

RCC OLIGOMETASTATICO

La necessità di un

Approccio Multidisciplinare

Sabato 11 Novembre 2017



Radioterapia: non solo palliazione

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Radiation Therapy (RT) in XXI century

Oligometastatic Renal Cell Carcinoma (RCC) and Role of RT in XXI century

- Palliative?
- Ablative?

Setting:

- Primary RCC
- Intracranial OligoMetastases
- Extracranial OligoMetastases

Radiation Therapy (RT) in XXI century

Better Therapeutic Ratio!

5D: BIOLOGIC BASED NAVIGATION

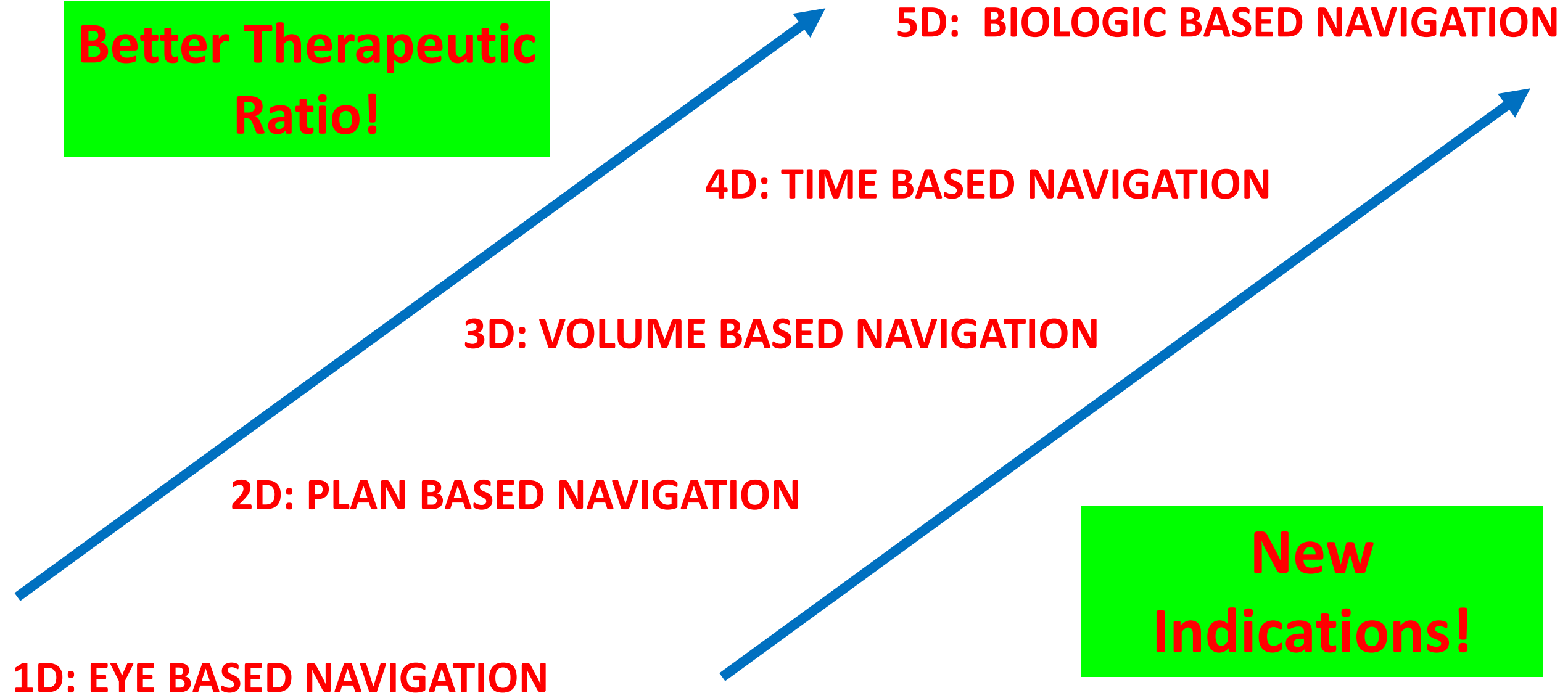
4D: TIME BASED NAVIGATION

3D: VOLUME BASED NAVIGATION

2D: PLAN BASED NAVIGATION

New Indications!

1D: EYE BASED NAVIGATION



Imaging Informed Radiation Therapy (I²RT)

Imaging per il PrePlanning RT

Imaging per il Planning RT

Imaging per il RT Delivery

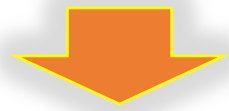
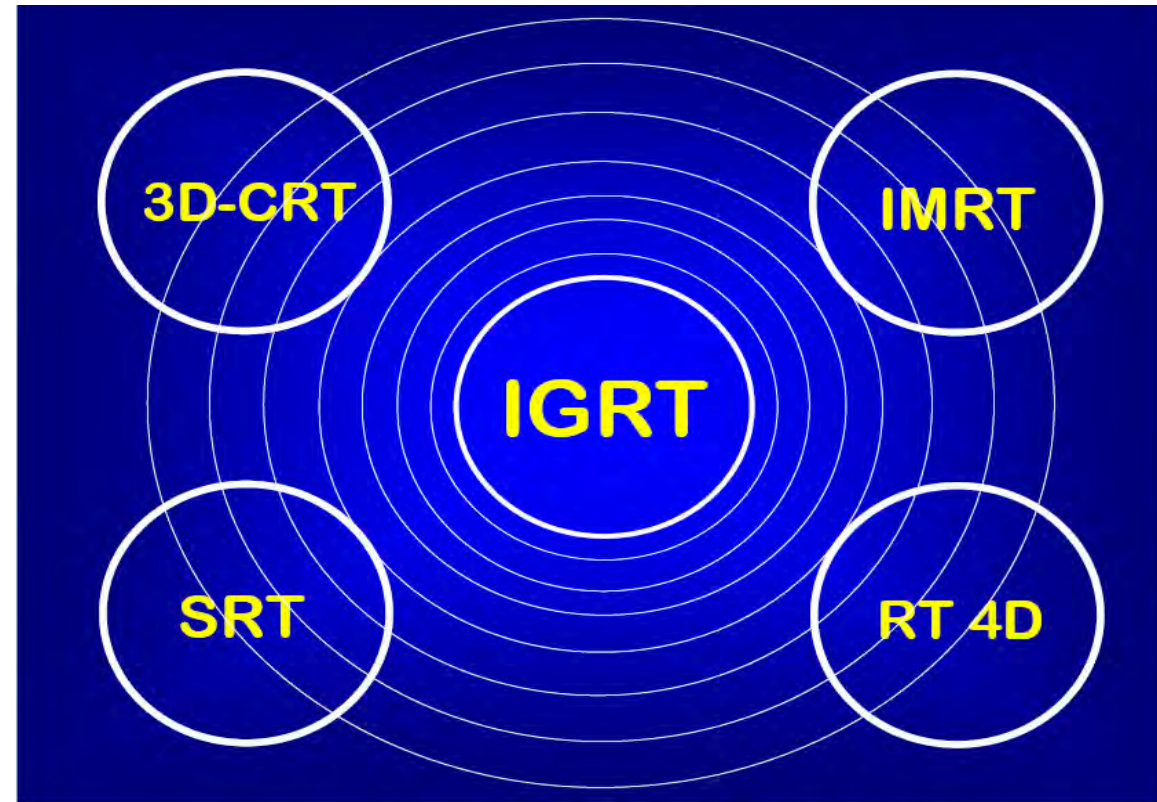


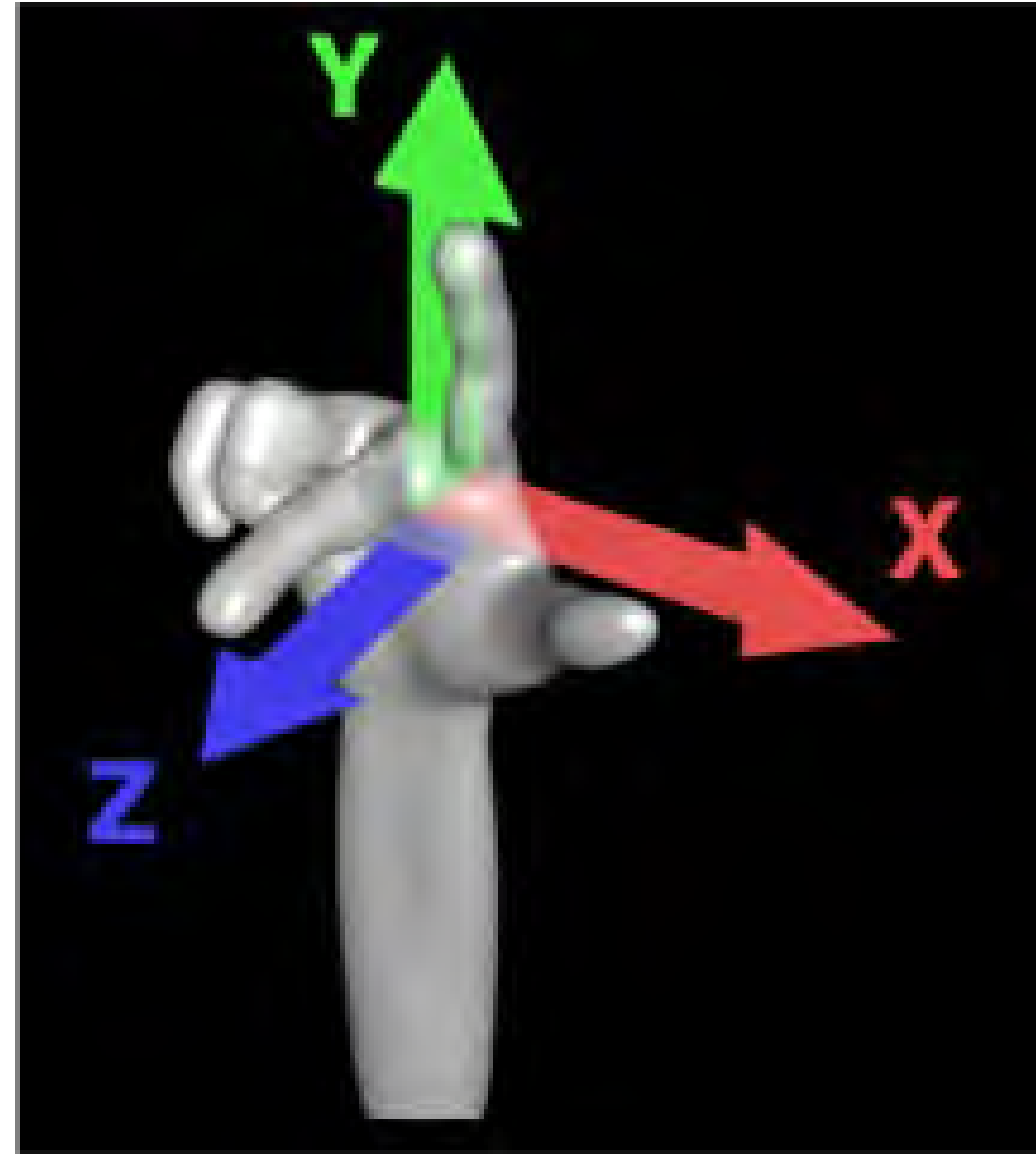
Image Guided RT



Stereotactic Body Radiotherapy (SBRT)



1. **High Dose Radiation**
2. **Reduced number of fractions (1-5)**
3. **Precise, Accurate & Reproducible delivery:**
 - a. **Reduced margins**
 - b. **Excellent tumour localization**
 - c. **Effective patient immobilization**
 - d. **Accurate to within 1 to 2 mm of target**



Stereotactic Body Radiotherapy (SBRT)

- With large dose per fraction, many data suggest **vascular effects** as more significant than other.
- This implies that acute cell killing from direct exposure is supplemented by a delayed **ischemic and/or immunologic** component of cell killing, not accounted for in alpha/beta



Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial



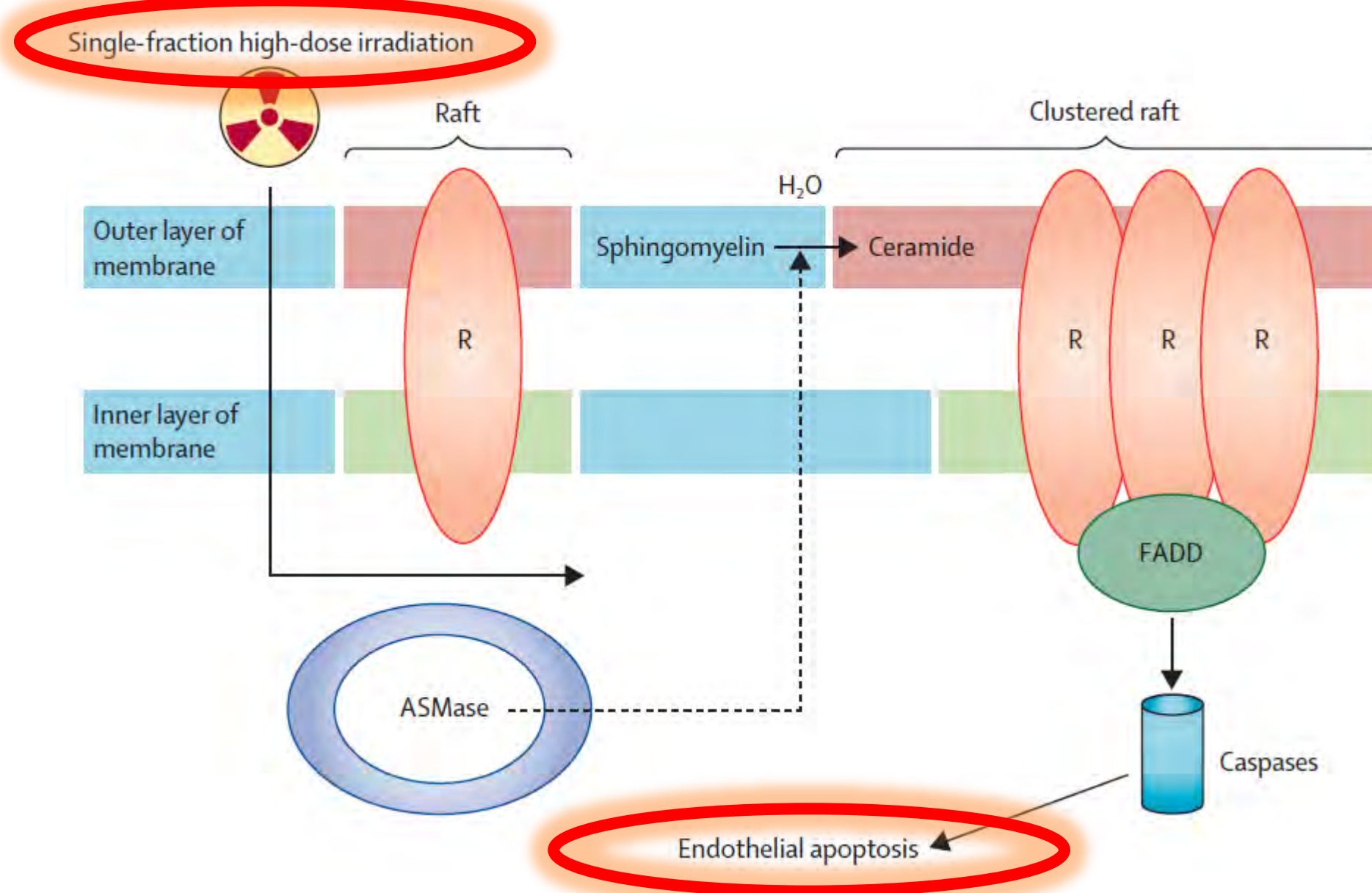
Lancet Oncol 2015; 16:795-803

Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti

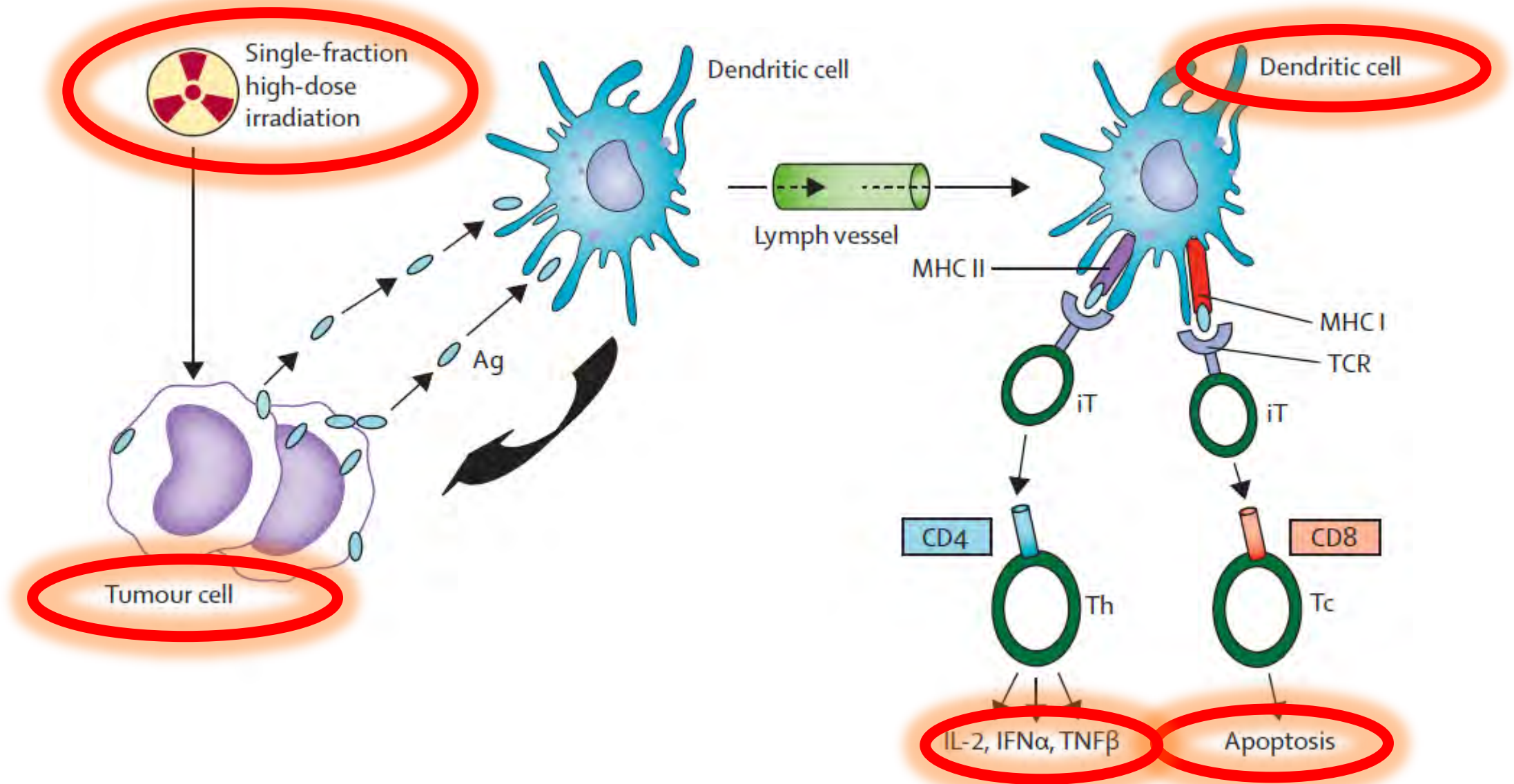
Interpretation The combination of radiotherapy with granulocyte-macrophage colony-stimulating factor produced objective abscopal responses in some patients with metastatic solid tumours. This finding represents a promising approach to establish an in-situ anti-tumour vaccine. Further research is warranted in this area.

Activation of ceramide pathway by single-fraction high-dose irradiation

ASMase=acid sphingomyelinase. R=receptor. FADD=FAS-associated death domains.



Immunological interpretation of the abscopal effect



Ag=antigen. TCR=T-cell receptor. iT=immature T-cell. Th=T-helper cell. Tc=cytotoxic T cell. IL2=interleukin 2. IFN α =interferon α . TNF β =tumour necrosis factor β .

Setting: RCC and Stereotactic Body Radiotherapy (SBRT)

Stereotactic Ablative Body Radiation Therapy for Primary Kidney Cancer: A 3-Dimensional Conformal Technique Associated With Low Rates of Early Toxicity



Pham D. et Al.: IJROBP, Vol. 90, No. 5, pp. 1061-1068, 2014

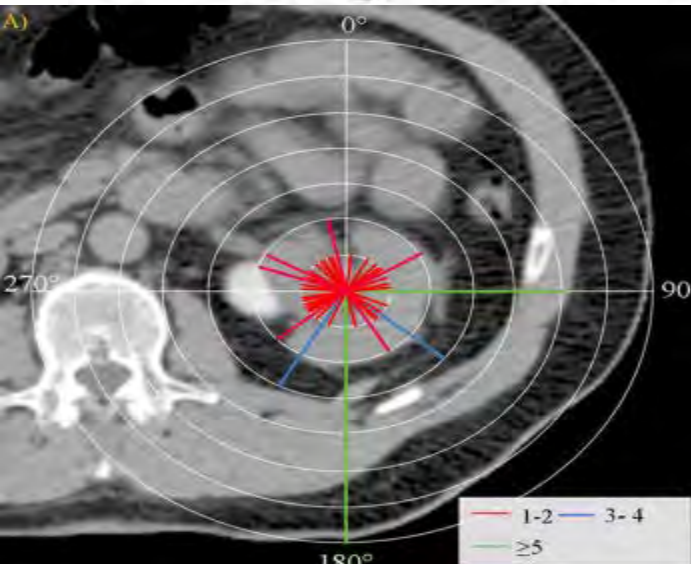
BJUI
BJU International

Trial

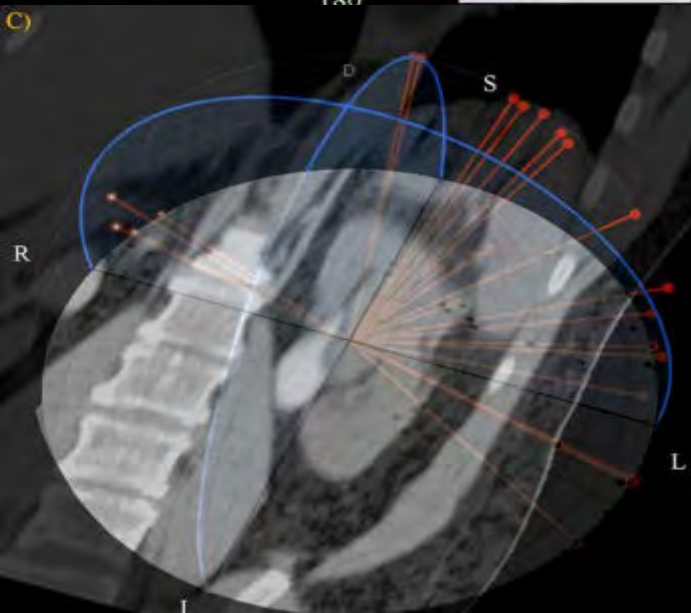
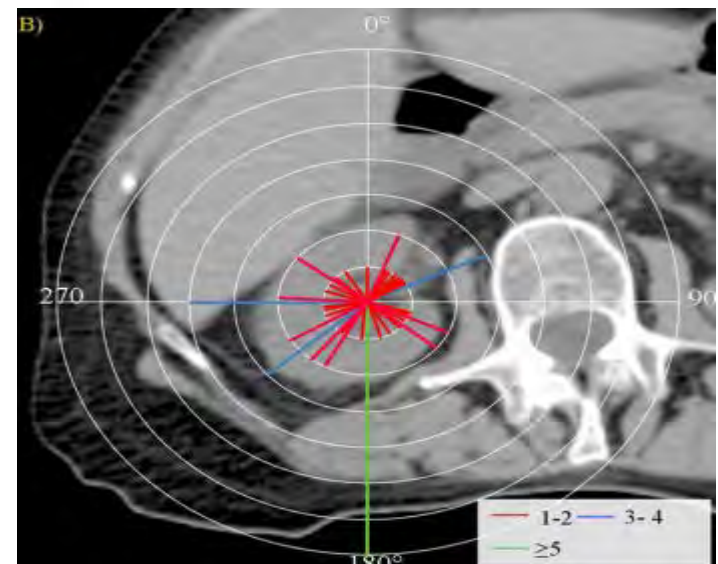
Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial

Siva S. et Al.: BJU Int 2017; 120: 623–630

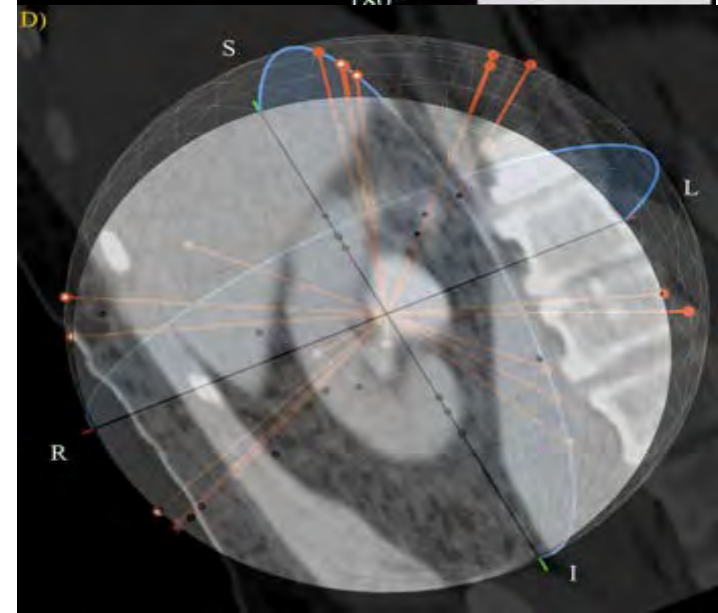
Stereotactic Ablative Body Radiation Therapy for Primary Kidney Cancer: A 3-Dimensional Conformal Technique Associated With Low Rates of Early Toxicity



Target < 5 cm	26Gy/1F
Target > 5 cm	42Gy/3F



Planning required a minimum of 8 fields prescribing to the minimum isodose surrounding the PTV generated from a 5-mm isotropic expansion of the ITV



Toxicity grade within 6 months of treatment completion for fractionated and single-fraction prescriptions (N = 20)

Patient no.	Dyspnea	Nausea	Diarrhea	Gastritis	Chest wall pain	Fatigue	Dermatitis	Hematuria	Asymptomatic
Total prescribed dose of 26 Gy in 1 fraction									
1									1
2	1	2				2	2		
3					1	1			
4		1				1	1		
5							1		
6						1			
7									1
8					1				
9		2			1	1			
10									1
11									1
Total	1	3	1	-	3	5	4	-	4
Total prescribed dose of 42 Gy in 3 fractions									
12					1	2			
13						1			
14					1				
15				2		2	2		
16					1				1
17									1
18		1				1			
19									1
20									1
Total	-	2	-	1	4	4	1	-	4

Within the 6-month assessment period:

- No grade 3 or 4 toxicities,
- 12 of 20 patients (60%) grade 1-2 intensity.

• In the single-fraction group, fatigue (7 of 11 pts, 73%) was the main symptom; then dermatitis, chest wall pain and nausea.

• In the multifraction group, fatigue and chest wall pain in 5 of 9 pts (56%).

Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial

33/37 patients (median age 78 years) and 34 kidneys received all prescribed SABR fractions (89% feasibility) Median follow-up was 24 months

Glomerular Filtration baseline vs post	Grade 1-2 Toxicity	Grade 3 Toxicity	Grade 4-5 Toxicity
55 mL/min vs 44 mL/min (P < 0.001)	78%	3%	0%

Follow up	Local Control	Overall Survival	Freedom from Distant Progression
2 yrs	100%	92%	89%

Primary RCC: focus on Stereotactic Body RadioTherapy (SBRT)

14 clinical studies (8 retrospective; 6 prospective) and 215 patients.

No size or site restrictions (no excluded tumors based on proximity to collecting vessels or renal vasculature)

Grade 1-2 Toxicity	Grade 3 Toxicity
21,4% (2-78%)	0-19%

Most common toxicities: fatigue and nausea, then dermatitis and enteritis.

Follow up (median)	Local Control (12/14)	Estimated weighted 2-year Local Control rate
9 - 57.5 ms	84-100%	93,1%

Primary RCC: focus on Stereotactic Body RadioTherapy (SBRT)

- **SBRT for both small and large primary RCC appears tolerable and is associated with encouraging local cancer control at 2 years and early survival in inoperable cohorts.**
- Ten groups used conventional gantry-operated LINACs.
- SBRT fractionation schedule: 40 Gy over 5 F; SRS (radiosurgical approach): 26 Gy in 1 F to targets <5 cm.; the outcomes are similar between single and multifraction regimens.
- **Prospective multicenter validation is essential to confirm the efficacy and safety of this non-invasive, ablative technique and to help refine patient selection and develop better biomarkers of response**

Setting: Intracranial OligoMetastases (WBRT and SBRT)

Sheehan JP, Sun MH et al (2003) Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control. J Neurosurg 98(2):342–349

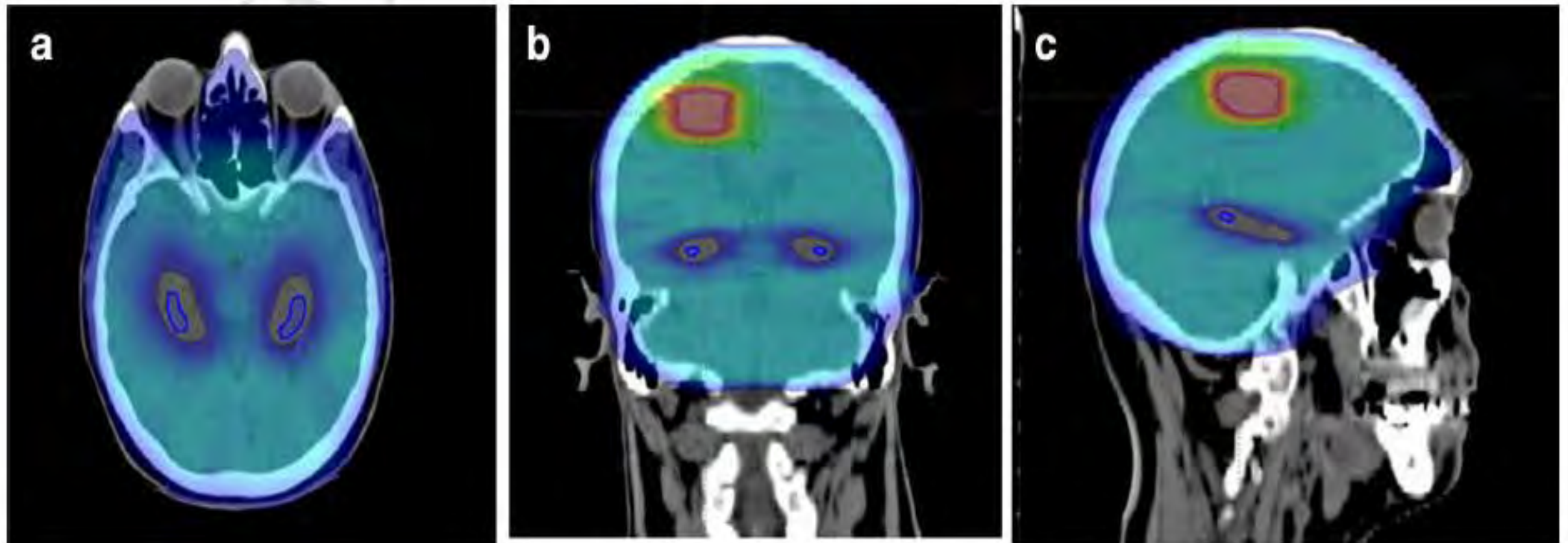


Retrospective review: 69 patients undergoing SRS for a total of 146 RCC cancer metastases. Factors affecting the rate of survival were: 1) younger patient age ($p = 0.0076$); 2) KPScale score ($p=0.0012$); 3) time from initial cancer diagnosis to brain metastasis diagnosis ($p=0.0017$); 4) treatment dose to the tumor margin ($p=0.0252$); 5) maximal treatment dose ($p=0.0127$); and 6) treatment isodose ($p=0.0354$).

Stereotactic radiosurgery provides local tumor control in 96% of patients and a median length of survival of 15 months. Early detection of brain metastases, aggressive treatment of systemic disease and **a therapeutic strategy including SRS can offer patients an extended survival.**

**WHOLE BRAIN RADIOTHERAPY WITH HIPPOCAMPAL AVOIDANCE AND
SIMULTANEOUS INTEGRATED BOOST FOR 1–3 BRAIN METASTASES: A
FEASIBILITY STUDY USING VOLUMETRIC MODULATED ARC THERAPY**

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NIMET NURANEY, R.T.T.,† RICHARD LEE, PH.D.,§ ERMIAS GETE, PH.D.,§ FRANCES WONG, M.D.,†
MOIRA SCHMULAND, M.SC.,§ MANRAJ HERAN, M.D.,¶ AND KARL OTTO, PH.D.‡



**WBRT plus SIB with HP avoidance with VMAT and
hypofractionated prescription is feasible**

Setting: Extracranial OligoMetastases

Clinical Investigation

Safety and Efficacy of Stereotactic Ablative Radiation Therapy for Renal Cell Carcinoma Extracranial Metastases



IJROBP, Vol. 98, No. 1, pp. 91-100, 2017

175 metastatic lesions from 84 patients.

Acute and late grade 3 toxicities were 1.7% and 2.9%, respectively.

The 1-year LC rate was 91.2% (median follow-up, 16.7 months).

Local failures were associated with prior radiation therapy (hazard ratio [HR], 10.49; $P < .0001$), palliative-intent radiation therapy (HR, 4.63; $P < .0189$), spinal location (HR, 5.36; $P = .0041$), previous systemic therapy status (0-1 vs >1 ; HR, 3.52; $P = .0217$), and BED <115 Gy (HR, 3.45; $P = .0254$).

Conclusions: SAbR demonstrated excellent LC of metastatic RCC with a favorable safety profile when an adequate dose and coverage were applied.

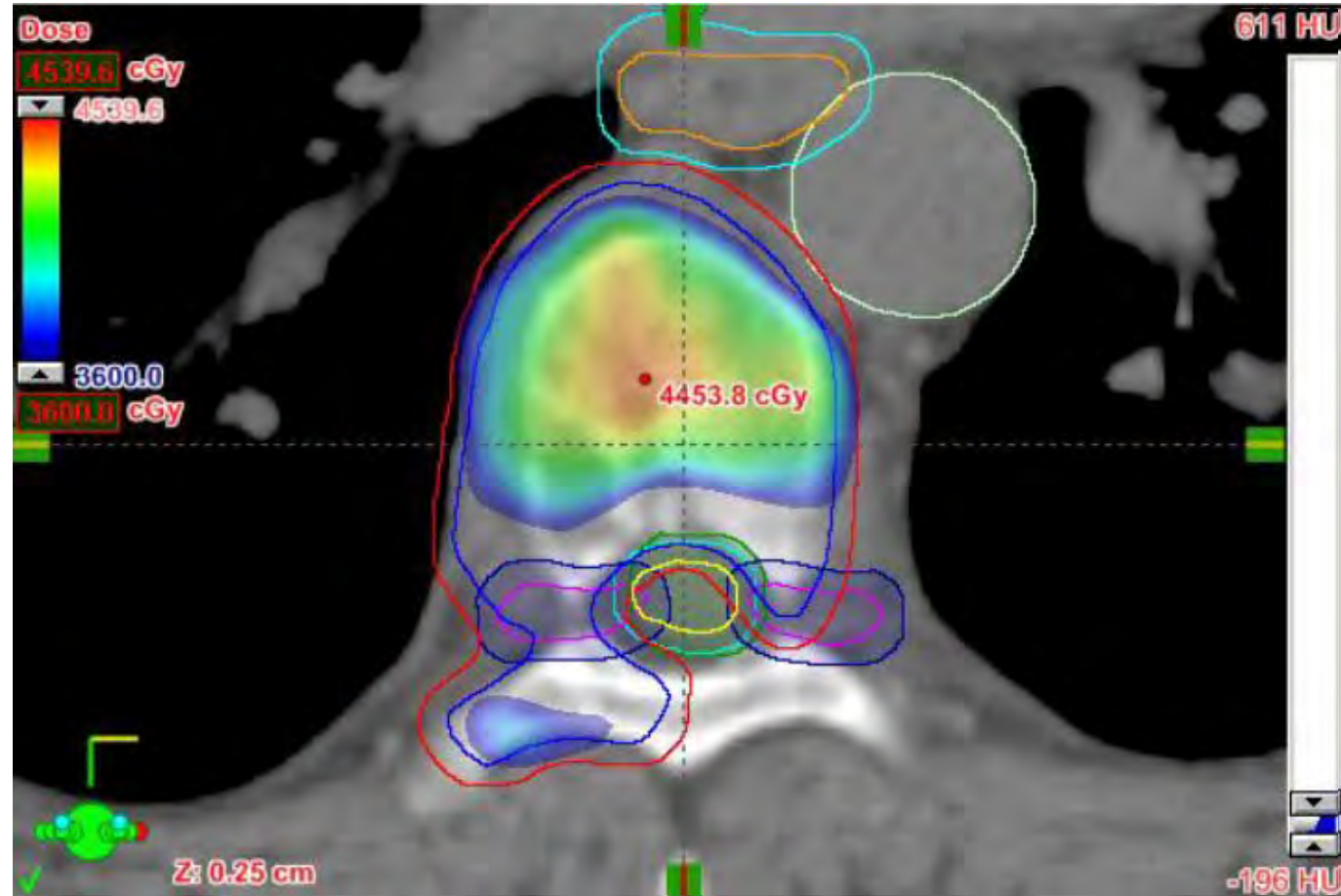
Typical spine case: 3x10Gy

20 Gy

23 Gy

30 Gy

36 Gy



Setting: Extracranial OligoMetastases (SBRT)

Stereotactic Ablative Radiotherapy Prolongs Surveillance and Delays Initiation of Systemic Therapy in Patients with Renal Cancer Metastases



Retrospective study to evaluate the use of SBRT to delay the initiation of systemic therapy in 25 mRCC patients.

14 patients had not received systemic therapy with a median follow up time at 24 months. For those who started on systemic therapy after SAbR, **the median time to start of systemic therapy was 32.9 months (95% CI: 10.8 - not reached).**

The median time to progression on systemic therapy after SAbR in this cohort was 7.7 months, which is comparable to the median time to progression on first line systemic therapy for mRCC patients (6.5 - 10.7 months).

Conclusion: SAbR may be used to treat selective mRCC patients to delay systemic therapy or time to progression on systemic therapy.

Radiation and Immune Checkpoint Blockade: From Bench to Clinic



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Clinical Trials of Radiation and Anti-PD-1/PD-L1 Therapy

Malignancy	Immunotherapeutic Agent	Radiation Fractionation	Phase	Clinical Trial Identifier
Metastatic RCC	Nivolumab	SBRT	II	NCT02781506
Metastatic RCC	Pembrolizumab	SBRT	II	NCT02599779
Metastatic RCC	Pembrolizumab	SBRT (18-20Gy 1F)	II	NCT02855203

Conclusions



- In all the settings of RCC, the RT is, at least, a good option for **Palliative Care**
- SBRT and/or SRS are **safe and effective**.
- SBRT and/or SRS offer a better therapeutic ratio, an **Ablative role** and a **biological/immunological modulation** for integration with the “Target Therapy and ImmunoTherapy”.

Conclusions



- SBRT and/or SRS may be used to **delay systemic therapy or time to progression on systemic therapy**
- The knowledge, promotion, initiation of prospective trials on SBRT and/or SRS could induce **a major shift in the treatment of renal-cell carcinoma**
- The patients need the engagement of **dedicated radiation oncologists** and development of **multidisciplinary meetings** for all professionals to discuss overall management of RCC