Radiotherapy in Renal Cell Carcinoma

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ORIGINAL REPORTS

Cancer Statistics, 2020: Report From National Cancer Registry Programme, India

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TABLE 2. Projected Incidence of Cancer Statistics in India, 2020

	Male			Female			Both Sexes		
	Patients	CR	Cum Risk	Patients	CR	Cum Risk	Patients	CR	Cum Risk
	679,421	94.1	1 in 9	712,758	103.6	1 in 9	1,392,179	98.7	1 in 9
	139,018	19.2	1 in 41	49,951	7.3	1 in 112	188,969	13.4	1 in 60
	39,902	5.5	1 in 147	13,870	2.0	1 in 401	53,772	3.8	1 in 215
	57,380	7.9	1 in 103	22,483	3.3	1 in 241	79,863	5.7	1 in 144
	3,029	0.4	1 in 1,793	1,102	0.2	1 in 5,475	4,131	0.3	1 in 2,701
	38,707	5.4	1 in 137	12,496	1.8	1 in 476	51,203	3.6	1 in 213
	163,845	22.7	1 in 32	110,137	16.0	1 in 50	273,982	19.4	1 in 39
	32,622	4.5	1 in 159	20,206	2.9	1 in 264	52,828	3.7	1 in 198
	32,713	4.5	1 in 160	17,430	2.5	1 in 319	50,143	3.6	1 in 213
	2,155	0.3	1 in 2,492	1,451	0.2	1 in 3,901	3,606	0.3	1 in 3,044
	20,572	2.8	1 in 260	15,685	2.3	1 in 348	36,257	2.6	1 in 298
	21,915	3.0	1 in 244	14,985	2.2	1 in 372	36,900	2.6	1 in 295
	2,897	0.4	1 in 1,865	2,028	0.3	1 in 2,682	4,925	0.3	1 in 2,200
	26,678	3.7	1 in 189	10,732	1.6	1 in 514	37,410	2.7	1 in 277
	12,385	1.7	1 in 422	19,510	2.8	1 in 284	31,895	2.3	1 in 340
	11,908	1.6	1 in 429	8,110	1.2	1 in 657	20,018	1.4	1 in 519
	103,552	14.3	1 in 48	32,480	4.7	1 in 165	136,032	9.6	1 in 74
	27,146	3.8	1 in 184	3,316	0.5	1 in 1,633	30,462	2.2	1 in 331
	71,788	9.9	1 in 68	26,490	3.9	1 in 201	98,278	7.0	1 in 101
	4,618	0.6	1 in 1,273	2,674	0.4	1 in 2,156	7,292	0.5	1 in 1,600
	8,115	1.1	1 in 1,013	5,840	0.8	1 in 1,370	13,955	1.0	1 in 1,162
	8,047	1.1	1 in 842	6,590	1.0	1 in 1,052	14,637	1.0	1 in 936
	11,203	1.6	1 in 510	8,962	1.3	1 in 640	20,165	1.4	1 in 568

Placenta	—	—	—	313	0.0	1 in 30,912	313	0.0	1 in 30,912
Prostate	41,532	5.7	1 in 125	—	—	—	41,532	5.7	1 in 125
Testis	4,352	0.6	1 in 2,095	—	—	—	4,352	0.6	1 in 2,095
Penis and other genital, male	6,110	0.8	1 in 916	—	—	—	6,110	0.8	1 in 916
Urinary system	33,269	4.6	1 in 158	11,265	1.6	1 in 502	44,534	3.2	1 in 240
Urinary bladder	20,470	2.8	1 in 250	5,403	0.8	1 in 1,014	25,873	1.8	1 in 402
Kidney and renal pelvis	12,363	1.7	1 in 442	5,657	0.8	1 in 1,038	18,020	1.3	1 in 620
Ureter and other urinary organs	436	0.1	1 in 10,843	205	0.0	1 in 21,892	641	0.0	1 in 14,531
Eye and orbit	1,304	0.2	1 in 6,870	953	0.1	1 in 9,063	2,257	0.2	1 in 7,792
Brain and other nervous system	19,979	2.8	1 in 341	12,750	1.9	1 in 546	32,729	2.3	1 in 419
Endocrine system	9,263	1.3	1 in 709	26,665	3.9	1 in 279	35,928	2.5	1 in 402
Thyroid	8,570	1.2	1 in 759	26,095	3.8	1 in 285	34,665	2.5	1 in 416
Adrenal gland	693	0.1	1 in 10,797	570	0.1	1 in 14,053	1,263	0.1	1 in 12,209
Lymphoma	32,695	4.5	1 in 197	20,247	2.9	1 in 296	52,942	3.8	1 in 236
Hodgkin lymphoma	7,294	1.0	1 in 1,150	3,936	0.6	1 in 1,871	11,230	0.8	1 in 1,418
Non-Hodgkin lymphoma	25,344	3.5	1 in 238	16,263	2.4	1 in 352	41,607	3.0	1 in 284
Malig Imn Prol D	57	0.0	1 in 101,774	48	0.0	1 in 164,355	105	0.0	1 in 126,050
Multiple myeloma	10,725	1.5	1 in 465	7,756	1.1	1 in 646	18,481	1.3	1 in 541
Leukemia	32,481	4.5	1 in 239	21,132	3.1	1 in 353	53,613	3.8	1 in 284
Lymphoid leukemia	14,159	2.0	1 in 608	7,419	1.1	1 in 1,138	21,578	1.5	1 in 789
Myeloid leukemia	14,913	2.1	1 in 474	11,275	1.6	1 in 617	26,188	1.9	1 in 536
Leukemia uns	3,409	0.5	1 in 2,287	2,438	0.4	1 in 2,980	5,847	0.4	1 in 2,583

- >50% - incidental
- 75% - localised
- Median age – 65 yrs
- Smoking, HTN, Obesity, CKD
- M:F 1.65
- Sx is the mainstay
- Motzer criteria

Radioresistant

- Survival after 2Gy - Low alpha beta
- Clonogenic survival assays - a/b-ratios of 6.9 and 2.6
- Experience from 1970s and 80s

Fertil B, Malaise EP. Inherent radiosensitivity as a basic concept for human tumor radiotherapy. Int J RadiatOncolBiol Phys. 1981;7:621-629.
Deacon J, Peckham MJ, Steel GG. The radioresponsiveness of human tumours and the initial slope of the cell survival curve. RadiotherOncol 1984;2(4):317-323.Deschavanne PJ, Fertil B. A review of human cell radiosensitivity in vitro. Int J Radiat Oncol Biol Phys. 1996;34:251-66.
Ning S, Trisler K, Wessels BW, Knox SJ. Radiobiologic studies of radioimmunotherapy and external beam radiotherapy in Vitro and in Vivo in human renal cell carcinoma xenografts. Cancer 1997;80:2519–28.

- VHL tumor suppressor loss & HIF-α
- RCC radioresistance & HIF-2α
- Radiosensitization by Zoledronic A, fludarabine and siRNA - via STAT 1

Gordan, J.D.; Lal, P.; Dondeti, V.R.; Letrero, R.; Parekh, K.N.; Oquendo, C.E.; Greenberg, R.A.; Flaherty, K.T.; Rathmell, W.K.; Keith, B.; et al. Hif-alpha effects on c-myc distinguish two subtypes of sporadic VHL-deficient clear cell renal carcinoma. Cancer Cell 2008, 14, 435-446.
Bhatt, R.S.; Landis, D.M.; Zimmer, M.; Torregrossa, J.; Chen, S.; Sukhatme, V.P.; Iliopoulos, O.; Balk S.; Bubley, G.J. Hypoxia-inducible factor-2α: Effect on radiation sensitivity and differential regulation by an mTOR inhibitor. BJU Int. 2008, 102, 358-363.
Hui, Z.; Tretiakova, M.; Zhang, Z.; Li, Y.; Wang, X.; Zhu, J.X.; Gao, Y.; Mai, W.; Furge, K.; Qian, C.N.; et al. Radiosensitization by inhibiting STAT1 in renal cell carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 2009, 73, 288-295.

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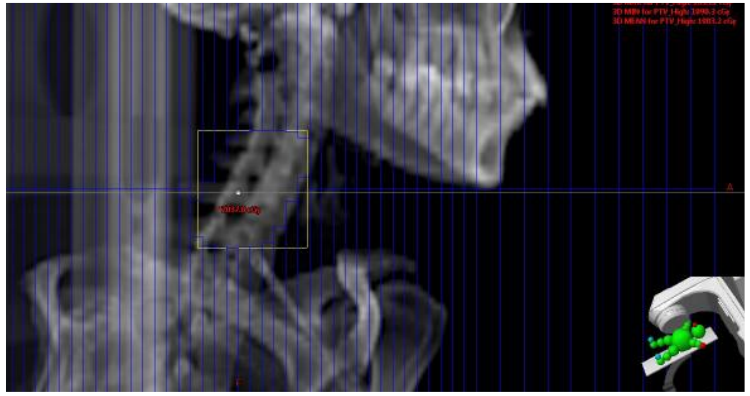
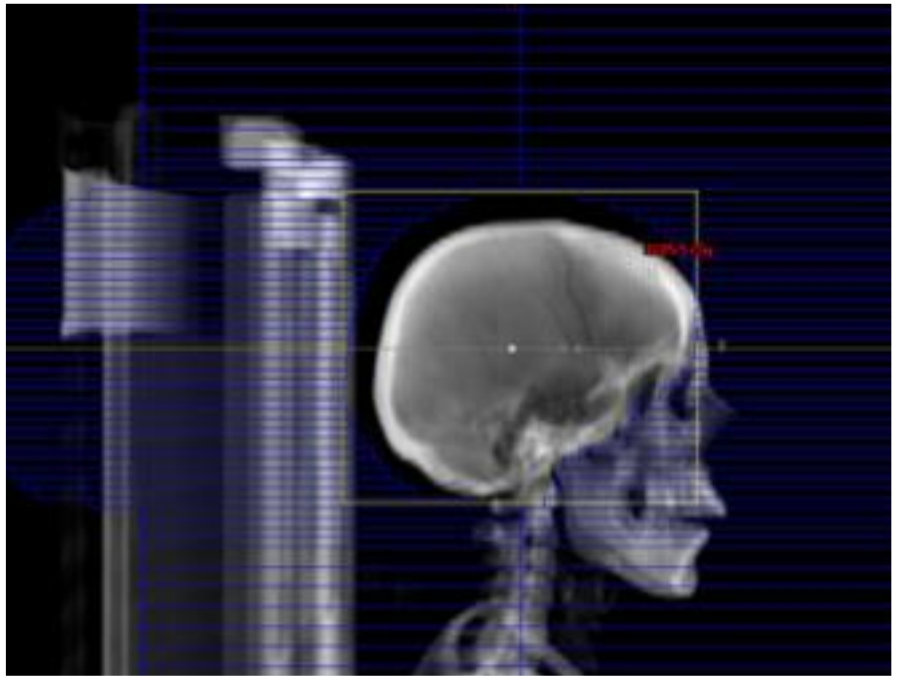
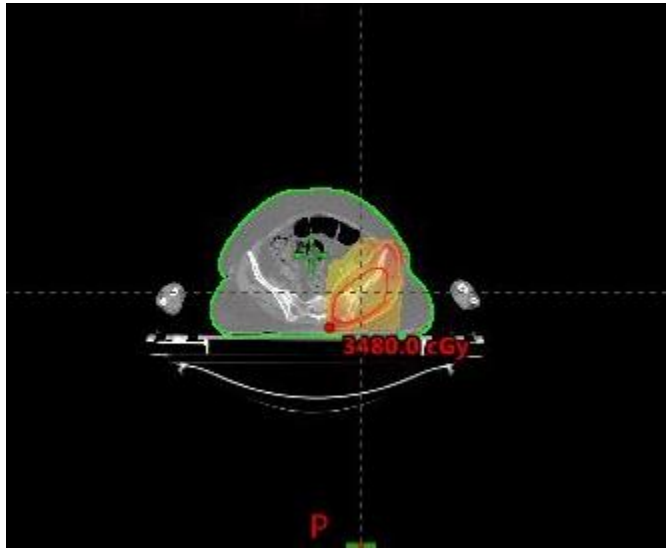
Role

- Primary
- Adjuvant
- Palliative

Palliative







- Lung
- Bone
- Brain
- WBRT - median survival 4.4 months; death from neurologic causes in 76%

Wronski, M.; Maor, M.H.; Davis, B.J.; Sawaya, R.; Levin, V.A. External radiation of brain metastases from renal carcinoma: A retrospective study of 119 patients from the MD Anderson Cancer Center. Int. J. Radiat. Oncol. Biol. Phys. 1997, 37, 753-759.

BED for pall

- Alpha beta 10; 86% palliative response (49% CR)
- Multivariate analysis – PS; higher BED

- Alpha beta 3 and 7; 73% palliative response. Not predictive

DiBiase, S.J.; Valicenti, R.K.; Schultz, D.; Xie, Y.; Gomella, L.G.; Corn, B.W. Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: Support for dose escalation based on a biological model. J. Urol. 1997, 158, 746-749.
Wilson, D.; Hiller, L.; Gray, L.; Grainger, M.; Stirling, A.; James, N. The effect of biological effective dose on time to symptom progression in metastatic renal cell carcinoma. Clin. Oncol. (R. Coll. Radiol.) 2003, 15, 400-407.

30Gy in 10

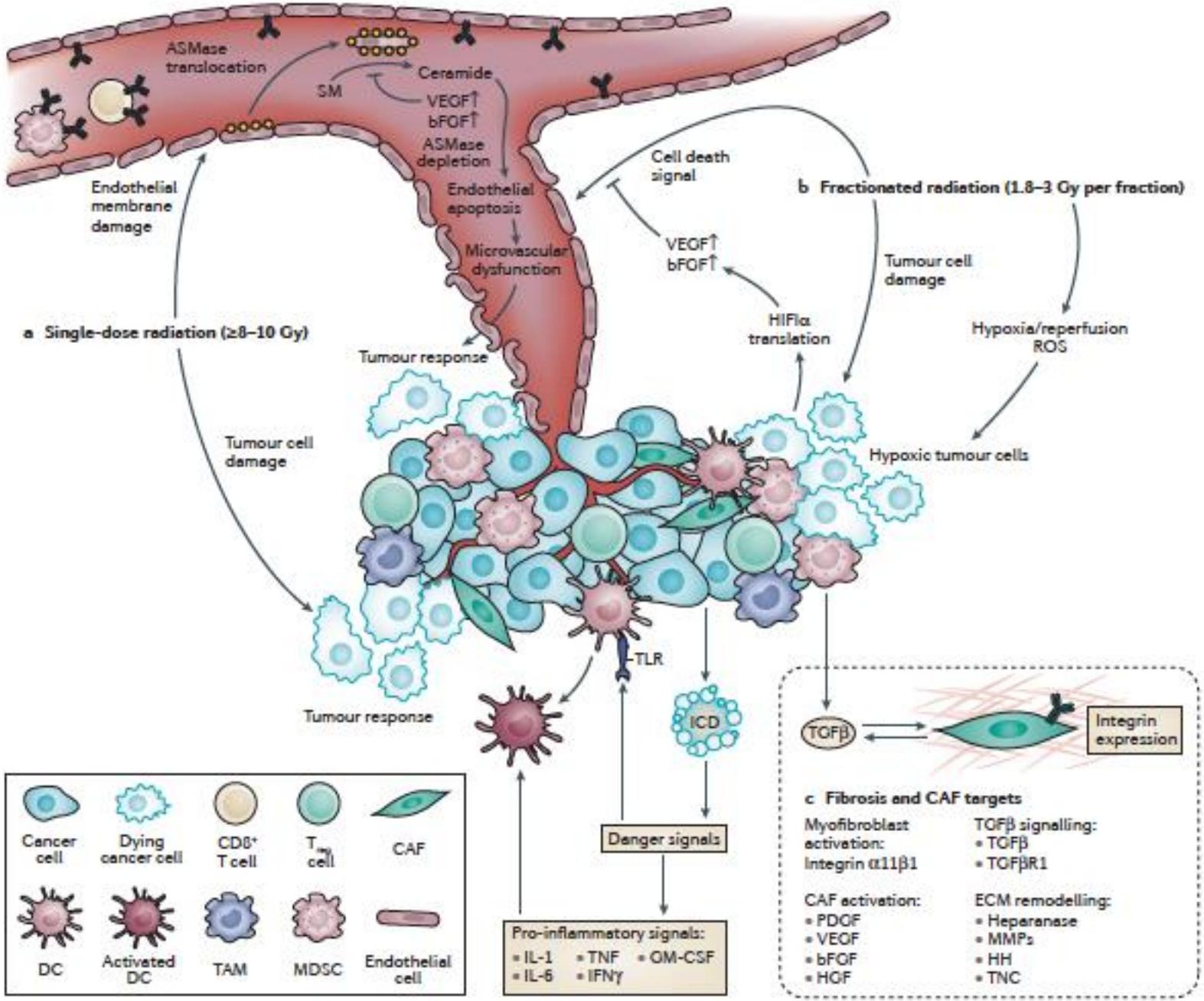
- Phase II trial; 31 patients
- 83% pain relief
- Limited follow-up
- BED_{10} – 39Gy

Lee, J.; Hodgson, D.; Chow, E.; Bezjak, A.; Catton, P.; Tsuji, D.; O'Brien, M.; Danjoux, C.; Hayter, C.; Warde, P.; et al. A phase II trial of palliative radiotherapy for metastatic renal cell carcinoma. Cancer 2005, 104, 1894-1900.

Stereotactic Radiation

- Ceramide induced endothelial cell apoptosis (Vascular tumour) through acid sphingomyelinase pathway
- ASMase 20 times more in endothelial cells
- Abscopal effect – through CD 4 and 8 T cells; intact p53

Kothari G, Foroudi F, Gill S, et al. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. Acta Oncol. 2015;54:148-57.
Walsh L, Stanfield JL, Cho LC, et al. Efficacy of ablative high-dose-per-fraction radiation for implanted human renal cell cancer in a nude mouse model. Eur Urol 2006, 50:795– 800.
De Meerleer G, Khoo V, Escudier B, et al. Radiotherapy for renal-cell carcinoma. Lancet Oncol. 2014 Apr;15(4):e170-7.
Sathishkumar S, Boyanovsky B, Karakashian AA, Rozenova K, Giltiay NV, Kudrimoti M, et al. Elevated sphingomyelinase activity and ceramide concentration in serum of patients undergoing high dose spatially fractionated radiation treatment: implications for endothelial apoptosis. Cancer Biol Ther 2005;4:979–86.


ASMase translocation
SM
Ceramide
VEGF↑
bFOF↑
ASMase depletion
Endothelial membrane damage
Endothelial apoptosis
Microvascular dysfunction
Cell death signal
b Fractionated radiation (1.8–3 Gy per fraction)
VEGF↑
bFOF↑
Tumour cell damage
HIFIα translation
Hypoxia/reperfusion ROS
a Single-dose radiation (≥8–10 Gy)
Tumour response
Tumour cell damage
Hypoxic tumour cells
TLR
Tumour response
ICD
TGFβ
Integrin expression
c Fibrosis and CAF targets
Myofibroblast activation:
Integrin α11β1
TGFβ signalling:
• TGFβ
• TGFβR1
CAF activation:
• PDGF
• VEGF
• bFGF
• HGF
ECM remodelling:
• Heparanase
• MMPs
• HH
• TNC
Danger signals
Pro-inflammatory signals:
• IL-1 • TNF • GM-CSF
• IL-6 • IFNγ
Cancer cell
Dying cancer cell
CD8+ T cell
T reg cell
CAF
DC
Activated DC
TAM
MDSC
Endothelial cell

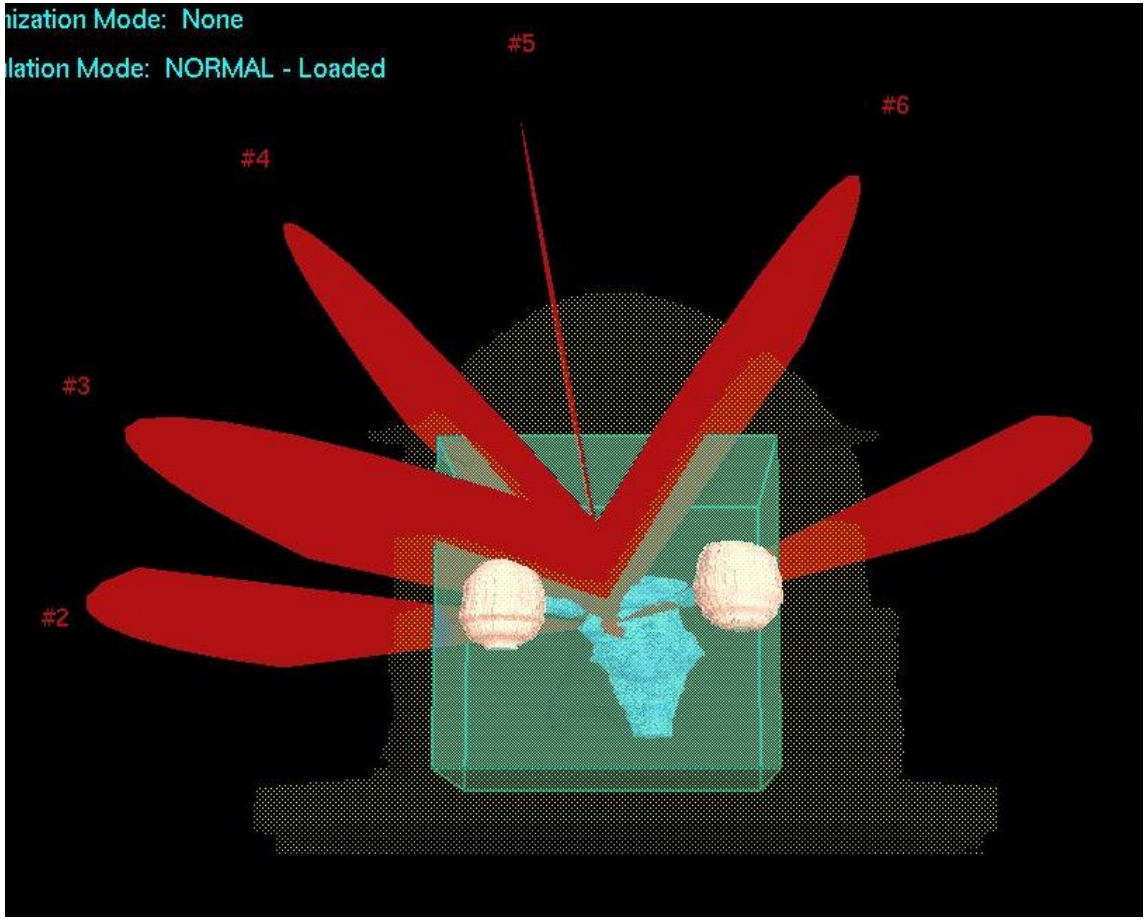

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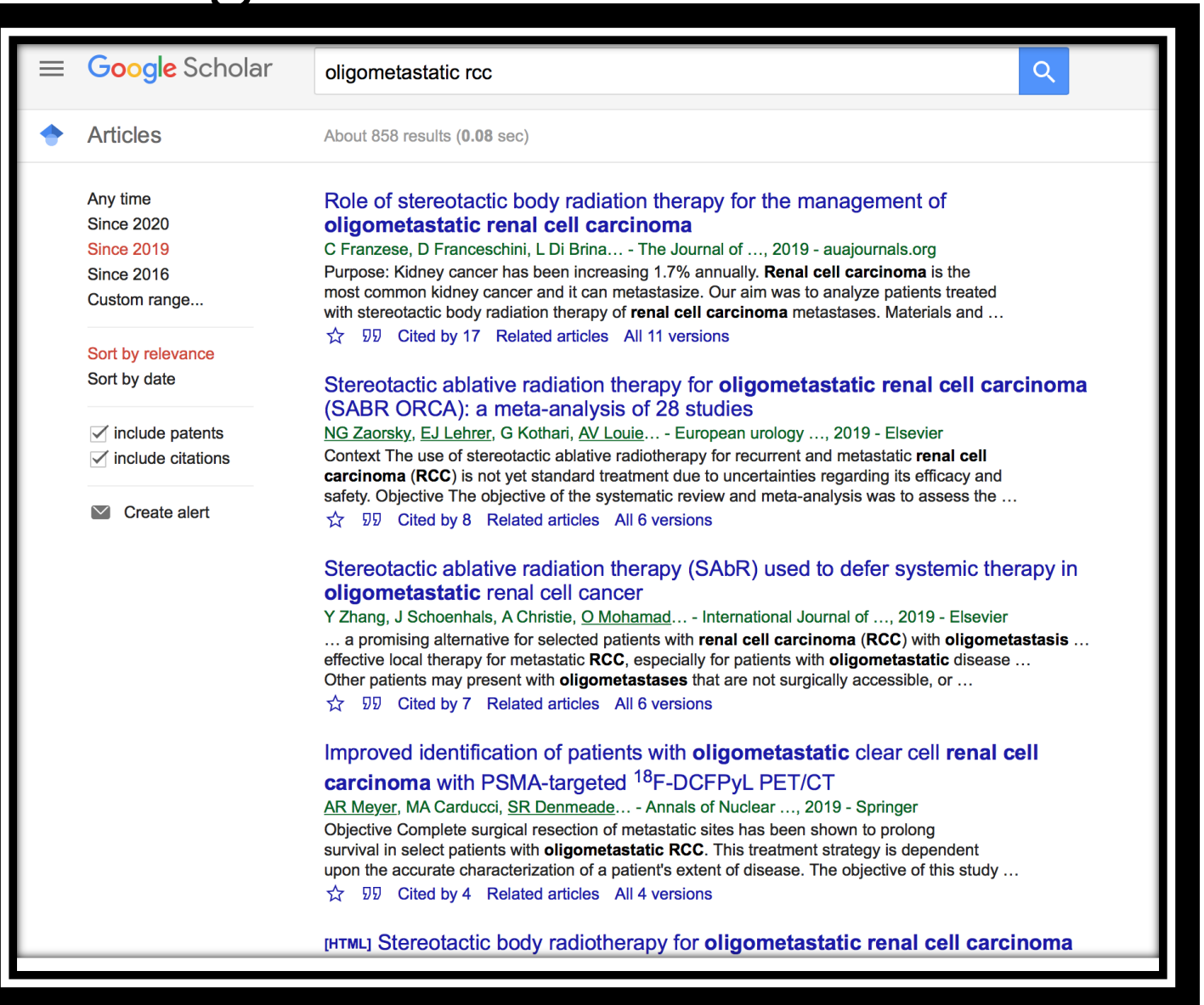
Table 1. Selected SRS series in RCC brain metastases.

Author	No. of Lesions Treated	SRS Type	Median Marginal Dose (Gy)	Tumor Control Rate (%)	Distant Failure Rate (%)	Median Survival (m)	Death From Brain Disease (%)
Payne *et al.* [27]	37	GK	20	100	50	8	0
Noel *et al.* [28]	65	LINAC	17.3	97	N/A	11	29
Muacevic *et al.* [29]	376	GK	21.2	94	33	11.1	10
Shuto *et al.* [30]	444	GK	22	84	39	12	17.2
Kano *et al.* [31]	531	GK	18	92	36	8.2	N/A

Shuto, T.; Matsunaga, S.; Suenaga, J.; Inomori, S.; Fujino, H. Treatment strategy for metastatic brain tumors from renal cell carcinoma: Selection of gamma knife surgery or craniotomy for control of growth and peritumoral edema. J. Neurooncol. 2010, 98, 169-175.

Kano, H.; Iyer, A.; Kondziolka, D.; Niranjan, A.; Flickinger, J.C.; Lunsford, L.D. Outcome predictors of gamma knife radiosurgery for renal cell carcinoma metastases. Neurosurgery , Volume 69, Issue 6, December 2011, Pages 1232–1239.

Oligometastases



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Editorial by Nguyen on pp. 524–525 of this issue

Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies

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Stereotactic ablative radiation therapy
Kidney cancer
Systematic review

Abstract

Context: The use of stereotactic ablative radiotherapy for recurrent and metastatic renal cell carcinoma (RCC) is not yet standard treatment due to uncertainties regarding its efficacy and safety.

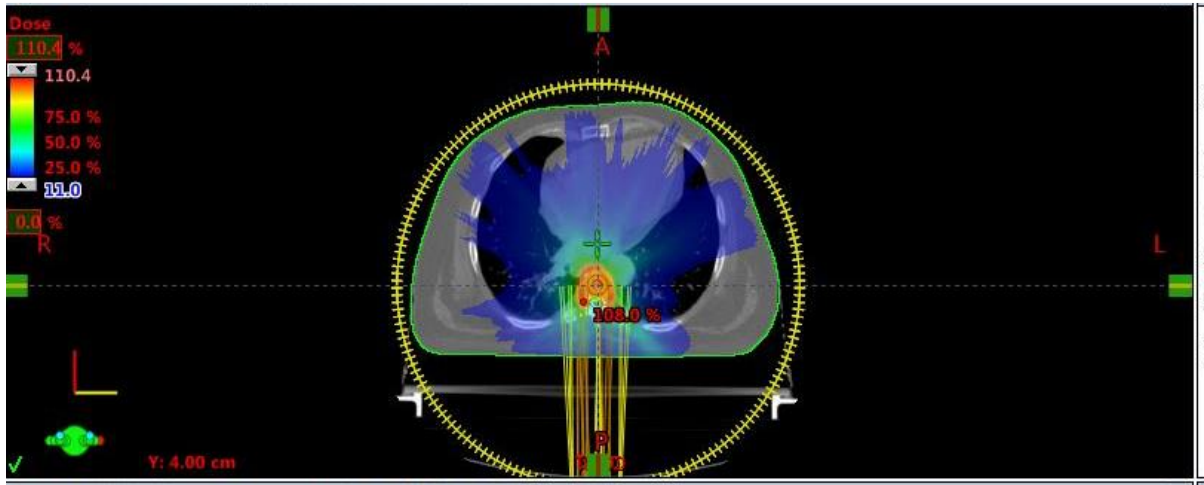
Objective: The objective of the systematic review and meta-analysis was to assess the efficacy and safety of stereotactic radiotherapy for metastatic RCC.

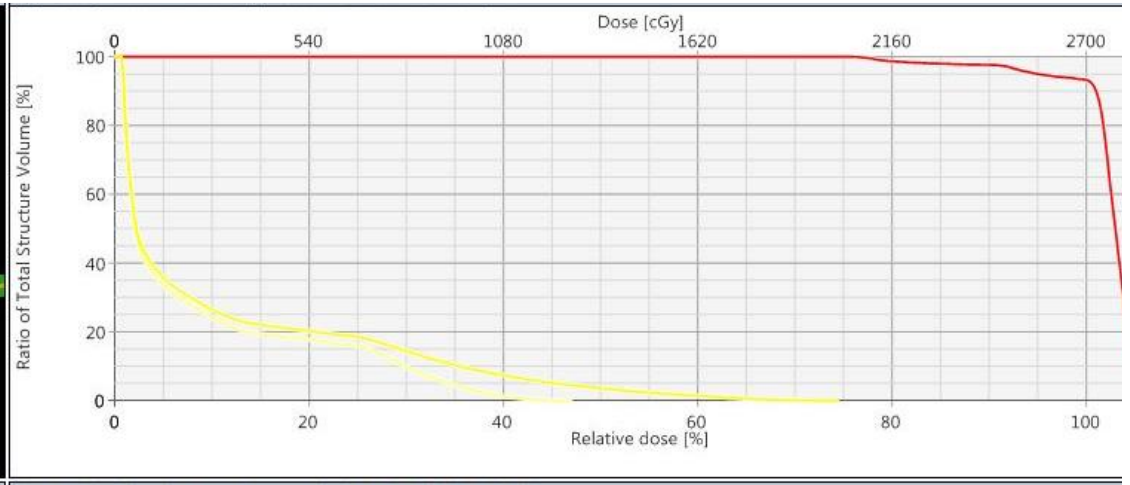
Evidence acquisition: A Population, Intervention, Control, Outcome, Study Design (PICOS)/Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)/Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocol was utilized to select studies published during 1998–2019. The primary outcome was 1 year local control and 1 year overall survival; the secondary outcome was Common Terminology Criteria for Adverse Events grade 3–4 toxicity. Weighted random-effect meta-analyses were conducted using the DerSimonian and Laird method, heterogeneity was evaluated using the I^2 statistic and Cochran Q test, and the Egger test assessed publication bias.

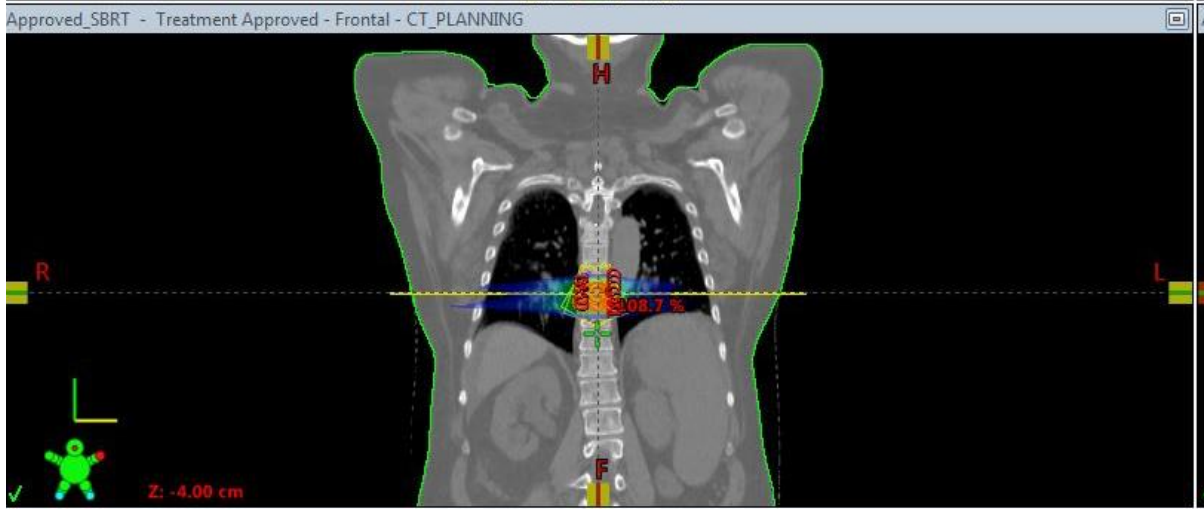
Evidence synthesis: A total of 265 studies were screened and 28 studies were included. There were 1602 mutually exclusive patients (679 extracranial/923 intracranial) and 3892 lesions (1159 extracranial/2733 intracranial). The median age was 62 yr. The median treatment volume was 59.7 cc for extracranial (interquartile range: 31.1–71.4) and 2.3 cc for intracranial (interquartile range: 1.3–4.3) lesions. Under the random-effect model, the summary effect size for 1-yr local control was 89.1% (95% confidence interval [CI]: 83.6–93.7%, $I^2 = 71\%$) and 90.1% (95% CI: 83.5–95.3%, $I^2 = 74\%$) for extracranial and intracranial disease, respectively. The 1-yr survival rates were 86.8% (95% CI: 62–99.8%, $I^2 = 95\%$) and 49.7% (95% CI: 41.1–58.3%, $I^2 = 74\%$) for extracranial and intracranial disease, respectively. The incidence of any grade 3–4 toxicity was 0.7% (95% CI: 0–2.1%, $I^2 = 0\%$) for extracranial disease and 1.1% (95% CI: 0–7.4%, $I^2 = 53\%$) for intracranial disease.

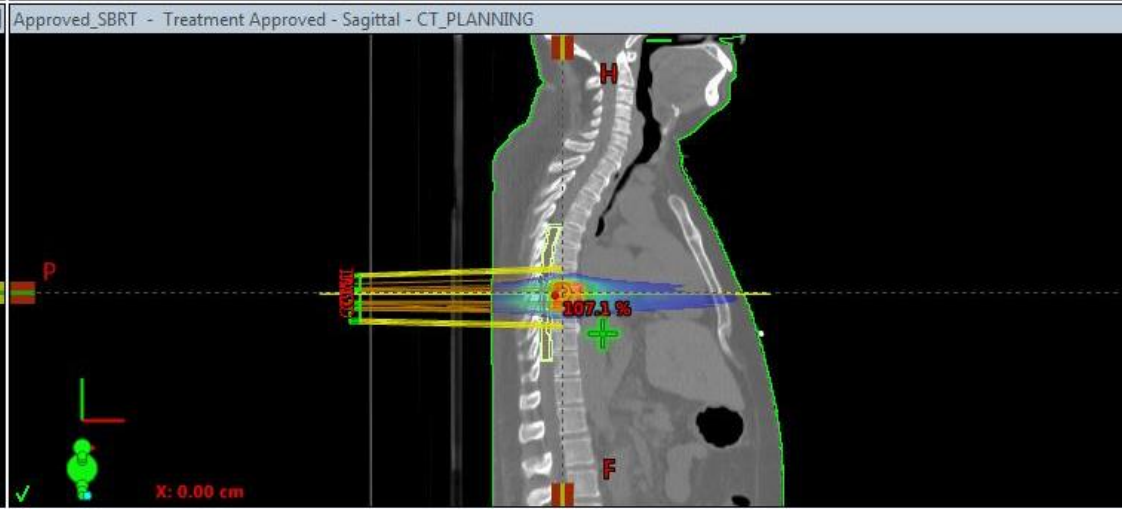
- 1- and 3-year local control - 98.1% and 91.9%
- 1- and 3-year OS - 84.3% and 43.8%
- BED at least 100 Gy
- Fraction size >9 Gy

Hoerner-Rieber J, Duma M, Blanck O, Hildebrandt G, Wittig A, Lohaus F, et al. Stereotactic body radiotherapy (SBRT) for pulmonary metastases from renal cell carcinoma-a multicenter analysis of the German working group ‘‘Stereotactic Radiotherapy”. J Thorac Dis 2017;9:4512–22.
Altoos B, Amini A, Yacoub M, Bourlon MT, Kessler EE, Flaig TW, et al. Local control rates of metastatic renal cell carcinoma (rcc) to thoracic, abdominal, and soft tissue lesions using stereotactic body radiotherapy (SBRT). Radiat Oncol 2015;10:218.


Dose
110.4 %
110.4
75.0 %
50.0 %
25.0 %
11.0
0.0 %
A
L
R
P
108.0 %
Y: 4.00 cm


Dose [cGy]
0
540
1080
1620
2160
2700
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
20
40
60
80
100
Relative dose [%]


Approved_SBRT - Treatment Approved - Frontal - CT_PLANNING
H
R
L
F
108.7 %
Z: -4.00 cm


Approved_SBRT - Treatment Approved - Sagittal - CT_PLANNING
H
P
F
107.1 %
X: 0.00 cm

Adjuvant

- No benefit even if N + or R1 resection
- Bad case selection, low dose RT , low patient numbers, old techniques [hemi abdominal with no liver / small bowel shielding]
- In both - positive margins and vena cava infiltration
- RILF in one trial; 20% RT induced deaths in the other

Finney R. The value of radiotherapy in the treatment of hypernephroma–a clinical trial. Br J Urol 1973;45(3):258–69.
Kjaer M, Iversen P, Hvidt V, et al. A randomized trial of postoperative radiotherapy versus observation in stage II and III renal adenocarcinoma. A study by the Copenhagen Renal Cancer Study Group. Scand J Urol Nephrol. 1987;21:285-9.

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However

- Meta analysis of 7 trials in 735 patients - Local control better; survival same

- Retrospective analysis of 325 patients
- 5 yr OS 72% versus 20% for capsular invasion
- 85 versus 33% with renal pelvis involvement
- Maybe after Partial nephrectomy if margins positive

Tunio MA, Hashmi A, Rafi M. Need for a new trial to evaluate postoperative radiotherapy in renal cell carcinoma: a meta-analysis of randomized controlled trials. Ann Oncol 2010;21(9):1839–45.
Rafla S., Parikh KJ. Role of adjuvant radiotherapy in management of renal cell carcinoma. Int J Radiat Oncol Biol Phys 1980;6(10):1418.

Preop RT

- Randomised
- 30-33Gy
- One trial – better survival at 18 mo, no difference at 5 yrs; especially benefited advanced disease.
- Other - worse

van der Werf-Messing B. Proceedings: carcinoma of the kidney. Cancer 1973;32(5):1056–61.
Juusela H, Malmio K, Alfthan O, Oravisto KJ. Preoperative irradiation in the treatment of renal adenocarcinoma. Scand J Urol Nephrol. 1977;11:277-81.

IORT

- Local recurrence/ advanced disease

- 22 patients, Median dose 12.5 Gy
- 77% incomplete resection
- 5 year in field local recurrence 9%
- Grade 3 to 5 toxicities 23%

Hallemeier CL, Choo R, Davis BJ, et al. Long-term outcomes after maximal surgical resection and intraoperative electron radiotherapy for loco regionally recurrent or loco regionally advanced primary renal cell carcinoma. Int J Radiat Oncol Biol Phys. 2012;82(5):1938-43.
Paly JJ, Hallemeier CL, Biggs PJ, et al. Outcomes in a multi-institutional cohort of patients treated with intraoperative radiation therapy for advanced or recurrent renal cell carcinoma. Int J Radiat Oncol Biol Phys. 2014;88(3):618-23.

Particle Therapy

- 60% reduction in integral dose
- Sharper penumbra
- 10 patients – 100% PFS, Local control; OS 74%
- Very slow shrinkage pattern

Nomiya T, Tsuji H., Hirasawa N., et al. Carbon ion radiation therapy for primary renal cell carcinoma:initial clinical experience. Int. J. Radiation Oncology Biol. Phys., 2008;72(3):828–833.

Primary

- Standard Of Care – Surgery

- Metastatic Disease (Alternative To Cytoreductive Nephrectomy)
- Bilateral Renal Tumors
- Contralateral Recurrence After Nephrectomy

Retrospective

Author and Year	Patients (N)	Inclusion Criteria	Dose/ Fractionation	Local Control	Toxicity	Other
Kaidar 2017[18]	6	• Nonsurgical candidates with tumors > 4 cm	• 39 Gy in 3 fractions	• 100%	• 33% grade 1 nausea • 17% grade 2 colitis	• 5–6 mm of target motion in each direction, on average
Chang 2016[17]	16	• Any primary tumor treated with SBRT (including patients with metastatic disease)	• 30–40 Gy in 5 fractions	• 100%	• 6% grade 2 nausea • 13% grade 4 renal toxicity (2 patients with CKD required dialysis after treatment) • Mean GFR decrease of 14.4%	
Sun 2016[20]	40 (RCC, 60%)	• Any primary tumor treated with SBRT	• 21–48 Gy in 3 fractions	• 92.7%	• NR	• Reduced tumor size and growth rate • No change in enhancement pattern
Yamamoto 2016[36]	14	• Tumors ≤ 5 cm • Inoperable or patient refused surgery	• 50–70 Gy in 10 fractions	• NR	• No ≥ grade 2 toxicity	• 20–30 Gy in 10 fractions was correlated with renal atrophy assessed on imaging
Lo 2014[19]	3	• Inoperable patients treated with SBRT for RCC	• 40 Gy in 5 fractions	• 100%	• No ≥ grade 2 toxicity	
Wang 2014[30]	9	• History of radical nephrectomy for previous RCC • ECOG ≤ 2	• 60–85 Gy in 5–7 fractions with gamma-SBRT	• 64.8%	• 22% grade 1 leukocytopenia • 22% grade 1 colitis • 22% grade 2 colitis	

Prospective

Author and Year	Patients (N)	Inclusion Criteria	Median Follow-Up	Dose/ Fractionation	Outcome	Toxicity
Siva 2017[28]	33	• ECOG 0–2 • Single lesion • Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery	• 24 months	• 26 Gy in 1 fraction for tumors ≤ 5 cm • 42 Gy in 3 fractions for tumors > 5 cm	• 100% 2-year local control • 90% freedom from distant progression	• 58% grade 1 (mostly chest wall pain and fatigue) • 21% grade 2 (mostly fatigue and nausea) • 3% grade 3 (fatigue)
Siva 2016[27]	21	• ECOG 0–2 • Single lesion • Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery	• 13 months	• 26 Gy in 1 fraction for tumors ≤ 5 cm • 42 Gy in 3 fractions for tumors > 5 cm	• NR	• Average GFR decrease of 8.7 mL/min at 1 year after treatment
Staehler 2015[21]	40 (RCC, 75%)	• Unable to spare kidney during surgery • Tumors < 4 cm	• 28 months	• 25 Gy in 1 fraction	• 98% local control at 9 months	• 3% grade 1 erythroderma • 8% grade 1 fatigue • 5% grade 1 nausea
Ponsky 2015[24]	19	• Poor surgical candidates • KPS ≥ 60	• 14 months	• 24–48 Gy in 4 fractions • 2 Gy per fraction dose escalation	• NR	• 5% grade 2 fatigue • 5% grade 4 duodenal ulcers • 5% grade 2 urinary incontinence • 11% grade 3 renal toxicity
Pham 2014[26]	20	• ECOG 0–2 • Single lesion • Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery	• NR	• 26 Gy in 1 fraction for tumors ≤ 5 cm • 42 Gy in 3 fractions for tumors > 5 cm	• NR	• 60% grade 1–2 side effects • Fatigue most common, followed by dermatitis, chest wall pain, and nausea
McBride 2013[23]	15	• Medically inoperable • Tumors ≤ 5 cm • KPS ≥ 70	• 37 months	• 21–48 Gy in 3 fractions • 2 Gy per fraction dose escalation	• 87% local control • 1 failure occurred in 21-Gy and 27-Gy arms	• 13% grade 1 nausea • 33% grade 1 fatigue • 13% late grade 3 renal dysfunction • Mean GFR decrease, 18 mg/dL
Kaplan 2010[25]	12	• Medically inoperable • Tumors ≤ 5 cm • KPS ≥ 70	• 14 months	• 21–39 Gy in 3 fractions • 2 Gy per fraction dose escalation	• 92% local control • 1 failure in 21-Gy arm	• Two patients with chronic renal failure had worsening of renal function
Svedman 2006[13]	4 with localized disease; 26 with metastatic disease; 10 received SBRT to the kidney	• Locally recurrent or inoperable RCC • Life expectancy > 3 months	• 52 months for living patients • 22 months for deceased patients	• 5–15 Gy in 2–5 fractions	• 98% local control	• 57% grade 1–2 cough, fatigue, skin rash, and/or local pain

- Meta analysis of 126 patients data - estimated weighted 2-year local control rate - 92.9%
- Grade 3+ toxicity of 4%
- Average FU - 13 to 52 months.
- Local Control Rates - 87% to 100%.
- For 3-fraction, minimum of 11 Gy /#.
- For 5-fraction, 8-10Gy/#.

Siva S, Pham D, Gill S, Corcoran NM, Foroudi F: A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. BJU Int 2012;110:E737-743.

Technical considerations

- Setup Reproducible
- Respiratory Motion Management
- On-board Imaging
- PTV – 3 to 5mm

Author and Year	Treatment System	Immobilization	Respiratory Management	On-Treatment Imaging	Dosage	Target Volumes	Fiducial Markers
Siva 2017[28]	• LINAC-based (Varian TrueBeam™ STx or Trilogy™)	• Vacuum immobilization (Elekta BodyFIX® dual vacuum device using both thoracic and pelvic setups)	• 4D CT simulation	• Pre-, mid-, and post-treatment cone beam CT	• 26 Gy in 1 fraction • 42 Gy in 3 fractions for tumors > 5 cm • 99% of PTV to full prescription dose	• ITV created using maximum inspiration, maximum expiration, and MIP datasets • PTV = ITV + 5 mm	• No
Siva 2016[27]	• LINAC-based (Varian TrueBeam™ STx or Trilogy™)	• Vacuum immobilization (Elekta BodyFIX® dual vacuum device using both thoracic and pelvic setups)	• 4D CT simulation	• Pre-, mid-, and post-treatment cone beam CT	• 26 Gy in 1 fraction • 42 Gy in 3 fractions for tumors > 5 cm • 99% of PTV to full prescription dose	• ITV created using maximum inspiration, maximum expiration, and MIP datasets • PTV = ITV + 5 mm	• No
Staehler 2015[21]	• CyberKnife	• NR	• Target tracking	• NR	• 25 Gy in 1 fraction • Prescribed to the 70% isodose line	• NR	• Yes—3 gold fiducials
Ponsky 2015[24]	• CyberKnife	• Synchrony vest • Vacuum cushion	• Expiratory phase CT • Expiratory phase MRI	• NR	• 24 Gy in 4 fractions • Increased by 2 Gy per fraction	• PTV = GTV + 0–3 mm	• Yes—3 or more gold fiducials
Pham 2014[26]	• LINAC-based (Varian TrueBeam™ STx or Trilogy™)	• Vacuum immobilization (Elekta BodyFIX® dual vacuum device using both thoracic and pelvic setups)	• 4D CT simulation	• Pre-, mid-, and post-treatment cone beam CT	• 26 Gy in 1 fraction (42 Gy in 3 fractions for tumors > 5 cm) • 99% of PTV to full prescription dose	• ITV created using maximum inspiration, maximum expiration, and MIP datasets • PTV = ITV + 5 mm	• No
McBride 2013[23]	• Robotic radiosurgical device	• NR	• NR	• NR	• 21–48 Gy in 3 fractions • 2 Gy per fraction dose escalation	• NR	• NR
Kaplan 2010[25]	• CyberKnife	• NR	• NR	• NR	• 21–39 Gy in 3 fractions • 2 Gy per fraction dose escalation	• PTV = GTV + 3 mm	• Yes—gold fiducials
Svedman 2006[13]	• LINAC-based	• Stereotactic frame • Vacuum pillow • Abdominal compression	• CT scan with abdominal compression	• NR	• 5–15 Gy in 2–5 fractions • 50% higher dose to center of target compared with periphery	• PTV = CTV + 5–10 mm (transverse) or 10 mm (CC)	• NR

Response Evaluation

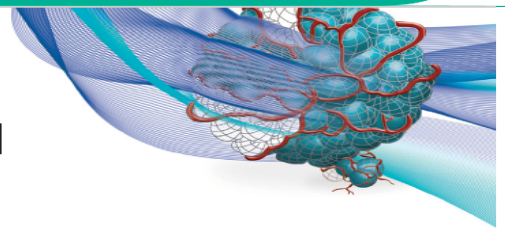
- Slow Radiographic Response
- No Significant Changes in Enhancement on CT or MRI
- Bx ??

Toxicities

- Mostly only grade I – fatigue nausea etc
- GFR decreased by 5.5- 8.7 mL / minute average at 1 year
- Underlying CKD
- 20-30 Gy in 10#; 13 Gy in 1#
- Long term ???????????

Siva S, Jackson P, Kron T, et al. Impact of stereotactic radiotherapy on kidney function in primary renal cell carcinoma: establishing a dose-response relationship. Radiother Oncol. 2016;118:540-6.

Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma



Shankar Siva*[1], Rodney J Ellis[2], Lee Ponsky[2], Bin S Teh[3], Anand Mahadevan[4], Alexander Muacevic[5], Michael Staehler[5], Hiroshi Onishi[6], Peter Wersall[7], Takuma Nomiya[8] & Simon S Lo[2]

Aim: To provide a multi-institutional consensus document for stereotactic body radiotherapy of primary renal cell carcinoma. **Materials & methods:** Eight international institutions completed a 65-item survey covering patient selection, planning/treatment aspects and response evaluation. **Results:** All centers treat patients with pre-existing hypertension and solitary kidneys. Five institutions apply size constraints of 5–8 cm. The total planning target volume expansion is 3–10 mm. All institutions perform pretreatment imaging verification, while seven institutions perform some form of intrafractional monitoring. Number of fractions used are 1–12 to a total dose of 25 Gy–80 GyE. Imaging follow-up for local tumor response includes computed tomography (n = 8), PET-computed tomography (n = 1) and MRI (n = 5). Follow-up frequency is 3–6 months for the first 2 years and 3–12 months for subsequent 3 years. **Conclusion:** Key methods for safe implementation and practice for stereotactic body radiotherapy kidney have been identified and may aid standardization of treatment delivery.

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KEYWORDS
• ablation • kidney cancer
• patterns of practice
• radiotherapy • SABR • SBRT
• stereotactic

Renal cell carcinoma (RCC) is one of the top ten most common malignancies in the developed world [1]. According to the American Cancer Society, kidney cancer incidence rates increased by 4.1% per year in men and 3.3% per year in women between 2004 and 2008 [2]. It affects predominantly the older population with a median age at diagnosis of 65 years, with a slight male preponderance. Surgery is the standard of care for primary RCC, however, many patients in this population have medical comorbidities that may preclude them from extirpative therapies. Patients undergoing partial or radical nephrectomy for renal cancer experience postoperative nephron loss, which may result in *de novo* chronic kidney disease or advancement of pre-existing renal dysfunction [2–5].

Nonsurgical definitive treatment options for this population of patients are limited. Radiofrequency ablation (RFA) and cryotherapy are two alternative ablative therapies available for patients with inoperable disease. RFA is a treatment technique that involves percutaneous insertion of electrodes to achieve thermal ablation of a renal tumor. Cryotherapy is based

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[7]Karolinska University Hospital / Karolinska Institute, Stockholm, Sweden,
[8]National Institute of Radiological Sciences, Chiba, Japan
*Author for correspondence: Tel.: +61 3 9656 1111; Fax: +61 3 9656 1424; shankar.siva@petermac.org

Future Medicine part of fsg

No head to head comparison with ablations

- No size limit
- Any location

- Small Number
- No Long-term Follow-up
- Dose Fractionation
- No HPR
- Selection bias

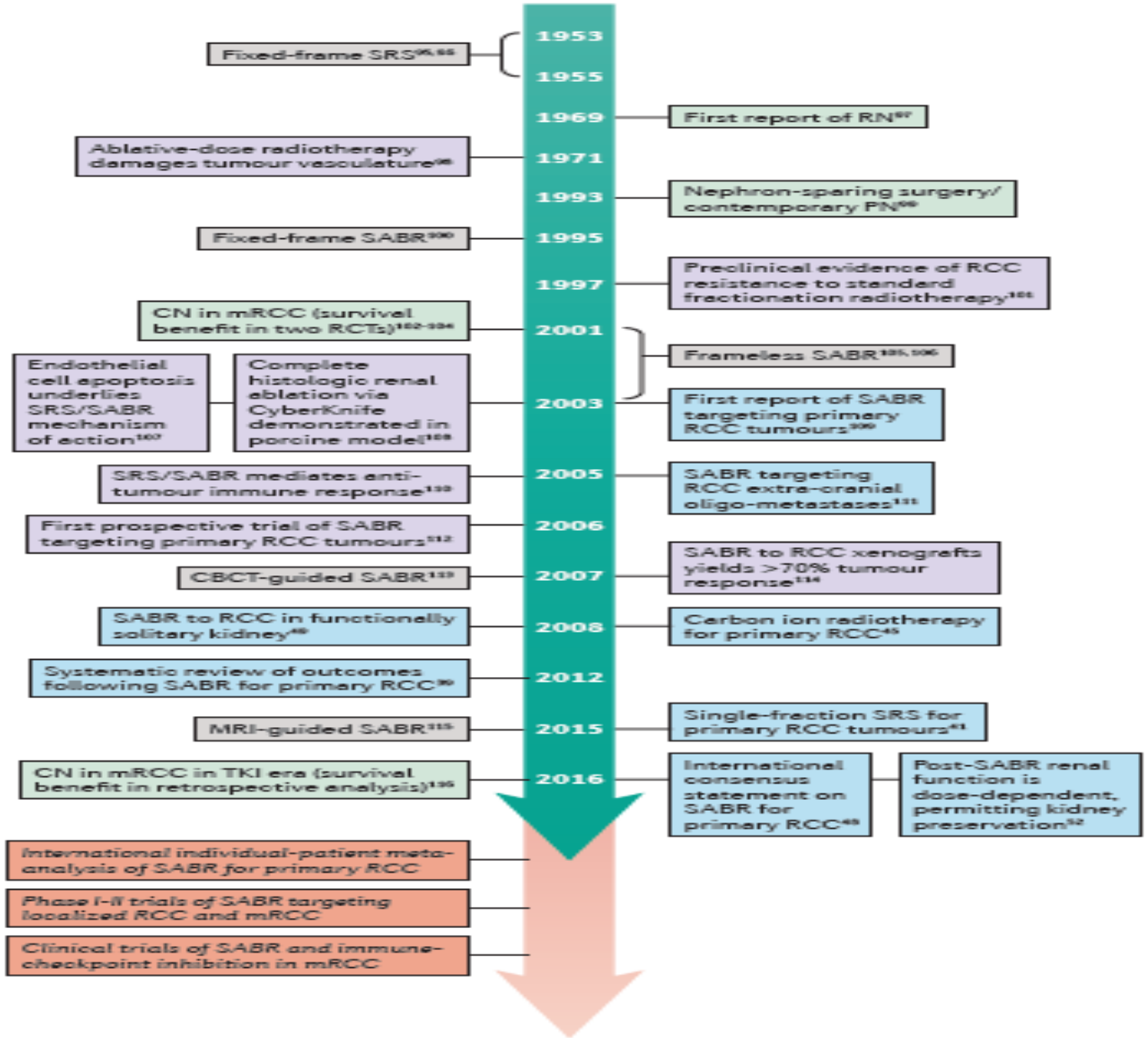
Immune therapy with RT

- Upregulation of antigenic expression, antigen processing, MHC molecules, co-stimulatory signals
- Increasing the production of immunostimulatory cytokines
- Recruiting antigen-presenting and immuneeffector cells to the tumor microenvironment
- VEGF and FGF families, check point inhibitors

Liu Y, Dong Y, Kong L, et al. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. J Hematol Oncol 2018;11(1):104.
Ko EC, Formenti SC. Radiotherapy and checkpoint inhibitors: a winning new combination? Ther Adv Med Oncol 2018;10.

Future Directions

- Renal impairment, QoL, Cost effectiveness.
- Combination with other local / systemic Rx
- Abscopal effect??
- Versus RFA/ cryo
- Versus sx ???
- Sequencing TKI


1953
Fixed-frame SRS
1955
1969
First report of RN
1971
Ablative-dose radiotherapy damages tumour vasculature
1993
Nephron-sparing surgery/ contemporary PN
1995
Fixed-frame SABR
1997
Preclinical evidence of RCC resistance to standard fractionation radiotherapy
2001
CN in mRCC (survival benefit in two RCTs)
Frameless SABR
2003
Endothelial cell apoptosis underlies SRS/SABR mechanism of action
Complete histologic renal ablation via CyberKnife demonstrated in porcine model
First report of SABR targeting primary RCC tumours
2005
SRS/SABR mediates anti-tumour immune response
SABR targeting RCC extra-cranial oligo-metastases
2006
First prospective trial of SABR targeting primary RCC tumours
2007
CBCT-guided SABR
SABR to RCC xenografts yields >70% tumour response
2008
SABR to RCC in functionally solitary kidney
Carbon ion radiotherapy for primary RCC
2012
Systematic review of outcomes following SABR for primary RCC
2015
MRI-guided SABR
Single-fraction SRS for primary RCC tumours
2016
CN in mRCC in TKI era (survival benefit in retrospective analysis)
International consensus statement on SABR for primary RCC
Post-SABR renal function is dose-dependent, permitting kidney preservation
International individual-patient meta-analysis of SABR for primary RCC
Phase I-II trials of SABR targeting localized RCC and mRCC
Clinical trials of SABR and immune-checkpoint inhibition in mRCC

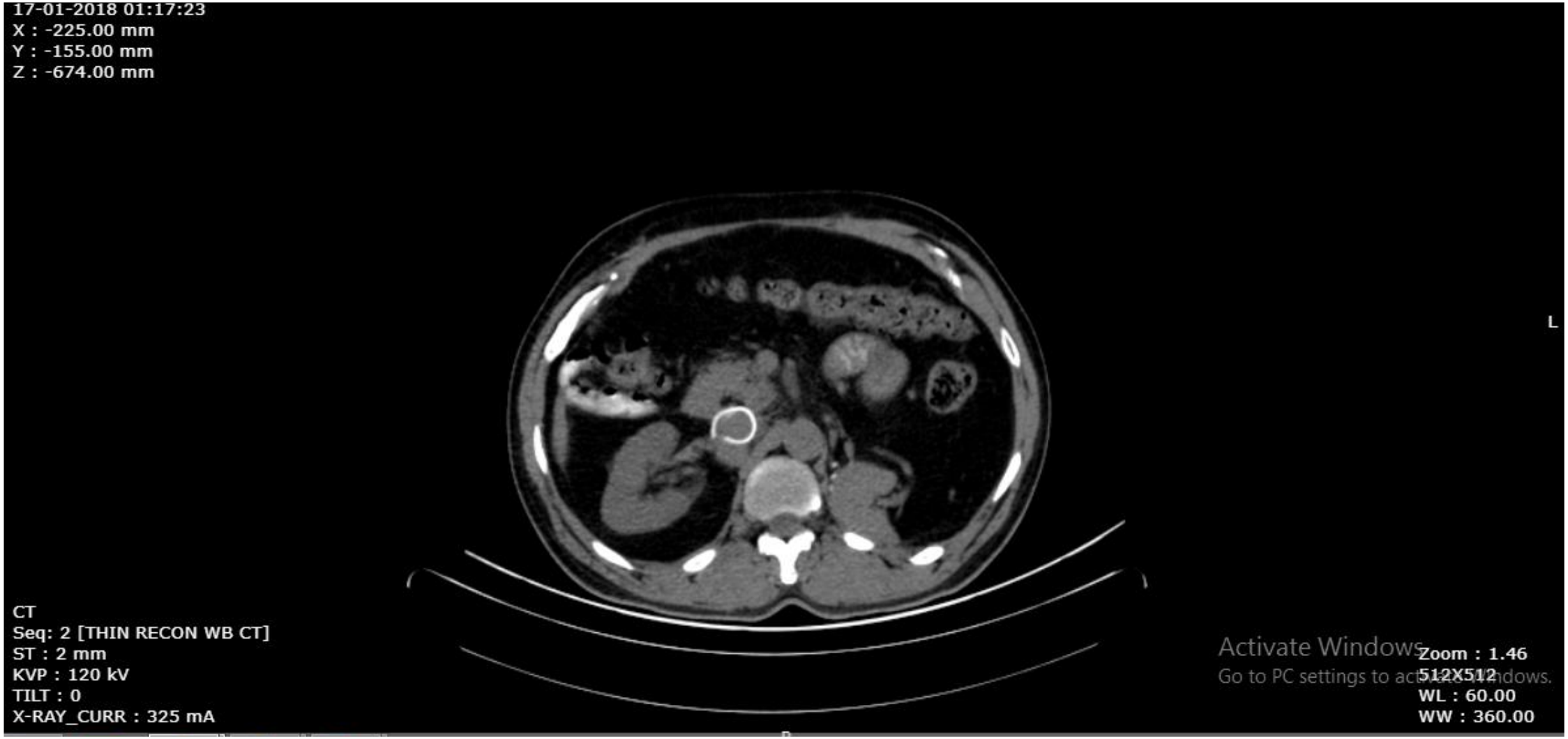
Few scenarios..

58/M

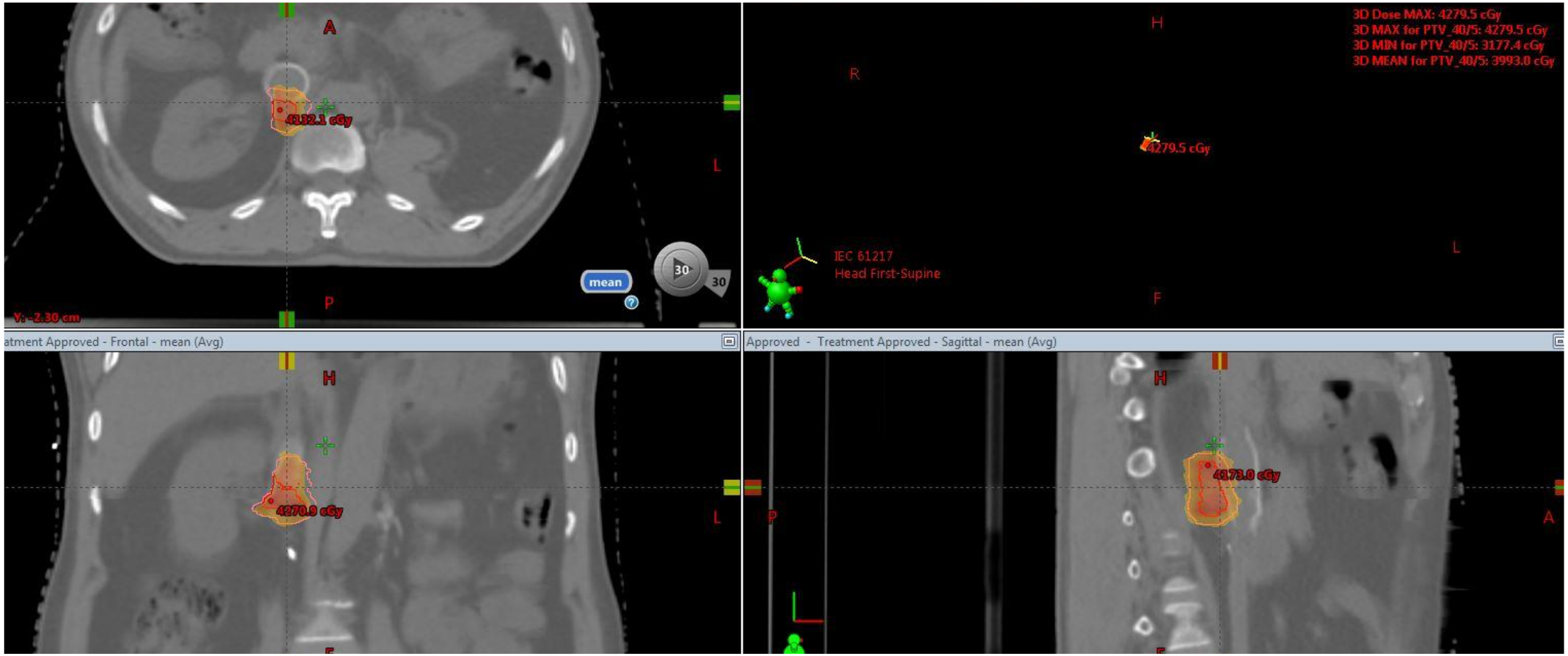
- Hematuria- in April 2015- single episode
- CT with contrast : large lobulated mass involving lower pole of the kidney, renal vein, infra hepatic short segment IVC thombus. Multiple subcentimetric lung nodules.
- Left Radical Nephrectomy With IVC Thrombectomy and Graft on 21/05/2015.
- Per op - Thrombus removed with IVC wall as it was infiltrating the wall.

- HPR - Renal Cell Carcinoma-Left Kidney -pT3
- Fuhrman grade 2
- Tumour size-12 cm.
- Tumour is limited to the kidney.
- Tumour is infiltrating into the renal vein at the hilum.
- Margins free


17-01-2018 01:17:23
17-01-2018 13:36:21
10 cm
A
R
L
P
CT: Series: 4/ Slice: 106
PT: Series: 763730/ Slice: 83
PT
Width:360 Level:60
Zoom : 1.68
445X493
WL : 128.00
Activate Windows
Go to PC settings to activate Windows.


17-01-2018 01:17:23
X : -225.00 mm
Y : -155.00 mm
Z : -674.00 mm
L
CT
Seq: 2 [THIN RECON WB CT]
ST : 2 mm
KVP : 120 kV
TILT : 0
X-RAY_CURR : 325 mA
Activate Windows
Go to PC settings to activate Windows.
Zoom : 1.46
512X512
WL : 60.00
WW : 360.00

40 Gy/5#

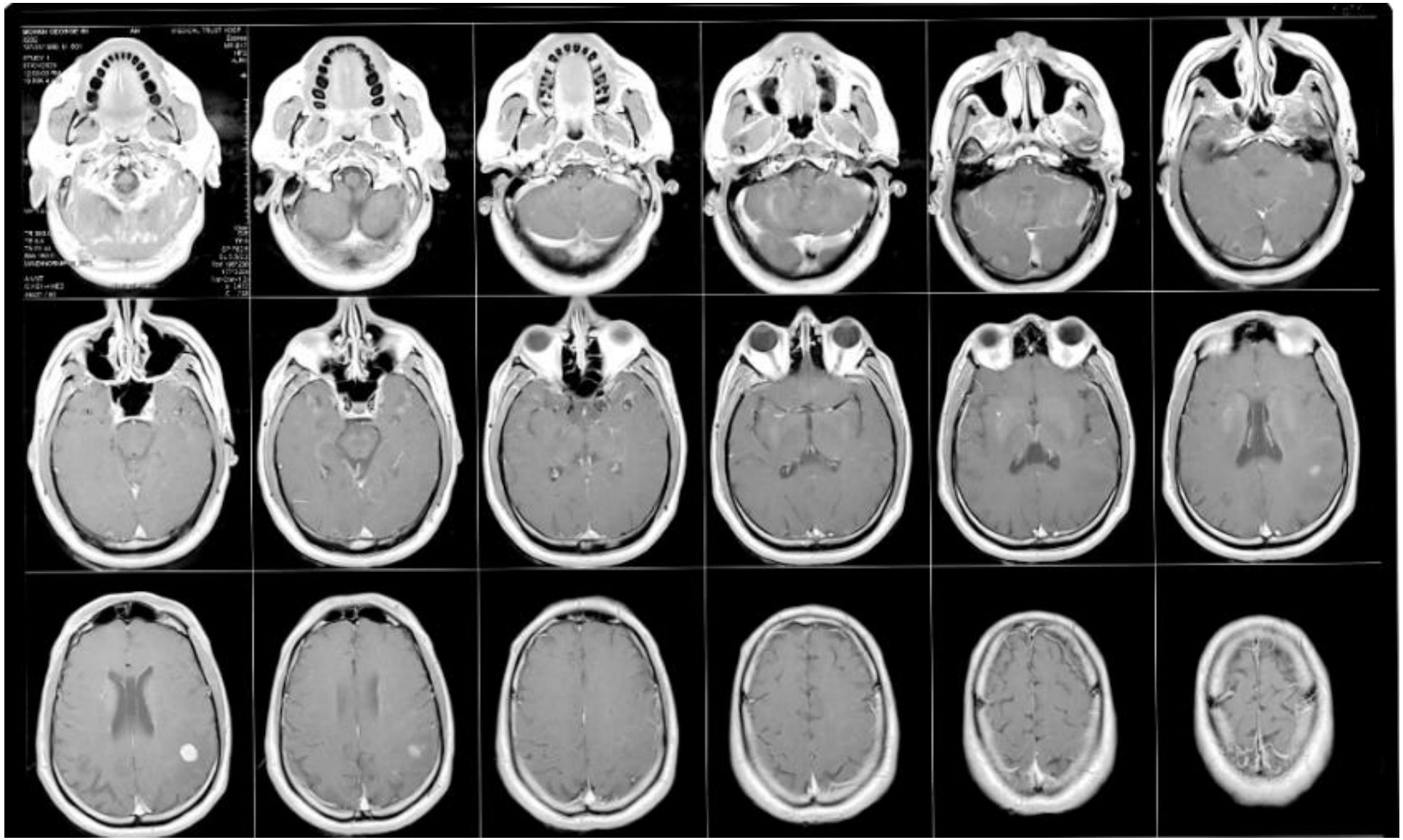

A
4132.1 cGy
L
mean
30
30
P
V: -2.30 cm
H
R
3D Dose MAX: 4279.5 cGy
3D MAX for PTV_40/5: 4279.5 cGy
3D MIN for PTV_40/5: 3177.4 cGy
3D MEAN for PTV_40/5: 3993.0 cGy
4279.5 cGy
IEC 61217
Head First-Supine
L
F
atment Approved - Frontal - mean (Avg)
H
4270.9 cGy
L
Approved - Treatment Approved - Sagittal - mean (Avg)
H
4173.0 cGy
P
A
L


05-03-2019 08:52:48
X : -190.30 mm
Y : -5.30 mm
Z : 850.10 mm
CT

60/M

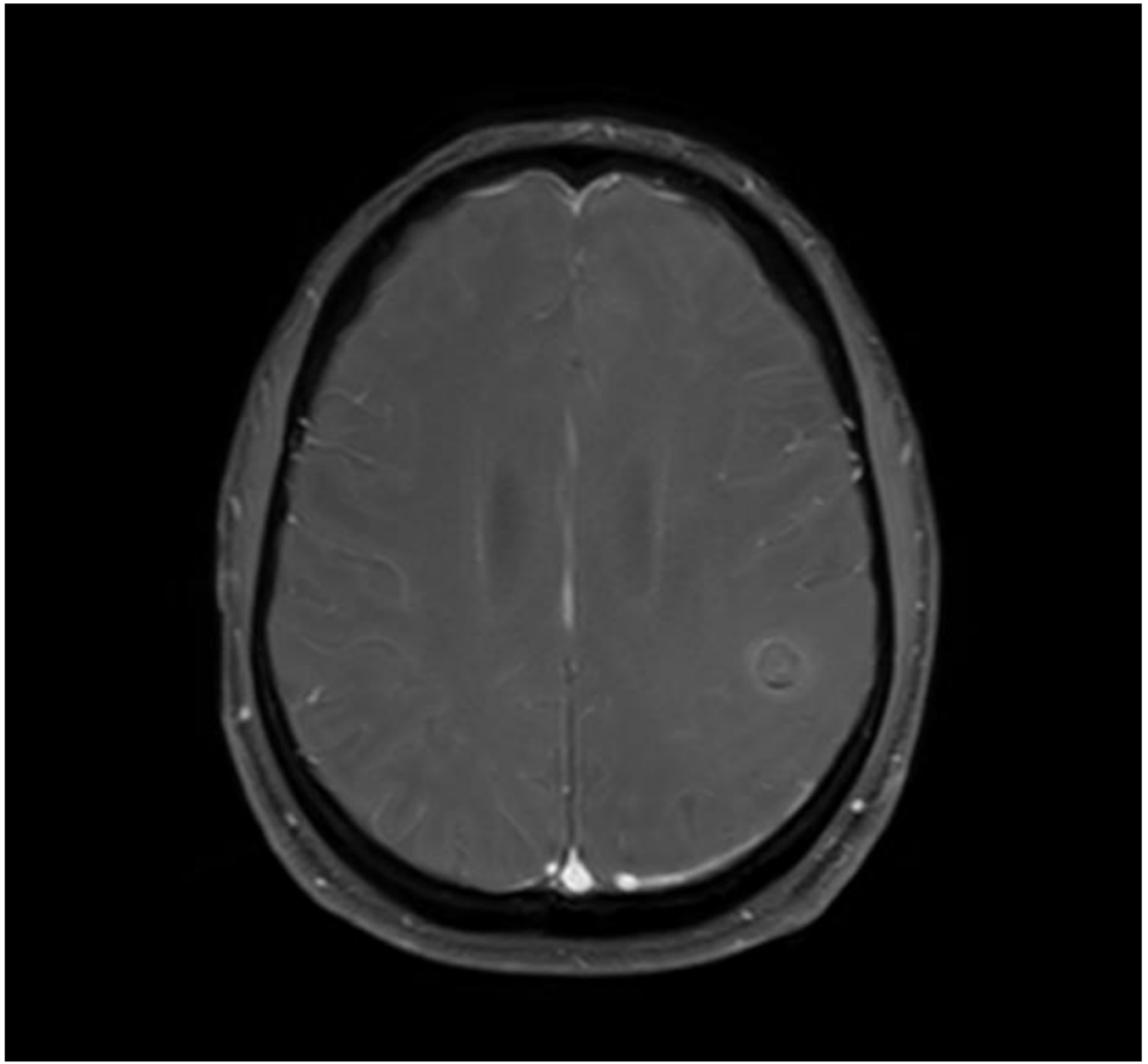
- Cough and congestion X 2 months.
- Chest x-ray - right upper lobe collapse.
- Chest CT - 2 enhancing upper lobe lesions and hilar adenopathy with collapse consolidation. Left renal mass in CT cuts of Upper abdomen
- CECT abdomen: a large necrotic enhancing middle and upper polar mass arising from left kidney with probable invasion
- Bronchoscopy - vascular necrotic mass in the right middle bronchus; Bx - inconclusive.
- He underwent left open nephrectomy on 11/4/2006 -mass was completely excised along with the adrenal gland and parts of diaphram.

- Histopathology - Furhmans Type 4 Clear Cell Carcinoma with rhabdoid features infiltrating into sinus, pelvis and perinephric fat, psoas muscle. Stage T4 N0M1
- On follow up
- Seizures – 1 episode – April 2008

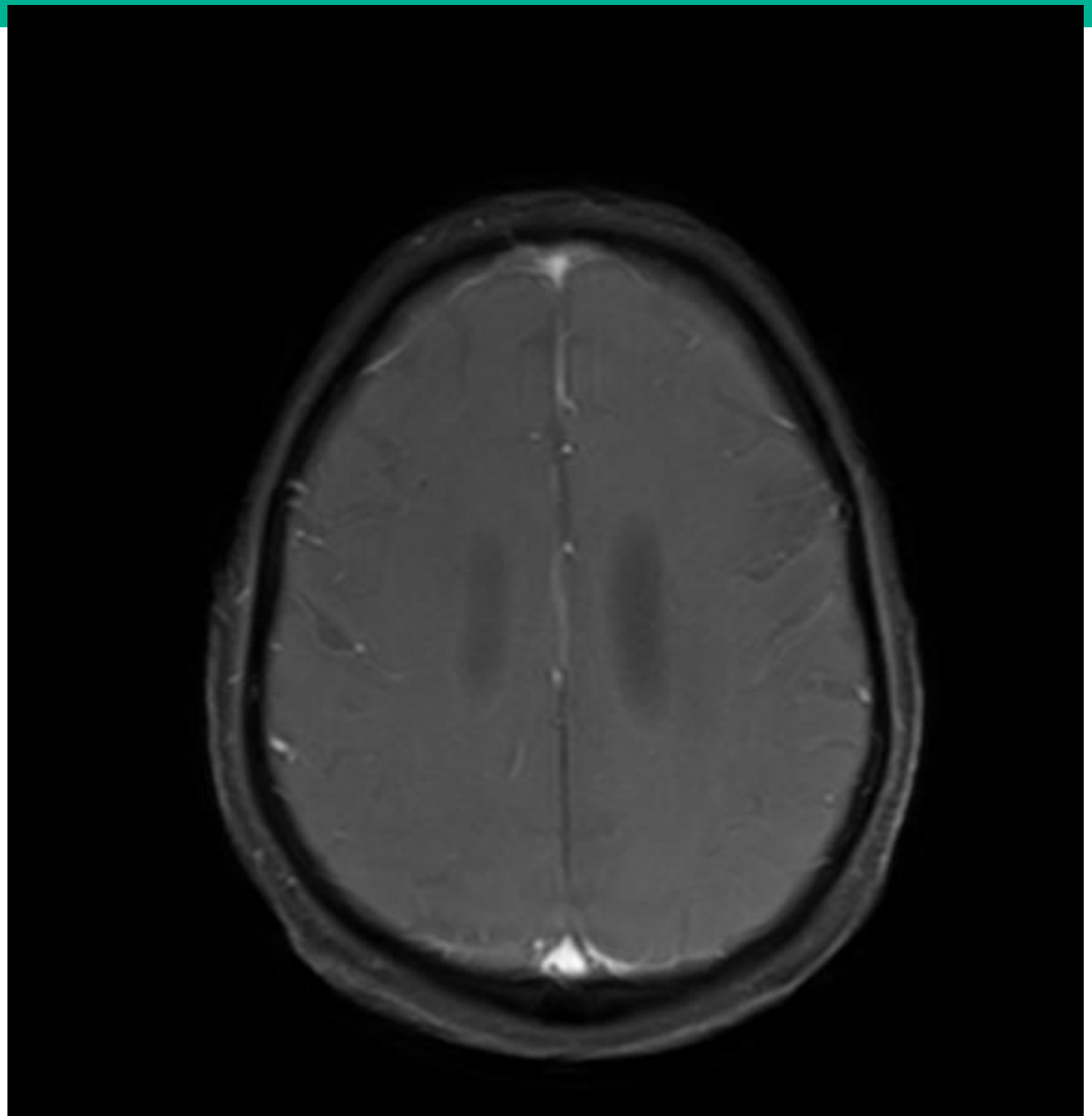


18Gy prescribed to the 85% isodose line

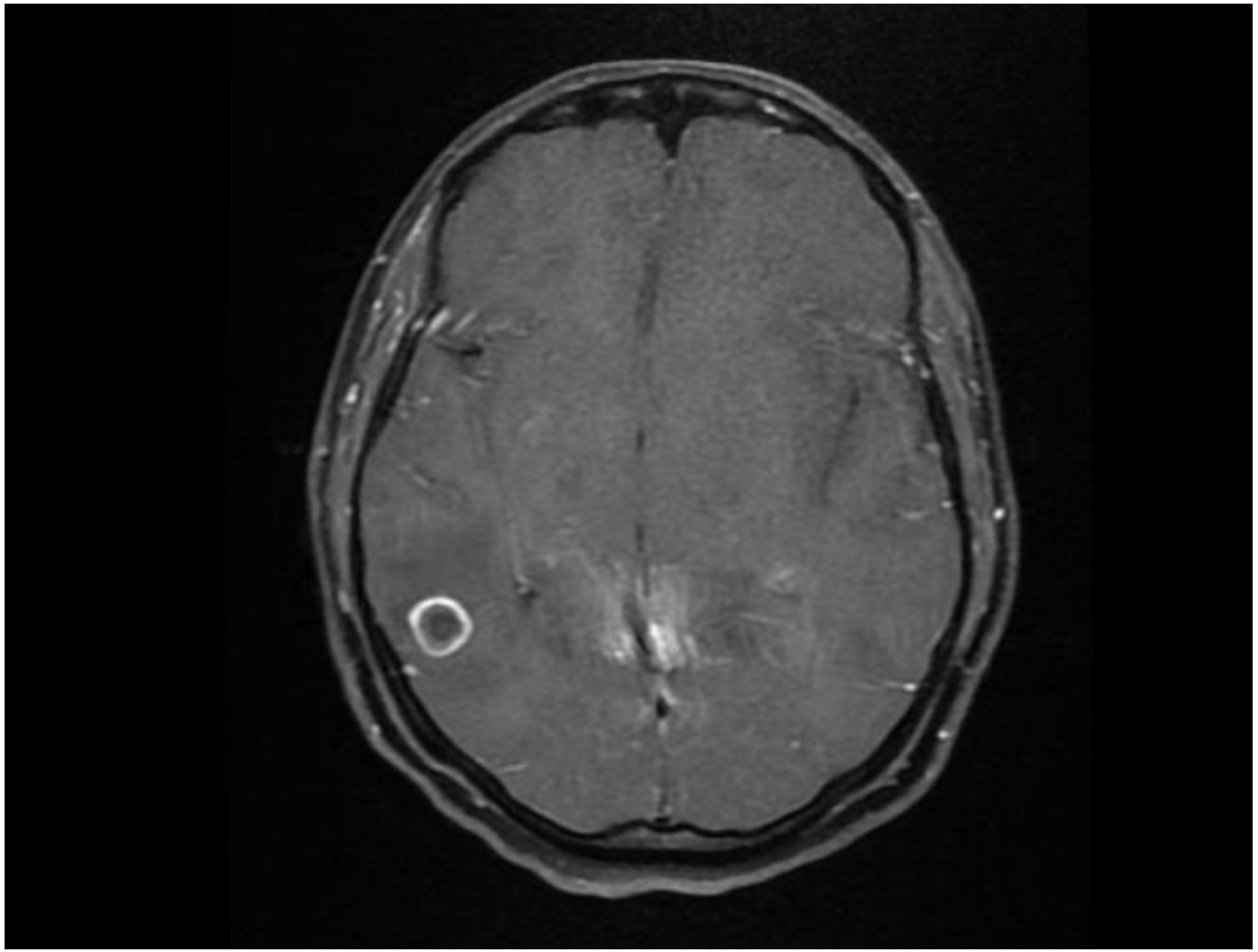
6 months

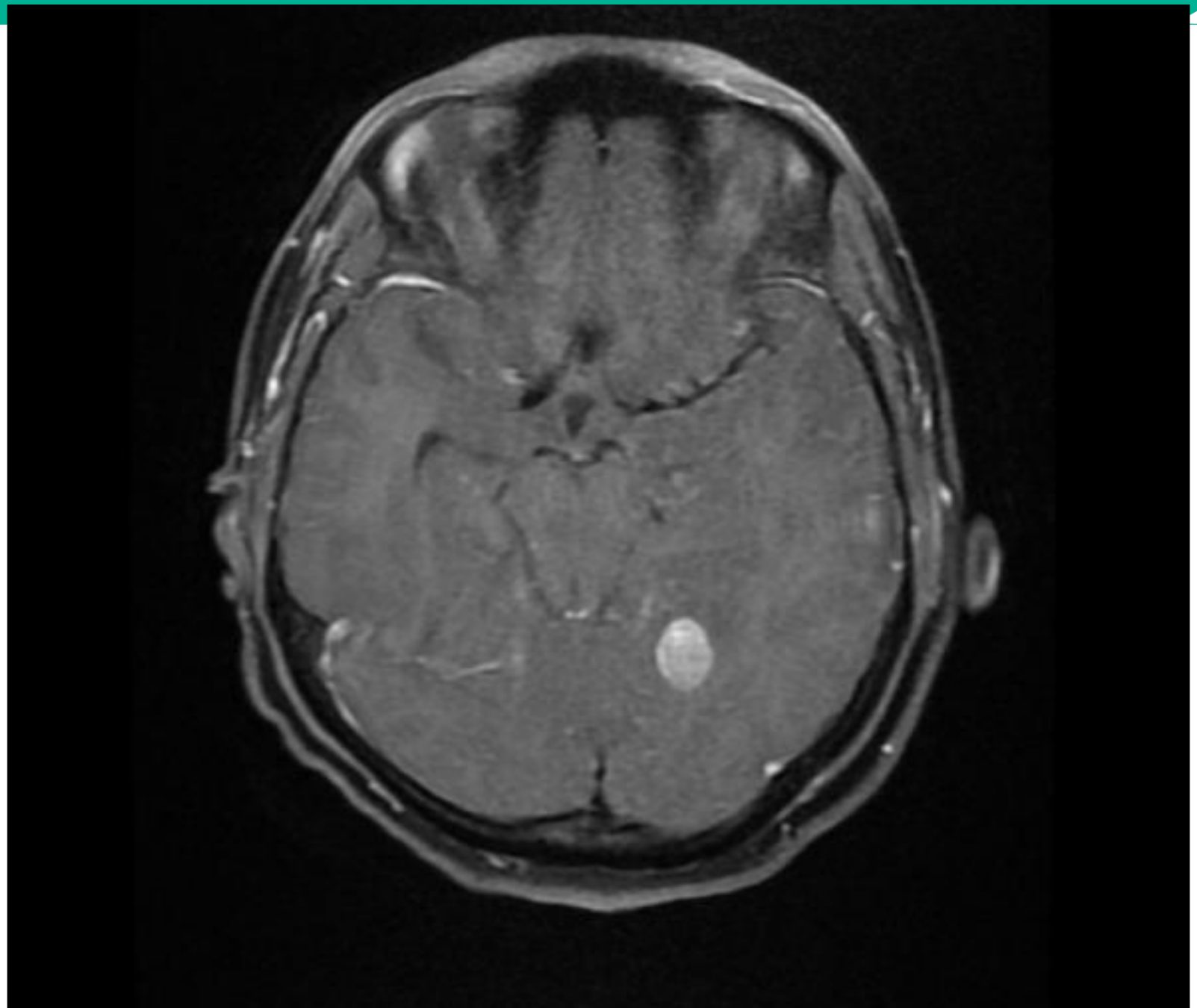


6 years



April 2016





https://www.theguardian.com/commentisfree/picture/2020/mar/28/coronavirus-everything-must-change-cartoon