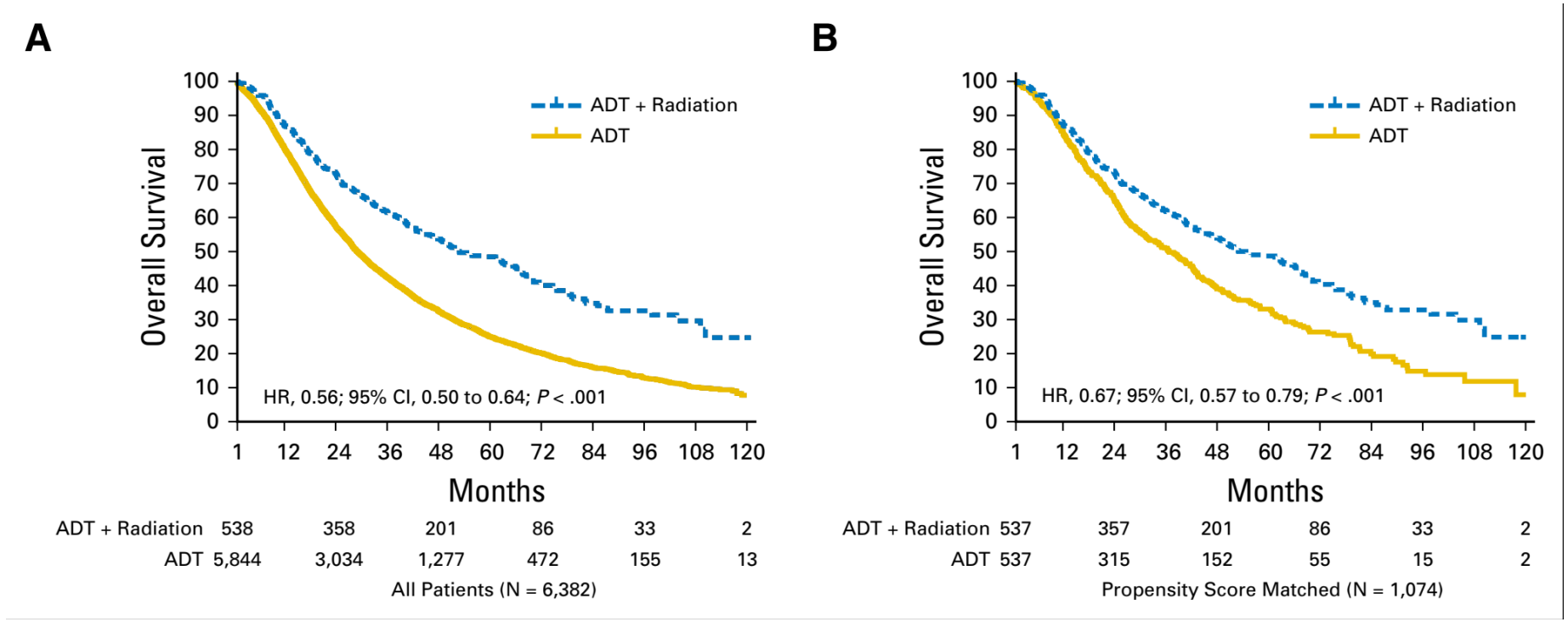
Mets: metastases, NSCLC: non-small cell lung cancer, SABR: stereotactic ablative radiotherapy, SOC: standard of care, CT: chemotherapy, RT: radiotherapy, OS: overall survival, PFS: progression-free survival, ADT: androgen deprivation therapy.

Cancers **2019**.

Table 2. Major prognostic factors for patients with oligometastatic cancers evident across multiple studies, colloquially termed the "four aces"

Prognostic factor	Common definitions
Young age	Usually defined as <65 or <70, or analyzed as a continuous variable
Patient fitness	Karnofsky performance status ≥70
Slow-growing cancers	Metachronous presentation of oligometastases
	Longer disease-free interval between original tumor and development of metastases
Minimal disease burden	Presence of fewer metastatic sites
	Single-organ oligometastases
	Lack of extracranial disease

Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer



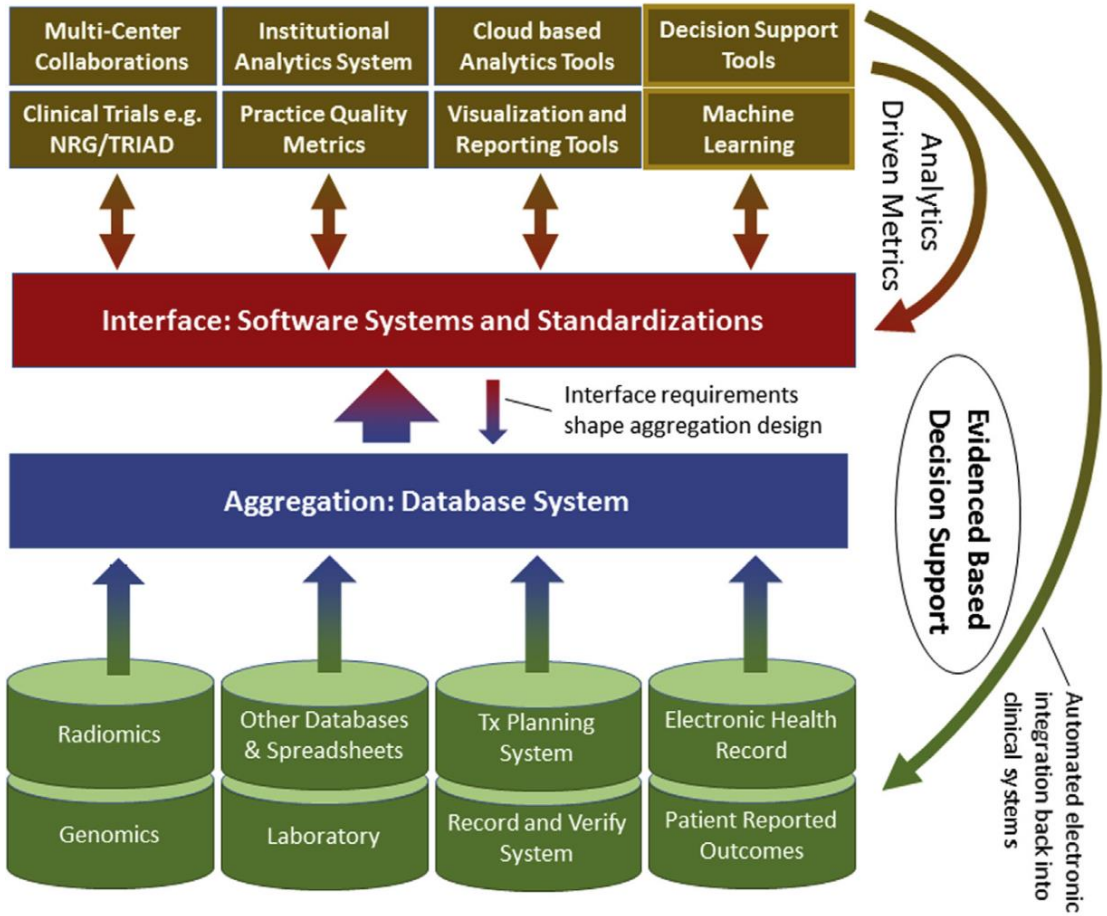
Rusthoven et al *J Clin Oncol 34:2835-2842. © 2016*

Critical Review

The big data effort in radiation oncology: Data mining or data farming?

Charles S. Mayo PhD [a,*], Marc L. Kessler PhD [a],

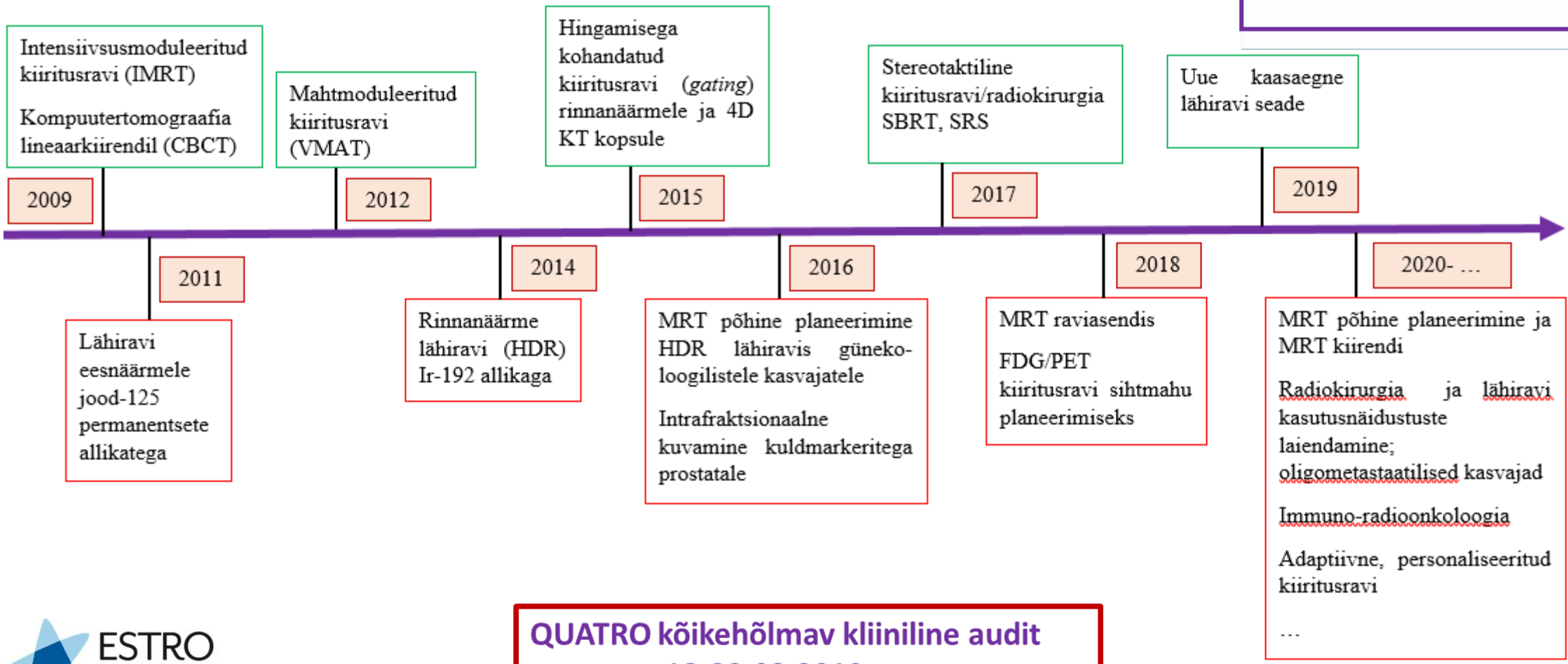
1. **Andmete standardiseerimine/struktureerimine**
2. IT infrastruktuur toetamaks andmevahetust, andmete taaskasutust, raviotsust (**TI , masin-ja süvaaõpe**)
3. RT protsesside **automatiseerimine**
4. Ravivastust ja prognoosi ennustavad mudelid- **CDSS***, integreerida kuvamise, molekulaarsed ja kliinilised andmed



Advances in Radiation Oncology (2016) **1**, 260-271

*CDSS- *Clinical Decision-Support Systems*

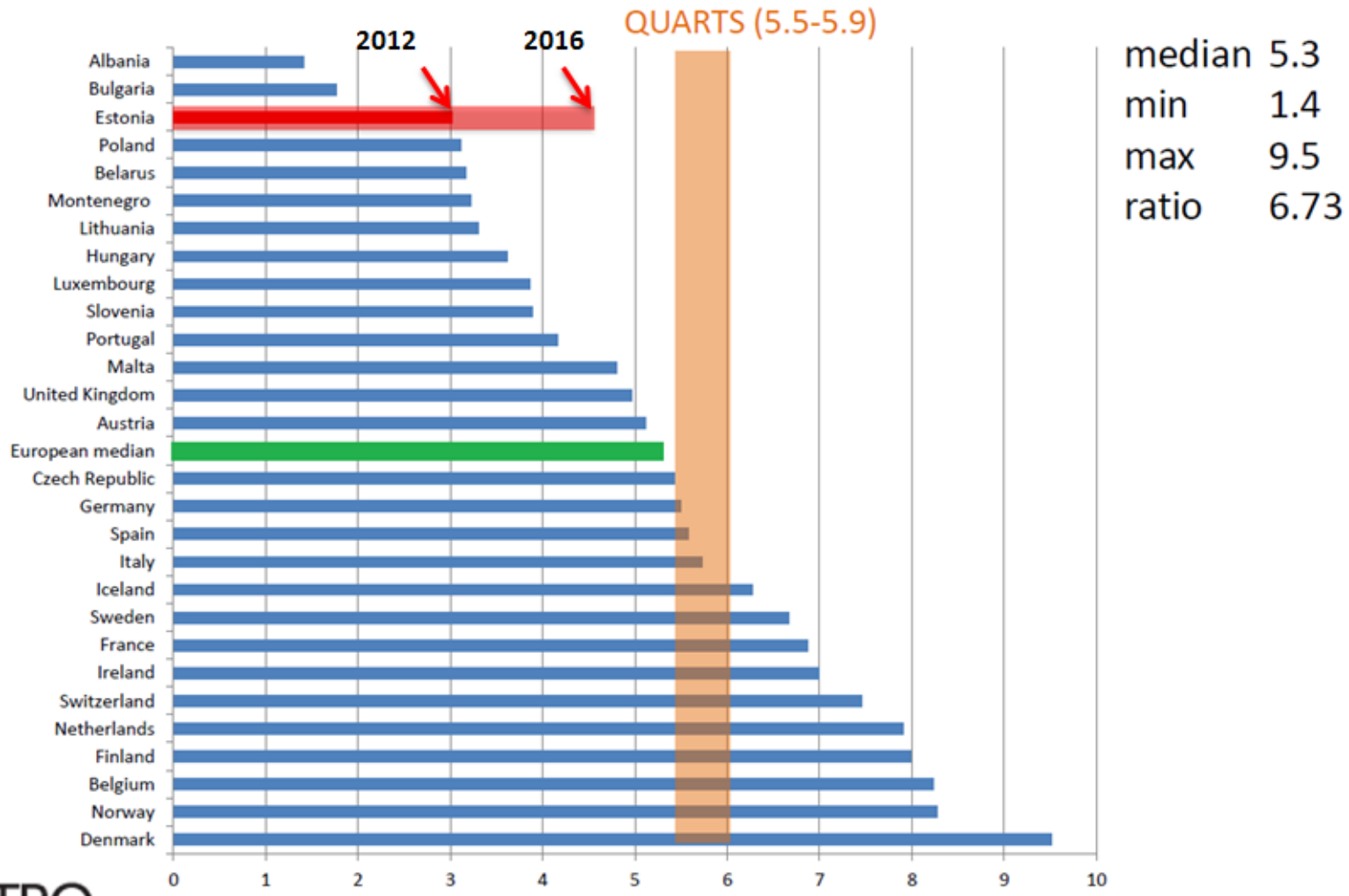
Kiiritusravi areng PERH-s



QUATRO kõikehõlmav kliiniline audit
18-22.03.2019
Kompetentsikeskus

Access of RT in Europe: LA per mln people

2016 **3 uut kiirendit**
Kokku PERH (4) + TÜK (2) = **6** **4.6 LA/per mln**



ESTRO European SocieTy for RADIOTHERAPY & ONCOLOGY

Slotman et al, Radiother Oncol 2005
Grau et al, Radiother Oncol 2014

The ESTRO ECF White Paper and EU Policy Forum