Radiotherapy in Renal Cell Carcinoma

Dr Durgapoorna
Aster Medcity, Kochi.
durgapoorna@gmail.com
TABLE 2. Projected Incidence of Cancer Statistics in India, 2020

<table>
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<th>Patients</th>
<th>CR</th>
<th>Cum Risk</th>
<th>Patients</th>
<th>CR</th>
<th>Cum Risk</th>
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Original Reports

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

Prashant Mathur, DNB, PhD; Krishnan Sathishkumar, MSc; Meesha Chaturvedi, MBBS; Priyanka Das, B-Level; Kondalli Lakshminarayana Sudarshan, MSc; Stephen Santhappan, MSc, MPhil;...

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</table>
• >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

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

WELL SARGE, THIS LOOKS LIKE ONE OF YOUR CLASSIC OPEN AND SHUT CASES
Role

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

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

30Gy in 10

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

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


Role of stereotactic body radiation therapy for the management of oligometastatic renal cell carcinoma

C Francesco, D Francoeschini, L Di Brina... - The Journal of... 1999 - eos-journals.org

Purpose: Kidney cancer has been increasing 1.7% annually. Renal cell carcinoma is the most common kidney cancer and it can metastasize. Our aim was to analyze patients treated with stereotactic body radiation therapy of renal cell carcinoma metastases. Materials and ...

Cited by 17 Related articles All 11 versions

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

NG Zaorsky, ED Leherer, G Kohari, AV Louis... - European urology... 2019 - Elsevier

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 ...

Cited by 8 Related articles All 6 versions

Stereotactic ablative radiation therapy (SABR) used to defer systemic therapy in oligometastatic renal cell cancer

Y Zhang, J Schoenhals, A Christie, O Mohamed... - International Journal of... 2019 - Elsevier

...a promising alternative for selected patients with renal cell carcinoma (RCC) with oligometastases ... effective local therapy for metastatic RCC, especially for patients with oligometastatic RCC that are not surgically accessible, or ...

Cited by 7 Related articles All 6 versions

Improved identification of patients with oligometastatic clear renal cell carcinoma with PSMA-targeted 18F-DCFPyl PET/CT

AR Meyer, MA Carducci, SR Denmeade... - Annals of Nuclear... 2019 - Springer

Objective: Complete surgical resection of metastatic sites has been shown to prolong survival in selected patients with renal cell carcinoma. This treatment strategy is dependent upon the accurate characterization of a patient’s extent of disease. The objective of this study ...

Cited by 4 Related articles All 4 versions

Stereotactic body radiotherapy for oligometastatic RCC
• 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

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


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

Preop RT

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

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%

Particle Therapy

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

Primary

• Standard Of Care – Surgery

• Metastatic Disease (Alternative To Cytoreductive Nephrectomy)
• Bilateral Renal Tumors
• Contralateral Recurrence After Nephrectomy
<table>
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<th>Patients (N)</th>
<th>Inclusion Criteria</th>
<th>Dose/Fractionation</th>
<th>Local Control</th>
<th>Toxicity</th>
<th>Other</th>
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<td>Kaidar 2017[18]</td>
<td>6</td>
<td>Nonsurgical candidates with tumors &gt; 4 cm</td>
<td>39 Gy in 3 fractions</td>
<td>100%</td>
<td>33% grade 1 nausea</td>
<td>5–6 mm of target motion in each direction, on average</td>
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<td>Chang 2016[17]</td>
<td>16</td>
<td>Any primary tumor treated with SBRT (including patients with metastatic disease)</td>
<td>30–40 Gy in 5 fractions</td>
<td>100%</td>
<td>6% grade 2 nausea</td>
<td>13% grade 4 renal toxicity (2 patients with CKD required dialysis after treatment)</td>
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<td>Sun 2016[20]</td>
<td>40 (RCC, 60%)</td>
<td>Any primary tumor treated with SBRT</td>
<td>21–48 Gy in 3 fractions</td>
<td>92.7%</td>
<td>NR</td>
<td>Reduced tumor size and growth rate</td>
</tr>
<tr>
<td>Yamamoto 2016[36]</td>
<td>14</td>
<td>Tumors ≤ 5 cm</td>
<td>50–70 Gy in 10 fractions</td>
<td>NR</td>
<td>No ≥ grade 2 toxicity</td>
<td>20–30 Gy in 10 fractions was correlated with renal atrophy assessed on imaging</td>
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<td>Lo 2014[19]</td>
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<td>Inoperable patients treated with SBRT for RCC</td>
<td>40 Gy in 5 fractions</td>
<td>100%</td>
<td>No ≥ grade 2 toxicity</td>
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<td>Wang 2014[30]</td>
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<td>History of radical nephrectomy for previous RCC</td>
<td>60–85 Gy in 5–7 fractions with gamma-SBRT</td>
<td>64.8%</td>
<td>22% grade 1 leukocytopenia</td>
<td>22% grade 1 colitis</td>
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<td>Siva 2017[28]</td>
<td>33</td>
<td>- ECOG 0–2</td>
<td>24 months</td>
<td>- 26 Gy in 1 fraction for tumors ≤ 5 cm</td>
<td>100% 2-year local control</td>
<td>58% grade 1 (mostly chest wall pain and fatigue)</td>
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<tr>
<td></td>
<td></td>
<td>- Single lesion</td>
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<td>- 42 Gy in 3 fractions for tumors &gt; 5 cm</td>
<td>90% freedom from distant progression</td>
<td>21% grade 2 (mostly fatigue and nausea)</td>
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<tr>
<td></td>
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<td>- Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery</td>
<td></td>
<td>- 26 Gy in 1 fraction for tumors ≤ 5 cm</td>
<td>98% local control at 9 months</td>
<td>3% grade 3 (fatigue)</td>
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<td>Siva 2016[27]</td>
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<td>- ECOG 0–2</td>
<td>13 months</td>
<td>- 25 Gy in 1 fraction for tumors ≤ 5 cm</td>
<td>NR</td>
<td>Average GFR decrease of 8.7 mL/min at 1 year after treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Single lesion</td>
<td></td>
<td>- 42 Gy in 3 fractions for tumors &gt; 5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staehler 2015[21]</td>
<td>40 (RCC, 79%)</td>
<td>- Unable to spare kidney during surgery</td>
<td>28 months</td>
<td>- 24–48 Gy in 3 fractions per fraction dose escalation</td>
<td>NR</td>
<td>3% grade 1 erythroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tumors ≤ 4 cm</td>
<td></td>
<td></td>
<td></td>
<td>5% grade 1 nausea</td>
</tr>
<tr>
<td>Ponsky 2015[24]</td>
<td>19</td>
<td>- Poor surgical candidates</td>
<td>14 months</td>
<td>- 25 Gy in 1 fraction for tumors ≤ 5 cm</td>
<td>NR</td>
<td>5% grade 2 fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- KPS ≥ 60</td>
<td></td>
<td>- 42 Gy in 3 fractions for tumors &gt; 5 cm</td>
<td></td>
<td>5% grade 4 duodenal ulcers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5% grade 2 urinary incontinence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11% grade 3 renal toxicity</td>
</tr>
<tr>
<td>Pham 2014[26]</td>
<td>20</td>
<td>- ECOG 0–2</td>
<td>NR</td>
<td>- 26 Gy in 1 fraction for tumors ≤ 5 cm</td>
<td>NR</td>
<td>60% grade 1–2 side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Single lesion</td>
<td></td>
<td>- 42 Gy in 3 fractions for tumors &gt; 5 cm</td>
<td></td>
<td>Fatigue most common, followed by dermatitis, chest wall pain, and nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McBride 2013[23]</td>
<td>15</td>
<td>- Medically inoperable</td>
<td>37 months</td>
<td>- 21–48 Gy in 3 fractions per fraction dose escalation</td>
<td>87% local control</td>
<td>13% grade 1 nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tumors ≤ 5 cm</td>
<td></td>
<td>- 2 Gy per fraction dose escalation</td>
<td></td>
<td>33% grade 1 fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- KPS ≥ 70</td>
<td></td>
<td>- 27-Gy arms</td>
<td></td>
<td>13% late grade 3 renal dysfunction</td>
</tr>
<tr>
<td>Kaplan 2010[25]</td>
<td>12</td>
<td>- Medically inoperable</td>
<td>14 months</td>
<td>- 21–39 Gy in 3 fractions per fraction dose escalation</td>
<td>92% local control</td>
<td>Mean GFR decrease, 18 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tumors ≤ 5 cm</td>
<td></td>
<td>- 2 Gy per fraction dose escalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- KPS ≥ 70</td>
<td></td>
<td>- 21-Gy arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Two patients with chronic renal failure had worsening of renal function</td>
</tr>
<tr>
<td>Svedman 2006[13]</td>
<td>4 with localized disease; 26 with metastatic disease; 10 received SBRT to the kidney</td>
<td>- Locally recurrent or inoperable RCC</td>
<td>52 months for living patients</td>
<td>- 5–15 Gy in 2–5 fractions</td>
<td>98% local control</td>
<td>57% grade 1–2 cough, fatigue, skin rash, and/or local pain</td>
</tr>
</tbody>
</table>
• 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, 8-10 Gy/#

Technical considerations

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

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

• Most 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 ???????????

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

Shankar Siva1, Rodney J Ellis2, Lee Ponsky3, Bin S Teh4, Anand Mahadevan5, Alexander Muacevic6, Michael Staehler7, Hiroshi Onishi8, Peter Wersall9, Takuma Nomiyama2 & Simon S Lo2

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 were 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 MRT (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.

First draft submitted: 26 October 2015; Accepted for publication: 6 January 2016; Published online: 3 February 2016

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 predominance. 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 [3–5].

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

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

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9Author for correspondence. Tel: +61 3 9665 1111, Fax: +61 3 9665 1426, shankar.ariv@petermac.org
WE'RE NOT HERE TO MOURN, BUT TO CELEBRATE BECAUSE, FRANKLY, NO ONE IS SORRY TO SEE HIM GO...
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 immune-effector cells to the tumor microenvironment
• VEGF and FGF families, check point inhibitors

Future Directions

• Renal impairment, QoL, Cost effectiveness.
• Combination with other local / systemic Rx
• Abscopal effect??
• Versus RFA/ cryo
• Versus sx ???
• Sequencing TKI
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 thrombus. 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
40 Gy/5#
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 diaphragm.
• Histopathology - Furfhans 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
When this is all over, what should change? Everything.