

Organization: American Society for Radiation Oncology
Address: 251 18th St South, 8th Floor, Arlington, VA, 22202
Phone: 703.502.1550
Fax: 703.502.7852
Email: ClinicalPracticeStatement@astro.org

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NCCN Guidelines Panel: Kidney Cancer

The American Society for Radiation Oncology has reviewed the kidney cancer guideline for gaps relative to radiation therapy and offers eight recommendations supported by evidence-based rationales for your consideration.

Recommendation One: There is currently only one radiation oncologist on the panel and radiation oncology should have more representation.

Rational: As with medical oncology and urology, which each have multiple representatives, there should be more than one representative for radiation oncology to make sure that the radiation therapy perspectives are well balanced.

Recommendation Two: On page KID-1, stereotactic body radiotherapy (SBRT) is not included for primary treatment. SBRT should be listed as a treatment option for T1a disease in patients who are not surgical candidates or failed any ablative treatment. It should also be included for T1a disease if there is local relapse after probe-based ablative procedures and, after multidisciplinary group discussion, for selected patients with stage I-III kidney cancer who are not fit for open surgery.

These changes should be made in both the algorithms and the Discussion.

Rational: SBRT has emerged as a non-surgical ablative therapy for medically inoperable primary renal cell carcinoma and the clinical outcomes are favorable.

References:

- De Meerleer G, Khoo V, Escudier B, et al. Radiotherapy for renal-cell carcinoma. *Lancet Oncol.* 2014;15(4):e170-177.
- Panje C, Andratschke N, Brunner TB, Niyazi M, Guckenberger M. Stereotactic body radiotherapy for renal cell cancer and pancreatic cancer: Literature review and practice recommendations of the DEGRO Working Group on Stereotactic Radiotherapy. *Strahlenther Onkol.* 2016;192(12):875-885.

- Ponsky L, Lo SS, Zhang Y, et al. Phase I dose-escalation study of stereotactic body radiotherapy (SBRT) for poor surgical candidates with localized renal cell carcinoma. *Radiother Oncol.* 2015;117(1):183-187.
- 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(11 Pt B):E737-743.
- Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma. *Future Oncol.* 2016;12(5):637-645.
- Siva S, Pham D, Kron T, et al. Stereotactic Ablative Body Radiotherapy for Inoperable Primary Kidney Cancer: A Prospective Clinical Trial. *BJU Int.* 2017. [Epub ahead of print]

Recommendation Three: On page KID-2, SBRT is not offered as an option for primary treatment for stage IV. SBRT should be listed as an alternative to “nephrectomy + surgical metastatectomy” for patients with stage IV disease and a solitary metastasis depending on the site of the metastasis (brain, bone or other pertinent site). For patients with multiple mets, SBRT should also be added as an option for patients with up to 3 to 5 mets.

These changes should be made in both the algorithms and the Discussion.

Rational: Radiation therapy in stage IV is an effective treatment for palliation and there is an emerging role for radiation in treating the synchronous or metachronous development of oligometastases in critical sites. For bone and brain metastases, local radiation therapy (either as single fraction or as fractional course) can provide relief of symptoms. Therefore, SBRT should be listed as an option for patients with up to 5 metastases.

References:

- Cheung P, Thibault I, Bjarnason GA. The emerging roles of stereotactic ablative radiotherapy for metastatic renal cell carcinoma. *Curr Opin Support Palliat Care.* 2014;8(3):258-264.
- De Meerleer G, Khoo V, Escudier B, et al. Radiotherapy for renal-cell carcinoma. *Lancet Oncol.* 2014;15(4):e170-177.
- Kothari G, Foroudi F, Gill S, Corcoran NM, Siva S. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. *Acta Oncol.* 2015;54(2):148-157.
- Taunk NK, Spratt DE, Bilsky M, Yamada Y. Radiosurgery in the Management of Renal Cell Carcinoma Metastases. *J Natl Compr Canc Netw.* 2015;13(6):801-809.

Recommendation Four: There is no mention on page KID-1 of post-operative radiation as primary treatment, especially for advanced stage disease. Radiation after nephrectomy for high-risk patients should be added to the algorithm.

Rational: A 2010 meta-analysis demonstrated a significant decrease in local-regional failure when radiation therapy was used in high-risk patients, although it showed no survival benefit. Ulutin et al. identified tumors ≥ 7 cm as a high-risk feature in patients with kidney cancer and

other high-risk factors may include positive margins, invasion of the Gerota's fascia, presence of adenopathy, renal vein and/or inferior vena cava involvement, and sarcomatoid features.

References:

- De Meerleer G, Khoo V, Escudier B, et al. Radiotherapy for renal-cell carcinoma. *Lancet Oncol.* 2014;15(4):e170-177.
- Stein M, Kuten A, Halpern J, Coachman NM, Cohen Y, Robinson E. The value of postoperative irradiation in renal cell cancer. *Radiother Oncol* 1992;24:41–44.
- Scherer E, Wirtz C. The role of postoperative radiotherapy in the treatment of hypernephroid carcinoma. *Strahlenther Onkol* 1988;164:371-385.
- Kao GD, Malkowicz SB, Whittington R, D'Amico AV, Wein AJ. Locally advanced renal cell carcinoma: low complication rate and efficacy of postnephrectomy radiation therapy planned with CT. *Radiology* 1994;193:725-730.
- Makarewicz R, Zarzycka M, Kulińska G, Windorbska W. The value of postoperative radiotherapy in advanced renal cell cancer. *Neoplasma* 1998;45:380–383.
- Tunio M, Hashmi A, and 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):1839-1845.
- Ulutin HC, Aksu G, Fayda M, Kuzhan O, Tahmaz L, and Beyzadeoglu M. The Value of Postoperative Radiotherapy in Renal Cell Carcinoma: A single-institution experience. *Tumori.* 2006;92(3):202-206.
- Shaikh T, Handorf EA, Murphy CT, et al. Contemporary Trends in the Utilization of Radiotherapy in Patients with Renal Cell Carcinoma. *Urology.* 2015;86(6):1165-1173.

Recommendation Five: On page KID-3 and KID-4, radiation therapy is not included for treatment after relapse or in stage IV patients who are unresectable. The use of local aggressive therapy such as SBRT for treatment of oligometastases (up to 3 to 5 lesions) or oligoprogression should be included in both the algorithms and the Discussion.

Rational: SBRT for oligometastases can improve local control and may modulate immune response. SBRT for oligoprogressive disease can allow patients to continue on the current line of systemic therapy.

References:

- Altoos B, Amini A, Yacoub M, 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.
- Ranck MC, Golden DW, Corbin KS, et al. Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. *Am J Clin Oncol.* 2013;36(6):589-595.
- Seung SK, Curti BD, Crittenden M, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2--tumor and immunological responses. *Sci Transl Med.* 2012;4(137):137ra74.

Recommendation Six: Intraoperative radiation is not included on pages KID-2 and KID-3 as an option after surgery for locally recurrent or advanced tumors undergoing resection and should be added for these scenarios.

Rational: The risk of local recurrence in locally advanced tumors or recurrent disease after partial or radical nephrectomy is high. Some series suggest lower recurrence rates in this cohort of patients when treated with intraoperative radiotherapy. The data are not strong, but may be worth discussing in the guideline.

References:

- 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):618-623.

Recommendation Seven: The guideline does not provide a “Principles of Radiation Therapy” section comparable to the “Principles of Surgery” on page KID-A and offers limited information on palliative RT for metastases. A description of RT principles should be added and should address palliative RT, including for brain and spine metastases and oligometastases. The description of palliative RT in the Discussion (page MS-23) should also be expanded to include oligometastases.

Rational: From a practical perspective, the role of radiation in kidney cancer is primarily for palliation, and it is a relatively frequent problem for radiation oncologists. It would likely be worthwhile to discuss the dose/fractionations (8 Gy x 1 vs. longer palliative regimens), and the role of SBRT and SRS.

Recommendation Eight: The guideline would benefit from more elucidation of ablative techniques. Currently, there is little description of these treatments and they are under “Principles of Surgery,” although they are significantly different. The description of ablative techniques should be expanded and a separate section on “Principles of Ablative Therapies” added.

Rational: Ablative therapy with cryoablation or radiofrequency ablation are options for select patients with small renal cell carcinomas, but there is limited discussion in the guideline on these approaches. Given they are being increasingly utilized, some guidance would be worthwhile.

We hope you find these recommendations useful to your panel as you review and update the guidelines.

Sincerely,



Laura I. Thevenot
Chief Executive Officer
American Society for Radiation Oncology