

Specialne tehnike v radioterapiji

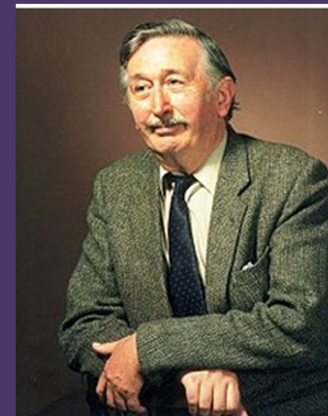
Računalniška tomografija

(klinični aspekt)

doc. dr. Uroš Smrdel dr. med.

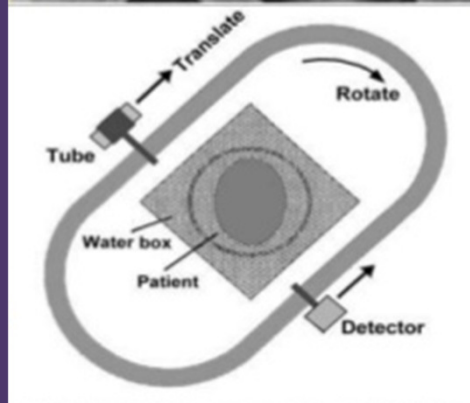
Zgodovina

- 1917 Radonova transformacija
- 1937 Stefan Kaczmarz matematični model za približno rešitev velikega sistema algebraičnih enačb
- Godfrey Hounsfield adaptira tehniko algebraične rekonstrukcije za prvi CT skener



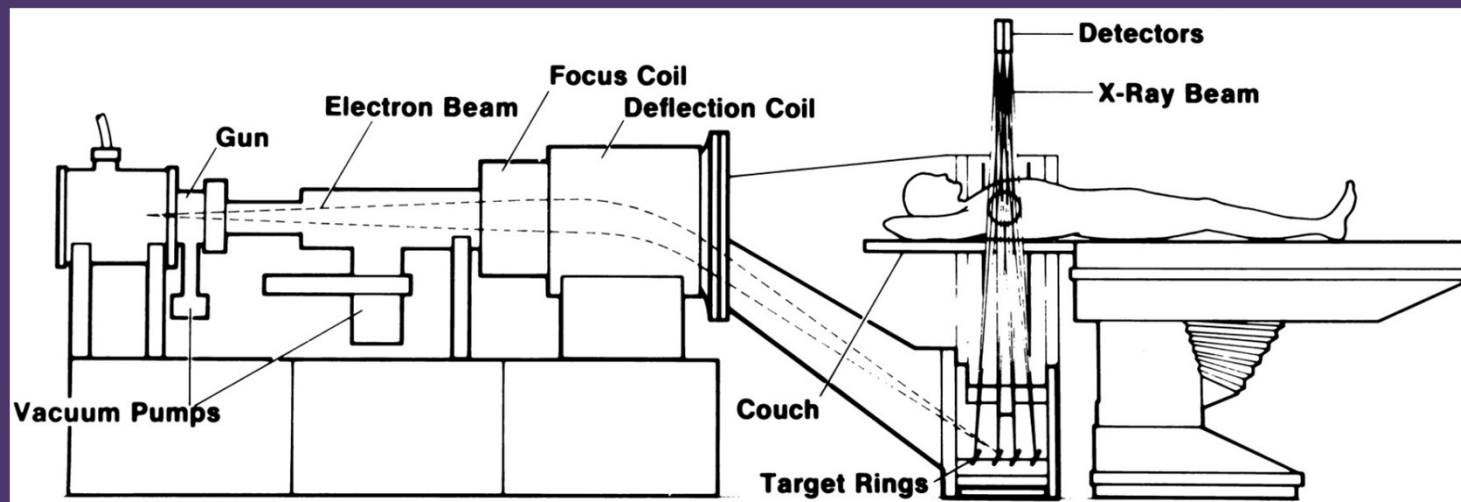
Zgodovina

- Prvi CT skener 1971, Atkinson Morley Hospital



Tipi

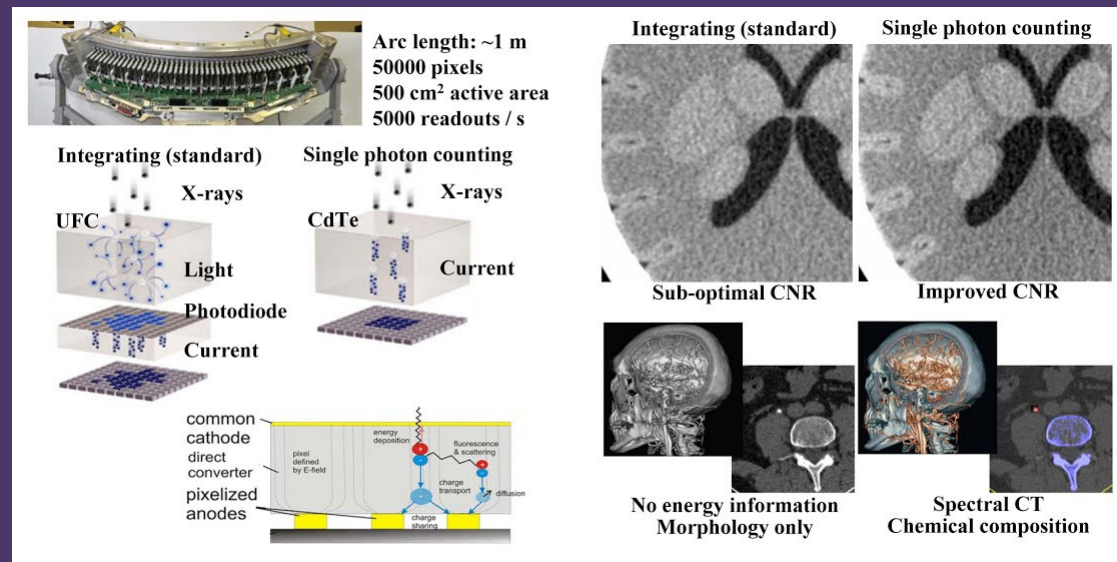
- „spiralni CT“
- tomografija z elektronskim žarkom
 - ne več od 2006



draga, večja, hitrejša

Tipi

- CT s štetjem fotonov
 - eksperimentalna (3 inštalirane 2016)
 - izboljša signal, zniža odmerek, izboljša resolucijo
 - individualni fotoni in energije



Simulator

- prehod iz planarne slike na 3D rekonstrukcijo
- prehod v prvi polovici 80tih let
- FDA odobreno konec 80tih
- princip JE ENAK principu CT
 - problem fiksacijskih pripomočkov (large bore CT)
 - resolucija mehkih tkiv
 - kontrastno sredstvo

Fiksacija

- couch top CT vs Linac
- koordinatni sistem
- pozicioniranje izven centra FOV
- pozicioniranje pripomočkov znotraj simulatorja



Mehka tkiva

- osnovna pomankljivost CT je pomanjkanje možnosti razločevanja med mehкими tkivi brez kontrastnega sredstva
- nekaj redkih področij, kjer je to manjši problem: pljuča in maščevje
- rešitev kontrastno sredstvo
- vpliv uporabe kontrastnega sredstva pri simulaciji na izračun doze:

- manj kot 1 %
- zanemarljiv

(J Med Imaging Radiat Oncol. 2009)

- niso zanemarljive reakcije
 - alergija na jodno KS
 - 70 % urtika in srbenje
 - ponovna izpostavljenost 2,5 -44 % reakcij
- Int J Angiol. 2013
- diabetiki - metformin

Table 1. HU Values of Non-contrast and Contrast-enhanced Blood Streams

	Non-contrast image (n=22)				Contrast-enhanced image (n=20)			
	Min	Max	Mean	SD	Min	Max	Mean	SD
Superior vena cava	36	53	43.86	4.3	150	465	279.3	84.51
Right atrium and ventricle	35	53	45.18	4.63	128	215	165.8	26.32
Pulmonary artery	31	53	44.27	5.78	126	221	163.2	29.58
Left atrium and ventricle	38	57	45.18	4.83	132	242	175.3	29.57
Aorta	32	58	44.82	5.7	128	287	196.95	42.89
Total	31	58	44.66	5.01	126	465	196.11	63.89

Min, the minimum HU value; Max, the maximum HU value; SD, standard deviation

Table 2. Dose Variation Between the Simulated Non-contrast Scenario (45 HU) and the Other Contrast Scenarios for PTV

	HU value	D99 (% difference)*			D95 (% difference)			D90 (% difference)			D80 (% difference)			D50 (% difference)		
		Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	Min	Max
Primary contrast		-0.04±0.09	-0.19	0.23	-0.02±0.11	-0.22	0.37	0.00±0.12	-0.18	0.42	-0.03±0.10	-0.16	0.35	0.00±0.07	-0.08	0.29
Simulated	145	-0.02±0.06	-0.13	0.09	0.00±0.07	-0.13	0.15	-0.02±0.07	-0.13	0.19	-0.02±0.06	-0.15	0.14	-0.01±0.03	-0.09	0.08
Contrast	245	-0.04±0.15	-0.25	0.3	-0.02±0.13	-0.24	0.37	-0.03±0.14	-0.25	0.44	-0.04±0.12	-0.27	0.35	0.00±0.07	-0.15	0.22
	345	-0.06±0.24	-0.43	0.59	-0.05±0.22	-0.41	0.59	-0.07±0.22	-0.46	0.69	-0.08±0.19	-0.48	0.56	-0.02±0.11	-0.27	0.34
	445	-0.11±0.35	-0.62	0.85	-0.11±0.31	-0.65	0.79	-0.13±0.03	-0.7	0.92	-0.13±0.26	-0.69	0.71	-0.04±0.14	-0.38	0.43
Extreme	1000	-0.65±0.94	-1.99	2.36	-0.58±0.86	-2.17	2.04	-0.59±0.76	-2.11	1.89	-0.50±0.68	-1.76	1.86	-0.08±0.38	-0.77	1.24
scenario	-1000	-0.61±1.45	-3.35	2.77	-0.87±1.33	-3.65	2.24	-0.83±1.27	-3.58	2.31	-0.57±1.14	-2.73	2.67	0.09±0.76	-0.68	3.11

*D99 (% difference) is the percent variation of the dose that 99% of the planning target volume (PTV) receives between the simulated non-contrast scenario (45 HU) and the other contrast scenarios, and so on for D95–D50

Klinične indikacije za simulacijo brez CT

- če ni CT simulatorja vse!
- klasični simulator ima prednost pri kostnih zasevkih ko gre za paliativno RT– hitrost
 - paliativna RT – VS vzame več časa, da pa boljši podatek o dozi

CŽS

- simulacija z CT z KS:
 - kostne lezije?
 - paliativna RT m cerebri
 - pri MR simulaciji z KS????
 - SRS?
 - prim možganski tu?
 - meningeomi?

CT simulacija pri SRS/SRT

- razen maske in debeline reza se postopek ne razlikuje od klasične simulacije
- NUJNO če MR starejši od 7 dni KS
- CT rezina zaradi DRR 1 mm!
- psihološki vidik maske odpade pri novih maskah

Adaptivna RT

- prilagajane obsevalnega načrta spremenjenim anatomskim in patološkim razmeram
- načrtovane zaporedne simulacije
- CBCT
- adaptacija načrta
 - na novo
 - avtomatska adaptacija
- ??

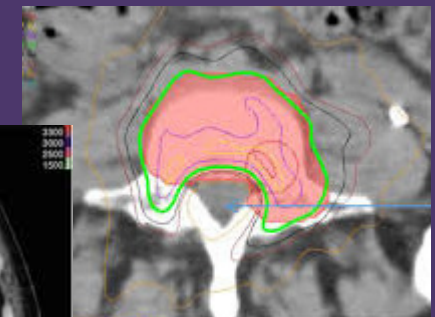
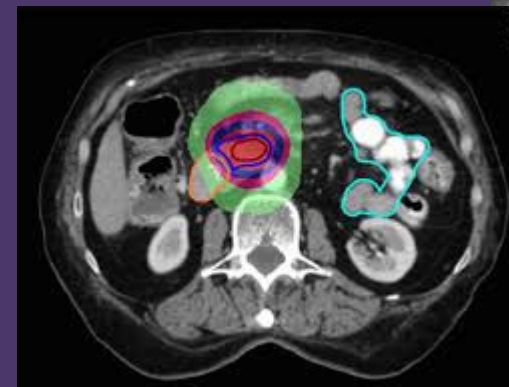
SBRT

- pljuča, jetra, hrbtenica, pankreas
- prostata?
- 4DCT
 - posnetki v različnih fazah dihanja
 - vrisujemo na?
 - ITV – motion tracking – mid expiratory - ...
- fiksacija na pripravi?
- poročanje ICRU

Suresh R 2014



Kang JI 2012

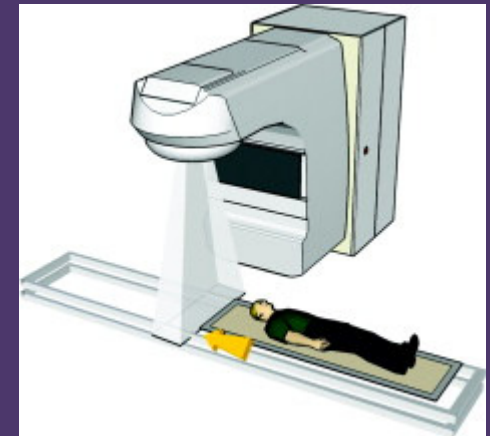


Huo M 2017

Chhabra A 2015

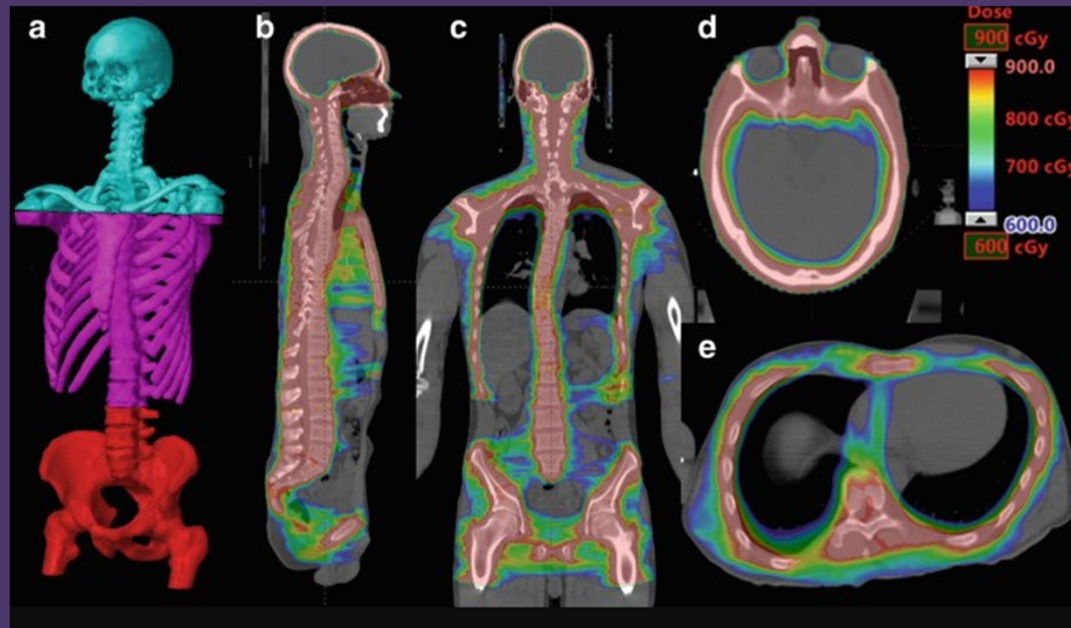
TBI

- CT ocena debeline torakalne stene
 - pri odmerku na pljuča 12 Gy – fibroza
 - ščitenje pljuč
 - dodatek na torakalno steno z e-
 - debelino stene ocenimo s CT
- načrtovanje obsevanja z e- na CT?



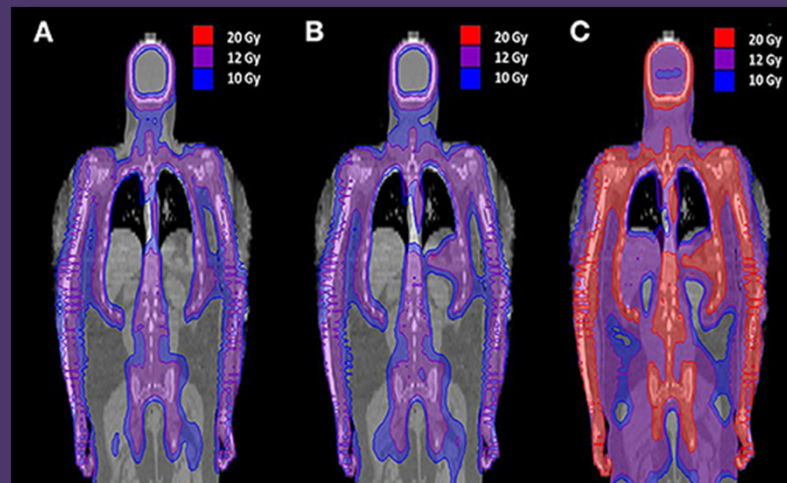
TBI

- TBMi



•Kang-Hyun Ahn, Bulent Aydogan 2020

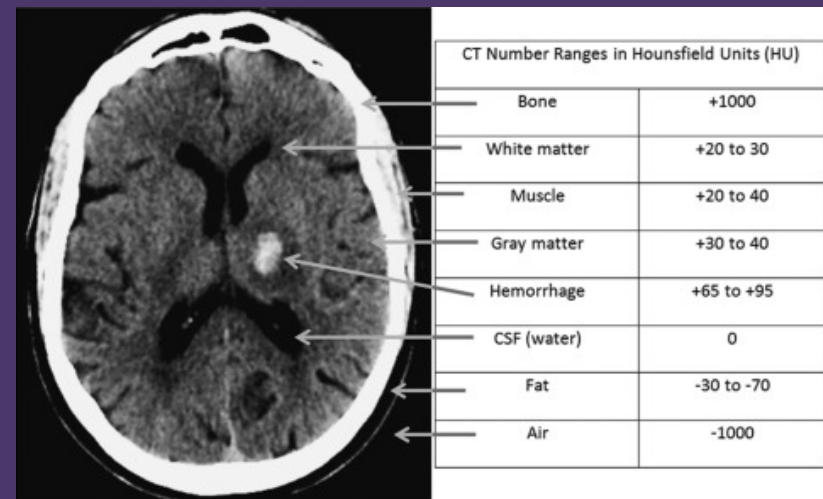
- TLI



Hoeben BA et al 2021

Opustitev CT načrtovanja

- Potrebno pridobiti elektronsko gostoto iz MR slik
 - Lahko atlas based (Gudur M et al 2014)
 - Pridobljeno iz predhodnih slikanj
- Ni še v splošni uporabi



Specialne tehnike v radioterapiji

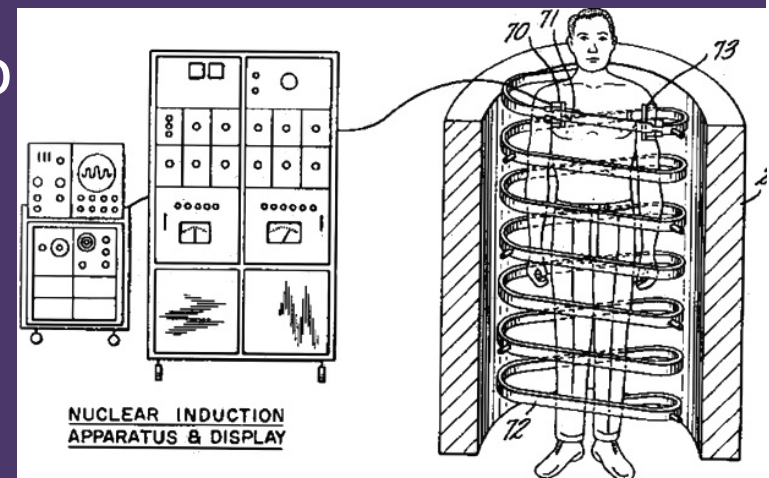
Magnetna resonanca

(klinični aspekt)

doc. dr. Uroš Smrdel dr. med.

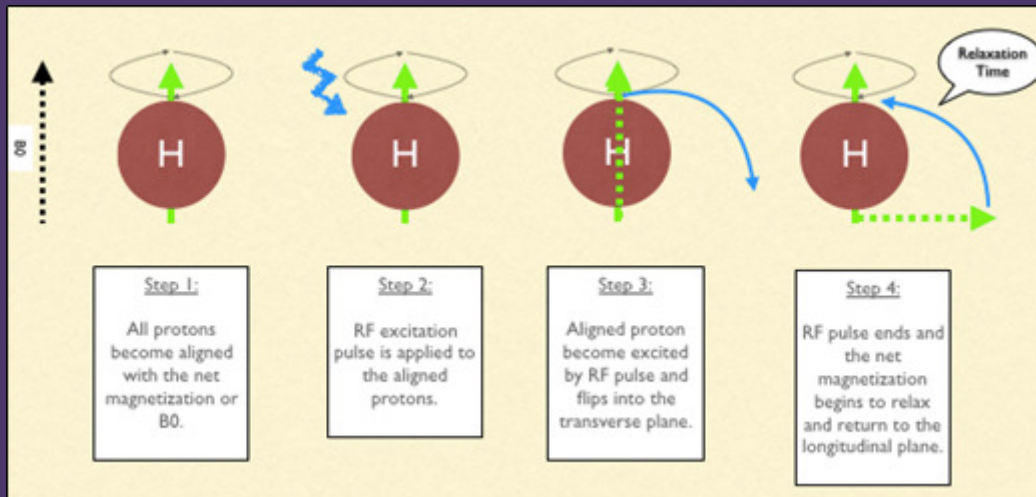
Zgodovina

- Paul C. Lauterbur 1971
- Raymond Damadian 1971 – tumorje in normalno tkivo lahko razlikujemo z NMR
 - ni primerno za praktično rabo
- John Mallard prvi MR v klinični rabi



Princip delovanja

- magnetno polje – poravna protone
- protoni (vodik v vodi) prejmejo eksitacijski signal
- kontrast med tkivi je odvisen od tega kako hitro se protoni vrnejo v ravnotežno stanje



<http://teachmeanatomy.info>

Uporaba

- Diagnostika
 - morfologija
 - funkcionalna diagnostika
- Terapija
 - predvsem načrtovanje RT
 - Načrtovanje stereotaktičnih posegov

Sekvence

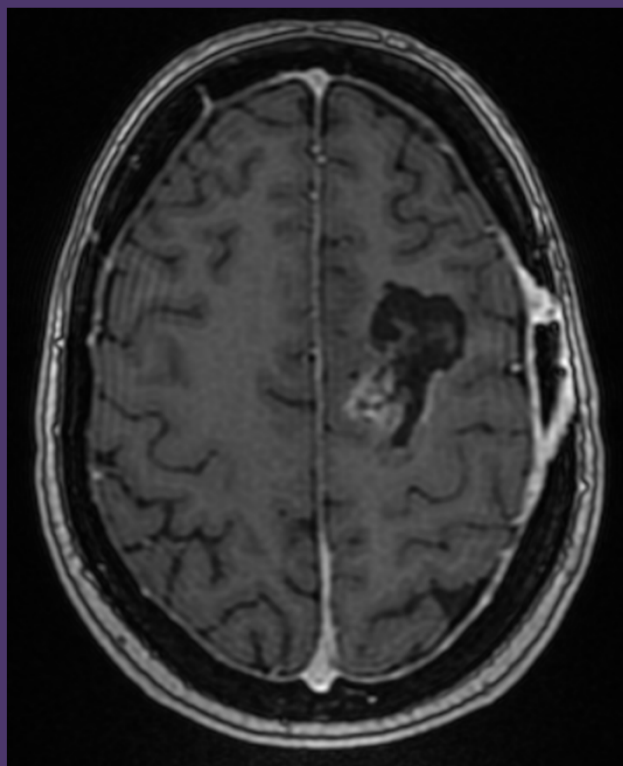
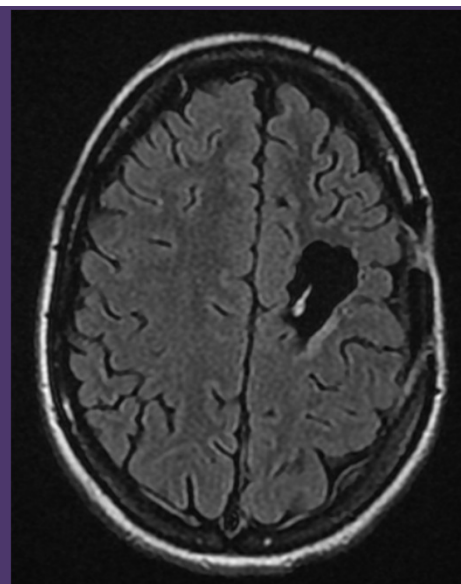
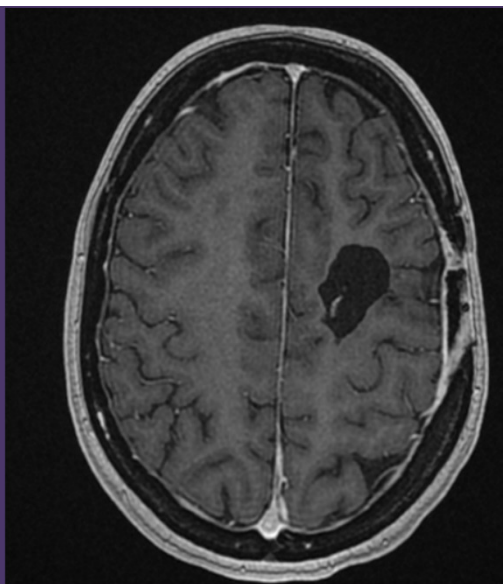
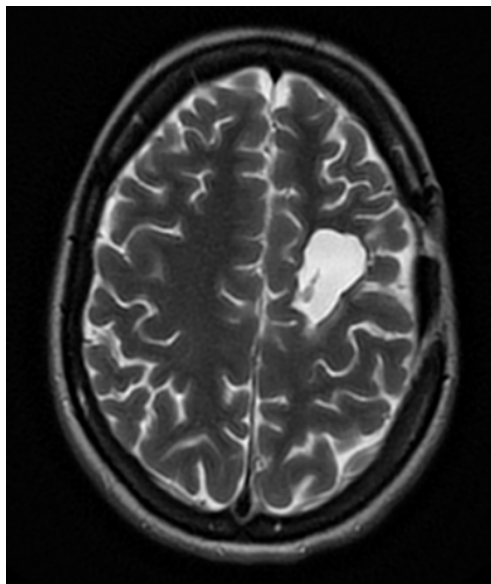
- T1 – v smeri magnetnega polja
- T2 – transverzalno na magnetno polje

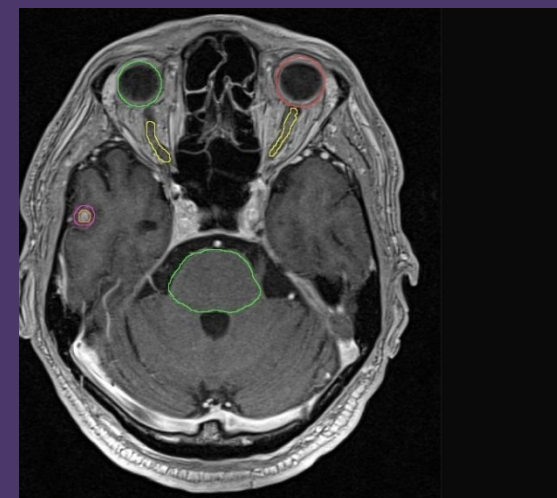
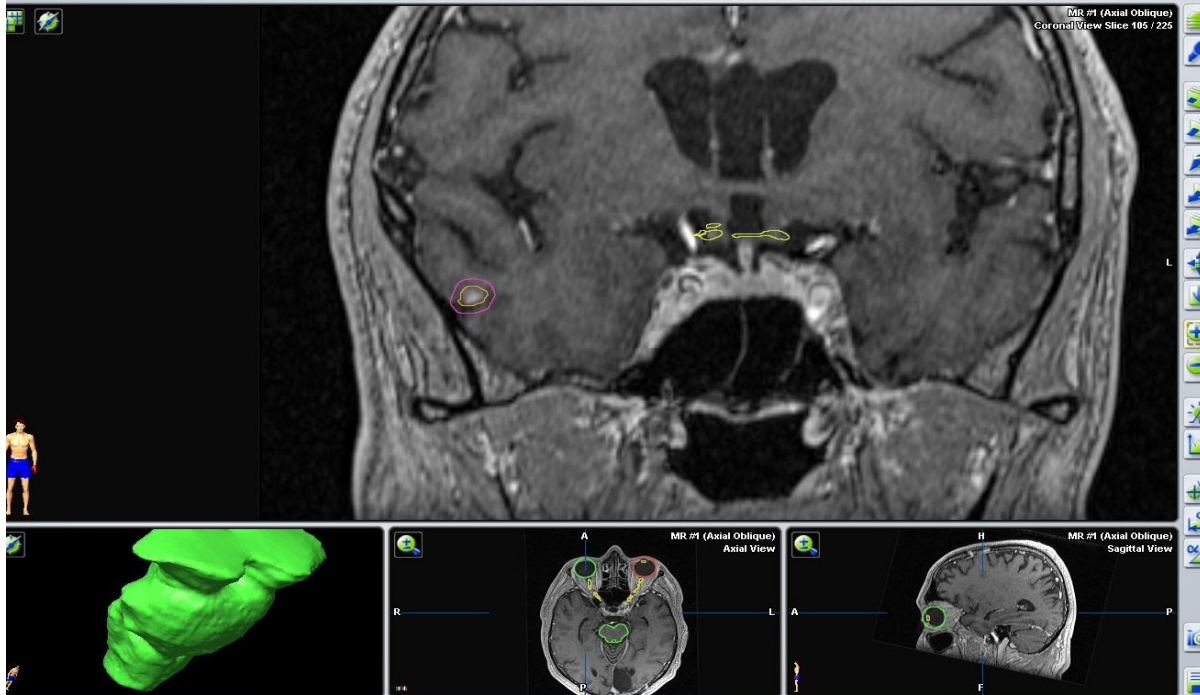
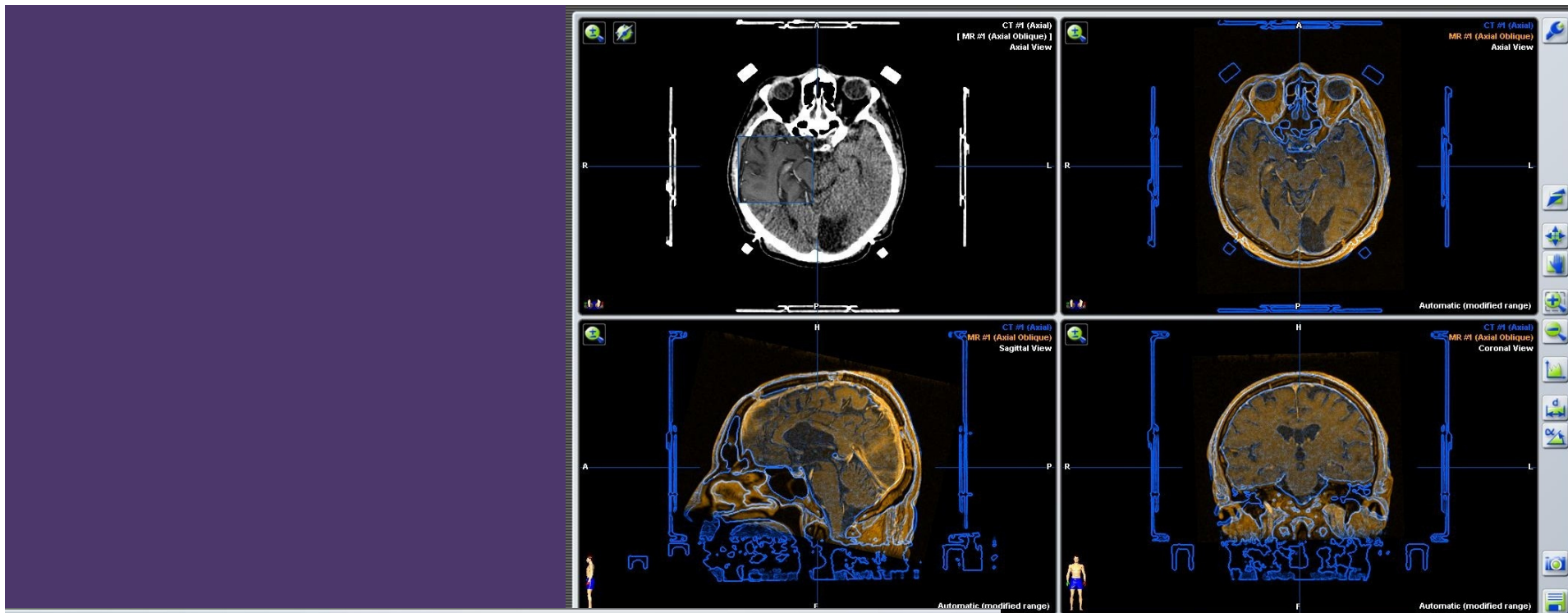
https://en.wikipedia.org/wiki/MRI_pulse_sequence#T1_and_T2

Signal	T1-weighted	T2-weighted
High	• Fat • Subacute hemorrhage • Melanin • Protein-rich fluid • Slowly flowing blood • Paramagnetic substances, such as gadolinium, manganese, copper • Cortical pseudolaminar necrosis	• More water content, as in edema, tumor, infarction, inflammation and infection • Extracellularly located methemoglobin in subacute hemorrhage
Inter-mediate	Gray matter darker than white matter	White matter darker than grey matter
Low	• Bone • Urine • CSF • Air • More water content, as in edema, tumor, infarction, inflammation, infection, hyperacute or chronic hemorrhage • Low proton density as in calcification	• Bone • Air • Fat • Low proton density, as in calcification and fibrosis • Paramagnetic material, such as deoxyhemoglobin, intracellular methemoglobin, iron, ferritin, hemosiderin, melanin • Protein-rich fluid

CŽS

- načeloma najbolj uporabna metoda
 - prednost pred CT
 - kontrast
 - resolucija
 - različne sekvence za različne namene
 - slabost pred CT
 - počasna
- praktično vedno paramagnetno kontrastno sredstvo
 - Včasih lahko uporabimo T2 cube pri bolnikih z alergijo





CŽS

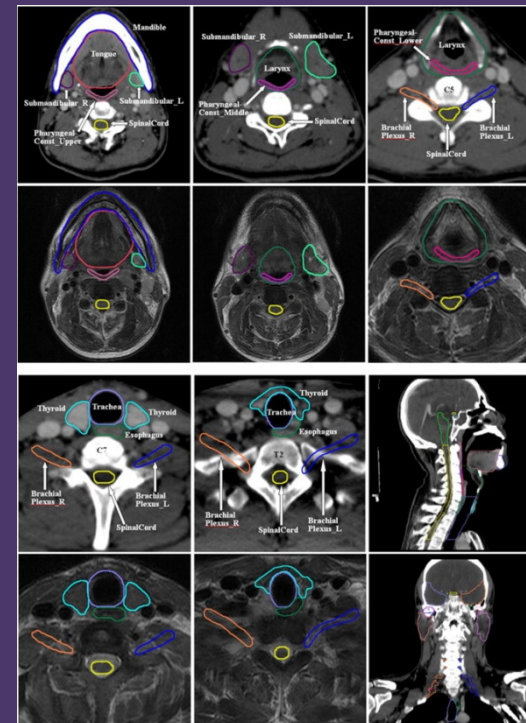
- RT
 - pri zdravljenju prim možganskih tumorjev obvezna
 - zaradi pooprativnih sprememb v 72 urah po op
 - Nevrokirurgija v LJ običajno, MB včasih
 - LJ – cca 1 mesec po op simulator
 - Nezanestljiva za oceno resekcije
 - konturiranje
 - na preoperativni MR in na pooprativni MR
 - odvisno od uporabljene sekvence

CŽS

EORTC treatment volumes (EORTC 22981/22961, 26071/22072 (Centric), 26981–22981, and AVAglio trials)	RTOG treatment volumes (RTOG 0525, 0825, 0913, and AVAglio trials)
Phase 1 (to 60 Gy in 30 fractions)	Phase 1 (to 46 Gy in 23 fractions)
GTV = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans).	GTV1 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans) plus surrounding oedema (hyperintensity on T2 or FLAIR MRI scans).
CTV = GTV plus a margin of 2 cm*	CTV1 = GTV1 plus a margin of 2 cm (if no surrounding oedema is present, the CTV is the contrast enhancing tumour plus 2.5 cm).
PTV = CTV plus a margin of 3–5 mm	PTV1 = CTV1 plus a margin of 3–5 mm
	Phase 2 (14 Gy boost in 7 fractions)
	GTV2 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans)
	CTV2 = GTV2 plus a margin of 2 cm
	PTV2 = CTV2 plus a margin of 3–5 mm

ORL

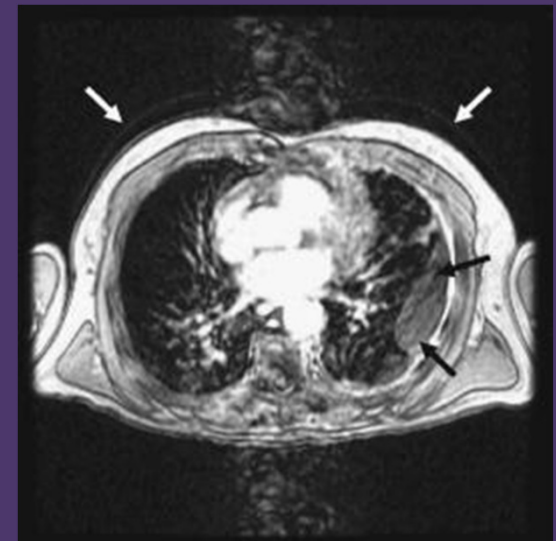
- osnova še vedno CT s KS
- klinični pregled
- MR predvsem v pomoč pri brahialnem pletežu in nekaterih OAR



Ying Sun et al, Radiotherapy
and Oncology, 2014

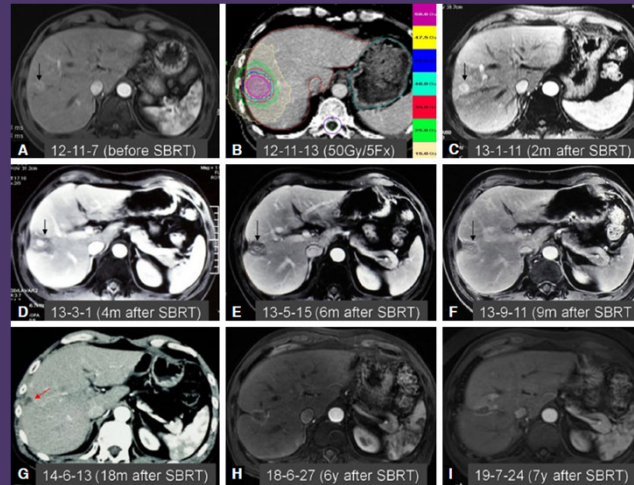
Torakalni organi

- pljuča so na MR slabo pregledna
- indikacija pri RT torakalne stene in nekaterih mediastinalnih organov (T3 – T4 tumor pljuč)
- torakalna hrbtenica
- CT z KS superioren
 - Razen pri paraspinalnih tumorjih

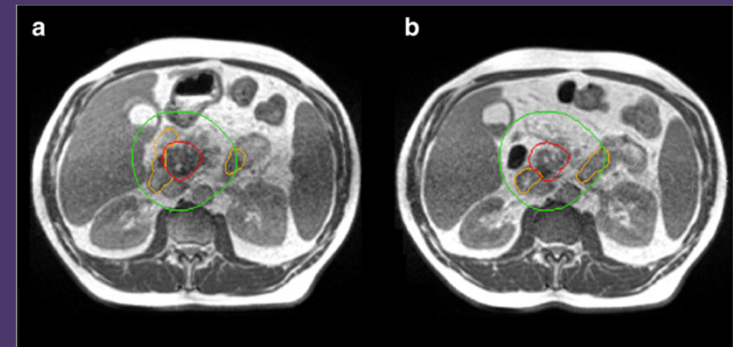


Abdominalni organi

- jetra
- pankreas
- želodec?



Zeng ZC 2020



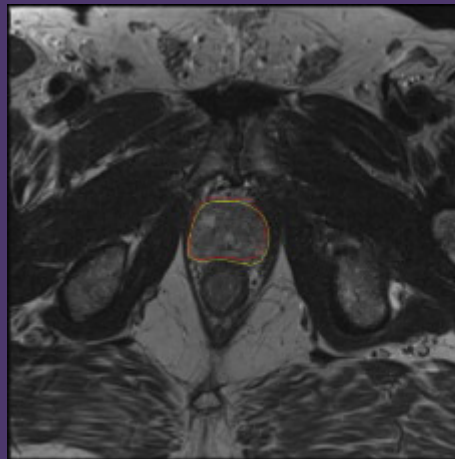
Boldrini L et al 2019

- predvsem pri SBRT – nujno
- premiki – fiksacija da/ne

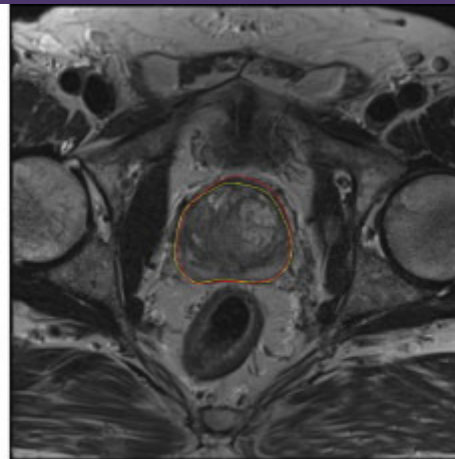
Prostata

- Osnova je še vedno CT z KS
- MR medenice, T1, T2, T1+ Gd
- boljša delineacija tumorja
- boljša delineacija OAR
- MR načrtovanje brez CT?

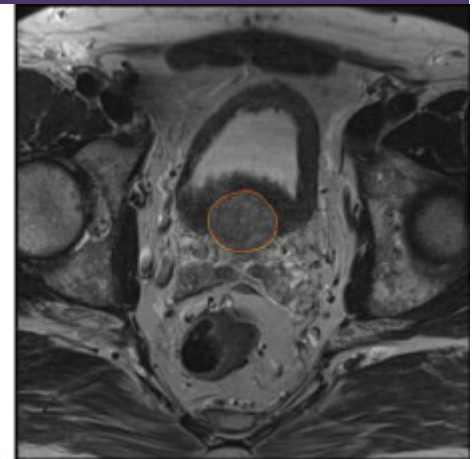
Litjens et al, Medical
Image Analysis, 2014



(a) Apex



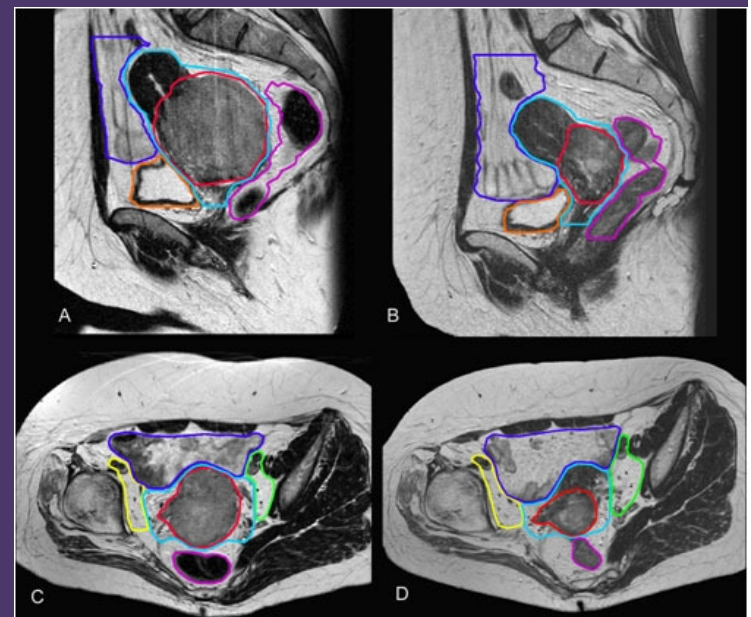
(b) Center



(c) Base

Ginekološki raki

- Osnova CT z KS
- MR medenice, T1, T2, T1+ Gd
- boljši kontrast med tkivi – GTV
- prizadetost bezgavk – MR vs PET CT

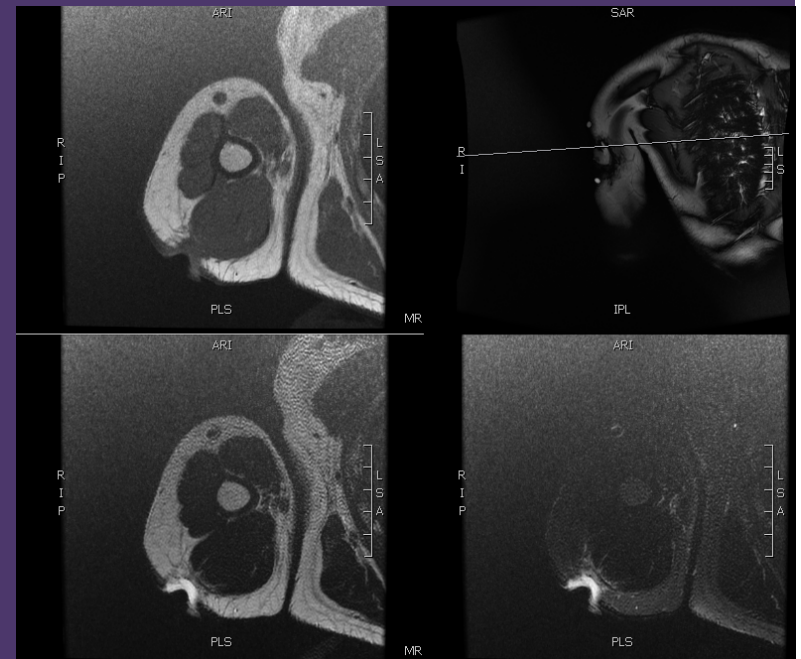
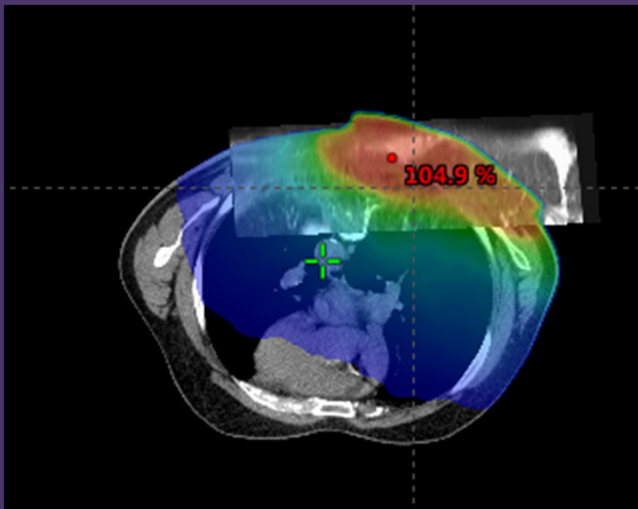


Rak danke

- MR nujna preiskava za zamejitev bolezni
- pri načrtovanju RT ni nedvoumnih dokazov za izboljšanje preživetja razen pri postavitvi stadija in zato prilagoditvi terapije

Tumorji mehkih tkiv

- MR simulacija pri predoperativni RT
- pooperativna RT: preoperativni MR + pooperativni MR če sum na makroskopski ostanek (mikroskopski na histologiji ?)
- ev. skip metastaze



MR v RT

- Nujna je fuzija slikovnih preiskav
- Različni algoritmi
- Prilagoditev MR za simulator
- SRS – Ljubljana tuljave ne omogočajo maske
- MR za izračun elektronske gostote

Zaključki

- V predelih medenice, CŽS..., je MR osnovna preiskava, ki omogoča izboljšanje natančnosti
- Ponekod inferiorna drugim slikovnim metodam (pljuča)

Specialne tehnike v radioterapiji

Pozitronska emisijska tomografija
(klinični aspekt)

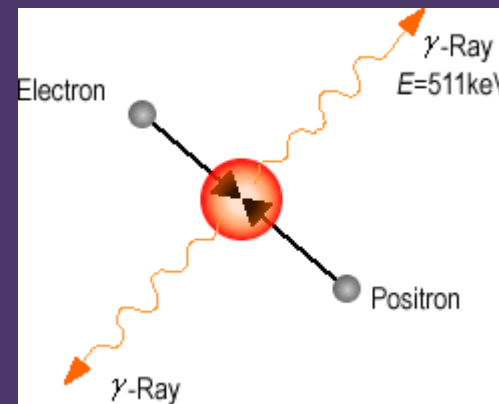
doc. dr. Uroš Smrdel dr. med.

Zgodovina

- David Townsend (univerza v Pittsburgu) in Ronald Nutt (CPS Innovations, Knoxville)
- prvi klinični skener 1998
- prvi komercialni sistem 2001

Princip

- β^+ razpad
 - proton se spremeni v nevtron in odda pozitron in nevtrino
 - interakcija z elektronom
 - anihilacija – nastaneta 2 fotona, ki se gibata v nasprotni smeri
 - detekcija, rekonstrukcija



PET

- Informacija o tkivnem metabolizmu
- ^{18}F Fluoro deoksi glukoza najpogosteje uporabljan tracer
 - privzem v tkivo proporcionalno z stopnjo glikolize (povečana v neoplastičnem tkivu)
 - vendar tudi v nekaterih normalnih tkivih (sublingvalne slinavke, Waldajerjev obroč, mišice, rjavo maščevje, možgani – skoraj ekskluzivno metabolizem glukoze)

PET

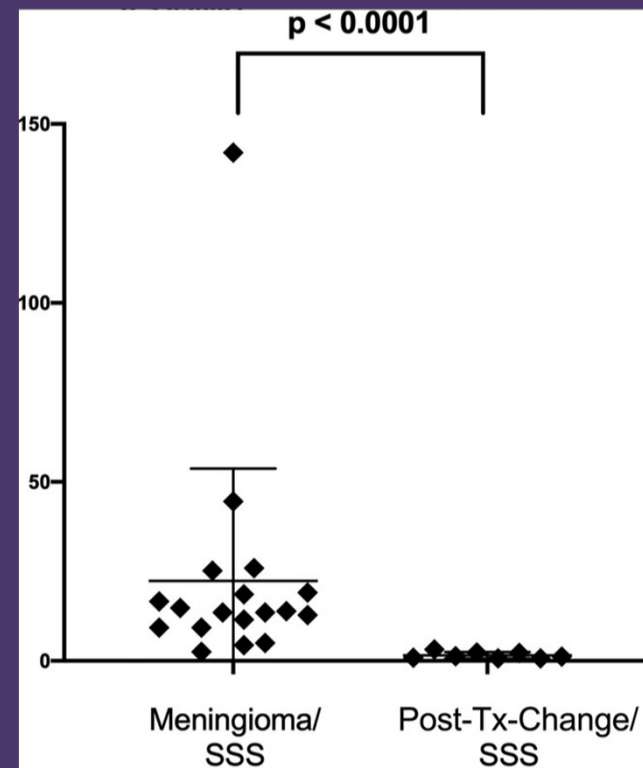
- v predelu CŽS zaradi visokega metabolizma glukoze drugi ligandi (tudi drugi radionuklidi)
 - ^{11}C Metionin – metabolizem proteinov
 - ^{18}F Fluoroetil-L-Tirozin – FET – metabolizem proteinov

Tracer	Specific remarks	References
^{18}F FDOPA	First introduced for the diagnosis of Parkinson's disease. Now, also used in neuroendocrine tumour imaging.	[25–33]
^{11}C Methionine	Authentic tracer (no structural alteration). Short half-life. Mainly used in brain tumour imaging.	[30,33–42]
^{18}F FET	Longer-lived alternative to ^{11}C methionine. Discussed to be able to distinguish between inflammation and residual tumour tissue.	[30,37,43–46]
^{11}C AMT	Used only in clinical trials so far.	[47–51]

Wadsak W, Mitterhauser M. European Journal of Radiology 2010

PET

- Galijev PET scan DOTATATE
 - Nevroendokrini tumorji
 - Recidivni meningeomi



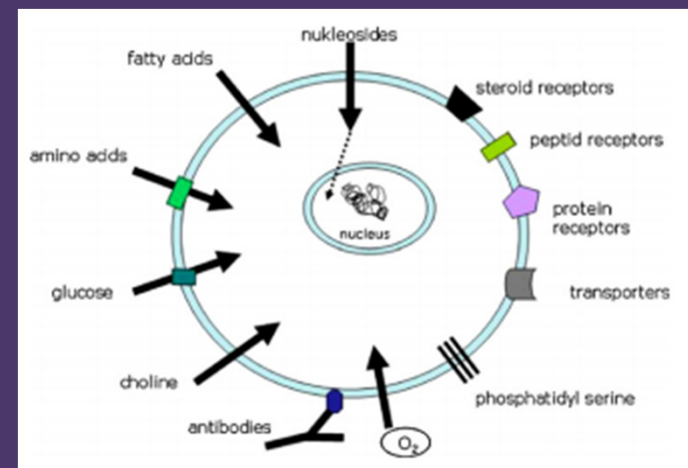
Značilnosti radiofarmakov za PET

- radionuklid + nosilna molekula

- nosilna molekula

- receptorski sistem
 - antigeni
 - encimi
 - transportni mehanizmi
 - metabolične spremembe (energija, tvorba proteinov)
 - hipoksija
 - vaskularizacija in perfuzija

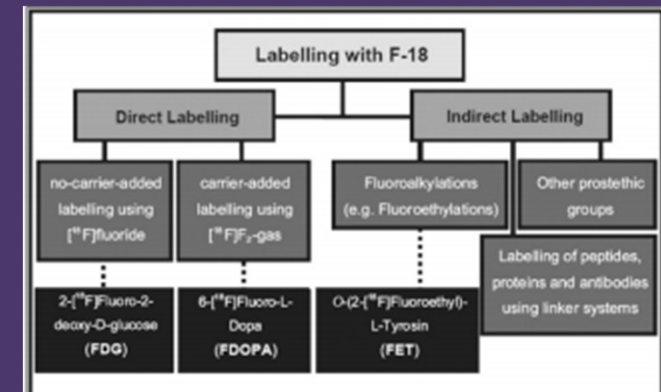
Wadsak W 2010



Značilnosti radiofarmakov za PET

— radionuklid

- nuklidi, ki izsevajo pozitrone
- kratek razpolovni čas
 - samo ^{18}F in ^{68}Ga če ni ciklotrona

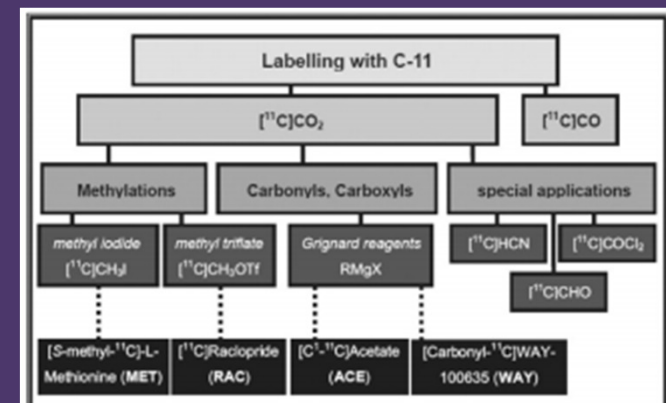


• označitev nosilca z radionuklidom

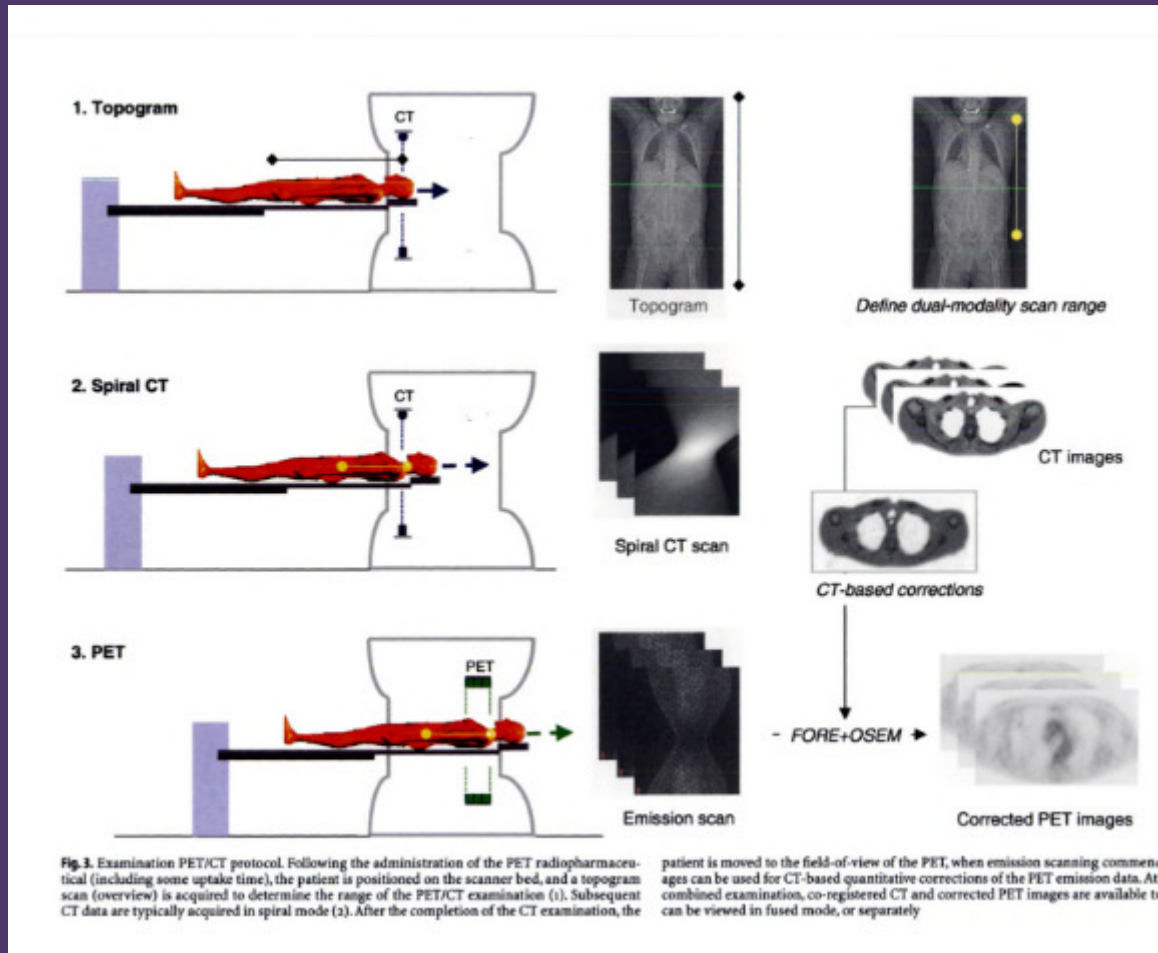
— več vrst označevanja

- direktno v molekuli
- preko dodatnih poti

Wadsak W, Mitterhauser M. European Journal of Radiology 2010



Protokol preiskave



Uporaba

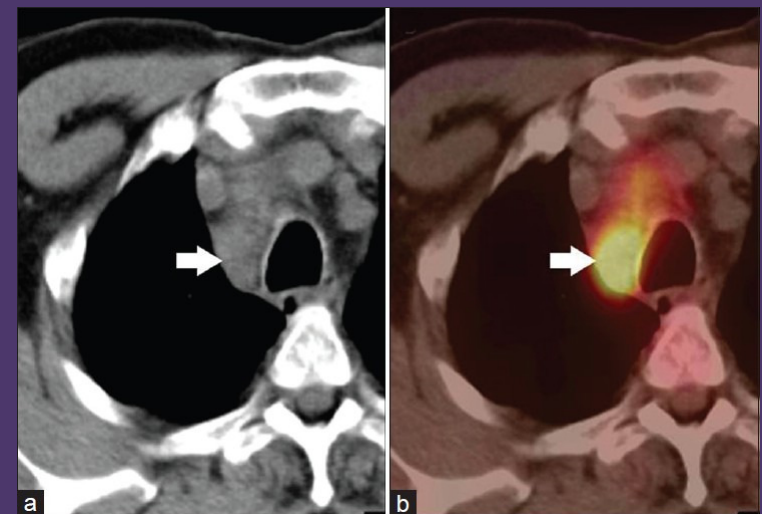
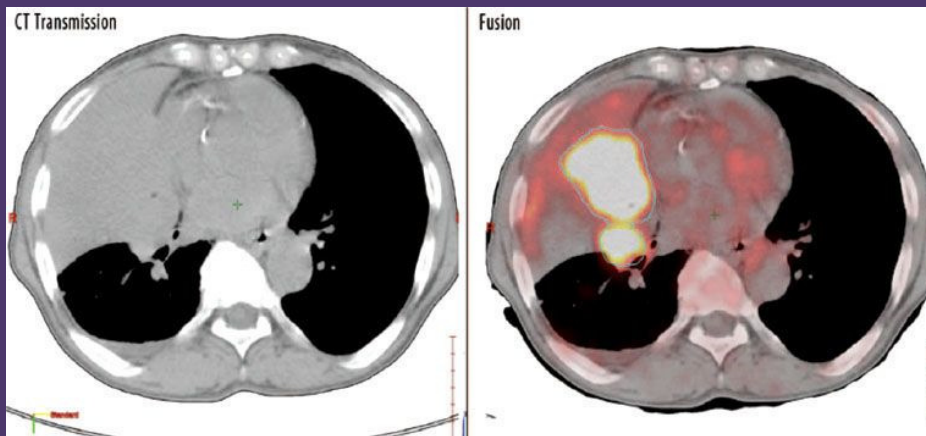
- Diagnostika
 - tumorji
 - vnetje
 - metabolizem (npr. kardiologija, nevrologija)
- Spremljanje učinka
 - po KT, RT...
- Načrtovanje zdravljenja

Načrtovanje RT z PET CT

- posebej pri slabo omejenih tarčah
 - IAEA report 2006 – 2007
 - lezije, ki niso očitne na CT ali MR
 - izogib tkivom brez tumorja (atelektaza)
 - radiokemoterapija
 - adaptivna terapija
 - dodatno
 - IMRT z differentnimi odmerki (dose painting/dose sculpting) (Ling CC et al. IJROBP 2000)

Pljučni rak

- največ raziskav
 - Nestle et al, uporaba PET CT vpliva na GTV, CTV, PTV
 - predvsem zaradi bezgavk
 - manjši volumen pri atelektazi



Sharma P et al, SAJC 2013

ORL

- Deisner et al, GTV se najbolj približa realnemu stanju pri uporabi PET CT
- Burri et al, SUV 40% maksimalnega je najboljši približek
- Greven et al, adaptivna RT glede na PET CT?
- 18Fluoromisonidazol in 18Fluoroazomicin-arabinozid kot markerja hipoksije
- Zlati standard je še vedno klinični pregled

Požiralnik

- vpliv na delineacijo pri od 20 – 94% bolnikov (Muijs et al)
- delineacija na PET CT zmanjša napake pri vrisovanju pri 30 – 60% bolnikov (Leong et al, Schreurs et al)
- avtomatske in na pol avtomatske metode vrisovanja – NE ŠE (Muijs et al)

Maternični vrat

- Zlati standard je MR
- Esthappen et al, PET CT vodena IMRT na paraaortno regijo z boostom na PET pozitiven ostanek
- Kidd et al, manj toksičnih efektov po načrtovanju z PET CT (6% vs 17% GII ali več)

Prostata

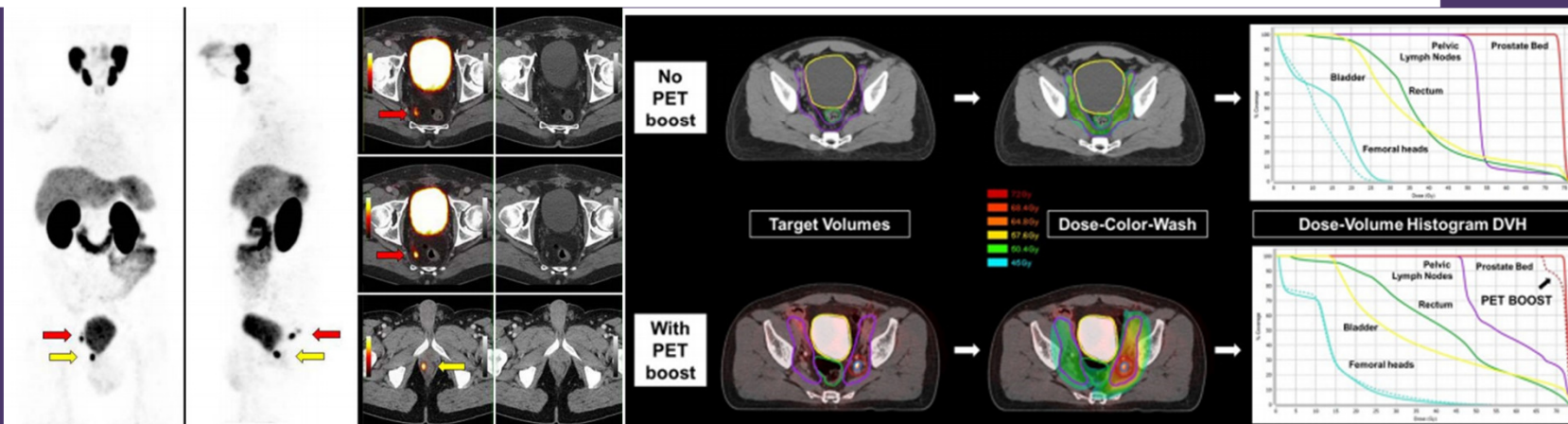
- PET CT načrtovano obsevanje je študijska metoda
 - drugi tracerji (FDG slabše občutljiv)
 - ^{11}C -Acetat
 - ^{18}F -FACBC
 - ^{11}C in ^{18}F -Holin
 - vprašanje je obsevanje radiološko negativnih bezgavk (RTOG 0924, RTOG 0534, NCT00567580)

Prostata

- Več raziskav glede uporabe

Calais J et al 2018

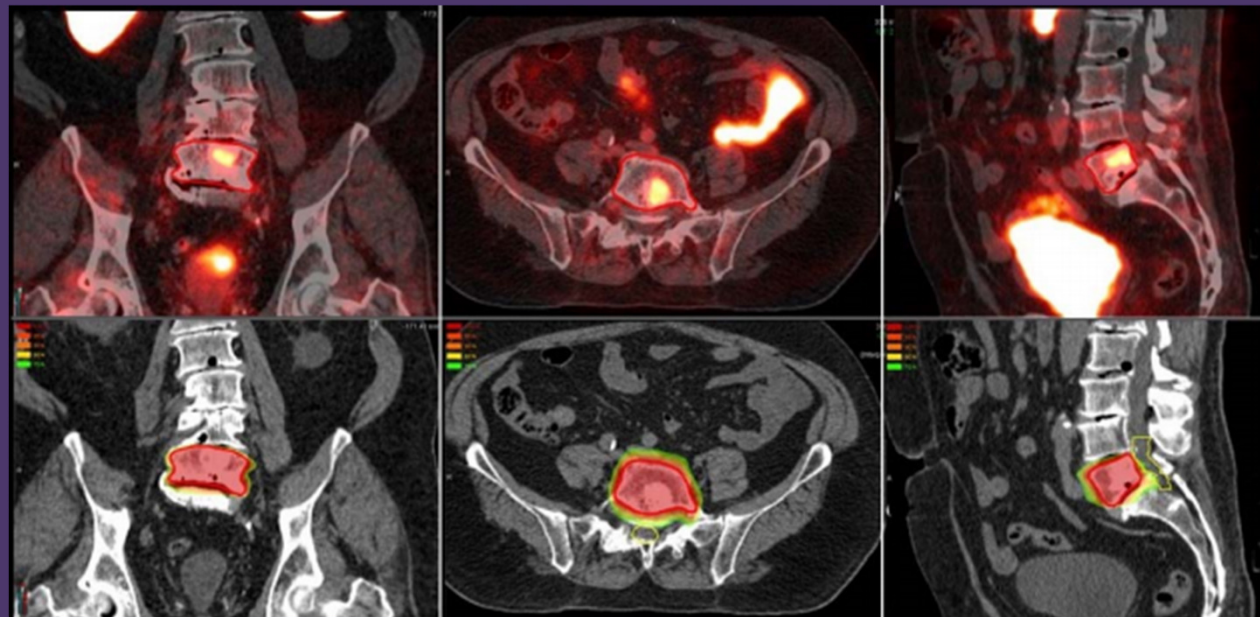
Author	Year	PET/CT Probe	Median PSA (range)	n	PET +	% PET +	Change in RT Plan (%)
Würschmidt	2011	¹⁸ F-Choline	10.4 (2.5-731)	7	7	100%	28.50%
Vees	2012	¹⁸ F-Choline	30.5 (6.4-66.5)	19	NA	NA	22%
Jereczek-Fossa	2014	¹¹ C-Choline	NA	16	NA	NA	12.50%
Garcia	2015	¹¹ C-Choline	(6.3-30.4)	61	61	100%	24.50%
Lopez	2015	¹¹ C-Choline	18.18 (4.90–55.40)	9	NA	NA	44%
Alongi	2015	¹⁸ F-Choline	6.5 (4.1-143)	60	57	95%	21.60%
Sterzing	2016	⁶⁸ Ga-PSMA	7.04 (0.28–45)	15	9	60%	26.50%
Dewes	2016	⁶⁸ Ga-PSMA	13.5 (8.2-63.9)	15	15	100%	33.30%
Schreibmann	2016	¹⁸ F-FACBC	0.43 (0.02-11.15)	41	32	78%	73%



Prostata

- Subklinični recidivi
- Boost glede na PET CT
- SBRT solitarnih zasevkov
-

Calais et al, Journal of
Nuclear Medicine,
2018

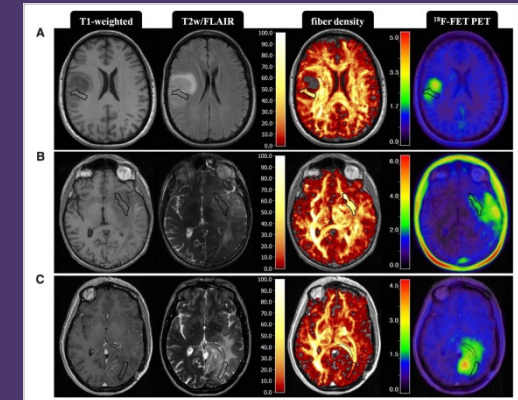


CŽS

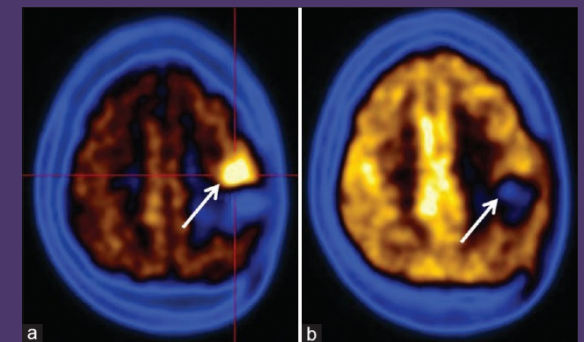
- **FDG PET CT ima omejeno uporabnost**
 - visok metabolizem glukoze v možganih
 - glukoza je edini vir energije
 - alternativa je aminokislinski PET CT
 - zlati standard ^{11}C met
 - razpolovni čas 20 minut = ciklotron v ustanovi
 - alternativa ^{11}C met je FET
 - ^{18}F kot pri FDG

CŽS

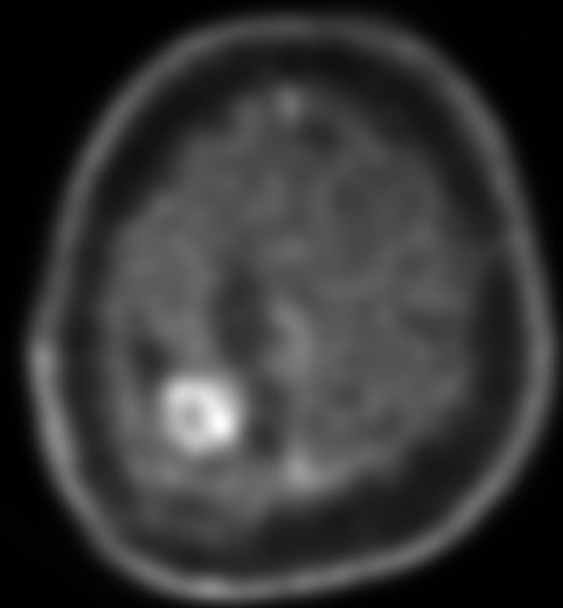
- Nizko maligni gliomi
 - PET za razmejitev infiltracije od edema
- Visoko maligni gliomi
 - pred ev reiradiacijo za razmejitev od poobsevalnih sprememb
- zasevki
 - po SRS ob progresu za razlikovanje od radionevroze



Stadlbauer et al, jnm
2011

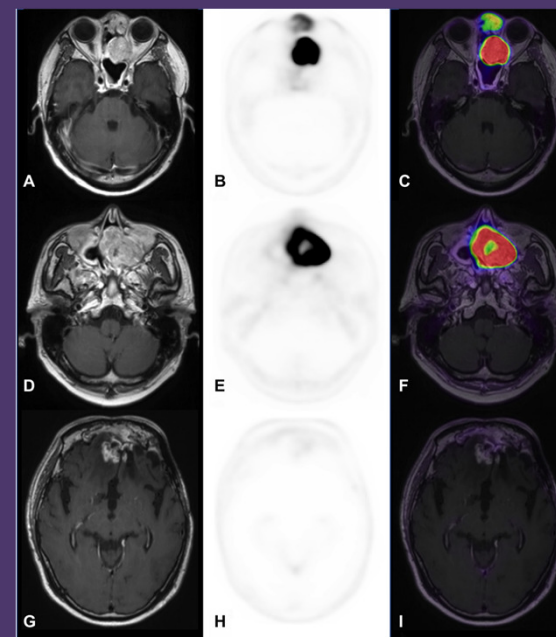


Sharma et al, ijnm 2016



CŽS

- Meningeomi PET CT DOTATATE
 - Preoperativno
 - Ocena radikalnosti resekcije
 - Pomembno WHO G II (RT da ali ne)
 - Relaps po RT
 - Relaps znotraj polja = omejen odmerk pri RT
 - DOTATATE korelira z izražanjem somatostatinskih receptorjev
 - Tarčno zdravljenje s somatostatinskimi analogi?



Ivanidze J et al 2019

Prospective Studies (n = 5)							
Chamberlain, 2007, USA [36]	16	WHO grade 1, 2, and 3	Sandostatin LAR im	PFS-6 *: 44%	Partial radiological response: 31% of patients	Ocreotide scintigraphy positive	Minimal toxicity
Graillon, 2020, France [40]	20	WHO grade 1, 2, and 3	Everolimus po + ocreotide LAR im	PFS-6: 55%	Anti-tumor activity (3D tumor growth rate)	SSTR2a detected in most patients using IHC	Stomatitis in 55% of patients, discontinuations of two patients
Johnson, 2011, USA [37]	11	WHO grade 1, 2, and 3	Ocreotide sc	None	None	SSTR status partly known	Mild adverse effects: diarrhea, nausea, anorexia, transaminitis
Norden, 2015, USA [38]	34	WHO grade 1, 2, and 3	Pasireotide LAR im	WHO grade 1: 50% WHO grade 2 + 3: 17%	None	High ocreotide uptake	Treatment well tolerated
Simó, 2014, Spain [39]	9	WHO grade 2 and 3	Ocreotide im	PFS-6: 44.4%	None	Positive ocreotide SPECT scanning	Minimal toxicity reported
Retrospective Studies (n = 3)							
Cardona, 2019, Colombia [33]	15 received ocreotide	WHO grade 2 or 3	Ocreotide ± everolimus	No difference in survival when comparing everolimus ± ocreotide, and sunitinib	Not reported	Confirmed overexpression of SSTR2	Fatigue and oedema
Furtner, 2016, Austria [34]	9 received somatostatin analog	WHO grade 2 and 3	Somatostatin analog	Not reported	No reduction in peritumoral edema or tumor size	SSTR status not reported	Not reported
Le Van, 2021, France [35]	8	WHO grade 1, 2, and 3	Everolimus + ocreotide	PFS-6 *: 60%, combination of ocreotide + everolimus	Not reported	SSTR status not reported	Not reported

* Progression-Free Survival at 6 months. Abbreviations: subcutaneous (sc), intramuscular (im), per oral (po), long-acting release (LAR), immunohistochemistry (IHC).

4. Conclusions

In conclusion, various efficacy of somatostatin analogs is reported by the included studies. None of the studies are randomized or controlled, and the overall quality of evidence is low. Further, the lack of standardized endpoints, imaging protocols and heterogenous case selection, and variation in drugs and doses limit the comparison of results across studies. In any case, the reported side effects of somatostatin analogs are sparse and well-known from other patient groups. **Given the possible effect observed in some studies, somatostatin analogs may present a safe last-option treatment in severely ill patients with treatment-refractory meningiomas.** However, only a properly controlled study, preferably a RCT study could clarify the efficacy on somatostatin analogs. Also, detection of potential treatment effects may perhaps be easier if done in a treatment-naïve and not a treatment-refractory clinical setting.

Zaključek

- PET CT v različnih oblikah prihaja v radioterapijo
- FDG je zlati standard ekstrakranialno (razen pri prostati)
- aminokislinski PET intrakranialno
- Kdaj in kje standard?

Povezave:

http://www.eanm.org/publications/guidelines/PET_in_Radiotherapy_Planning.pdf

http://www.eanm.org/content-eanm/uploads/2016/11/gl_PET-CT_Radiotherapy_Planning_Part_3.pdf

https://www-pub.iaea.org/MTCD/Publications/PDF/te_1603_web.pdf

Specialne tehnike v radioterapiji

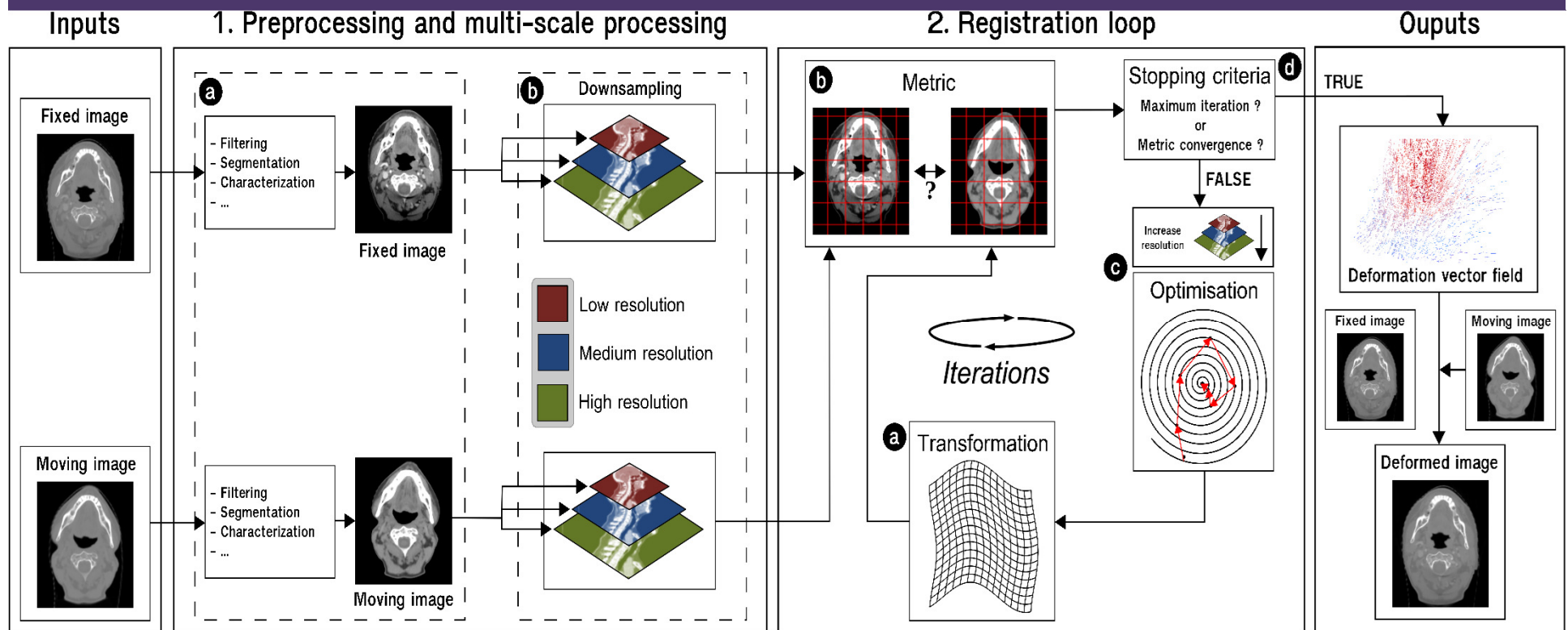
Registracija medicinskih slik
doc. dr. Uroš Smrdel dr. med.

Slikanja, ki se uporabljajo v RT

- Planarna RTG slika
- aksialni CT
- MR
- PET-CT
- UZ
- Funkcionalni MR
- 4D CT

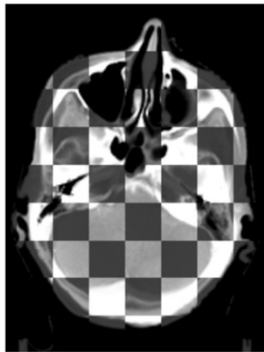
- Pravilna razporeditev doze je možna samo če je planirna slika posnetek bolnikove anatomije in patologije v daljšem opazovanem obdobju
(Seungjong Oh, Siyong Kim, Radiat Oncol J. 2017)
- Registracija slik je način kako najti prostorsko ujemanje med dvema ali večimi slikovnimi preiskavami
- $F(x) = M(T(x')) = M(x' + u(x'))$
 - $F(x)$: fiksni set, $M(x)$: premični set, $T(x')$: transformacija, ki zmanjša razliko med $F(x)$ in $M(T(x'))$, x' : pozicijski vektor gibljive slike, $u(x')$: vektor premika

- 2 skupini registracij
 - Rigidna registracija
 - vsi piksli (voksli) se premikajo in rotirajo enako
 - odnos med piksli (voksli) je pred in po registraciji enak
 - Nerigidna (deformabilna) registracija
 - odnosi med piksli (voksli) registrirane slike se po registraciji spremenijo

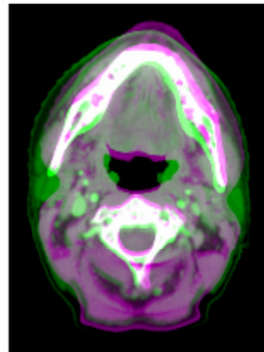


A Visual criteria

Checkerboard



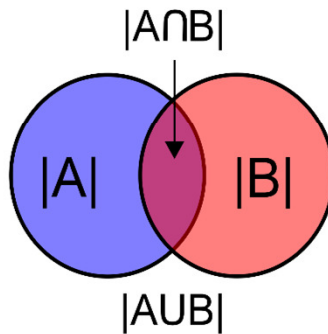
Overlay



Absolute difference



B Delineation scores



$$DSC = 2 \times \frac{|A \cap B|}{|A| + |B|}$$

$$JACCARD = 2 \times \frac{|A \cap B|}{|A \cup B|}$$

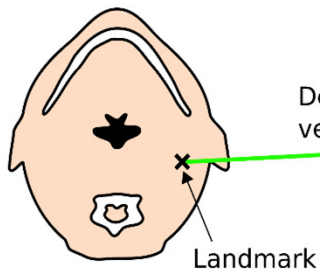
$$OVERLAP = \frac{|A \cap B|}{\min(|A|, |B|)}$$

$$HD = \max\{d(A, B), d(B, A)\}$$

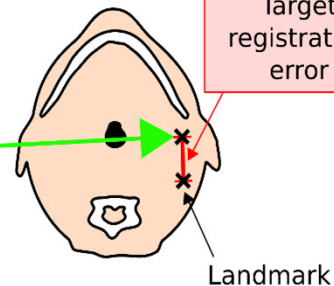
where: $d(X, Y) = \max_{x \in X} \min_{y \in Y} \|x - y\|$

C Landmarks

Fixed image



Moving image

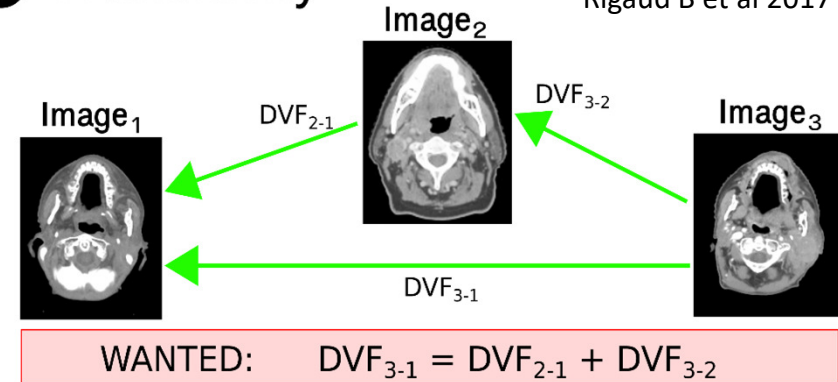


Deformation
vector field

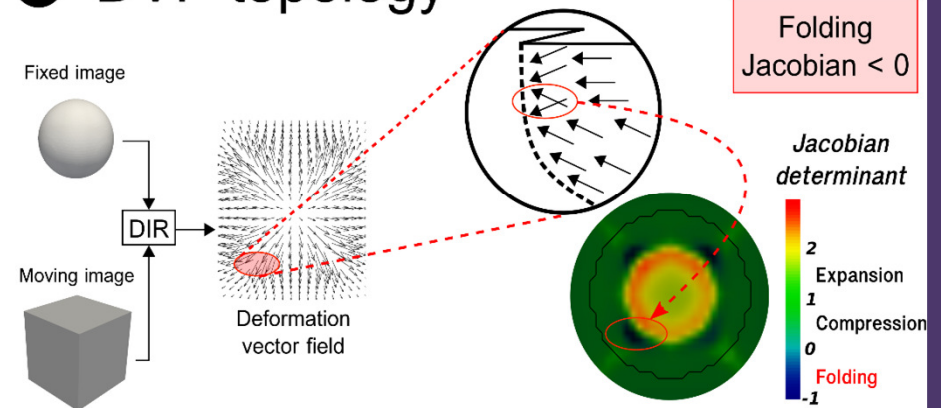
Target
registration
error

D Transitivity

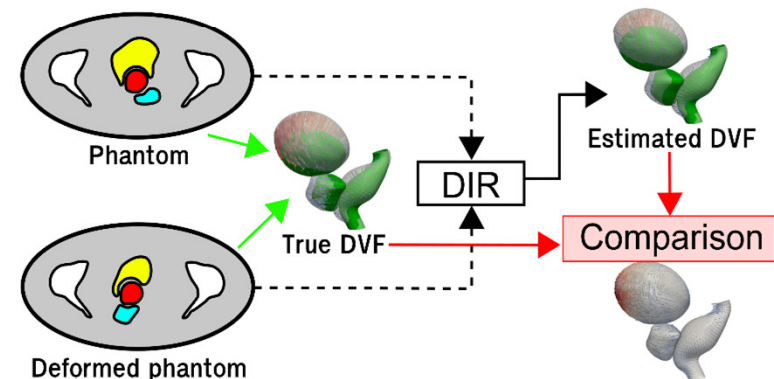
Rigaud B et al 2017



E DVF topology



F Phantom evaluation



- Več metod deformabilne registracije
 - Demons algoritem
 - Izračunan premik vsakega voksla, minimizira razliko v intenziteti – optimiziran za iste metode – CT-CT
 - „Prosta“ deformacija
 - Set kontrolnih točk, ki se vektorsko preoblikujejo
 - Deformacija prek izstopajočih točk
 - Geometrijska metoda, posebej uporabna npr. Pri CT-MR registraciji
 - Biomehainčni model
 - Upošteva Hookov zakon in obravnava mehka tkiva kot elastičen material
 - Hibridna registracija
 - Združuje prej opisane metode

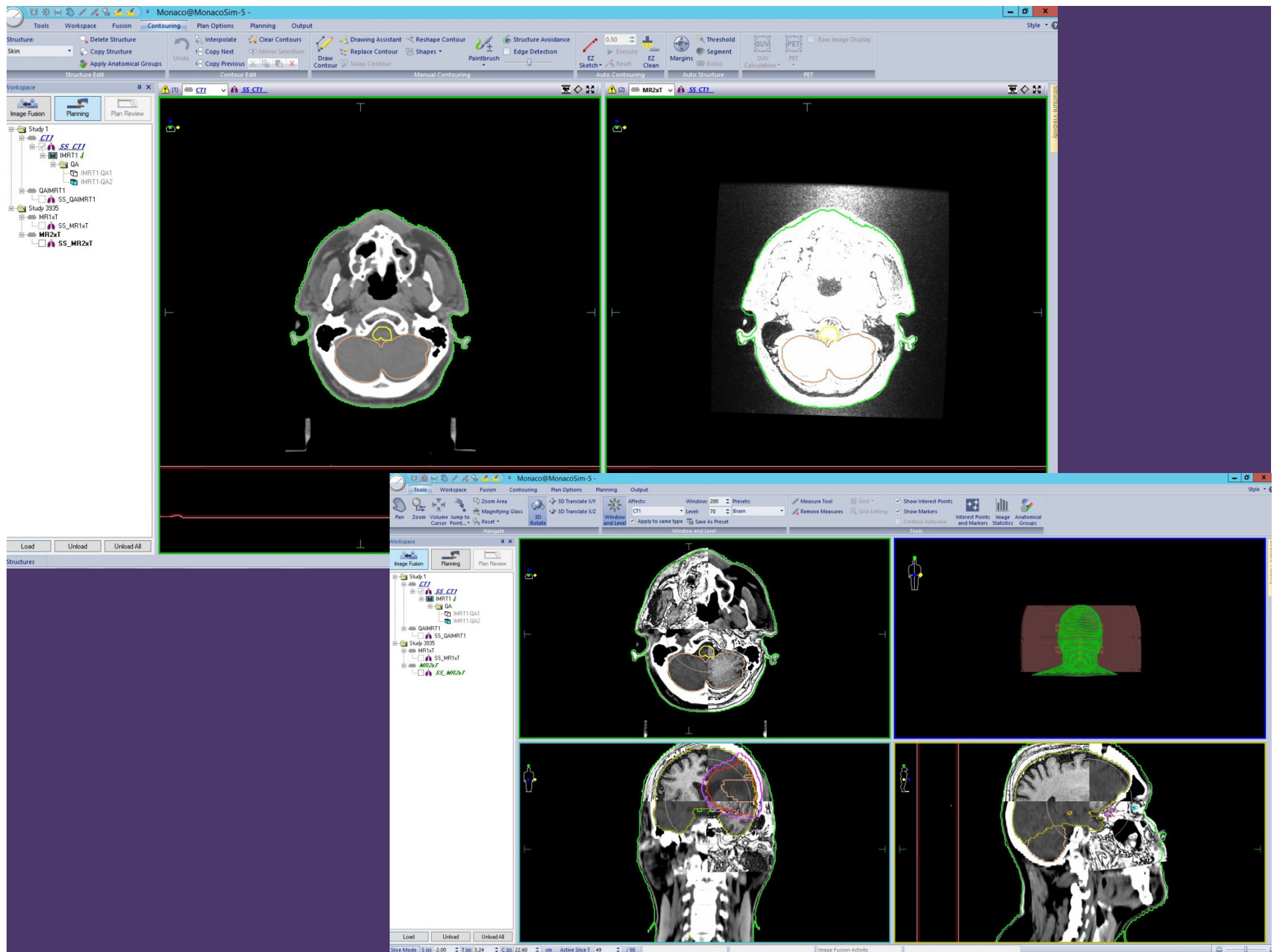
- Vse metodo potrebujejo verifikacijo
 - Vizualna
 - Primerjava segmentov
 - Izračun točkovnih napak
 - Izračun deformacije vektorskih polj
 - Deformabilni fantomi

Rigaud et al Acta oncologica 2017

- Najenostavnejša
 - kjer ne pričakujemo sprememb v anatomiji
 - primer CT – MR glava
 - algoritem je odvisen od načrtovalnega sistema
 - Monaco – kvazi 3D (nova verzija 3D, tudi ne rigidna)
 - Eclipse – 3D (načeloma tudi ne rigidna)
 - BrainLab – 3D (načeloma tudi ne rigidna)

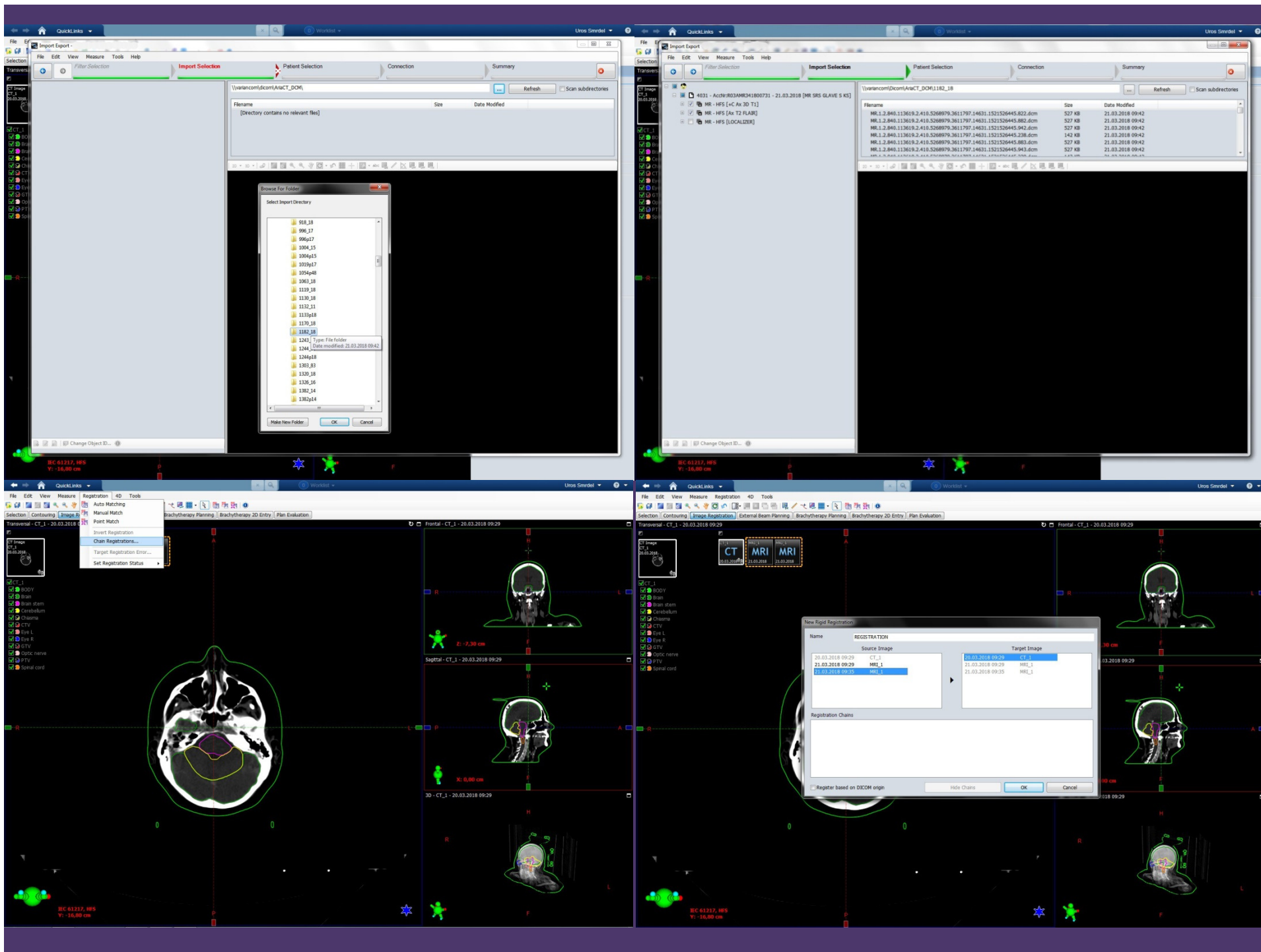
Primer: CŽS

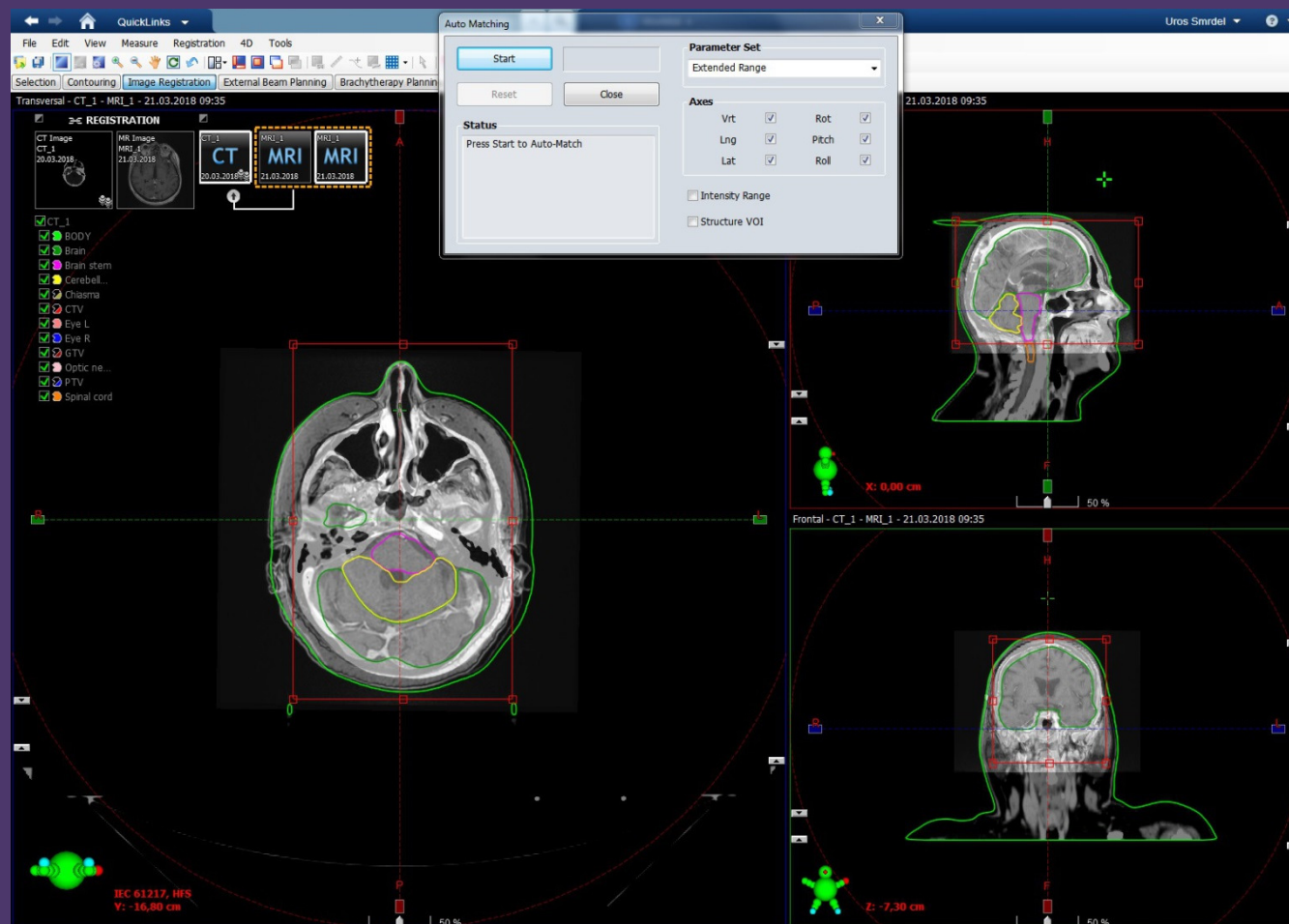
- Monaco: registracija pri RT možganskega tumorja
 - posebnost sistema je, da Monaco obravnava volumne kot vektorske slike
 - nujne so aksialne rezine
 - možna rotacija do 15°
 - 3D sekvenca zaobide omejitve

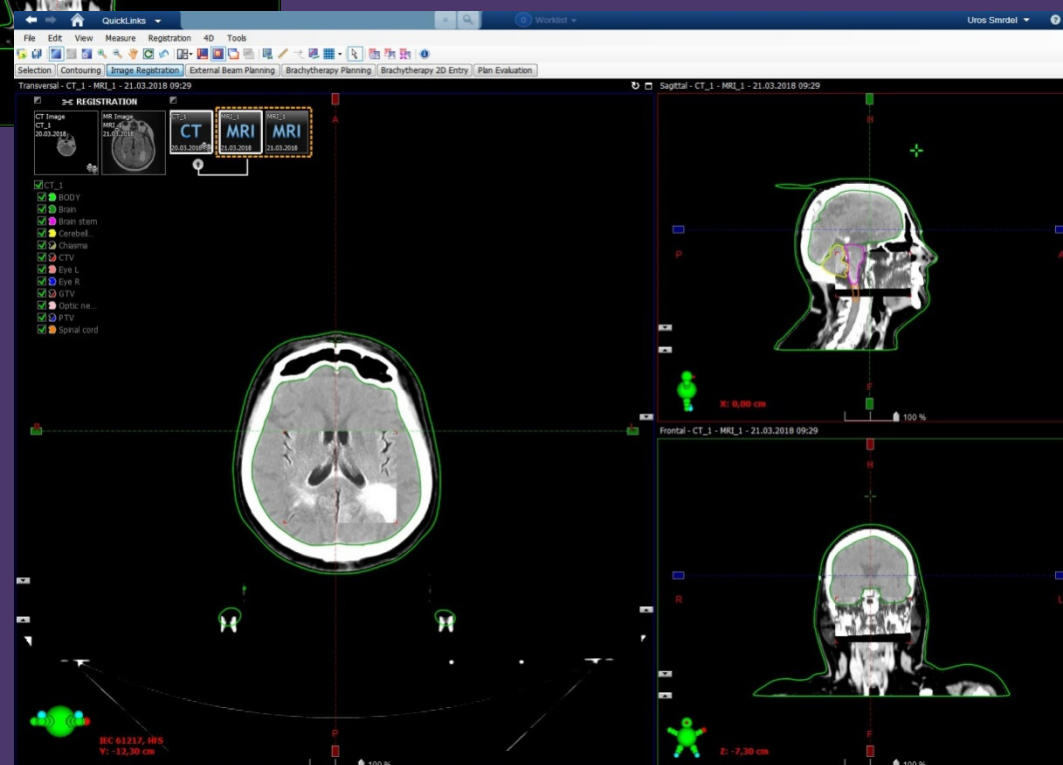


Primer: CŽS

- Eclipse: registracija pri RT možganskega tumorja
 - volumni obravnavani kot rastrske slike
 - lahko tudi sagitalne in koronalne ravnine
 - vrisovanje na aksialnih slikah, je pa tudi možno v koronarni in sagitalni ravnini
 - 3D sekvenca zaobide omejitve

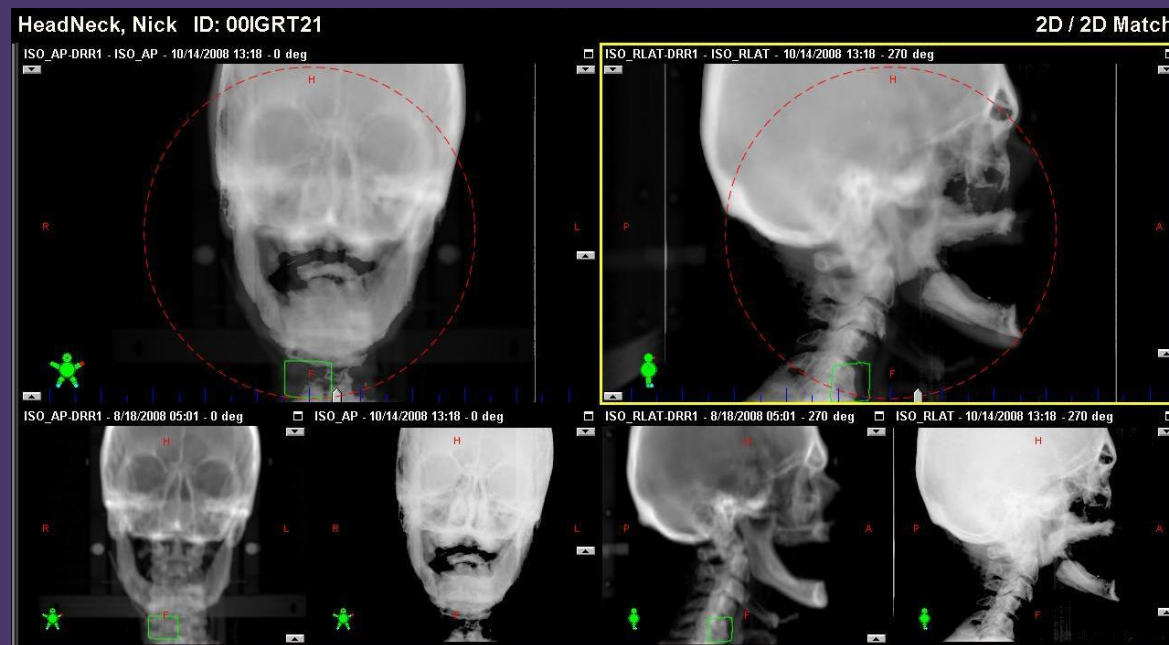






Primer CŽS

- primer registracije slik je tudi portalno slikanje
- rigidna transformacija, kjer pridobiš podatke



Varian Medical Systems

Primer CŽS

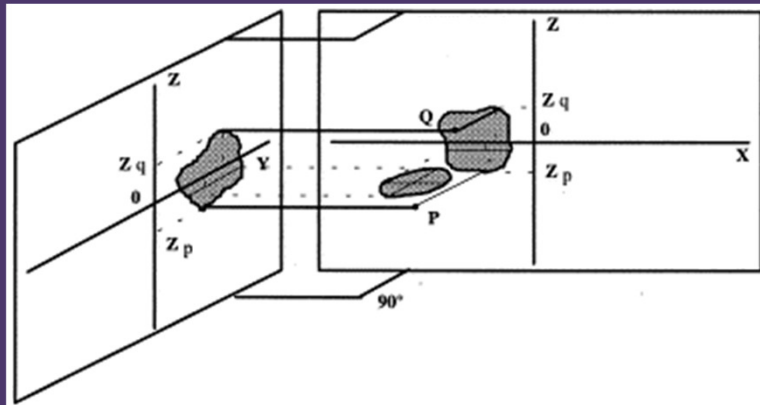
- podobno kot pri portalnem slikanju
- rigidna transformacija $\longrightarrow$ premik



MedIND

Primer CŽS

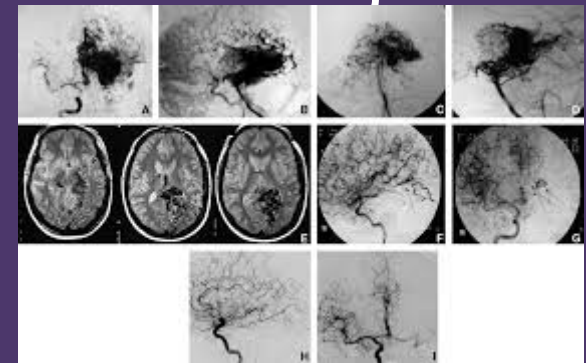
- pri radiokirurgiji arteriovenskih malformacij
 - planarna slika DSA
 - planirni CT
 - problem distorzije – distorzijska plošča



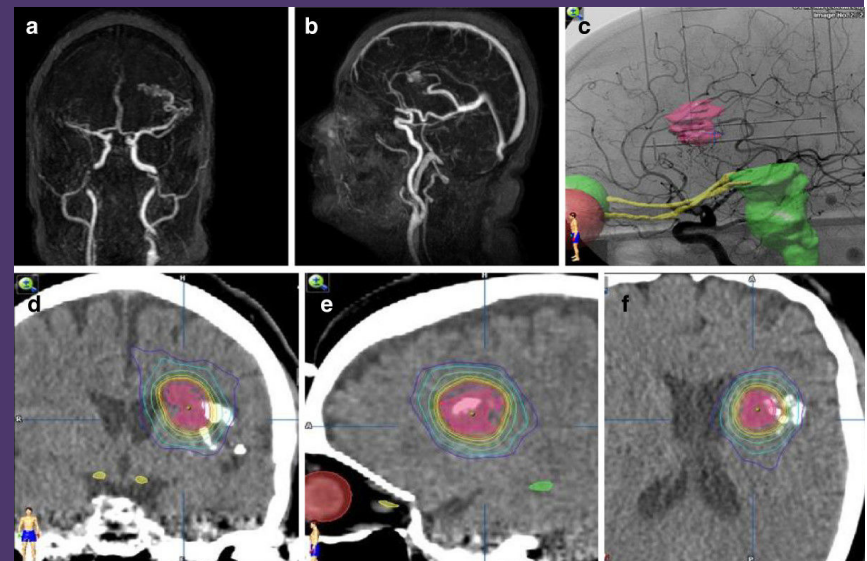
Coste E et al, IJROBP 2001

– MRA brez DSA?

Boström J et al, Radiation Oncology 2013



Neurosurgery Blog

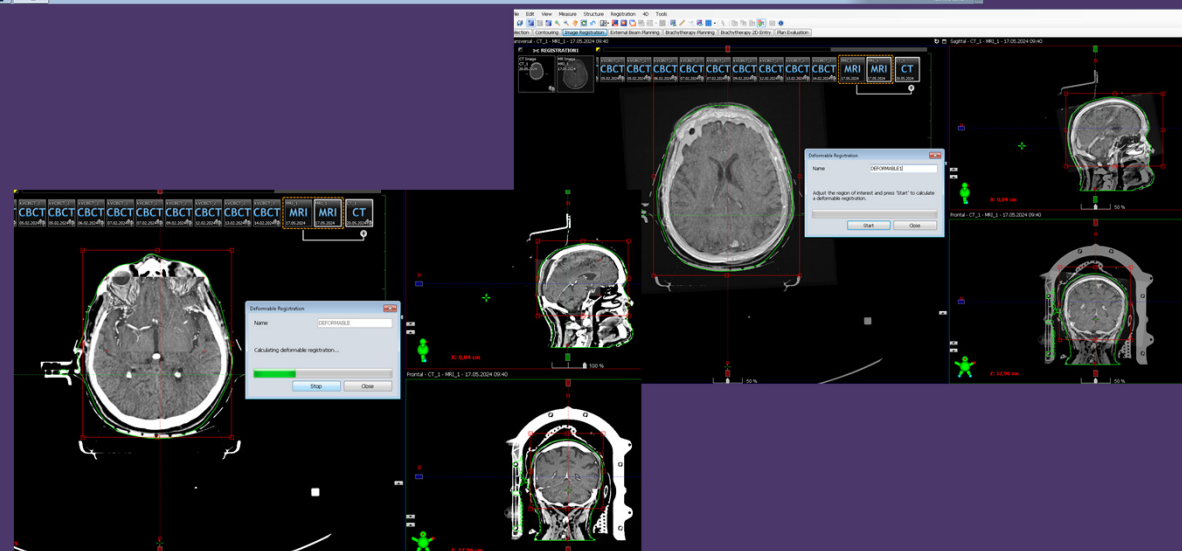
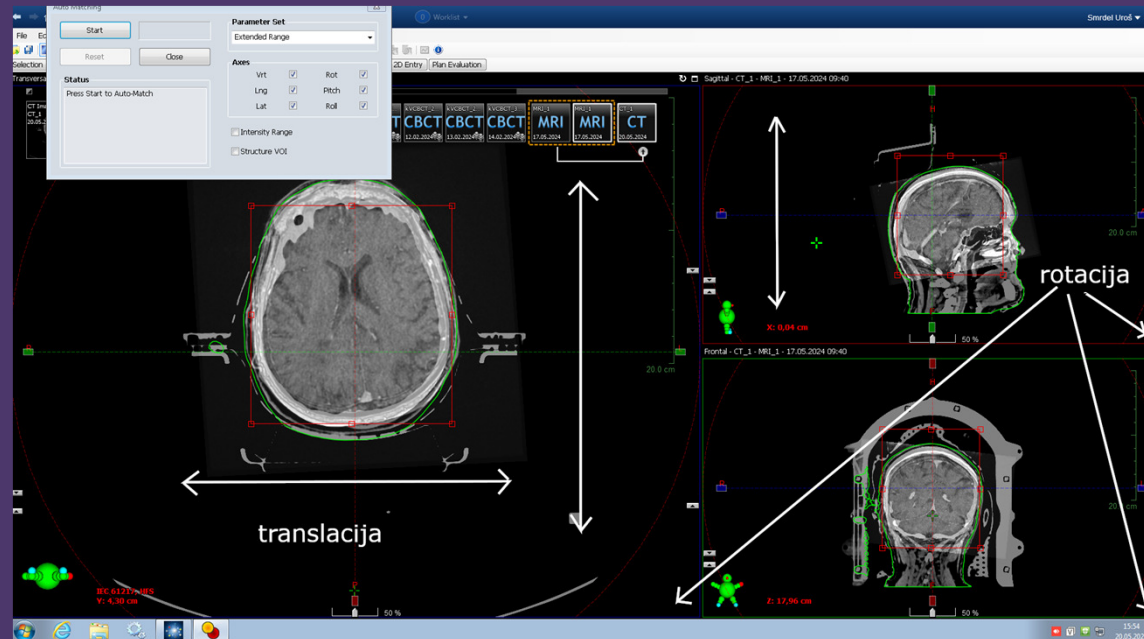


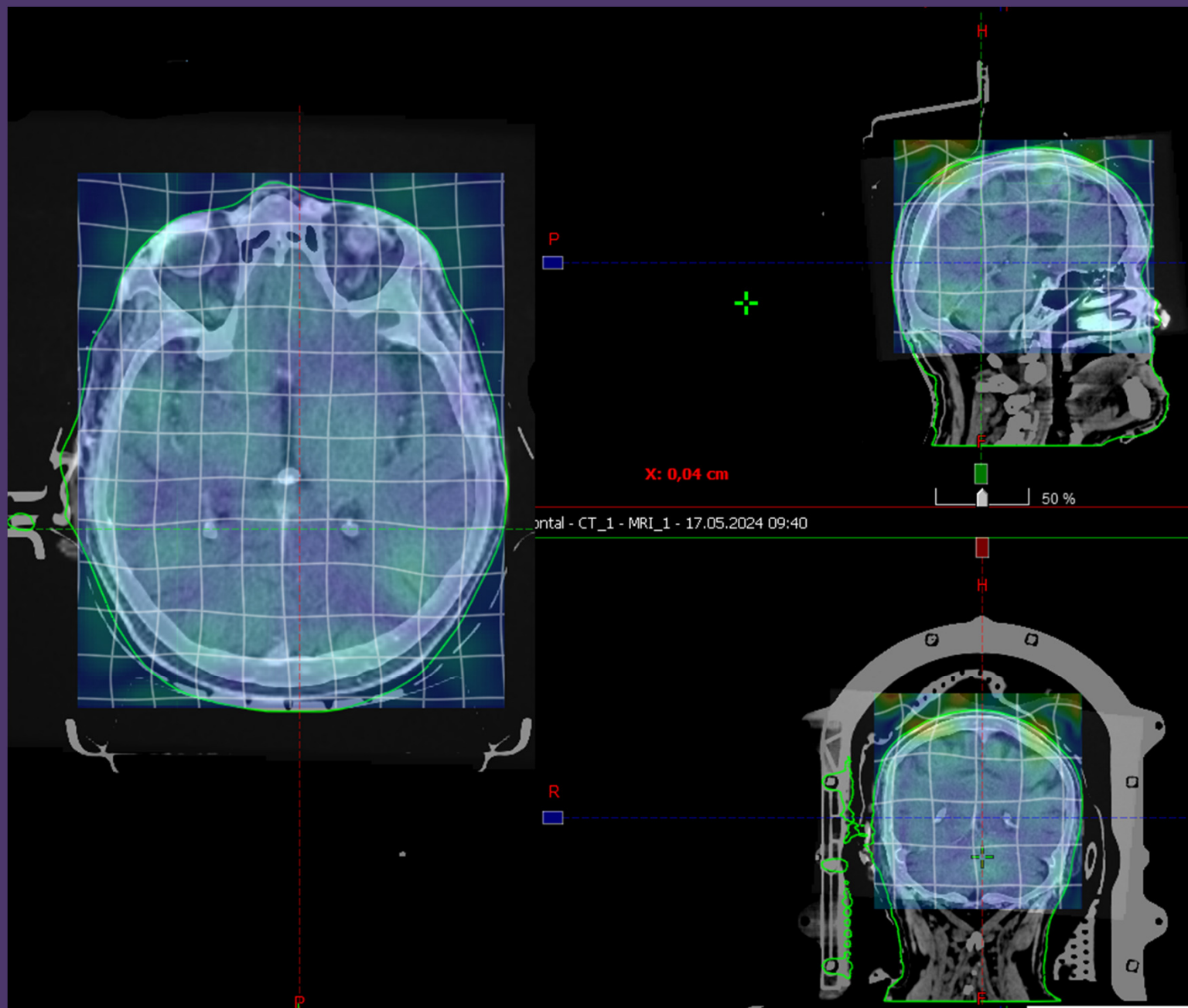
Primer CŽS

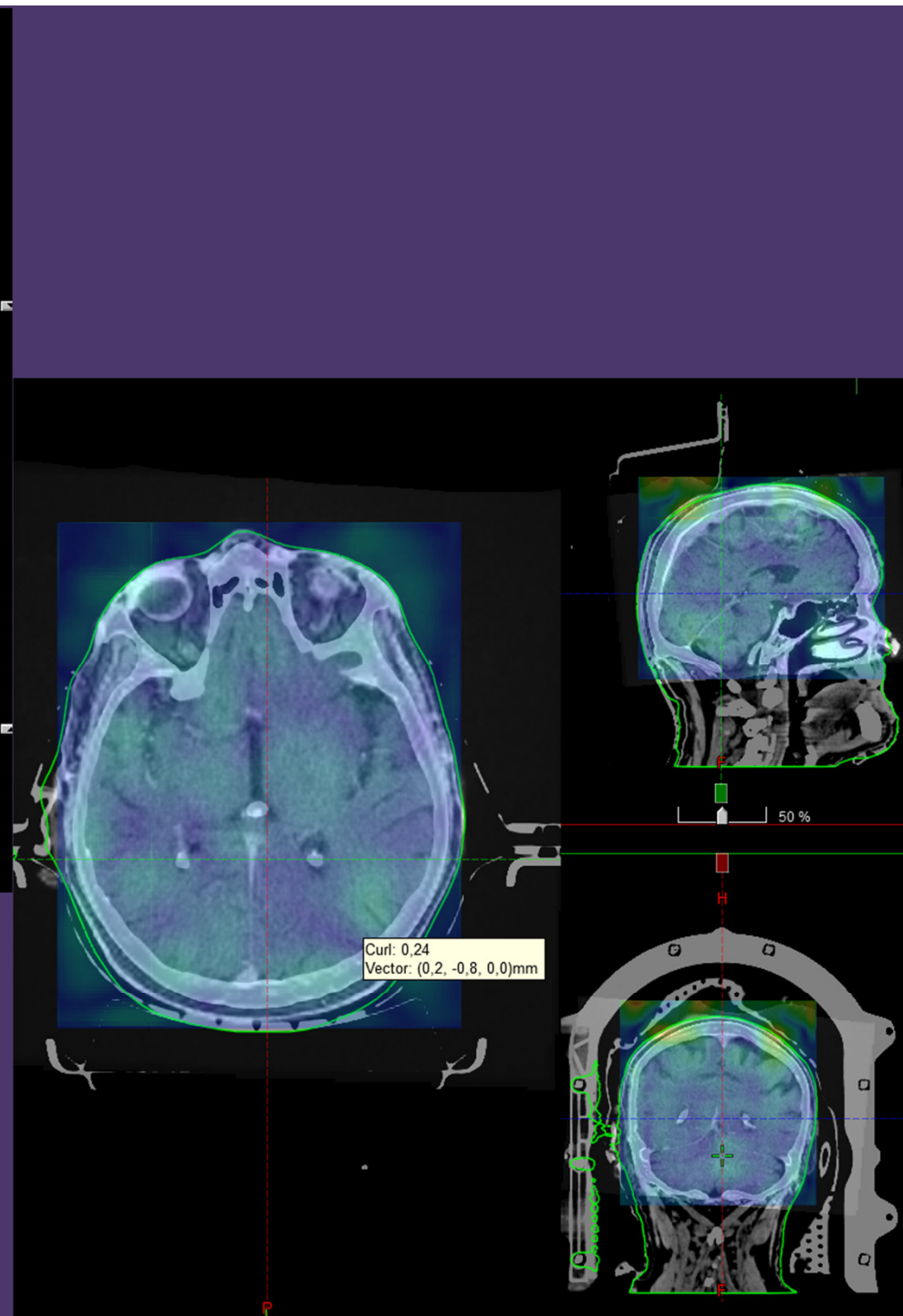
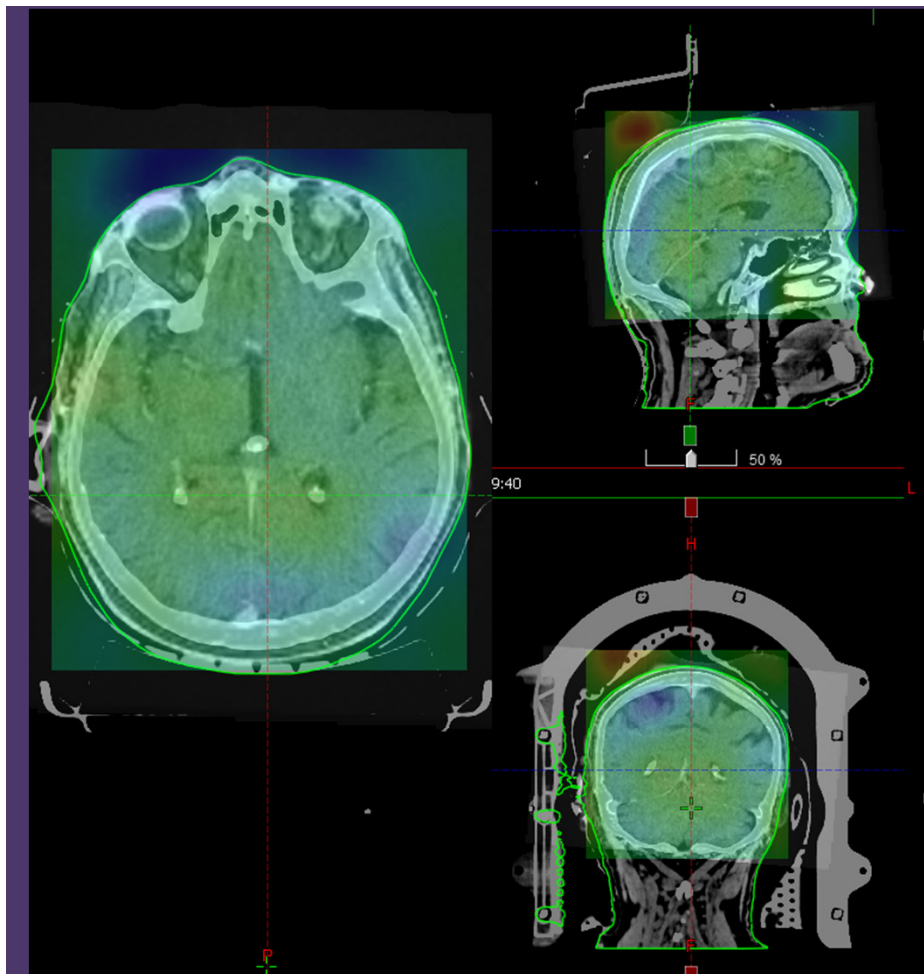
- HyperArc

— Rigidna

— deformabilna





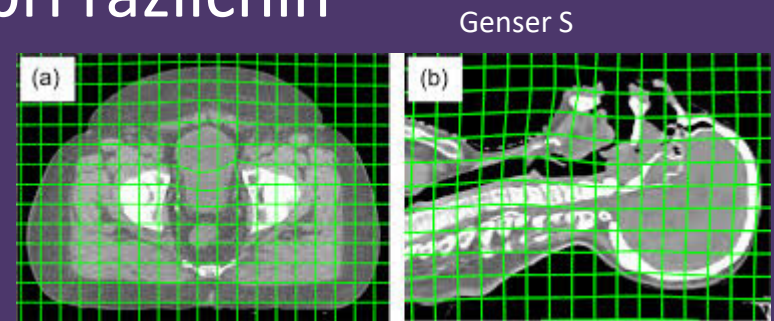


Primer CŽS

- Bolj kot metodi podobni lažja je registracija
 - CT-portalna slika samo večji premiki
 - CT-MR problem signala tkiv manjši pa glede na sivine
 - CT-FETPET v RT uporaba FETPET seta z že opravljeno registracijo z diagnostičnim Ctjem
 - Registracija je odlična, datoteke so velike

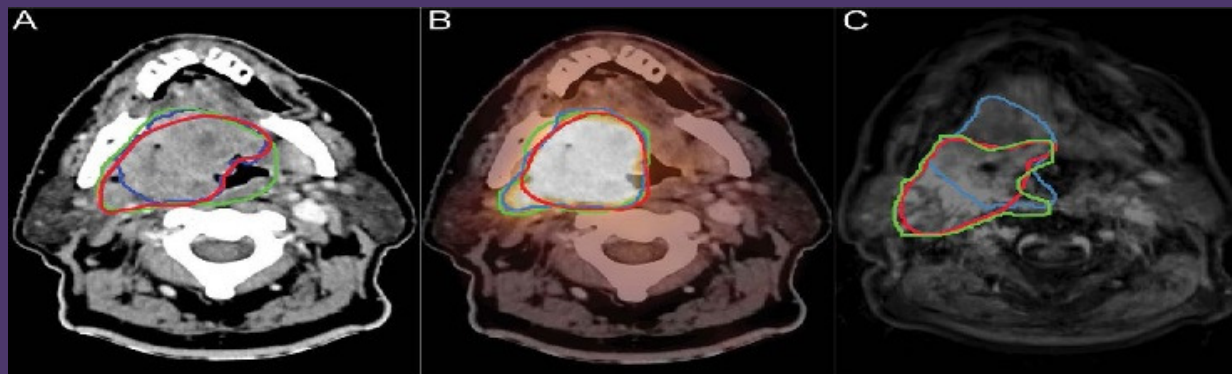
ORL

- za razliko od CŽS, rigidna transformacija manj primerna
 - problem nastavitve bolnika pri različnih modalitetah
 - MRI simulator $\pm$ CT simulator
 - PET-CT simulator
 - elastična transformacija



Obeidat M et al, Biomedical Physics & Engineering Express 2016

Anderson CM et al, Jacobs Journal of Radiation Oncology 2014



Mott SL 2014

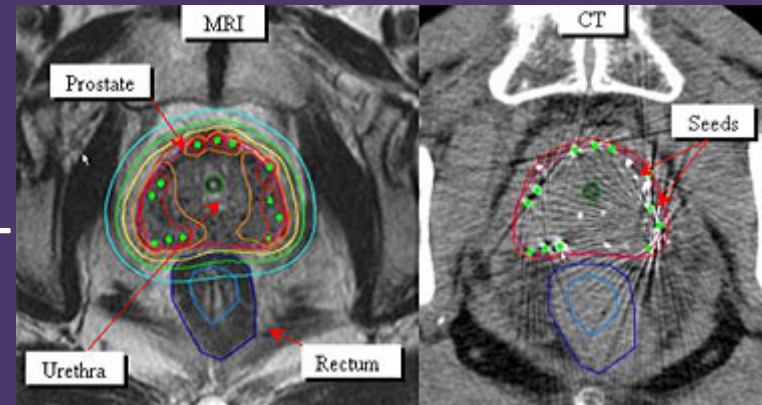
- Najpogostejše pri uporabi PET
 - Rigidna registracija napake do 11 mm brez imobilizacije
 - Z nerigidno registracijo so napake do velikostnega reda 5 mm

Medenica

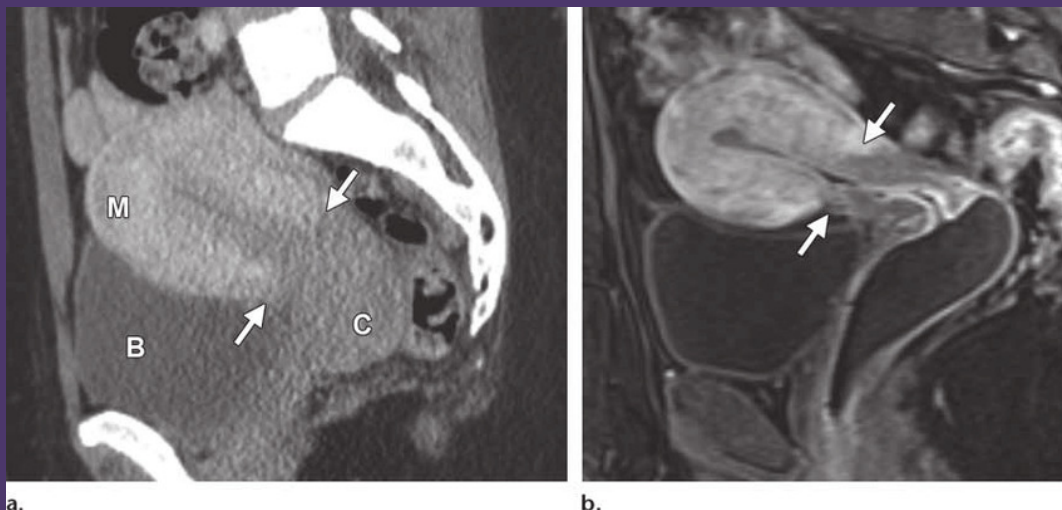
- številne kostne strukture – omogočajo fuzijo kost – kost
- organi v medenice se premikajo glede na:
 - polnjenost mehurja
 - polnjenost rektuma
 - običajni premiki

Medenica

- implantacija markerjev
 - fuzija na markerje in CBCT ne na kosti
- enaki fiziološki pogoji
 - pitje tekočin, dieta...

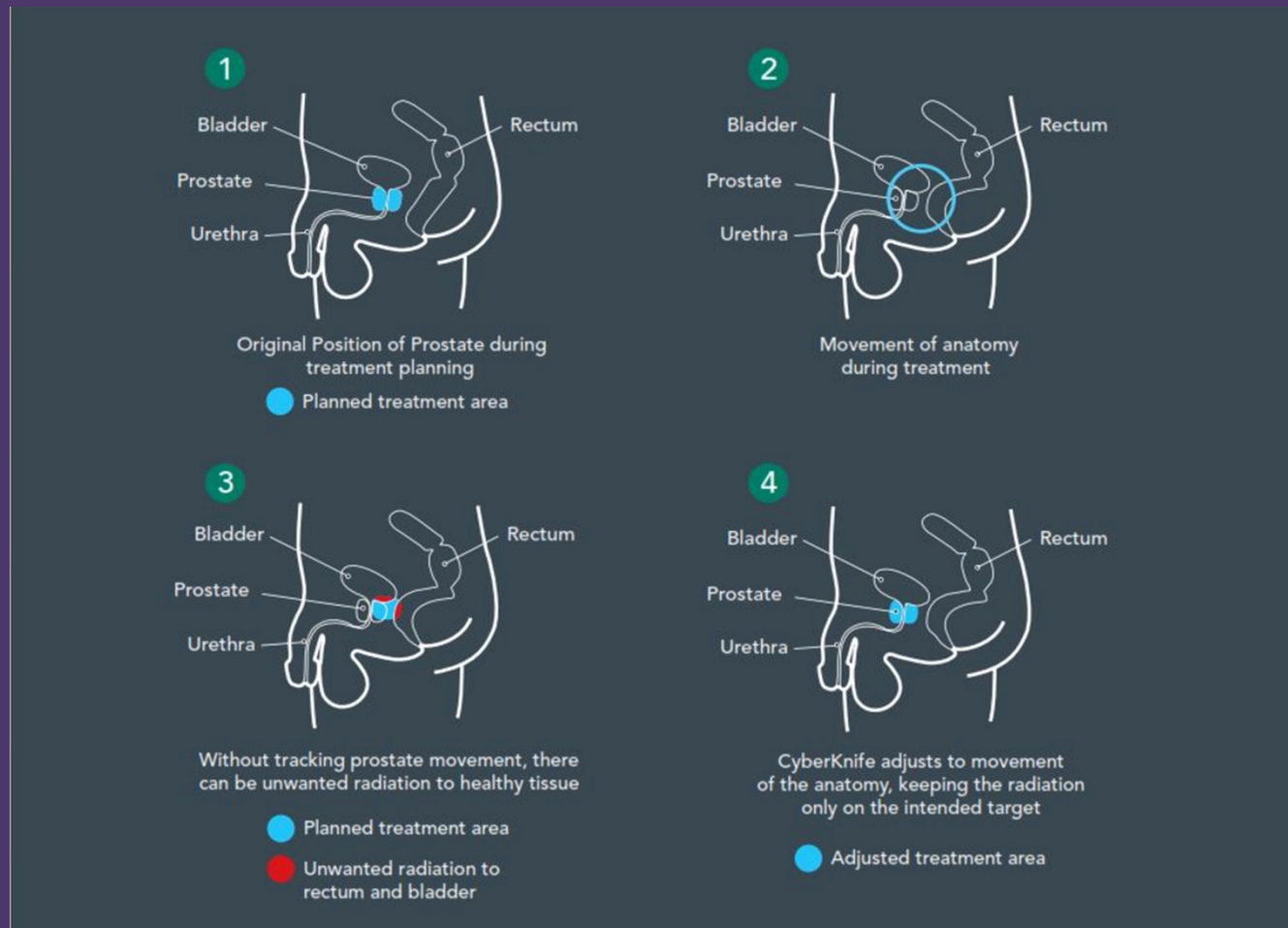


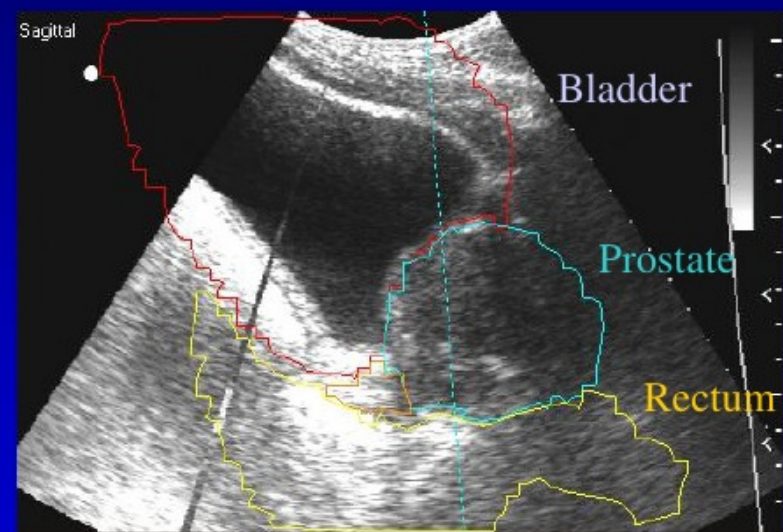
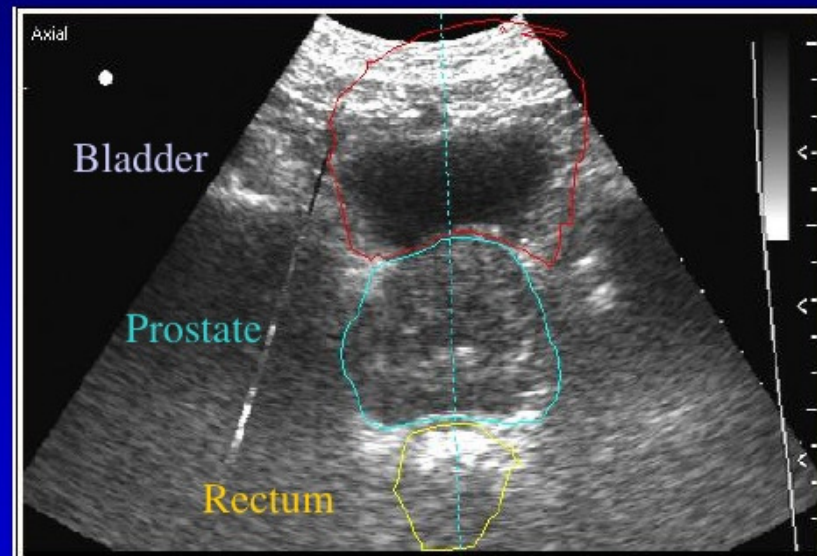
<https://www.mygenesishhealth.com/treatment-options/genesis-prostate-cancer-center/images/figures.htm>



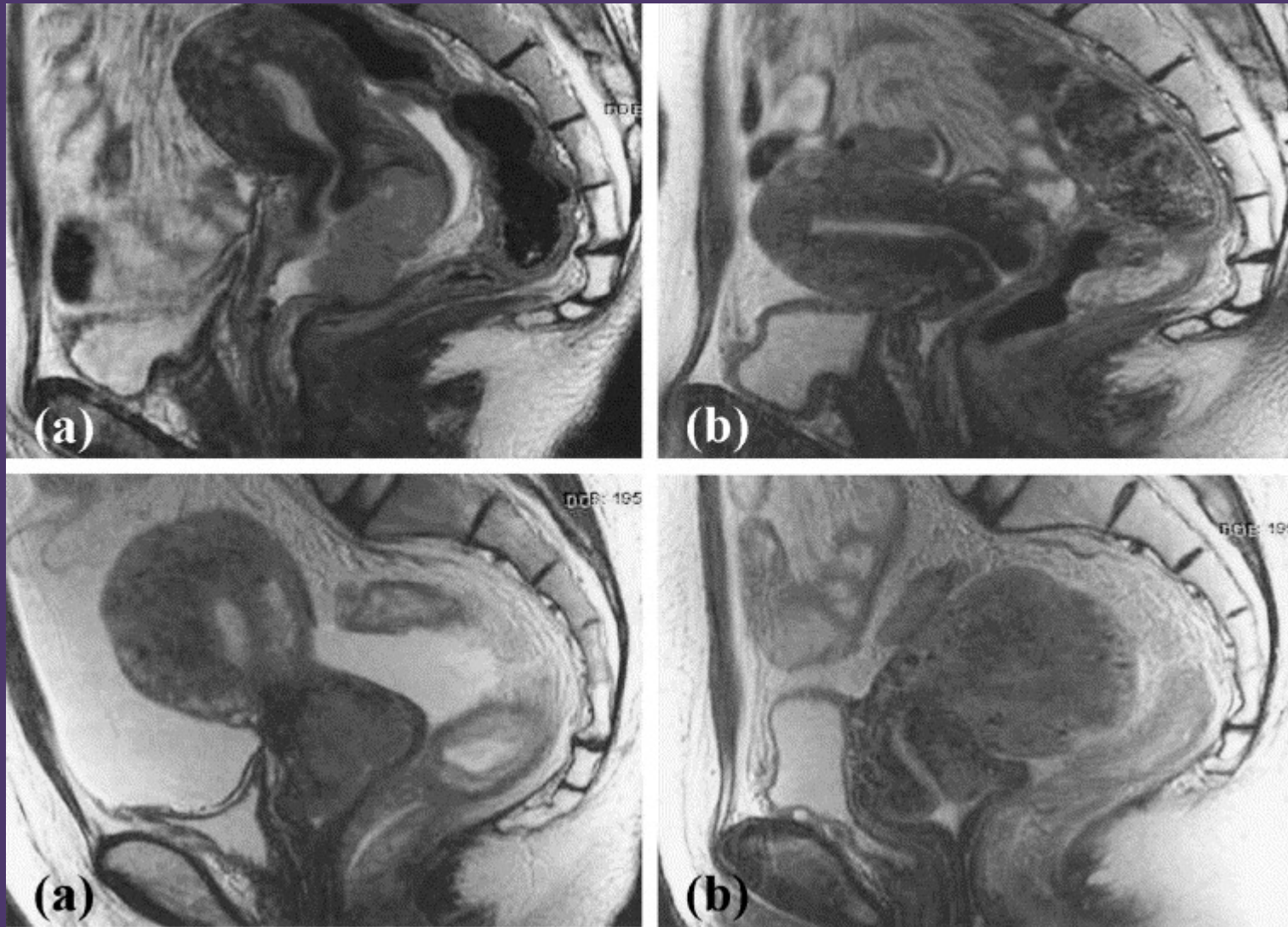
Yitta et al, research gate

Medenica





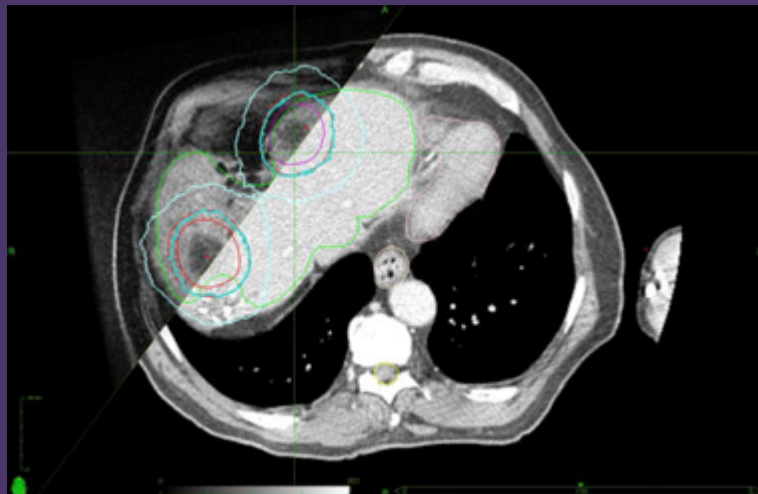
Medenica



Yae Hun S, Radiotherapy and Oncology 2004

Jetra

- jetra so organ, kjer je prisotno premikanje v dihalnem ciklusu
- rešitev:
 - kompresija
 - fuzija z implantiranimi markerji



Mendez Romero A et al, Best Practice & Research Clinical Gastroenterology 2016

Hrbtenica

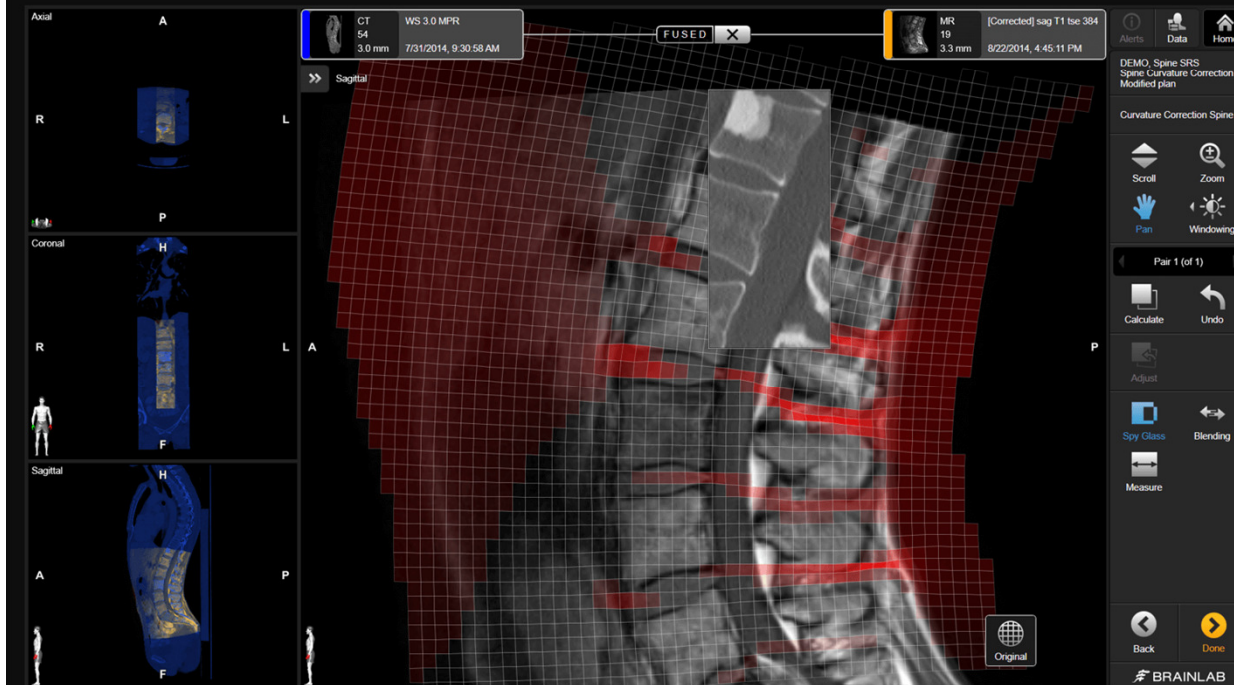
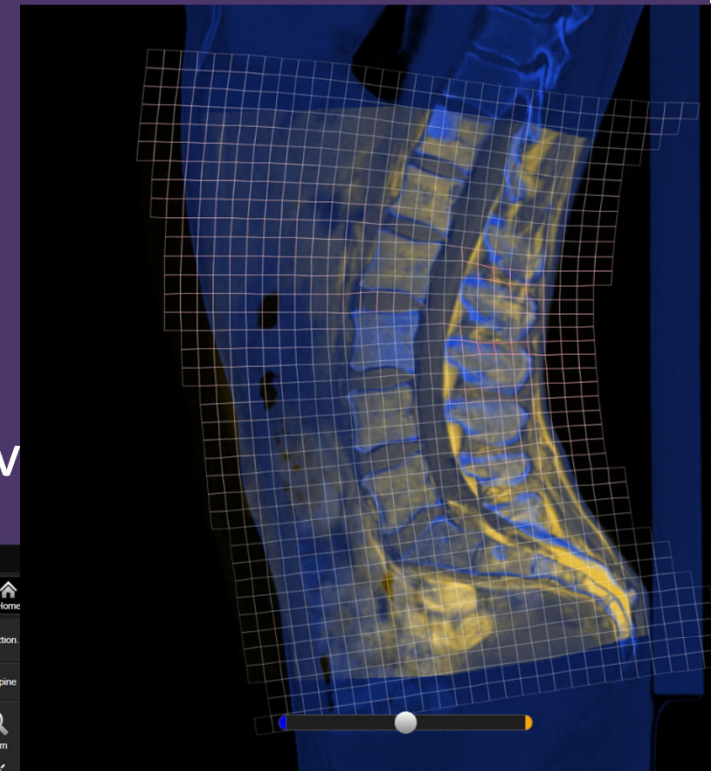


http://digitalimaginggroup.ca/ispine/spine_image_fusion.html

- sicer se ne premika
- se pa pri različnih slikanjih ukrivljenost spreminja
 - elastična fuzija
 - MRI simulacija

Hrbtenica

- Vretenca NISO deformabilna
- Mehka tkiva SO deformabilna
 - Edino BrainLab upošteva to dejstvo



Specialne tehnike v radioterapiji

Slikovno vodena radioterapija
(praktični pogled)

doc. dr. Uroš Smrdel dr. med.

Definicije

- Image-guided radiation therapy (IGRT) is the use of imaging during radiation therapy to improve the precision and accuracy of treatment delivery (www.radiologyinfo.org)
- Image guided radiotherapy (IGRT) is a type of conformal radiotherapy. Conformal radiotherapy can shape the radiotherapy beams around the area of the cancer. (www.cancerresearchuk.org)
- Image-Guided Radiation Therapy (IGRT) refers to the use of imaging, usually CT scans and X rays, to help precisely target the cancer with radiation therapy (www.targetingcancer.com.au)
- Image-guided radiation therapy (IGRT) is the process of frequent two and three-dimensional imaging, during a course of radiation treatment, used to direct radiation therapy utilizing the imaging coordinates of the actual radiation treatment plan (<http://advancedradiationcenters.com>)
- Vse definicij držijo vsaka pove samo malo

- RT razvojno povezana s slikovnimi metodami
- 3D metode (diagnostika, konturiranje, izračun)
  prileganje doze tarči
- Integracija slikovnih metod v obsevalni prostor
  zmanjšanje nesigurnosti

**IGRT je nujen in naraven del vsakega
natančnega obsevanja v radioterapiji**

Problemi

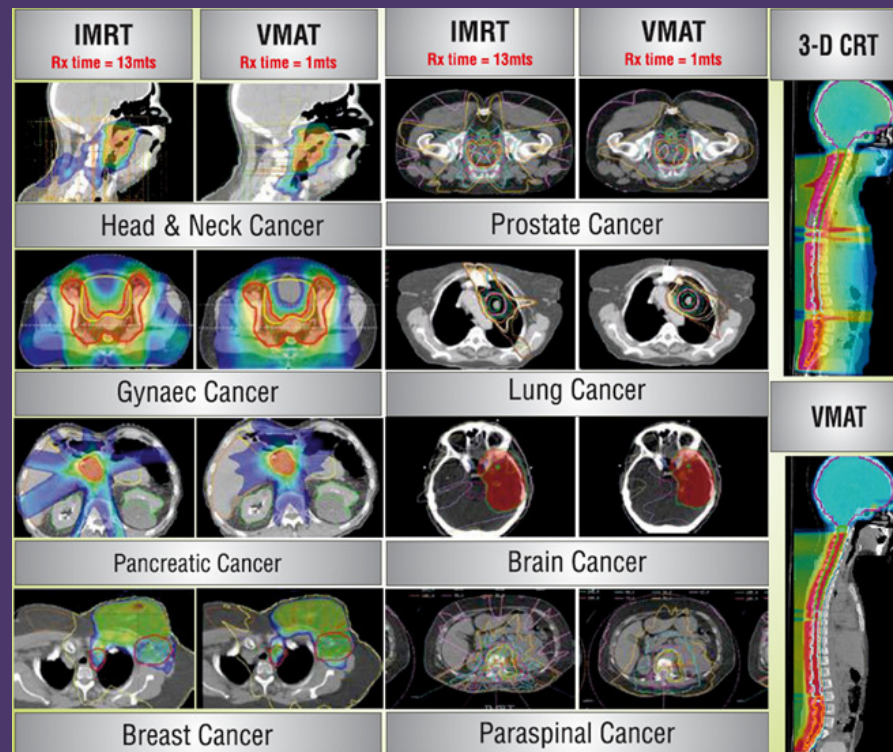
- Potratno z resursi
- Dodatna doza zaradi slikanja

AMPAK

- Natančnost = znižanje doze na zdrava tkiva
- Posledično dvig TD
 - Izboljšan terapevtski indeks
 - Več ozdravljenih z manj stranskimi učinki
- Prihranek za zavarovalnico

KDAJ

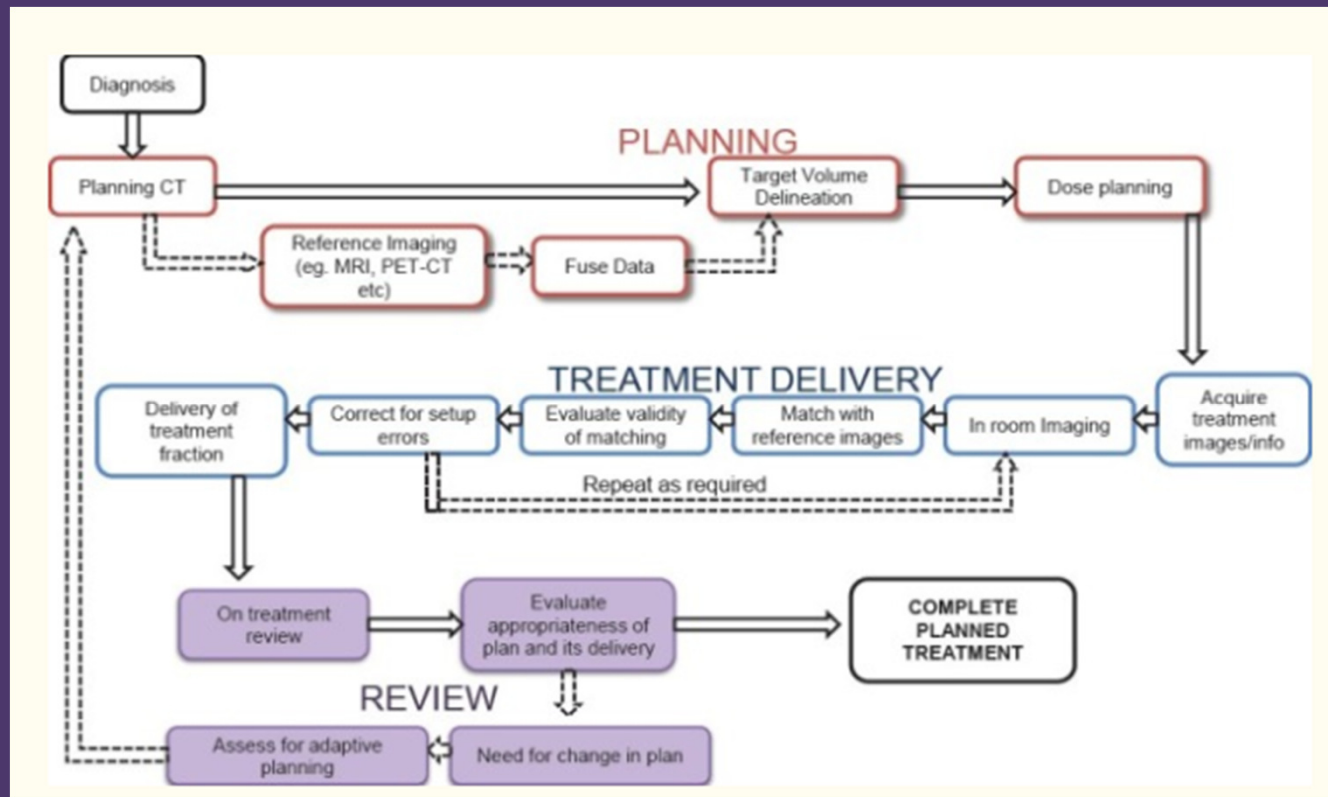
- 3D-CRT?, IMRT, SRS/SRT, SBRT, VMAT!
 - Tudi 3D-CRT, če zaradi tega intervencija
 - Ostale tehnike so odvisne od IGRT



3 nujni koraki

- Slikanje
 - Registracija
 - Analiza
-
- Intervencija (če potrebna)
 - Strategije za ukrepanje





Gupta T, Anand Narayan C., J Med Phys. 2012

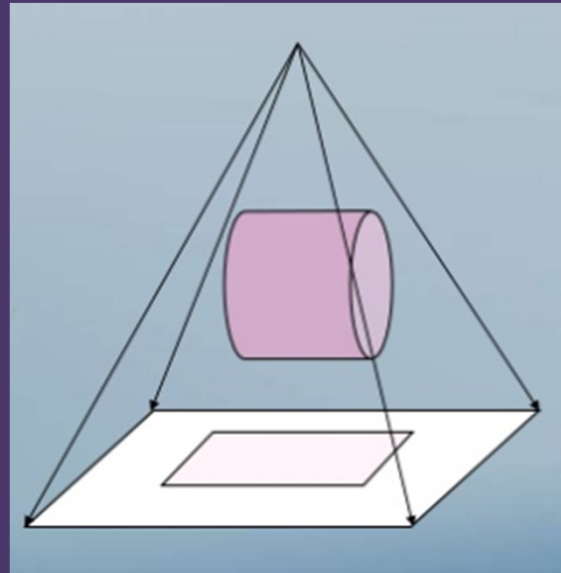
Cilji

<i>Attributes</i>	<i>Outcome</i>	<i>Results</i>
Technical performance	Set-up error	Can be quantified and minimized
	Intra-fraction organ motion	Early data, needs further validation
	Inter-fraction organ motion	Can be quantified and corrected
Feasibility	Patient compliance	Fair
	Learning curve	Steep
	Cost	Expensive
Safety	Acute adverse event/toxicity	Significant reduction
	Late adverse event/toxicity	Data not mature
Clinical efficacy	Surrogate outcomes	Significant improvement in selected tumors (prostate, head-neck)
	• Tumor response	
	• Local control	
	Secondary outcomes	Significant positive impact on quality of life in most sites
	• Disease-free survival	
	• Quality of life	
	Primary outcomes	No robust data as yet
	• Disease-specific survival	
	• Overall survival	

Gupta T, Anand Narayan C., J Med Phys. 2012

Tehnike

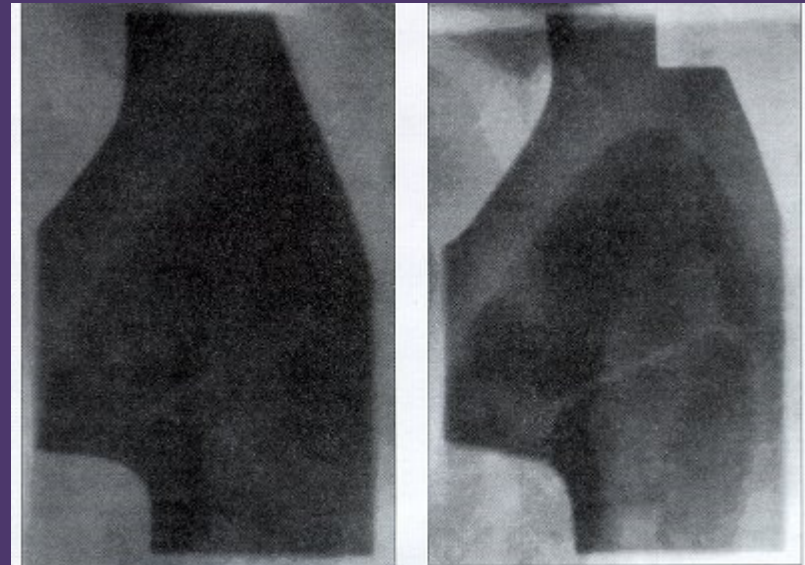
- Število dimenzij
- Modaliteta
 - Gama
 - MV
 - kV
 - CBCT
 - MR
 - UZ



Basran PS 2015

Gamagrafija

- V realnosti začetek IGRT
- Časovno požrešna
- Ni on line
- Natančnost slaba
- Najde velika odstopanja
- Pod 0,5 cm???



These two portal localization radiographs of the chest (left anterior oblique projection with shaping blocks in place, made at 6 MV) show the difference in image quality using a conventional direct exposure screen-film combination (left) and the Kodak EC-L film system (right).

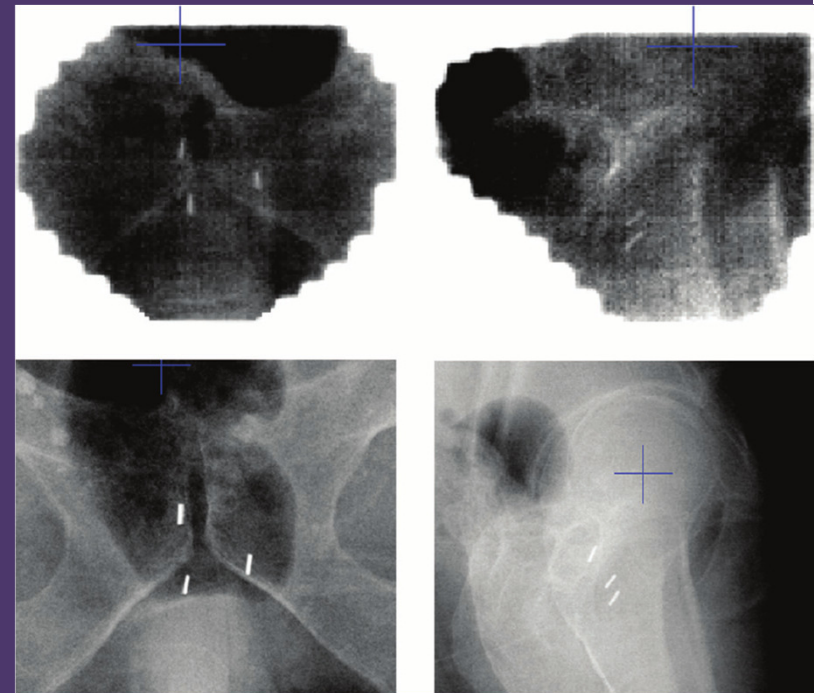
<http://www.cancernetwork.com> 1997



Frascino V et al 2013

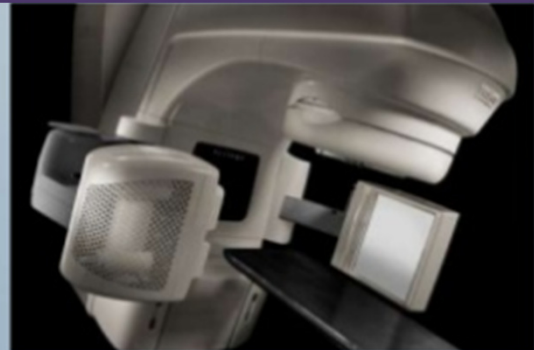
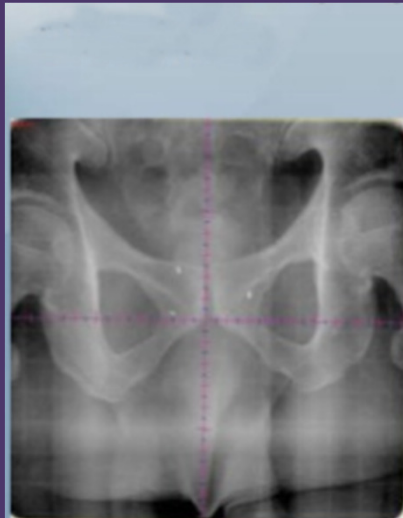
MV portalno slikanje

- Jasen napredek od gamagrafije
- Realnočasovno
- Resolucija slabša
- Kontrast običajno boljši
- Registracija boljša
- Odvisno od proizvajalca



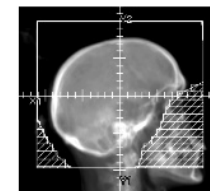
KV portalno slikanje

- Realno časovno
- Izboljšanje resolucije
- Izboljšanje kontrasta
- Avtomatiziran izračun (Cyberknife),
polavtomatski (Varian, Elekta, BrainLab)

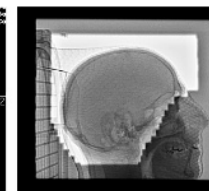


Anees K 2014

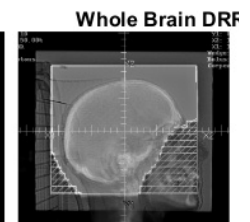
Treatment Verification: Portal Imaging



Reference DRR Right Lat

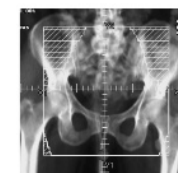


Treatment day Right lat portal image

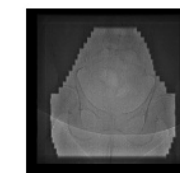


Registered DRR and portal image

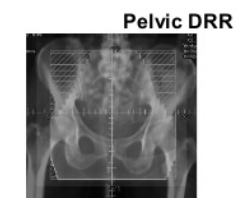
Whole Brain DRR



Reference Planning PA DRR



Treatment day PA portal image



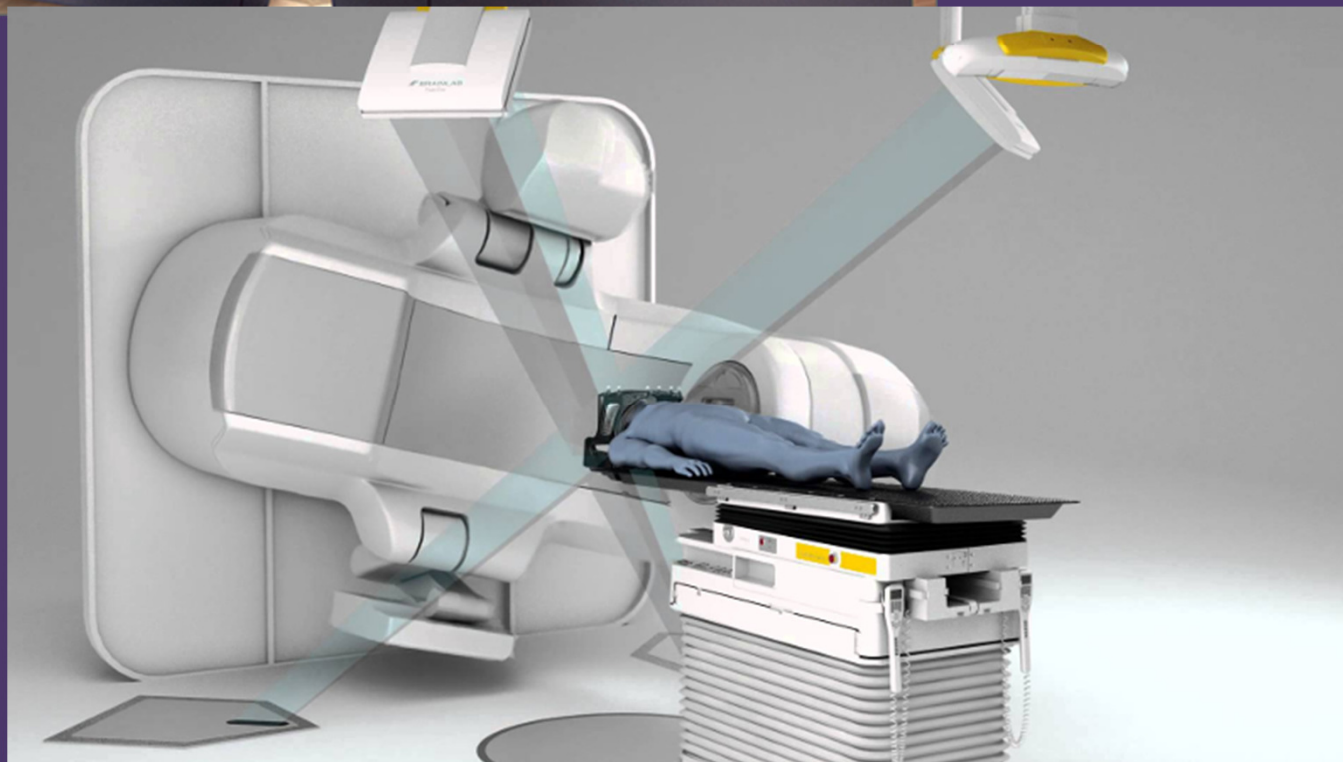
Registered PA images

Pelvic DRR

Ingram I 2021



Cicalese V et al 2019



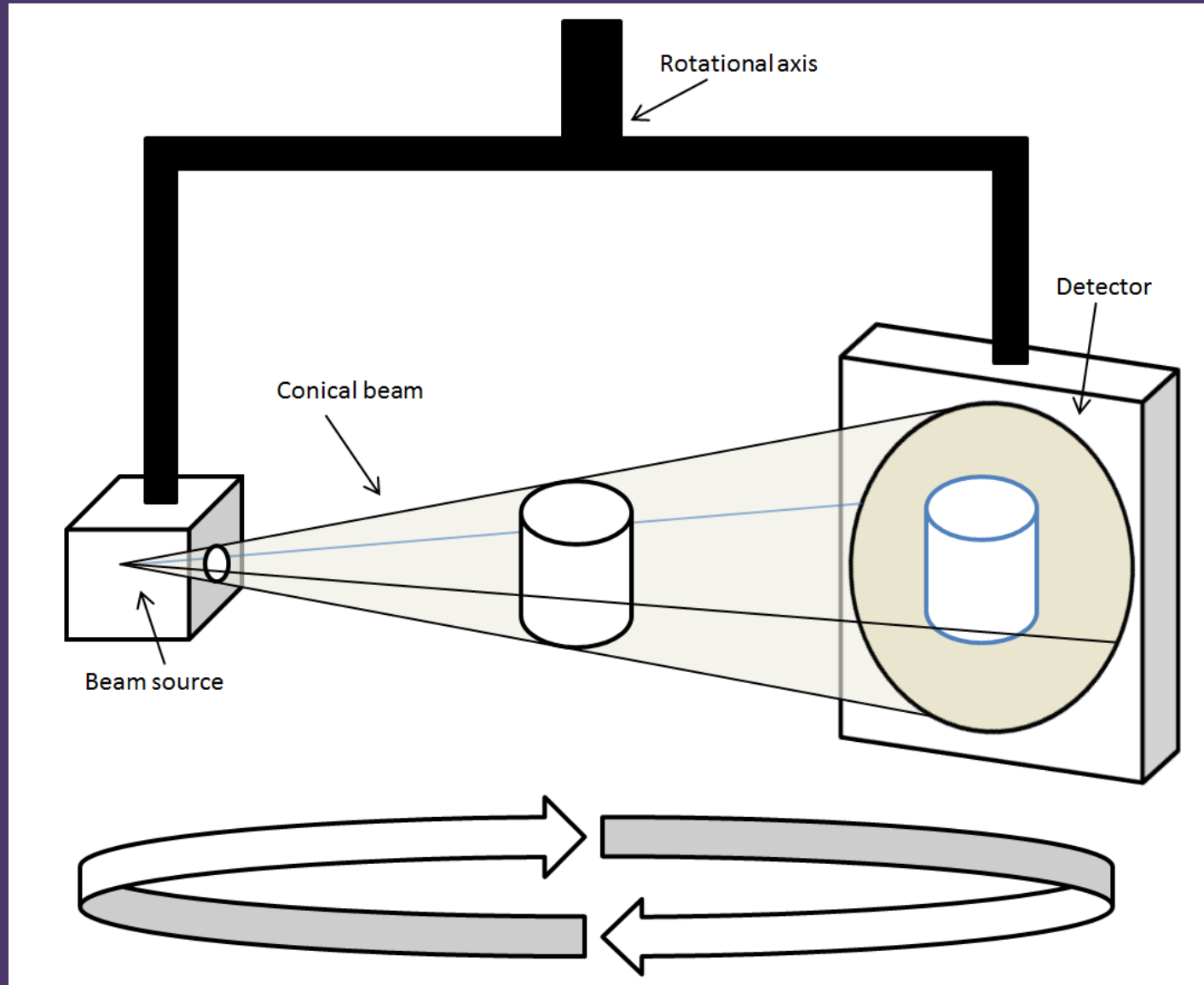
CBCT

- Začetki CT v RT = CT on rails



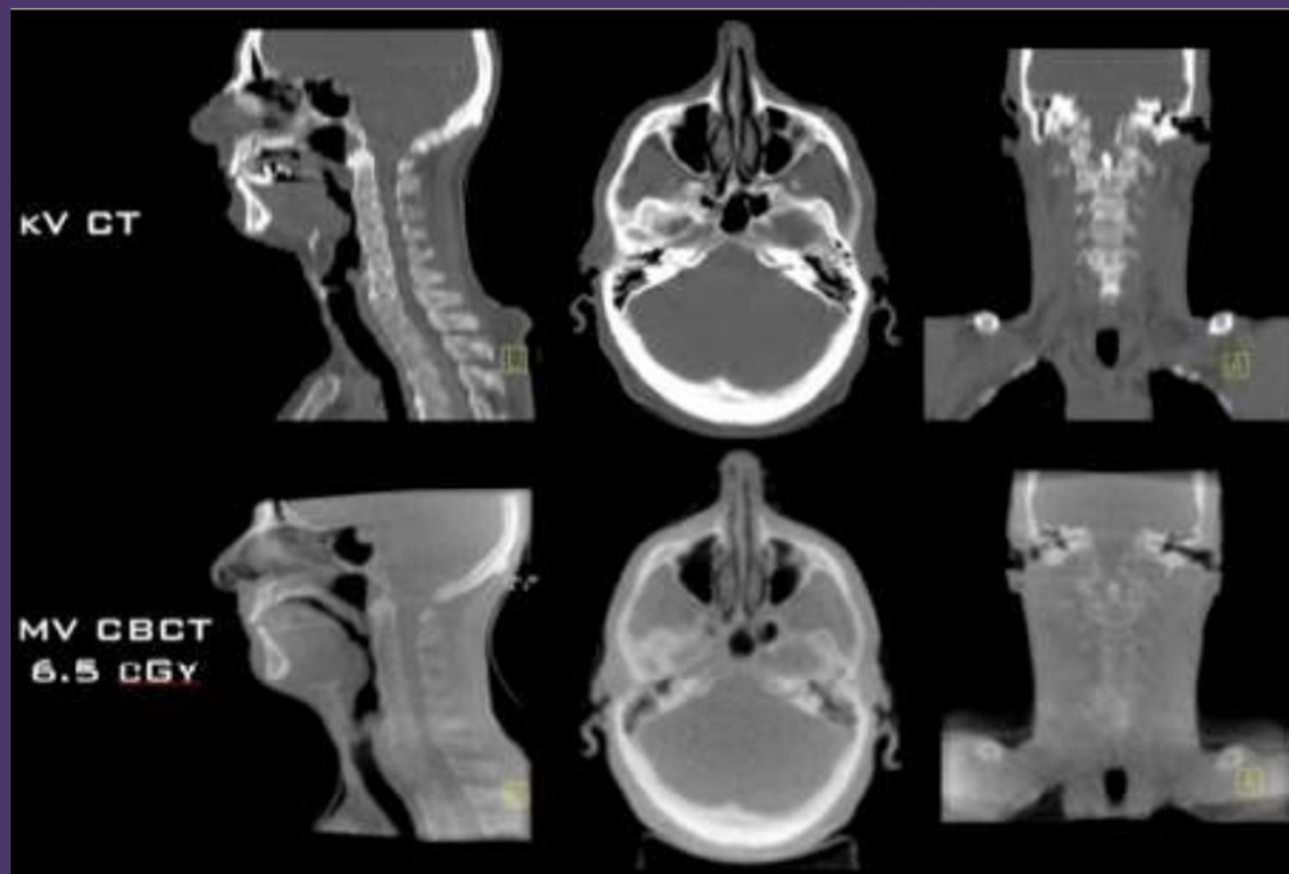
itn 2009

CBCT

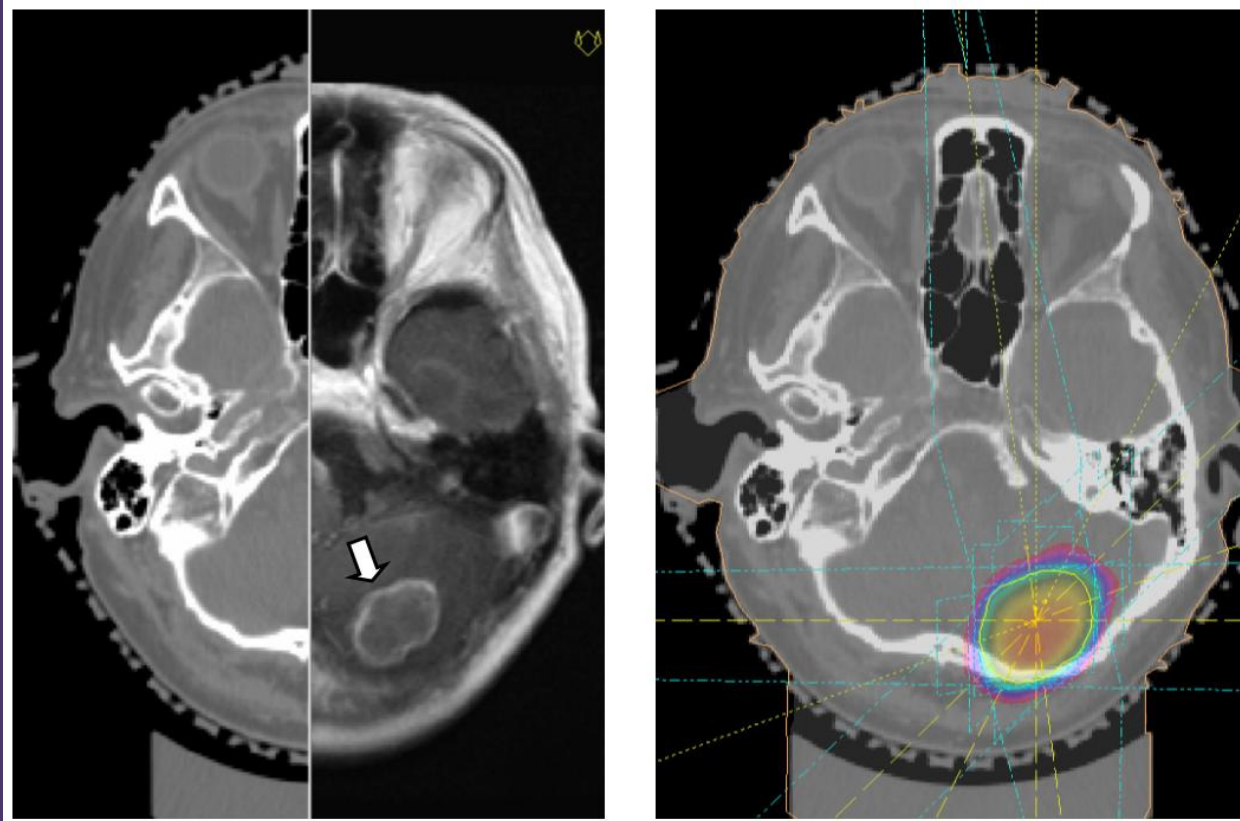


CBCT

- MV vs kV



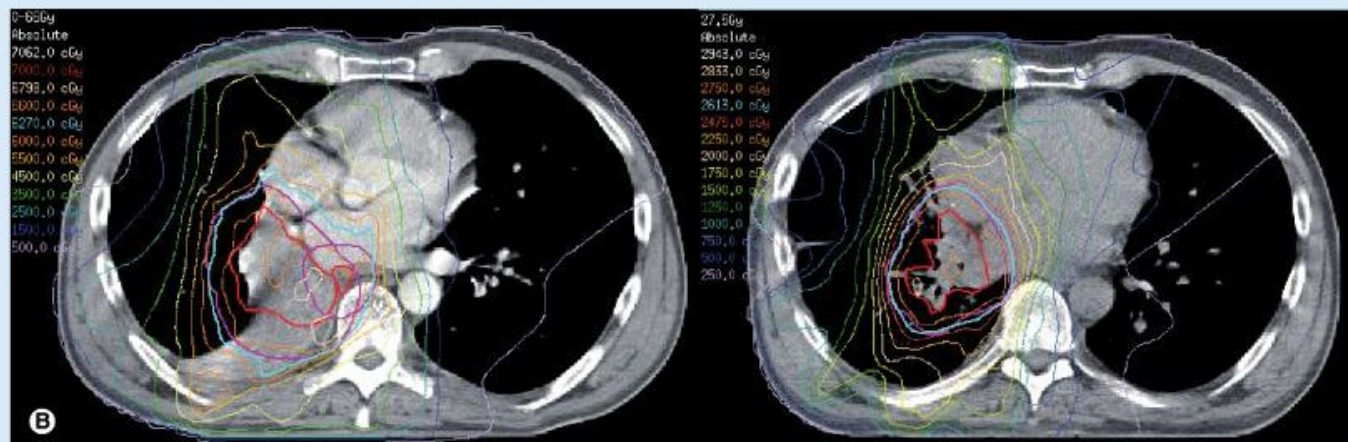
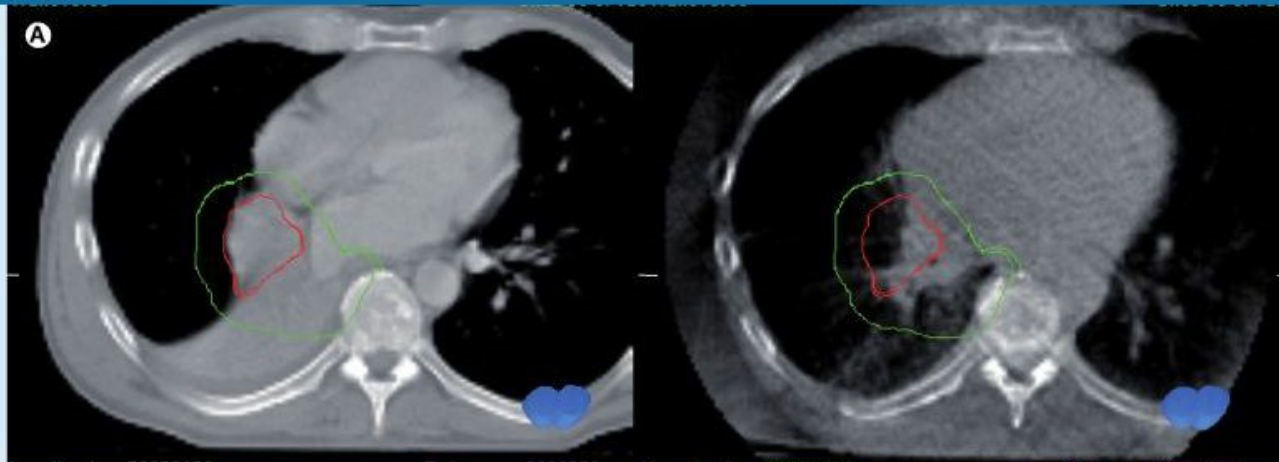
CBCT



Oslo University Hospital Research

CBCT

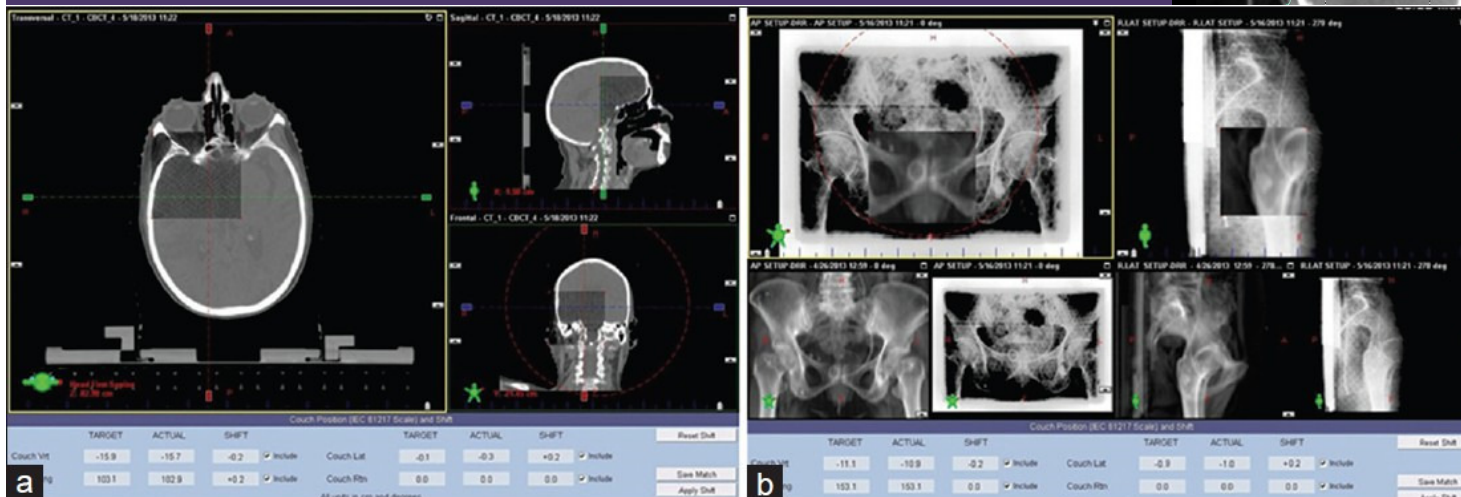
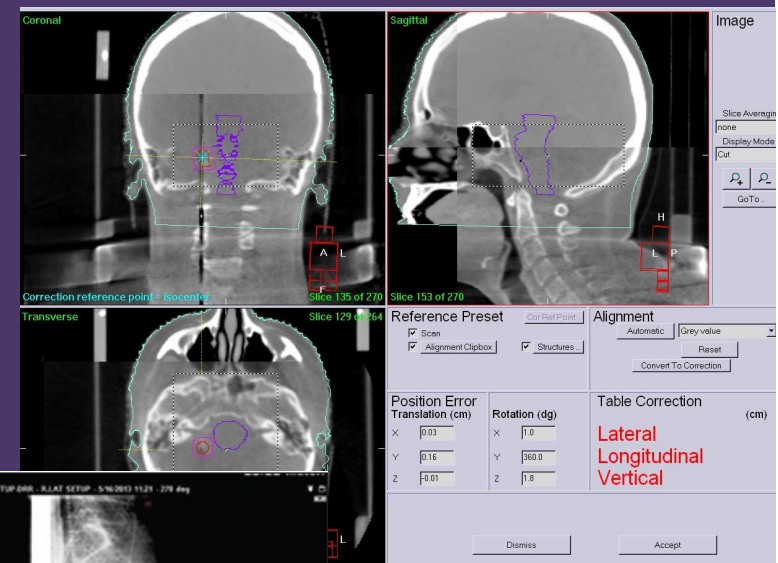
Medscape



Source: Expert Rev Anticancer Ther © 2009 Expert Reviews Ltd

CBCT

- Seveda je resolucija slabša kot običajen CT
- Realnočasovna registracija
- Sistem



Ingrosso G 2012

CBCT

- FoV
- Filtri
- Kolizija vs in room
- Hitrost rotacije
- Ergonomija
- ...

kvaliteta

varnost

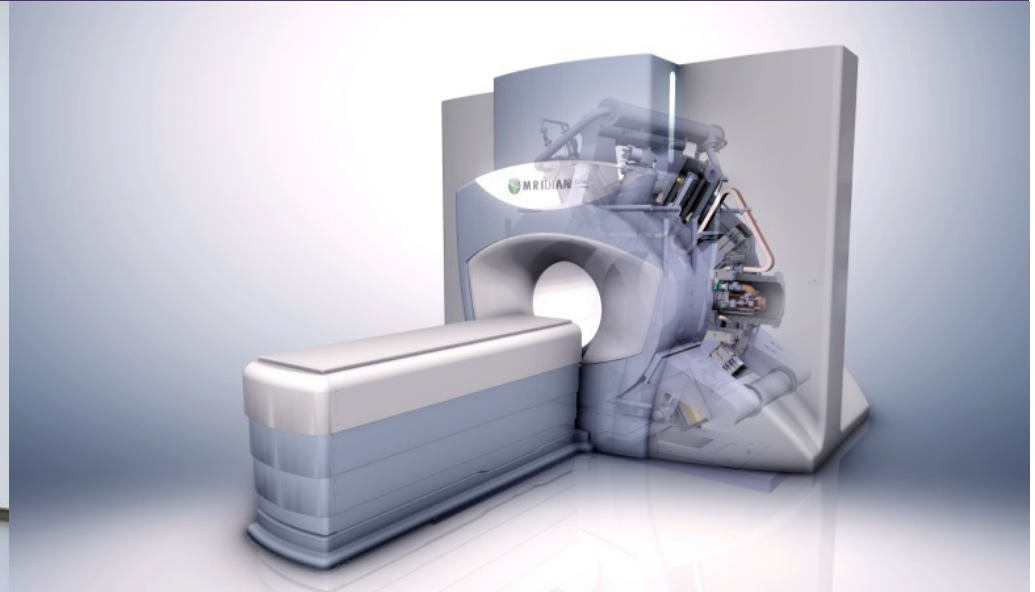
cena

MR - linac



2017 predstavljen

Casey B, Rebekah M 2017

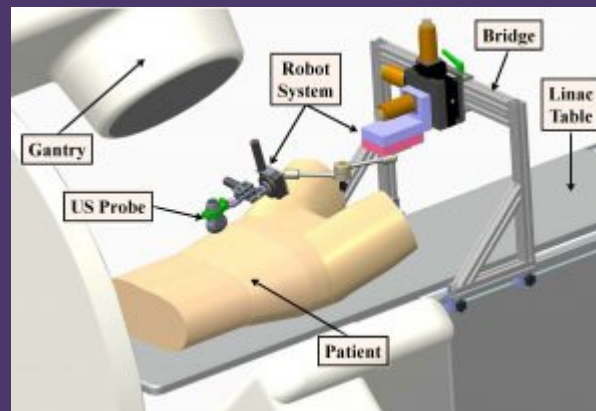
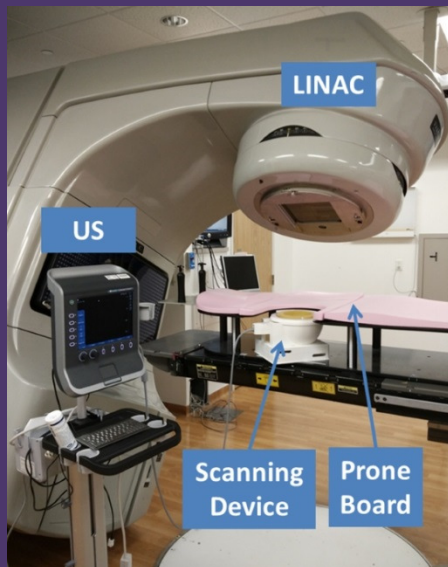


2017 Michigan operativen?

<https://radonc.wustl.edu/department-of-radiation-oncology-to-install-new-mridian-linac-system/>

UZ

- UZ vodena RT
 - predvsem medenica in jetra, dojka?
 - kot pri registraciji problem subjektivnost
 - razmeroma poceni



Sen et al., Frontiers in Robotics and AI, 2016

Ostale dileme

- Orodja za analizo
- Translacije, rotacije
 - 6D miza,
- Registracija
- Mehanske omejitve aparata
- Finance
 - tehnologija
 - osebje
 -

Specialne tehnike v radioterapiji

Adaptivna radioterapija
(klinični aspekt)

doc. dr. Uroš Smrdel dr. med.

ADAPTIVNA RT

Cilj adaptivne radioterapije je prilagoditi obsevalni načrt vsakega bolnika na za bolnika specifične spremembe z oceno in karakterizacijo naključnih in sistematičnih sprememb povratno informacijo preko slik in jih vključiti v adaptivno načrtovanje.

Seminars in Radiation Oncology, 2005

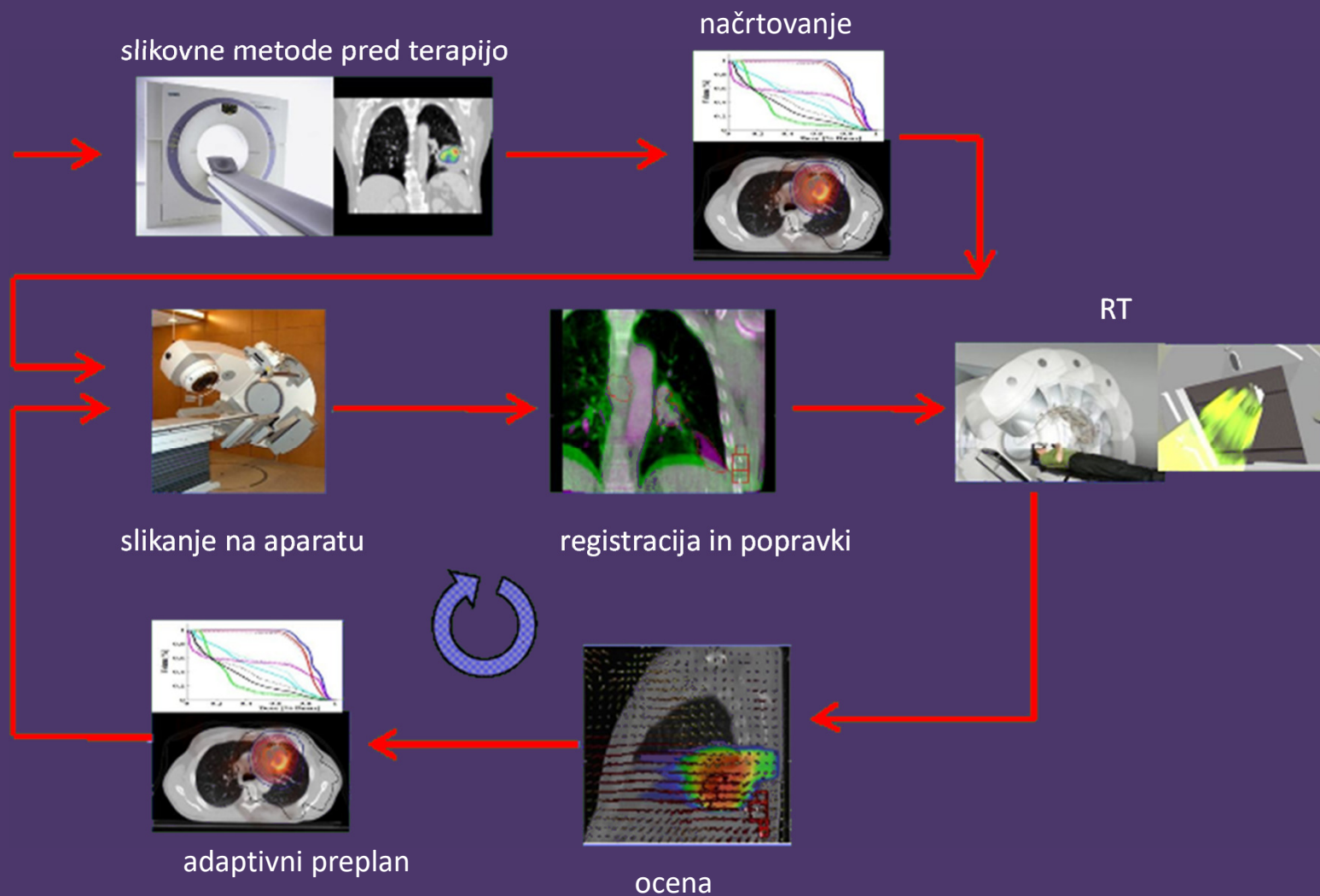
ADAPTIVNA RT

- Yan D, Vicini F, Wong J, Martinez A. Adaptive radiation therapy. Phys Med Biol. 1997 Jan;42(1):123-32

Adaptive radiation therapy is a closed-loop radiation treatment process where the treatment plan can be modified using a systematic feedback of measurements. Adaptive radiation therapy intends to improve radiation treatment by systematically monitoring treatment variations and incorporating them to re-optimize the treatment plan early on during the course of treatment. In this process, field margin and treatment dose can be routinely customized to each individual patient to achieve a safe dose escalation.

- IGRT
 - premik bolnika brez spremembe načrta obsevanja
- ART
 - vključuje spremembo osnovnega načrta obsevanja tako žarkovnih snopov kot intenzitete
 - predvsem na račun notranjih anatomskih sprememb med potekom obsevanja

PROCES ADAPTIVNEGA NAČRTOVANJA



ADAPTIVNA RT

ADAPTACIJA PREMIKOV

račit dneva

BIOLOŠKO ADAPTIVNA

terapevtsko načrtovanje
(več funkcionalnih metod)

ODZIV NA ODGOVOR

spremembe GTV
in OAR

ČASOVNO ADAPTIVNA

CT med zdravljenjem
in preplan

MORFOLOŠKE SPREMEMBE

interfrakcijsko

PREMIKANJE

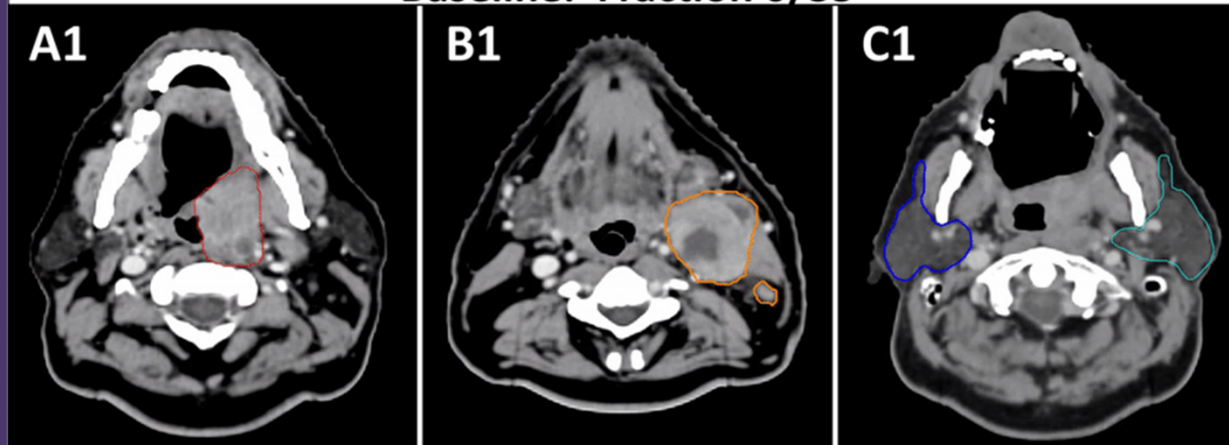
intrafrakcijsko

ADAPTIVNA RT

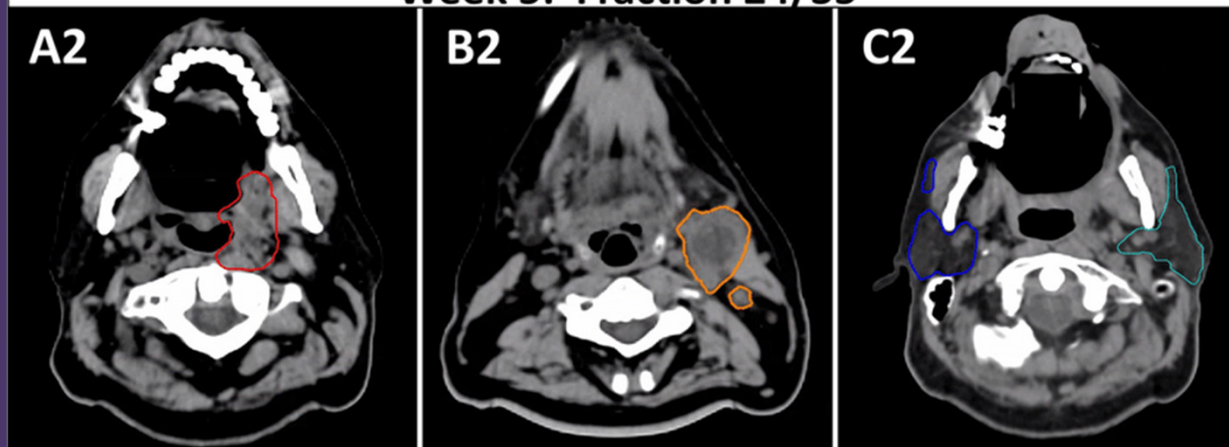
- spremembe
 - velikost in oblika tumorja
 - regres (vrat, retroperitonej), povečanje ciste...
 - bolnikove geometrije
 - hujšanje, zmanjšanje edema
 - OAR
 - neenakomerna polnjenost, atrofija med RT...
 - biološke spremembe
 - nova mesta privzema izotopa, hipoksija

ADAPTIVNA RT

Baseline: Fraction 0/35

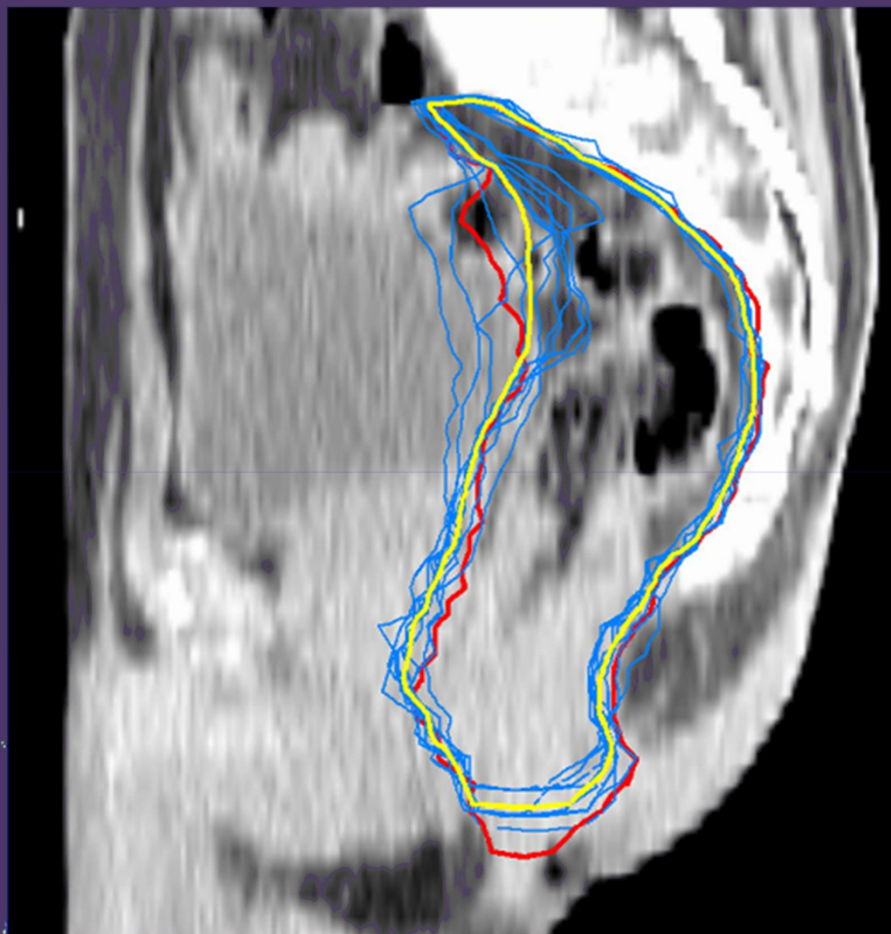


Week 5: Fraction 24/35



sprememba geometrije - tumor

ADAPTIVNA RT



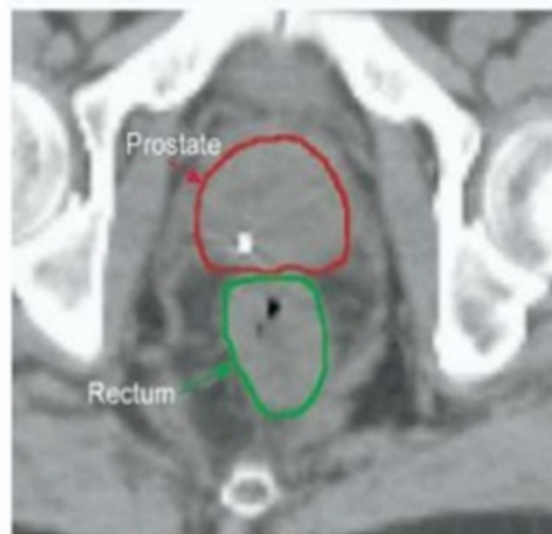
planirni CTV

dnevni CTV

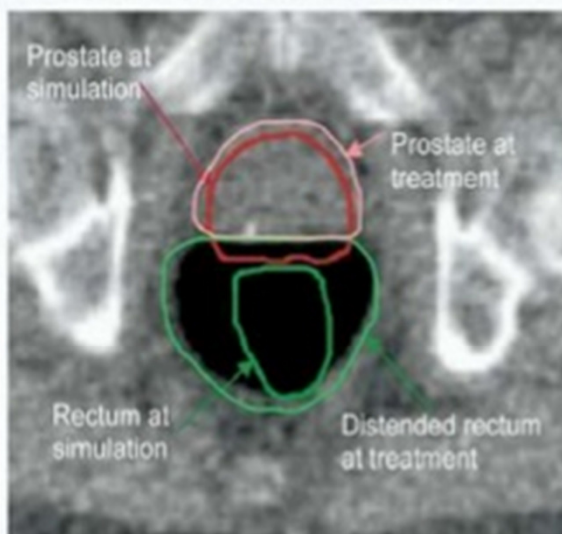
povprečni CTV

sprememba obsevalnega načrta zaradi premikanja organov

Patient #1. Simulation CT



Patient #1. Treatment day MVCT



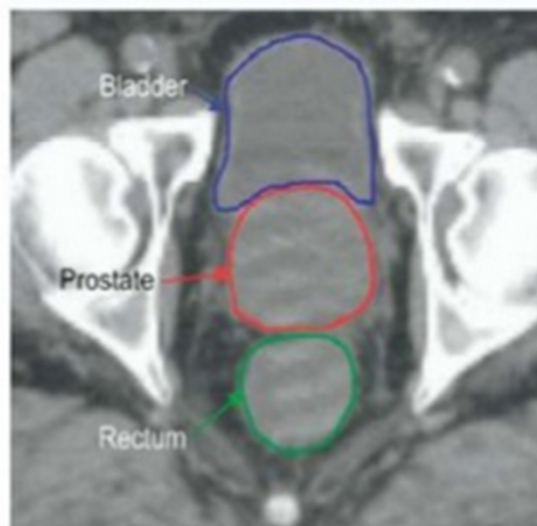
Kupelian PA et al 2008

prostata

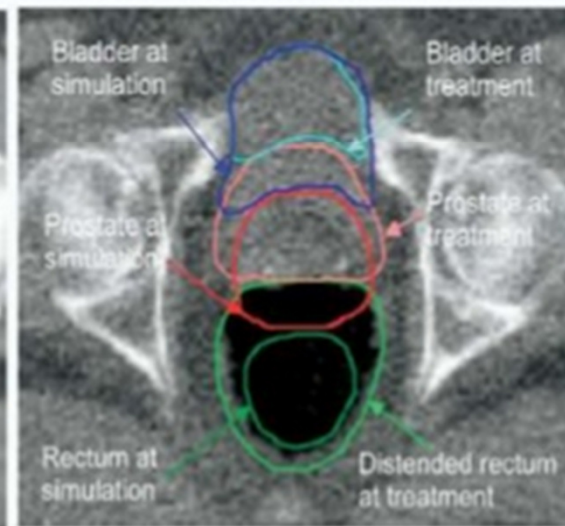
nizek $\alpha/\beta < 2$
spremembe niso
povezane z tu

premikanje
organov

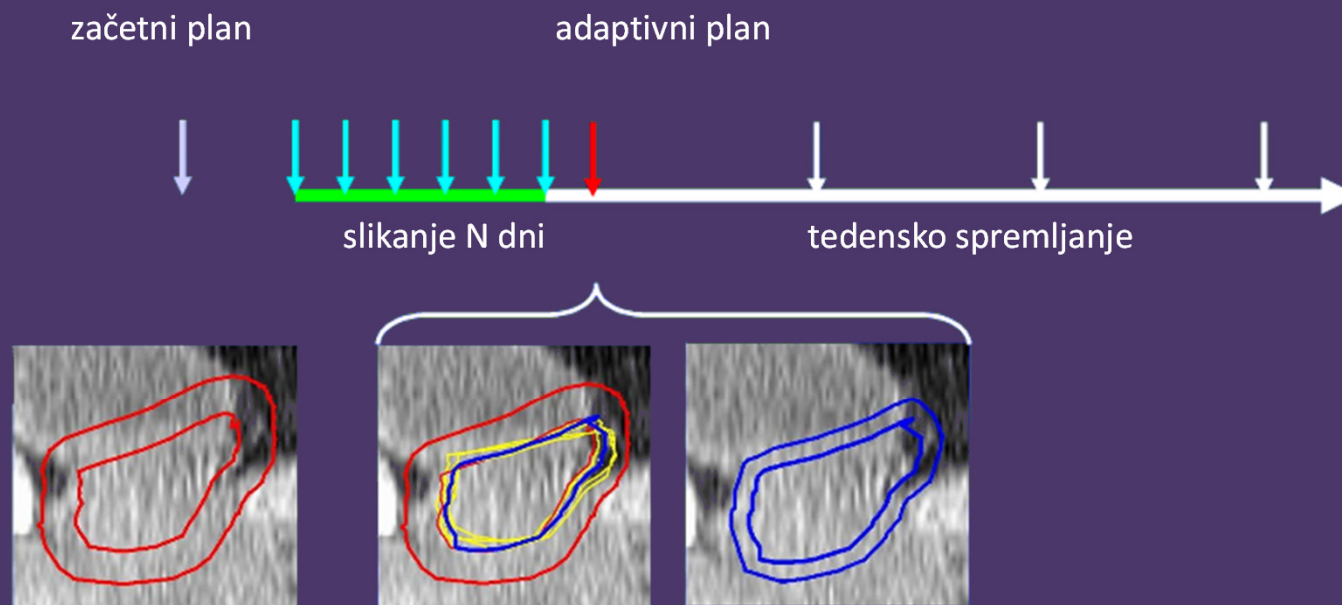
Patient #2. Simulation CT



Patient #2. Treatment day MVCT



PRIMER - PROSTATA



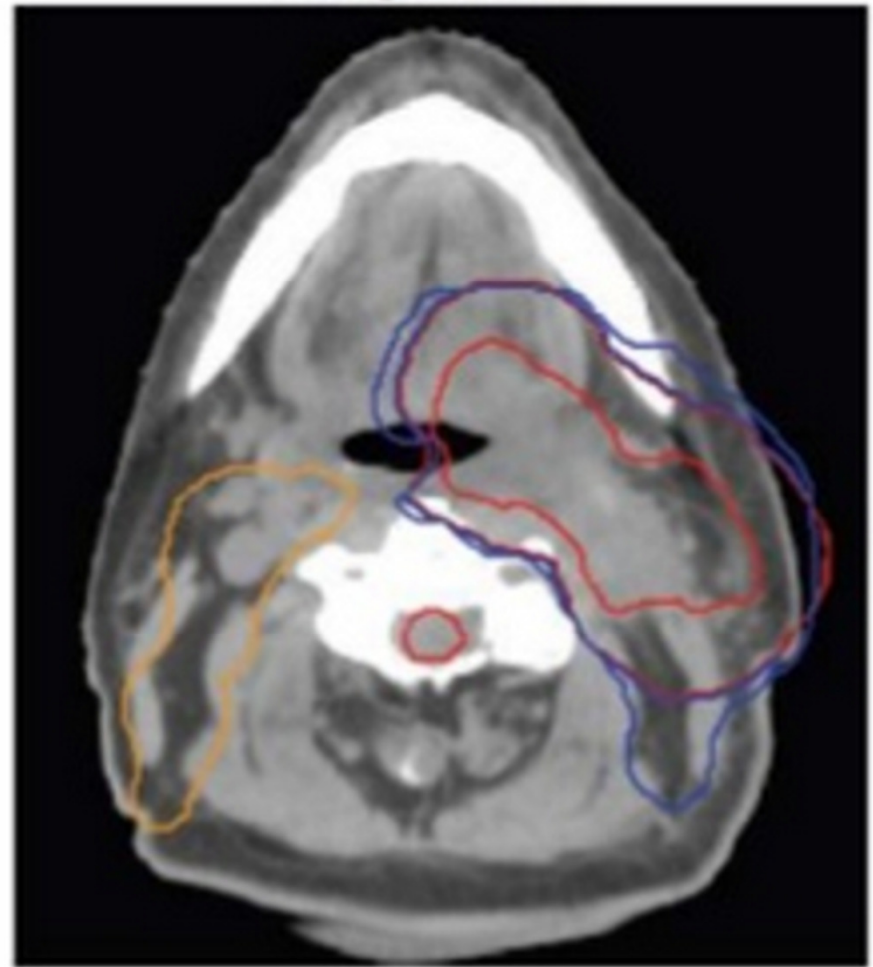
**ADAPTIVE RADIOTHERAPY FOR PROSTATE CANCER USING KILOVOLTAGE
CONE-BEAM COMPUTED TOMOGRAPHY: FIRST CLINICAL RESULTS**

JASPER NIJKAMP, M.Sc., FLORIS J. POS, M.D., Ph.D., TONNIS T. NUVER, Ph.D.,
RIANNE DE JONG, R.T.T., PETER REMEIJER, Ph.D., JAN-JAKOB SONKE, Ph.D.,
AND JOOS V. LEBESQUE, M.D., Ph.D.

Planning CT



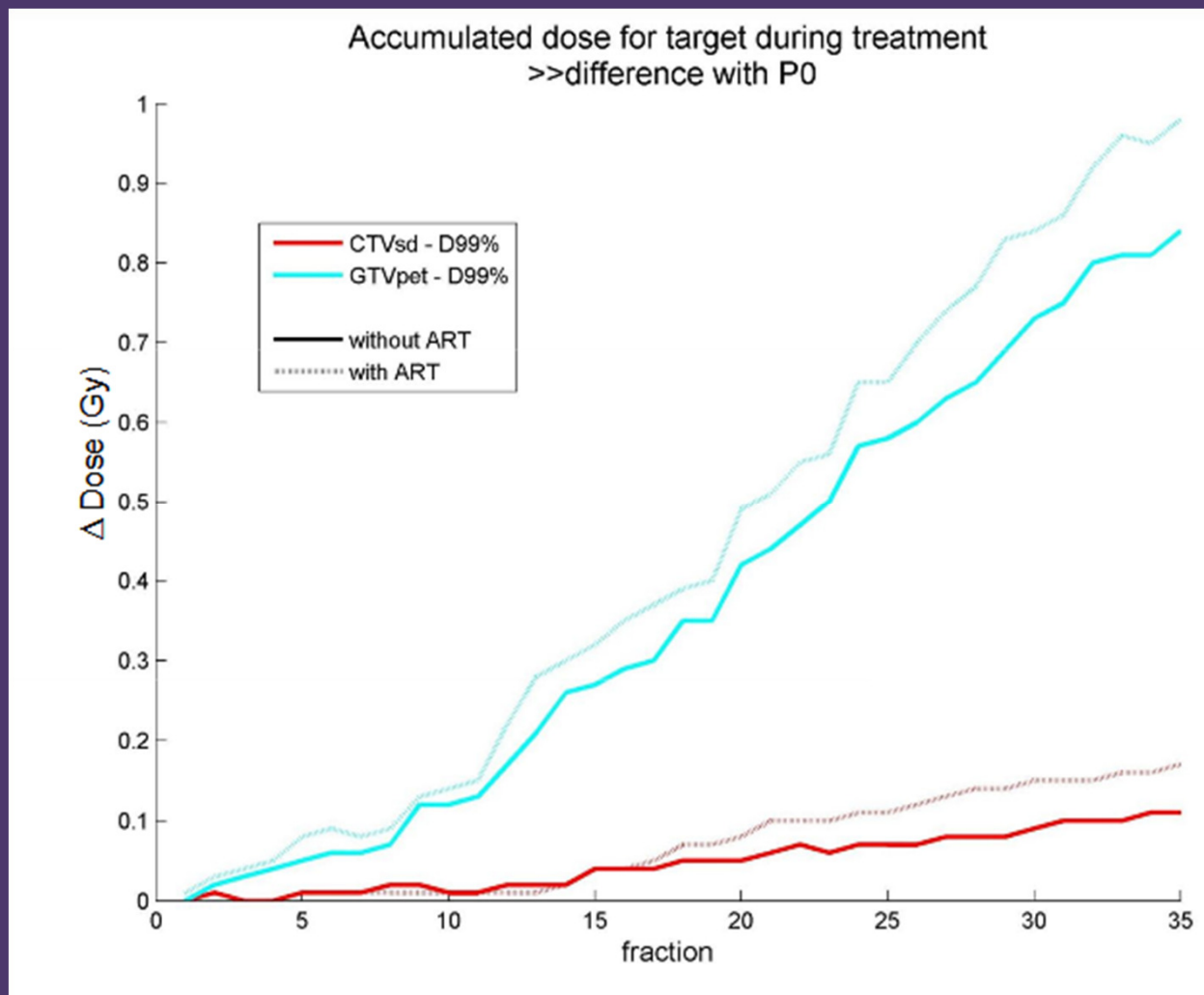
During treatment



ORL – regres tumorske mase med RT

Schwartz DL et al 2010

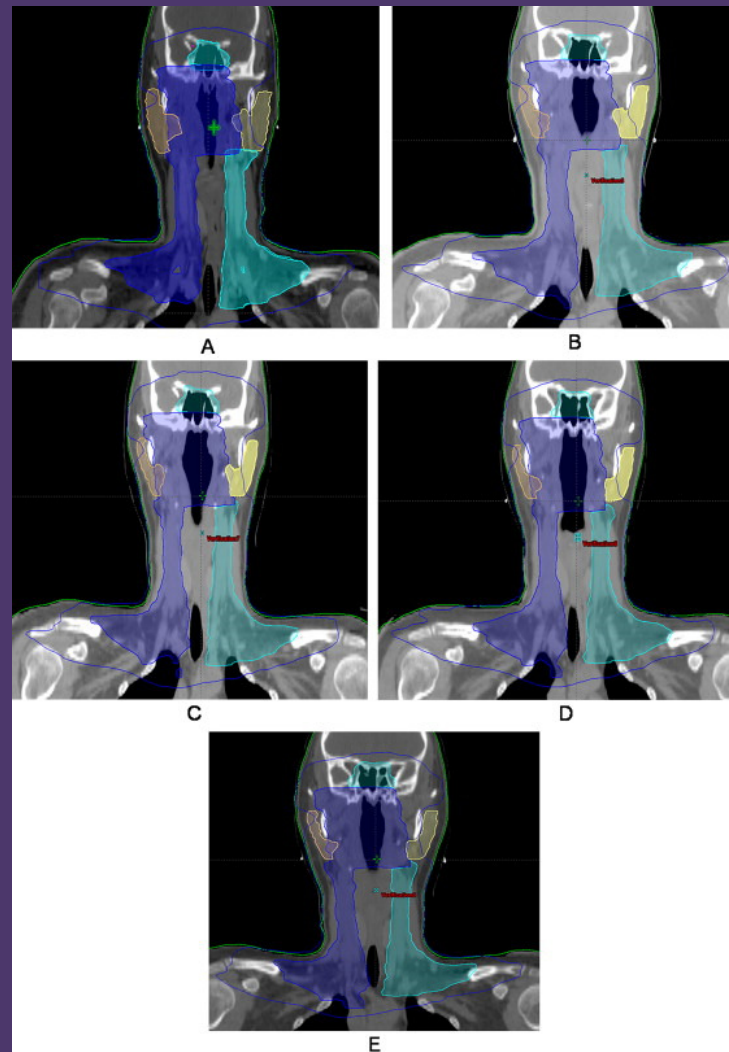
ADAPTIVNA RT



from: Subrata Roy
2019

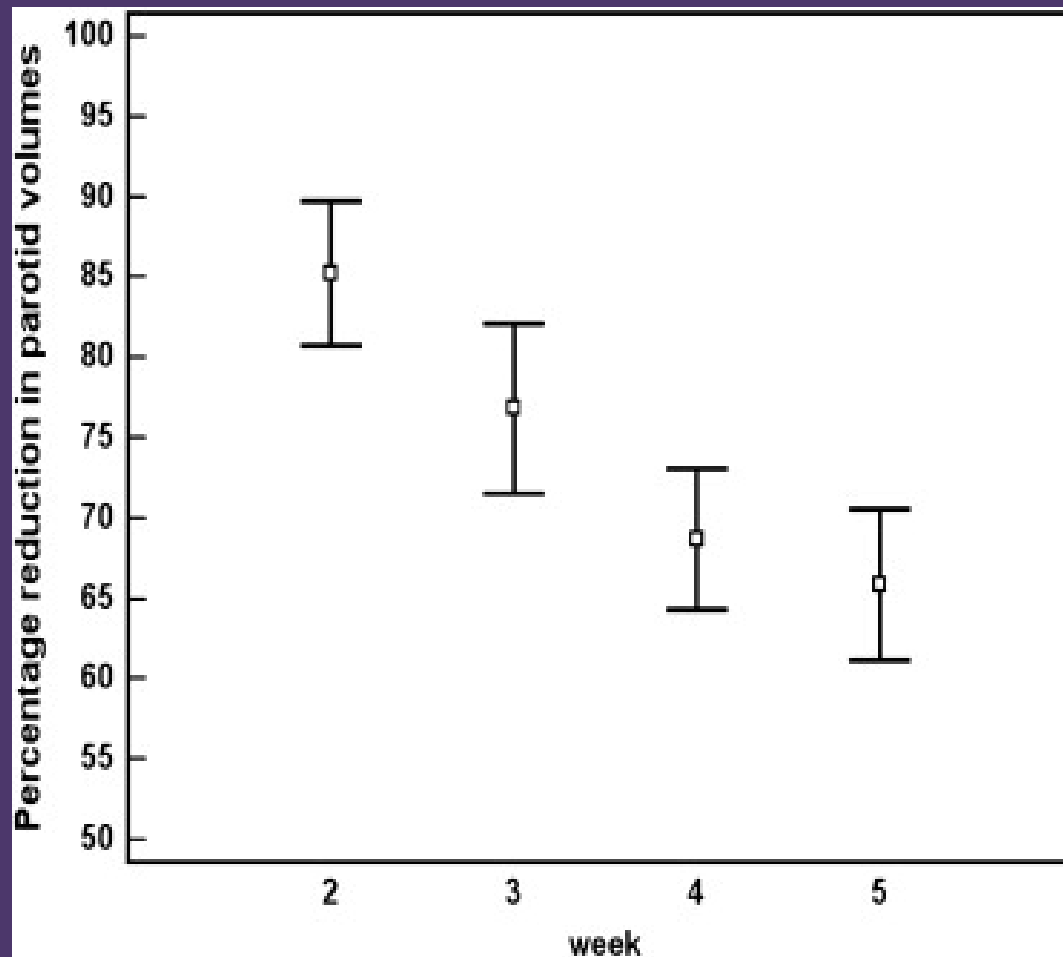
s prilagoditvijo obsevalnega načrta dosežemo višji odmerek na tumor

ADAPTIVNA RT



Bhide SA et al 2010

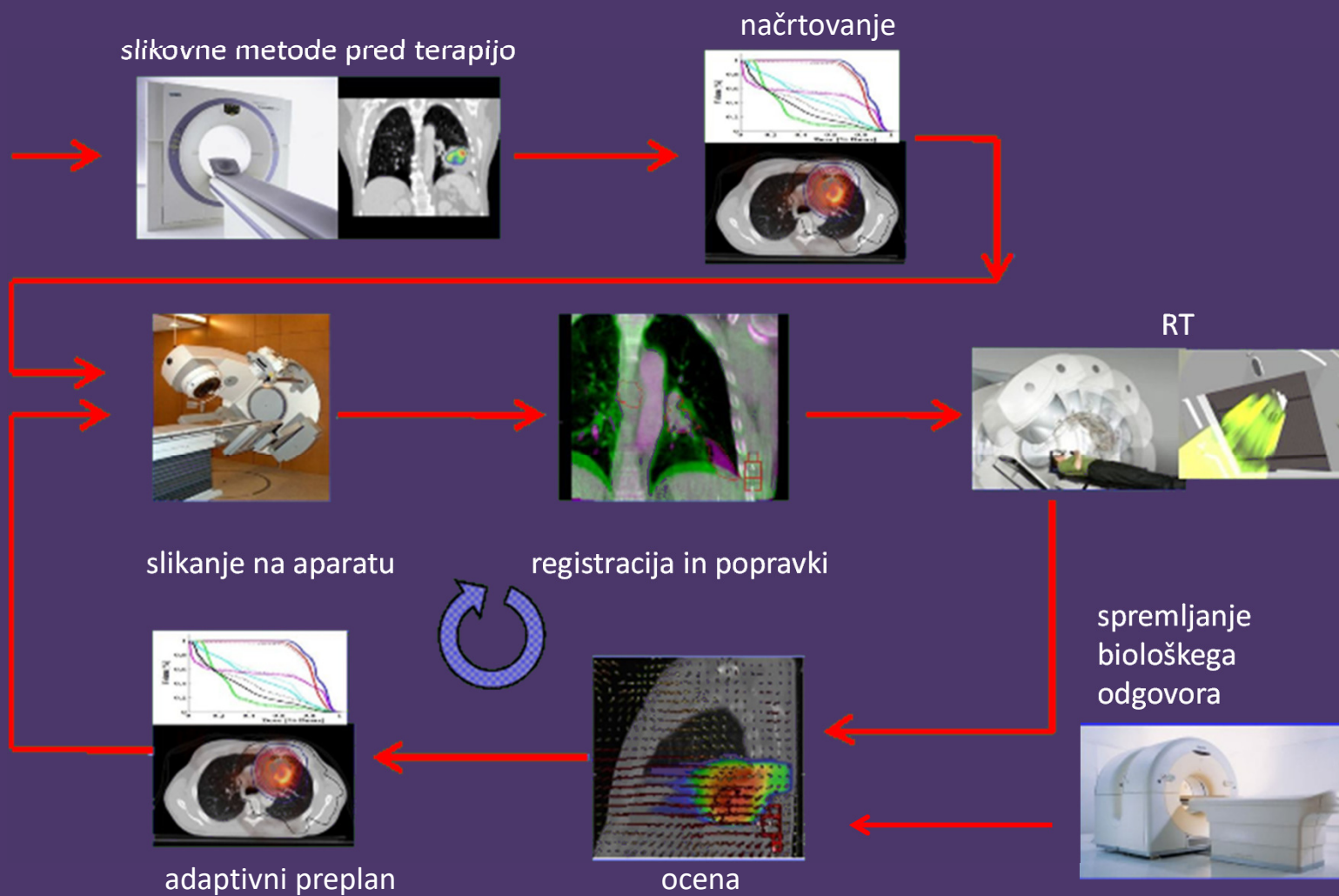
ADAPTIVNA RT



Sprememba volumna parotide med RT

Bhide SA et al 2010

BIOLOŠKI MONITORING?



BIOLOŠKI MONITORING

- Aerts s sodelavci 2009, Radiother oncol
 - PET-CT ostanek po RT – sovpada z metabolično najbolj aktivnim področjem tumorja pred RT
 - slabše preživetje
 - rešitev spremljanje metabolične aktivnosti in boost?
 - problem specifičnost

BiGART = (Biology Guided ART)

- Molekularno profiliranje
 - hipoksija
 - proliferacija
 - apoptoza
 - angiogeneza
 - receptorski status
- Markerji
 - ^{18}F -FAZA, ^{18}F -HX4
 - ^{18}F -FLT, ^{11}C Met, Holin
 - Annexin V
 - ^{18}F Galacto-RGD
 - ^{18}F -FES

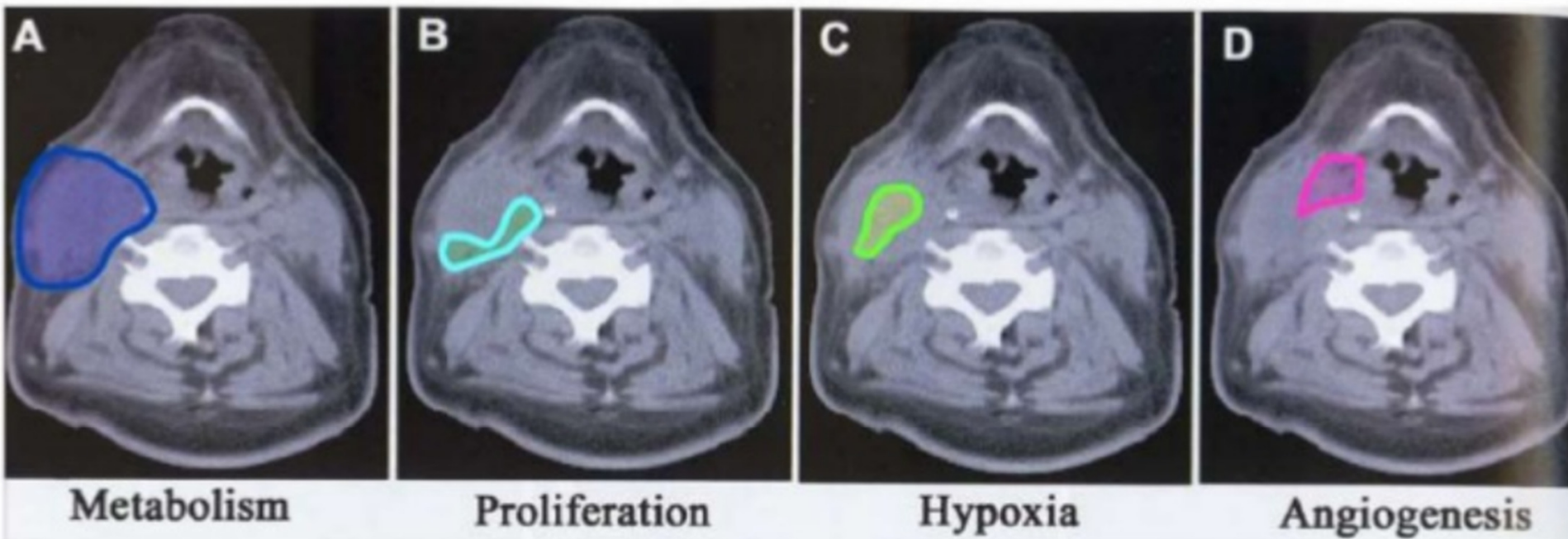
Muramaki, Boers, Beer,...

FDG

FLT

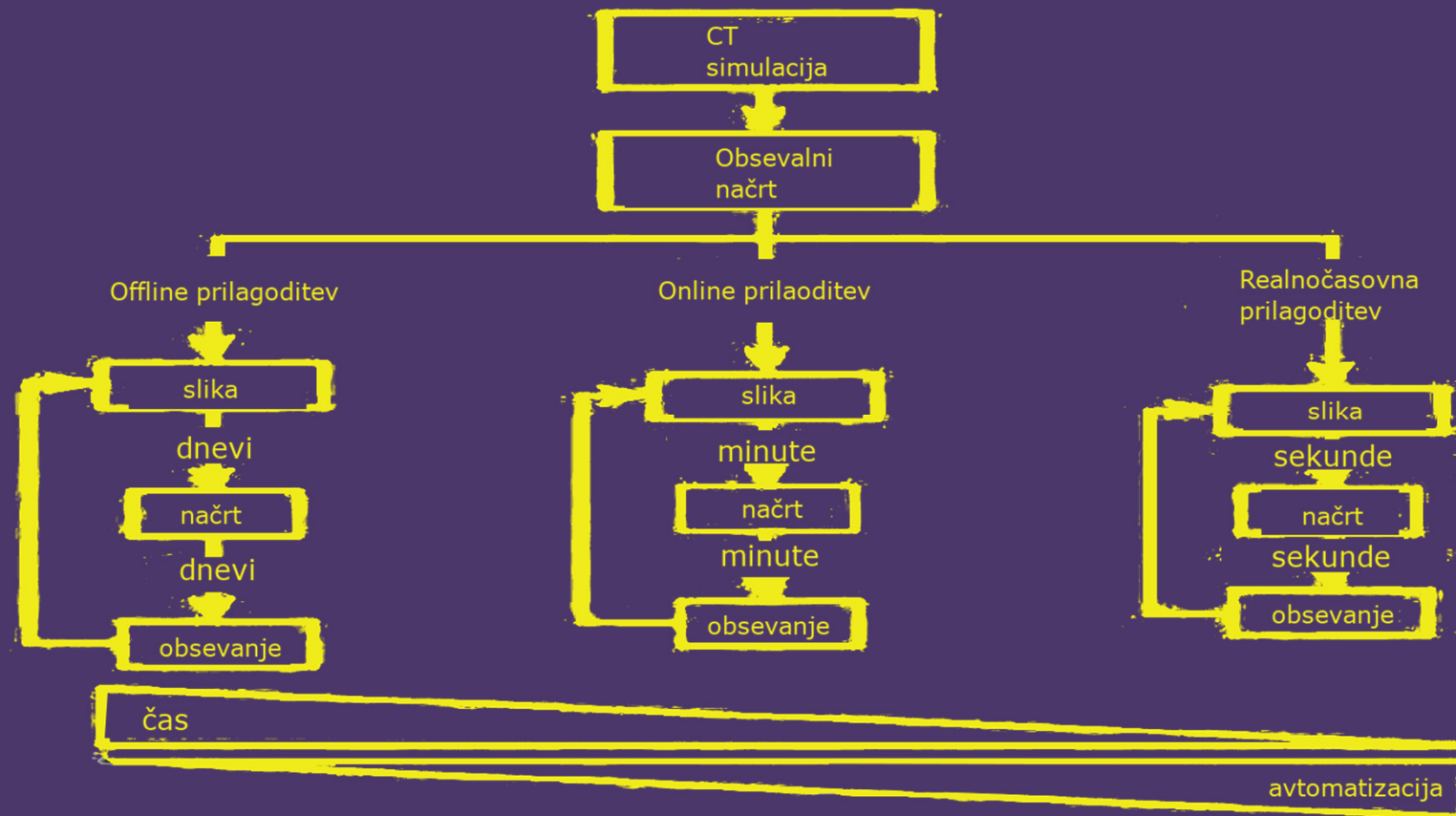
Cu-ATSM

MMP



Apisanthanrax, Rad. Res. 163, 2005

SPREMEMBA PLANA



KJE

- prostata
- ORL
- pljuča
- colli uteri
- mehur

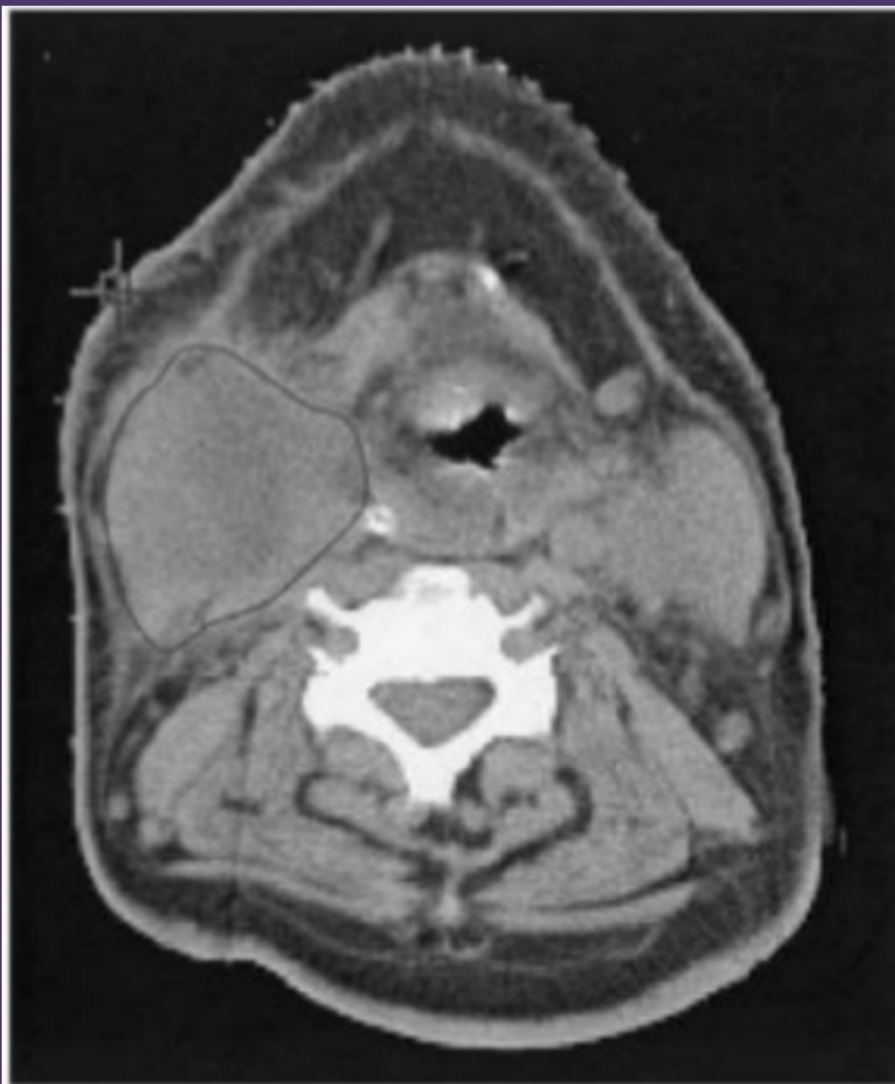
ORL

QUANTIFICATION OF VOLUMETRIC AND GEOMETRIC CHANGES OCCURRING DURING FRACTIONATED RADIOTHERAPY FOR HEAD-AND-NECK CANCER USING AN INTEGRATED CT/LINEAR ACCELERATOR SYSTEM

JERRY L. BARKER, JR., M.D.,* ADAM S. GARDEN, M.D.,* K. KIAN ANG, M.D., Ph.D.,*
JENNIFER C. O'DANIEL, M.S.,† HE WANG, Ph.D.,† LAURENCE E. COURT, Ph.D.,†
WILLIAM H. MORRISON, M.D.,* DAVID I. ROSENTHAL, M.D.,* K. S. CLIFFORD CHAO, M.D.,*
SUSAN L. TUCKER, Ph.D.,‡ RADHE MOHAN, Ph.D.,† AND LEI DONG, Ph.D.†

Departments of *Radiation Oncology, †Radiation Physics, and ‡Biomathematics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

- GTV decreased throughout the course of fractionated RT, at a median rate of 0.2 cm³/per treatment day (range, 0.01–1.95 cm³/d).
- With respect to initial volume, the GTVs decreased at a median rate of 1.8%/treatment day (range, 0.2–3.1%/d).
- On the last day of treatment, this corresponded to a median total relative loss of 69.5% of the initial GTV (range, 9.9 –91.9%).
- The center of the mass of shrinking tumors changed position with time, indicating that GTV loss was frequently asymmetric.
- Parotid glands also decreased in volume (median, 0.19 cm³/d range, 0.04–0.84 cm³/d), and generally shifted medially (median, 3.1 mm; range, 0–9.9 mm) with time.
- This medial displacement of the parotid glands correlated highly with the weight loss that occurred during treatment



(a)



(b)

REPEAT CT IMAGING AND REPLANNING DURING THE COURSE OF IMRT FOR HEAD-AND-NECK CANCER

ERIC K. HANSEN, M.D.,* M. KARA BUCCI, M.D.,* JEANNE M. QUIVEY, M.D.,*
VIVIAN WEINBERG, PH.D.,[†] AND PING XIA, PH.D.*

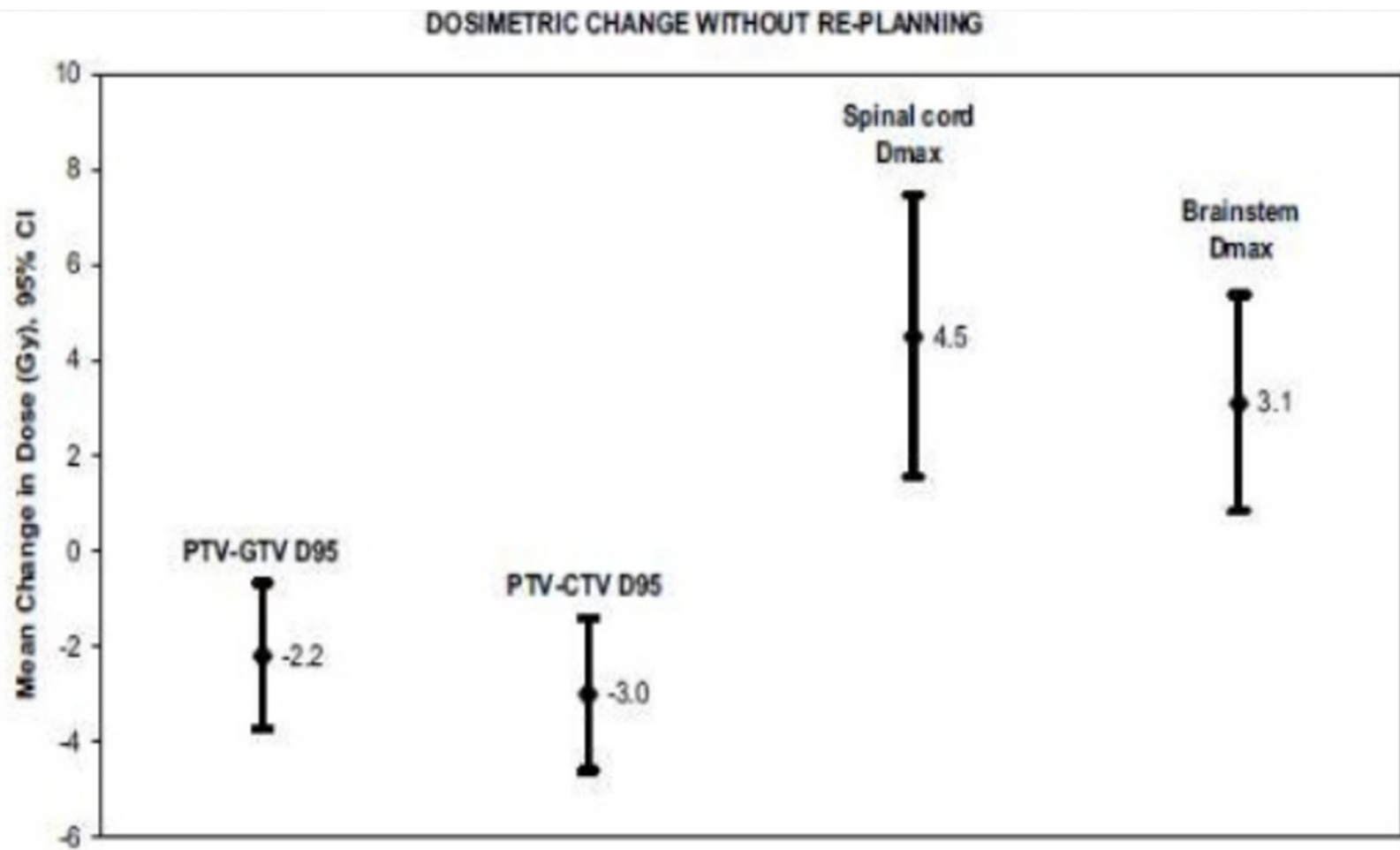
*Department of Radiation Oncology and [†]Comprehensive Cancer Center Biostatistics Core, University of California,
San Francisco, San Francisco, CA

Table 1. Patient characteristics

Patient ID	Age (years)/gender	Stage	Primary site	Indication for second CT scan
1	22/M	T3N3a	NPX	Tumor shrinkage
2	26/M	T1N2	NPX	Weight loss
3	52/W	T3N3b	NPX	Tumor shrinkage
4	61/M	T4N1	NPX	Weight loss, tumor shrinkage
5	49/M	T4N3a	NPX	Tumor shrinkage
6	55/M	T4N2	NPX	Tumor shrinkage
7	50/M	T2N2c	BOT	Weight loss, tumor shrinkage
8	59/M	Recurrent (T4Nx)	BOT	Tumor shrinkage
9	52/M	T4N2c	BOT	Weight loss, tumor shrinkage
10	81/M	T1N2a	Right BOT	Weight loss
11	58/M	T2N2b	Left tonsil	Weight loss, tumor shrinkage
12*	69/M	T4bN1	Right tonsil	Weight loss
13	54/M	TXN2b	Unknown primary	Weight loss, tumor shrinkage

Table 3. Dosimetric comparisons of the 2nd portion of treatment with and without replanning

Dosimetric end point (mean values)	1st portion of treatment (1st CT/1st plan)	2nd portion of treatment		<i>p</i> value
		Replanned (2nd CT/2nd plan)	Not replanned (2nd CT/1st plan)	
PTV _{GTV}				
D ₉₉	38.1 Gy	28.3 Gy	26.0 Gy	0.05
D ₉₅	40.3 Gy	30.3 Gy	28.1 Gy	0.02
V ₉₃	99.5%	99.4%	92.5%	<0.001
PTV _{CTV}				
D ₉₉	30.9 Gy	22.9 Gy	18.3 Gy	<0.001
D ₉₅	34.0 Gy	25.7 Gy	22.7 Gy	0.003
V ₉₃	98.7%	98.7%	90.5%	<0.001
Spinal cord				
D _{max}	25.7 Gy	19.3 Gy	23.3 Gy	0.003
D _{1 cc}	23.0 Gy	17.1 Gy	20.2 Gy	0.04
Brainstem				
D _{max}	28.2 Gy	22.3 Gy	24.9 Gy	0.007
D _{1 cc}	25.0 Gy	19.4 Gy	21.7 Gy	0.20
D _{1%}	26.1 Gy	20.2 Gy	22.9 Gy	0.12
Right parotid (<i>n</i> = 12)				
D _{mean}	15.5 Gy	12.0 Gy	14.9 Gy	0.05
D ₅₀	13.0 Gy	10.6 Gy	13.6 Gy	0.06
V ₂₆	44.6%	45.5%	55.5%	0.04
Left parotid				
D _{mean}	15.2 Gy	11.9 Gy	12.1 Gy	0.81
D ₅₀	13.2 Gy	10.2 Gy	11.2 Gy	0.47
V ₂₆	45.2%	42.9%	42.2%	0.89
Mandible (<i>n</i> = 9)				
D _{max}	39.2 Gy	29.6 Gy	31.3 Gy	0.01
V ₆₀	11.0%	11.3%	18.2%	0.08
V ₇₀	0.04%	0.05%	4.5%	0.32



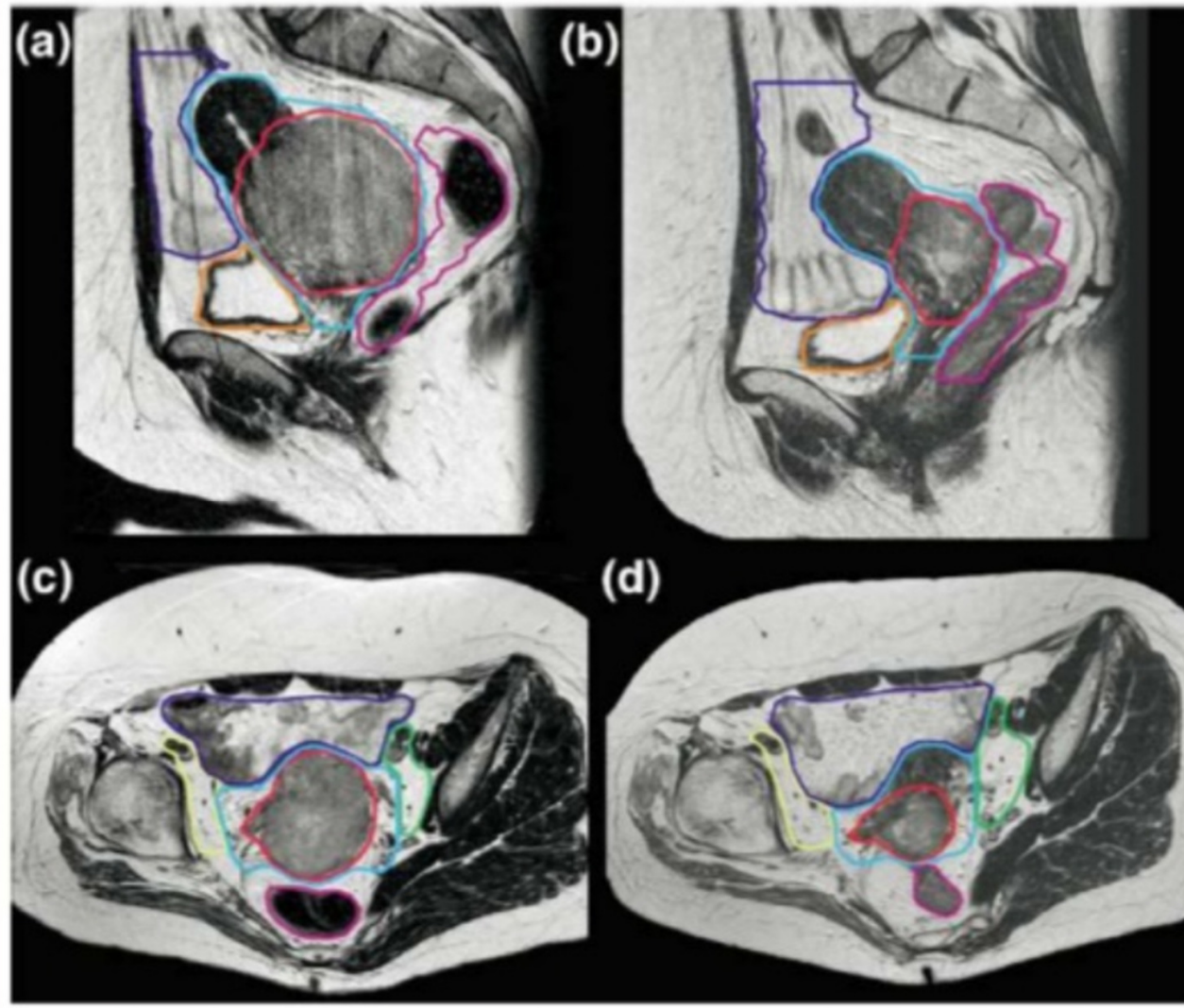
Conclusions: Repeat CT imaging and replanning during the course of IMRT for selected patients with H&N cancer is essential to identify dosimetric changes and to ensure adequate doses to target volumes and safe doses to normal tissues. Future prospective studies with larger sample sizes will help to determine criteria for repeat CT imaging and IMRT replanning for H&N cancer patients undergoing radiotherapy. © 2006 Elsevier Inc.

CONVENTIONAL, CONFORMAL, AND INTENSITY-MODULATED RADIATION THERAPY TREATMENT PLANNING OF EXTERNAL BEAM RADIOTHERAPY FOR CERVICAL CANCER: THE IMPACT OF TUMOR REGRESSION

LINDA VAN DE BUNT, M.D.,* UULKE A. VAN DER HEIDE, PH.D.,* MARTIJN KETELAARS, PH.D.,*
GERARD A. P. DE KORT, M.D.,[†] AND INA M. JÜRGENLIEMK-SCHULZ, M.D., PH.D.*

Departments of *Radiation Oncology and [†]Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

- The average volume receiving 95% of the prescribed dose (43 Gy) by the conventional, conformal, and IMRT plans was, respectively, for the bowel 626 cc, 427 cc, and 232 cc; for the rectum 101 cc, 90 cc, and 60 cc; and for the bladder 89 cc, 70 cc, and 58 cc.
- The volumes of critical organs at this dose level were significantly reduced using IMRT compared with conventional and conformal planning ($p < 0.02$ in all cases).
- After having delivered about 30 Gy external beam radiation therapy, the primary gross tumor volumes decreased on average by 46% (range, 6.1–100%).
- The target volumes on the intra treatment MR images remained sufficiently covered by the 95% isodose.
- Second IMRT plans significantly diminished the treated bowel volume, if the primary gross tumor volumes decreased >30 cc.



Conclusions: Intensity-modulated radiation therapy is superior in sparing of critical organs compared with conventional and conformal treatment, with adequate coverage of the target volumes. Intensity-modulated radiation therapy remains superior after 30 Gy external beam radiation therapy, despite tumor regression and internal organ motion. Repeated IMRT planning can improve the sparing of the bowel and rectum in patients with substantial tumor regression. © 2006 Elsevier Inc.

SERIAL MEGAVOLTAGE CT IMAGING DURING EXTERNAL BEAM RADIOTHERAPY FOR NON-SMALL-CELL LUNG CANCER: OBSERVATIONS ON TUMOR REGRESSION DURING TREATMENT

PATRICK A. KUPELIAN, M.D.,* CHESTER RAMSEY, PH.D.,[†] SANFORD L. MEEKS, PH.D.,*
TWYLA R. WILLOUGHBY, M.S.,* ALAN FORBES, M.D., PH.D.,* THOMAS H. WAGNER, PH.D.,*
AND KATJA M. LANGEN, PH.D.*

*Department of Radiation Oncology, M. D. Anderson Cancer Center Orlando, Orlando, FL; [†]Department of Radiation Oncology, Thompson Cancer Survival Center, Knoxville, TN

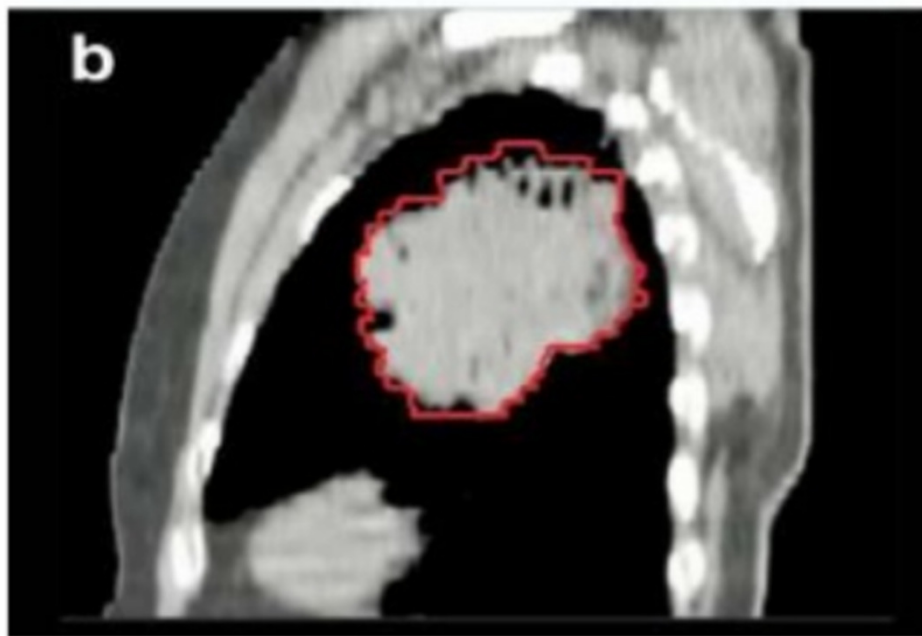
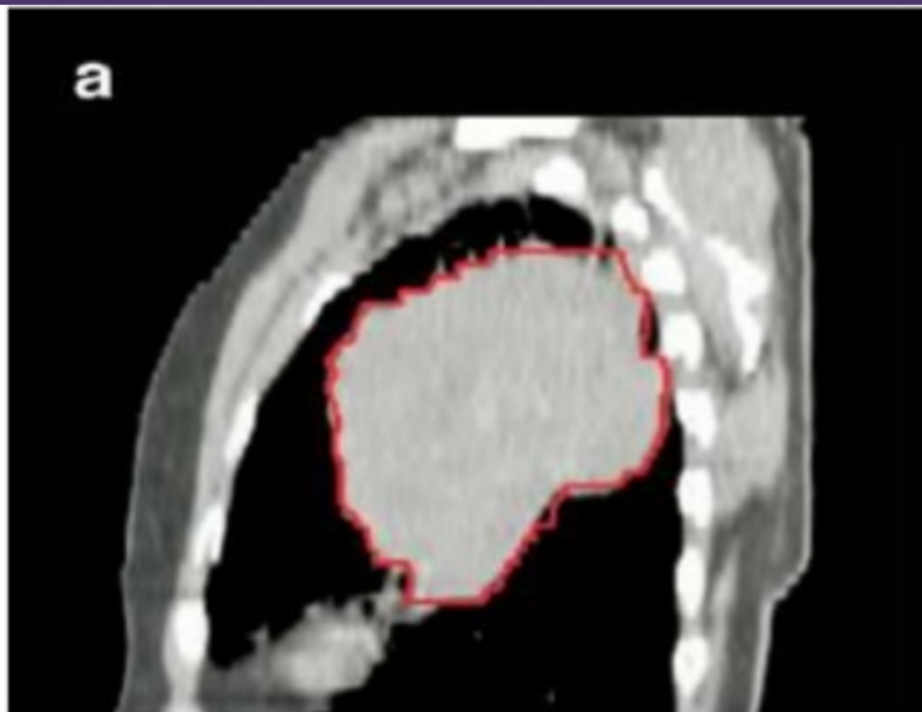
Results: Regression of all 10 lung tumors could be observed on the serial megavoltage CT scans. The decrease in volume was observed at a relatively constant rate throughout the treatments, with no obvious initial or final plateaus. For all 10 tumors, the average decrease in volume was 1.2% per day. However, individual tumor regression rates were observed with a range of 0.6% to 2.3% per day. The lowest rate of shrinkage was observed for the smallest lesion, and the highest rate was observed in the largest lesion. Of the 6 cases in which dose recalculations were performed, 5 demonstrated a small but noticeable gradual increase in deposited doses within the tumor, with the $D_{0.5}$ increases ranging from 0.02% to 0.1% per day.

A TECHNIQUE FOR ADAPTIVE IMAGE-GUIDED HELICAL TOMOTHERAPY FOR LUNG CANCER

CHESTER R. RAMSEY, PH.D.,* KATJA M. LANGEN, PH.D.,[†] PATRICK A. KUPELIAN, M.D.,[†]
DANIEL D. SCAPEROTH, M.D.,* SANFORD L. MEEKS, PH.D.,[†] STEPHEN L. MAHAN, PH.D.,*
AND REBECCA M. SEIBERT, M.S.*

*Department of Radiation Oncology, Thompson Cancer Survival Center, Knoxville, TN; [†]Department of Radiation Oncology, M. D. Anderson Cancer Center Orlando, Orlando, FL

- A total of 158 MVCT imaging sessions were performed on 7 lung patients.
- The GTV was reduced by 60–80% during the course of treatment.
- Based on these treatment planning studies, the absolute volume of ipsilateral lung receiving 20 Gy can be reduced between 17% and 23% (21% mean) by adapting the treatment delivery.
- The benefits of adaptive therapy are the greatest for tumor volumes >25 cm₃ and are directly dependent on GTV reduction during treatment.



simulacija

15 frakcija

Comparison of adaptive radiotherapy techniques for the treatment of bladder cancer

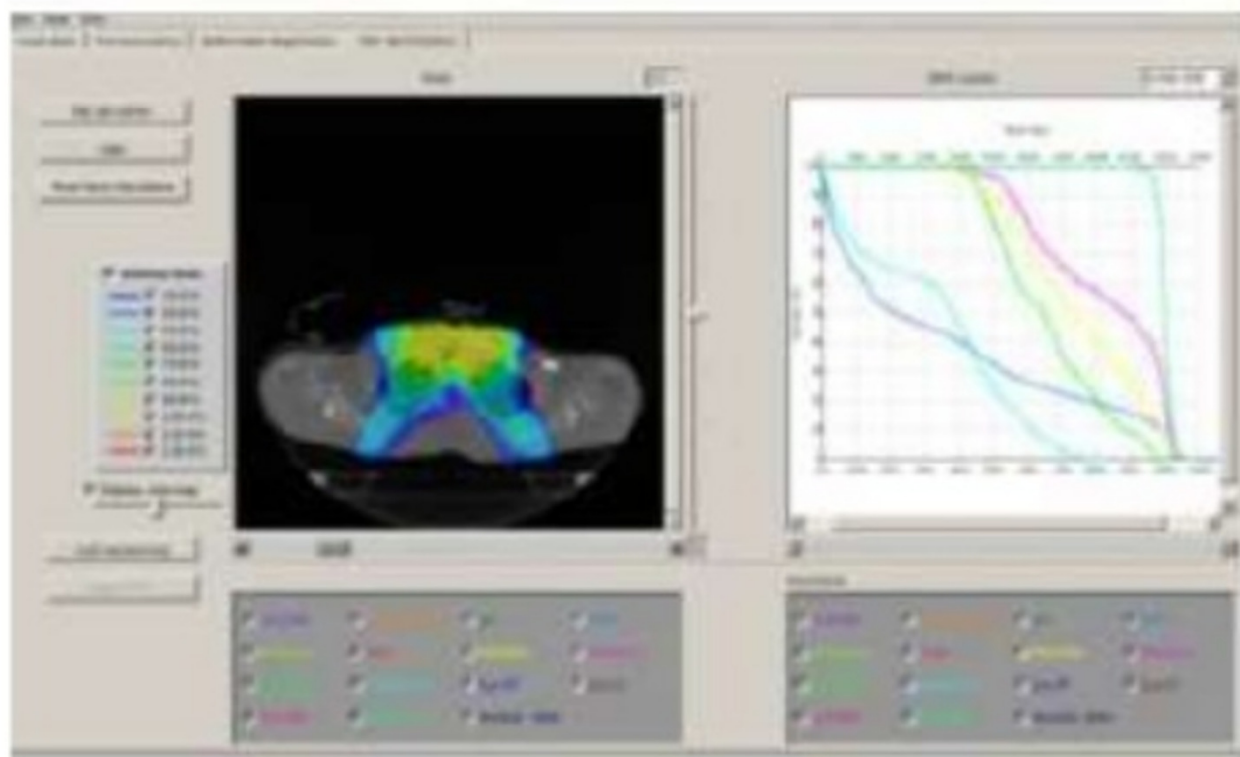
^{1,2}G J WEBSTER, PhD, ³J STRATFORD, DCR (T), ³J RODGERS, BSc, ⁴J E LIVSEY, FRCR, ⁵D MACINTOSH, FRCR and ^{2,4}A CHOUDHURY, FRCR

¹Christie Medical Physics & Engineering, Christie NHS Foundation Trust, Manchester, UK, ²University of Manchester, Manchester, UK, ³Wade Centre, Christie NHS Foundation Trust, Manchester, UK, ⁴Department of Clinical Oncology, Christie NHS Foundation Trust, Manchester, UK, and ⁵Beatson West of Scotland Cancer Centre, Glasgow, UK

- 20 patients were retrospectively planned using different three-dimensional conformal radiotherapy treatment strategies for whole-bladder carcinoma:
 - “conventional” treatment used isotropic expansion of the clinical target volume (CTV) by 15mm to the planning target volume (PTV) for daily treatment;
 - “plan of the day” used daily volumetric on-treatment imaging [cone beam CT (CBCT)] to select from four available plans with varying superior PTV margins;
 - “composite” strategies used on-treatment CBCTs from Fractions 1–3 to inform a composite CTV and adapted PTV (5- and 10-mm margins for composite 1 and composite 2, respectively) for subsequent treatment.
- Target coverage was evaluated from available CBCTs (the first three fractions then the minimum weekly thereafter), and the reduction in the irradiated volume (i.e. within the 95% isodose) was quantified.

- Plan of the day improved target coverage (i.e. all of the bladder within the 95% isodose throughout the treatment) relative to conventional treatment while no such benefit was observed with composite strategies.
- Target coverage was reduced with composite relative to conventional treatment.
- The mean irradiated volume was reduced by 17.2%, 35.0% and 14.6% relative to conventional treatment, for plan of the day, composite 1 and composite 2, respectively
- No parameters predictive of large changes in bladder volume later in the treatment were identified.

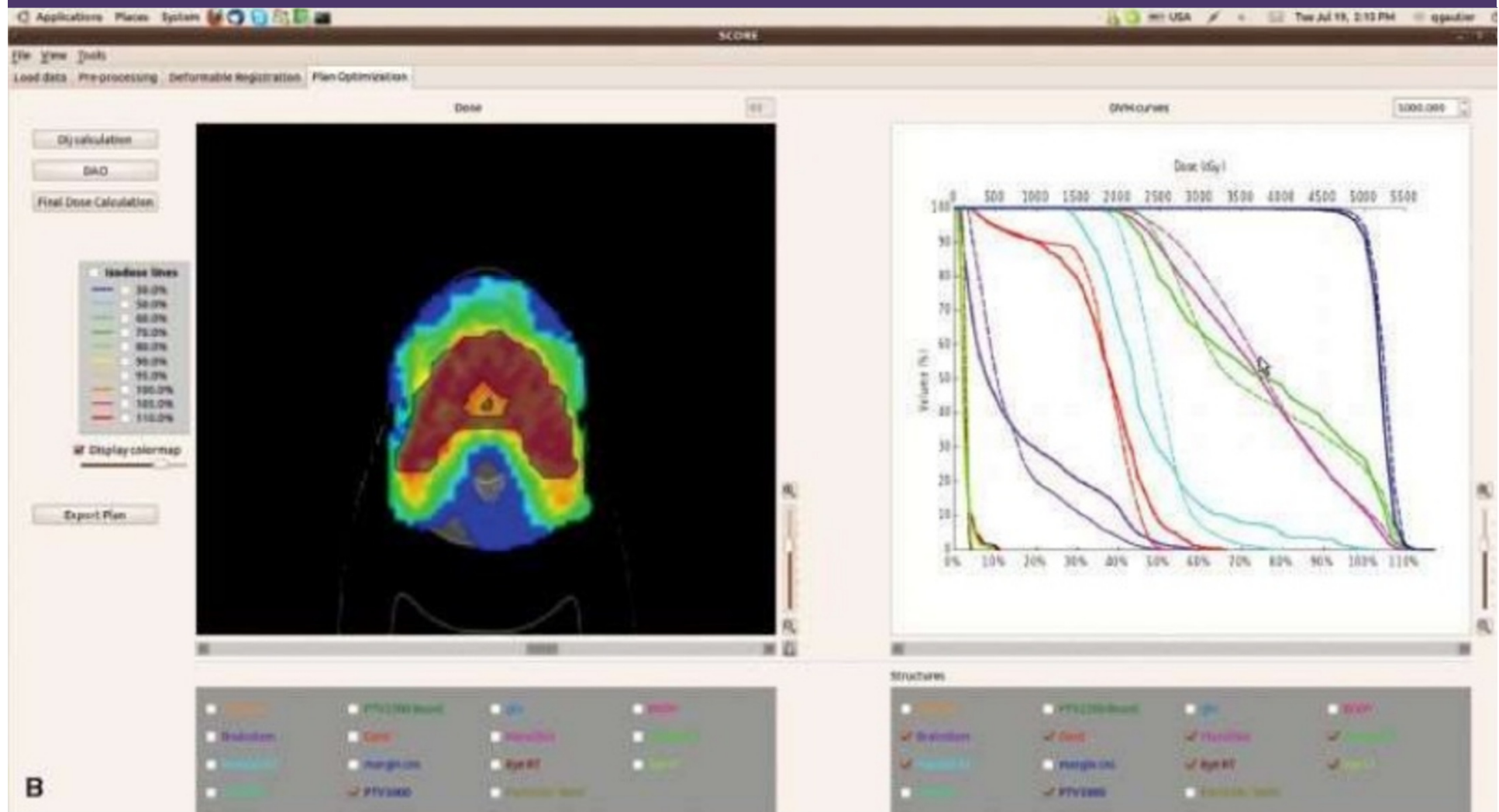
SCORE **Supercomputing On-line Re-planning Environment**



A GPU-based real-time re-planning system
A research platform for online ART

SCORE

- lokalno pridobivanje slikovnih podatkov
- rigidna registracija
- deformabila registracija
- pregled (anatomski, konture)
- reoptimizacija
- izračun doze
- primerjava
- izvoz v TPS



<https://www.utsouthwestern.edu/departments/radiation-oncology/facilities-equipment/mpe.html>

ČASOVNO ADAPTIVNA RT

- izbrana skupina bolnikov, ki pokažejo zmanjšanje tumorja
- upravljanje s podatki
- vzorci obnašanja po lokacijah
- nujen CT sredi zdravljenja

DILEME

- MVCT?
- robustnost sistema za delineacijo
- je varno zmanjšati GTV?
- nevarnosti IMRT+IGRT združene
- obremenitev osebja
- \$\$\$\$\$\$?
- dnevno?
- čas?
- upravičenost?

POVZETEK

- razvijajoče se orodje
- za bolnika specifična optimizacija plana
- še ovire
- NI KONSENZA O SMERNICAH
- BiGART?

Specialne tehnike v radioterapiji

Stereotaktična
radiokirurgija/radioterapija
(klinični aspekt)

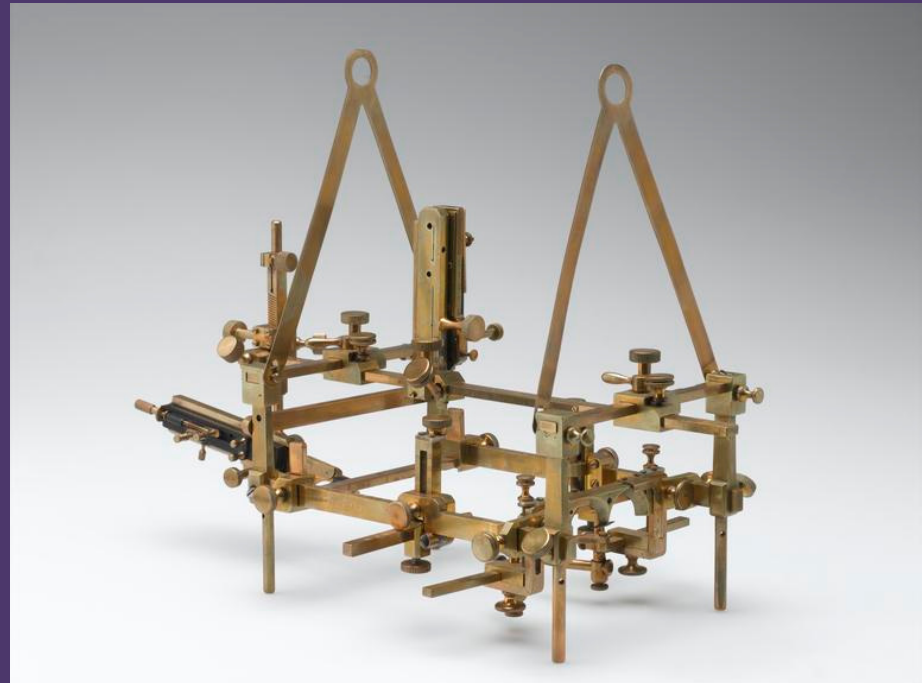
doc. dr. Uroš Smrdel dr. med.

STEREOTAKTIČNA RADIOKIRURGIJA SRS

- iz grškega στερεός (stereos) – soliden in latinskega taxis urejenost
- nanaša se na 3D koordinatni sistem, s katerim določimo virtualno tarčo na slikovnih preiskavah in realno tarčo znotraj bolnika

STEREOTAKSIJA

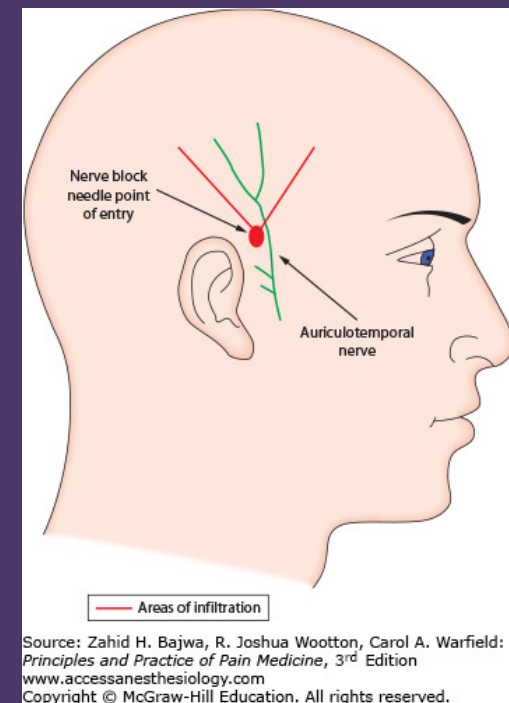
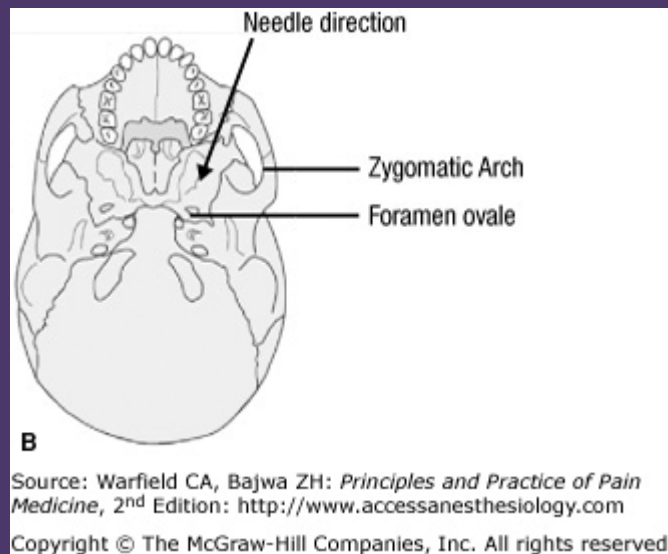
- Victor Horsley in Robert H. Clarke 1908
 - naprava z kartezijskim koordinatnim sistemom
 - uporaba za biopsijo lezij v možganih
 - samo živali



Science Museum London

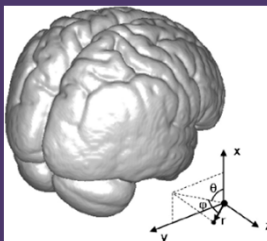
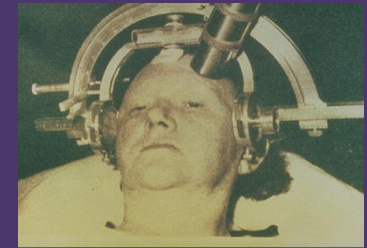
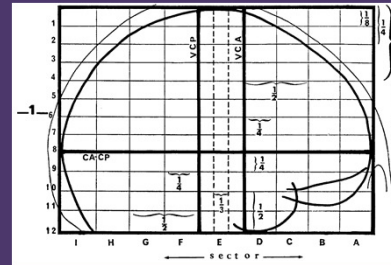
STEREOTAKSIJA

- 1933 Martin Kirschner
- prva stereotaktična kirurgija pri človeku
 - ablacija trigeminalnega ganglija



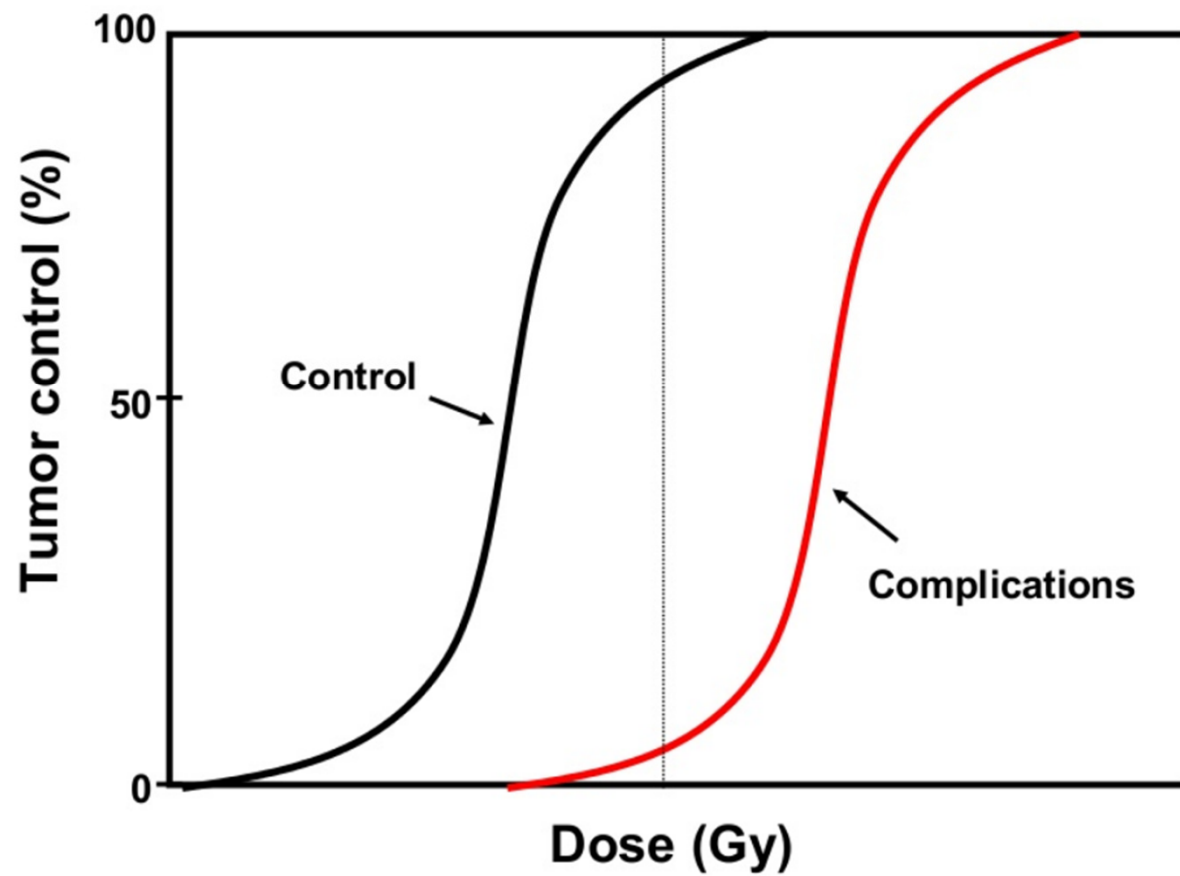
STEREOTAKSIJA

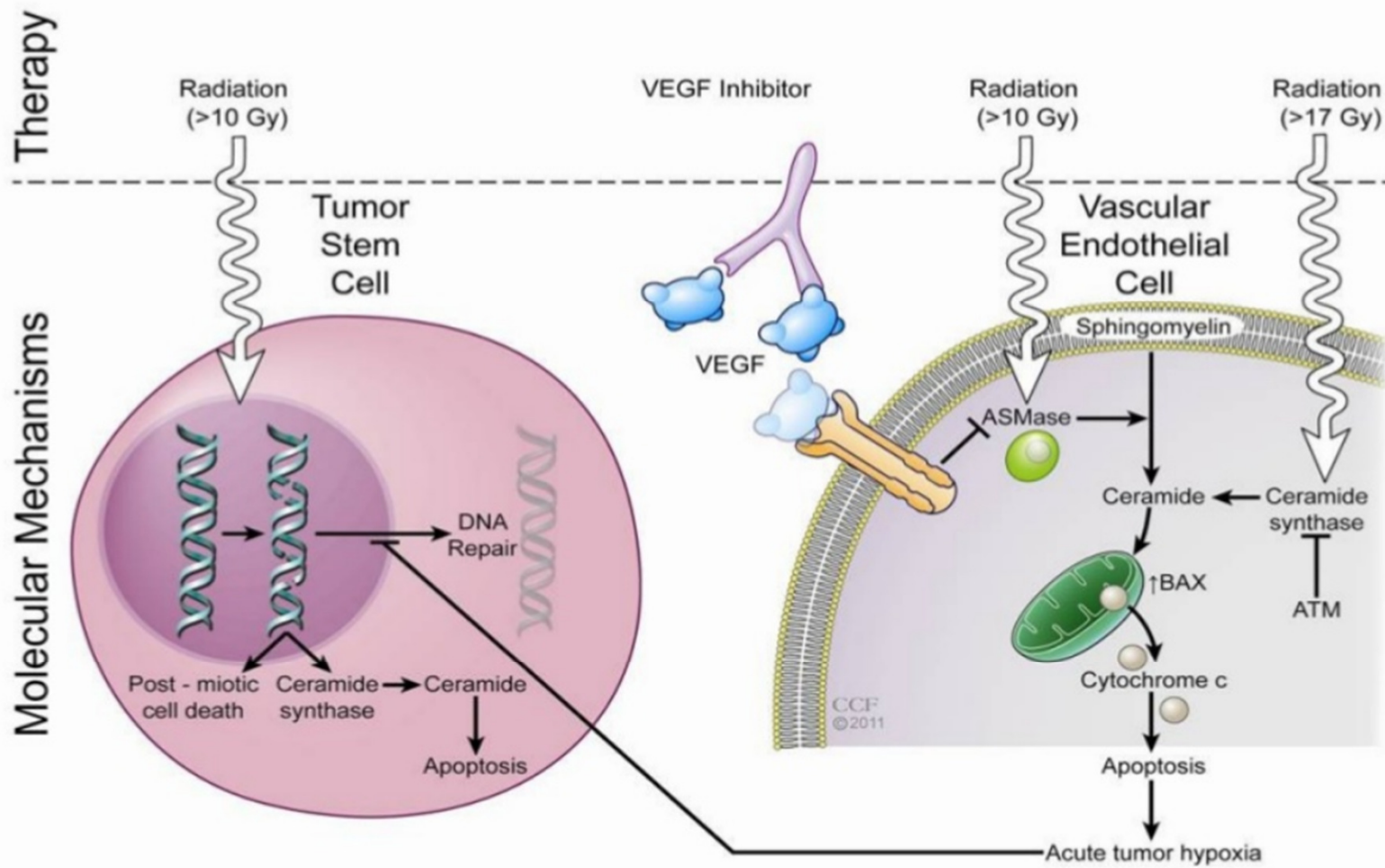
- Jean Talairach, Marcel David, Henri Hacaen, Julian de Ajuriaguerra, koordinatni sistem za človeške možgane (1949)
- Lars Leksell
 - polarni koordinatni sistem (1949)
 - usmerjena radiacija (ciklotron) z uporabo koordinatnega sistema (1951)
 - gama nož (1967) – Karolinska inštitut



SRS

Therapeutic Index



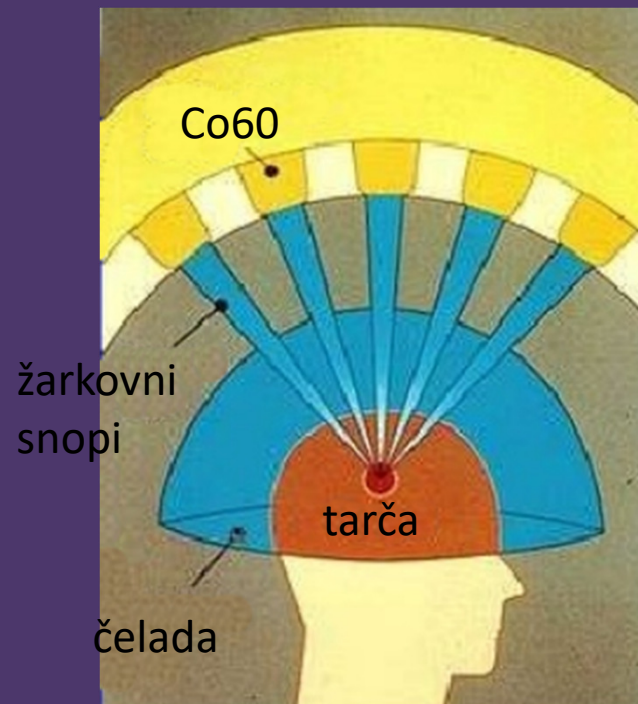


RADIOKIRURGIJA – METODE

- „GAMMA KNIFE“
- linearni pospeševalnik (1 izocenter)
 - večina pospeševalnikov, NovalisTx
- linearni pospeševalnik (več izocentrov)
 - „cyberknife“
- delci
 - protonski snop....

„GAMMA KNIFE“

- prva komercialno dostopna tehnika SRS

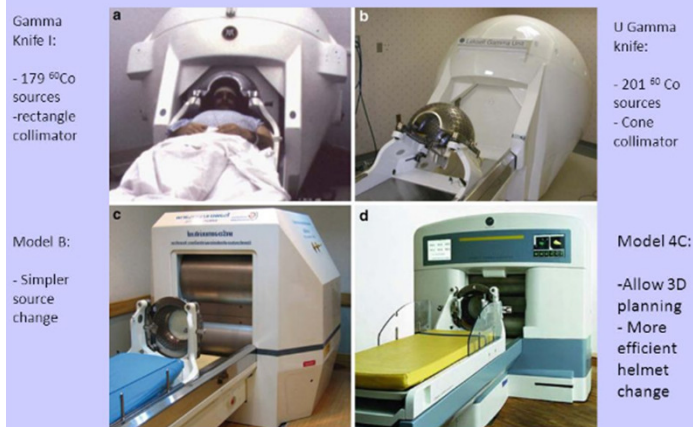


<http://www.mc.uky.edu/gammaknife/images/>

„GAMMA KNIFE“

- odlična stabilnost in mehanska natančnost
- okrogel kolimator do 1,8 cm (novi že MLC)
 - dosednji sistemi za nepravilne lezije multipli prekrivajoči se izocentri
- deklaracija na 50% izodozo
- conformity index vs homogeneity index

<https://www.elekta.com/products/catalog/gamma-knife-radiosurgery/leksell-gamma-knife-icon/leksell-gamma-knife-icon/>



Dr. Timothy D. Solberg et al. Historical Development of Stereotactic Ablative Radiotherapy

Solberg TD et al 2012



„GAMMA KNIFE“

$$Quality\ of\ coverage_{RTOG} = \frac{I_{min}}{RI}$$

where I_{min} = minimum isodose around the target, and RI = reference isodose.

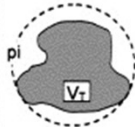
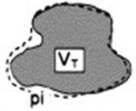
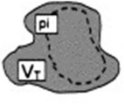
$$Homogeneity\ index_{RTOG} = \frac{I_{max}}{RI}$$

where I_{max} = maximum isodose in the target, and RI = reference isodose.

$$Conformity\ Index_{RTOG} = \frac{V_{RI}}{TV}$$

where V_{RI} = reference isodose volume, and TV = target volume.

ICRU 50
Feuvret L 2006

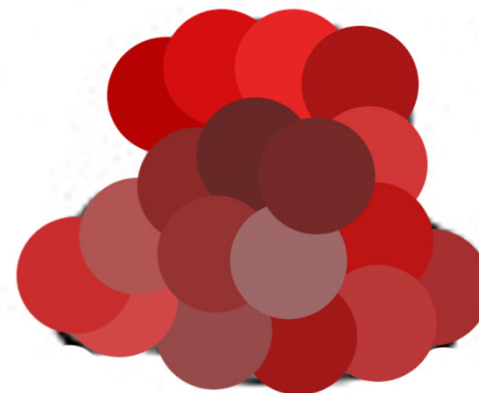
Case	1	2	3	4
Single slice showing target volume and prescription isodose				
Volume data	$V_T = 1.0$ $V_{pi} = 2.0$ $V_{T,pi} = 1.0$	$V_T = 1.0$ $V_{pi} = 1.2$ $V_{T,pi} = 0.95$	$V_T = 1.0$ $V_{pi} = 0.5$ $V_{T,pi} = 1.0$	$V_T = 1.0$ $V_{pi} = 1.0$ $V_{T,pi} = 0.5$
Coverage _{RTOG}	1.0	0.72	0.20	0.16
% Coverage	100%	95%	50%	50%
CI _{RTOG}	2.0	1.2	0.5	1.0
CI	0.5	0.79	1.0	0.5
CN	0.5	0.75	0.5	0.25

Lomax NJ 2003



TUMOR

TUMOR POKRIT S
HOMOGENIM
ODMERKOM,
KONFORMNOST JE
SLABA



TUMOR KONFORMNO
POKRIT,
HOMOGENOST JE
SLABA



„GAMMA KNIFE“

- do nedavno nepremičen okvir
- sedaj maske
- Elekta Icon – „image guided“



<https://www.elekta.com/products/>



SRS Z POSPEŠEVALNIKOM

- J. Barcia-Salorio 1982 najprej Co60, nato linac
— AVM in epilepsija

Acta Neurochirurgica, Suppl. 33, 385—390 (1984)
© by Springer-Verlag 1984

Hyperselctive Encephalic Irradiation with Linear Accelerator

O. O. Betti¹ and V. E. Derechinsky²

Linear Accelerator as a Neurosurgical Tool for Stereotactic Radiosurgery

Ken R. Winston, M.D. ✉, Wendell Lutz, Ph.D.

1988

- prva uporaba Boston Brigham and Women's Hospital 1986

SRS Z POSPEŠEVALNIKOM

- sedaj najpogosteje uporabljan NovalisTx
 - tudi svoj program:



- še vedno tudi modificirani obsevalni aparati
- Elekta svoj sistem za SRS



Suh JH 2013

Linac SRS Cleveland

1989 – 1997

adaptacija pospeševalnika

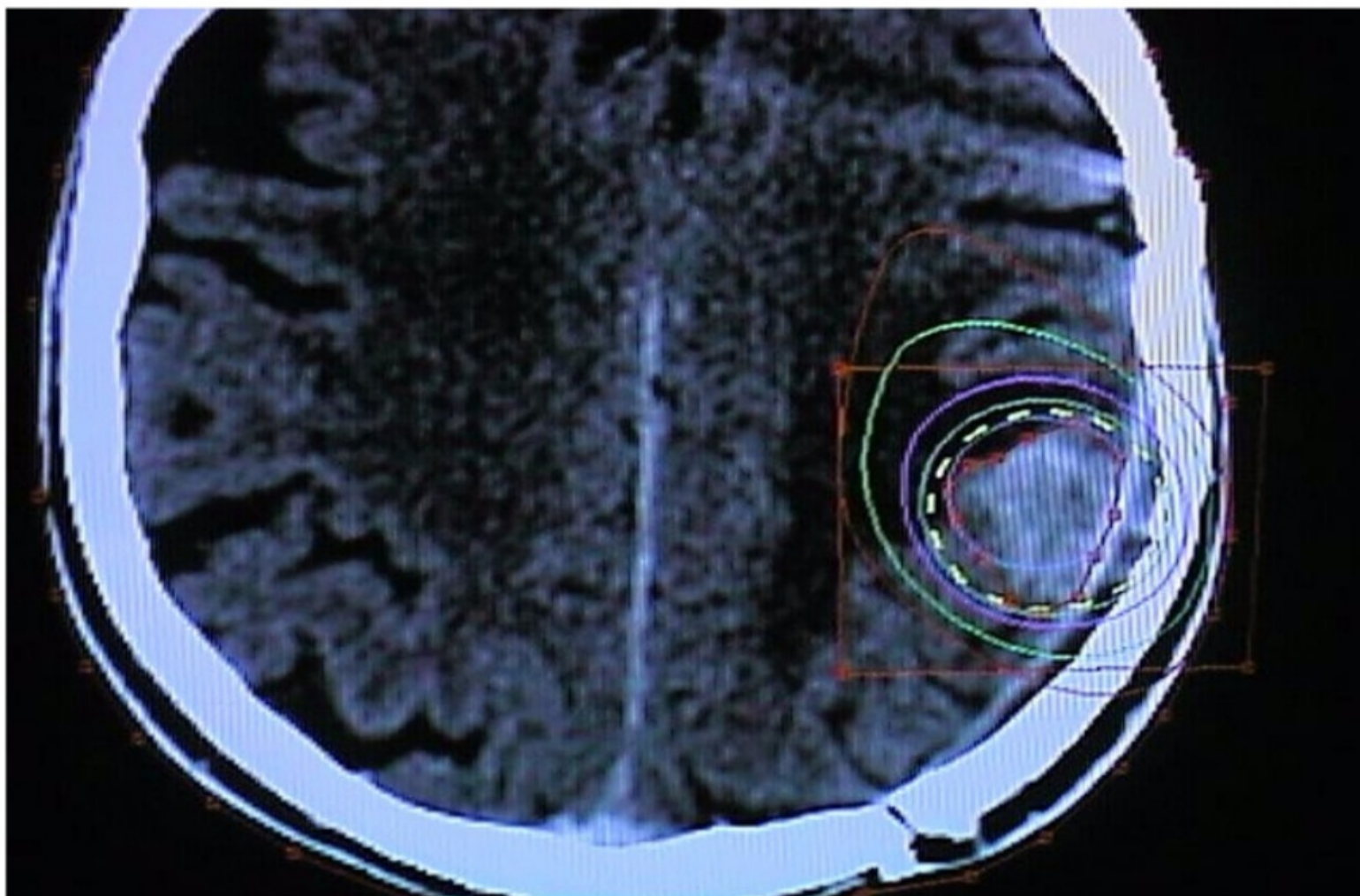
adaptacija mize

konični kolimator

5 nekoplanarnih lokov

ZNAČILNOSTI PRVIH
PROGRAMOV SRS

Treatment plan

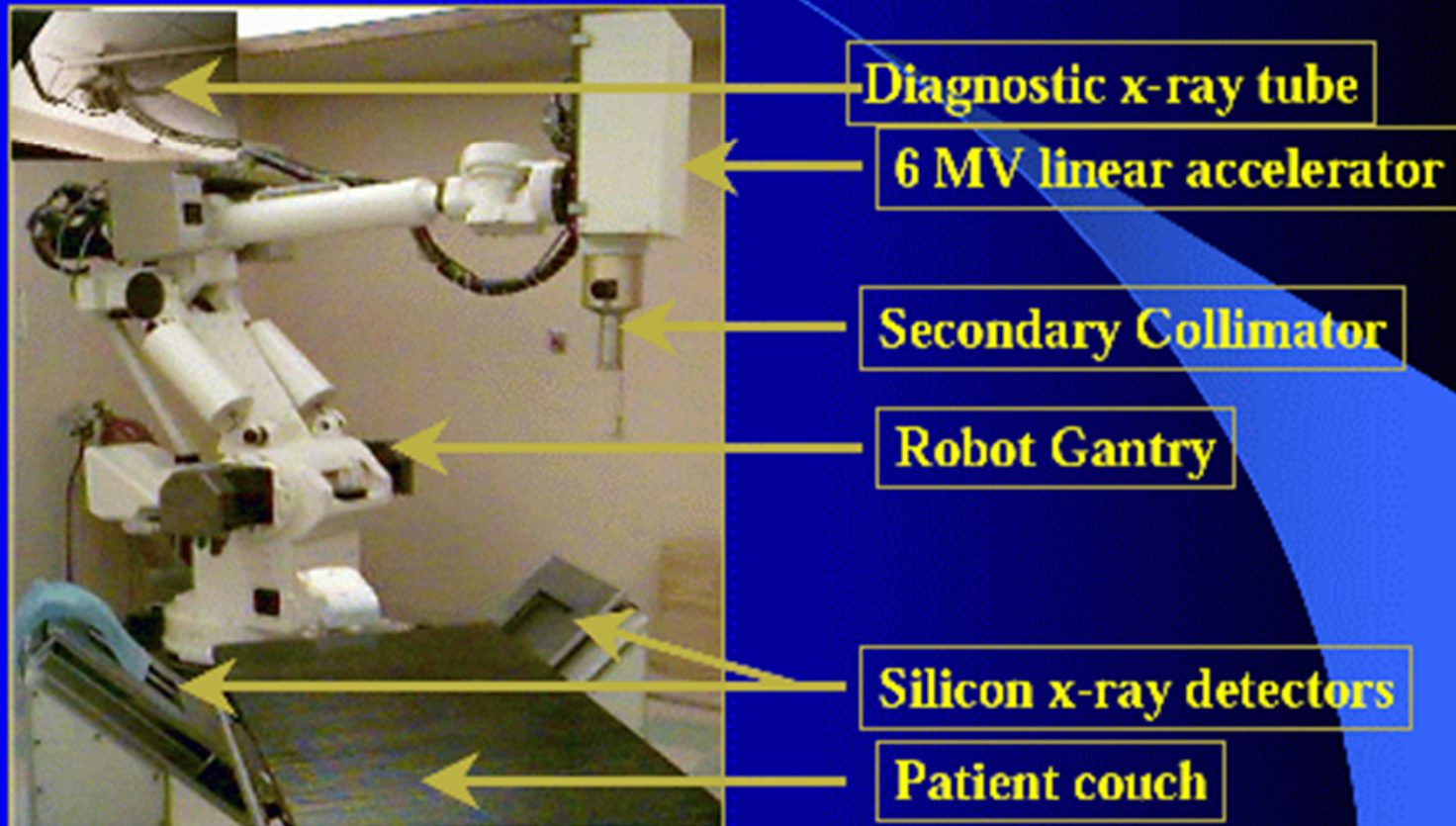




itn 2007

„CYBERKNIFE“

CYBERKNIFE™ Image-Guided Stereotactic Radiosurgery System

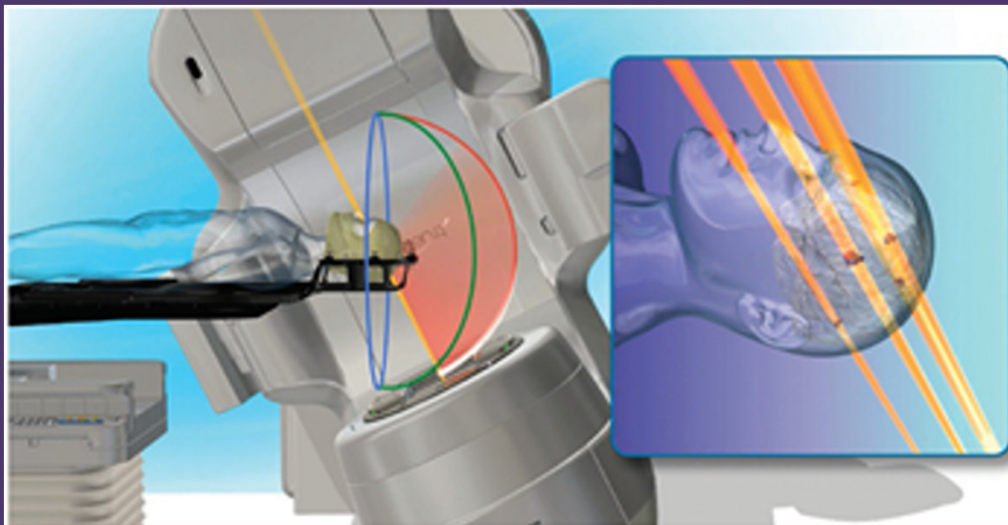


„CYBERKNIFE“

- 6 MV pospeševalnik na robotski roki
- SRS brez fiksacije
- spremlja gibanje tarče – bolnika in se prilagaja
- prednost pred GK ni samo za CŽS
- debata med CK in NovalisTx podporniki

HyperArc

- Varian
 - Uporaba enega izocentra za zdravljenje multiplih lezij
 - Glede na FFF hitra metoda cca 15 min

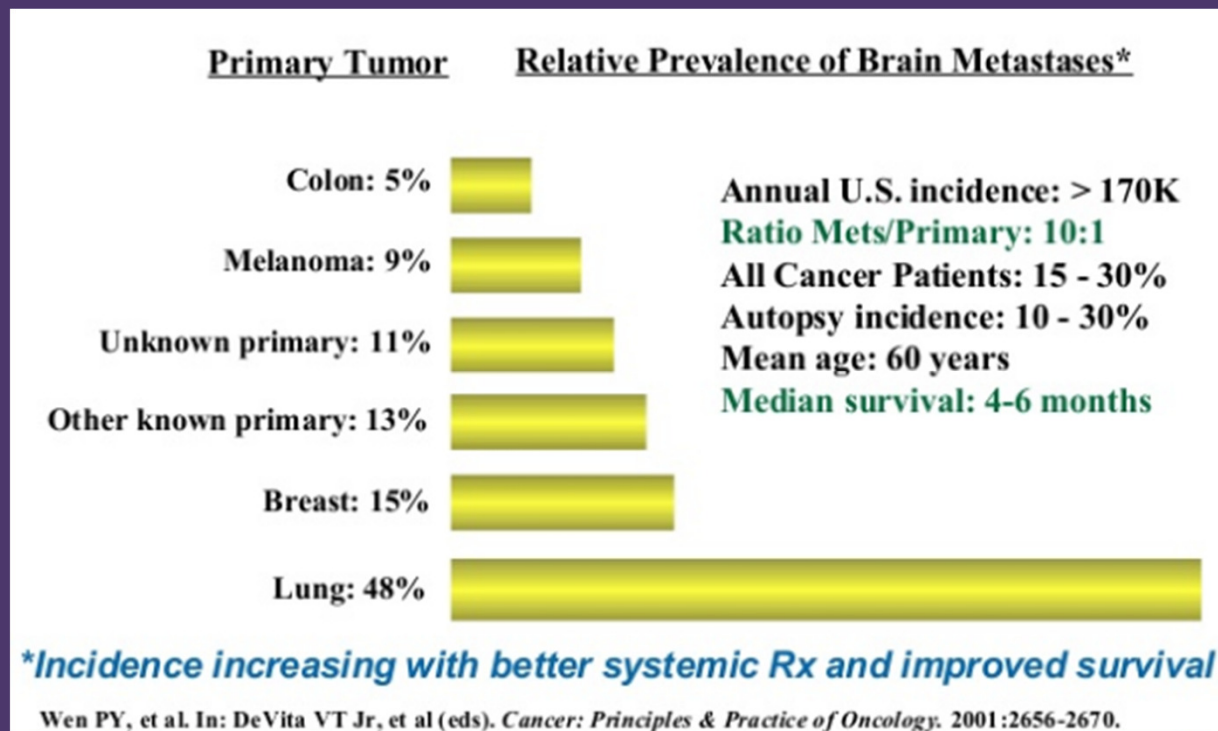


SRS – KDO?

- zasevki
- meningeomi
- schwanomi
- AVM
- tumorji hipofize
- ...
- ...
- funkcionalne lezije
- gliomi????

SRS – ZASEVKI

- najpogostejša indikacija

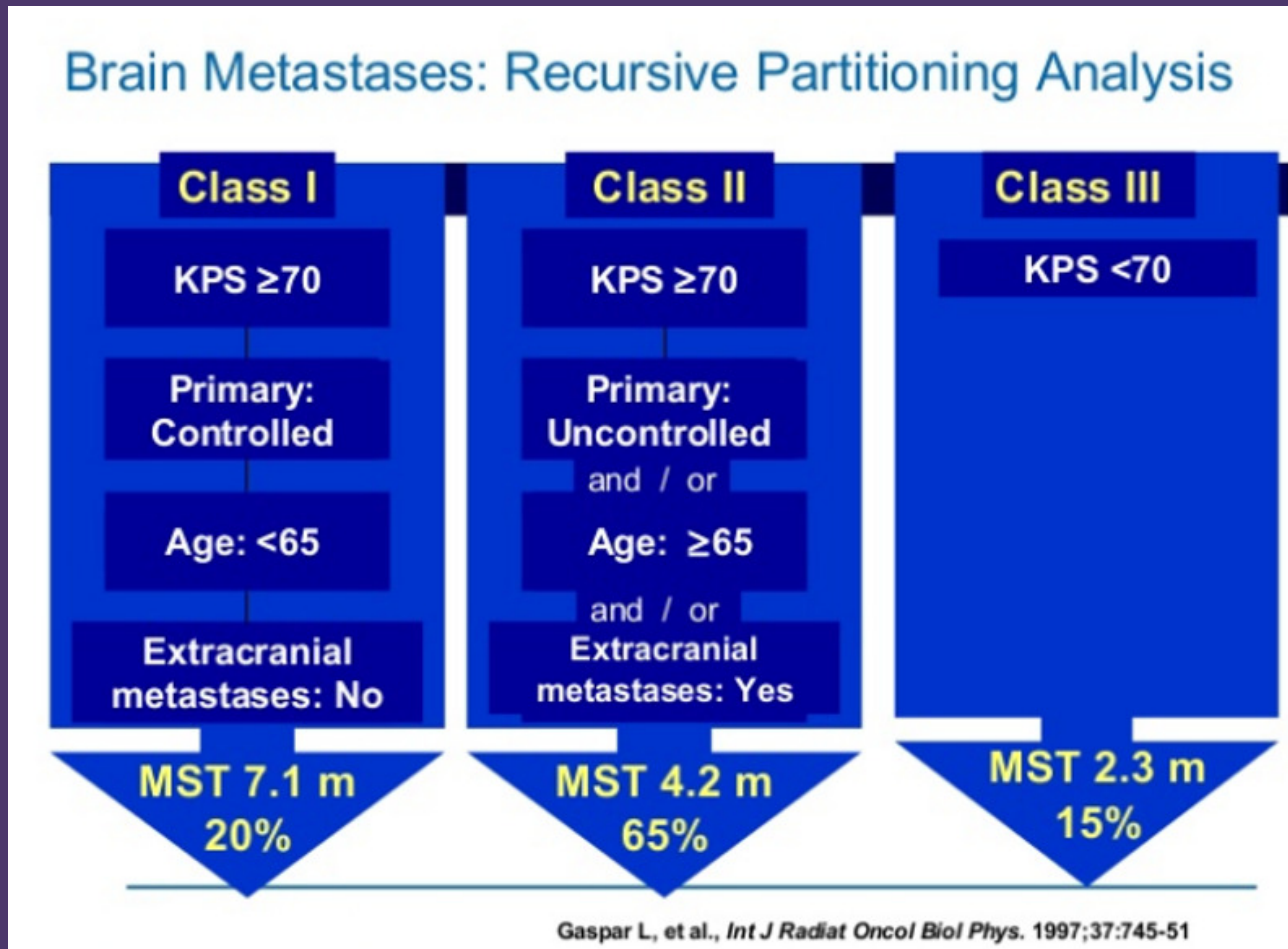


SRS – ZASEVKI

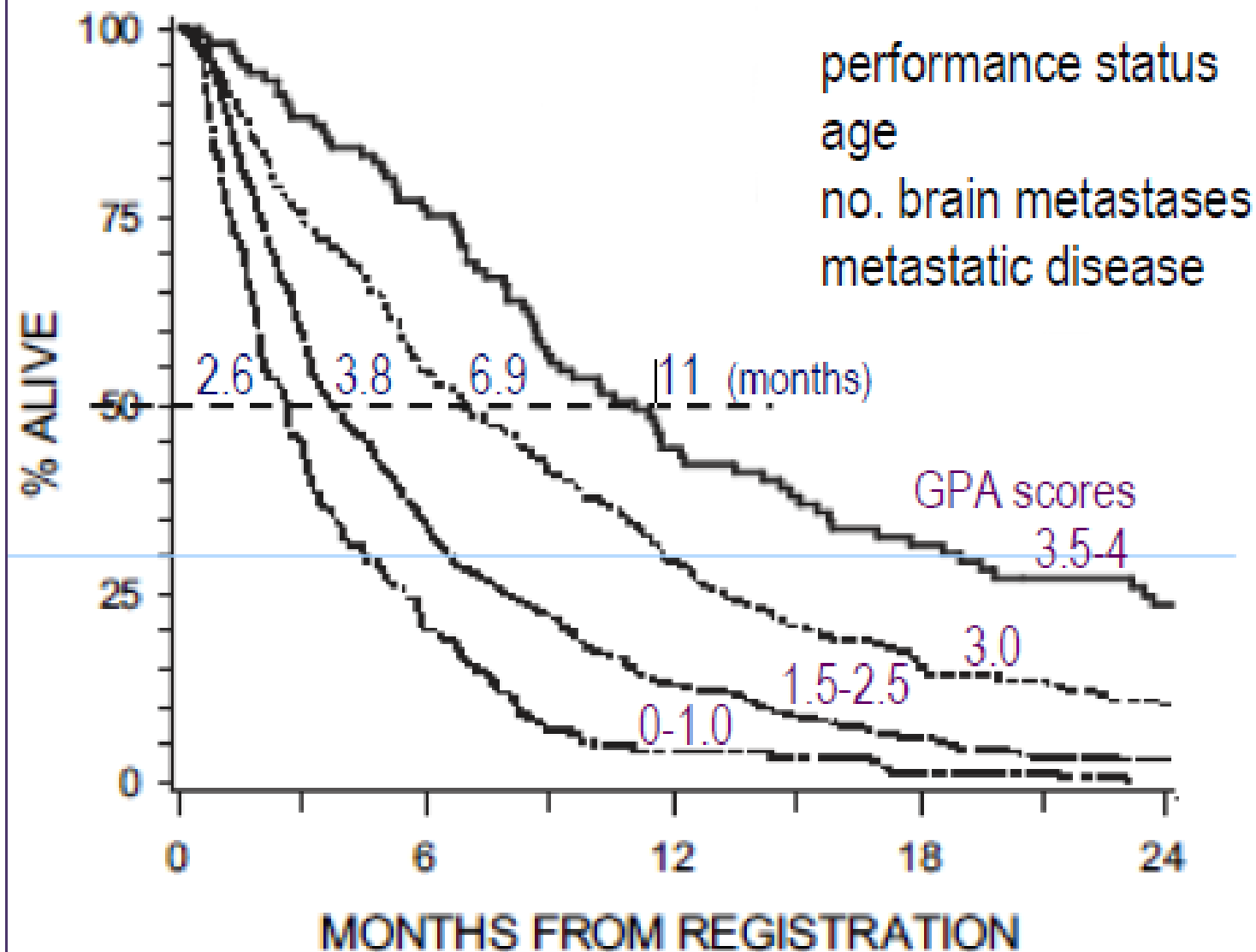
- odvisno od
 - število
 - velikost
 - mesto
 - deficit
 - starost/KPS
 - primarni tumor
 - bolezen izven CŽS
 - sodelovanje bolnika

SRS – ZASEVKI

- RPA



SRS – ZASEVKI



SRS – ZASEVKI

Sperduto et al. J Clin Oncol. 2012

A – dojka

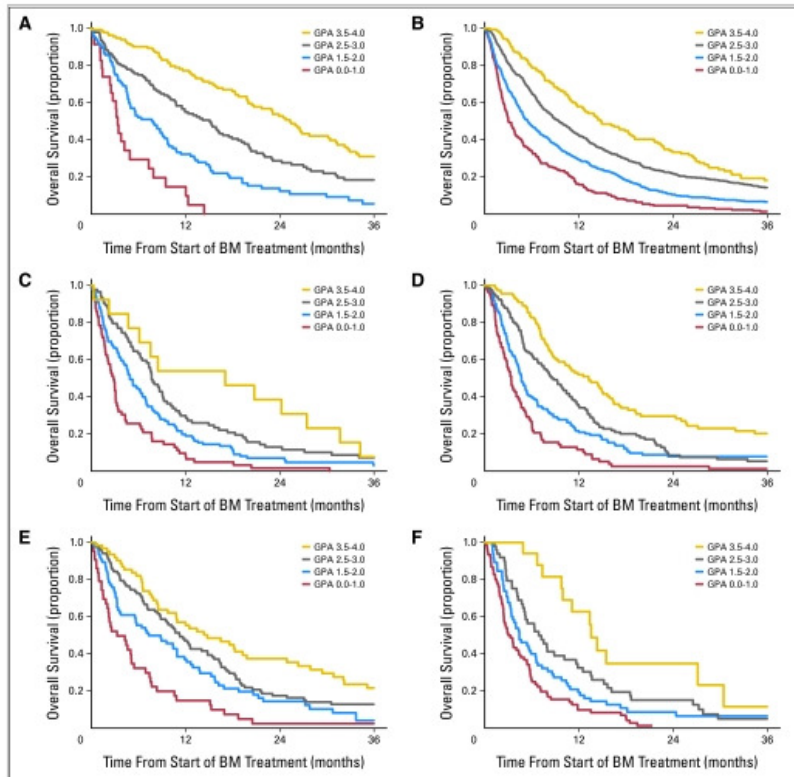
B – nedrobnocelični pljučni rak

C – drobnocelični pljučni rak

D – melanom

E – ledvica

F – gastrointestinalni tumorji



GRADED PROGNOSTIC ASSESSMENT

Non-small-cell and small-cell lung cancer		GPA Scoring Criteria			Patient
Prognostic Factor		0	0.5	1.0	Score
Age, years	> 60	50-60	< 50		_____
KPS	< 70	70-80	90-100		_____
ECM	Present	—	Absent		_____
No. of BM	> 3	2-3	1		_____
Sum total					_____
Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8					

Melanoma		GPA Scoring Criteria			Patient
Prognostic Factor		0	1.0	2.0	Score
KPS	< 70	70-80	90-100		_____
No. of BM	> 3	2-3	1		_____
Sum total					_____
Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2					

Breast cancer		GPA Scoring Criteria					Patient
Prognostic Factor		0	0.5	1.0	1.5	2.0	Score
KPS	≤ 50	60	70-80	90-100	n/a		_____
Subtype	Basal	n/a	LumA	HER2	LumB		_____
Age, years	≥ 60	< 60	n/a	n/a	n/a		_____
Sum total							_____
Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3							

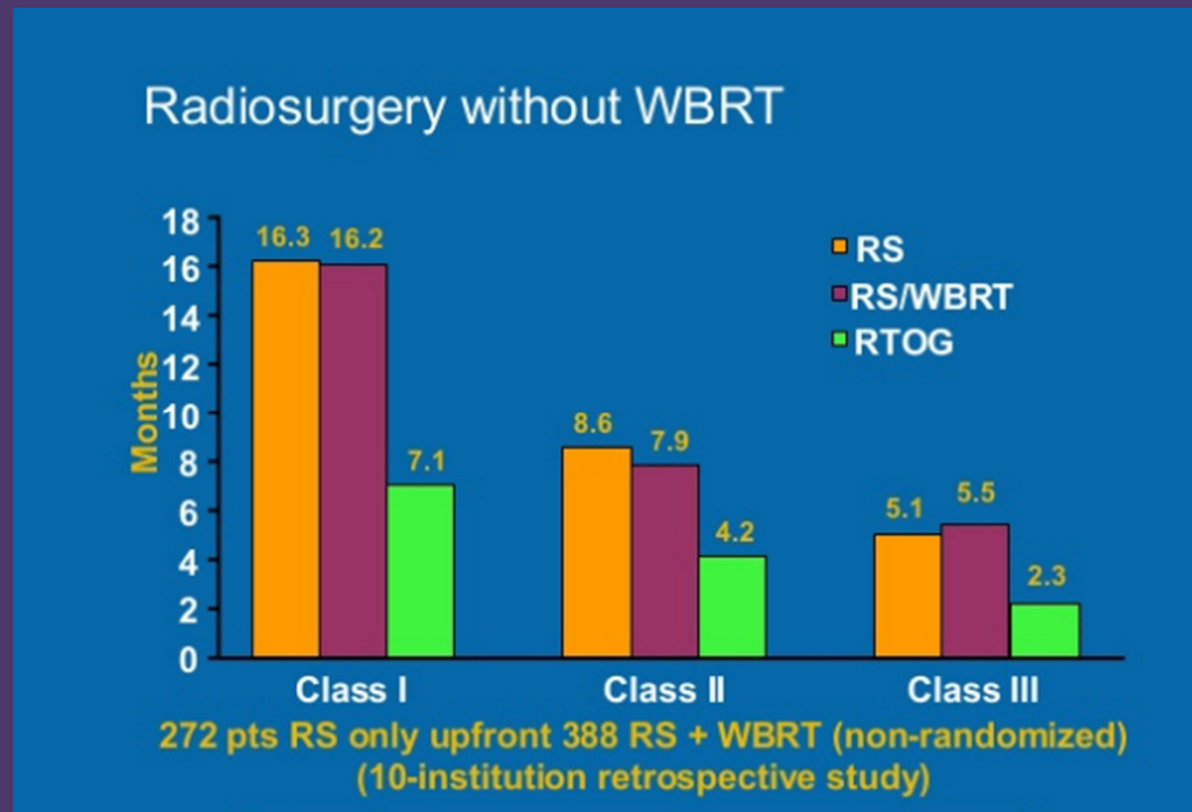
Renal cell carcinoma		GPA Scoring Criteria			Patient
Prognostic Factor		0	1.0	2.0	Score
KPS	< 70	70-80	90-100		_____
No. of BM	> 3	2-3	1		_____
Sum total					_____
Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8					

GI cancers		GPA Scoring Criteria				Patient	
Prognostic Factor		0	1	2	3	4	Score
KPS	< 70	70	80	90	100		_____
Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5							

SRS – ZASEVKI

- primerni za SRS zaradi
 - MR radiološko jasni
 - večinoma sferoidi
 - odrivajo možgane
 - malo invazije
 - pogosto pod 3 cm

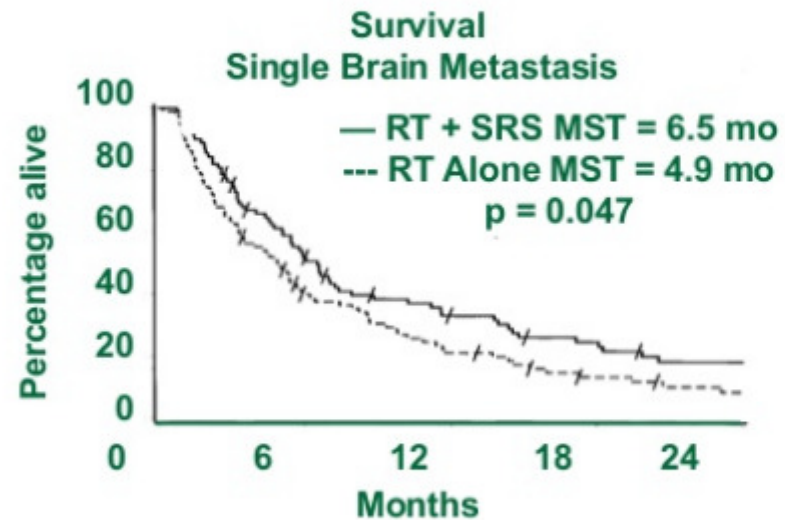
SRS – ZASEVKI



Suh JH 2013

SRS – ZASEVKI

KAPLAN-MEIER SURVIVAL RTOG 9508



Andrews DW et al. Lancet 363:1665-1672, 2004

SRS – ZASEVKI

Phase III randomized trial of SRS +/-WBRT

No prior surgery, SRS, or WBRT

No leukemias, lymphomas, germ-cell tumors, SCLC, leptomeningeal disease

RPA class I /II
patients with
1-3 lesions
from known
primary
58 pts

**R
A
N
D**

SRS (15, 18 or 24 Gy)

SRS + WBRT (30 Gy/12 fx)

Stratification by

- RPA class (I or II)
- number of lesions (1 or 2 vs 3)
- “radioresistant” histologies (melanoma or RCC vs other)

? Baseline neurocognitive function and medications (opioids, sedatives)

Primary endpoint: neurocognitive function

- Defined as a decrease in HVLT-R total recall at 4 months by more than 5 points
- Trial was closed early by data monitoring committee

SRS – ZASEVKI

Neurocognitive decline

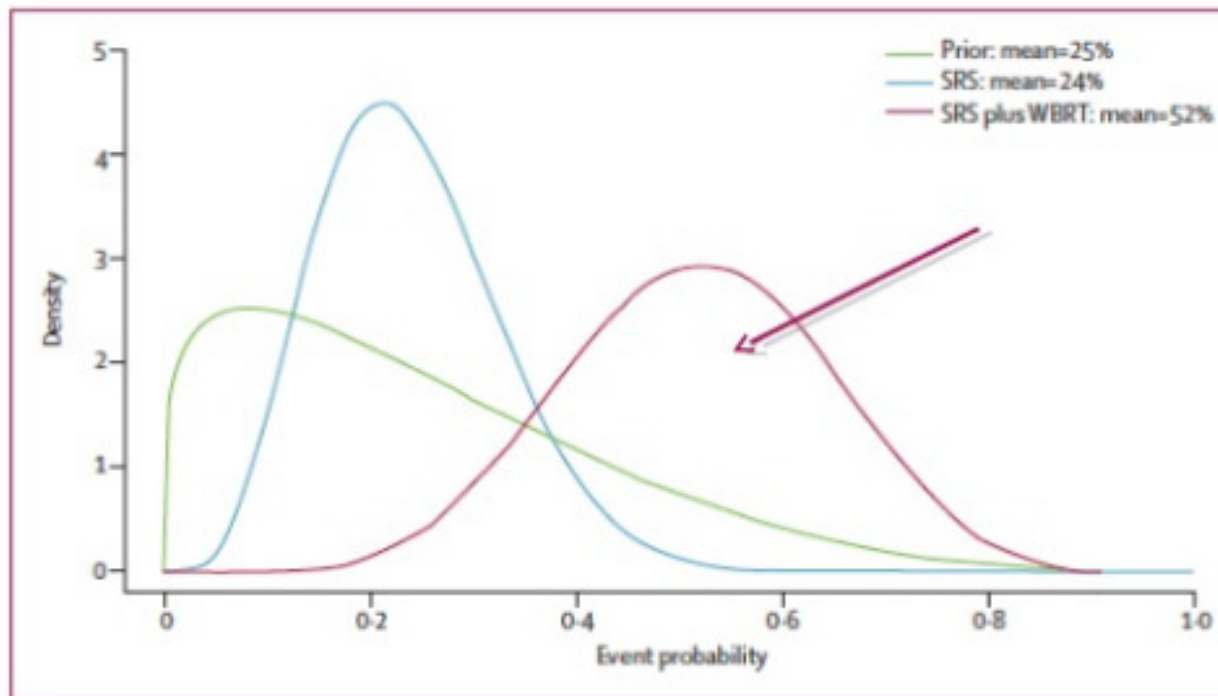


Figure 2: Prior and posterior distributions of probability of cognitive decline (5 points or greater fall from baseline) assessed by HVL-R (total recall)

SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.

“A mean posterior probability of [neurocognitive] decline of 52% for the SRS plus WBRT group and 24% for the SRS only group.” (96% confidence)

SRS – ZASEVKI

Phase III randomized trial of surgery or SRS +/-WBRT EORTC 22592-26001

	Observation	WBRT	p value
Median time WHO PS > 2	10 m	9.5 m	0.71
Median overall survival	10.9 m	10.7 m	0.89
2-year relapse at initial site			
Surgery	59%	27%	0.001
SRS	31%	19%	0.04
2-year relapse at new sites			
Surgery	42%	23%	0.008
SRS	48%	33%	0.023

SRS – ZASEVKI

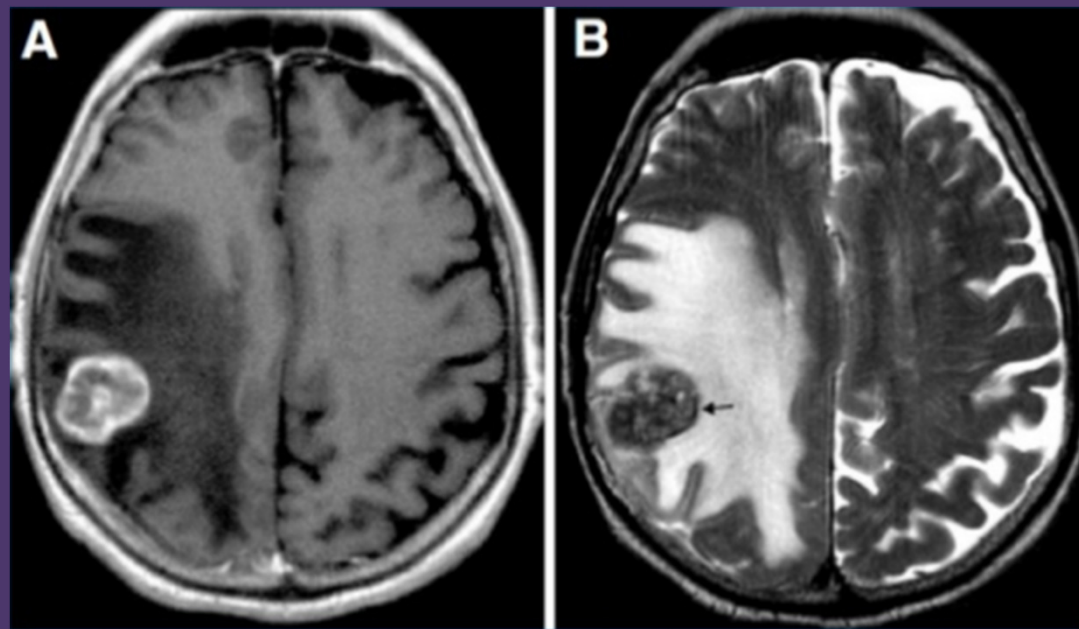
- Še vedno vprašanje koliko zasevkov je smiselno
 - Mogoče je obsevati veliko zasevkov



Klinični učinek pa je vprašljiv
pri bolnici progres izven CŽS
po 2 mesecih pokojna

SRS – ZASEVKI

- problem radionekroza ali ponovitev?



Suh JH 2013

SRS/SRT - MENINGEOMI

- najpogostejši primarni tu CŽS
 - večina radiološka diagnoza
 - 2:1 nad tentorijem
 - opazovanje
 - operacija
 - RT/SRS/SRT
- 

SRS/SRT - MENINGEOMI

Most Common Brain and CNS Tumors by Age CBTRUS Statistical Report: NPCR and SEER Data 2004-2006		
Age (yrs)	Most Common Histology	2nd Most Common Histology
0-4	Embryonal / Medulloblastoma	Pilocytic Astrocytoma
5-9	Pilocytic Astrocytoma	Malignant Glioma , NOS
10-14	Pilocytic Astrocytoma	Neuronal / Glial
15-19	Pituitary	Pilocytic Astrocytoma
20-34	Pituitary	Meningioma
35-44	Meningioma	Pituitary
45-54	Meningioma	Glioblastoma
55-64	Meningioma	Glioblastoma
65-74	Meningioma	Glioblastoma
75-84	Meningioma	Glioblastoma
85+	Meningioma	Neoplasm, unspecified

SRS/SRT - MENINGEOMI

University of Pittsburgh: long term results

- Updated their 18-year experience in a cohort of 972 patients with 1045 intracranial meningiomas
- 70% women
- 645 patients had middle and posterior fossa tumors
- Median dose 14 Gy

Kondziolka D, et al. Neurosurg 62(1):53-8, 2008

SRS/SRT - MENINGEOMI

University of Pittsburgh: long term results

- Among 75 patients with a minimum follow-up of 10 years, the local control rates for grade 1 meningiomas or lesions without histology were 91% and 95%, respectively.
- Local control for WHO II and III were 50% and 17%, respectively.
- Symptomatic peritumoral edema was 4 months at mean of 8 months.

Kondziolka D, et al. Neurosurg 62(1):53-8, 2008

SRS/SRT - MENINGEOMI



Contents lists available at [ScienceDirect](#)

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Benign meningiomas

Long-term efficacy of fractionated radiotherapy for benign meningiomas



Francesca Soldà^{a,1}, Beverley Wharram^{a,2}, Paul B. De Ieso^{a,3}, Jacob Bonner^{a,2}, Sue Ashley^a,
Michael Brada^{a,b,*}

^aNeuro-oncology Unit, The Royal Marsden NHS Foundation Trust; and ^bAcademic Unit of Radiotherapy and Oncology, The Institute of Cancer Research, London, UK

SRS/SRT - HIPOFIZA

- observacija
- kirurgija
- zdravila
- SRS
- RT
- multimodalno

SRS/SRT - HIPOFIZA

- kot primarno
- dodatno
- reševalno



Maurice Tillet, akromegalija

SRS/SRT - HIPOFIZA

- različne frakcionacije
 - 45 Gy # 25 frakcij (VB)
 - 20 Gy # 13 frakcij
 - 28 Gy # 5 frakcij....

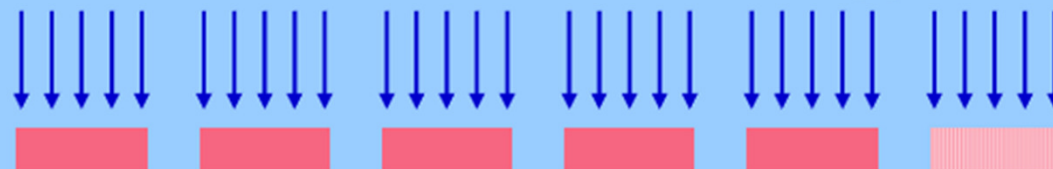
SCHWANOMI

- 8 – 10 % prim tumorjev CŽS
 - 80 – 90 % tumorjev cerebelopontinega kota
 - 99,9% benigni
 - lahko v sklopu NF1
-
- izguba sluha
 - tinitus
 - motnje ravnotežja
 - prizadetost možganskih živcev

SCHWANOMI

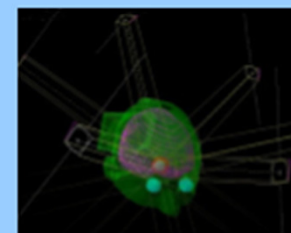
- opazovanje
- operacija
- SRS – do 1,5 cm
- SRT – nad 1,5 cm

Fractionated “stereotactic” radiotherapy

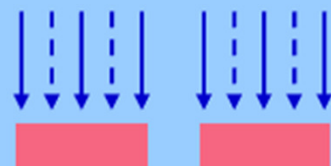


45 - 50Gy in 25 - 30 fractions

fractions
weeks



Hypofractionated “stereotactic” radiotherapy



20 - 30Gy in 6 - 10 fractions

Single fraction radiosurgery

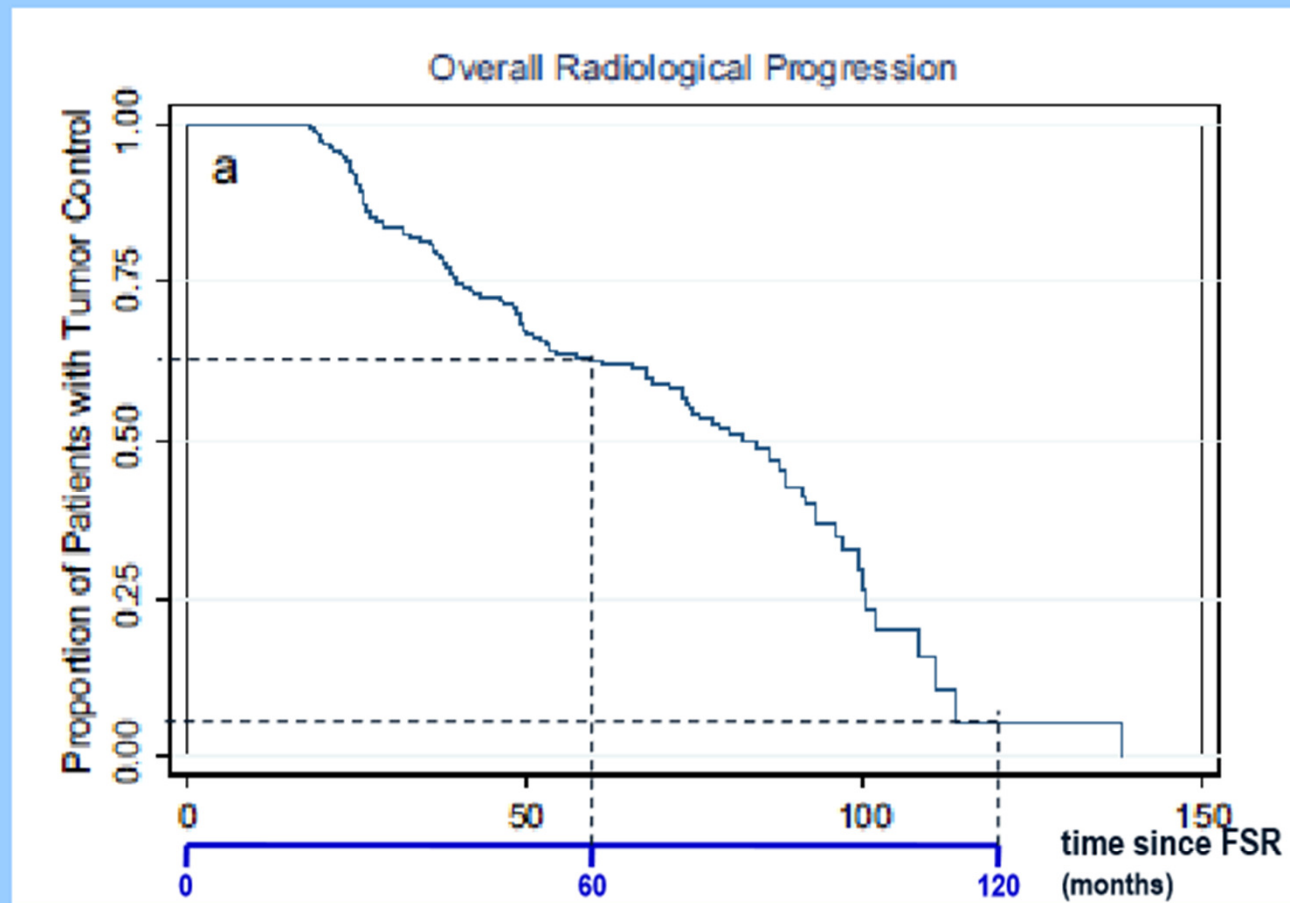


10 - 25Gy in 1 fraction



Fractionation in high precision radiotherapy

Tumour control



Fractionated stereotactic RT for acoustic neuroma

Kapoor et al 2010, Int J Rad Oncol Biol Phys, Johns Hopkins experience

SRS vs FSR: Jefferson Results

- Retrospective study of 125 patients with AN
 - 69 treated with SRS (12 Gy to the 50% IDL)
 - 56 treated with FSR (50 Gy/25 fx)

	Tumor Control	Preserv Trigem	Preserv Facial	Preserv Hearing	Tumor Control NF2
SRS	98%	95%	98%	33%	80%
FSR	97%	93%	98%	81%	67%
P value	0.6777	0.5893	0.8202	0.0228	0.6615

Dosing recommendation: 46.8 Gy/26 fx

Andrews D, et al., Int J Radiat Oncol Biol Phys 2001; 50:1265-1278

SRS vs FSR from Netherlands

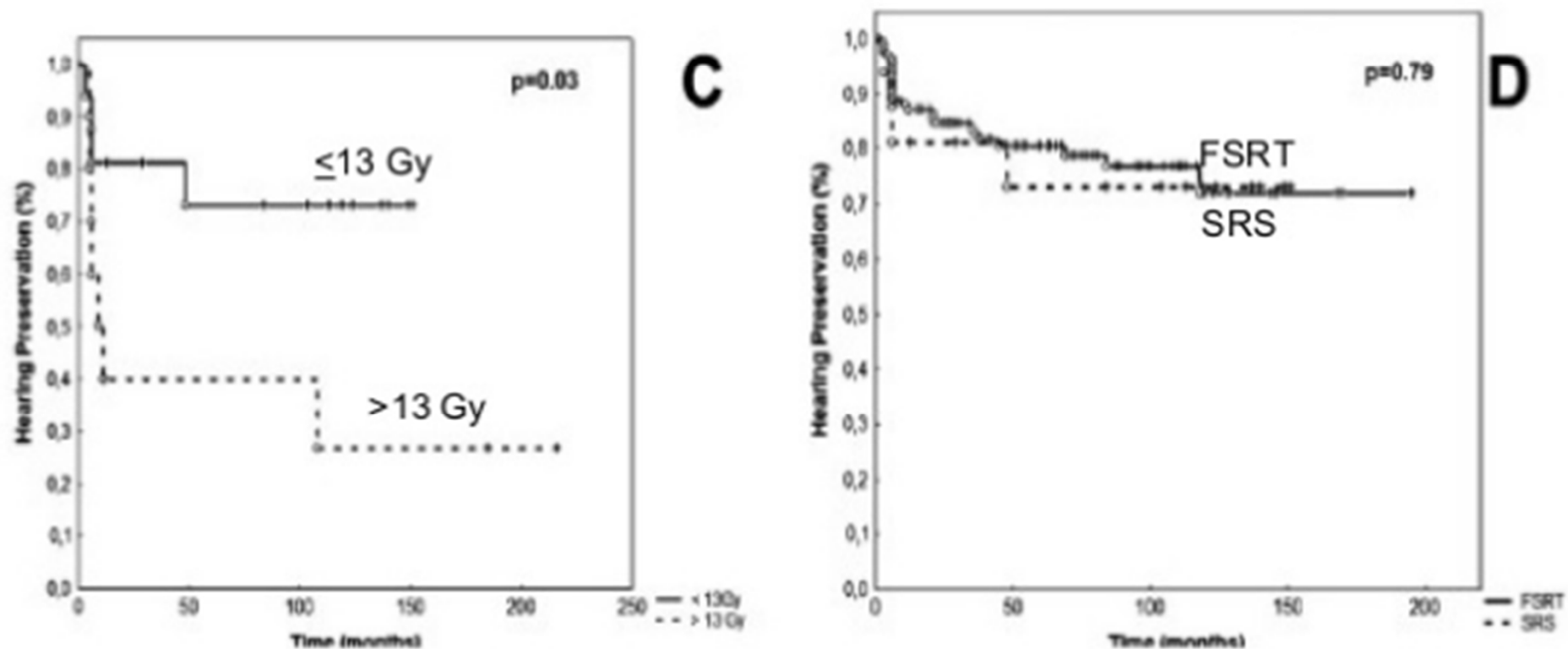
- All treatments were linac-based from 1992 to 1999
- 129 patients prospectively randomized to SRS vs. FSR
 - Dentate: FSR (20 Gy/5 fx and 25 Gy/5 fx)
 - Edentate: SRS (10 Gy and 12.5 Gy)
- Mean Tumor Diameter (FSR: 2.5 cm vs. SRS: 2.6 cm)

	Local Control	Preserved Hearing	Preserved VII Function	Preserved Vth Function
FSR	94%	61%	97%	98%
SRS	100%	75%	93%	92%

Meijer et al. Neurosurg 2003; 56(5): 1390-1396

SRS versus FSRT for vestibular schwannomas

200 patients treated at Heidelberg and DFKZ
Hearing preserv SRS ≤ 13 Gy and FSRT 57.6 Gy/32 fx



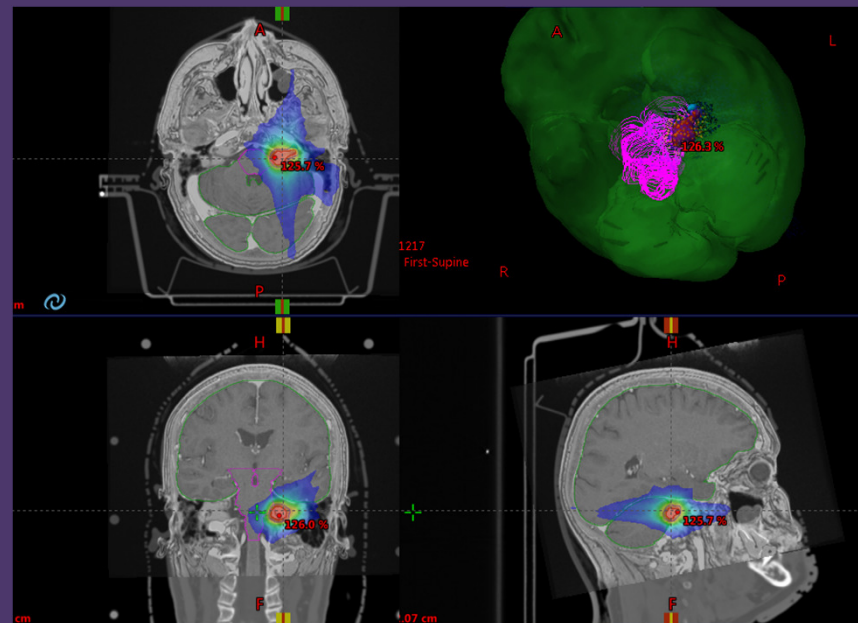
Combs S, et al. Int J Radiat Oncol Biol Phys 76:193-200, 2010

SCHWANOMI

- pri nas
 - $< 1,5$ cm lahko 13,5 Gy # 1 frakcija
 - $> 1,5$ cm 54 Gy # 30 frakcij
- lokalna kontrola $> 90\%$
- se izogibamo

SCHWANOMI

- Po podatkih EANO
 - Hipofrakcionirana SRS podoben učinek kot frakcionirana
 - Pri nas sedaj 21 Gy # 3 frakcije



Load Archives

Archive Name ▲

Data Format

Directory

 DICOM from VARIANCOM	DICOM	\\variancom\dicom\variaet_dcm\
 iPlan Patient Data	Advanced BrainLAB	\\variancom\va_data\filedata\brainlab\iplan_patients\
 PACS	DICOM	iplanet



New Archive

Settings

Delete

Logfile...

DICOM from VARIANCOM

Details

Back

Cancel

Next

Navigator

No Patient Loaded

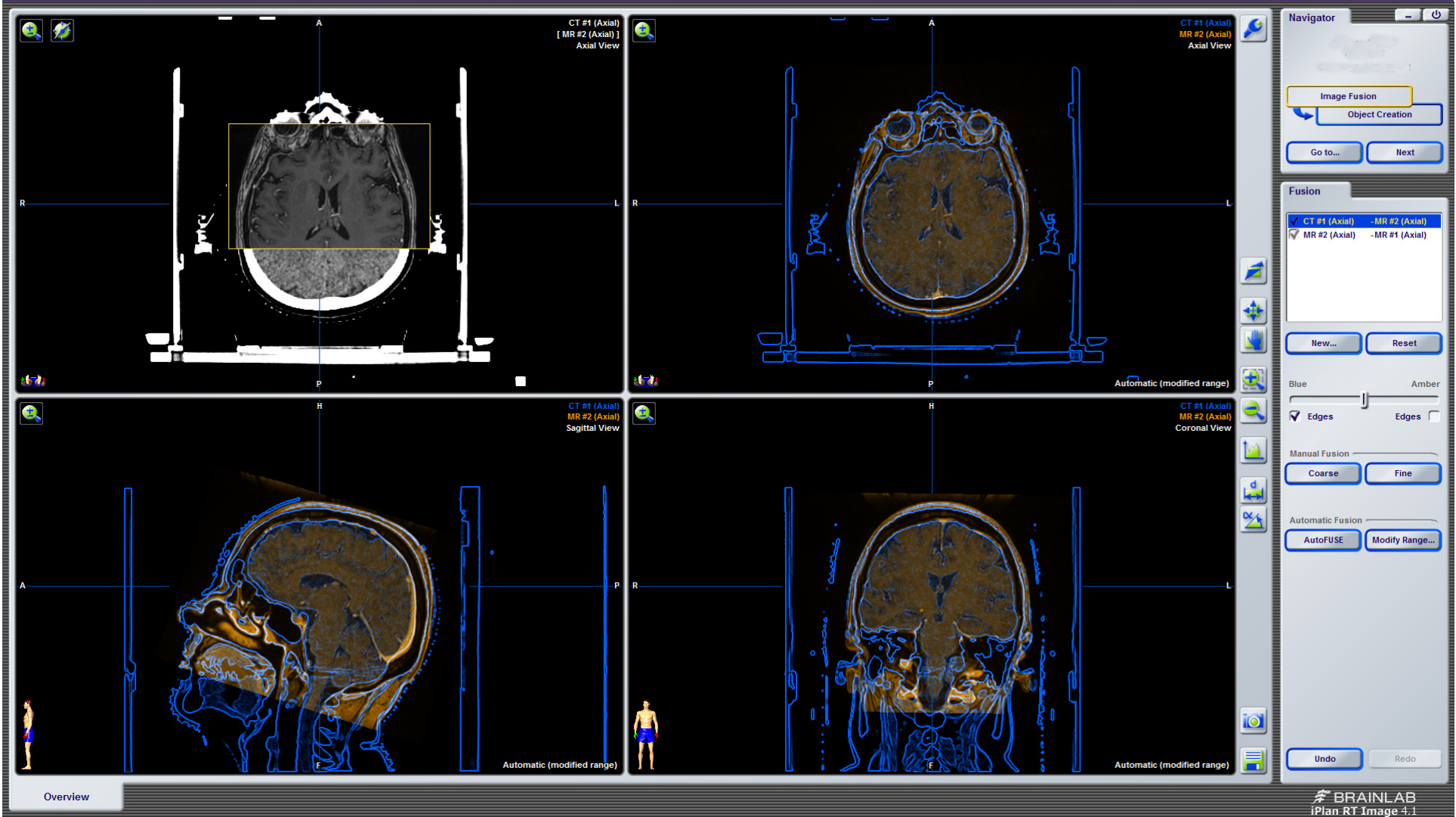
Load and Import

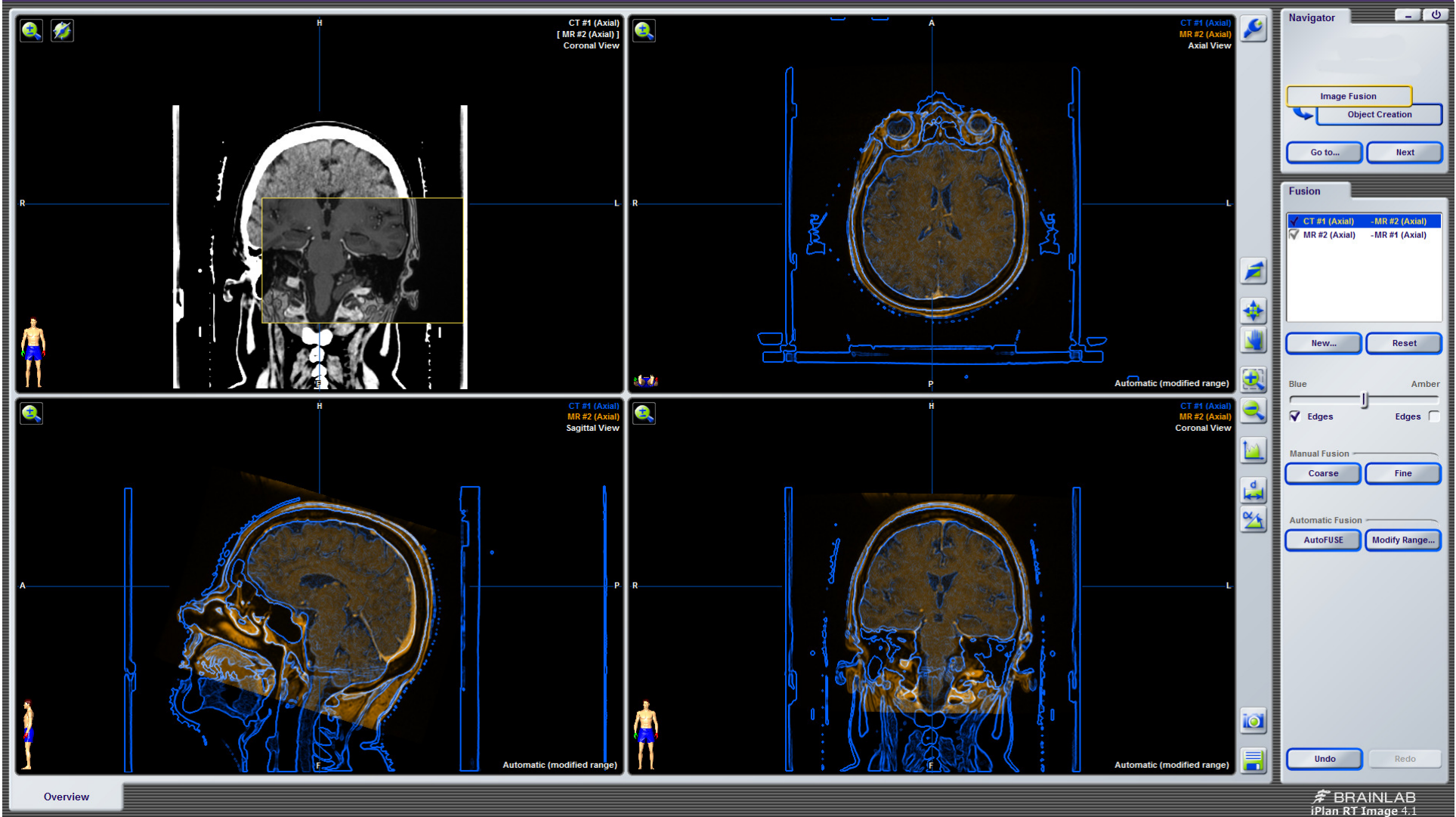
Statistics

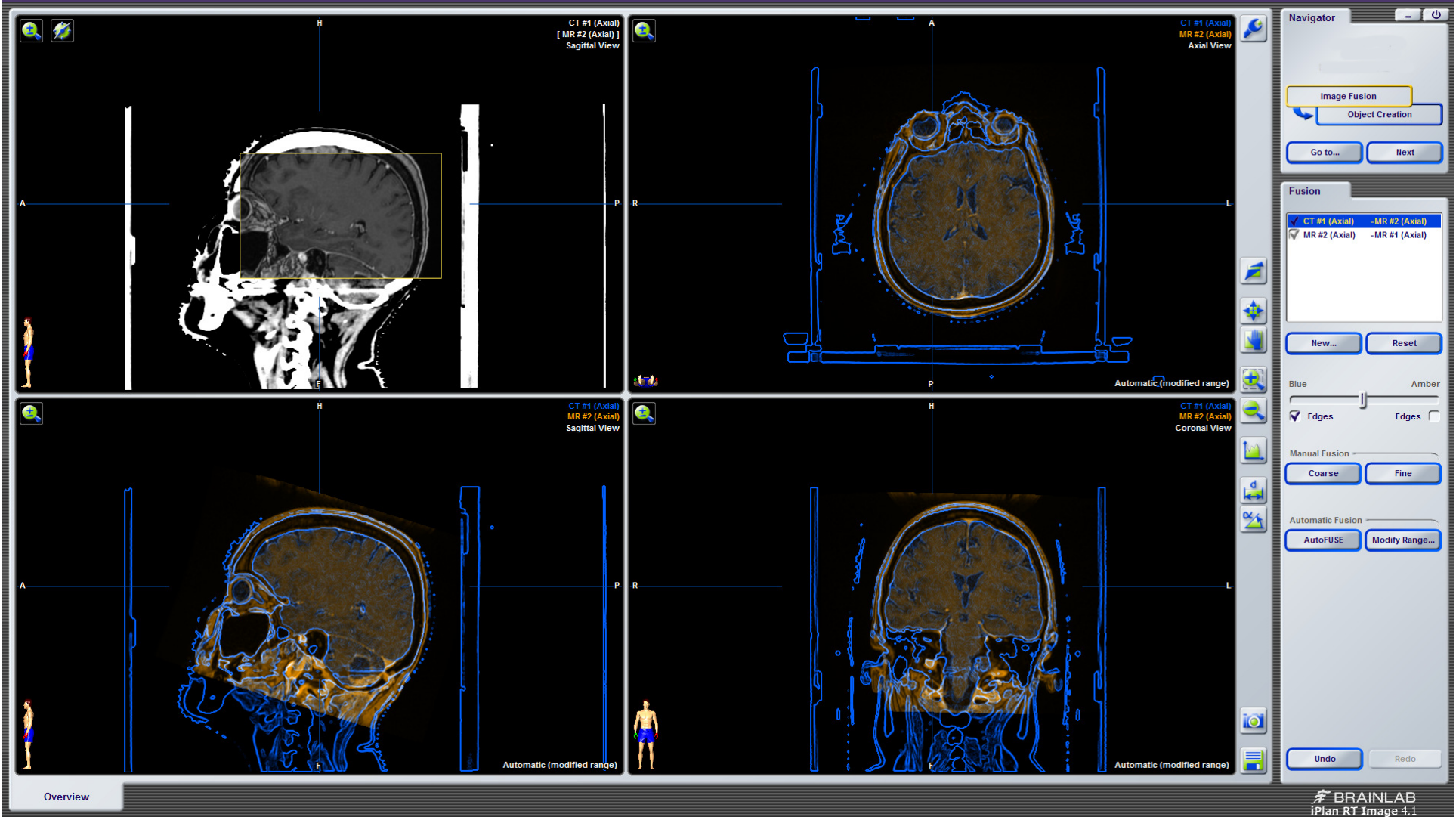
Go to...

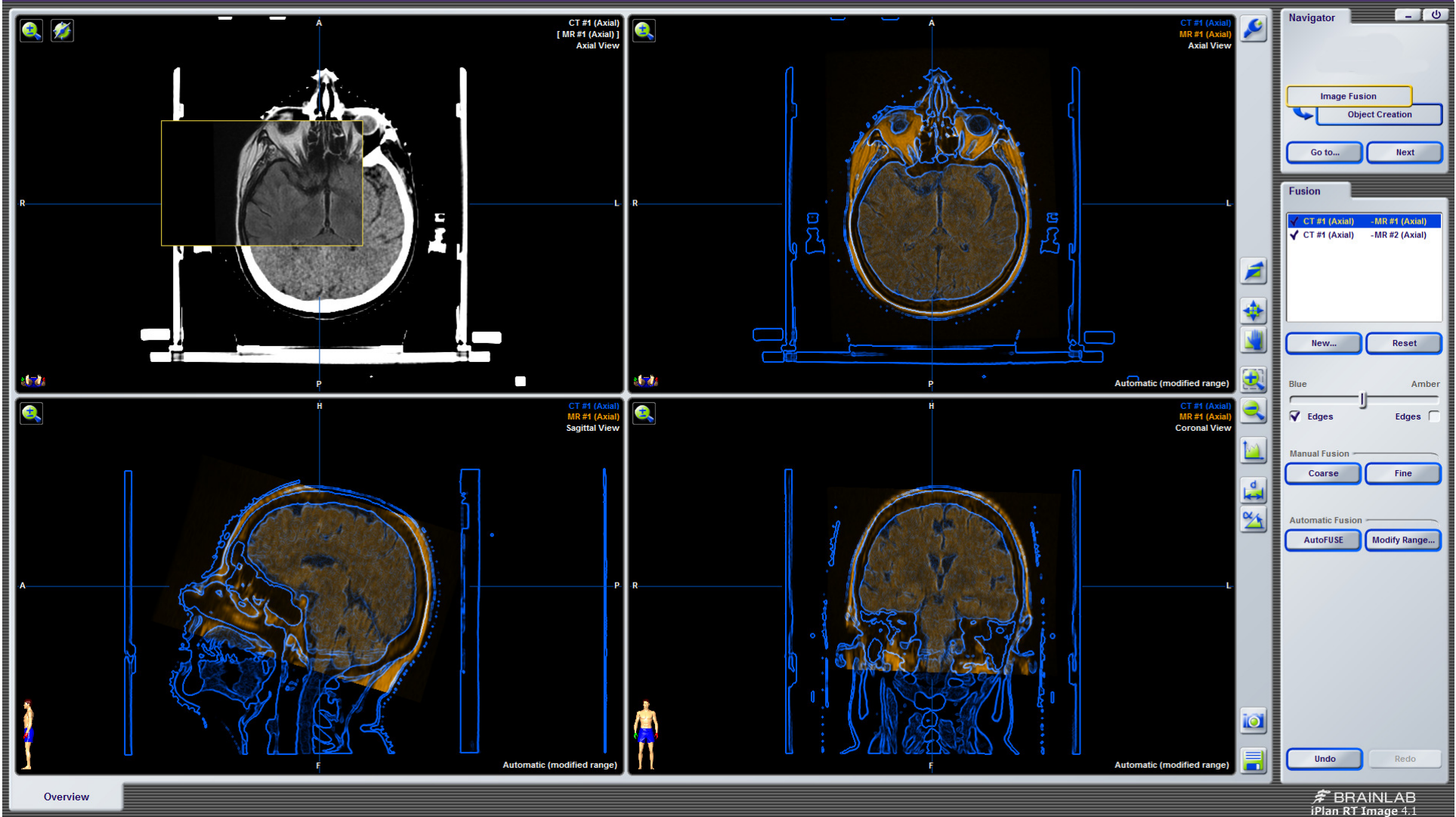
Next

Functions











MR #2 (Axial)
Slice 118 / 174

R



Single ObjectMultiple Objects

Treatment Templates

All Objects

Cranial Treatment

Extracranial Treatment

Prostate Treatment

Head And Neck Treatment

Remove

Objects

Hip Joint, Left

Hip Joint, Right

Hippocampus

Hippocampus, Left

Hippocampus, Right

Hyoid

Hypothalamus

Inner Ear, Left

Inner Ear, Right

Internal C. Artery, Left

Internal C. Artery, Right

Jugular Vein, Left

Jugular Vein, Right

Kidney, Left

Kidney, Right

Lens, Left

☐ Select All

New Template

OK

Cancel

Navigator

Object Creation
Verification

Go to...Next

Object

- Brainstem
- Chiasm
- Eye, Left
- Eye, Right
- Lens, Left
- Lens, Right
- Otic Nerve, Left

New...Remove

Auto Segmentation...

Brush Size
Contours

Outlining

BrushEraser

SmartBrushDraw Sphere

SmartShaper...

Auto FillInterpolation

Advanced Manipulation...

4-D Morphing...

UndoRedo

BRAINLAB
iPlan RT Image 4.1

Overview

Slices

Multiple Sets

Plan Content

A

P

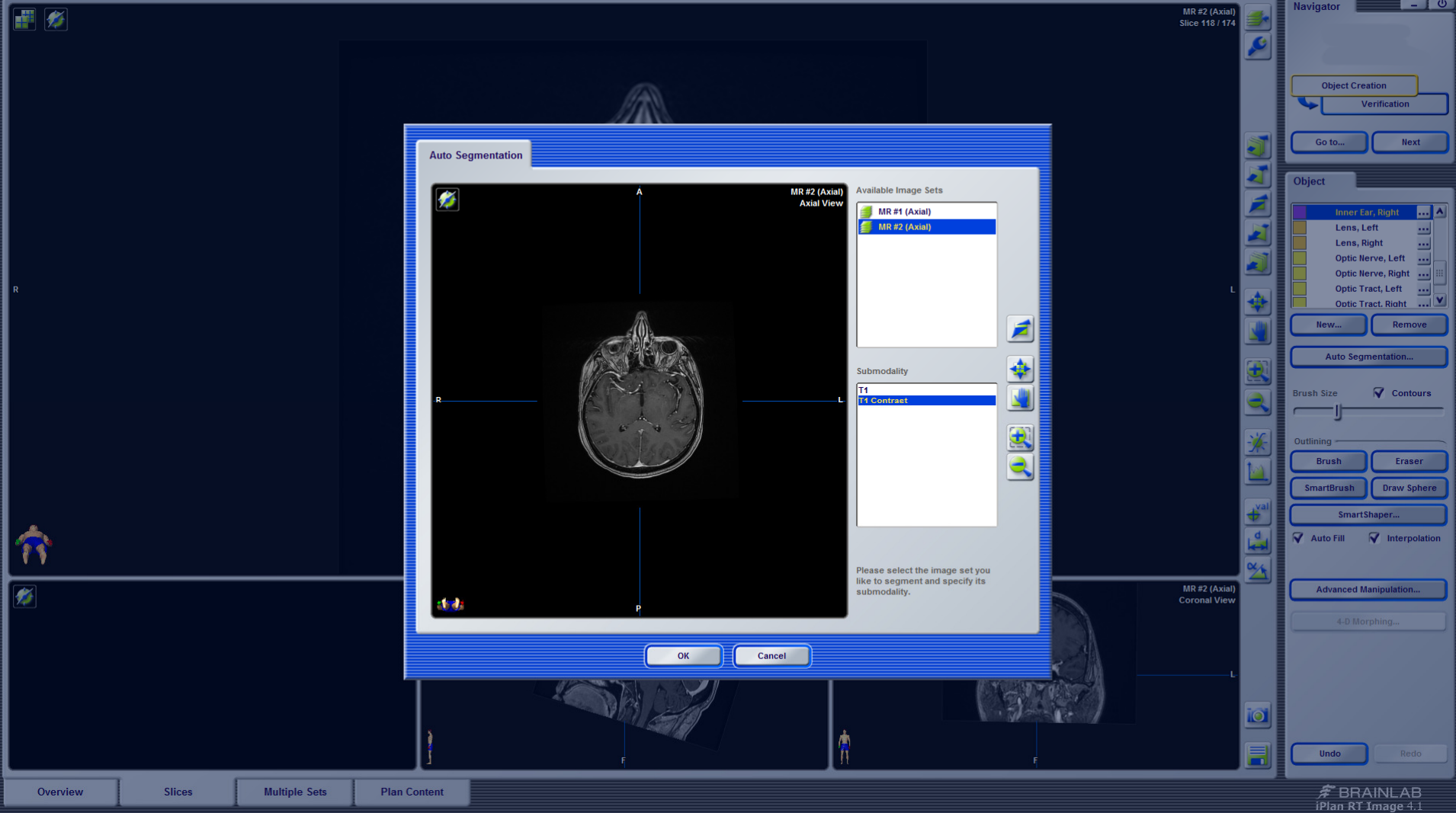
R

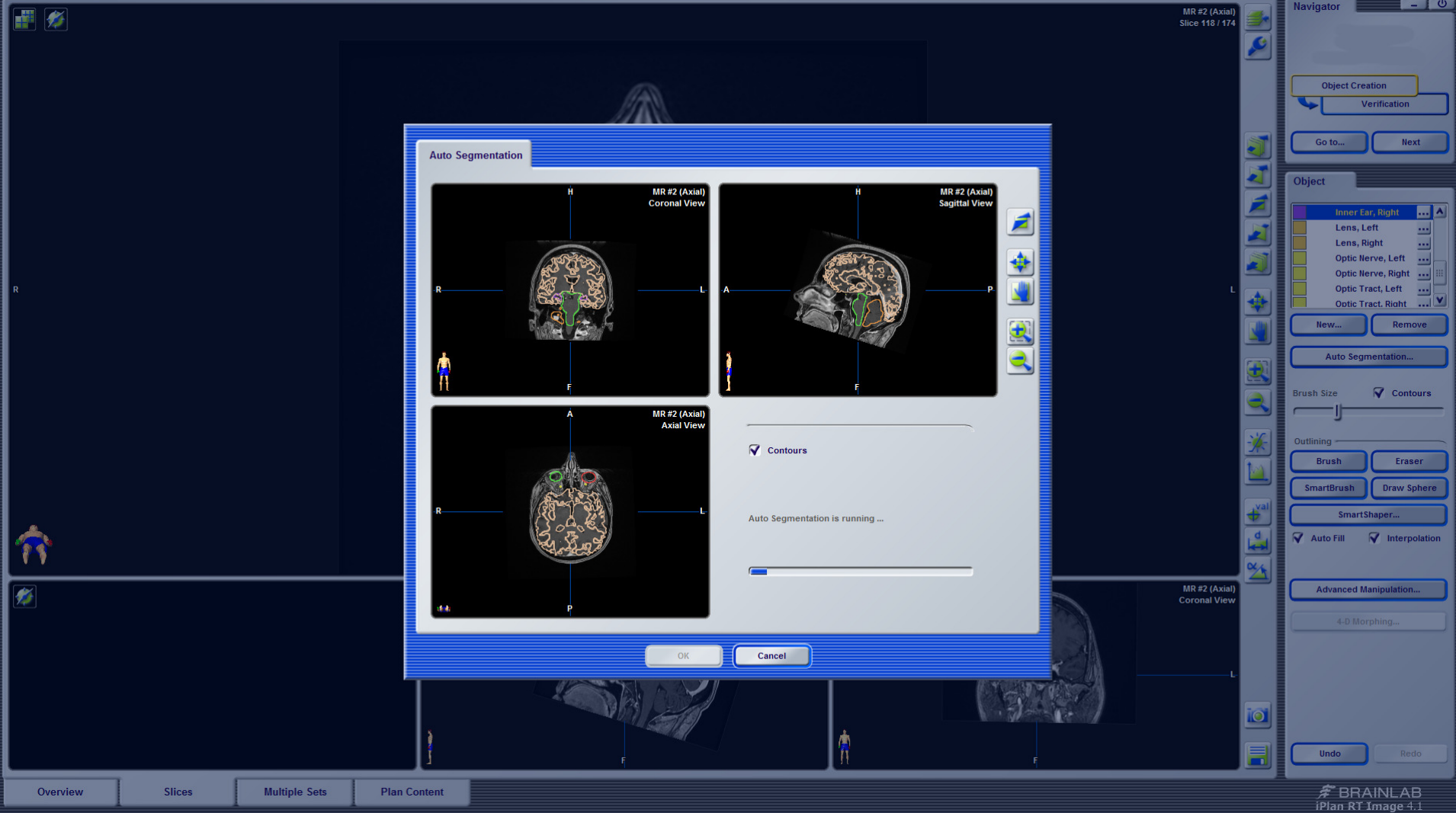
L

F

F

MR #2 (Axial)
Coronal View





MR #2 (Axial)
Slice 118 / 174

Object Creation
Verification
Go to...
Next

Object

- Inner Ear, Right
- Lens, Left
- Lens, Right
- Optic Nerve, Left
- Optic Nerve, Right
- Optic Tract, Left
- Optic Tract, Right

New... Remove

Auto Segmentation...

Brush Size
Contours

Outlining

- Brush
- Eraser
- SmartBrush
- Draw Sphere
- SmartShaper...

Auto Fill Interpolation

Advanced Manipulation...

4-D Morphing...

Undo Redo

Auto Segmentation

MR #2 (Axial)
Coronal View

MR #2 (Axial)
Sagittal View

MR #2 (Axial)
Axial View

Contours

Auto Segmentation has finished.
Verify that all segmented structures are outlined correctly in the original slice views!

OK Cancel

Overview

Slices

Multiple Sets

Plan Content

BRAINLAB

iPlan RT Image 4.1

BRAINLAB
iPlan RT Image 4.1



MR #2 (Axial)
Slice 114 / 174

SmartShaper

MR #2 (Axial)
Coronal View

MR #2 (Axial)
Sagittal View

MR #2 (Axial)
Axial View

Deform

Move

Tool Size

☒ Contours

Undo

Redo

OK

Cancel

Navigator

Object Creation

Verification

Go to...

Next

Object

Brainstem

Cerebellum

Cerebrum

Chiasm

Cochlea, Left

Cochlea, Right

Eve, Left

New...

Remove

Auto Segmentation...

Brush Size

☒ Contours

Outlining

Brush

Eraser

SmartBrush

Draw Sphere

SmartShaper...

☒ Auto Fill

☒ Interpolation

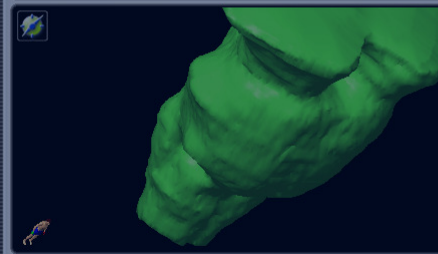
Advanced Manipulation...

4-D Morphing...

Undo

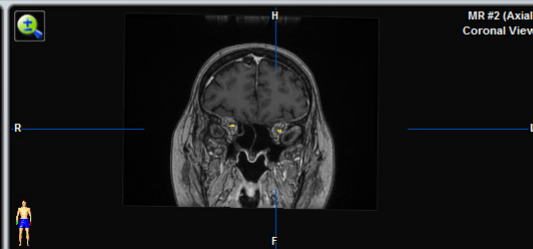
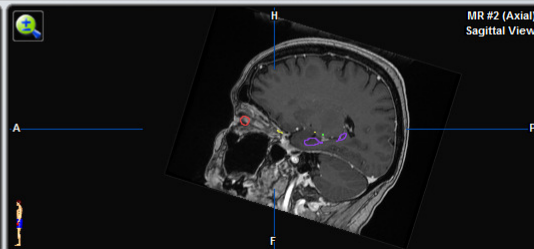
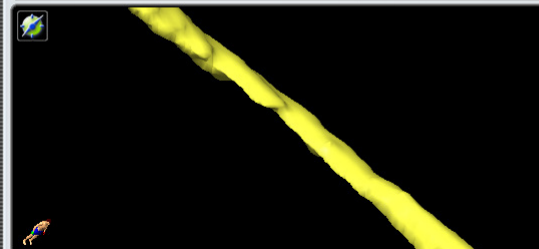
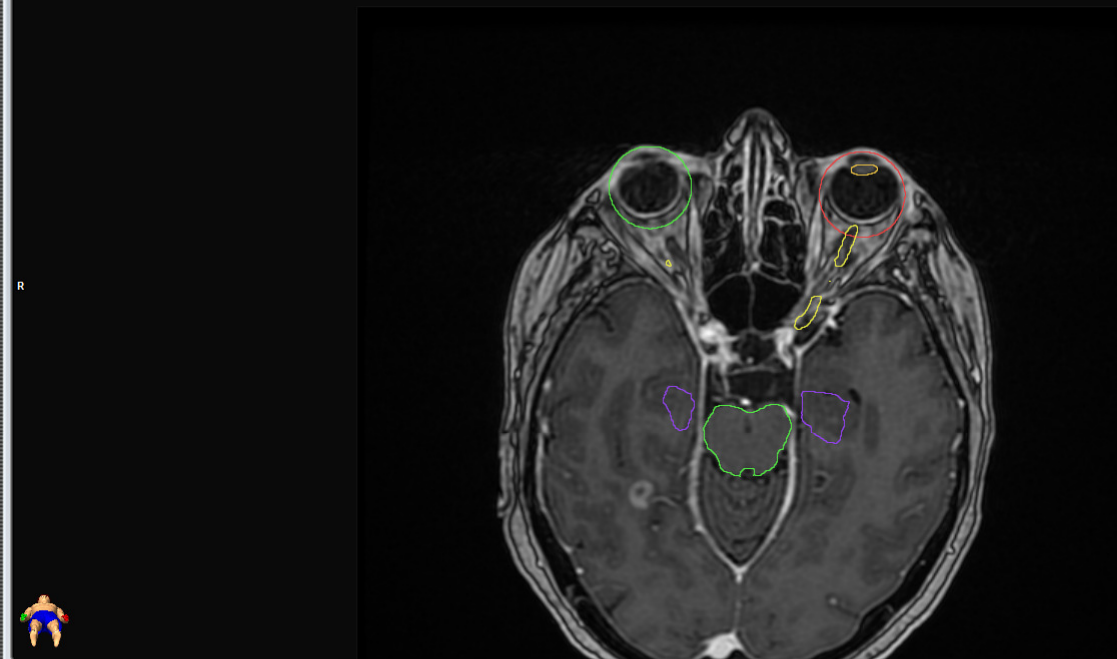
Redo

MR #2 (Axial)
Coronal View





MR #2 (Axial)
Slice 103 / 174



Navigator

Object Creation
Verification

Go to... Next

Object

- Inner Ear, Left
- Inner Ear, Right
- Lens, Left
- Lens, Right
- Optic Nerve, Left
- Optic Nerve, Right
- Optic Tract, Left

New... Remove

Auto Segmentation...

Brush Size
Contours

Outlining

Brush Eraser

SmartBrush Draw Sphere

SmartShaper...

Auto Fill Interpolation

Advanced Manipulation...

4-D Morphing...

Undo Redo

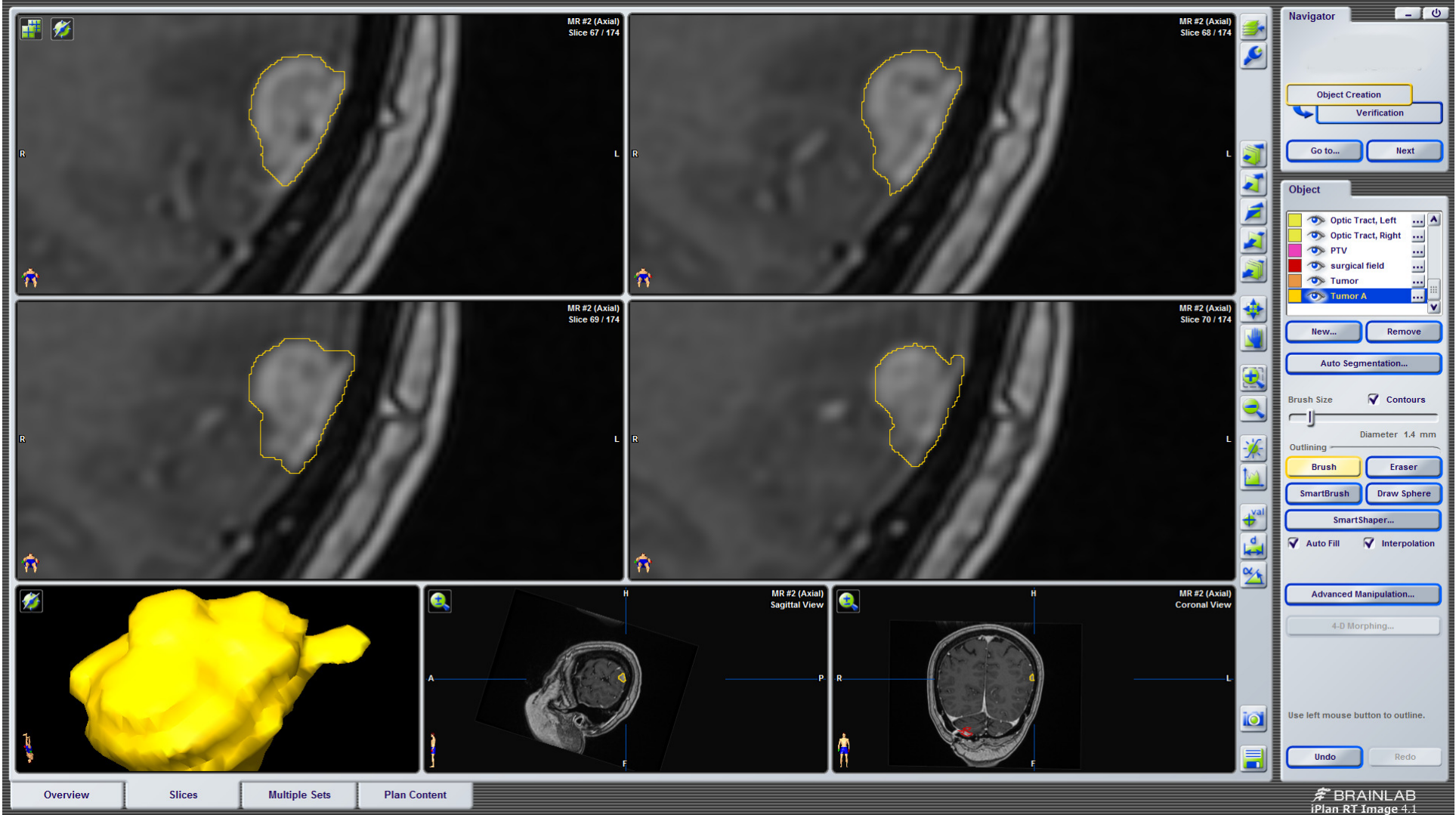
Overview

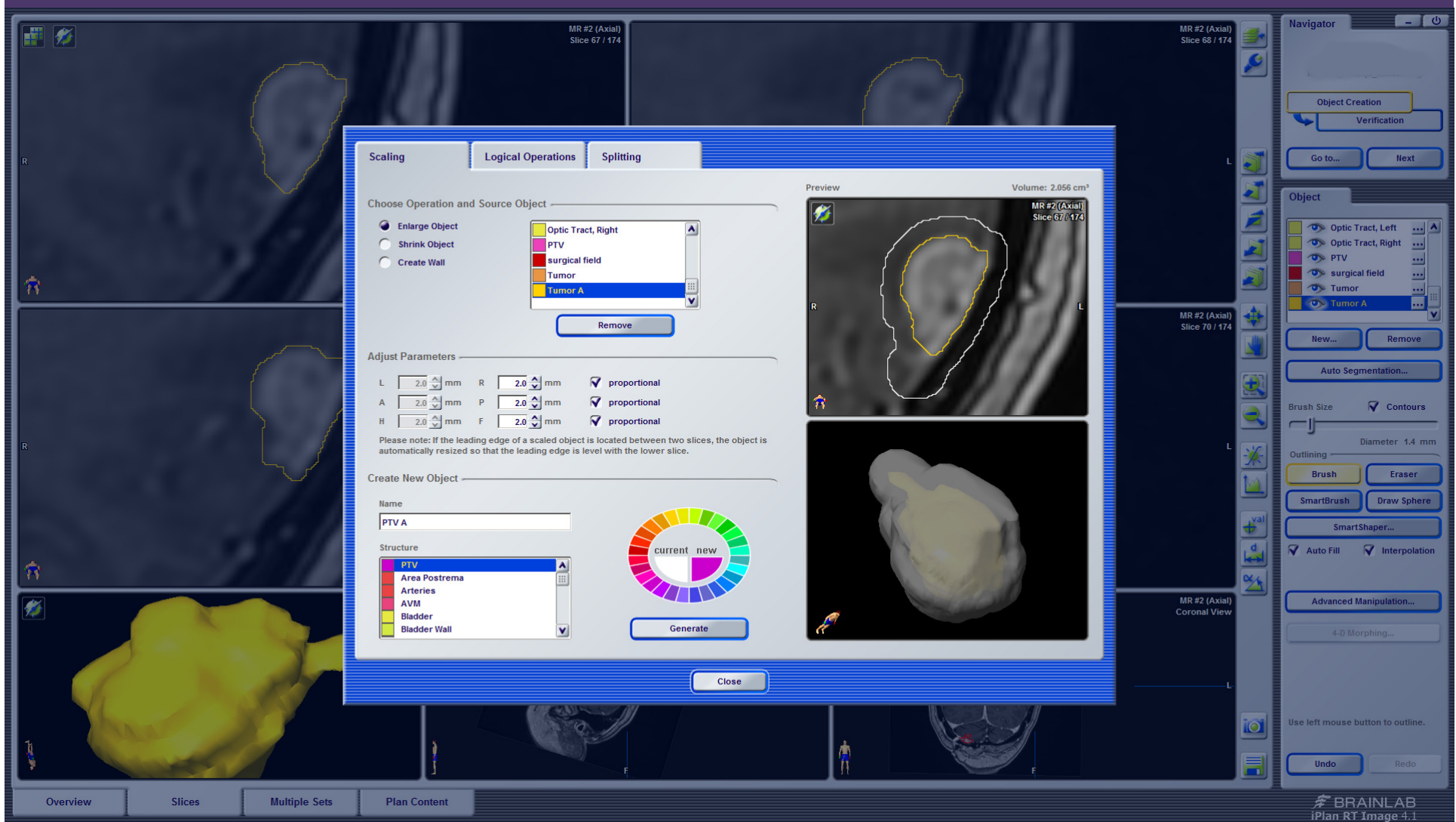
Slices

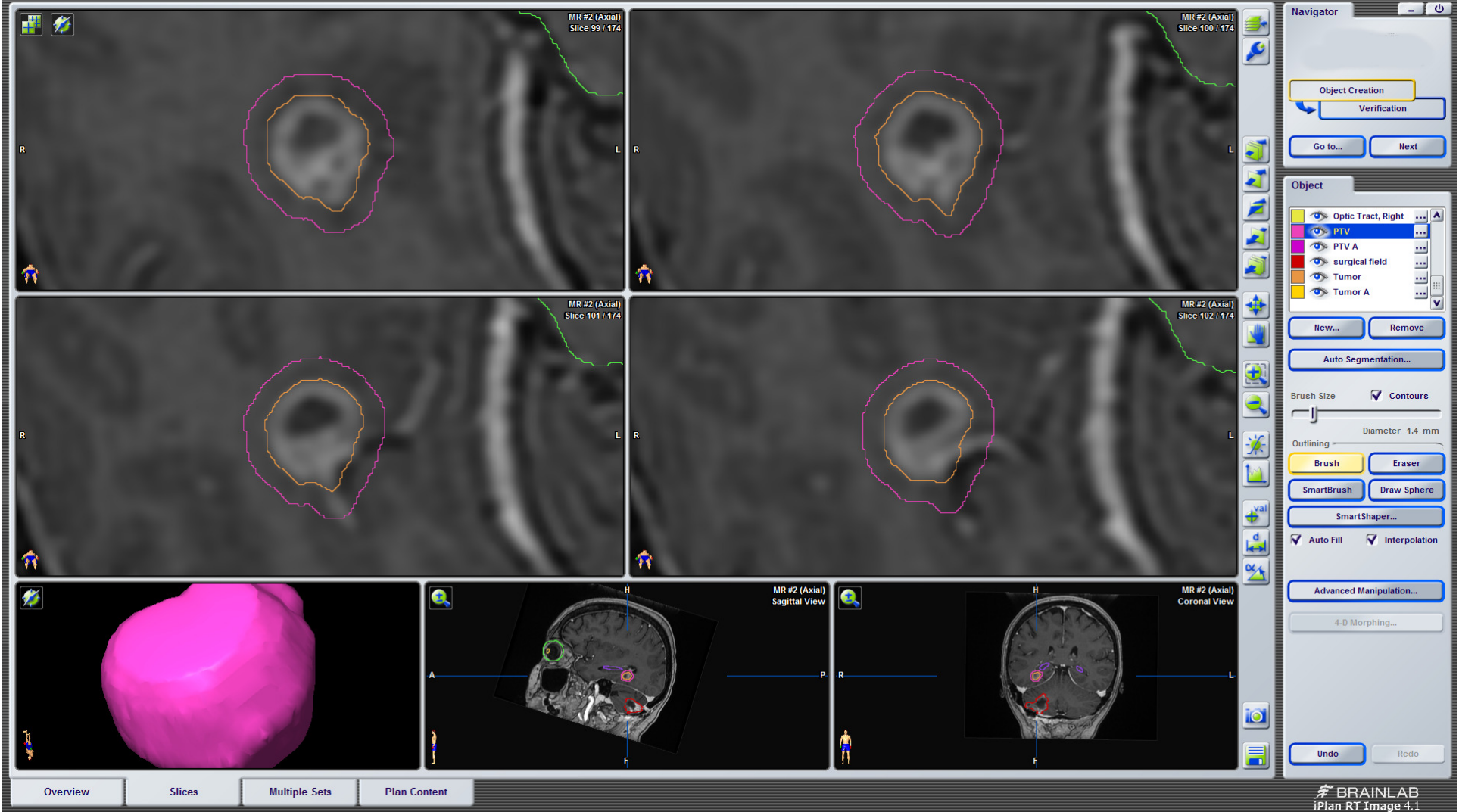
Multiple Sets

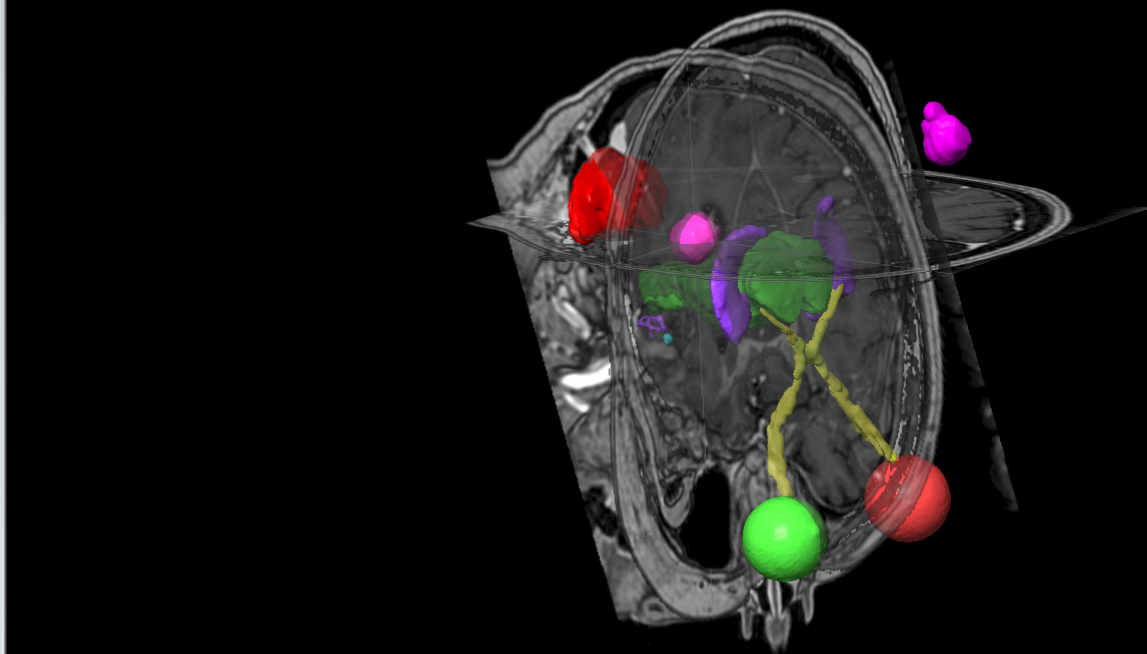
Plan Content

BRAINLAB
iPlan RT Image 4.1









Overview

Slices

Multiple Sets

Plan Content

Navigator

Object Creation

Verification

Go to...

Next

Object

- ☒ Optic Tract, Right
- ☒ PTV
- ☒ PTV A
- ☒ surgical field
- ☒ Tumor
- ☒ Tumor A

New...

Remove

Auto Segmentation...

Brush Size

☒ Contours

Outlining

Brush

Eraser

SmartBrush

Draw Sphere

SmartShaper...

☒ Auto Fill

☒ Interpolation

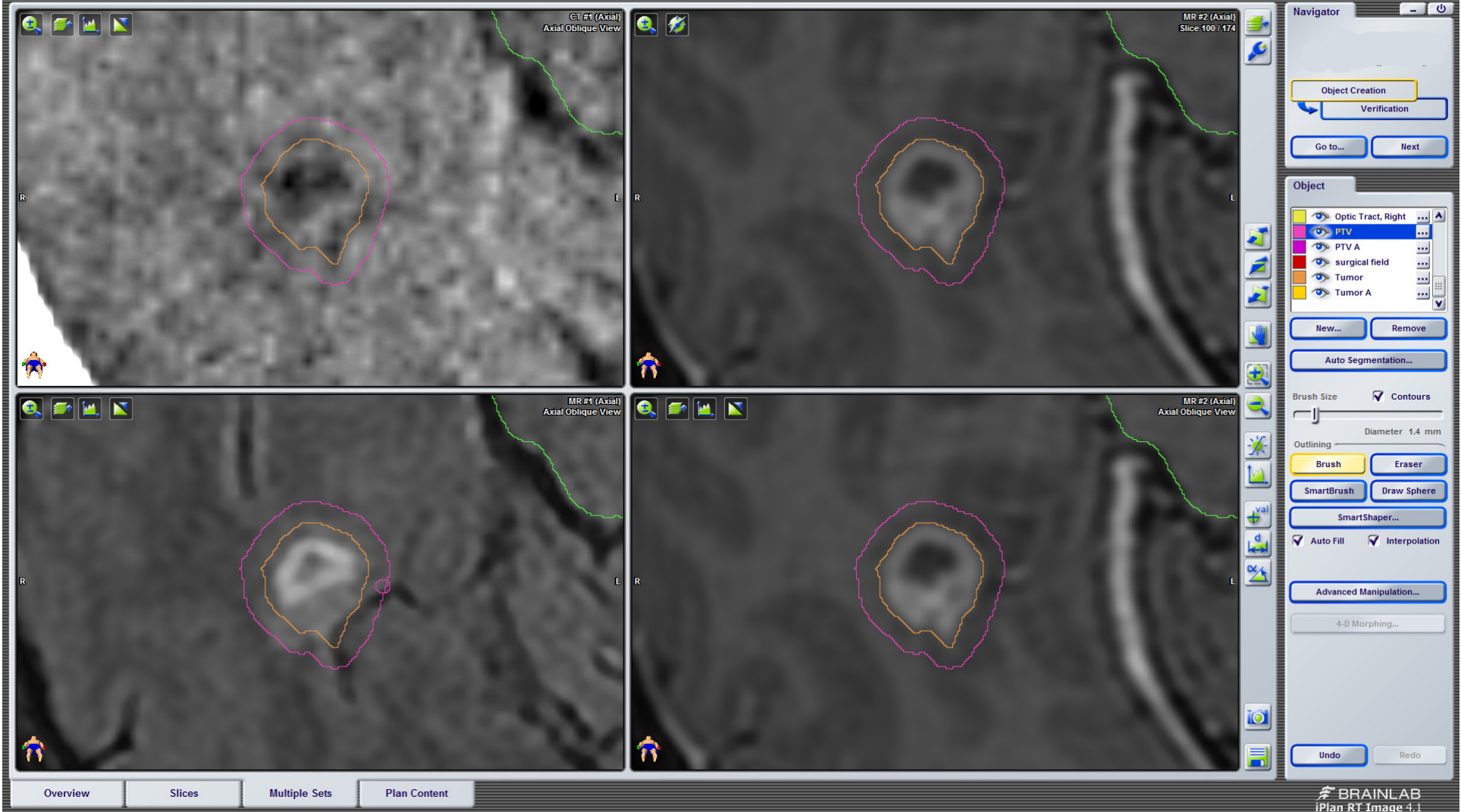
Advanced Manipulation...

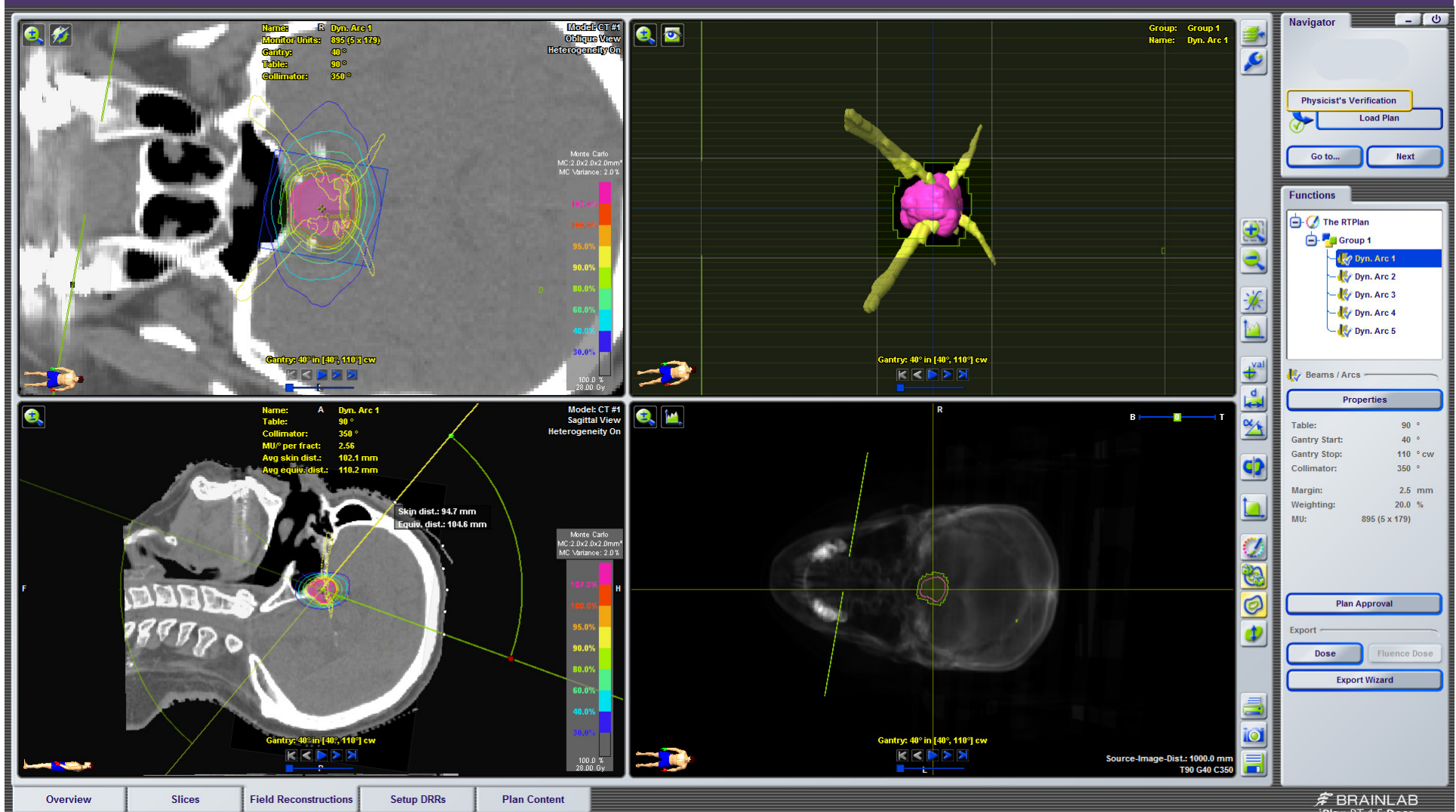
4-D Morphing...

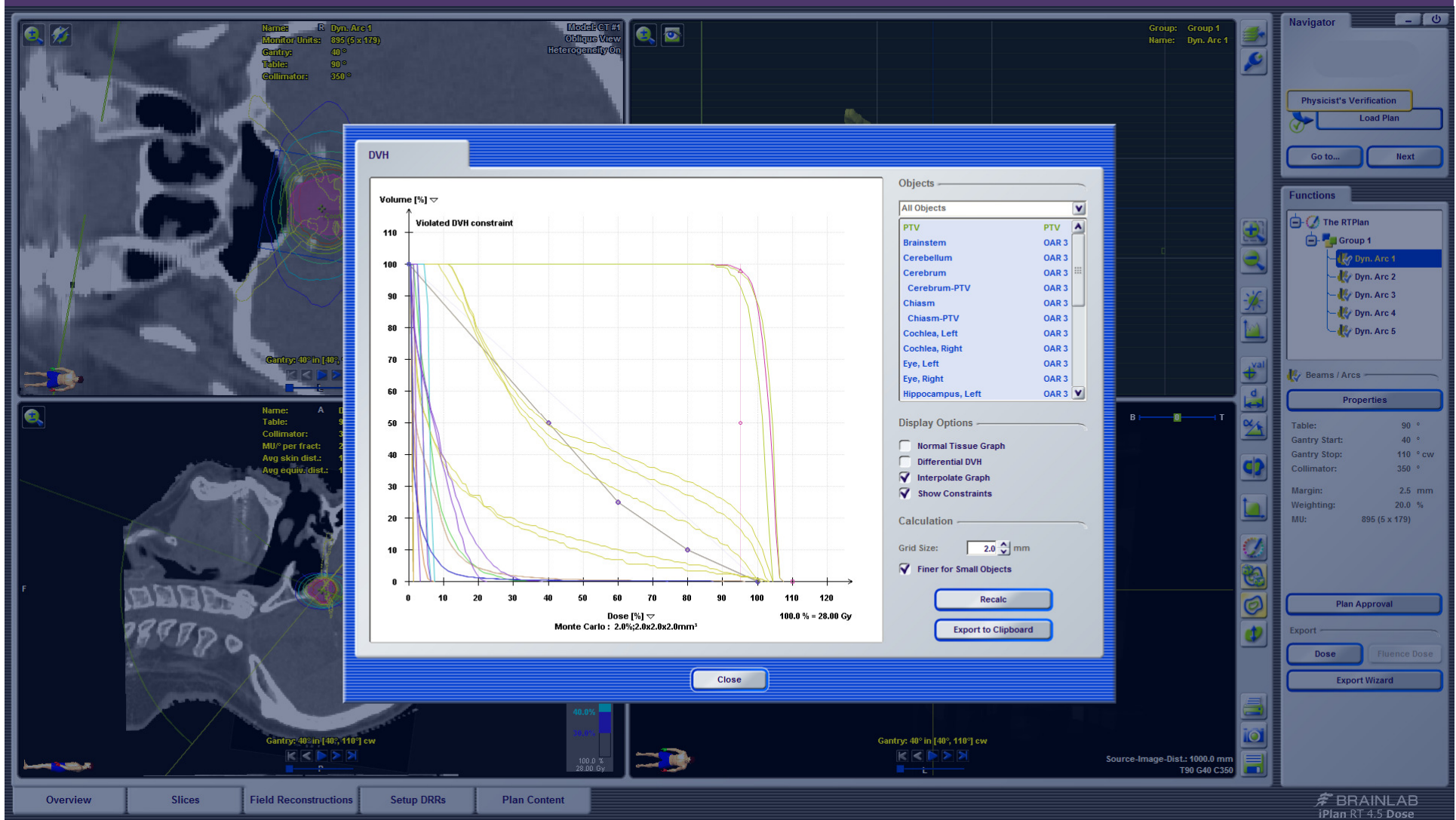
Undo

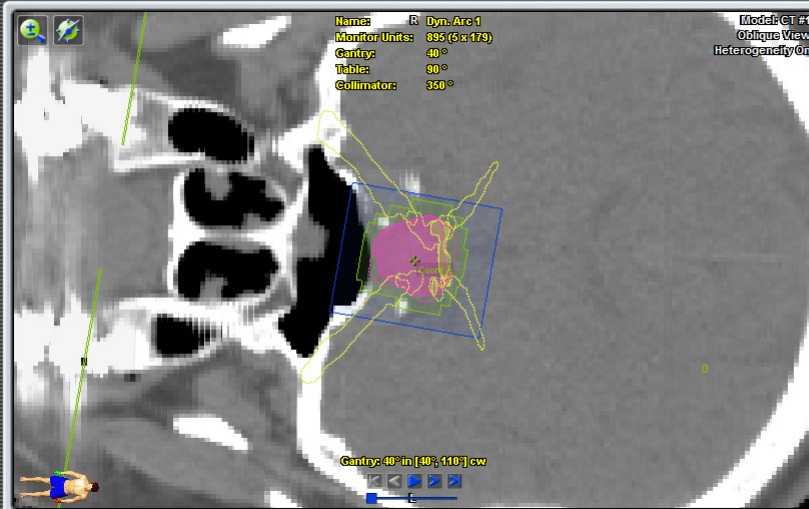
Redo

BRAINLAB
iPlan RT Image 4.1





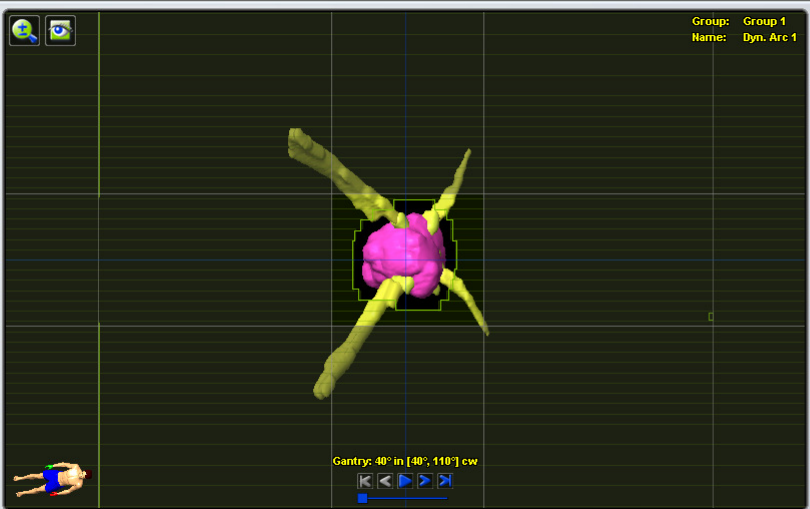




Name: R Dyn. Arc 1
Monitor Units: 895 (5 x 179)
Gantry: 40°
Table: 90°
Collimator: 350°

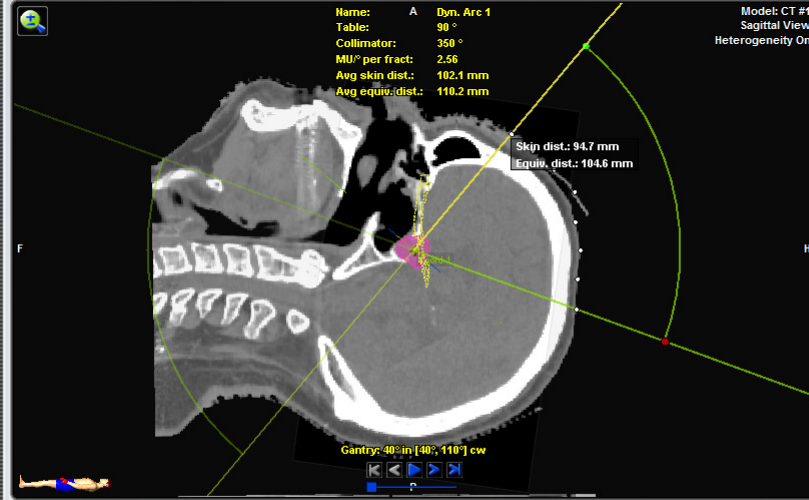
Model: CT #1
Oblique View
Heterogeneity On

Gantry: 40° in [40°, 110°] cw



Group: Group 1
Name: Dyn. Arc 1

Gantry: 40° in [40°, 110°] cw

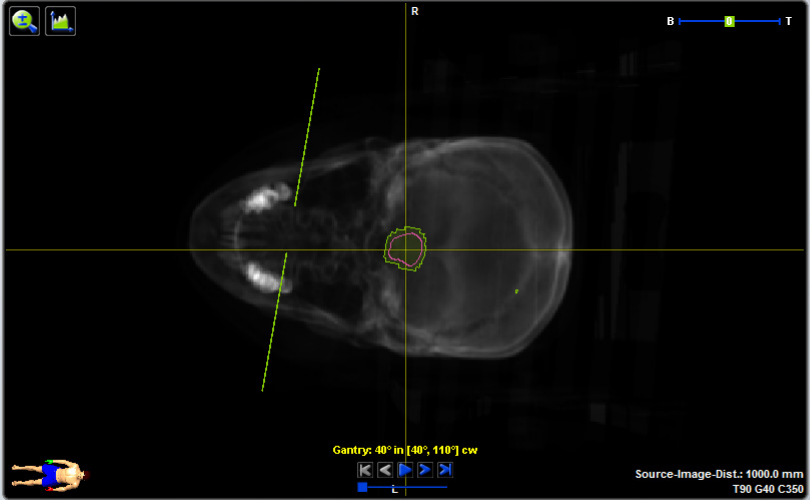


Name: A Dyn. Arc 1
Table: 90°
Collimator: 350°
MU° per fract: 2.56
Avg skin dist.: 102.1 mm
Avg equiv. dist.: 110.2 mm

Model: CT #1
Sagittal View
Heterogeneity On

Skin dist.: 94.7 mm
Equiv. dist.: 104.6 mm

Gantry: 40° in [40°, 110°] cw



Gantry: 40° in [40°, 110°] cw

Source-Image-Dist.: 1000.0 mm
T90 G40 C350

Overview

Slices

Field Reconstructions

Setup DRRs

Plan Content

Physicist's Verification

Load Plan

Go to... Next

Functions

The RTPlan

- Group 1
 - Dyn. Arc 1
 - Dyn. Arc 2
 - Dyn. Arc 3
 - Dyn. Arc 4
 - Dyn. Arc 5

Beams / Arcs

Properties

Table:	90°
Gantry Start:	40°
Gantry Stop:	110° cw
Collimator:	350°
Margin:	2.5 mm
Weighting:	20.0 %
MU:	895 (5 x 179)

Plan Approval

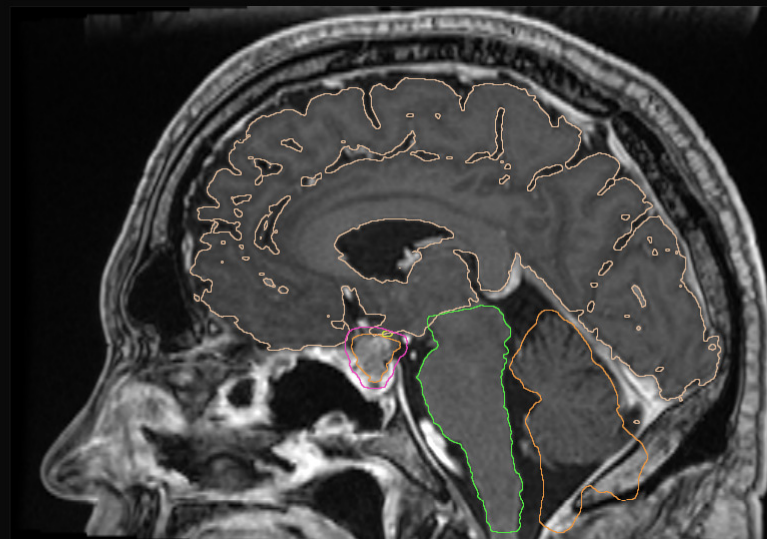
Export

Dose Fluence Dose

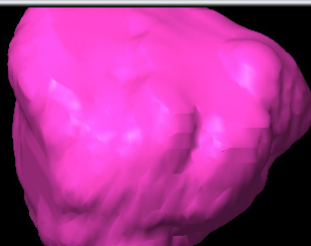
Export Wizard



BRAINLAB
iPlan RT 4.5 Dose



MR #2 (Axial)
Sagittal View Slice 84 / 171



MR #2 (Axial)
Coronal View



MR #2 (Axial)
Axial View

Overview

Slices

Multiple Sets

Plan Content

Navigator

Object Creation

Verification

Go to...

Next

Object

- ☐ Optic Nerve, Left
- ☐ Optic Nerve, Right
- ☐ Optic Tract, Left
- ☐ Optic Tract, Right
- ☒ PTV
- ☐ Tumor

New...

Remove

Auto Segmentation...

Brush Size

☒ Contours

Outlining

Brush

Eraser

SmartBrush

Draw Sphere

SmartShaper...

☒ Auto Fill

☒ Interpolation

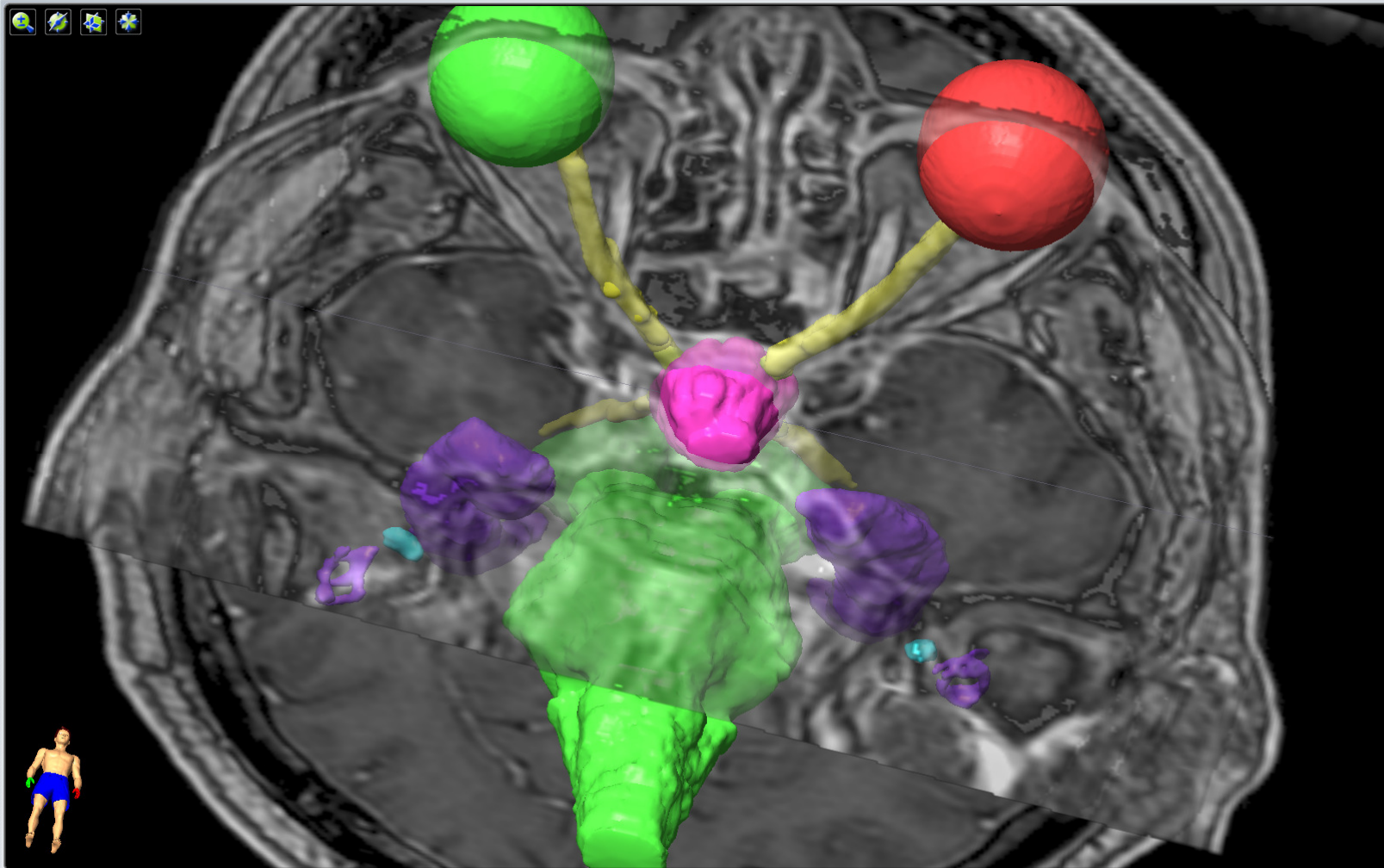
Advanced Manipulation...

4-D Morphing...

Undo

Redo

BRAINLAB
iPlan RT Image 4.1



Navigator

Object Creation

Verification

Go to...

Next

Object

- ☒ Brainstem
- ☒ Cerebellum
- ☒ Cerebrum
- ☒ Chiasm
- ☒ Cochlea, Left
- ☒ Cochlea, Right
- ☒ Eve, Left

New...

Remove

Auto Segmentation...

Brush Size ☒ Contours

Outlining ☐ Brush ☐ Eraser

SmartBrush ☒ Draw Sphere

SmartShaper...

☒ Auto Fill ☒ Interpolation

Advanced Manipulation...

4-D Morphing...

Undo

Redo

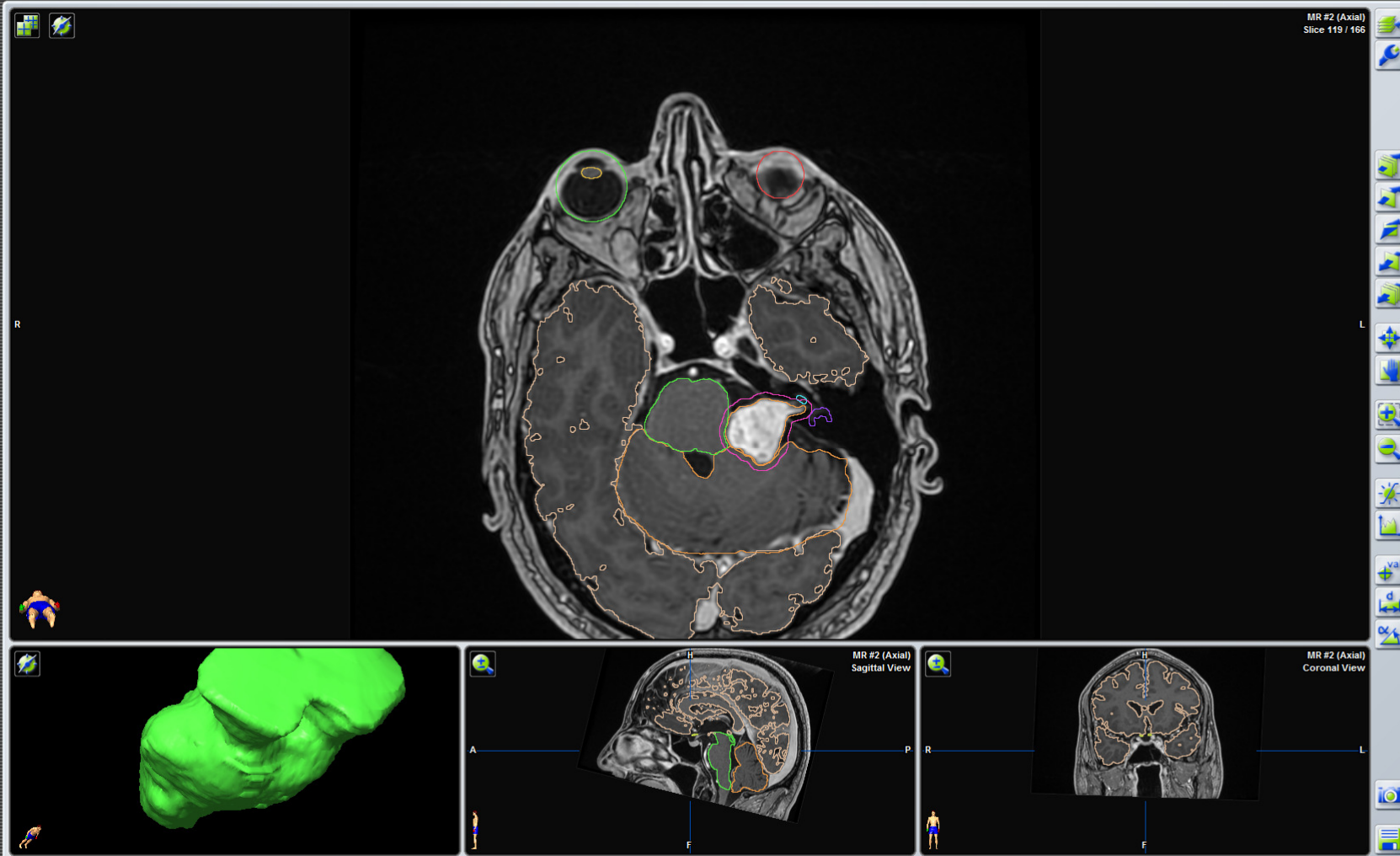
Overview

Slices

Multiple Sets

Plan Content

BRAINLAB
iPlan RT Image 4.1



MR #2 (Axial)
Slice 119 / 166

Navigator

Object Creation
Verification

Go to... Next

Object

- Brainstem
- Cerebellum
- Cerebrum
- Chiasm
- Cochlea, Left
- Cochlea, Right
- Eve, Left

New... Remove

Auto Segmentation...

Brush Size ☒ Contours

Outlining

Brush Eraser

SmartBrush Draw Sphere

SmartShaper...

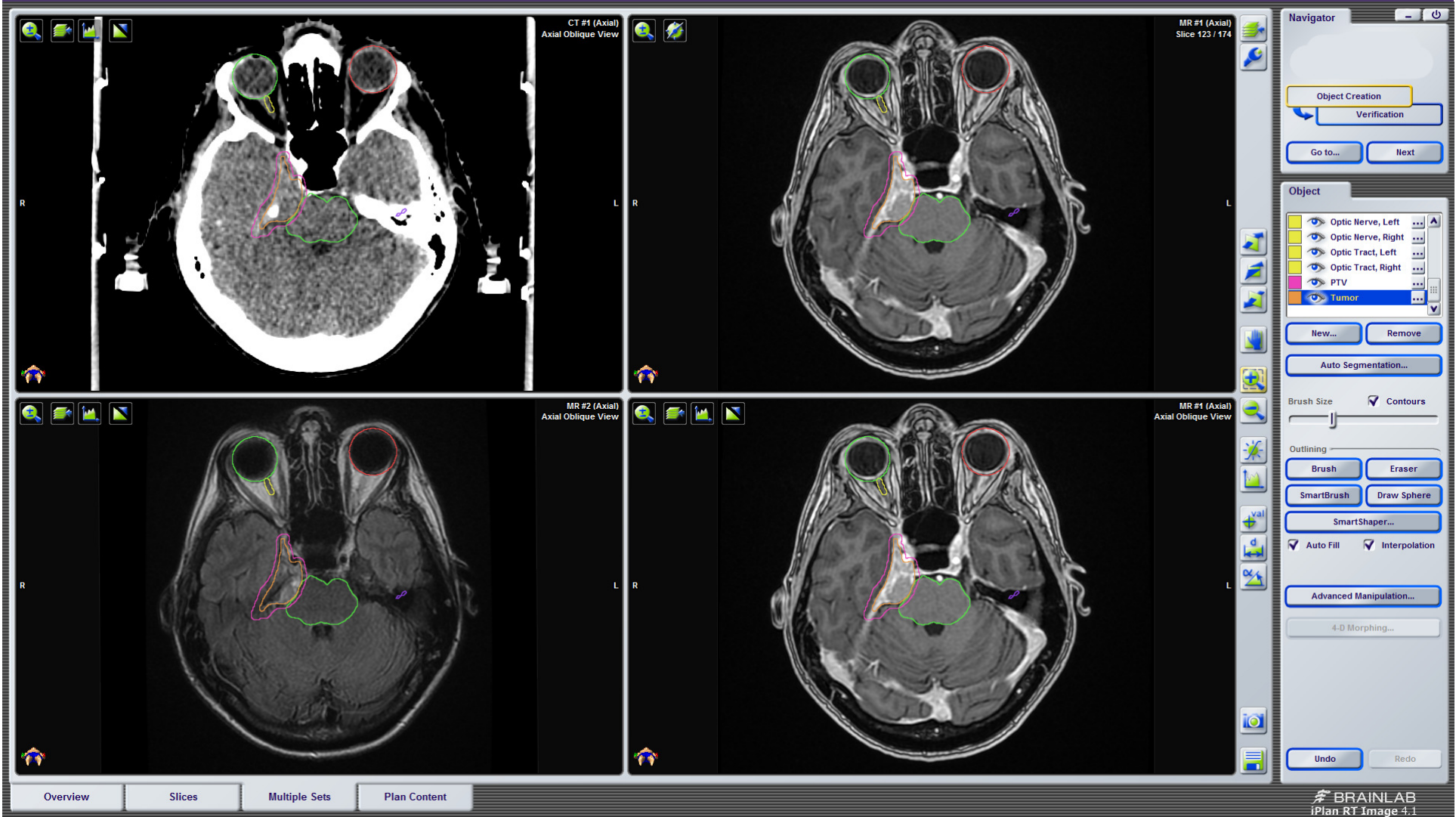
☒ Auto Fill ☒ Interpolation

Advanced Manipulation...

4-D Morphing...

Undo Redo

Overview Slices Multiple Sets Plan Content



Specialne tehnike v radioterapiji

SBRT

(klinični aspekt)

doc. dr. Uroš Smrdel dr. med.

SBRT

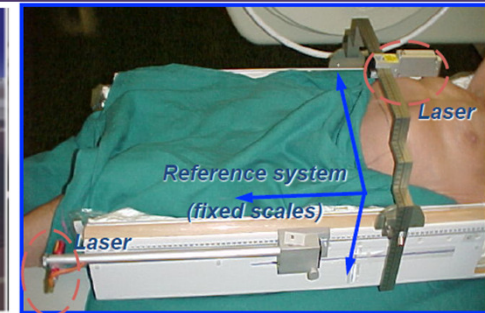
- sinonimi:
 - Stereotactic Body Radiotherapy
 - Stereotactic Ablative Radiotherapy
- Karolinska 1991:
 - Bromgren in Lax
 - pljuča
- Japonska 1994:
 - Uematsu, Arimoto
 - enako pljuča

SBRT

- KAJ?
 - pljuča
 - jetra
 - hrbtenica
 - pankreas
 - prostata

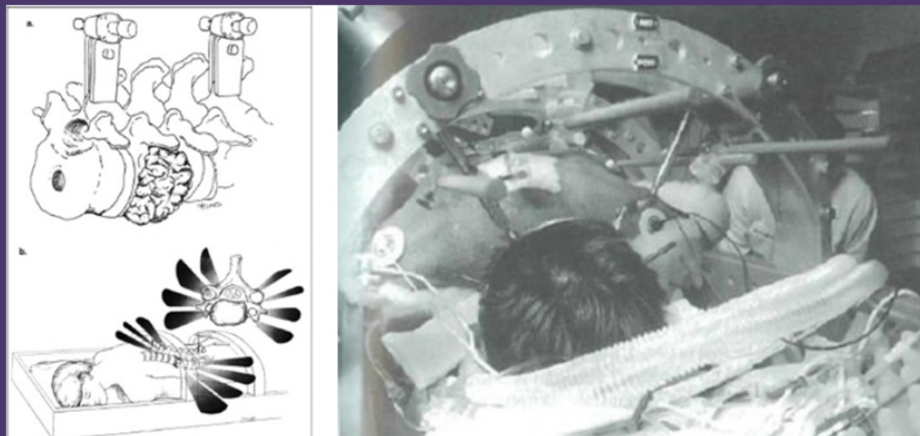
SBRT

- s stereotaktičnim okvirjem
- brez okvirja
 - slikovno vodena
- posebna fiksacija ±



„body frame“
kompresija trebuha
vakumska blazina

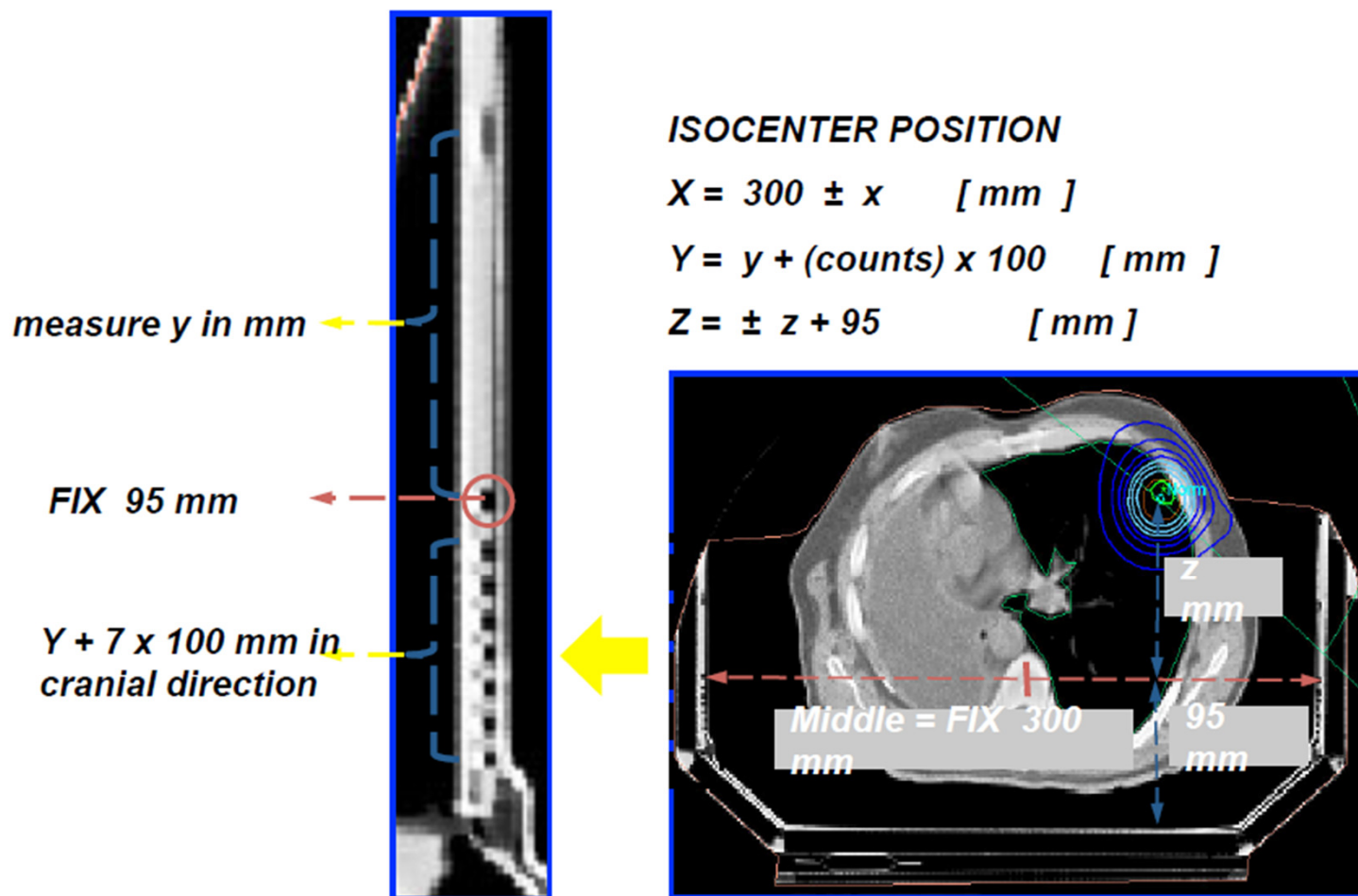
Schmidt WFO 2004



Hamiltonov rigidni stereotaktični okvir za hrbtenico

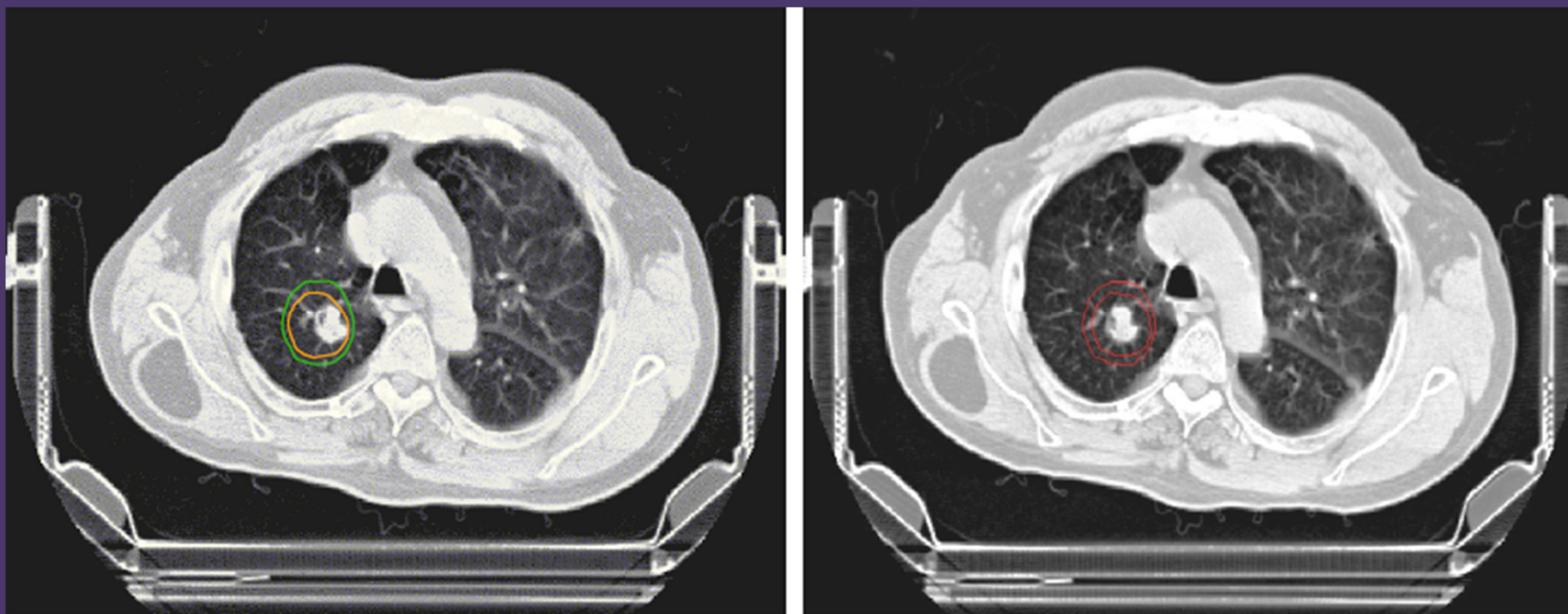
Hamilton et al. Neurosurgery 36 (2): 311-19, 1995
Hamilton et al. Stereotactic Funct NS, 1995

SBRT



SBRT

- zahteve:



visoka reproducibilnost lege bolnika
visoka reproducibilnost lege tarče
učinkovita imobilizacija
zmanjšanje gibanja organov
CT/MR kompatibilen sistem fiksacije

SBRT – HISTORIČNI REZULTATI

- pljuča

Single Fraction Stereotactic Irradiation

autor	Pts no	Follow up Months (median)	Dose	Results (median)
Nakagawa et al. 2000	22	2-82	18-25	OS 9,8 MO PD: n=1 NC: n=2 PR: n=7 CR: n=12
Hara et al 2002	23	3-24(13)	20-30	LC 13 months 63% < 30 Gy 88% >30Gy
Hof et al 2003	10	8,3-29,9 (14,9)	19-26	PD: n=2 act OS 80%; y act.OS 28%; 2 J act. LC 88,9%;1 J act. LC 71,1%; 2 J
Hof et al 2007	61		12-30	Actuarial OS 12months 78,4% 24 months 65,1% 36 months 47,8%

Guckenberger 2015

SBRT – HISTORIČNI REZULTATI

- pljuča **Fractionated Stereotactic Lung Irradiation**

autor	Pts no	Follow up (median) months	Fractions no	Dose Gy	Results
Uematsu et al 2000	66	3-31(11)	5-15	30-75	PD: n=2 SD+CR=64
Wulf et al	27	2-33 (8)	3	30	Act.LC 76% 1y Act. LC 76% 2y
Timmermann et al 2003	27		3	8-20	PR 60% CR 27%
Nagata et al 2003	55Lung Tu	2-51 (19)	4	40-48	PR 84% CR 12% OS 95%; ½ years OS 92%; 1 year OS 82%; 2 years
	T1:n=31 T2:n=15 T3: n=3 Meta:		4	48	OS 89% 1 y
	10 12		5	60	OS 65% 2 years

SBRT – HISTORIČNI REZULTATI

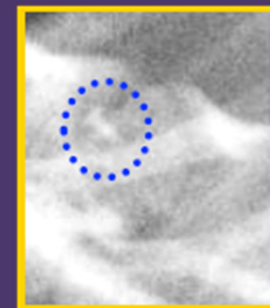
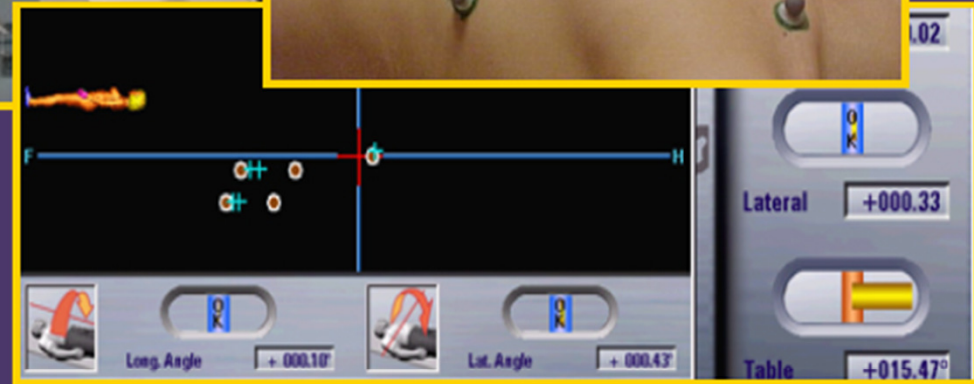
- jetra

ESTRO SBRT course
2015

Autor	No of Meta	Dose (Gy)	Local control	Median Follow up
Blomgren et al. 1998	21	20-45	95%	9,6 Mo
Sato et al. 1998	5	50-60	100%	10 Mo
Herfarth et al. 2001	56	14-26	76%	5,7 Mo
Wulf et al. 2001	23	28-30	83%	9 Mo
Schefer et al. 2005	22	36-60	K.A.	7 Mo
Katz et al. 2007	174	30-55	86%	14,5 Mo
AKH Wien	62	24-45	84%	13 Mo

SBRT – ALTERNATIVE OKVIRJU

- zunanji markerji in vakumska fiksacija



- notranji markerji in vakumska fiksacija

SBRT - INDIKACIJE

A Survey of Stereotactic Body Radiotherapy Use in the United States

Hubert Pan

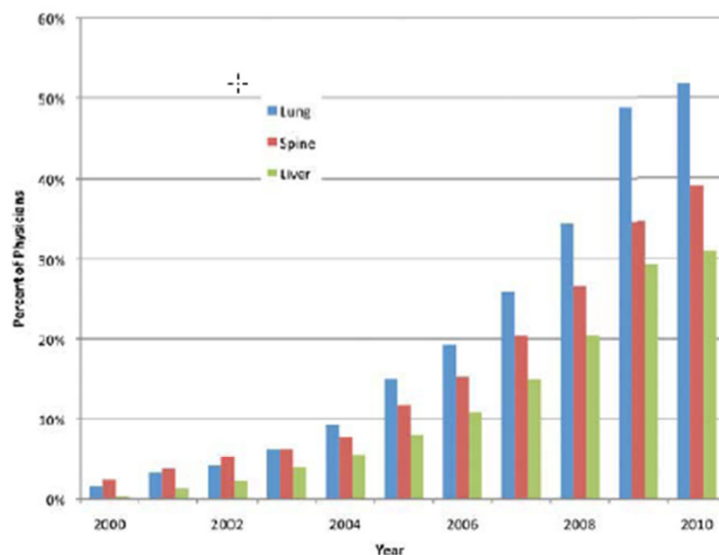


Figure 4. Cumulative adoption of stereotactic body radiotherapy is shown for the 3 most common disease sites treated: lung, spine, and liver.

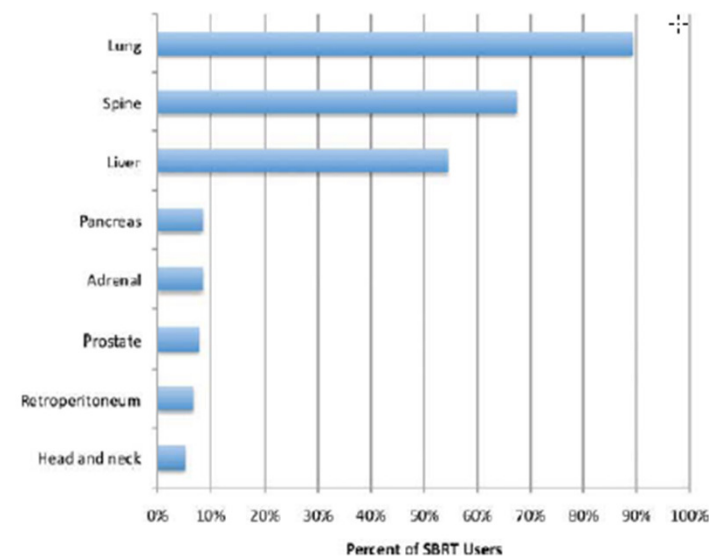
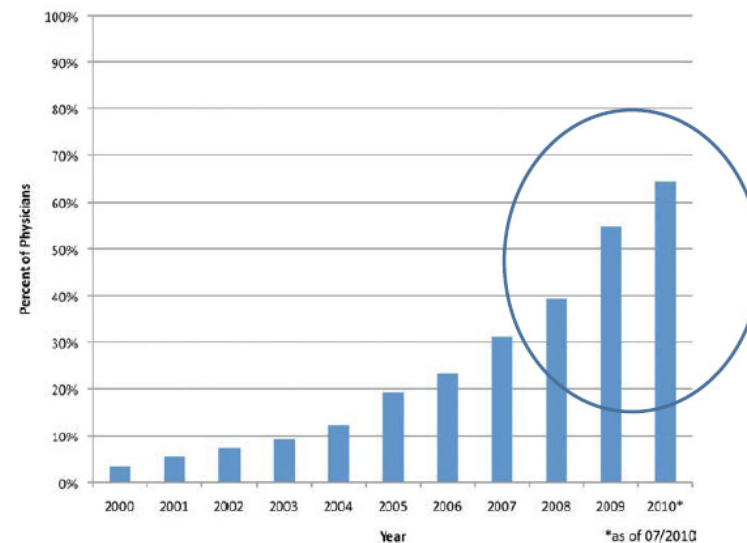


Figure 5. Disease sites treated by stereotactic body radiotherapy (SBRT) users who responded to the survey are shown.

SBRT – ZAKAJ UPORABITI

- višji odmerek od konvencionalnega
- reiradijacija

A Survey of Stereotactic Body Radiotherapy
Use in the United States Hubert Pan > 1300 physicians



SBRT – „WORKFLOW“

- pozicioniranje bolnika
- gibanje organov
- slikanje (CT/PET-CT/MR)

priprava

- fuzija
- konturiranje
- načrtovanje

načrtovanje

- pozicioniranje
- kontrola pred, med in po RT

obsevanje



SBRT – ZAKAJ BREZ OKVIRJA?

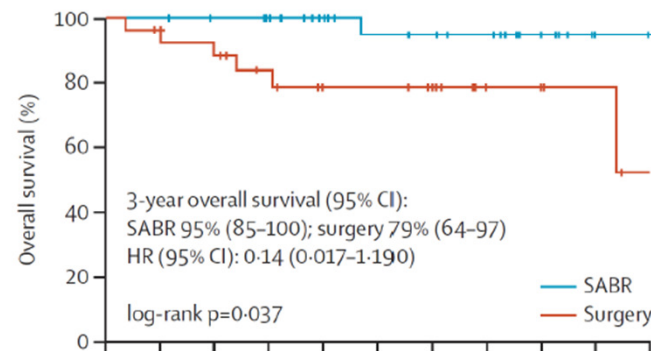
- SRS/SBRT – udobje, neboleče, fuzija na tumor ne na zunanji marker  natančnost
- fSBRT – udobje, fuzija na tumor ne na zunanji marker, **natančnost in ponovljivost**, večji volumni

SBRT - PLJUČA

- operabilni nedrobnocelični pljučni rak stadij I
primerjava SBRT in kirurgija
— gre tudi za zmogljivost

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien DeJaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*



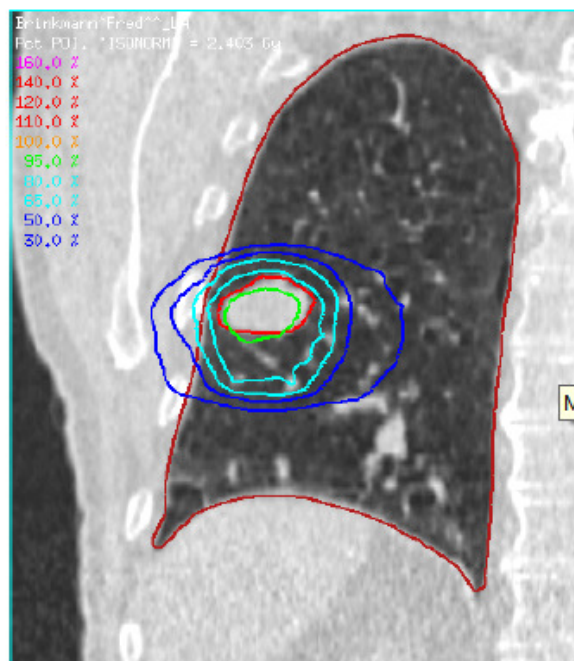
SBRT - PLJUČA

	# of fractions	Single fraction dose	Dose prescription	Local control
Nagata 2005	4	12Gy	@ isocenter	98%
Baumann 2009 Lindberg 2015	3	15Gy	@ 65%	92% @ 3 a 79% @ 5 a
Fakiris 2009	3	20-22Gy	@ 80%	88% @ 3 a
Ricardi 2010	3	15Gy	@ 80%	88% @ 3 a
Bral 2010	3-4	13 – 20Gy		84% @ 2a
Timmerman 2010	3	18Gy	@ 80%	98% @ 3a

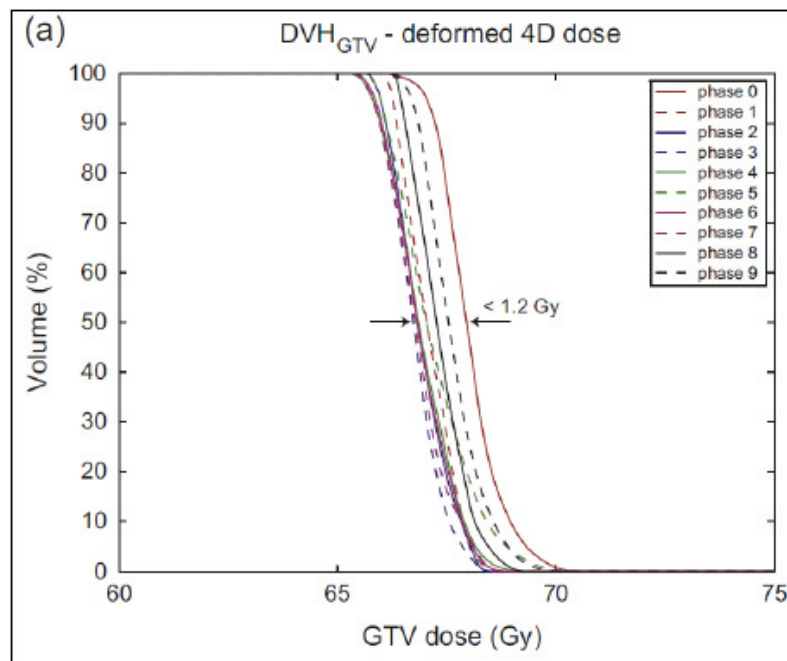
Matthias Guckenberger - DEGRO 2015 / 29.08.2015

SBRT - PLJUČA

- gibanje



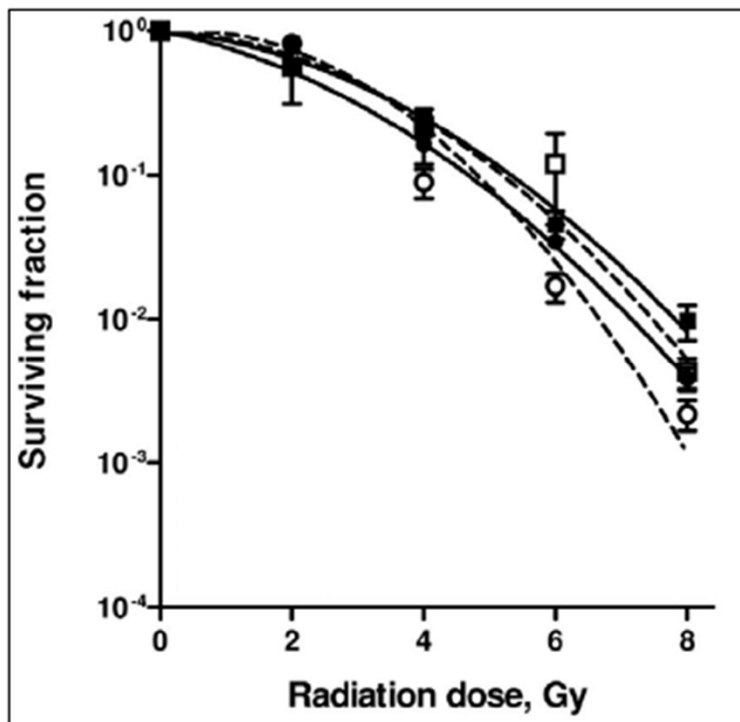
Mexner IJROBP 2009



Limited variation in **GTV dose** between all breathing phases, even end-inhalation and end-exhalation

SBRT - PLJUČA

- LQ model



$$SF = e^{-(\alpha D + \beta D^2)}$$

$$BED = nD (1 + (D/(\alpha/\beta)))$$

α – smrt celic /Gy začetne linearne komponente

β - smrt celic /Gy² kvadratnega dela krivulje

SBRT - PLJUČA

The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery

John P. Kirkpatrick, M.D., Ph.D.

*Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina 27710
(Tel: 919-668-7342, E-mail: kirkp001@mc.duke.edu)*

David J. Brenner, Ph.D., D.Sc.

*Center for Radiological Research, Columbia University, New York, New York 10032
(Tel: 212-305-9930, E-mail: djb3@columbia.edu)*

Colin G. Orton, Ph.D., Moderator

(Received 27 May 2009; accepted for publication 28 May 2009; published 1 July 2009)

[DOI: [10.1118/1.3157095](https://doi.org/10.1118/1.3157095)]

Published in final edited form as:

Semin Radiat Oncol. 2008 October ; 18(4): 234–239. doi:10.1016/j.semradonc.2008.04.004.

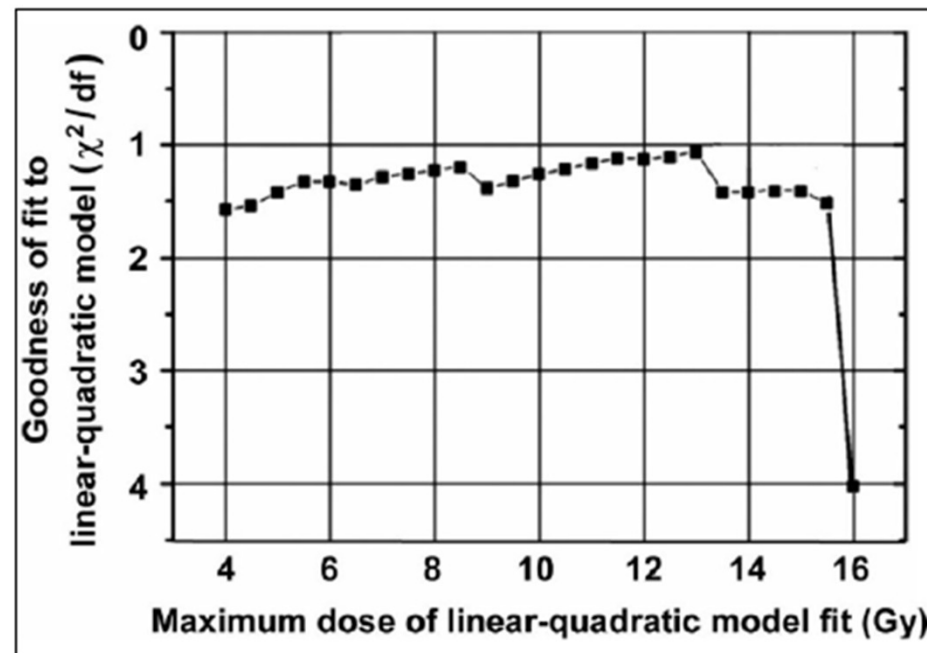
Point: The linear-quadratic model is an appropriate methodology for determining iso-effective doses at large doses per fraction

David J. Brenner, Ph.D., D.Sc.

From the Center for Radiological Research, Columbia University Medical Center, 630 West 168th Street, New York, NY.

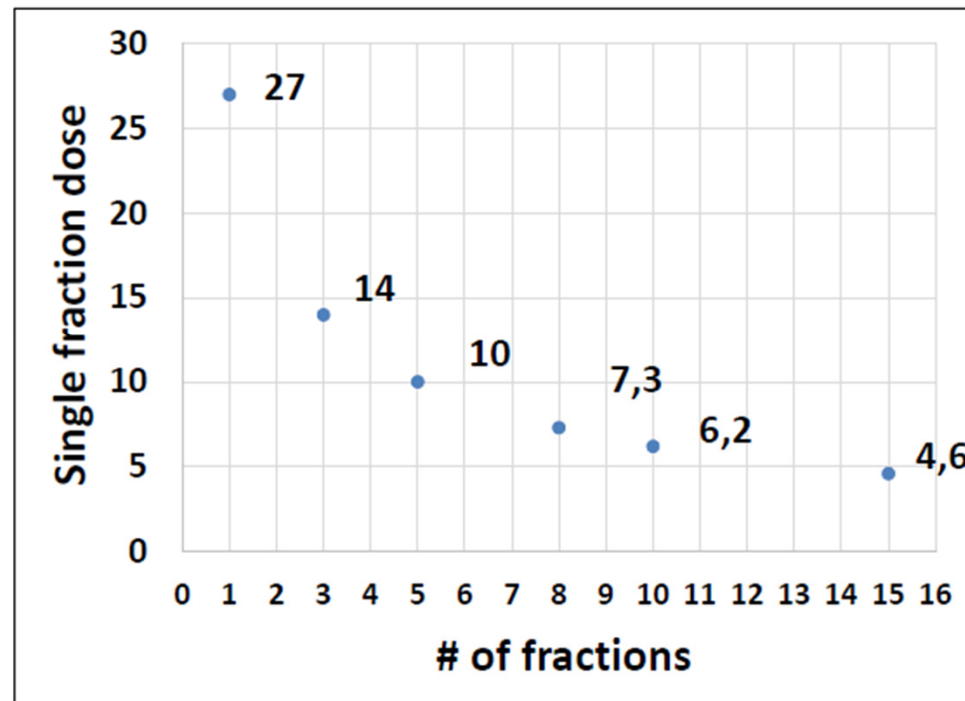
SBRT - PLJUČA

Brenner Semin Radiat Oncol 2008



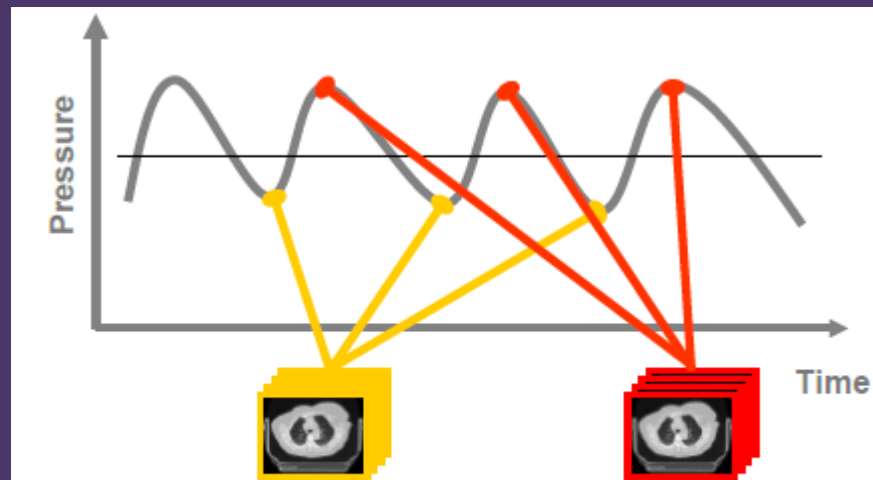
SBRT - PLJUČA

- „čarobni odmerek“ je BED 100 Gy



SBRT - PLJUČA

- priprava
 - respiratorno koreliran 4DCT
 - konvencionalni
 - 4DCT
 - rekonstrukcija faz dihanja

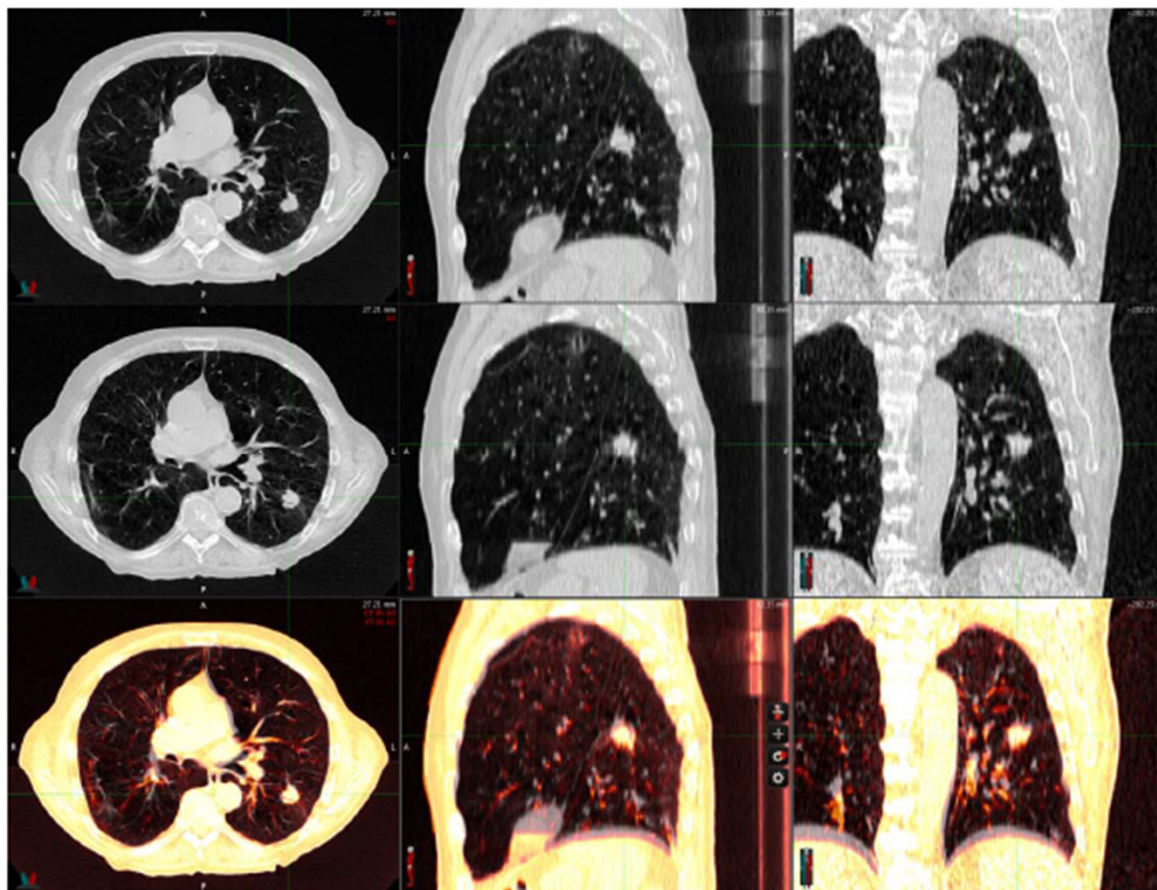


SBRT - PLJUČA

End-exhalation

End-inhalation

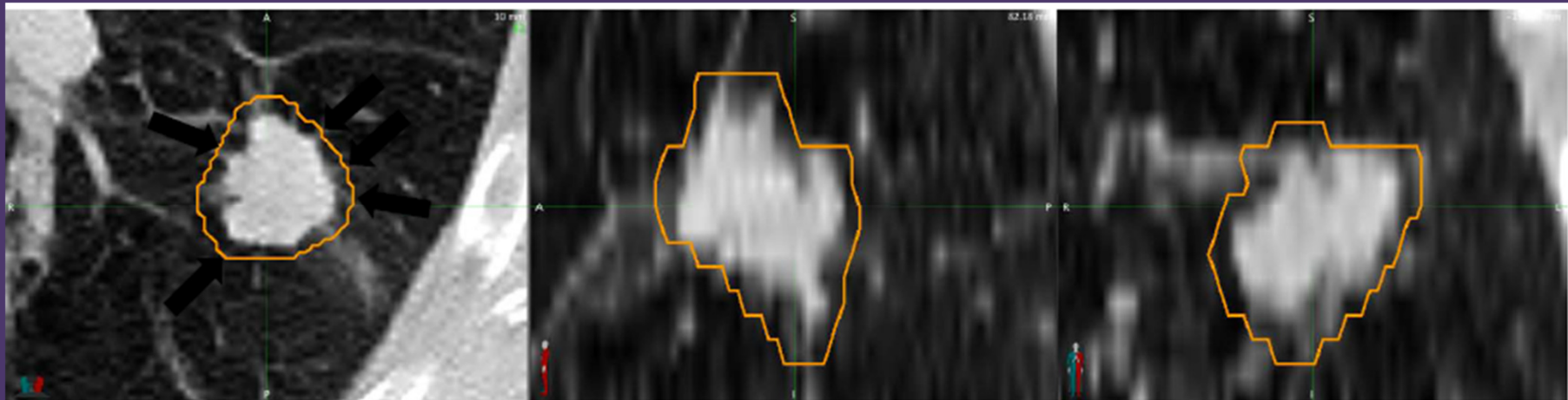
Fusion



primer: Mathias Gukenberger ESTRO SBRT 2015

SBRT - PLJUČA

- GTV
 - GTV pogosto CTV
 - spikule vključene v GTV

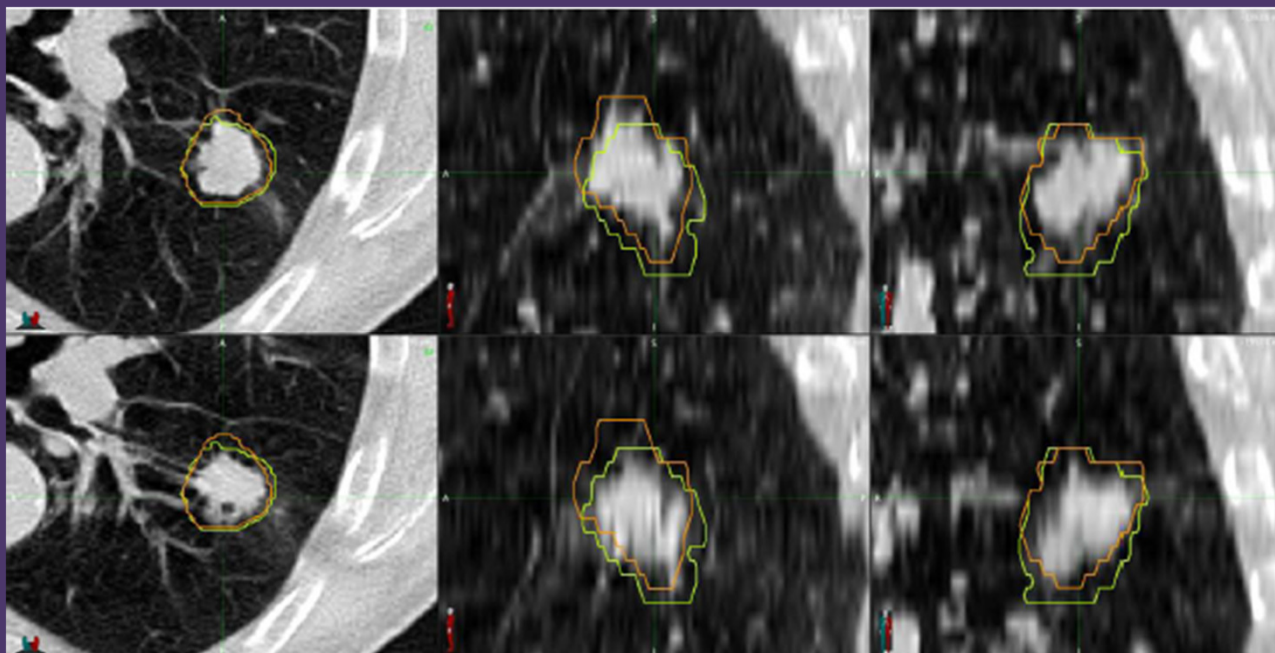


SBRT - PLJUČA

- GTV delineacija na koncu vdiha in koncu izdiha

konec izdiha

konec vdiha

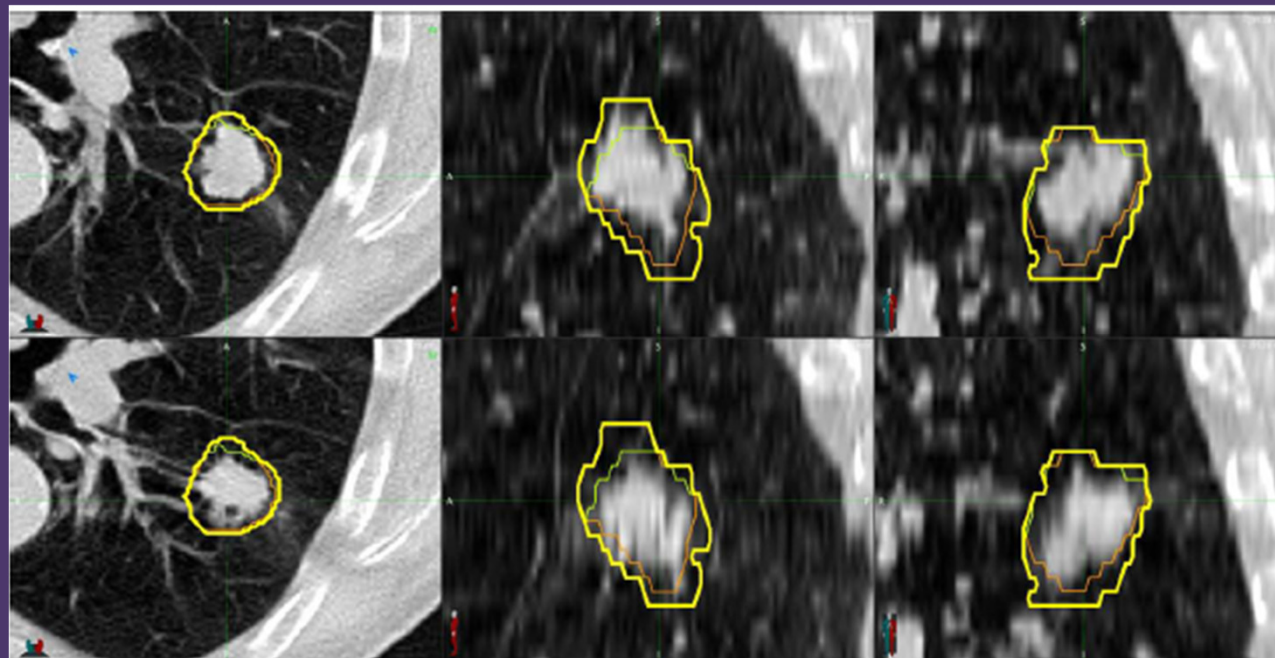


SBRT - PLJUČA

- ITV
– kompenzacija gibanja

konec izdiha

konec vdiha

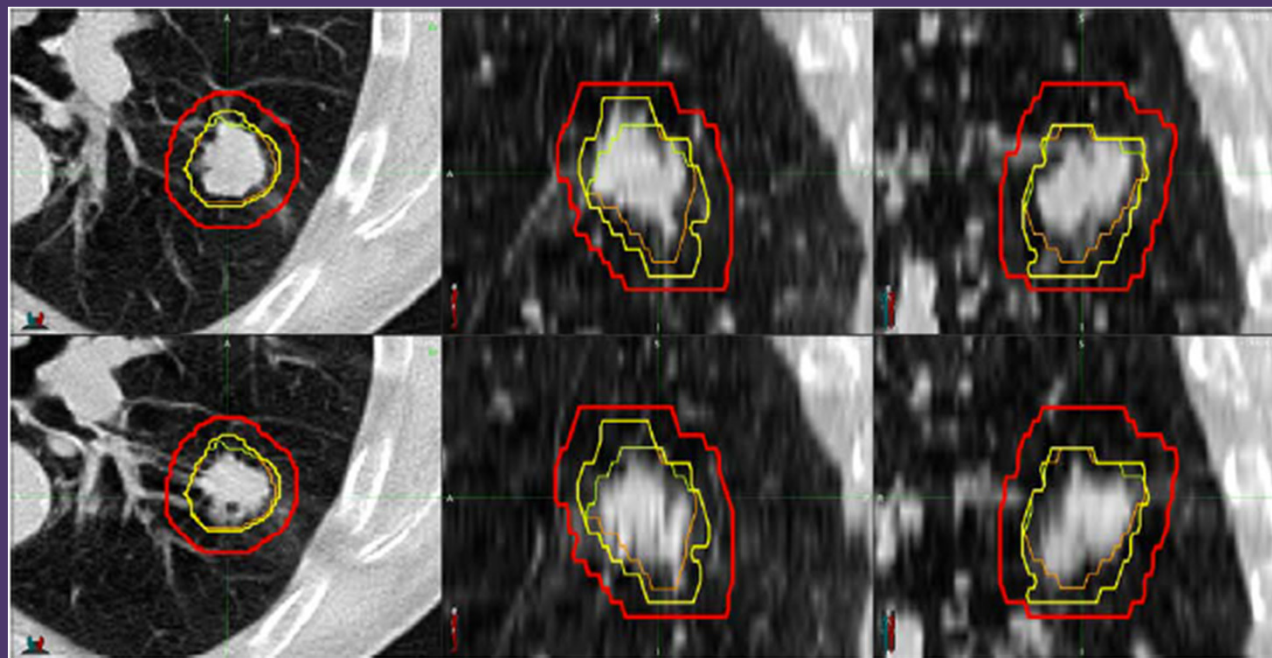


SBRT - PLJUČA

- $PTV = ITV + 5mm$

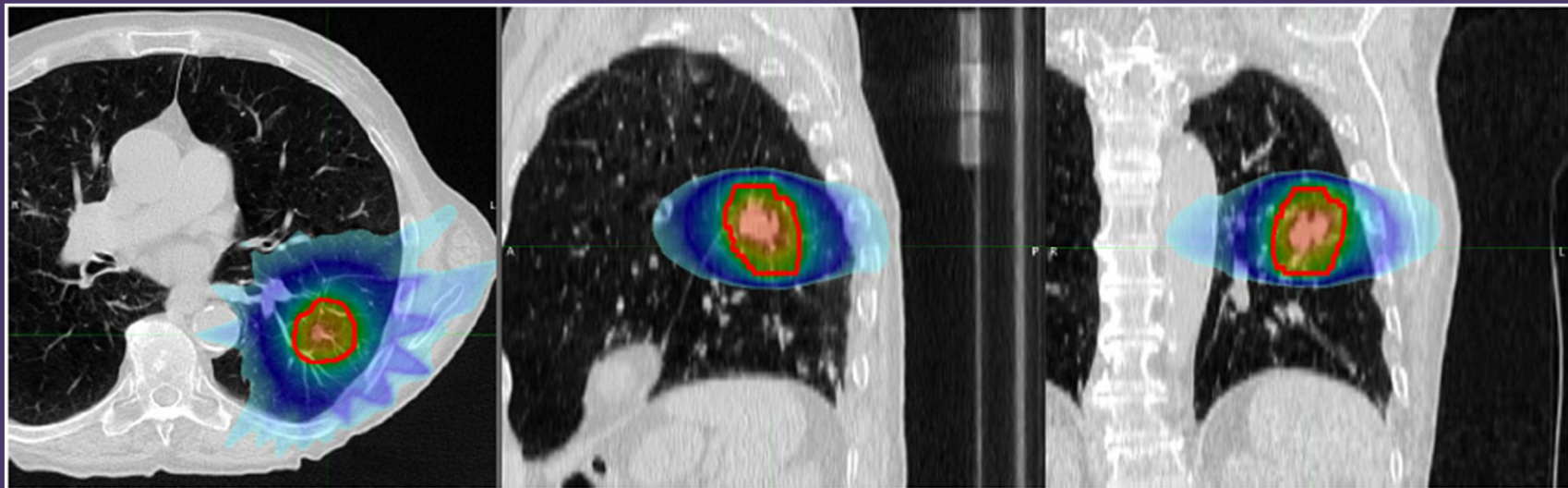
konec izdiha

konec vdiha

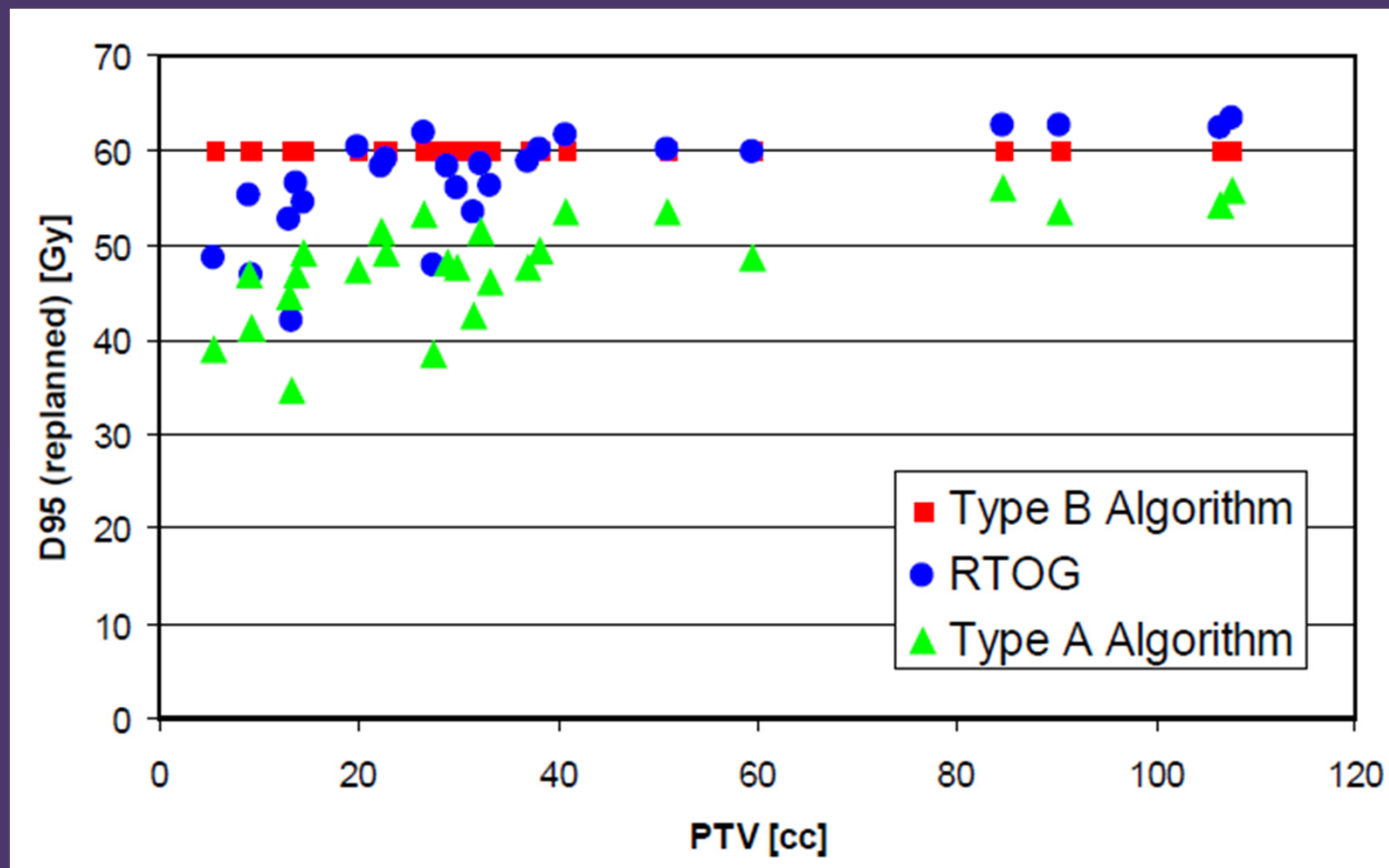


SBRT - PLJUČA

- izračun doze
 - algoritmi: **tip B**
 - Pinacle CC, Eclipse AAA, I plan MC, XiO superposition, XiO MC



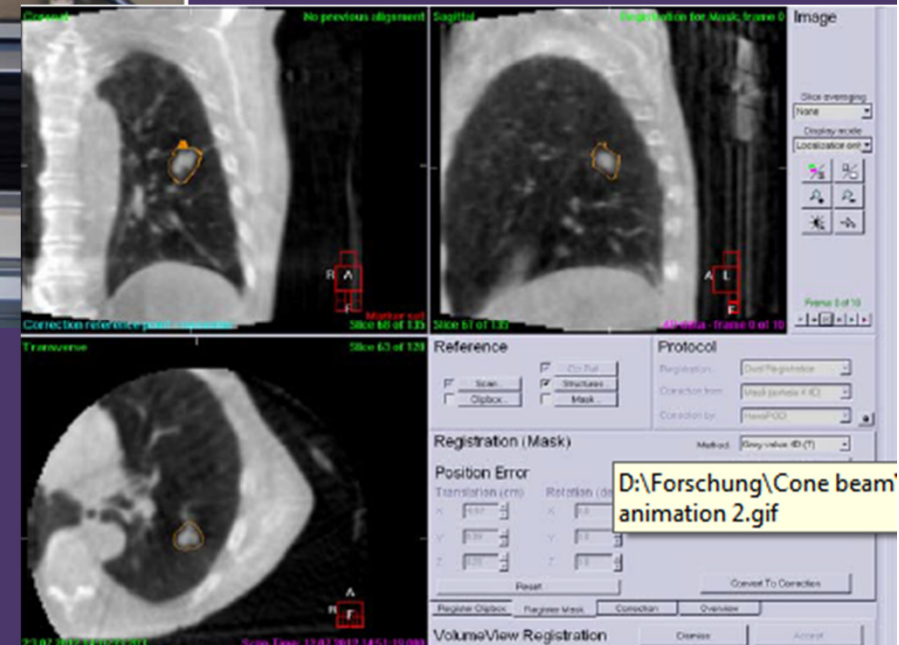
SBRT - PLJUČA



Hurkmans, Schuring. Rad Onc 2008

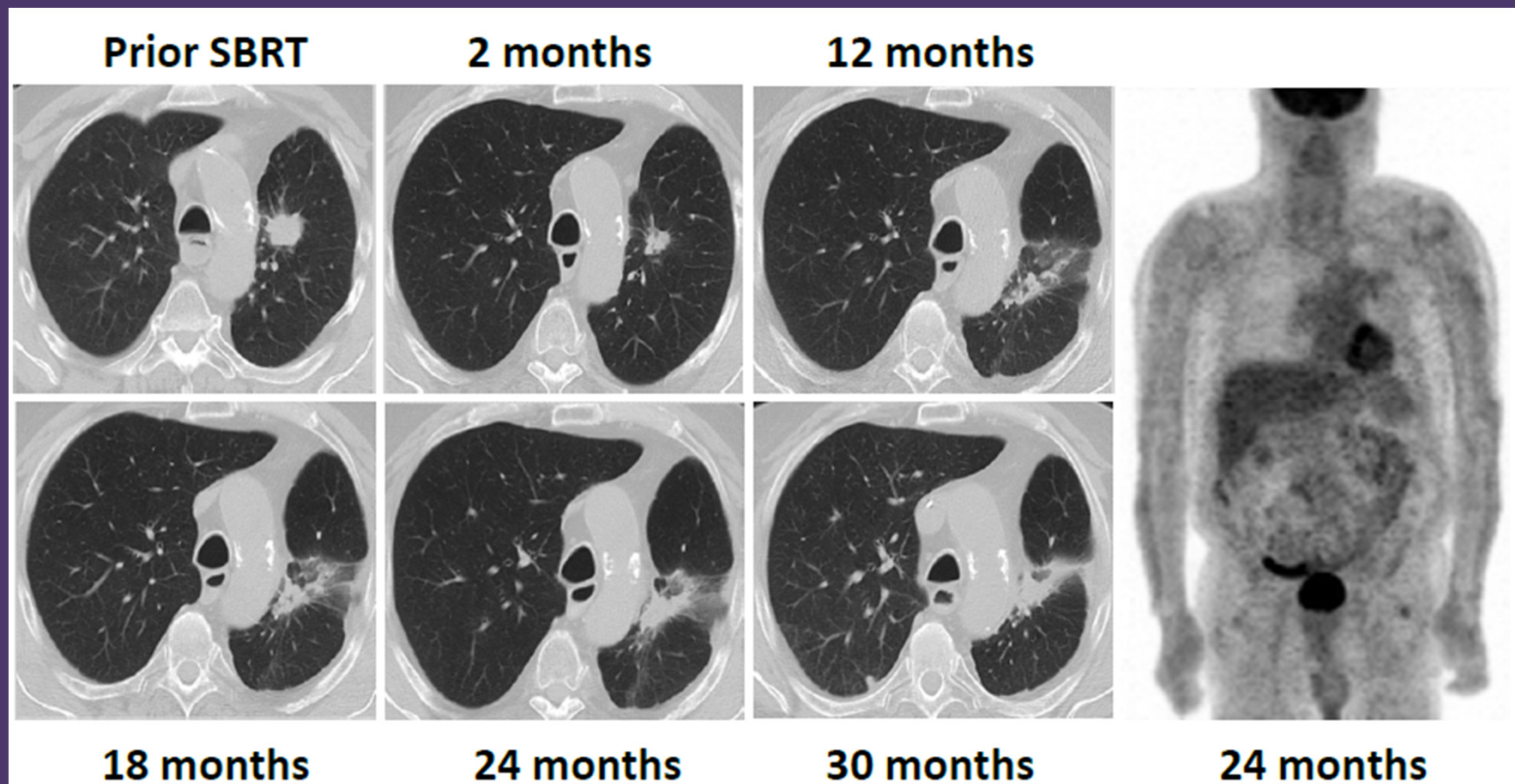
SBRT - PLJUČA

- zdravljenje



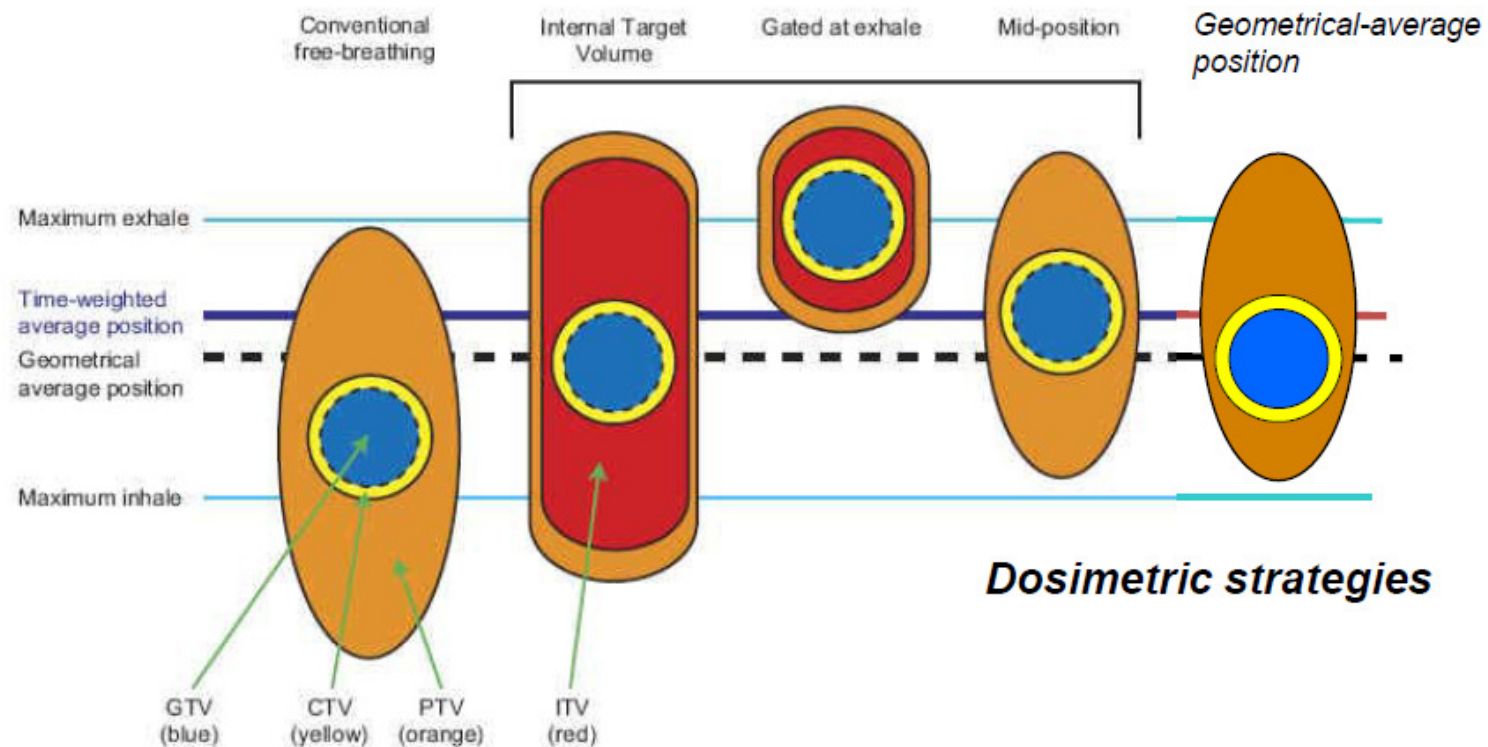
SBRT - PLJUČA

- spremljanje



SBRT - PLJUČA

- ITV ali kaj drugega

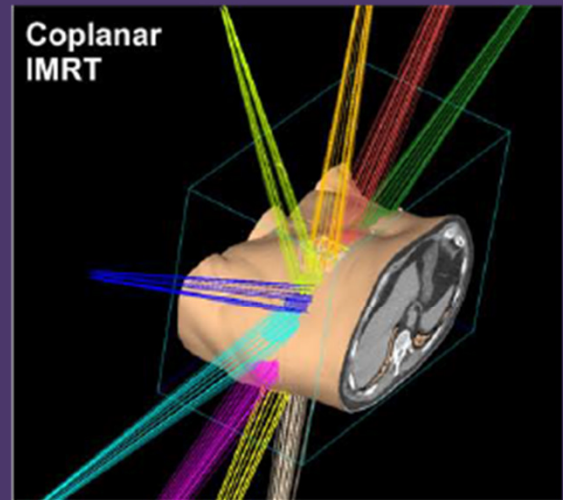
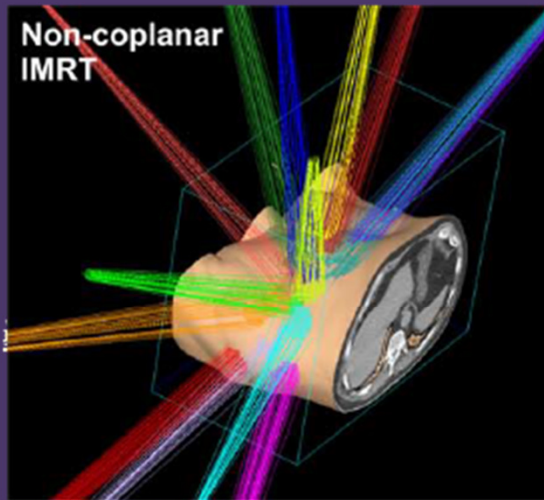
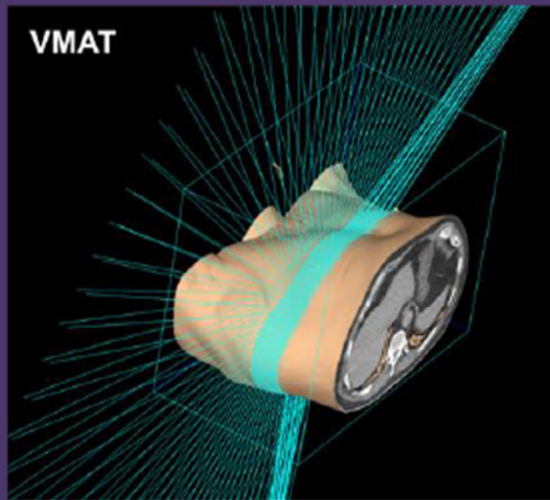


Wolthaus, IJROBP 70 (2008) p1229

Cuijpers et al, R&O 97 (2010) p443

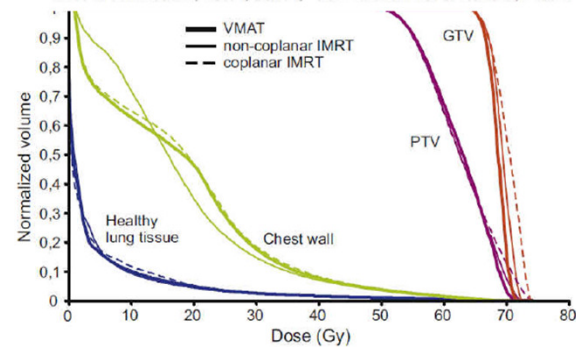
SBRT - PLJUČA

- VMAT vs IMRT

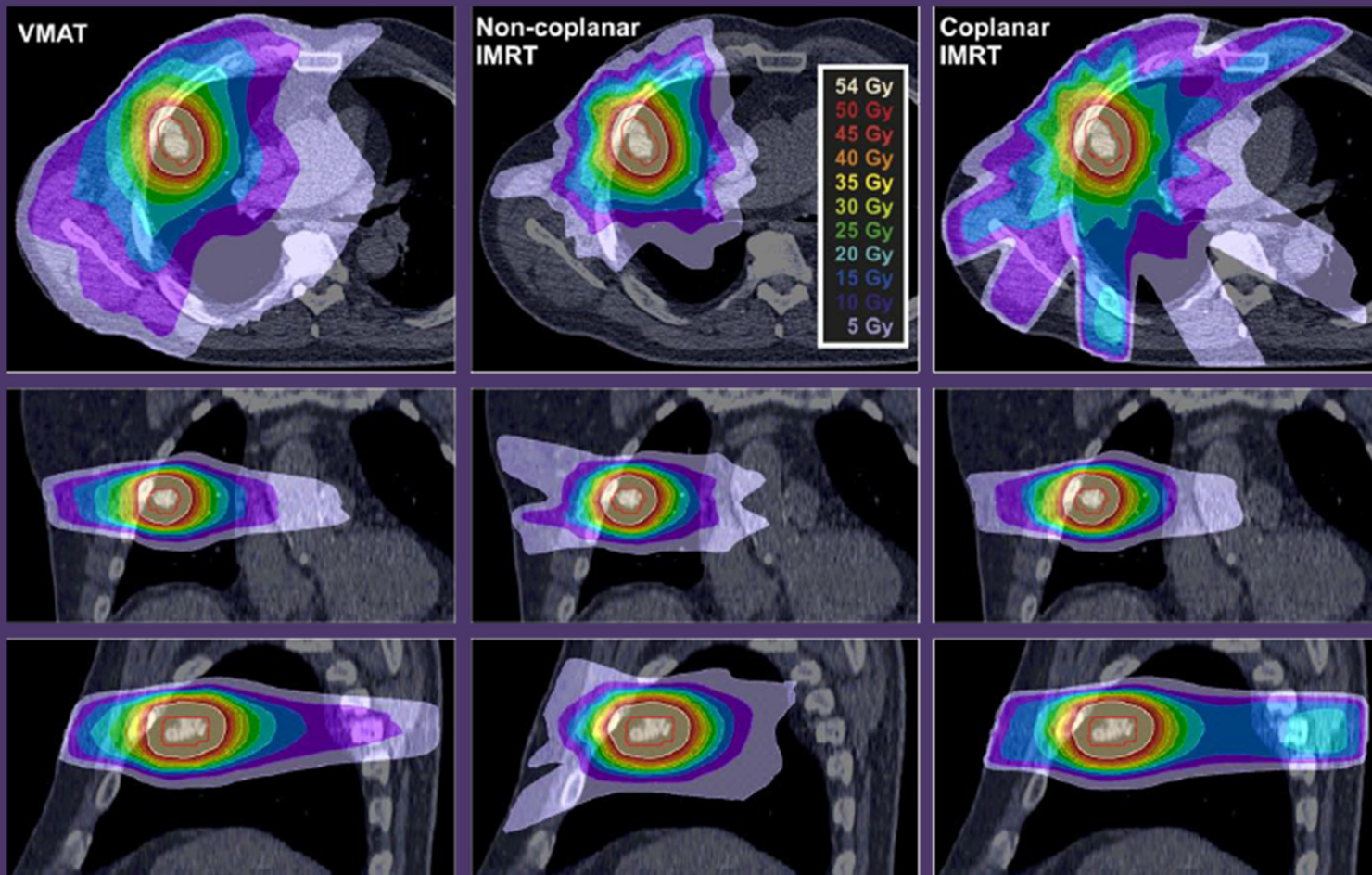


VOLUMETRIC-MODULATED ARC THERAPY FOR STEREOTACTIC BODY RADIOTHERAPY OF LUNG TUMORS: A COMPARISON WITH INTENSITY-MODULATED RADIOTHERAPY TECHNIQUES

ANDREA HOLT, PH.D.,* CORINE VAN VLIET-VROEGINDEWEIJ, PH.D.,* ANTON MANS, PH.D.,*
JOSÉ S. BELDERBOS, M.D., PH.D.,* AND EUGÈNE M. F. DAMEN, PH.D.*



SBRT - PLJUČA



SBRT - PLJUČA

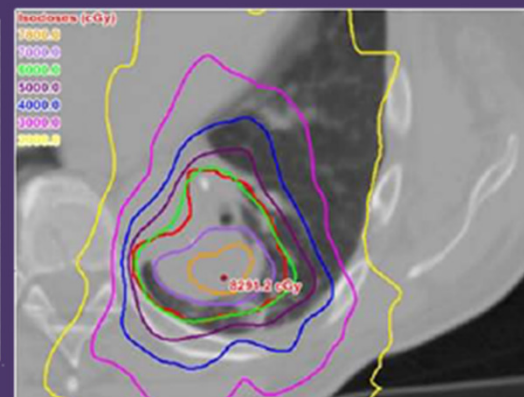
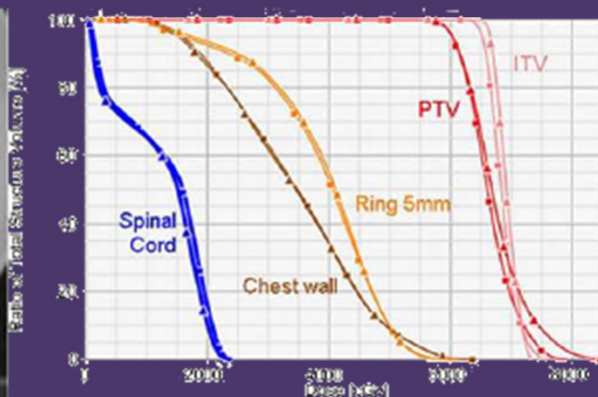
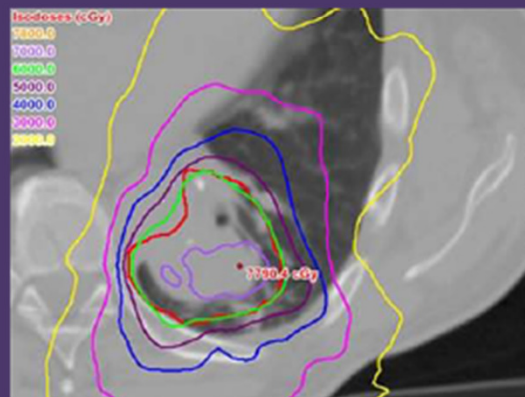
- konvencionalno ali 3F

Table 1 Summary of dosimetric metrics for FF and FFF plans

Sites	Metric	Unit	FF 6 MV	FFF 10 MV	<i>p</i>
	3 × 18 Gy (<i>n</i> = 4)	Lung	4.8 ± 0.4	2.6 ± 0.1	—
	5 × 11 Gy (<i>n</i> = 3)		3.2 ± 0.2	2.5 ± 0.1	—
	8 × 7.5 Gy (<i>n</i> = 3)		2.5 ± 0.1	2.5 ± 0.1	—
	1 × 16 Gy (<i>n</i> = 3)	Spine	9.9 ± 1.6	3.4 ± 0.4	—
	2 × 10 Gy (<i>n</i> = 3)		6.8 ± 1.8	2.7 ± 0.2	—
	3 × 9 Gy (<i>n</i> = 4)		4.3 ± 0.7	2.5 ± 0.1	—

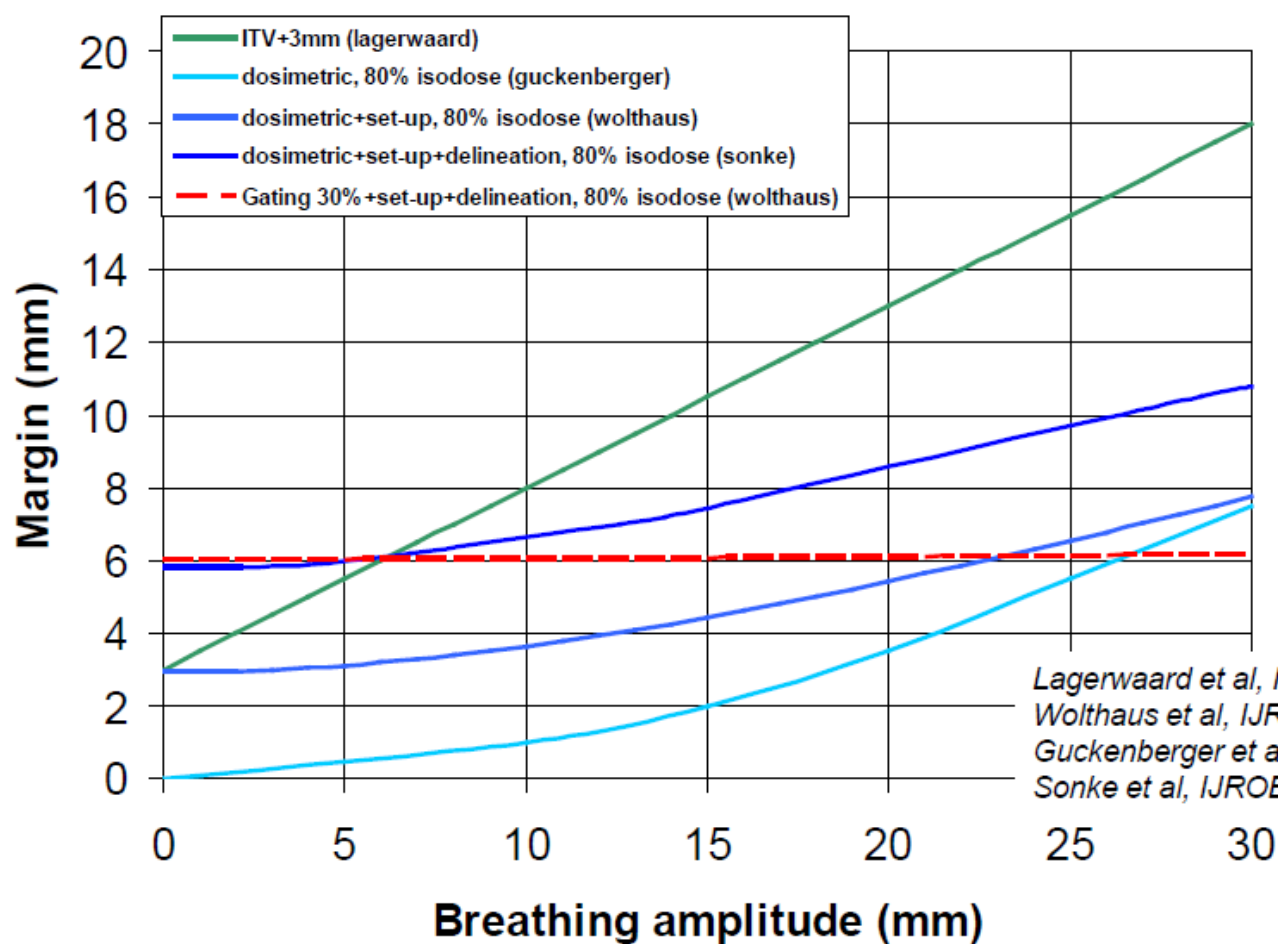
Abbreviations: FF = flattened beam; FFF = flattening filter-free; PTV = planning target volume; ITV = internal target volume; PRV = planning at risk volume.

Values are mean ± SD.



SBRT - PLJUČA

- robovi zaradi dihanja



Lagerwaard et al, IJROBP (2008) p685
Wolthaus et al, IJROBP (2008) p1229
Guckenberger et al, R&O 91(2009) p288
Sonke et al, IJROBP (2009) p567

SBRT - PLJUČA

- problem: rebra

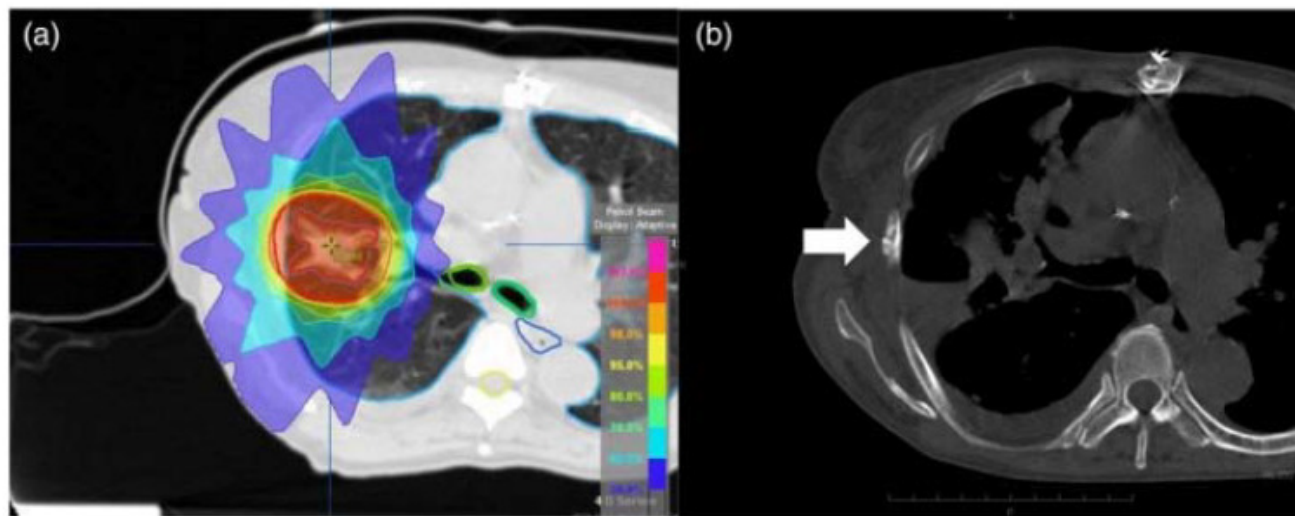


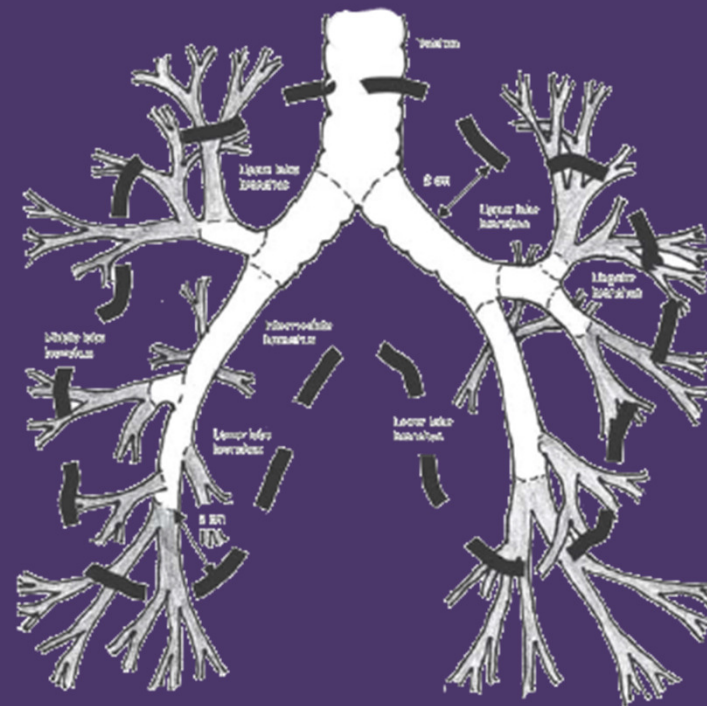
Fig. 1. (a) Dose distribution image shows the $D(0.5 \text{ cm}^3)$ prescribed dose to the rib as 49.6 Gy, with a BED3 of 254.6 Gy. (b) Bone window image shows a rib fracture (white arrow) 21 months after completion of SBRT.

Multivariate analysis showed that tumor location was a statistically significant risk factor for the development of Grade 1 RIRFs. Of the 77 RIRFs, 71 (92%) developed in the true ribs (ribs 1–7), and the remaining six developed in the false ribs (ribs 8–12).

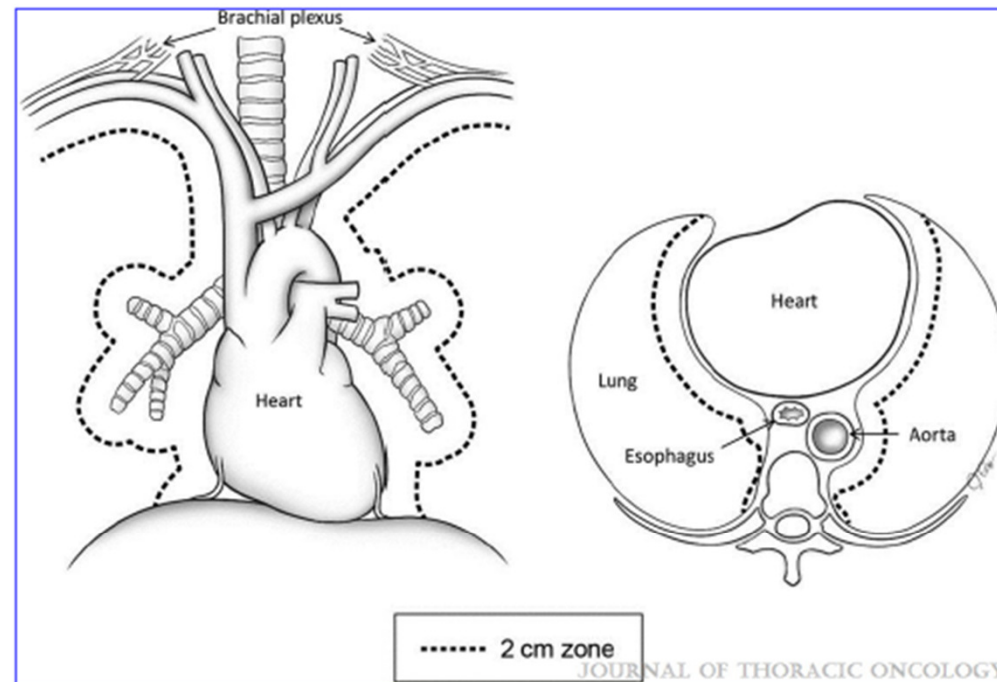
The $D(0.5 \text{ cm}^3)$ BED3 associated with 10% and 50% probabilities of RIRF were 55 and 210 Gy to the true ribs and 240 and 260 Gy to the false ribs. We conclude that RIRFs develop more frequently in true ribs than in false ribs.

SBRT - PLJUČA

- problem: centralno ležeči tumorji
 - proksimalno bronhialno drevo
 - 2 cm nad karino
 - do segmentnih razcepišč bronhov
 - tumorji ob plevri
- neprimerni za SBRT



SBRT - PLJUČA

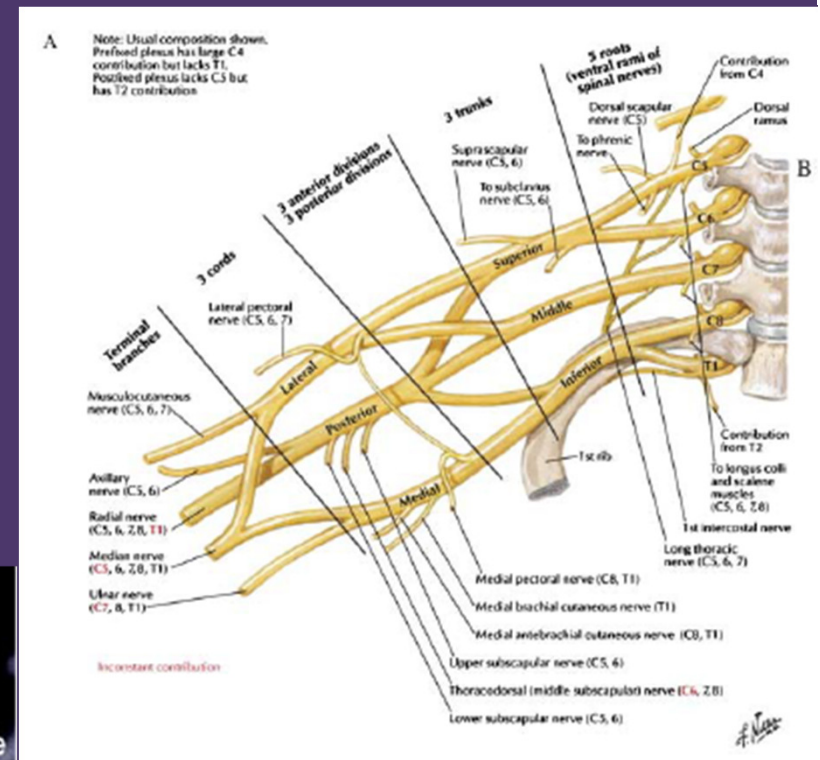
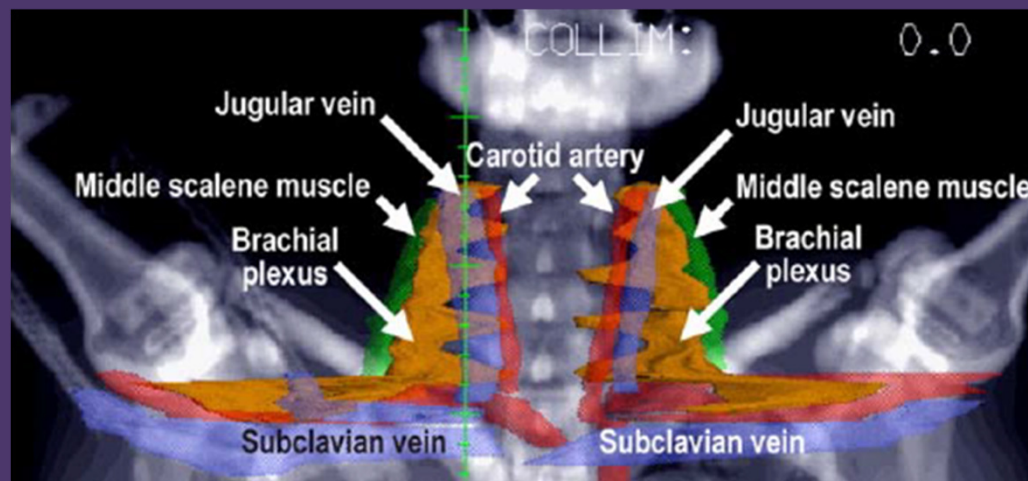


IASLC-ARTC [Chang JY, JTO 2015]

A tumor within 2 cm in all directions of any mediastinal critical structure, including bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve.

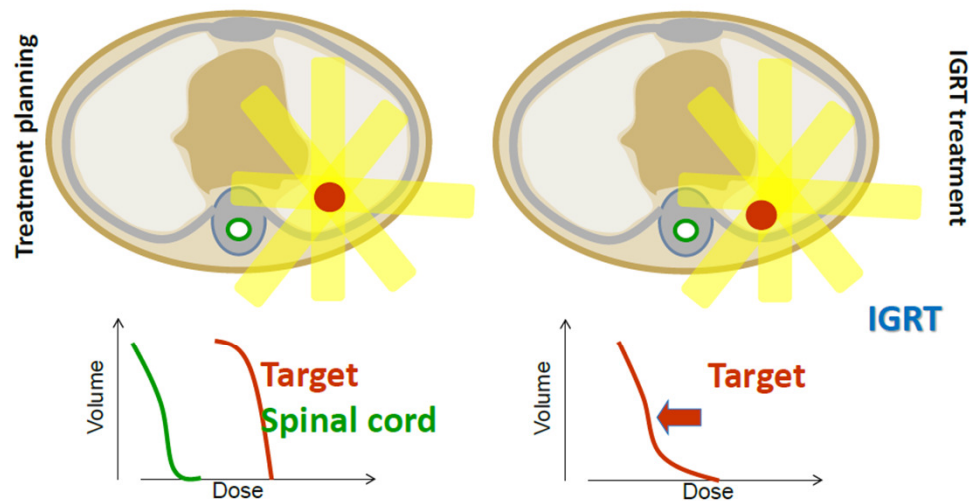
SBRT - PLJUČA

- problem: brahialni pletež – bolečina



SBRT - PLJUČA

4D volumetric image guidance:

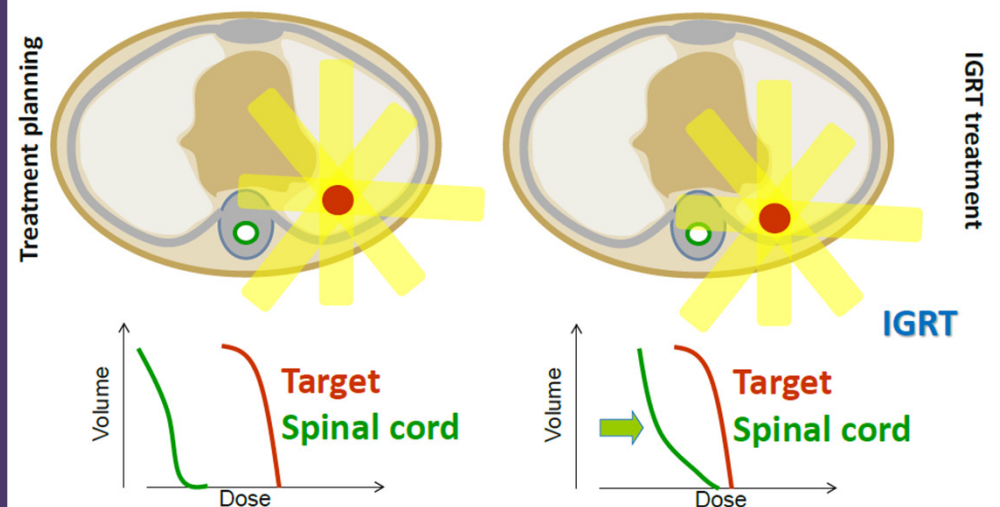


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4D volumetric image guidance:



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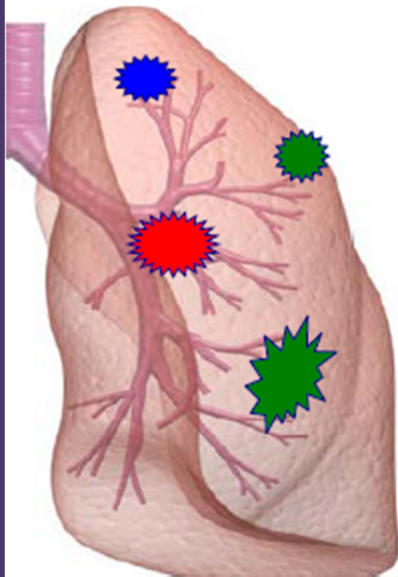
38

ESTRO

SBRT - PLJUČA

Fractionation** schemes used in Netherlands

** Prescribed to the encompassing isodose



● **3 fractions of 18Gy:** T1 lesions, not adjacent to chest wall

● **5 fractions of 11Gy:** T1 lesions with broad chest wall contact, and T2 lesions

● **8 fractions of 7.5Gy:** central lesions with limited overlap with mediastinum

Louie AV, 2014

druge frakcionacije, kjer je BED približno 100 Gy

50 Gy # 5 fr, 54 Gy # 6 fr, 56 Gy # 7 fr, 60 Gy # 8 fr

SBRT - HRBTENICA

- Glavna indikacija za SBRT hrbtenice je BOLEČINA
 - po 1x8 Gy popoln odgovor 1/3 do 1/2
- AKUTNA PAREZA/PLEGIJA NI INDIKACIJA ZA SBRT HRBTENICE
- SINS

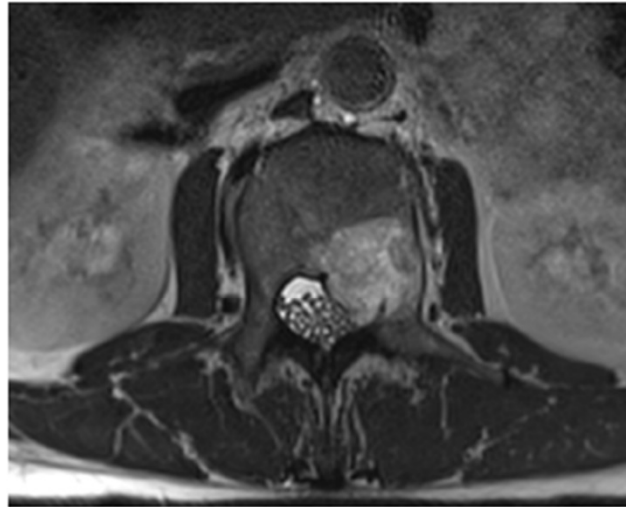
SBRT - HRBTENICA

	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain *	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements †	
Bilateral	3
Unilateral	1
None of the above	0

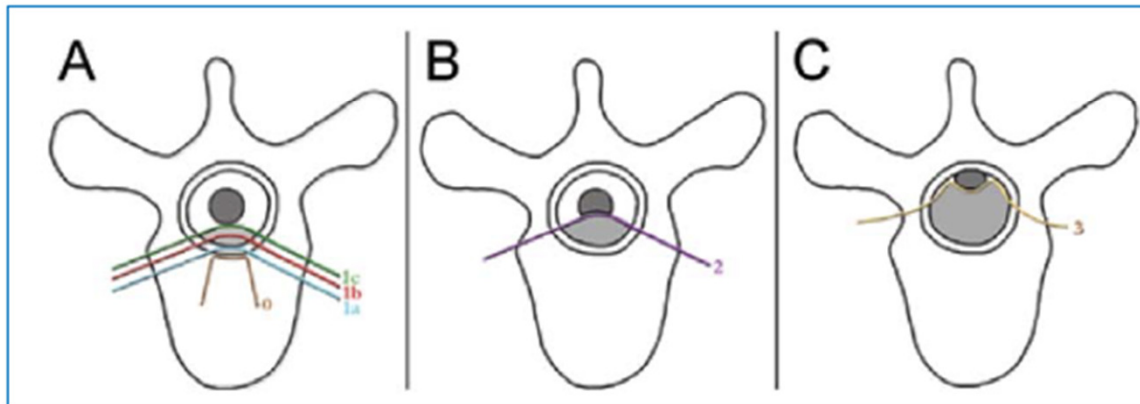
Total Score (0-18 SINS)	1	2	3	4	5	6		7	8	9	10	11	12		13	14	15	16	17	18
Three Clinical Categories (3-point)	Stability							Potentially Unstable							Unstable					
Binary Scale (2-point)	Stability							Current or potential instability; Surgical consultation recommended												

The SINS classification; Fisher et al.

SBRT - HRBTENICA



Score 2



Bilsky Score

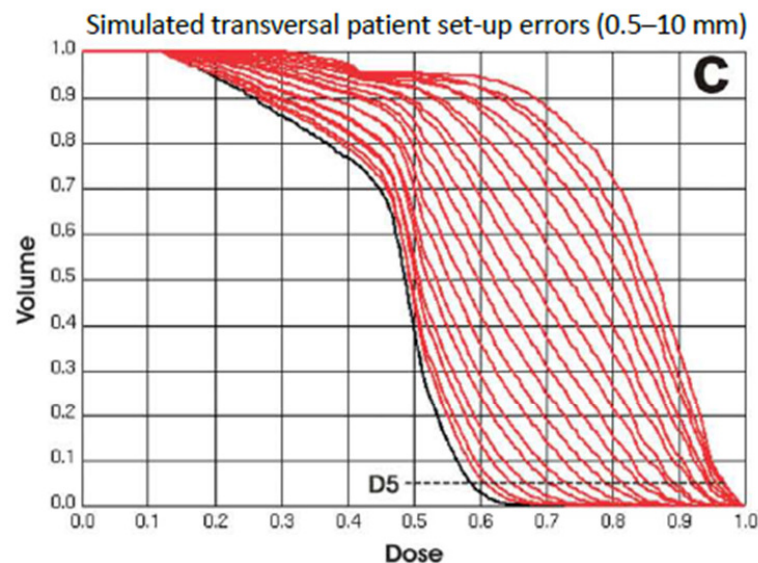
Bilsky J Neurosurg Spine 2010

SBRT - HRBTENICA

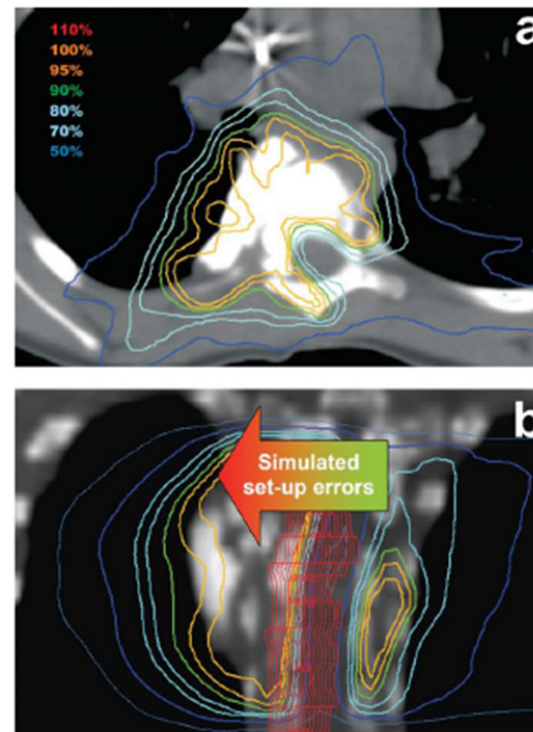
- INDIKACIJE
 - mehkotkivna masa
 - že paliativno obsevana hrbtenica

SBRT - HRBTENICA

Spine SBRT: Required accuracy



maximum tolerable errors on average :
1 mm (transversal plane)
4 mm (SI direction)
3.5°
(spinal cord dose within $\pm 5\%$ of prescribed dose)

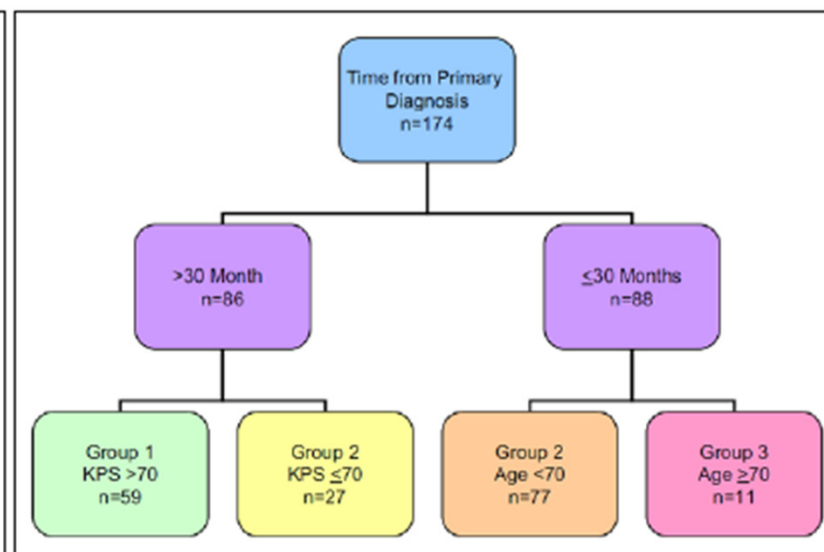
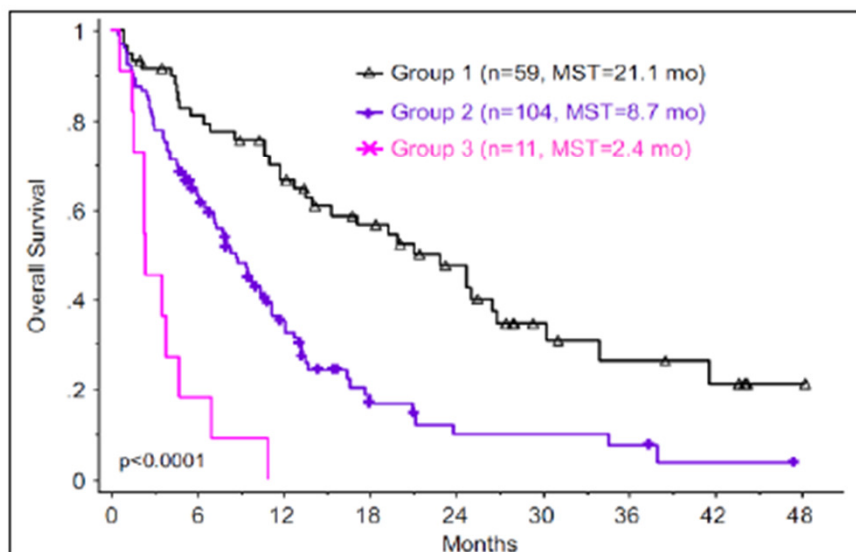


Guckenberger R&O 84, 2007 p56

SBRT - HRBTENICA

Overall survival after SBRT for vertebral metastases

Chao IJROBP 2012



Best OS after spinal SBRT

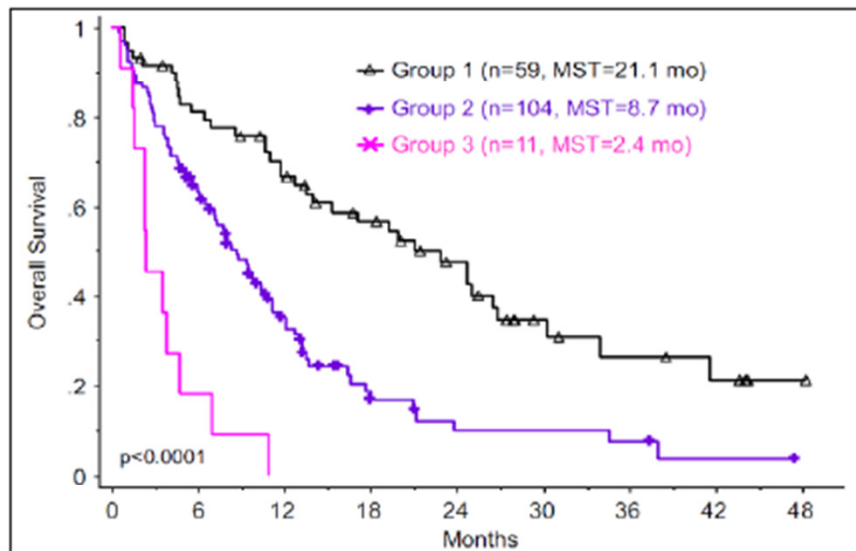
- Interval > 30 months after primary diagnosis
- KPS >70
- Age <70

SBRT - HRTENICA

Overall survival after SBRT for vertebral metastases

Mono-center

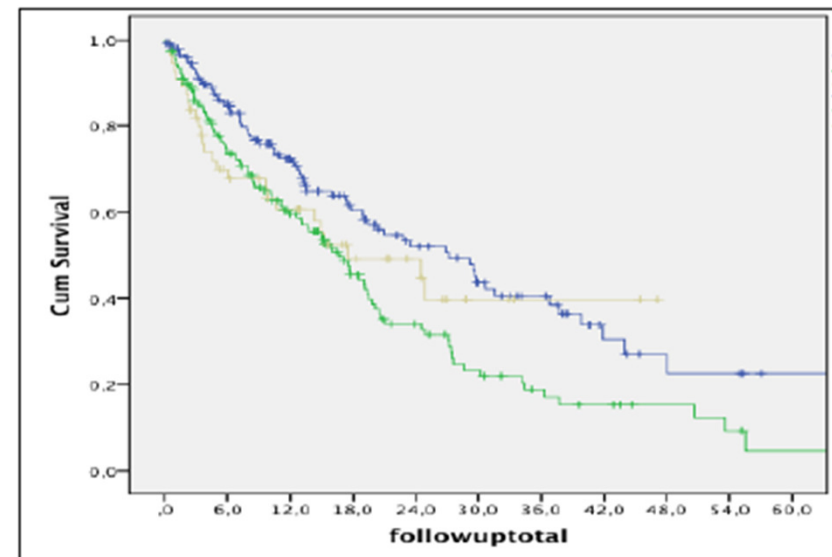
Cleveland Clinic: n=174



Chao IJROBP 2012

Multi-center

n=365

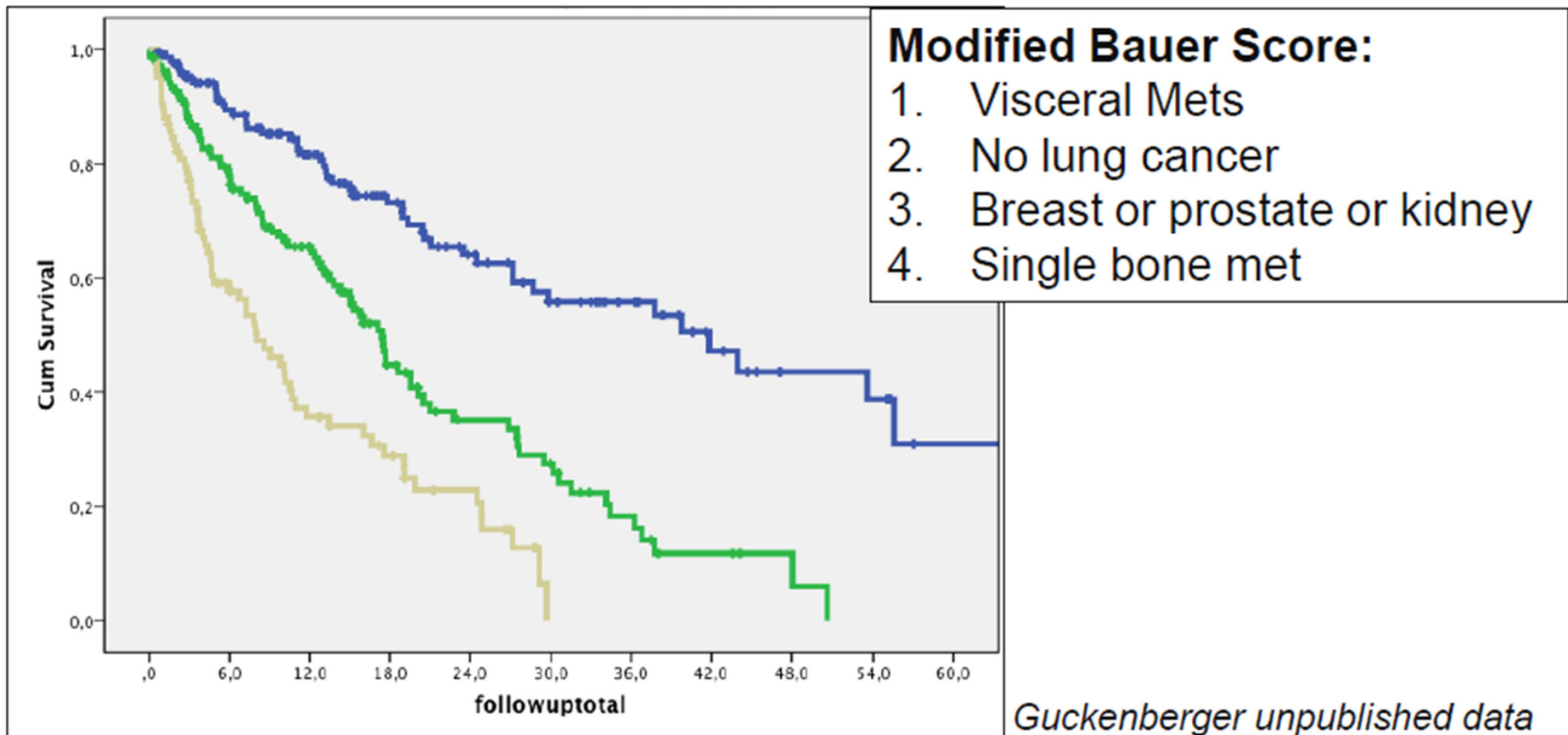


Guckenberger unpublished data

Chao RPA score not reproduced in a large multi-center analysis

SBRT - HRBTENICA

Overall survival after SBRT for vertebral metastases



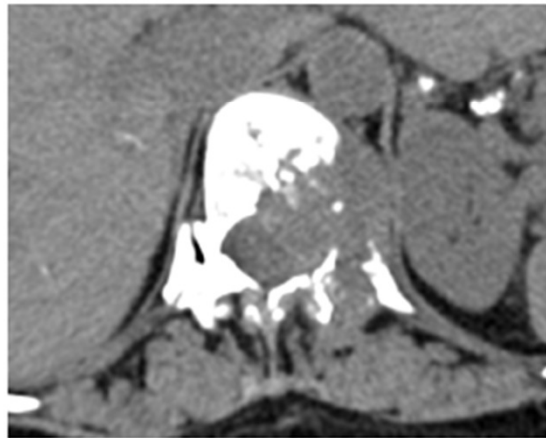
Simple, surgical modified Bauer score highly effective in predicting OS after spinal SBRT

SBRT - HRBTENICA

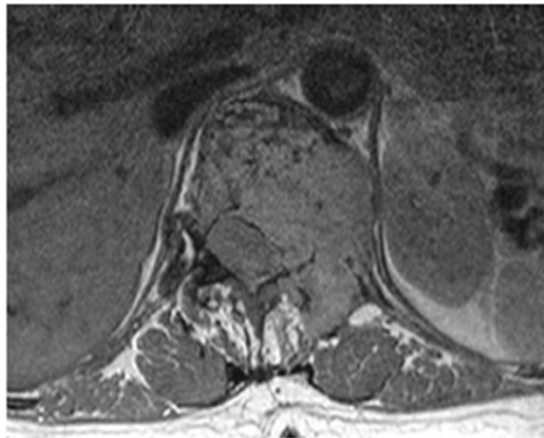
IMAGING FOR STEREOTACTIC SPINE RADIOTHERAPY: CLINICAL CONSIDERATIONS

Dahele IJROBP 2011

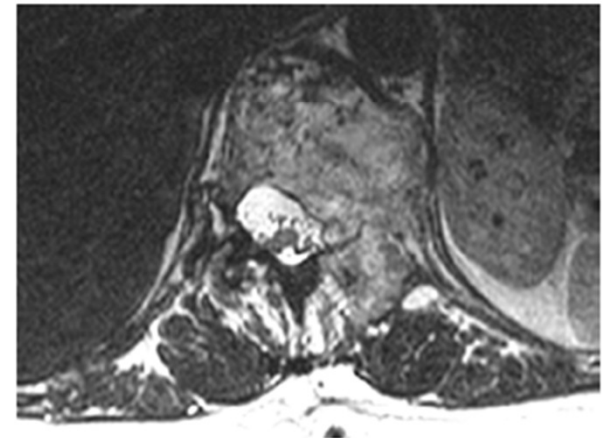
CT



MRI T1



MRI T2



CT imaging:

- Slice thickness 1- 2mm

MRI imaging:

- T1 with and w/o Gadolinium contrast
- T2
- Slice thickness $\leq$ 3mm or volumetric image acquisition

SBRT - HRBTENICA

Patterns of radiographic failure after spine SBRT:

	Total Failures	Adjacent vertebra	Epidural Space	Pedicles / posterior elements
Ryu 2004	9 / 61	33%		
Chang 2007	17 / 74		47%	17%
Gerszten 2007	6 / 51	0%		
Nelson 2008	4 / 33	0%	50%	50%
Nguyen 2010	12 / 55		50%	33%

Conclusions:

- Safety of treating the involved vertebra only
- Areas at risk: epidural space and untreated parts of vertebra

SBRT - HRBTENICA

Target volume concept of RTOG 0631

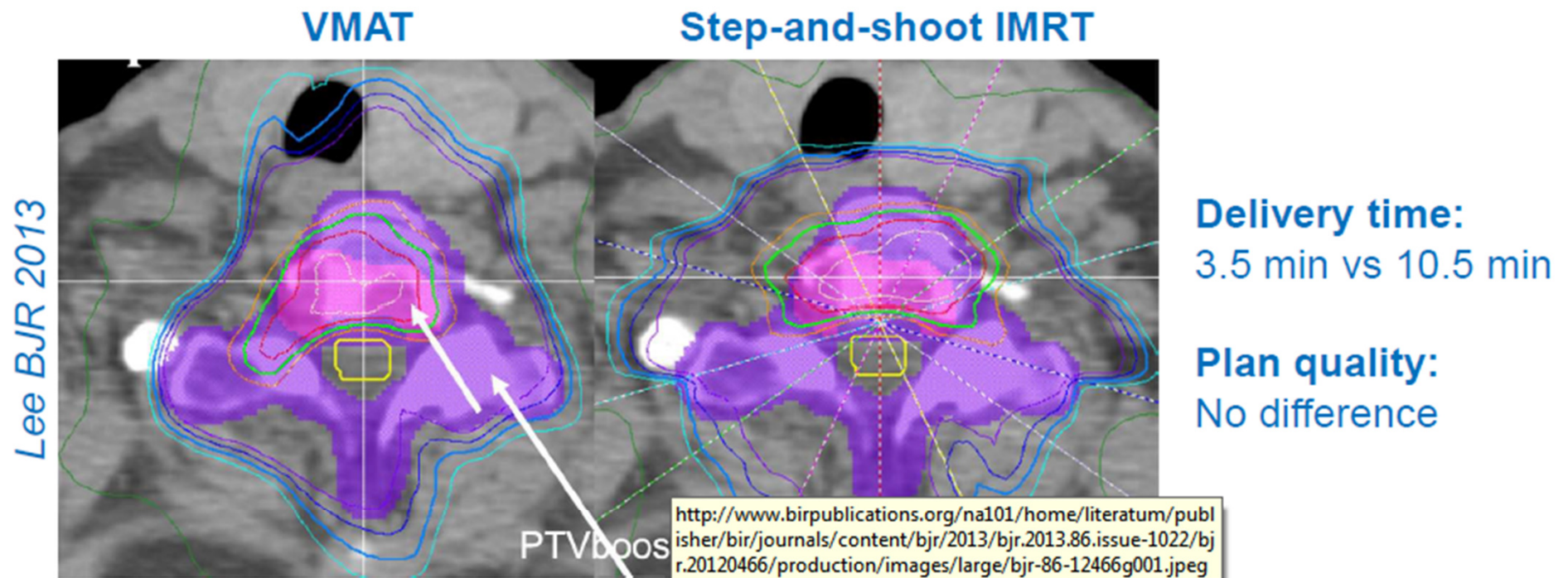


Anatomical target volume concept:

- Inclusion of „volumes-at-risk“ in target volume
- Exclusion of tumors within 3mm distance to spinal cord from practice of single fraction radiosurgery

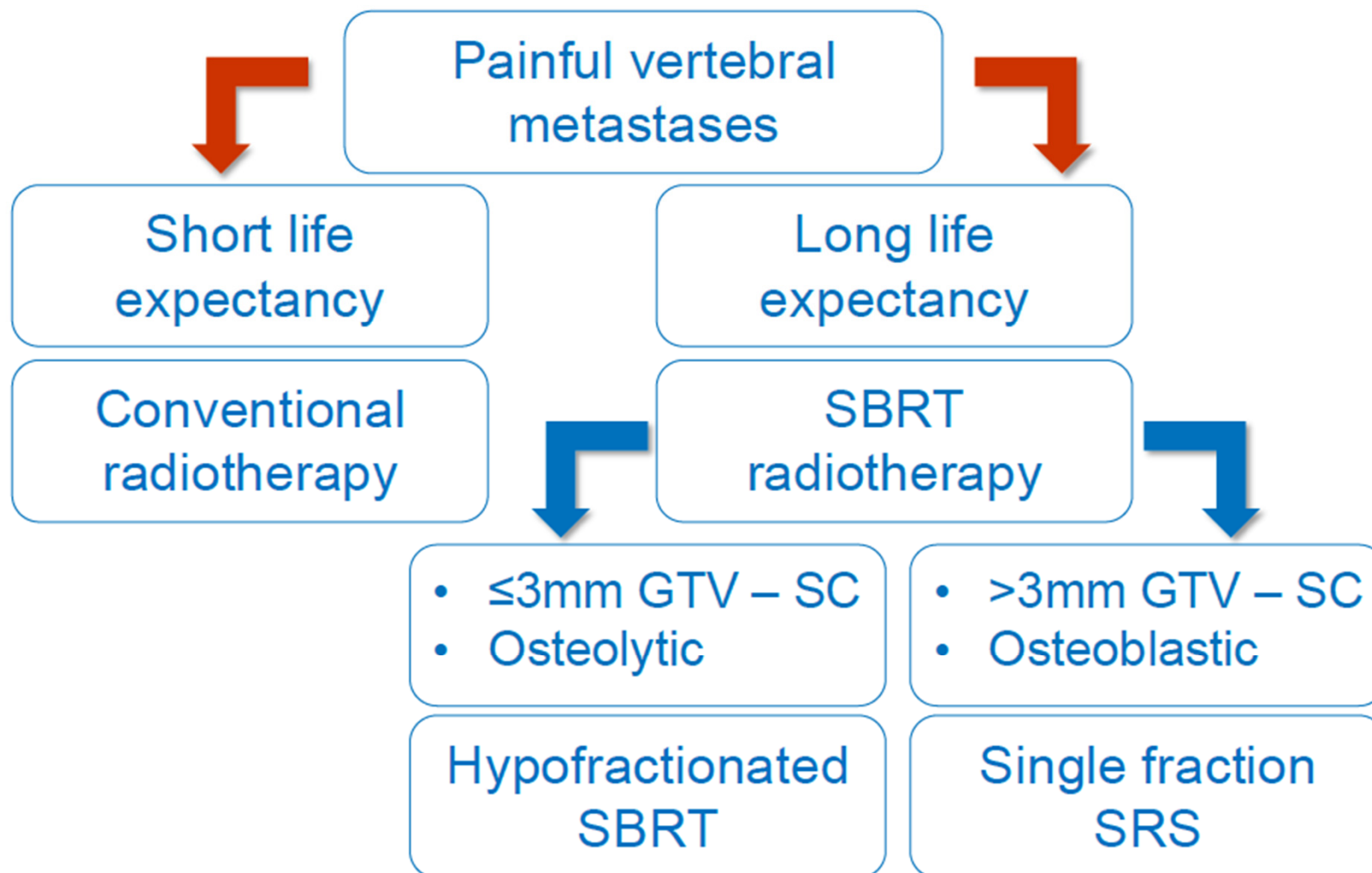
SBRT - HRBTENICA

IMRT versus VMAT for spine SBRT



- Substantially shorter delivery times
- Comparable dosimetric plan quality
- VMAT preferable for patients in pain

SBRT - HRBTENICA



SBRT - HRBTENICA

Positioning for spine SBRT

Before IGRT: (a)

M:-0.4 to 1.5, SD of 2-3 mm

(b) and (c)

M: of -6.2 to 0.8, SD of 4-7 mm



After IGRT: SD of 0.6 to 0.9 mm and 0.9° to 1.6°

Thus: IGRT resolves initial differences in set-up accuracy

However: Mean localisation to post treatment CBCT time 34 ± 7 min

6% of all fractions were within the tolerance (2mm) on localization CBCTs.

97% directly after IGRT

93% at mid-treatment,

82% at post-treatment. **Try to reduce treatment time!**

SBRT - HRBTENICA

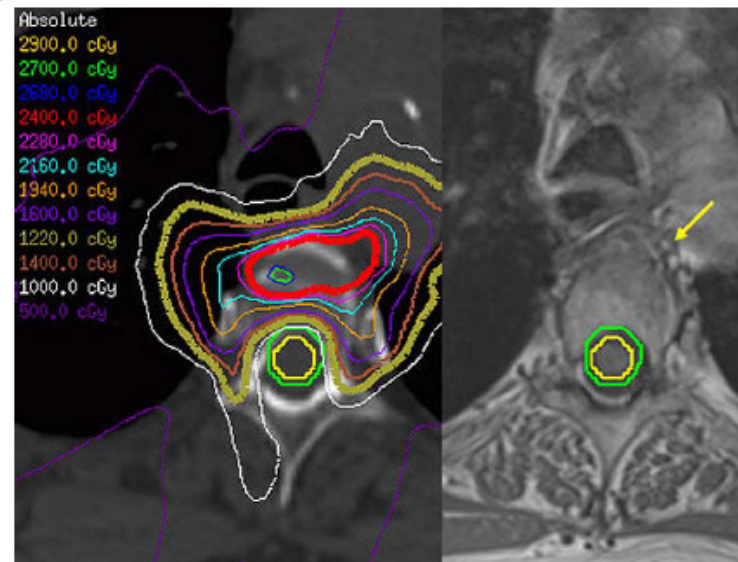
Positioning for spine SBRT

BodyFIX and Hexapod 6DOF table, Elekta CBCT.
(42 spine patients)

Small positioning errors after the initial CBCT setup were observed, with 90% within 1 mm and 97% within 1° (after 10 ± 3 min.).

Only half of patients within tolerance (1 mm and 1°) for the entire treatment (63 ± 4 min).

With intra-fraction IGRT every 15-20 min and using a 1-mm and 1 correction threshold, the target was localized to within 1.2 mm and 0.9° with 95% confidence.

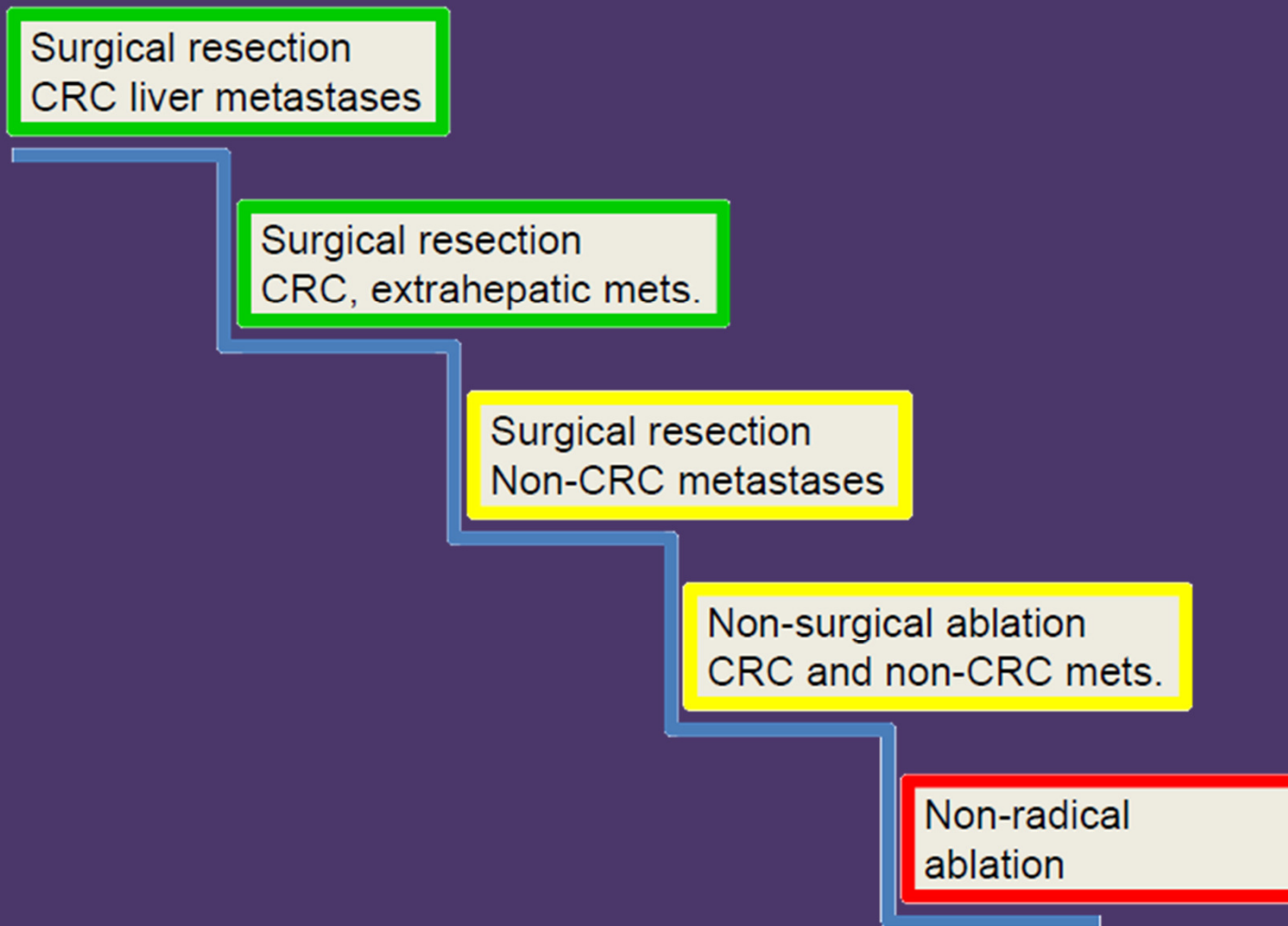


intrafractional imaging and corrections needed approximately every 15 to 20 min.

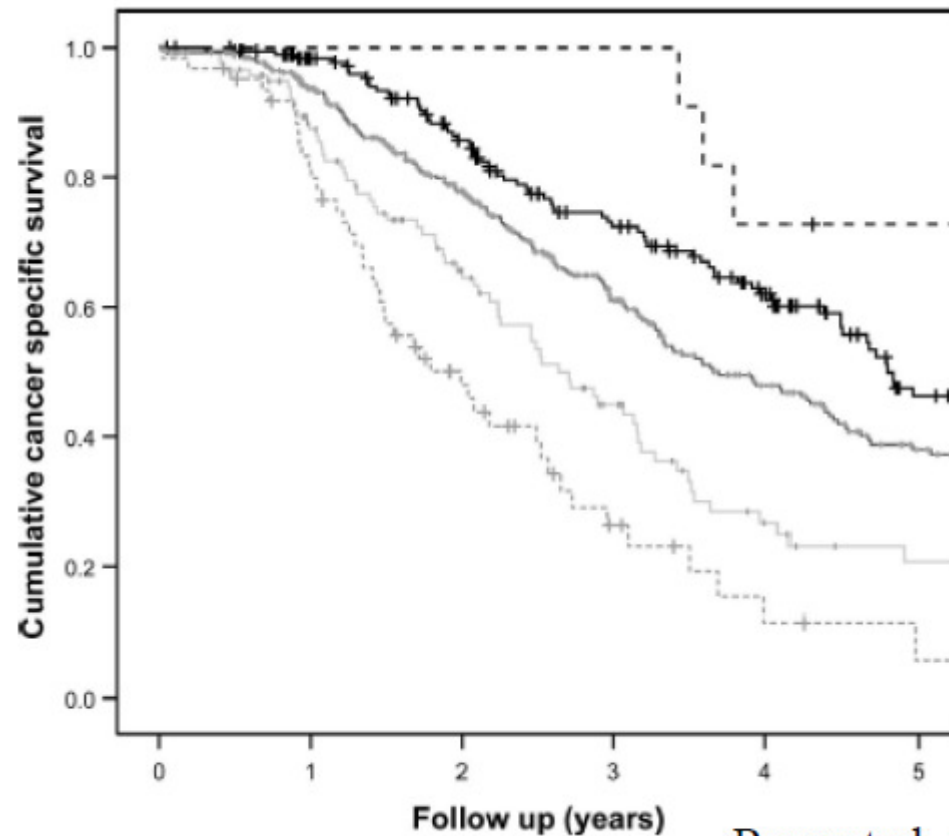
SBRT - HRBTENICA

- PROTOKOL
 - izbira bolnikov
 - odločitev glede fiksacije
 - slikovna diagnostika
 - +/- 1 vretence, T1 + ks, T2, 1-2 mm 3D
 - cela lumbalna ?
 - IGRT (exacTrac, CBCT)
 - FU

SBRT - JETRA



SBRT - JETRA



- Lymph node status (primary)
- Tumor differentiation (primary)
- CEA
- Number of metastases
- Diameter of largest metastasis
- Surgical resection margin
- Extrahepatic extension

Rees et al. Ann Surg (2008) 247: 125; N=929 pts.

SBRT - JETRA

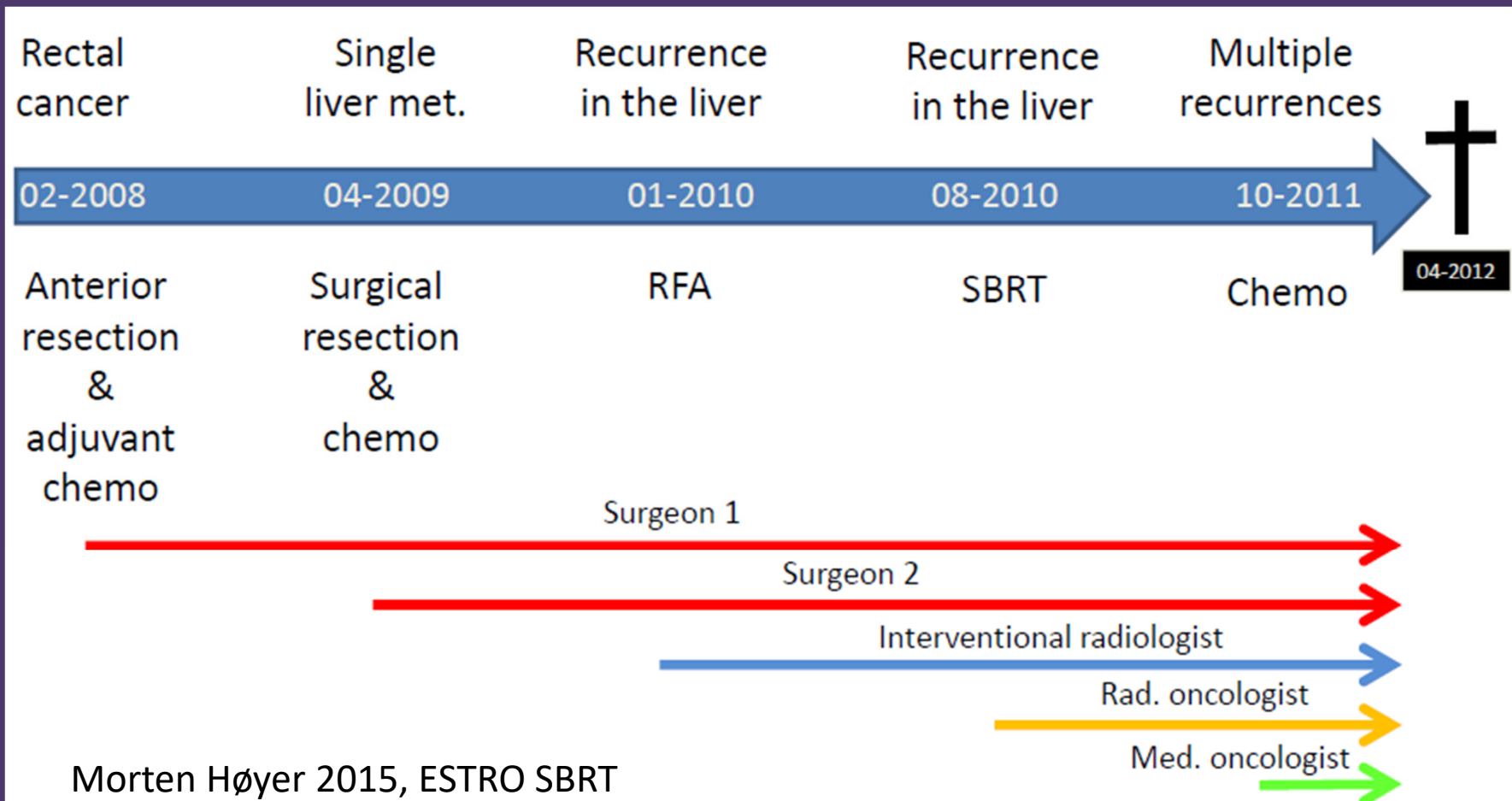
- morbiditeta po SBRT jeter

Acute morbidity	0	1	2	3	4	5
Deterioration of PS	296	22	2	-	-	1
Nausea	293	23	3	2	-	-
Pain	273	24	8	6	-	-
Gastritis	303	7	12	1	-	-
Skin	209	4	6	2	-	-
Liver function	294	23	4	-	-	1
Late morbidity						
Gastritis/ulcer/perforation	308	1	10	1	0	1
Rib fracture	311	-	10	-	-	-
Dyspnea	294	15	11	-	1	-
Skin reaction	308	4	7	2	-	-
Liver function	307	6	8	-	-	-

Fode et al. Radiother Oncol 2015 in press

SBRT - JETRA

- kdaj in kako?



Morten Høyer 2015, ESTRO SBRT

SBRT - JETRA

- kaj je boljše?

	Mortality	Severe complication	Local control	Survival
Resection Simmonds	2.8%	-	-	30% (5 yr)
RFA Wong	0-2%	6-9%	40-96% (crude)	14-55% (5 yr)
SBRT	0.5-1%	2%	74-92% (actuarial)	30-62% (2 yr)

Simmonds et al Br J Surgery 94: 982-99; 2006

Wong et al JCO 28:493-508 (ASCO 2009 syst. rev.)

Høyer et al IJROBP 83: 1047-57; 2012

SBRT - JETRA

Patient evaluation and
multidisciplinary assessment

Simulation:

- ✓ Immobilization devices
- ✓ 3 phases contrast-enhanced CT scan
- ✓ 4D CT scan
- ✓ Multi-imaging: PET-CT total body and/or MRI

- ✓ Counturing: target and organs at risk
- ✓ Dose prescription
- ✓ Treatment planning
- ✓ Review of dose distribution and plan approval

Treatment delivery:

- ✓ Verify patient position and radiation delivery

Follow-up:

- ✓ Clinical evaluation
- ✓ Laboratory tests and tumor markers
- ✓ Imaging: CT, MRI or PET-CT total body

Table 2

Selection criteria for SBRT

Selection criteria	Patients categories		
	Suitable	Cautionary	Unsuitable
Lesion number	<3	4	>4
Lesion diameter (cm)	1-3	>3 and ≤6	>6
Distance from OARs (mm)	>8	5-8	<5
Liver function	Child A	Child B	Child C
Free liver volume (cc)	>1,000	<1,000 and ≥700	<700

SBRT, stereotactic body radiation therapy; OARs, organs at risk.

SBRT - JETRA

Prescription dose in 3 fractions recommended according to lesion diameter

Lesion diameter	Prescription dose
≤ 3 cm	48-60 Gy
3-6 cm	60-75 Gy

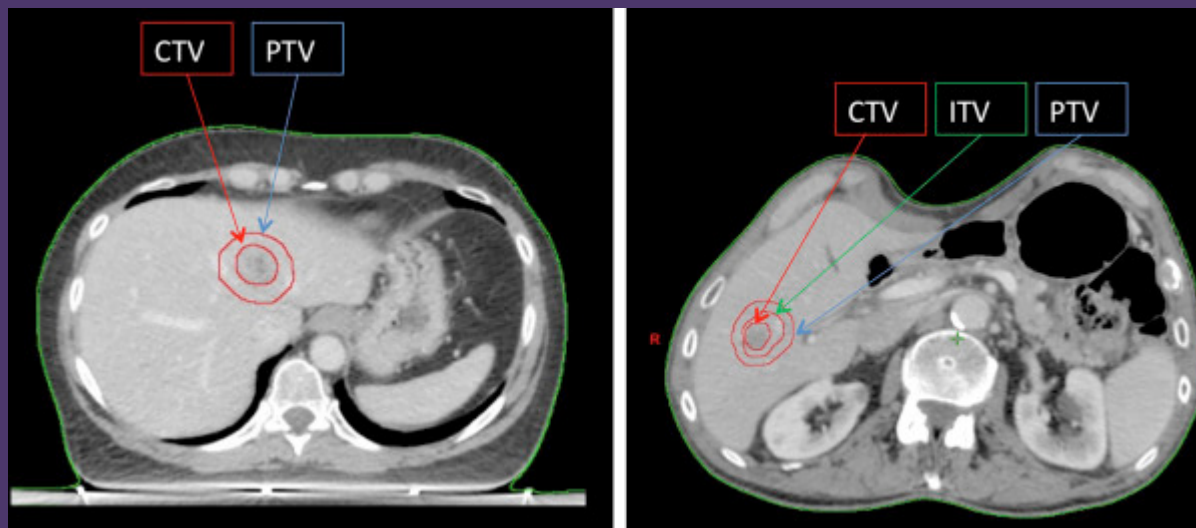
Recommended OARs dose constraints for liver SBRT in 3 fractions

Organ	Dose-volume limits
Healthy liver (total liver volume minus cumulative GTV)	$>700 \text{ cm}^3$ at <15 Gy
Spinal cord	D 1 cm^3 <18 Gy
Kidneys (R + L)	V15 Gy $<35\%$
Stomach, duodenum, small intestine	D 3 cm^3 <21 Gy
Heart	D 1 cm^3 <30 Gy
Rib	D 30 cm^3 <30 Gy

SBRT, stereotactic body radiation therapy; OARs, organs at risk; GTV, gross tumor volume.

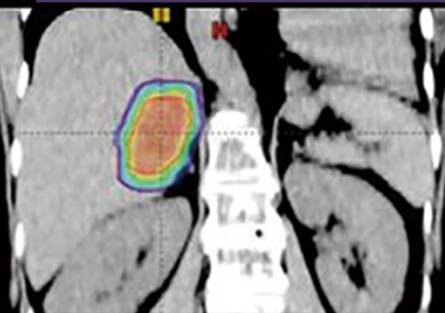
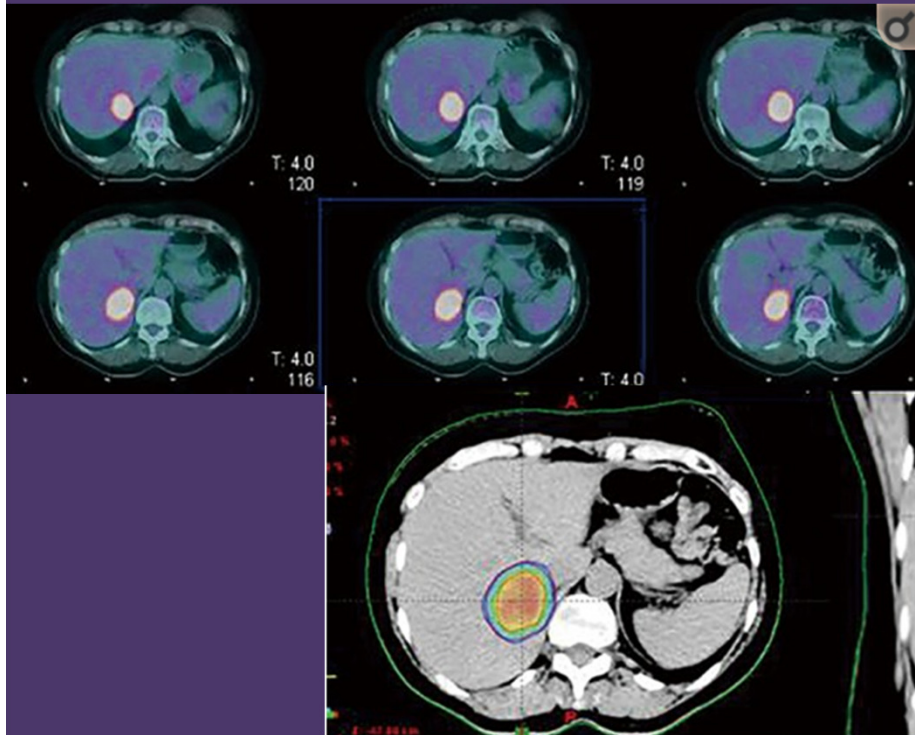
SBRT - JETRA

- definicija PTV
- markerji

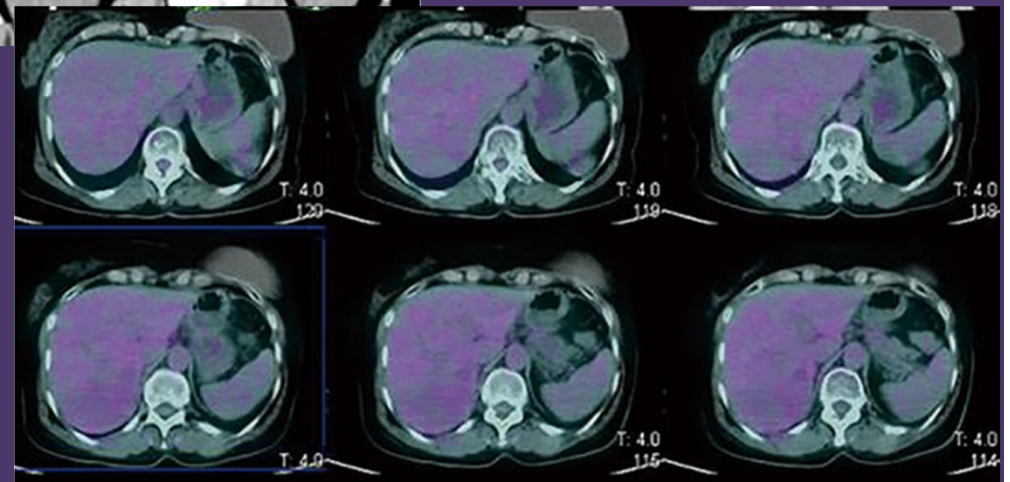


Tomito et al 2014

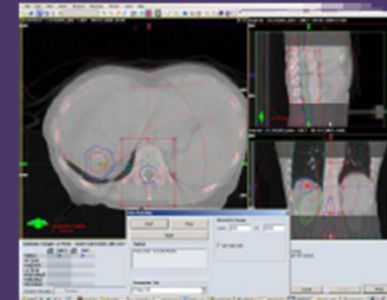
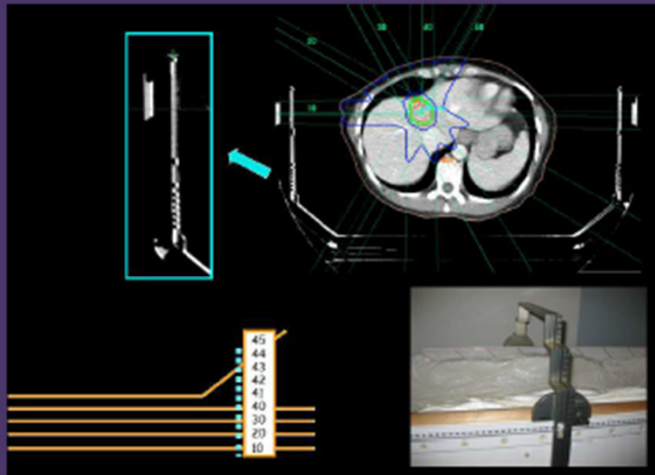
SBRT - JETRA



JGO 2014



SBRT - JETRA

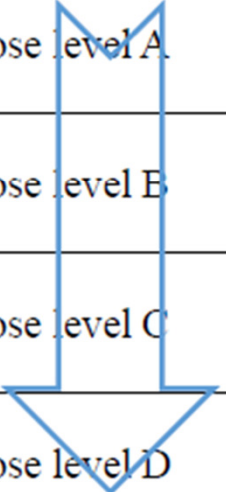


okvir vs brez okvirja

SBRT - JETRA

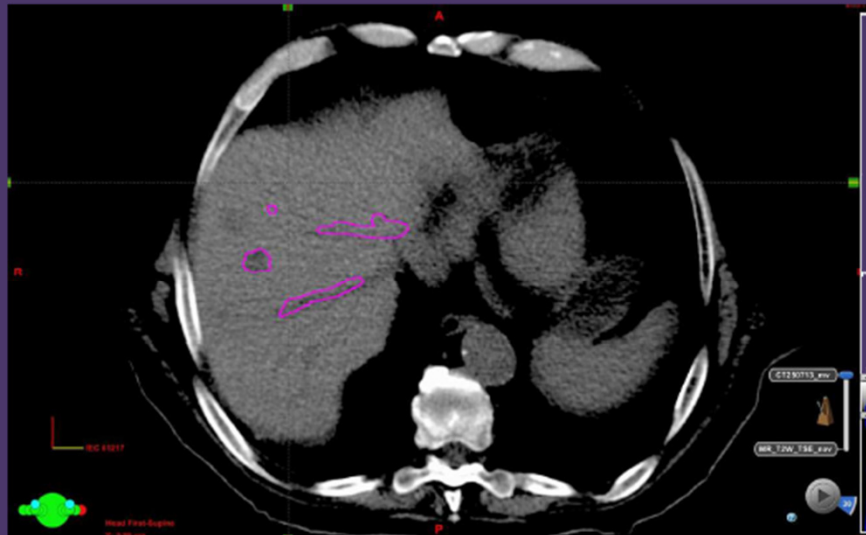
- RAS trial

	Prescribed PTV dose (67% isodose)	Maximum tumor dose (100%)
Dose level A	12.50 Gy	18.75 Gy
Dose level B	13.75 Gy	20.63 Gy
Dose level C	15.00 Gy	22.50 Gy
Dose level D	16.75 Gy	25.00 Gy



SBRT - JETRA

- kot pri pljučih problem žil



SBRT - JETRA

- omejitve pri 3 frakcijah

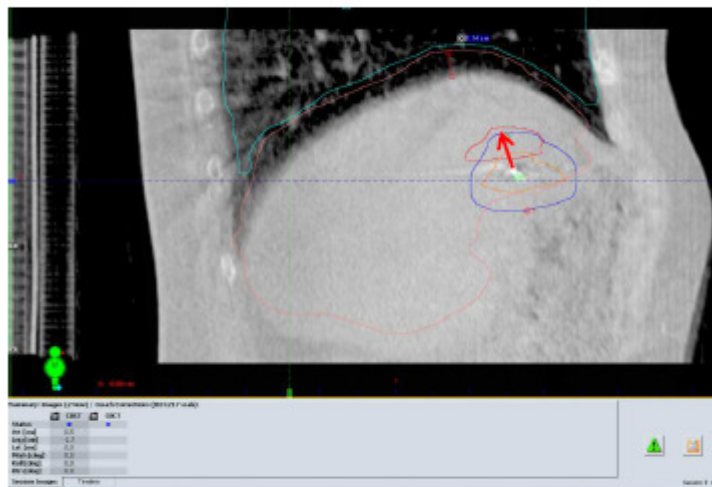
SBRT for liver metastases		Aarhus-Rotterdam
Liver (<15 Gy)	700 CC	
Liver (Dmean)	15 Gy	
Stomach, duodenum or bowel (D4ccm)*	28 Gy	
Ipsilateral kidney (<15 Gy)	35%	
Volume of both kidneys (<15 Gy)	50%	
Spinal cord (Dmax)	18 Gy	
Esophagus (Dmax)	21-27	
Heart (D1cc)	30	

Hoyer et al: IJROBP 82(3): 1047; 2012

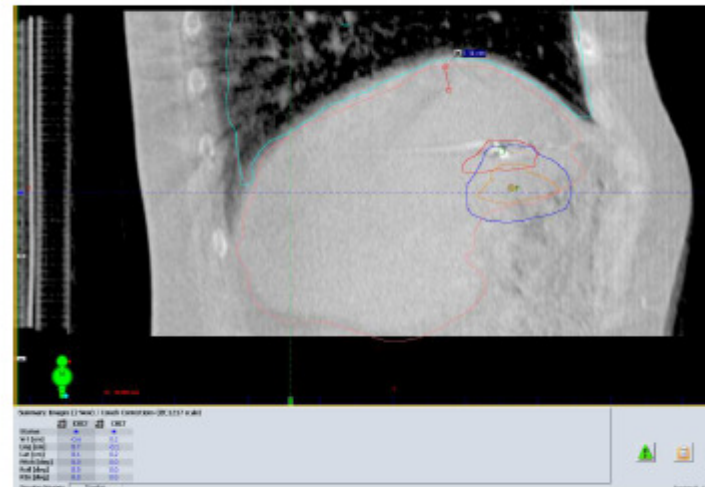
SBRT - JETRA

- lahko kostna fuzija ali pa na markerje

Match on bone



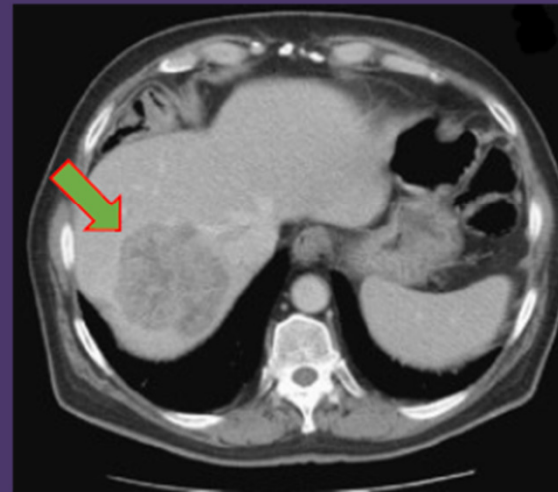
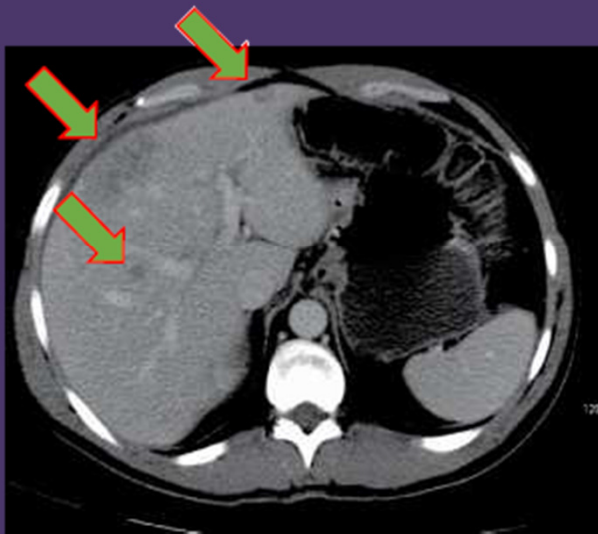
Match on gold markers



Esben Worm, Aarhus University Hospital

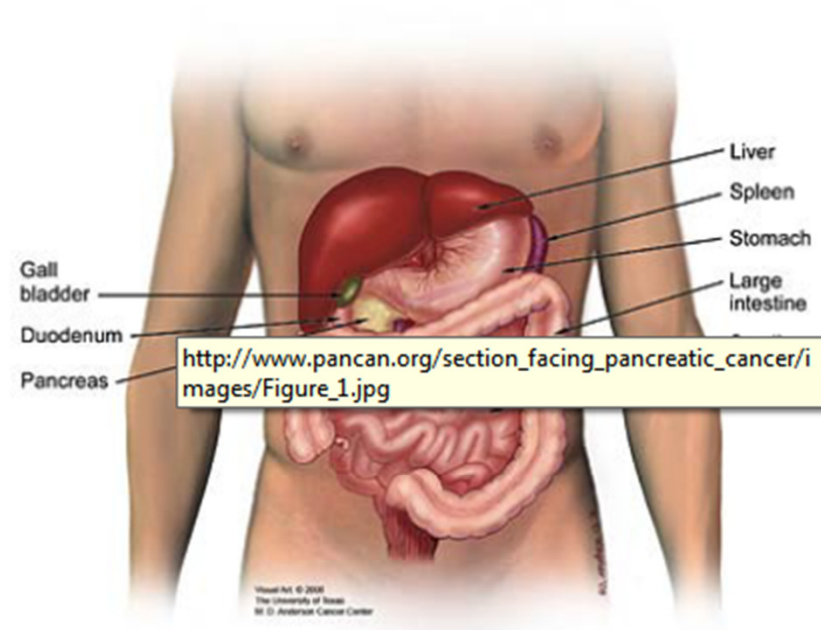
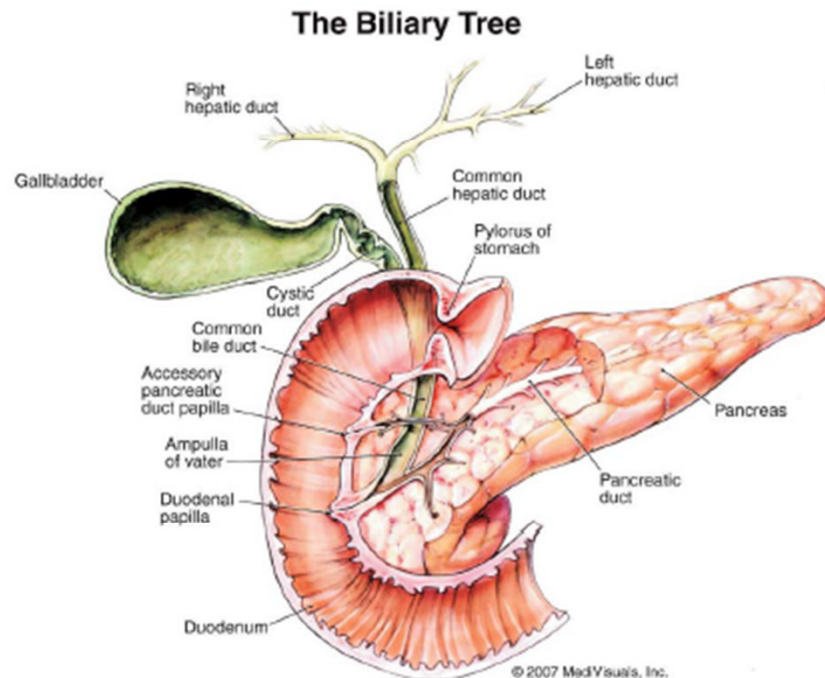
SBRT - JETRA

- izbira bolnikov
 - max 4 meta
 - max 6 cm
 - 1,5 cm od požiralnika/
želodca/dvanajstnika/črevesja
- lahko 1 velika



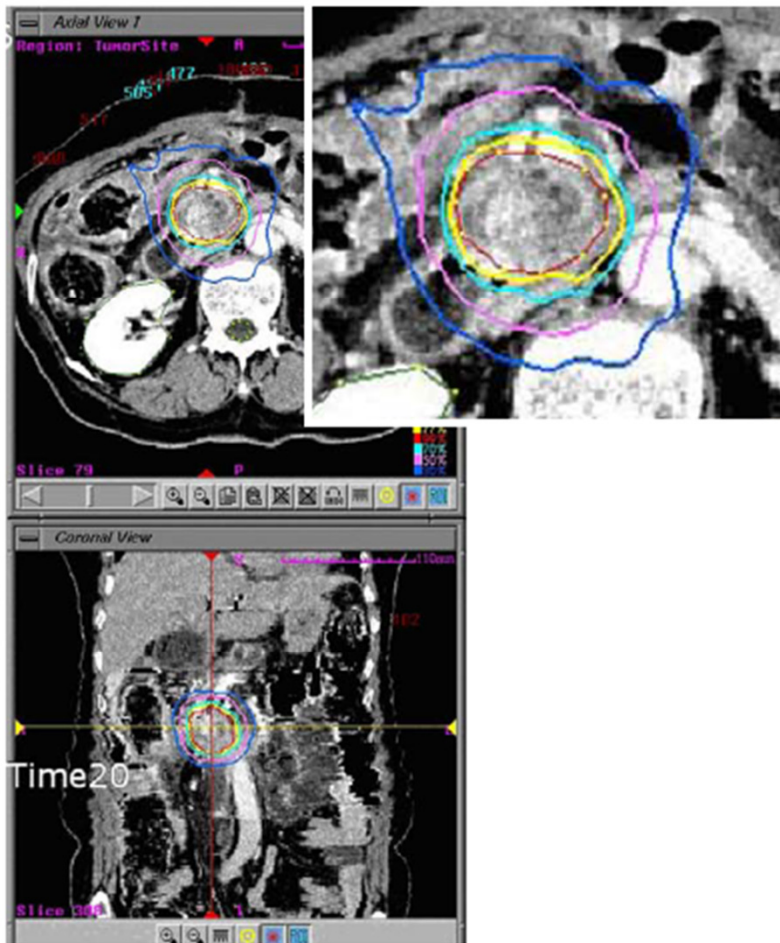
SBRT - PANKREAS

Pancreatic cancer



- Location: head 75% tail 25%
- Critical OARs VERY close to target: duodenum, stomach, small bowel

SBRT - PANKREAS



Published illustration of pancreatic SBRT:

No (obvious) safety margin:

- Imaging for extension of disease?
- Microscopic disease?
- Residual uncertainties?

Despite small (zero) safety margin:

- Full dose to adjacent duodenal wall
- Relevant doses to intestine

SBRT - PANKREAS

SBRT for locally advanced PC

	Study	Patients	Dose	Chemotherapy
Hoyer 2005	Phase II	22	3 x 15Gy	None
Koong 2005	Phase II	17	45Gy CF 1 x 25Gy Boost	5-FU during CF-RT
Schellenberg 2008	Phase II	16	1 x 25Gy	Between Gem
Schellenberg 2011	Phase II	20	1 x 25Gy	Between Gem

- Very small patient numbers
- How to integrate into systemic treatment ?

SBRT - PANKREAS

SBRT for locally advanced PC

	Study	Patients	Median OS	LC
Hoyer 2005	Phase II	22	5.4 months	57% @ 6m
Koong 2005	Phase II	17	8.3 months	16 / 17
Schellenberg 2008	Phase II	16	11.4 months	81%
Schellenberg 2011	Phase II	20	11.8 months	94% @ 1a

- (Very) short overall survival – similar to systemic treatment only
- Interpretation of promising LC considering OS ?

Guckenberger 2015

SBRT - PANKREAS

SBRT for locally advanced PC

	Study	Patients	Toxicity
Hoyer 2005	Phase II	22	5 cases with severe GI tox
Koong 2005	Phase II	17	2/17 acute G3 GI
Schellenberg 2008	Phase II	16	Late: 5x G2 ulcers 1x G3 duodenal stenosis 1x G4 duodenal perforation
Schellenberg 2011	Phase II	20	3x G2 ulcers 1x G4 duodenal perforation

- (Very) high rates of gastrointestinal toxicity DESPITE short FU
- Difficult (impossible) sparing of duodenum

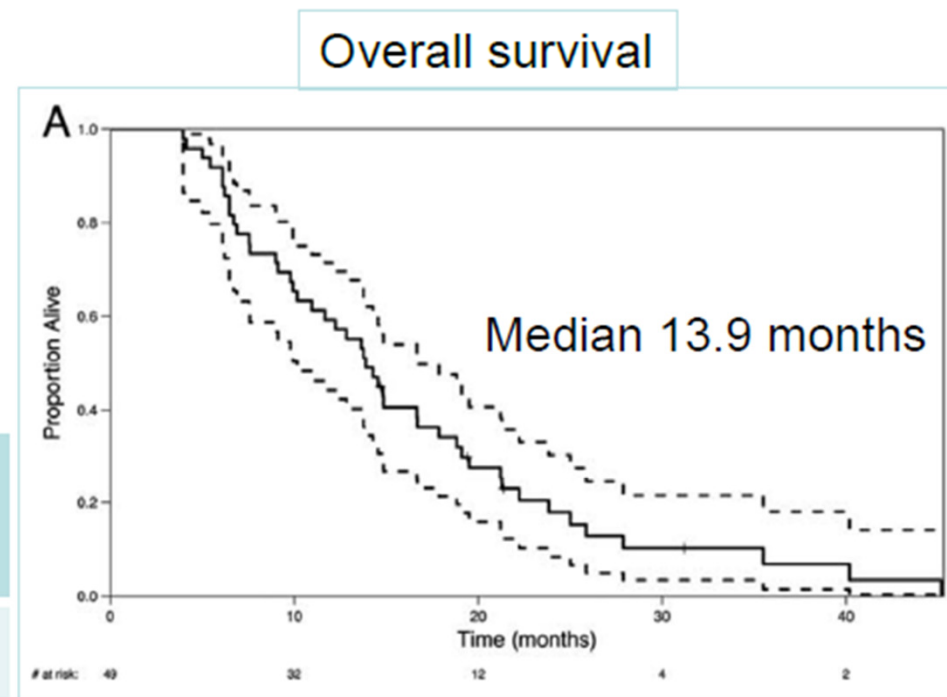
SBRT - PANKREAS

SBRT for locally advanced PC

Herman Cancer 2015

- 49 pat. with locally advanced PC
 - 3 x Gem (1000mg/m²)
 - 1 week break
 - SBRT with 5 x 6.6Gy
- Phase 2 multi-institutional study
- Median FU 14 months

Acute GI Tox G ≥2	Late GI Tox G ≥2
2%	11%

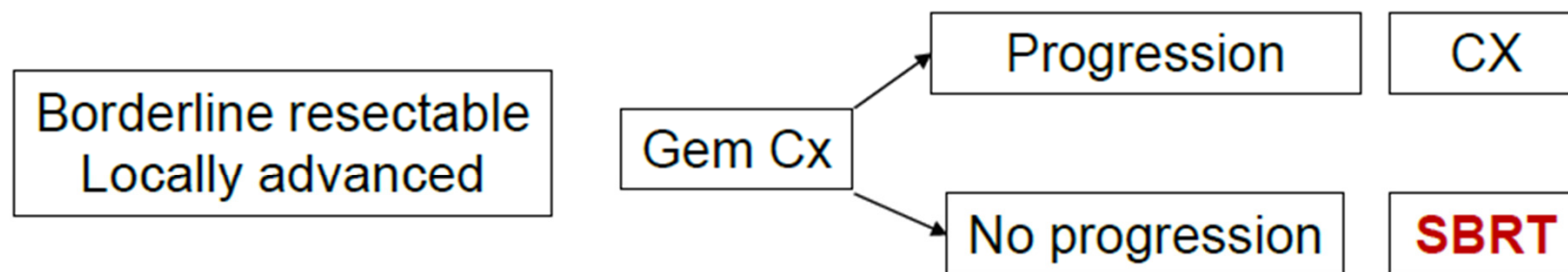


➤ Fractionated SBRT with lower SFD well tolerated

Guckenberger 2015

SBRT - PANKREAS

SBRT to achieve resectability



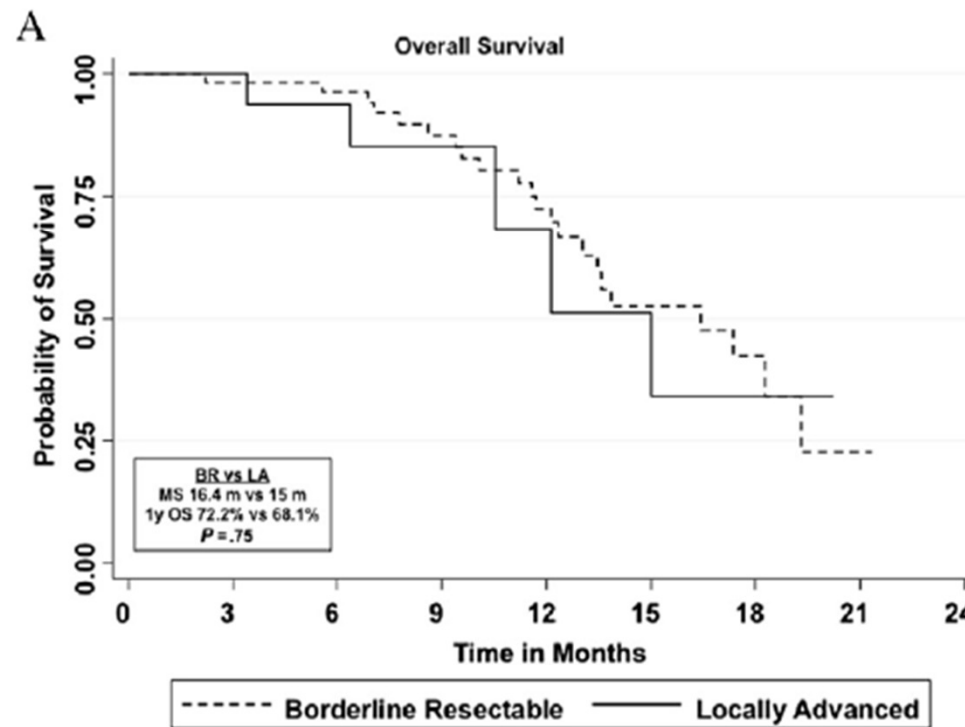
SBRT: 5 x 7Gy to vessle abutting region
5 x 5Gy to remaining tumor

Chuong IJROBP 2013

- N=73 with median FU 10.5 months
- Borderline resectable PC: 31/57 achieved R0 resection
- Locally advanced PC: 0 patient underwent resection
- Late GI grade 3+ toxicity: n=4 (GI bleeding)

SBRT - PANKREAS

SBRT to achieve resectability



Chuong JROBP 2013

Median OS:

- Borderline resectable PC: 16.4 months
- Locally advanced pC: 15 months

SBRT - PANKREAS

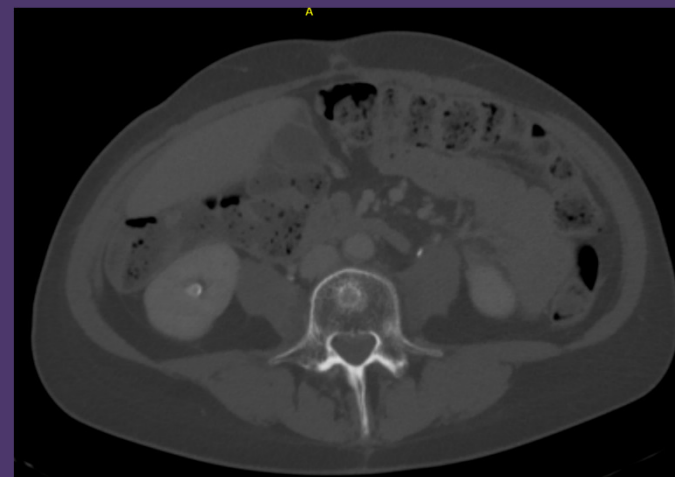
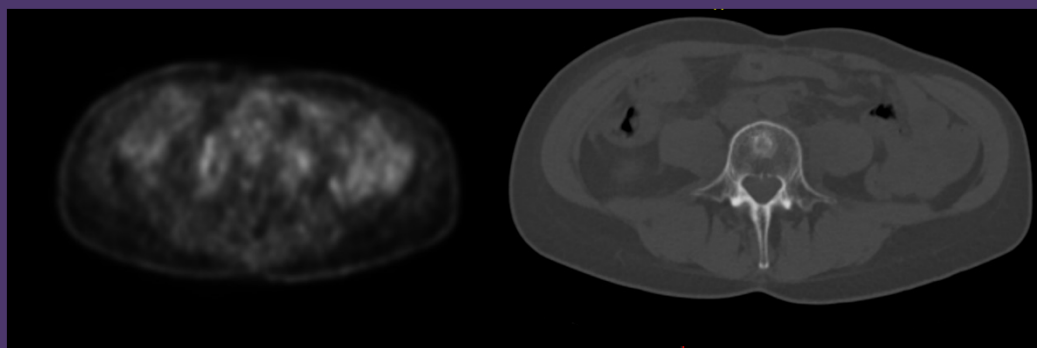
CONCLUSIONS

- Small patient numbers treated in prospective trials
- Local tumor control appears favourable
- Very limited overall survival, similar to Cx only
- High rates of severe GI toxicity

➤ **Should not be practiced outside of prospective trials**

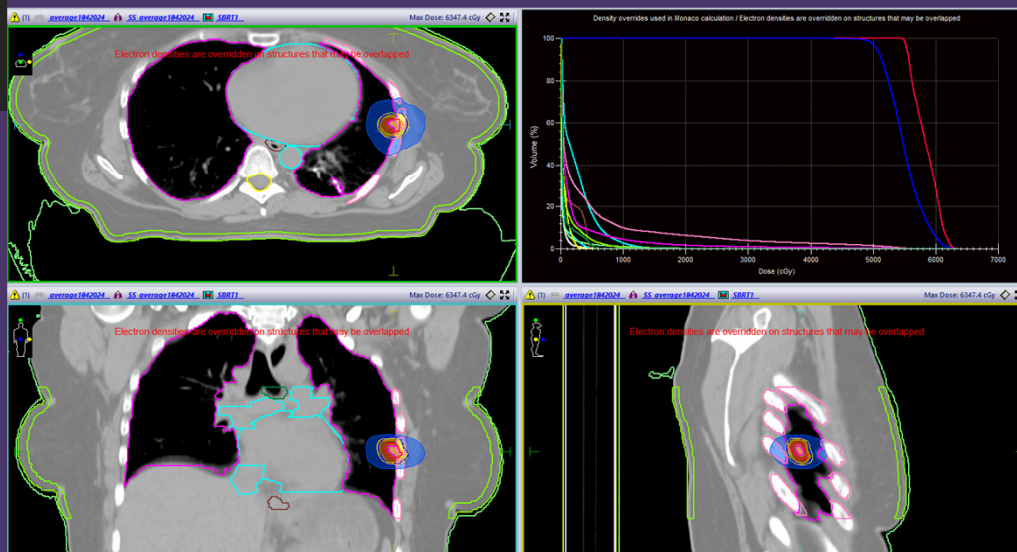
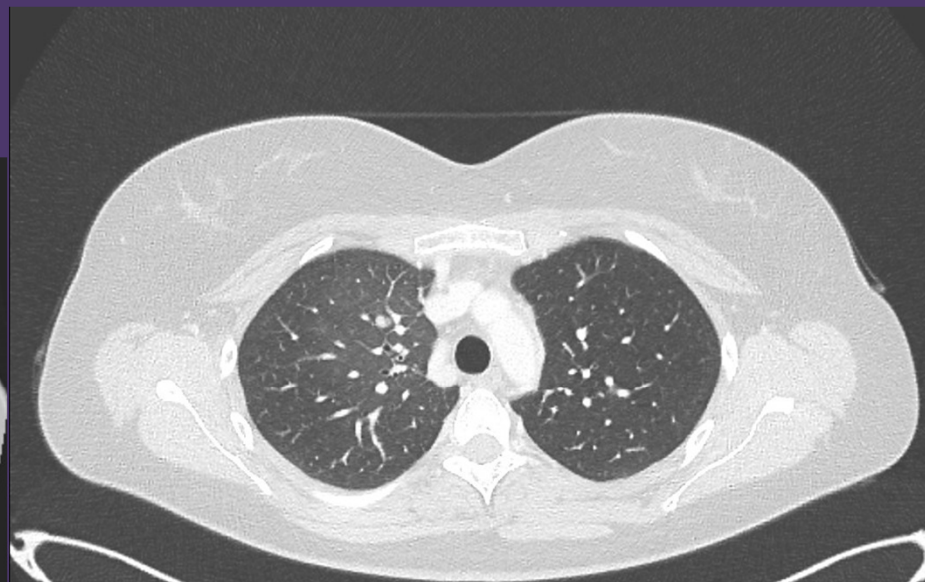
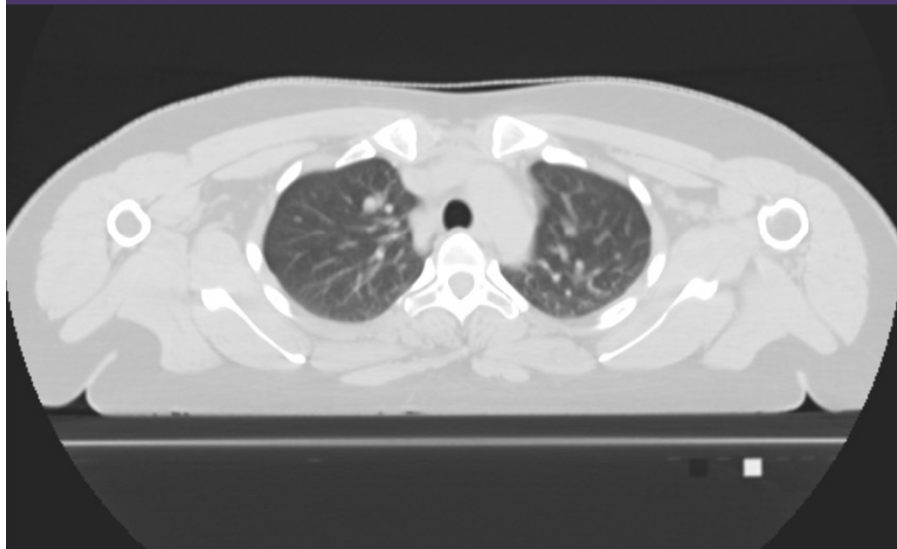
PRIMER HRBTENICA

- Sarkom zasevek L3
- SBRT 22 Gy # 1 fr
- Po letu dni skleroza



PRIMER PLJUČA

- Metastatski PECOM



Specialne tehnike v radioterapiji

Ocsevanje celega telesa (TBI)
(klinični aspekt)

doc. dr. Uroš Smrdel dr. med.

TBI

- Pripravljalni režim za:
 - Presaditev kostnega mozga
 - Presaditev krvnih matičnih celic
- Alternativa mieloablativna kemoterapija

TBI

- Levkemije
 - ALL
 - AML
 - KML
- Limfomi
 - Mb Hodgkin (recidivni ob doseženi remisiji)
 - Limfom plaščnih celic
- Plazmocitom
- Ewingov sarkom (v raziskavah (Burdach et al 1993, Meyers et al 2001))

TBI

- Ne onkološke bolezni
 - Imunske motnje
 - Aplastična anemija
 - Genetske motnje
 - Wiskott Aidrich sindrom
 - Osteopetroza
 - Tar sindrom
 - Fankonijeva anemija

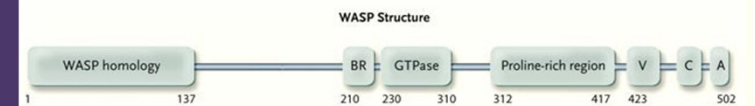
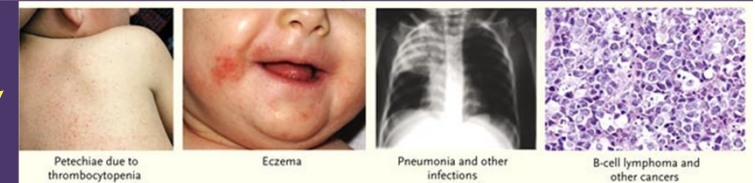
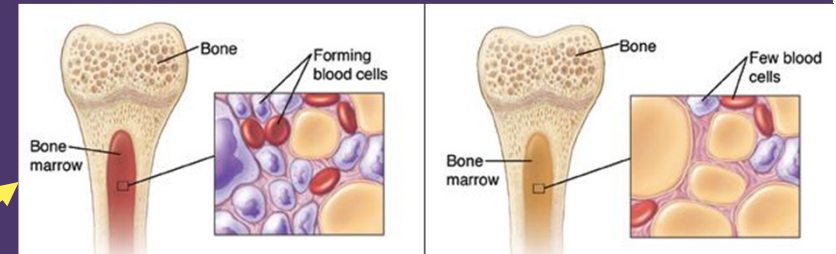


FIGURE 1: X-ray of arm prior to (A) and 6 months after (B) bone marrow transplantation. The high bone density, absent medullary



cavity, and abnormal epiphyseal plates of osteopetrosis have largely resolved following bone marrow transplantation.



TBI

- 4,5 Gy LD 50 brez agresivne terapije
- 10 – 12 Gy frakcionirano

TBI

- Običajno mieloablativna
 - Uniči KM, rezidualne tumorske celice
- Ne – mieloablativna
 - 2 Gy
 - Ne uniči KM
 - Zavre imunski odgovor
 - Graft vs host reakcija

TBI

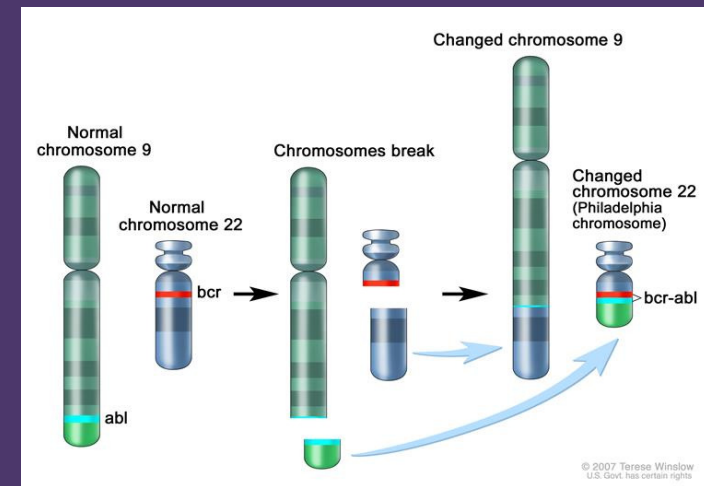
- Donnall Thomas 1956 (nobelova nagrada za medicino 1960)
- Končni stadiji levkemije



Joe DiMaggio, Dr. E. Donnall Thomas in bolnik
Darrell Johnson in LAF sobi

TBI

- Naloge
 - Uničiti KM
 - Zmanjšati tumorsko breme
 - Imunosupresija (limfociti)
 - Fizično naresiti prostor za darovan KM
 - Uničenje celic z genetskimi napakami
(npr Filadelfija kromosom pri kronični mieloični levkemiji)



<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/philadelphia-chromosome>

TBI

- Prednosti pred visokodozno kemoterapijo
 - Ni “zavetišč” – testisi, CŽS
 - Homogen odmerek – neodvisno od prekrvavitve
 - Neodvisno od ledvic in jeter
 - Ni problemov z izločanjem in razstrupljanjem
 - Možnost zaščite in boosta

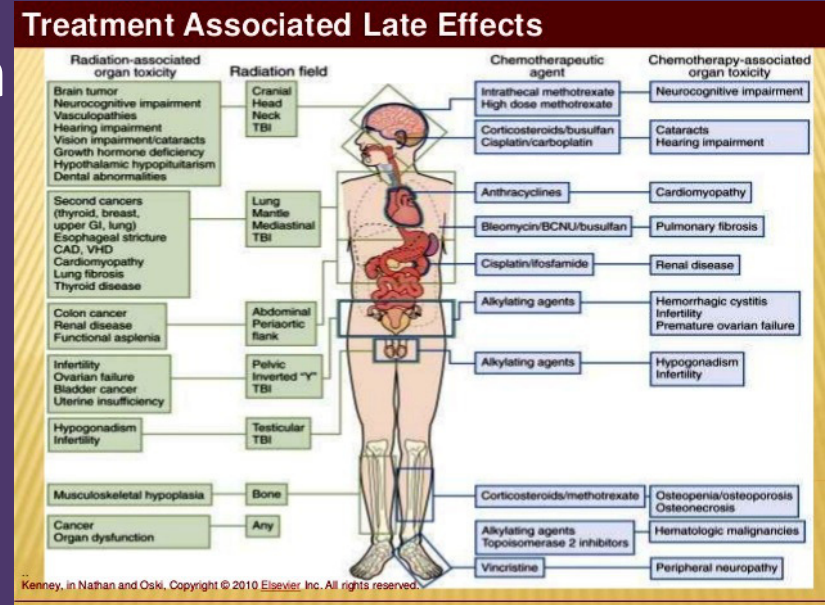
TBI

- Slabosti

- Pozni sopojavi (sterilnost, katarakta, rast, kognicija)

- Posledica obsevanja prizadetih organov, pri rasti tudi kontrolnih organov

- Potreba po kompenzatorjih (odvisno od tehnike)



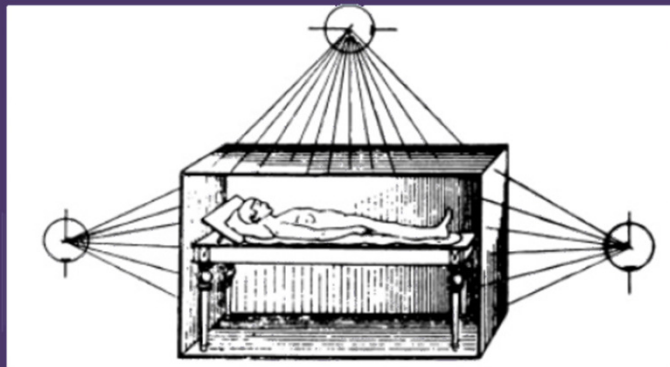
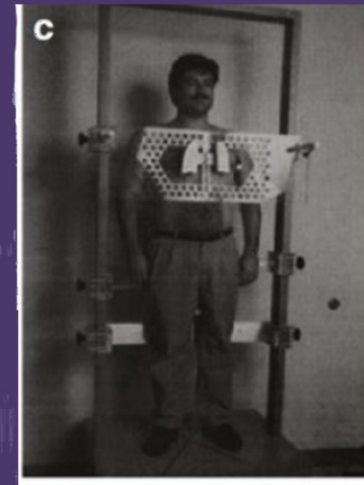
TBI

- Pogoji
 - Anamneza, status
 - Interdisciplinarni tim
 - Presaditev v istem centru
 - Nizko tvegabje za okužbe

TBI

- Tehnika
 - Reproducibilna
 - Pozicioniranje
 - Uniformnost
 - $\pm 10\%$ (zaželjeno 5)

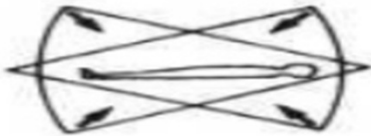
TBI



Sunny BP 2016

TBI

a) Four sources



b) Two horizontal beams



c) Two vertical beams



d) Single source, short SSD



e) Source scans horizontally



f) Patient moves horizontally



g) Head rotation



h) Direct horizontal, long SSD



i) Half body, direct and oblique fields

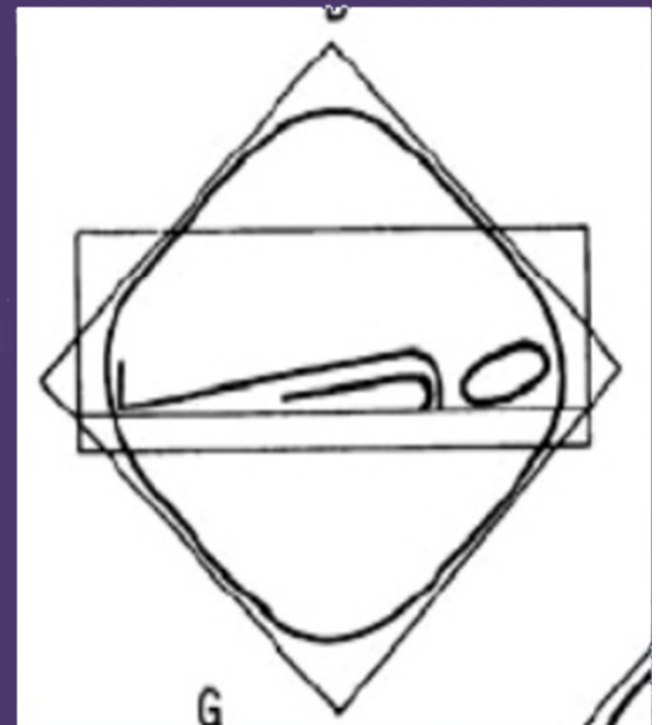


j) Half body, adjacent direct fields



TBI

- Bilateralna TBI (Khan et al)
 - Sede ali leže = udobje
 - Neenakomerna debelina = kompenzatorji
 - Distanca



TBI

- AP – PA
 - Bolj homogena
 - Lažje zaščite

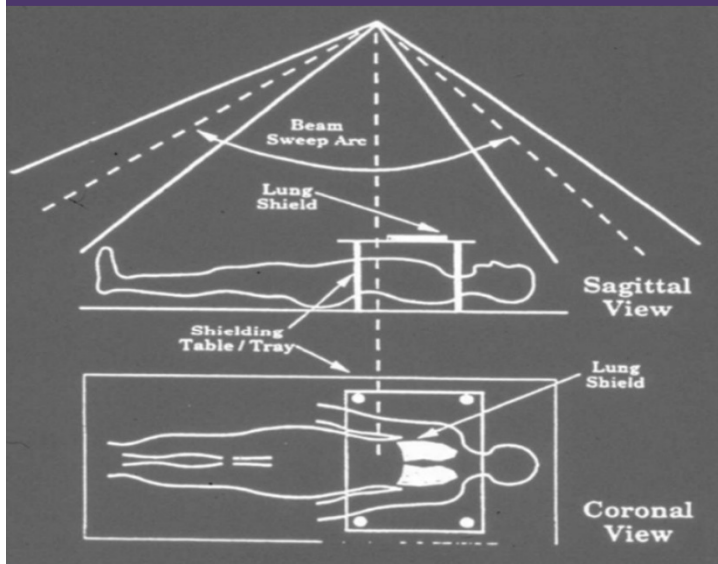
Grille S 2017



TBI

- Pometajoč žarek

Corns R et al 2000



- Mc Gill



TBI

- Potujoča miza
- Dolžina
- Lega
- Kompenzatorji
če predolg

Wilder B 2006



TBI

- Tarčni volumen
 - Vse maligne celice
 - Ves KM
- = celo telo vključno z kožo

TBI

- Odmerki
 - Visokodozni 13,6 Gy # 6 fr, 3 dni
 - Standardni 12 Gy # 6 fr, 3 dni
 - Mini 2 Gy # 1 fr
- OAR
 - Pljuča 10 Gy limitirajoča toksičnost
 - hipofiza, leče, rastni hrustanec, srce, ledvica
- Referenčna točka
 - Sredina telesa v višini popka
 - Lahko še dodatne

TBI

- Ker odmerek na površini pri 6MV ni 100%



TBI

- Zaradi zaščite pljuč
 - Torakalna stena nižji odmerek
 - Lahko dodatek z elektroni
 - (ne vedno)

TBI

- Zapleti – akutni
 - Slabost
 - Glavobol
 - Utrujenost
 - Suhe oči
 - Ezofagitis
 - Inapetenca
 - Eritem
 - Mukozitis
 - Driska
 - Vročina

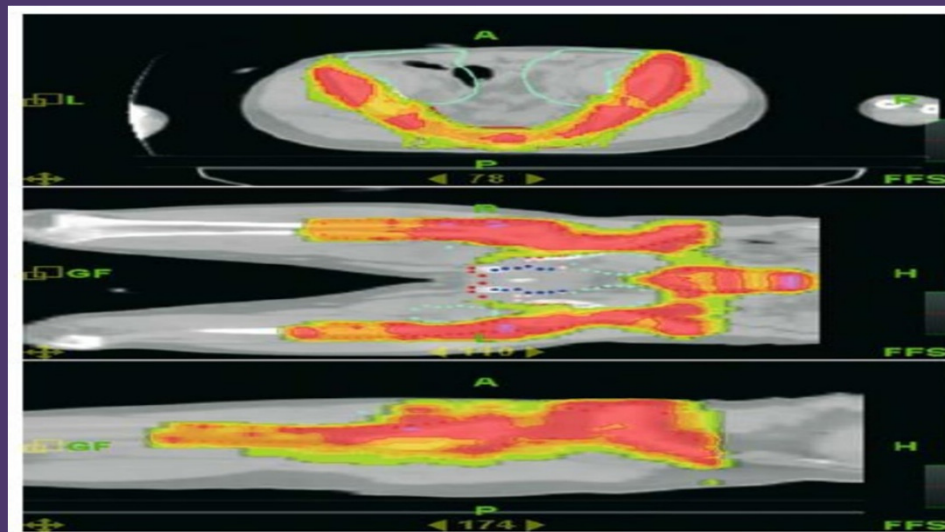
TBI

- Zapleti – pozni
 - Očesni
 - Slinovke, zobje
 - Pnevmonitis/fibroza
 - Jetra
 - Ledvica
 - Otroci – rast
 - Sterilnost
 - Sekundarni tumorji

<i>Toxicity</i>	<i>Methods of Risk Reduction and Intervention</i>
<i>Acute</i>	
Parotitis	Generally subsides in 1–2 days without intervention
Nausea/vomiting	Use of low dose-rate TBI Antiemetics 5HT ₃ receptor agonists (ondansetron, granisetron) Dopamine agonists (metoclopramide, prochlorperazine) NK1 receptor antagonists (aprepitant) H ₁ histamine receptor antagonists (diphenhydramine, meclizine) Benzodiazepines (midazolam, lorazepam) Steroids (dexamethazone)
<i>Sub-acute</i>	
Interstitial pneumonitis	Use of low-dose rate TBI Use of lung blocks Fractionation Avoidance of chemotherapies associated with lung toxicity Avoidance of infection, notably CMV
<i>Late and long-term</i>	
Venooclusive disease of the liver	Avoidance of concurrent use of drugs that are sources of toxic metabolites and/or modify the endothelium: Myeloablative drugs (BU, BCNU, MTX) Immunosuppressants (sirolimus, cyclosporine) Antimicrobials (ketoconazole, amphotericin B, vancomycin, acyclovir) Avoidance of BMT in the setting of active hepatitis or cirrhosis Close monitoring of fluid: sodium balance post transplant Role of heparin prophylaxis remains unclear
Cataract formation	Fractionation Eye shielding
Gonadal failure	Pretransplant sperm/oocyte banking or harvest Hormone replacement therapy if indicated
Renal toxicity/chronic kidney disease	Monitoring of blood urea nitrogen, creatinine, and GFR Treatment of post transplant chronic disease if indicated
Osteopenia/porosis	Bone density monitoring and treatment, if indicated
Xerostomia	Use of artificial salivary products Monitoring of nutrition and impact on quality of life
Dental complications	Frequent professional cleaning and care Addressing of sequelae that may impact self-care, including xerostomia, mucosal pain, and/or trismus
Endocrine dysfunction	Comprehensive endocrine monitoring with hormone replacement as indicated
Short stature ^a	Monitoring of growth hormone level during pubertal growth
Cardiometabolic traits	Hypertension screening, treatment if indicated Dyslipidemia screening, treatment if indicated Close monitoring of wt, body mass index and adipose distribution Screening for insulin resistance/diabetes mellitus, treatment if indicated
Second malignancy	Age-appropriate cancer screening Yearly pap smear Colonoscopy and/or fecal occult blood testing Yearly mammogram with consideration of screening breast MRI Close monitoring of patient-reported symptoms

TBI

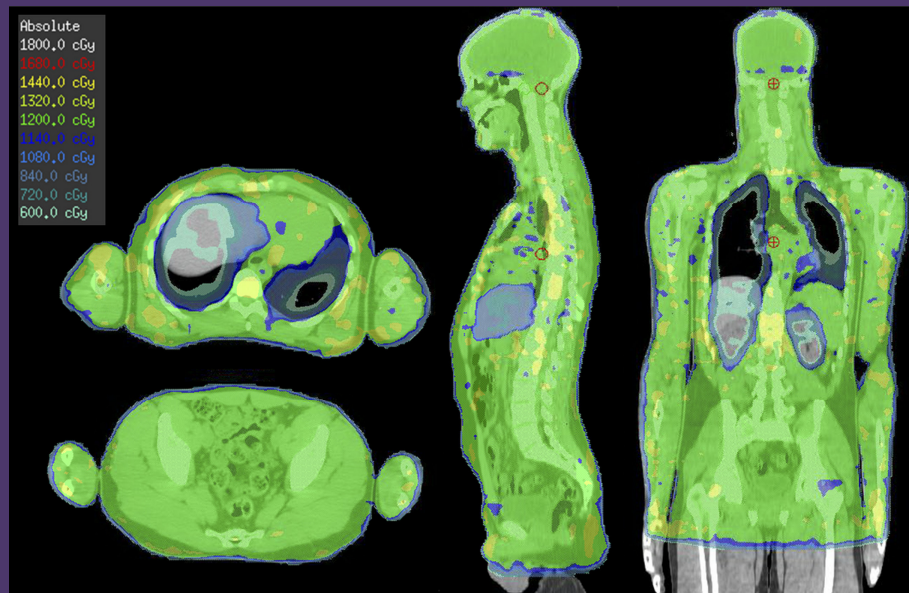
- Tarčna TBI
 - TMI – kosti pri plazmocitomu
 - TMLI – KM + limfatični sistem, jetra, možgnani in testisi pri nekaterih limfomih
- Tomoterapija



Dusenbery KE 2011

TBI

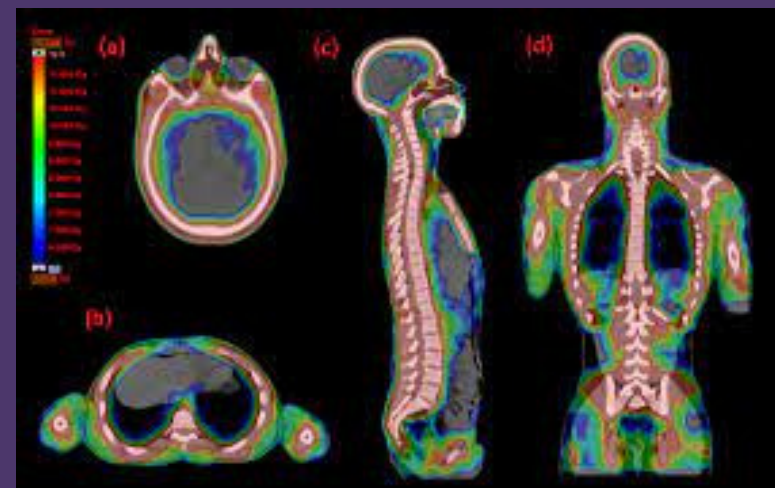
- VMAT TBI



Symons et al 2018

- VMAT TMI

Aydogan 2011



TBI

- Protoni
- Radioimunoterapija

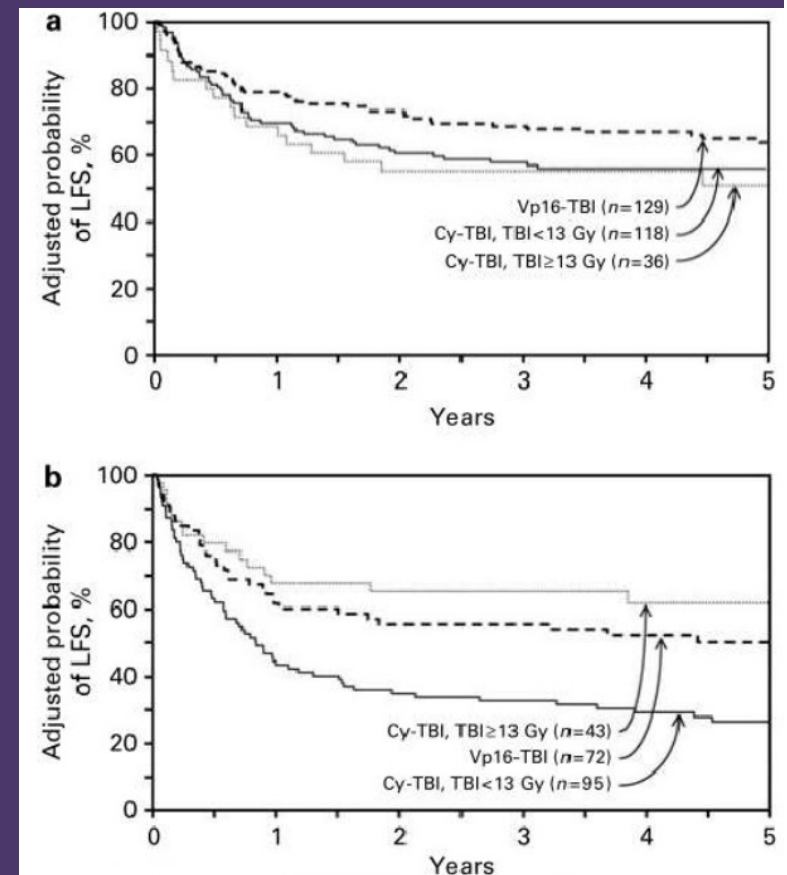
<i>Method</i>	<i>Description</i>	<i>Extent of current study</i>	<i>Potential benefits</i>
Helical tomotherapy	Rotating beam source with multileaf collimator moving in spiral pattern relative to patient	Dosimetric studies demonstrating reduction in median organ dose DVH analysis showing potential for safe dose escalation to marrow and other regions Treatment delivered to one patient with successful engraftment and limited toxicity	Reduction of dose to normal tissues Safe escalation of dose to BM, LN and spleen Delivery of myeloablative doses to broader range of patients through limiting toxicity
Proton radiotherapy	Heavy, charged particles that stop in tissue, producing Bragg-peak. The majority of radiation is delivered within the Bragg-peak region, and may be delivered to the target vol with minimal exit dose	Studied and applied clinically for delivery of CSI Allows reduction of dose to most vital organs during CSI Studies in TBI have not been published	Reduction of dose to normal vital organs through elimination of exit dose Specific dose deposition in the BM, LN and spleen.
Radioimmunotherapy	Radionucleotides conjugated to antibodies that recognize specific cell-surface Ags allows delivery of radiation to specific cell-types	Agents recognizing CD20 clinically available Used widely to treat B-cell NHL outside of BMT setting Phase II data demonstrating efficacy as part of RIC regimens during BMT for NHL Laboratory-based expansion of cell-surface targeting is currently underway.	An agent targeted to BM could allow delivery of entire radiation dose to marrow alone All cells not expressing a specific surface marker could then be spared, allowing extreme 'conformality' of radiation delivery.

Hill-Kayse CE et al 2010

TBI

- Kljub že dolgemu iskanju alternative TBI še vedno najpogosteje uporabljana
- Mieloablacija z KT
 - Manj poznih sopojavov
 - Več relapsov
 - Preživetje je enako

Biol Blood Marrow transplant 2006; 12: 438-53



Specialne tehnike v radioterapiji

Obsevanje s protoni in lahkimi ioni

klinični aspekt

doc. dr. Uroš Smrdel dr. med.

TIPI SEVANJA

ELEKTROMAGNETNO SEVANJE

NEIONIZIRAJOČE

mikrovalovi
radijsko
IR
vidna svetloba
UV

IONIZIRAJOČE (INDIREKTNO)

X
gama

DELCI

NABITI

α
 β
protoni
lahki ioni

NENABITI

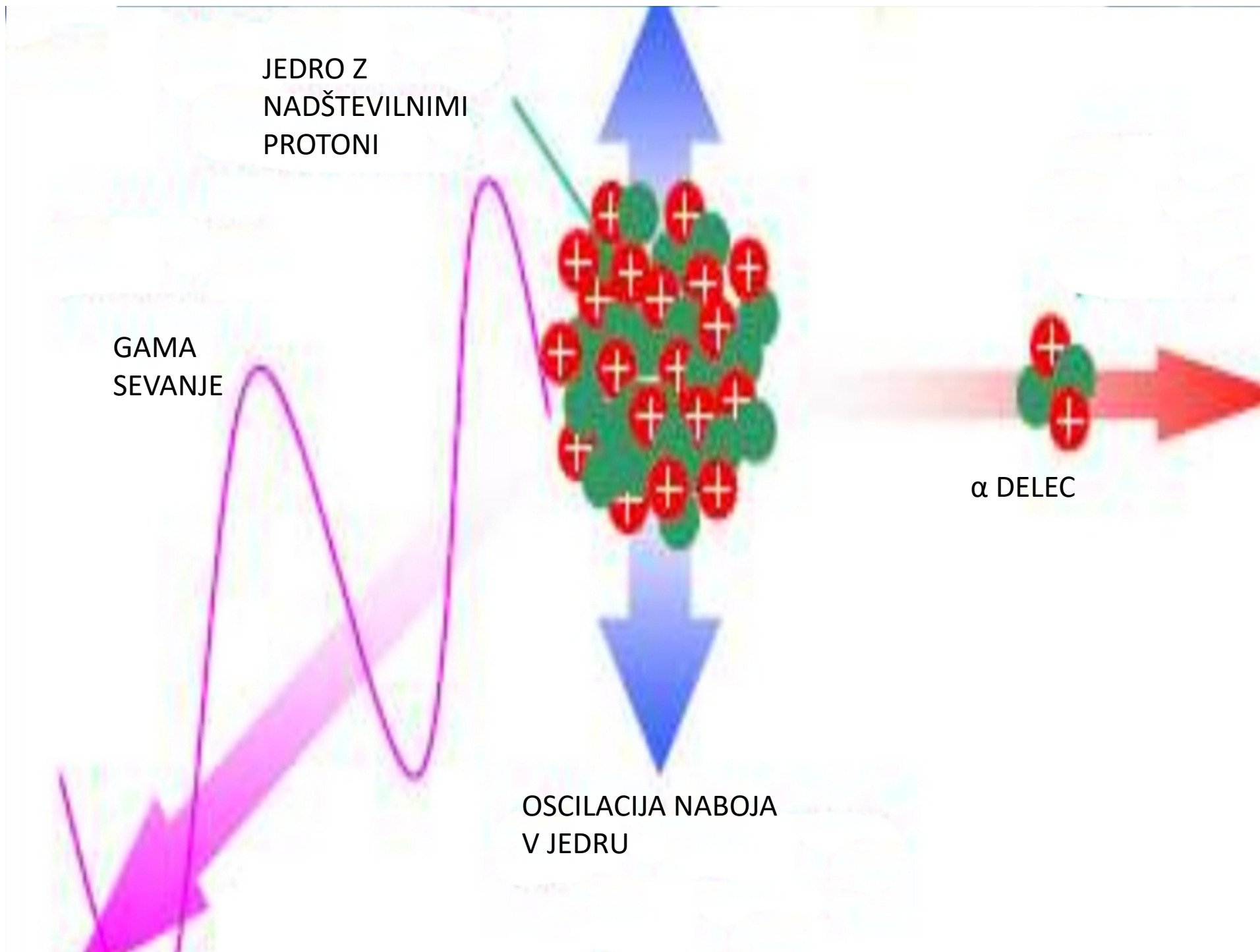
nevtroni

JEDRO Z
NADŠTEVILNIMI
PROTONI

GAMA
SEVANJE

OSCILACIJA NABOJA
V JEDRU

α DELEC



ZGODOVINA

- Robert Wilson 1946 – protoni bi se lahko uporabljali v terapiji
 - maksimalna doza znotraj tumorja
 - znižanje doze na kritičnih organih



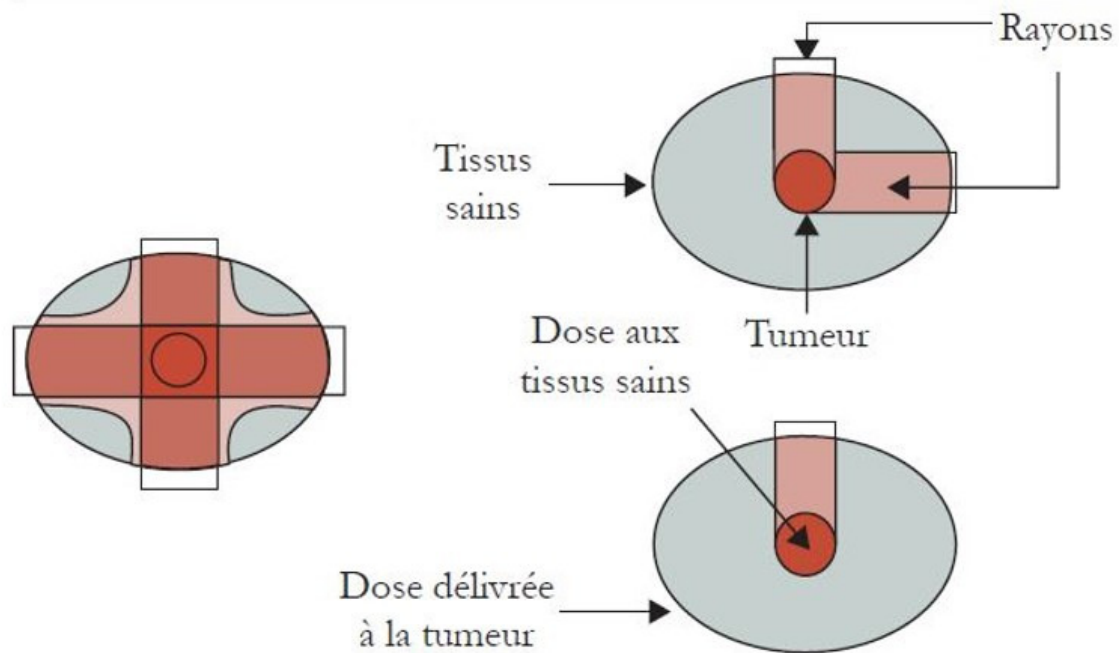
ZAKAJ?

- stabilen pozitivno nabit delec
- 1800 x masa elektrona
- malo sipanja na poti skozi tkivo
- ravna pot
- interakcije so drugačne

	FOTONI	PROTONI	OGLJIK
LET	Nizek	Nizek (?)	Visok
RBE	1	1,1 (-2?)	2-3
Poškodba DNK	Posredna	Posredna	Neposredna
Penumbra 80-20	Do globine prbl. 10-15 cm ožja pri protonih, nato širša		Ozka
		Odvisna od globine, zračne vrzeli, tehnike (aktivna / pasivna)	
Proizvodnja	Linearni pospeševalnik	Ciklotron / Sinhrotron	Sinhrotron
Čas proizvodnje	Kratek	Kratek / dolg	Dolg (EU / JP)

PHOTONS X

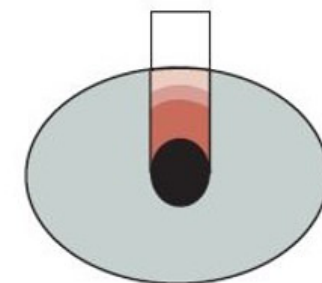
Efficacité biologique relative EBR = 1



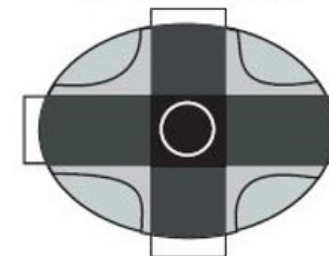
PROTONS

IONS CARBONE

EBR > 1



NEUTRONS



INTERAKCIJA S SNOVJO

- Coulomb interactions with atomic electrons .

Electronic (ionization ,excitation)



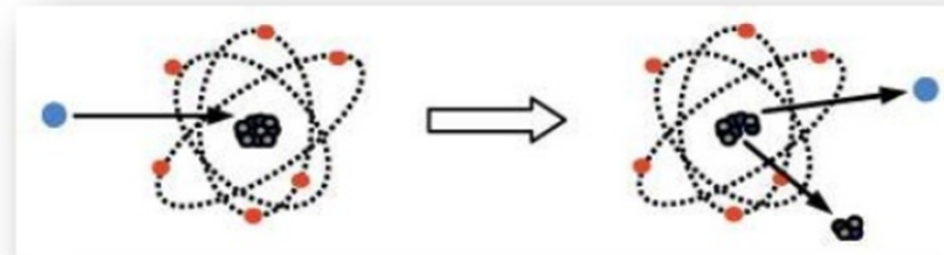
- Coulomb interactions with atomic nuclei .

“multiple Coulomb scattering.”



- Nuclear interactions with atomic nuclei .

- Elastic nuclear collision
- Non elastic nuclear collision



INTERAKCIJA S SNOVJO

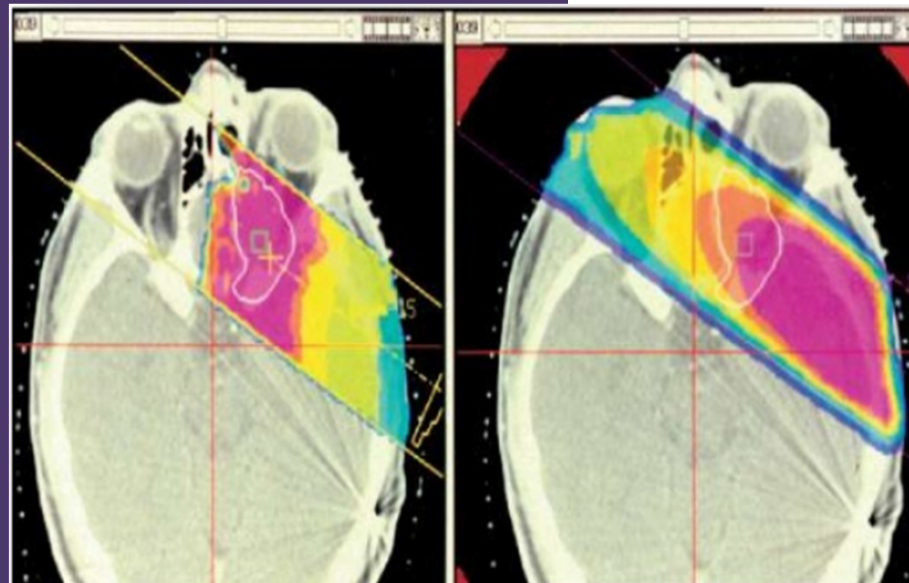
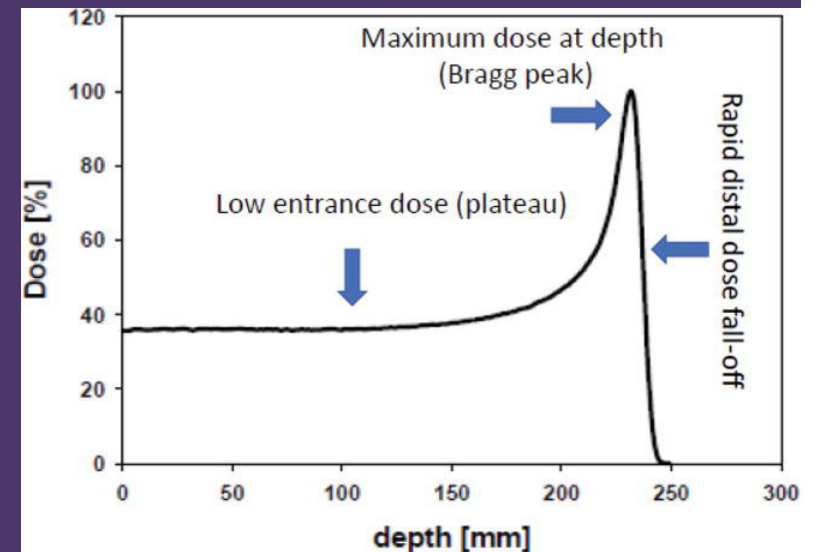
- kot posledica teh interakcij

— DRUGAČNA RAZPOREDITEV DOZE

RAZPOREDITEV DOZE

- nizka vstopna doza
- maksimalna doza v Braggovem vrhu
- za njim hiter padec doze

Hazem R 2023



Goitein M 2010

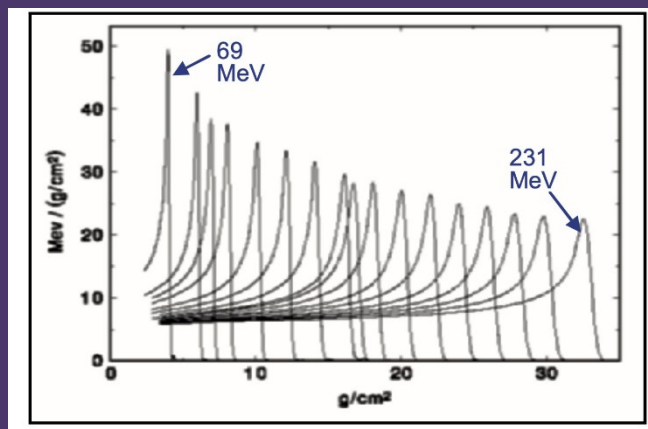
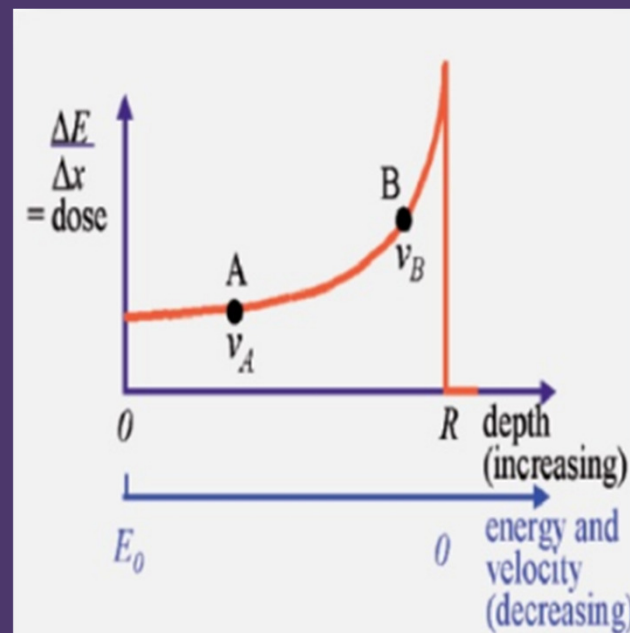
BRAGGOV VRH

<https://www.slideshare.net/slideshow/proton-therapy/11802130#21>

- Visok linearni prenos energije

$$\frac{dE}{dx} \propto \frac{1}{v^2} \left(\frac{Z}{A} \right) Z^2$$

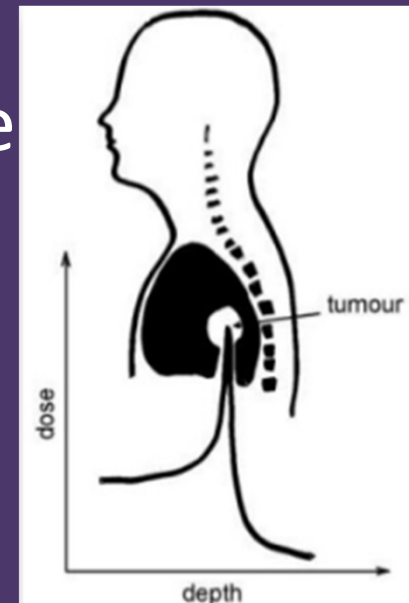
- Bethe Blokova formula
- Braggo vrh je odvisen od energije



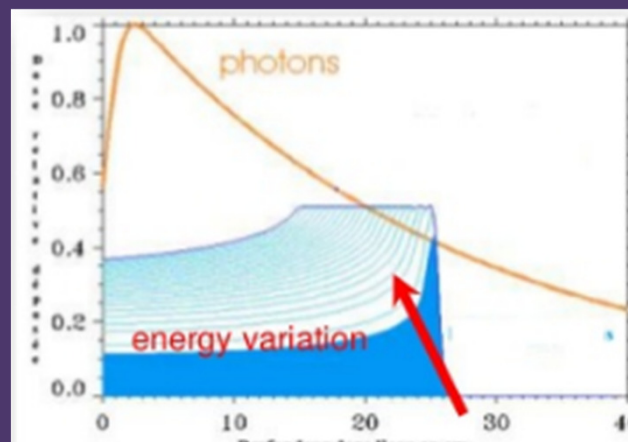
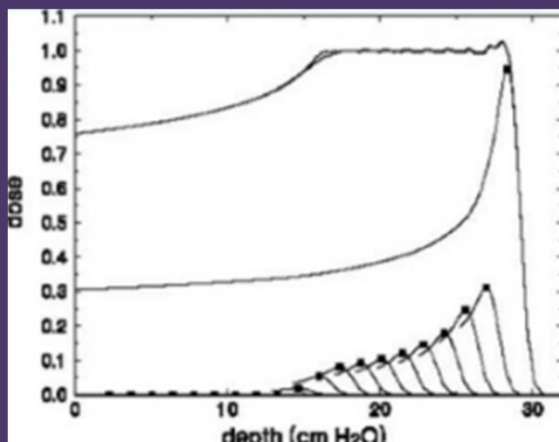
<https://geant4-forum.web.cern.ch/t/testem7-bragg-peak-incorrect-for-high-energy-particles/11999>

BRAGGOV VRH

- ne moremo dobiti uniformne doze ker je preozek
- zato raztegnitev
- številni žarkovni snopi z različno energijo
- energijo



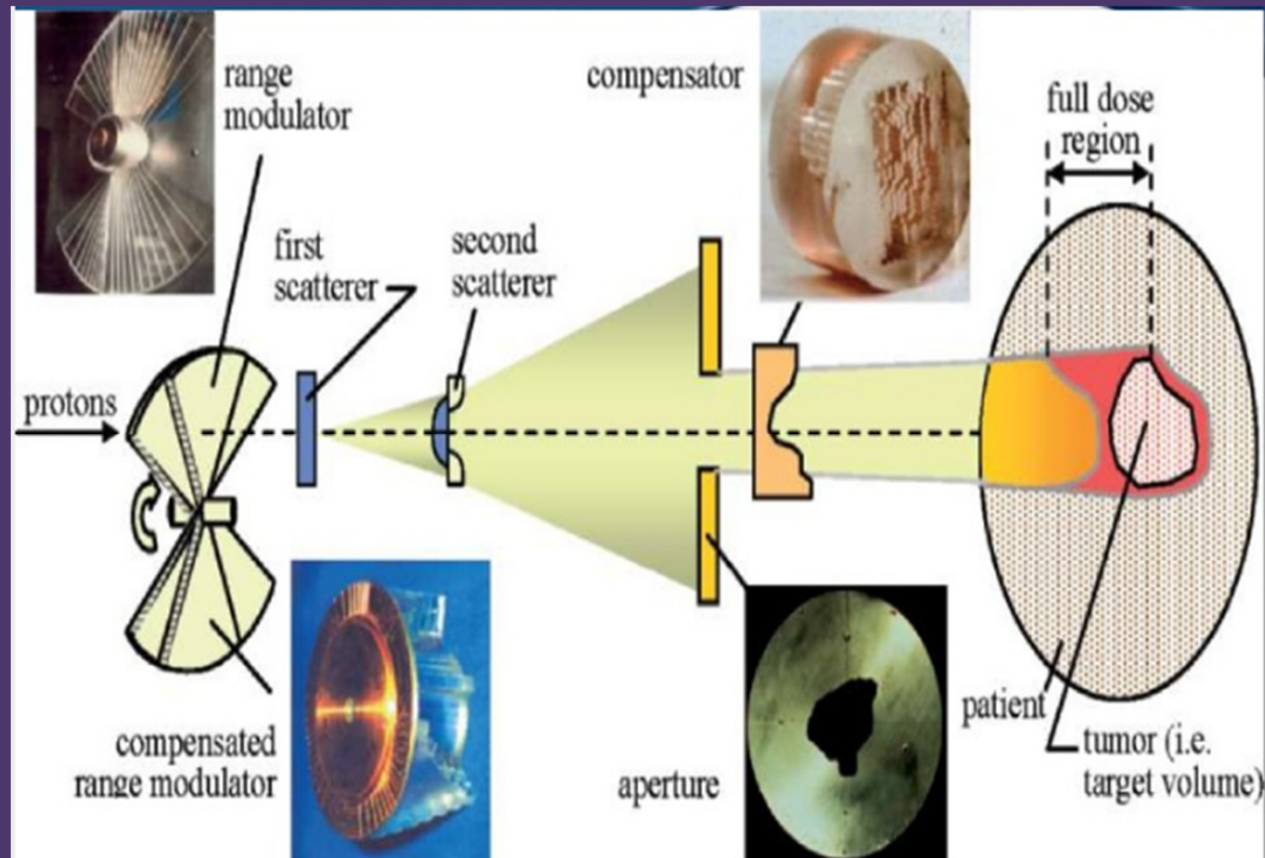
Dromey B 2019



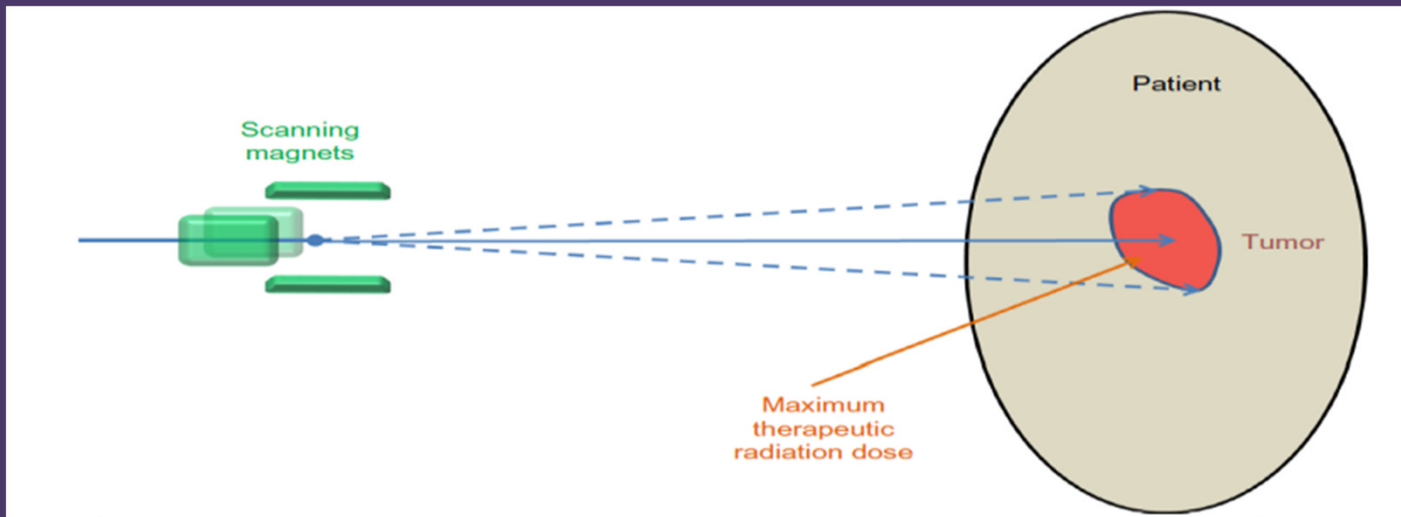
DOSEGANJE RAZTEGNITVE

- PASIVNI SCATTERING
- „SCANED BEAM“

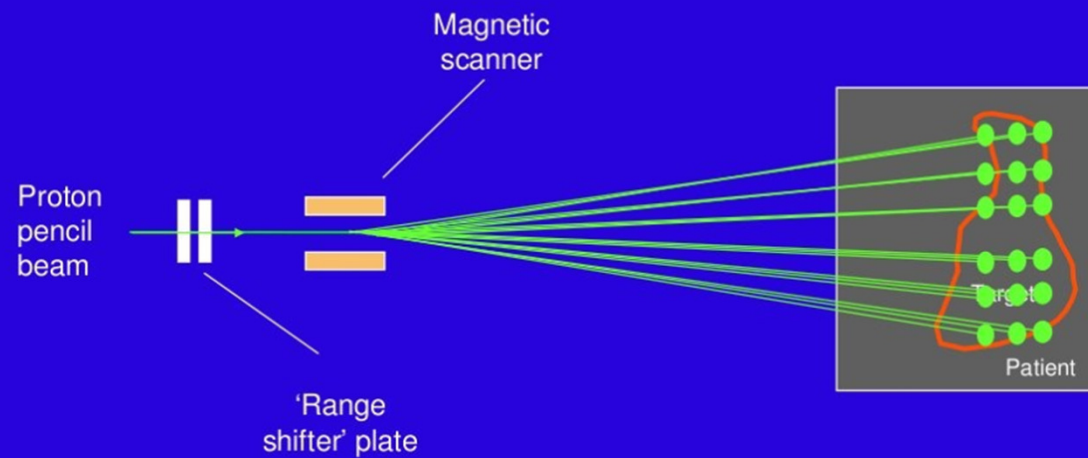
PASIVNI SCATTERING



„SCANED BEAM“



Putri WA et al 2023

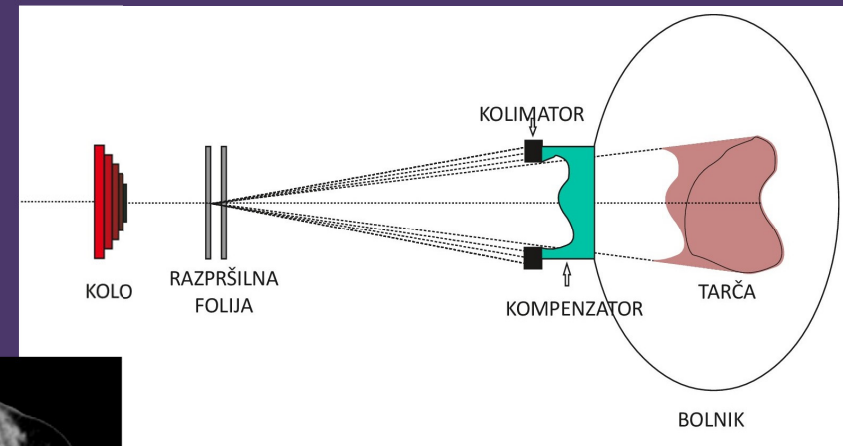
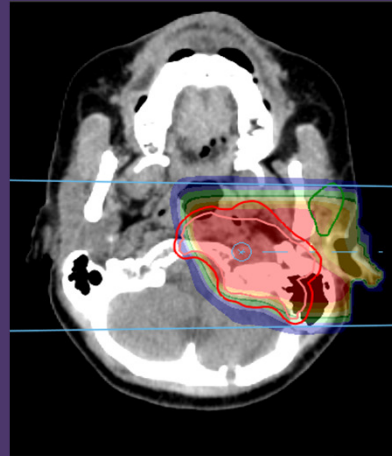


Böhlen T 2009

Pasivna in aktivna tehnika

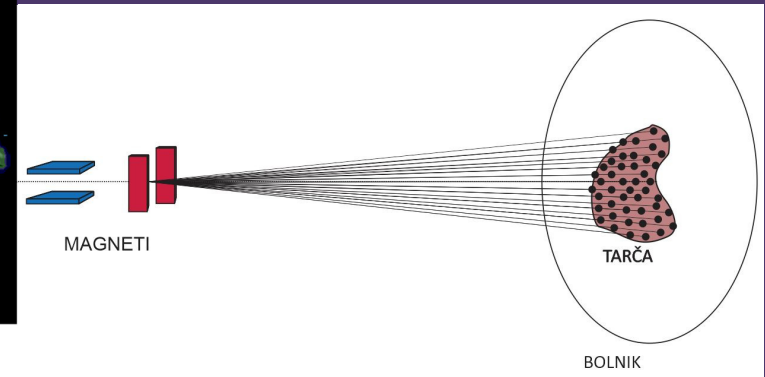
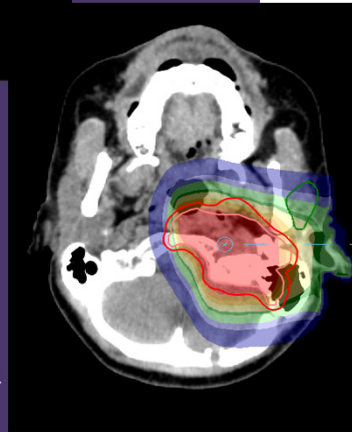
● PASIVNA TEHNIKA

- Ožja penumbra
- Robustnejša
- Hitrejša



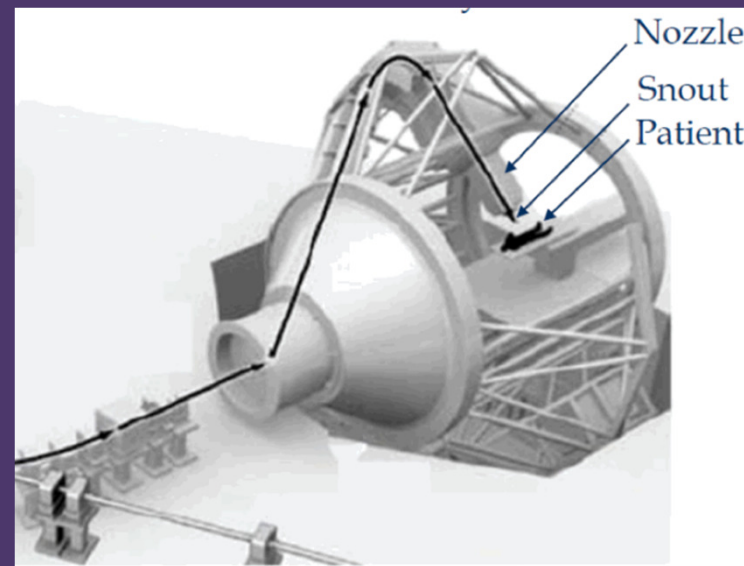
● AKTIVNA TEHNIKA

- Ugodnejša dozna porazdelitev
- Manj pasivnih elementov
 - Manj nevtronov
 - Ni potreba individualna izdelava
- Manj polj



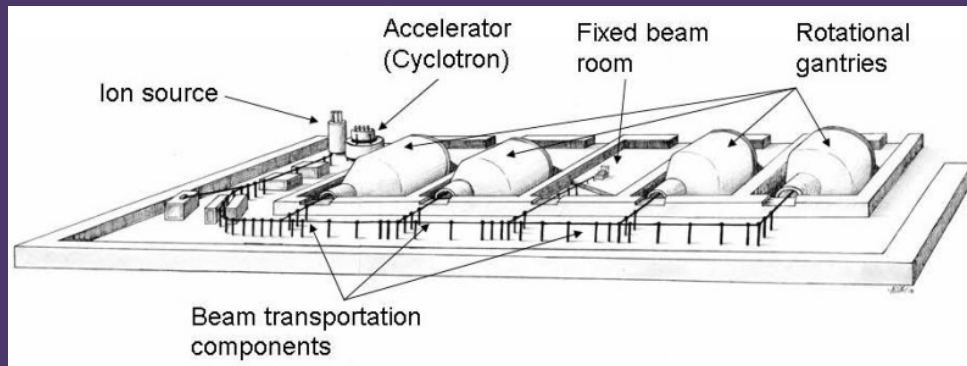
KOMPONENTE

- pospeševalnik
- transportni sistem
- bunker
- „gantry“
- miza



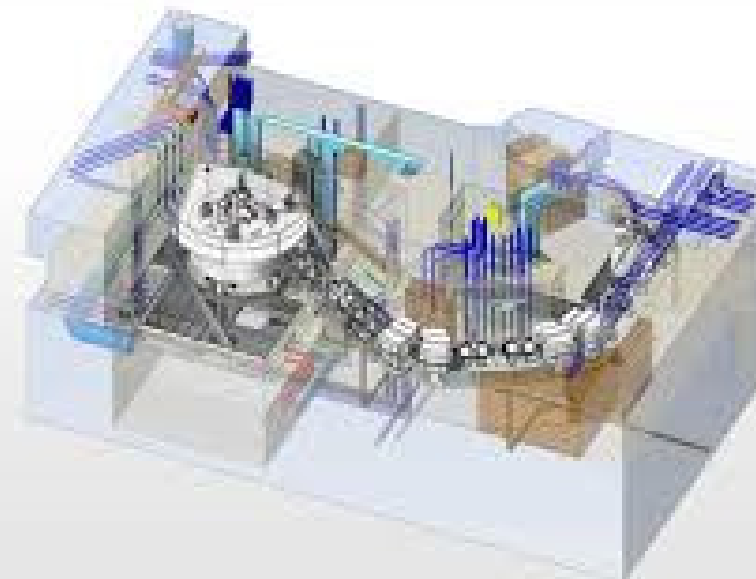
Dürr H 2019





Trikalinos TA 2009

<https://www.arup.com/projects/the-christie-proton-beam-therapy-centre> (2024)



RBE

- relativna biološka učinkovitost
- protoni imajo enako kot fotoni
- razlika je fizikalnih lastnostih in ne v biološkem učinku
- učinkovitost se povečuje, ko se povečuje LET (na skrajnem dometu)

- Photon therapy

the interactions are **stochastic** .
they not easy to control .

At point of entrance,

It receive large amount of dose.

As they reached the tumor,

Continue to pass through tissue

Used for treat superficial tumors.

Proton therapy

they are **deterministic** events .
They easier to control .

It receive very small dose .

a sharp burst of energy released
at tumor and none beyond it.

ideal for tumors in or near
critical structures (brain, heart,
eye) pediatric cancers.

	FOTONI	HADRONI	
Razporeditev doze	Konformna	Konformna	
Doza v zdravih organih	Večja	Manjša	Eskalacija doze Redukcija doze
Čas obsevanja	Krajši	Daljši	Jakost žarka Število plasti/polj
Cena	Nizka	Visoka	Padajo
Velikost naprave	1 soba	Večja (pospeševalnik)	Padajo
Robustnost	Visoka	Anatomske spremembe Domet delcev RBE	Robustna optimizacija Redne slikovne kontrole
Velikost polja	Večje (40 x 40 cm)	Manjše (30 x 40 cm)	Krpanje polj
Omejitve		Fiksna linija (ogljik)	Alternativna imobilizacija, napotitev v drugi center
Sekundarno sevanje	Nad 10 MV	Vedno prisotno (nevtroni)	Veliko nižje pri aktivni tehniki
Izocentrično obsevanje	DA	NE (protoni) DA (ogljik)	Modeliranje v planirnem sistemu

KLINIČNA RABA

- znižanje skupne doze v normalnih tkivih
- zvišanje doze v tumorju
- ščitenje organov v bližini (oči, možgansko deblo...)

KLINIČNA RABA

- pediatrični tumorji
 - meduloblastom – obsevanje cerebrospinalne osi
 - kraniofaringeom
 - sarkomi
- prostata
- tumorji baze lobanje
- obnosni sinusi
- GI tumorji – pankreas, HCC

KLINIČNA RABA

- ščitenje – baza lobanje
- lokalna kontrola – prostata
- izogibanje poznim posledicam – pediatrija
- geometrija – melanom žilnice
- velik volumen – meduloblastom pri otrocih

KLINIČNA RABA

Table 1. Particle RT of Uveal Melanomas

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Egger et al ¹⁷	2003	PSI, Switzerland	P	2,645	Proton RT	5-/10-year eye retention: 88.9%/86.2%; after optimization of technique: 100% small, 99.7% medium, 89.5% large tumors
Courdi et al ¹⁸	1999	Nice, France	R	538	Proton RT, 57.2 CGE	LC: 89%; OS: 73.8%; metastases rate: 8%
Char et al ¹²	1993	San Francisco, CA	Phase III	184	Helium-ion RT v ¹²⁵ I BT; maximum diameter < 15 mm; thickness < 10 mm	Recurrence/eye enucleation rate higher after BT, but more anterior segment complications after helium-ion RT
Fuss et al ¹⁰	2001	LLUMC, United States	R	78	Proton RT; medium and large tumors	5-year LC: 90.5%
Dendale et al ¹⁴	2006	CPO, France	R	1,406	Proton RT, 60 CGE	5-year LC: 96%; 5-year OS: 79%
Gragoudas et al ²¹	2000	MGH, Boston, MA	Phase III	188	Proton RT, 50 CGE v 70 CGE; small- and medium-sized tumors, near optic disc or macula	No difference for LC, less visual field loss after 50 CGE
Desjardins et al ²⁰	2003	Paris, France	R, 2 arms	1,272	¹²⁵ I BT for small anterior tumors; protons for tumors at equator and posterior equator < 12 mm	5-year LC: 96% (protons) v 96.25% (¹²⁵ I)
Castro et al ¹³	1997	San Francisco, CA	P	347	Helium-ion RT, 48-80 CGE; dose search trial	5-year LC: 96%; 5-year OS: 80%; at 48 CGE, 5-year LC: 87%
Damato et al ¹⁵	2005	Liverpool, United Kingdom	P	88	Proton RT, 53.1 CGE; iris melanoma	4-year LC: 96.7%
Hocht et al ¹⁶	2004	Berlin, Germany	P	245	Proton RT, 60 CGE	3-year LC: 95.5%; 3-year eye retention: 87.5%
Tsuji et al ²⁴	2006	NIRS, Japan	P	57	Carbon RT, 60-95 GyE; dose-escalation trial; large tumors	3-year LC: 97.4%; 3-year eye retention: 91.1%; 3-year OS: 88.2%

Abbreviations: RT, radiotherapy; PSI, Paul Scherrer Institut; P, prospective nonrandomized; R, retrospective nonrandomized; CGE, cobalt gray equivalents; LC, local control; OS, overall survival; phase III, prospective randomized phase III trial; ¹²⁵I, iodine-125; BT, brachytherapy; LLUMC, Loma Linda University Medical Center; CPO, Centre de Protontherapie d'Orsay; MGH, Massachusetts General Hospital Boston; NIRS, National Institute of Radiological Sciences, Chiba, Japan; GyE, gray equivalents.

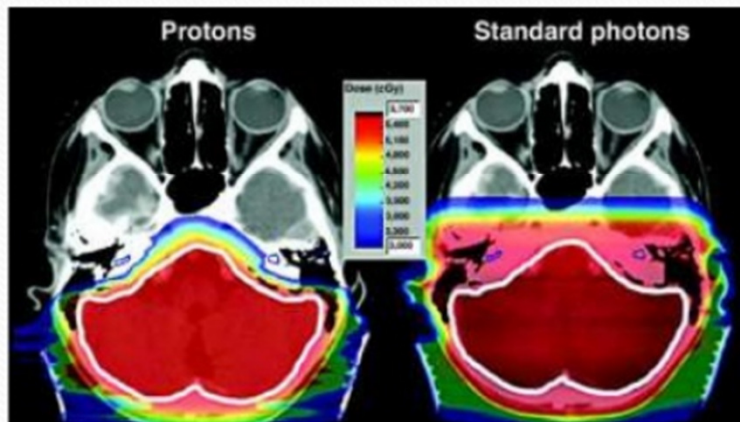
KLINIČNA RABA

Table 2. Proton RT in Pediatric Tumors

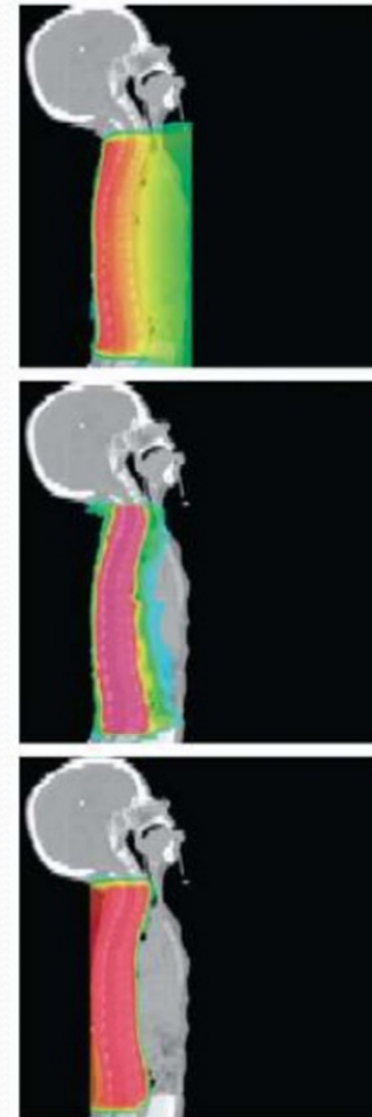
Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Yock et al ²⁷	2005	MGH, Boston, MA	R	7	Proton RT + standard chemotherapy; orbital rhabdomyosarcoma	LC comparable to photon trials, but dose to normal tissue can be reduced
McAllister et al ²⁸	1997	LLUMC, United States	R	28	Proton RT; pediatric brain, head, and neck tumors	Low acute toxicity
Habrand et al ²⁹	1999	CPO, France	R	8	Proton RT; pediatric CNS tumors	4 of 8 patients had treatment-related late toxicity
Yuh et al ³⁰	2004	LLUMC, United States	P	3	Proton RT; craniospinal RT; medulloblastoma	Elimination of exit dose, reduction of toxicity in children with a history of myelosuppression
Hug et al ³¹	2002	LLUMC, United States	R	27	Proton RT, 50.4-63 CGE; low-grade astrocytoma	Mean follow-up: 3.3 years; control rates comparable to photon RT; mild toxicity
Hug et al ³²	2002	MGH, Boston, MA	R	29	Proton RT or photons + protons; chordoma, n = 10; chondrosarcoma, n = 3; RMS, n = 4; other sarcoma, n = 3; benign tumors, n = 9	Mean follow-up: 40 months; 5-year LC: 72%; 5-year OS: 56%; severe late effects: 7%

Abbreviations: RT, radiotherapy; MGH, Massachusetts General Hospital Boston; R, retrospective nonrandomized; LC, local control; LLUMC, Loma Linda University Medical Center; P, prospective trial; CPO, Centre de Protontherapie d'Orsay; CGE, cobalt gray equivalents; RMS, rhabdomyosarcoma.

KLINIČNA RABA

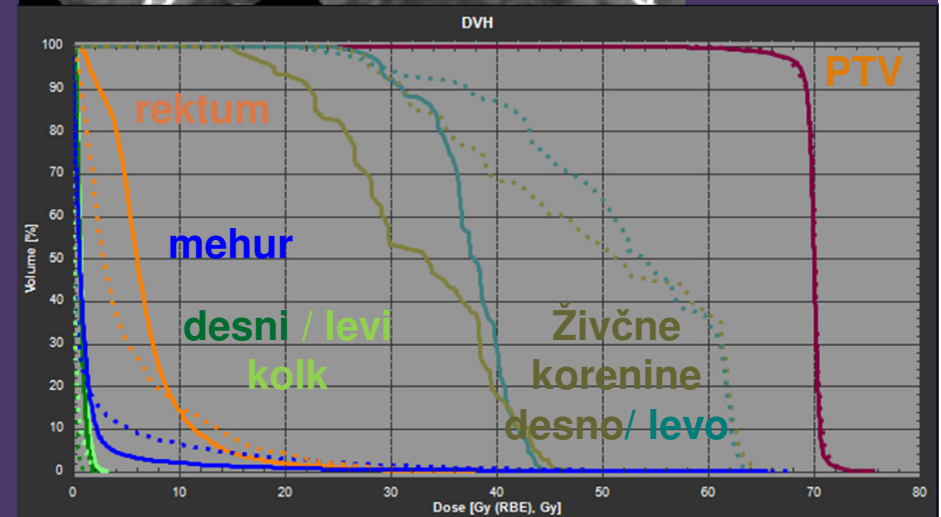
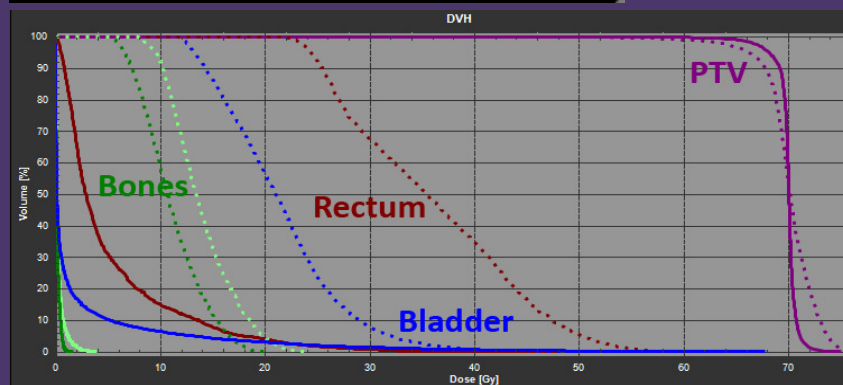
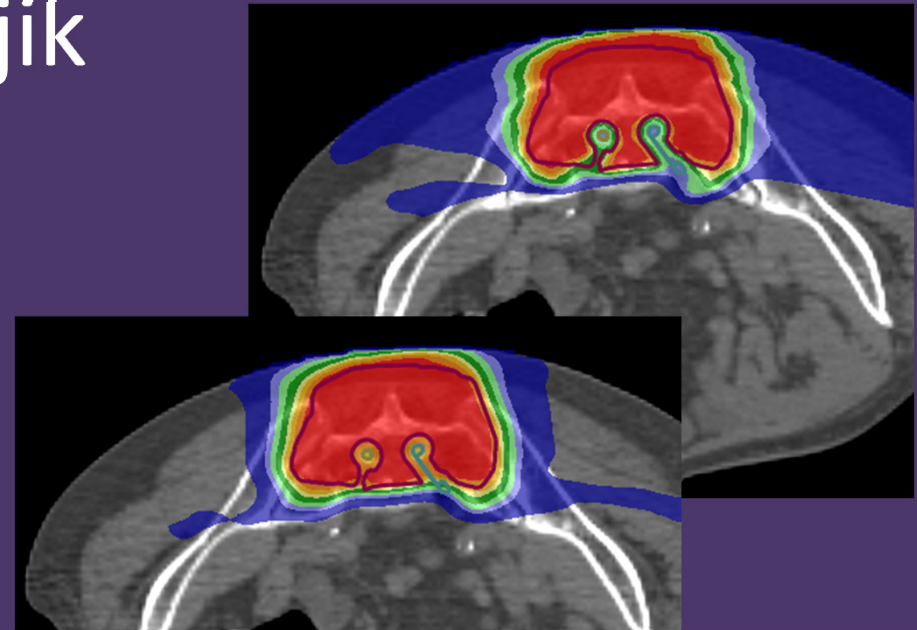
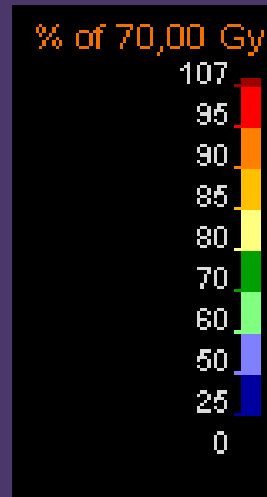
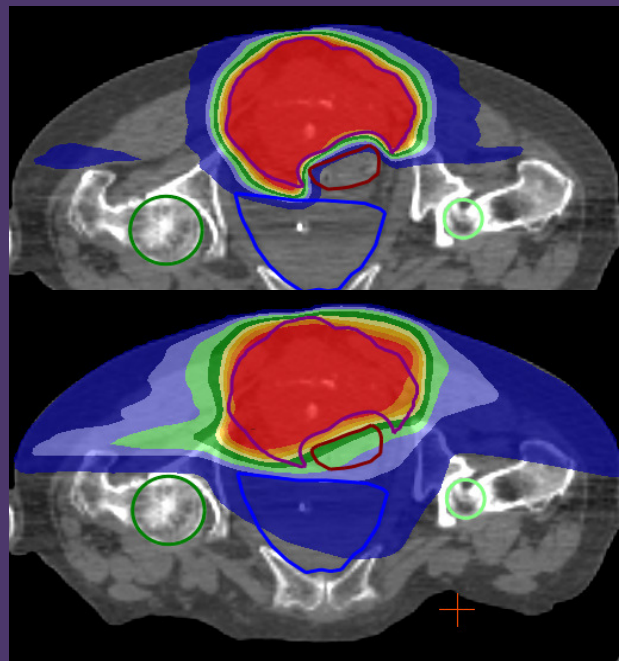


The Exit dose from photon therapy exposes the thyroid, heart, lung, gut, and gonads to functional and neoplastic risks that can be avoided with proton therapy.



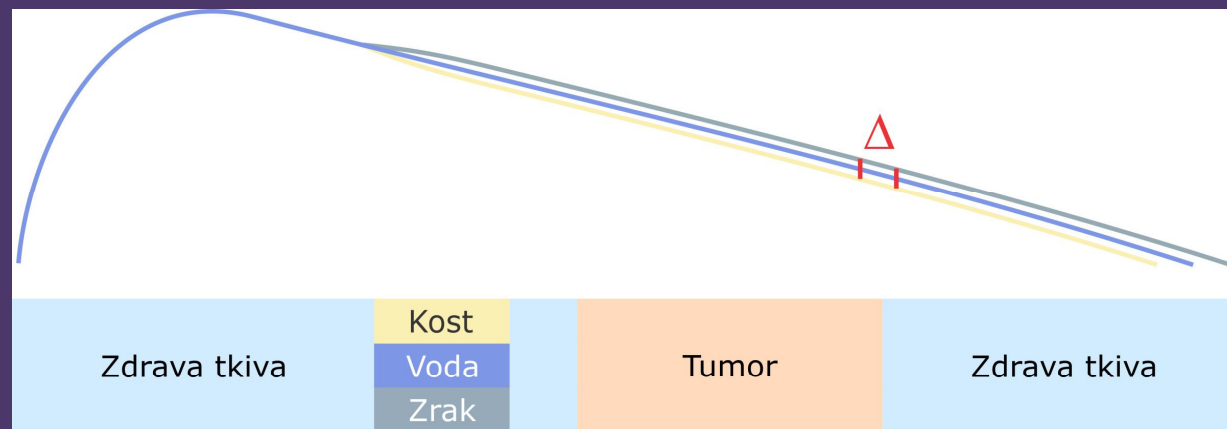
Deepak KD 2016

Hordom križnice: fotoni, protoni in ogljik

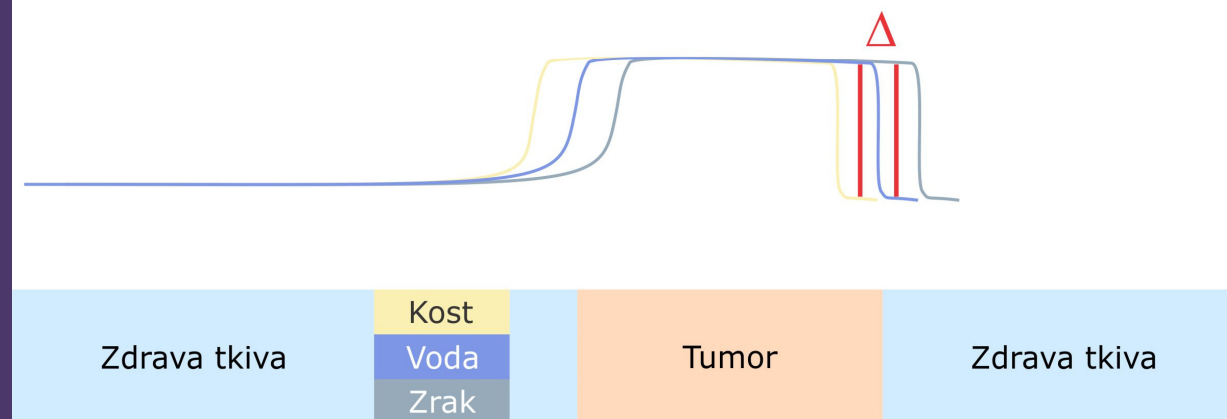


Negotovosti pri dometu / Robustnost

Fotoni

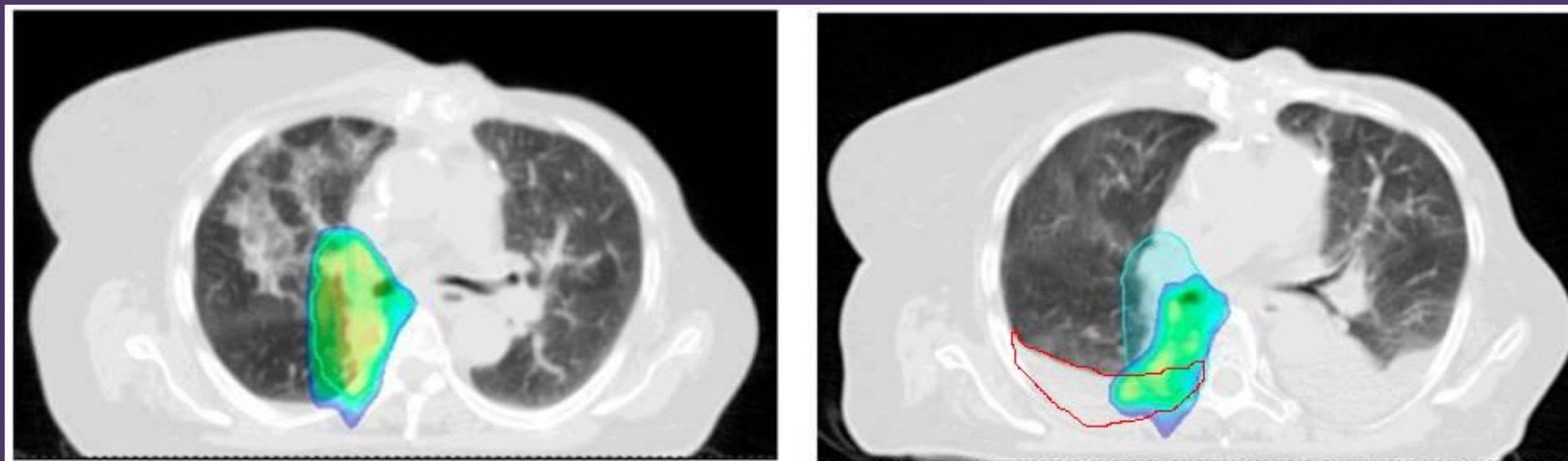


Hadroni

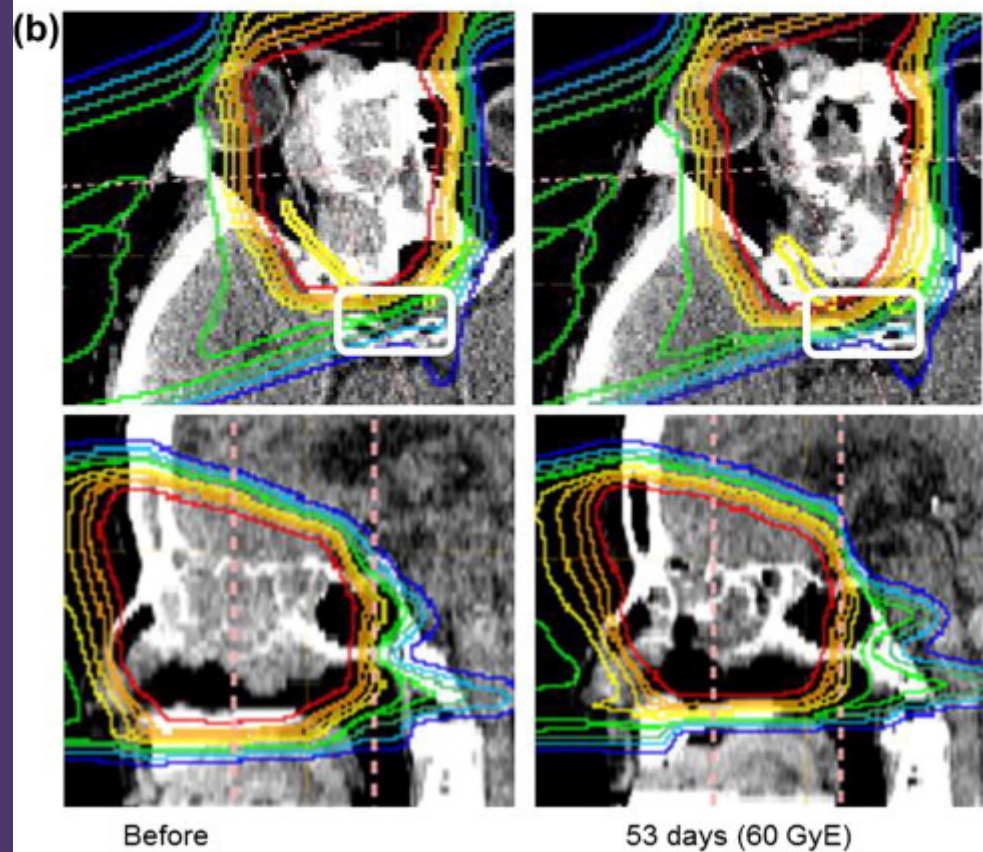
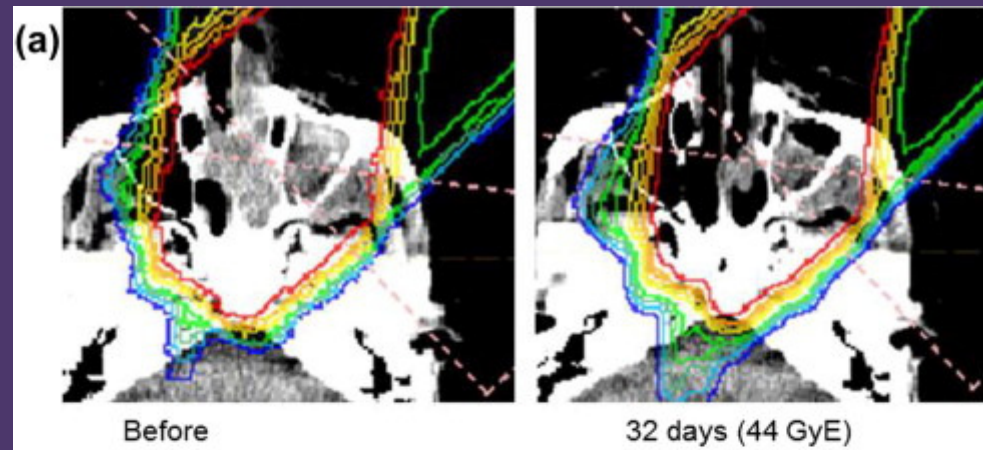


anatoMSKE SPREMEMBE

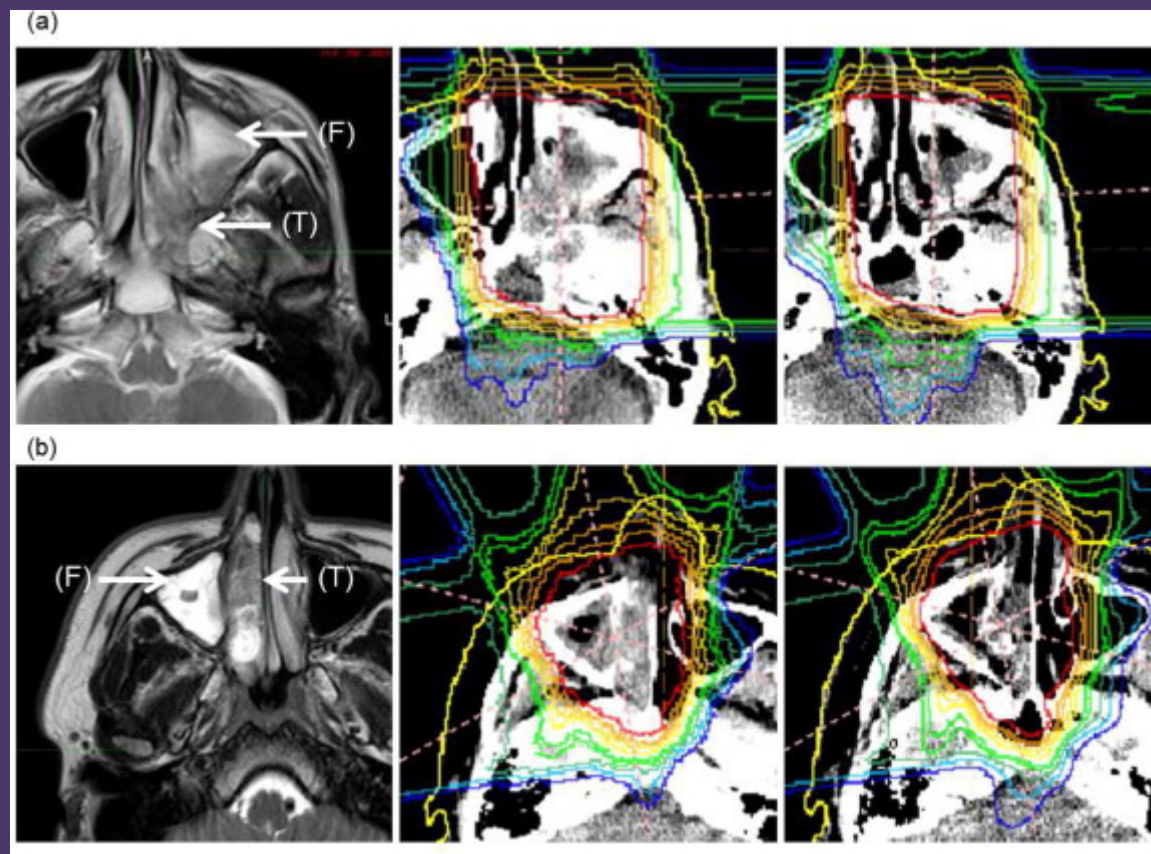
- Sprememba dometa žarkov
 - Premik visokodoznega območja v zdrava tkiva
 - Izguba pokritosti tarče



Berman AT et al 2015



Fukumitsu N et al 2014



Fukumitsu N et al 2014

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Medulloblastoma: Late Toxicity

Table 1 Estimated risk of radiation-induced cancer by radiation delivery technique following spinal irradiation for childhood medulloblastoma

Radiation delivery technique	Risk of radiation-Induced cancer, %
Intensity modulated x-ray beam	30
Electron beam	21
Conventional x-ray beam	20
Intensity modulated electron beam	15
Intensity modulated proton beam	4

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Table 3. Particle Therapy of Skull Base Chordomas

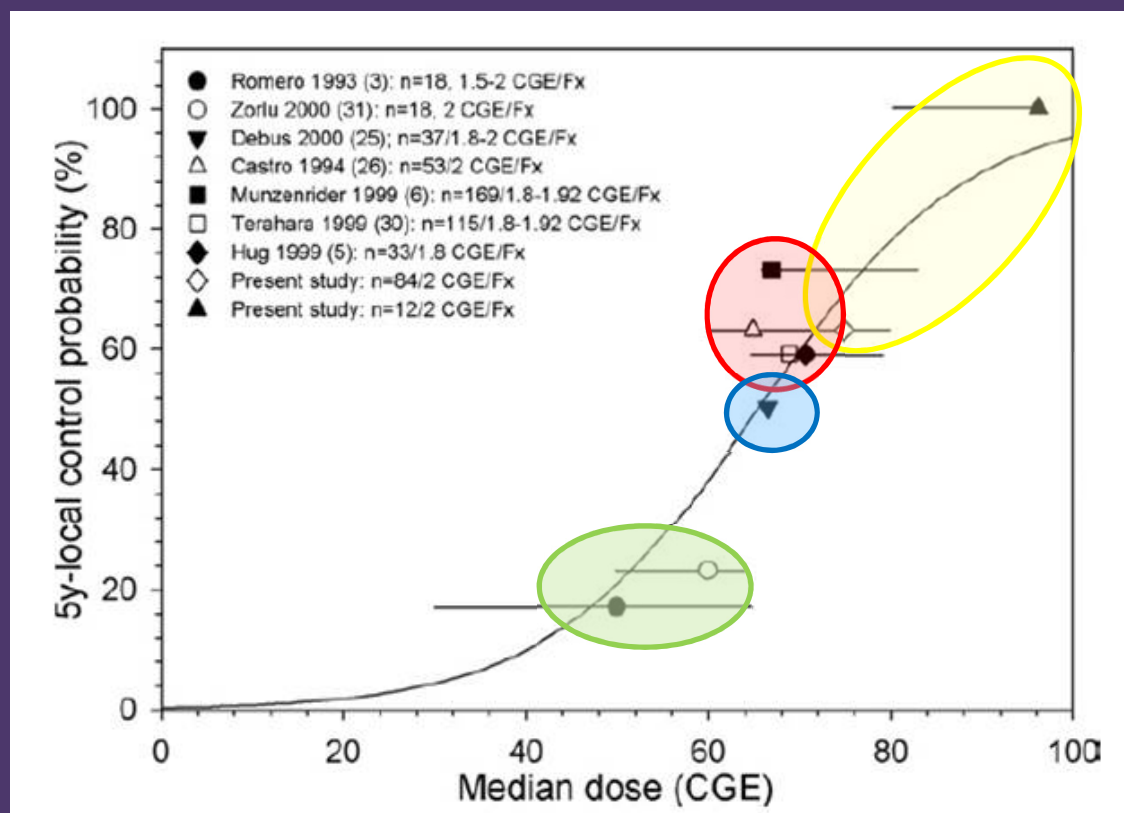
Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Colli and Al-Mefty ³⁴	2001	Sao Paulo, Brazil	R	53	Protons v conventional RT	4-year LC: 90.9% v 19.4%
Noel et al ³⁵	2005	CPO, France	P	100	Photons + protons, 67 CGE	4-year LC: 53.8%; 5-year OS: 80.5%
Weber et al ³⁶	2005	PSI, Switzerland	R	18	Proton RT, 74 CGE	3-year LC: 87.5%; 3-year OS: 93.8%; 3-year complication-free survival: 82.2%
Igaki et al ³⁷	2004	Tsukuba, Japan	R	13	Proton RT or protons + photons, 72 CGE	5-year LC: 46%; 5-year OS: 66.7%
Castro et al ³⁸	1994	LBL, United States	R	53	Helium/neon ions, 65 CGE	5-year LC: 63%
Terahara et al ³⁹	1999	MGH, Boston, MA	R	115	Proton RT, 68.9 CGE	5-year LC: 59%; 10-year LC: 44%
Hug et al ⁴⁰	1999	LLUMC, United States	R	33	Proton RT, 70.7 CGE	5-year LC: 59%
Schulz-Ertner et al ⁴³	2004	GSI, Germany	P	44	Carbon ion RT, 60 CGE	4-year LC: 74%; 4-year OS: 86%

Abbreviations: RT, radiotherapy; R, retrospective nonrandomized; LC, local control; CPO, Centre de Protontherapie d'Orsay; P, prospective trial; CGE, cobalt gray equivalents; OS, overall survival; PSI, Paul Scherrer Institute; LBL, Lawrence Berkeley Laboratory; MGH, Massachusetts General Hospital Boston; LLUMC, Loma Linda University Medical Center; GSI, Gesellschaft für Schwerionenforschung.

Hordom: protoni in ogljik

Avtor	Hug et al	Igaki et al	Weber et al	Ares et al	Schulz-Ertner et al	Hasegawa et al	Tsujii et al
Leto	1999	2004	2016	2009	2007	2009	2012
Bolniki	33	13	151	42	96	34	47
Delec	p ⁺	p ⁺	p ⁺	p ⁺	C ¹²	C ¹²	C ¹²
Doza	70,7 GyE	72 GyE	74 GyE	73,5 GyE	60 GyE (3 GyE / fx)	48-60,8 GyE (16 fx)	60,8 GyE (16 fx)
LC	5L: 59%	5L: 46%	7L: 70,9%	5L: 81%	5L: 70%	5L: 85% 10L: 64%	5L: 88% 10L: 80%
OS	5L: 79%	5L: 67%	7L: 81,7%	5L: 62%	5L: 88%	5L: 88% 10L: 67%	5L: 87%
G3+	7%	2 bolnika	8,1%	6%	5%	0	0

HORDOMI: Razmerje med dozo in odgovorom



- Carbon ion
- Protons
- FSRT
- Photon

Schulz-Ertner D et al 2007

hondrosarkomi: protoni in ogljik

Avtor	Hug et al	Weber et al	Ares et al	Schulz-Ertner et al	Combs et al	Tsujii et al	Uhl et al
Leto	1999	2016	2009	2007	2009	2012	2014
Bolniki	25	77	22	54	17	71	79
Delec	p ⁺	p ⁺	p ⁺	C ¹²	C ¹²	C ¹²	C ¹²
Doza	70,7 GyE	64-76 GyE	68,4 GyE	60 GyE	60 GyE	60,8 GyE	
LC	5L: 75%	8L: 89,7%	5L: 94%	4L: 90%	5L: 94%	5L: 60%	5L: 88% 10L: 88%
OS	5L: 100%	8L: 93,5%	5L: 91%	4L: 98%	5L: 100%	5L: 60%	5L: 96% 10L: 79%
G3+	7%	7,8%	6%	2%	0	4 bolniki	0

ORL: Ogljik + / - fotoni

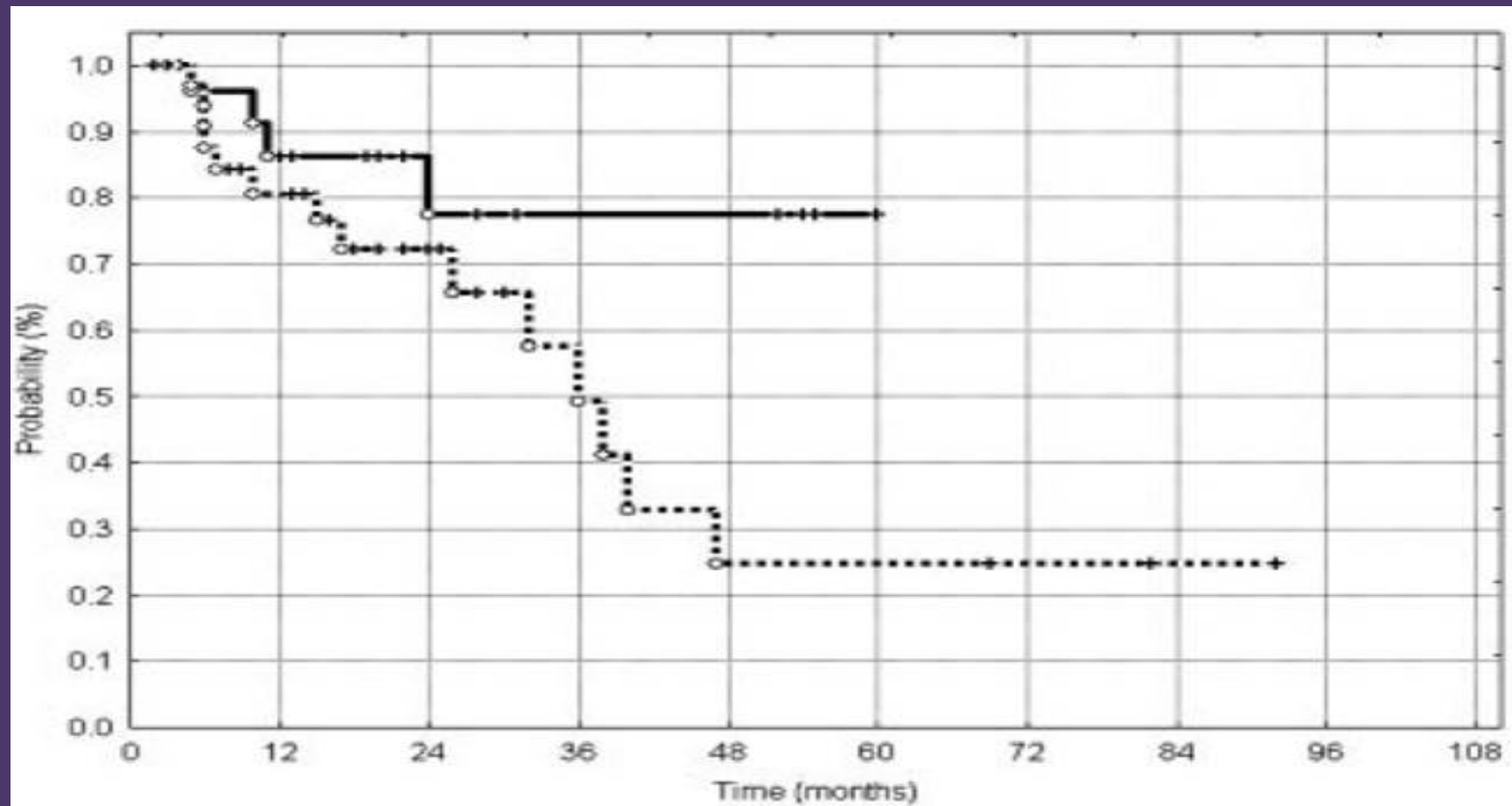
Avtor	Schultz-Ertner et al	Jensen et al	Jensen et al	Jensen et al	Hasegawa et al
Diagnoza	ACC	ACC & slinavke 89% ACC	ACC	Ne-ACC slinavke	ACC
Leto	2005	2015	2015	2016	2014
Bolniki	63	54	309	40	141
Doza	med f + C ¹² : 72 GyE med f: 66 Gy	f + C ¹² : 24 + 50 Gy GyE	f + C ¹² : 24 + 50 Gy GyE	med f + C ¹² : 74 GyE C ¹² : 66 GyE	C ¹² : 57,6-64 GyE
LC	4-year ph+c: 77,5% 4-year ph: 24,6%	3-year: 81,9%	3-year: 83,7% 5-year: 58,5%	3-year: 66,8%	5-year: 75,9%
OS	no difference	3-year: 78,4%	3-year: 88,9% 5-year: 74,6%	3-year: 72,8%	5-year: 72,2%
G3+	1 bolnik (f) mukoz G3	ak: 24% mucosa poz: 1 pt G4	ak: 16% muc, 3% skin poz: „tolerable“	ak: 15% muc, 20% disf G2+ poz: X G2+	

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Table 6. Particle Therapy for Prostate Cancer

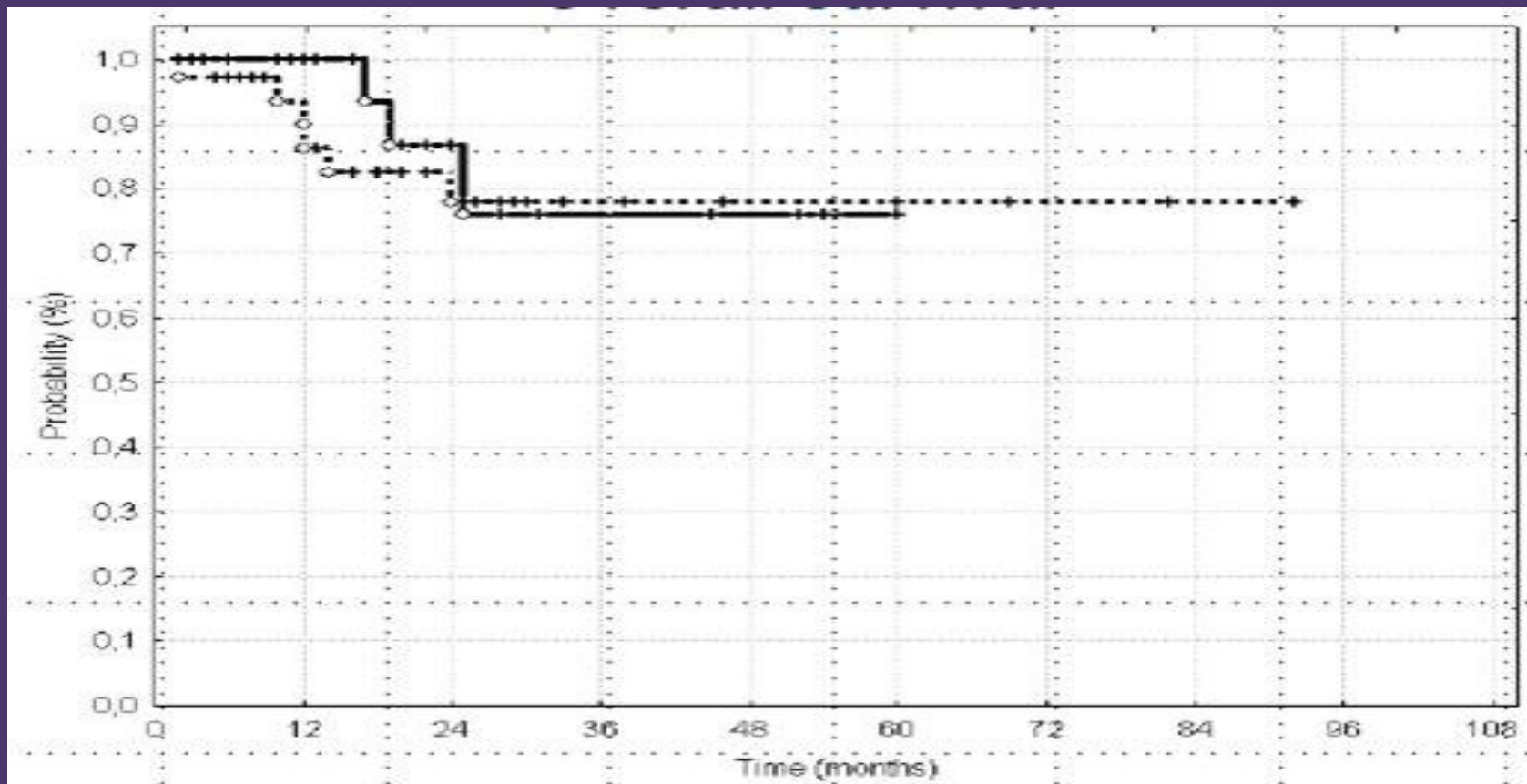
Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Slater et al ⁶⁶	2004	LLUMC, United States	R	1,255	Proton RT, 74-75 CGE; localized prostate cancer	DFS comparable with other forms of local therapy, minimal morbidity
Yonemoto et al ⁶⁷	1997	LLUMC, United States	P; phase I/II	106	Photons, 45 Gy pelvis + protons, 30 CGE prostate	2-year grade 1-2 toxicity: 12%; no grade 3-4 toxicity; 2-year PSA normalization: 96% (PSA 4-10 ng/mL), 97% (PSA 10-20 ng/mL), 63% (PSA > 20 ng/mL); 2.8% local recurrence
Nihei et al ⁶⁸	2005	NCCHE, Japan	P; phase II, one arm	30	Photons, 50 Gy prostate/vesicles + proton boost, 26 CGE; T1-3N0M0 prostate cancer	Late grade 2 toxicity; GU: 10%; GI: 10%; no late toxicity > grade 2; biochemical relapse in six of 30 patients
Zietman et al ⁶⁹	2005	MGH, Boston, MA	P; randomized phase III	393	Photon RT, 70.2 Gy v photon + proton RT, 79.2 CGE; T1b-2b, PSA < 15 ng/mL	5-year bDFS: 61.4% (photons) v 80.4% (photons + protons); late toxicity > grade 2: 2% v 1%
Slater et al ⁷⁰	1999	LLUMC, United States	R	119	Protons or protons + photons, 74-75 CGE; prostate cancer T1-2b, PSA < 15 mg/mL	5-year bDFS: 88%; no severe toxicity; biochemical control rates comparable to radical prostatectomy; no significant toxicity
Shipley et al ⁶⁰	1995	MGH, Boston, MA	P; randomized phase III trial	202	Photons, 67.2 Gy v photons, 50.4 Gy + perineal proton boost, 25.2 CGE; T3-4 prostate cancer	Median follow-up: 61 months; improved LC only in patients with poorly differentiated tumors treated with high-dose RT; grade 1-2 rectal bleeding rate significantly higher in the high-dose arm (32% v 12%) as well as urethral stricture (19% v 8%)

ORL – LOKALNA KONTROLA

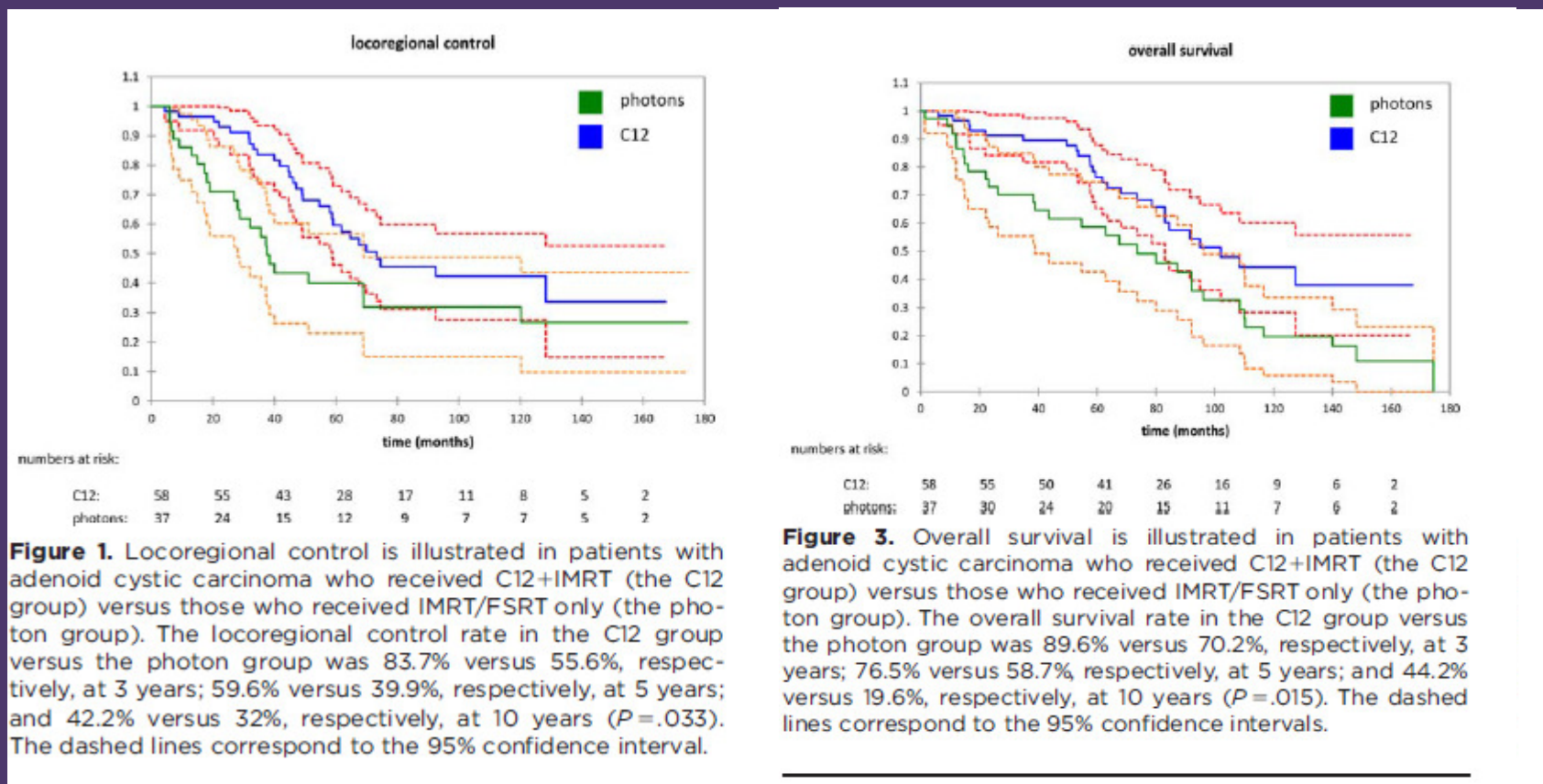


Schultz-Ertner et al., Cancer, 2005

ORL - PREŽIVETJE



Schultz-Ertner et al., Cancer, 2005



(Jensen et al., Cancer, 2015)

Schultz-Ertner et al., Cancer, 2015

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SECOND MALIGNANCY

- Harvard Cyclotron Laboratory
- Matched 503 HCL proton patients with 1591 SEER patients
- Median follow up: 7.7 years (protons) and 6.1 years (photon)
- Second malignancy rates
 - 6.4% of proton patients (32 patients)
 - 12.8% of photon patients (203 patients)
- **Photons are associated with a higher second malignancy risk: Hazard Ratio 2.73, 95% CI 1.87 to 3.98, $p < 0.0001$**

Chung et al. ASTRO 2008

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- trenutno še brez centra
- Trento, Pavia, Wilingen, Wiener Neustatt
- sodelovanje sedaj predvsem pri pediatričnih tumorjih s Trentom, zanimajo se tudi v Avstriji
- večinoma protoni
- največ izkušenj s ogljikom imajo v Evropi v Heidelbergu