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NCCN Guidelines Panel: Cervical/Uterine Cancers

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

Recommendation One: We advise revising how stage II disease is approached in the guideline.

- 1) On page ENDO-2, for gross cervical involvement, the guideline suggests external beam radiotherapy (EBRT) and brachytherapy to 75-80 Gy to point A/paracervical dose, but using image-guided brachytherapy (IGBT) is more standard now, and we recommend using volume-based target and detailing the high risk clinical target volume (HR-CTV) for those patients as detailed in the Principles of Radiation Therapy on page UN-A, 2 of 2.
- 2) NCCN recommends upfront surgery as the preferred option for patients with gross cervical involvement in the discussion (page MS-12) and the algorithm on page ENDO-2, but both total and radical hysterectomy are mentioned. Since preoperative RT followed by surgery is a category 2B recommendation, we suggest specifying which surgical resection is appropriate for patients with stage II disease on page ENDO-C, 1 of 6 and page MS-12.
- 3) On page ENDO-5, in superscript “s,” consider adding “without other high risk features” for patients for whom adjuvant vaginal brachytherapy (VBT) alone is considered in surgically staged Stage II. Also consider distinguishing these as microscopic Stage II patients, as opposed to macroscopic Stage II, who should not be considered for vaginal brachytherapy alone except after radical hysterectomy. Distinguishing between microscopic (pathologic only) and macroscopic (gross visualization of on exam) could be an important distinguishing factor of Stage II disease that would be helpful to use in the guideline.

Rational: Volume-based brachytherapy is now the standard of care and advising dose to point A can be avoided in the era of 3D brachytherapy. The incidence of parametrial involvement in endometrial cancer is not known. According to a retrospective study, parametrial spread cannot be predicted by cervical involvement alone. Studies of vaginal brachytherapy alone are often highly selected patients and those without additional risk factors of deep invasion or LVSI.

References:

- Vargo JA, Boisen MM, Comerci JT, et al. Neoadjuvant radiotherapy with or without chemotherapy followed by extrafascial hysterectomy for locally advanced endometrial cancer clinically extending to the cervix or parametria. *Gynecol Oncol.* 2014;135(2):190-5.
- Dankluchia P, Petsuksiri J, Chansilpa Y, Hoskin PJ. Image-guided high-dose-rate brachytherapy in inoperable endometrial cancer. *Br J Radiol.* 2014 Jul;87(1039):20140018.

- Gebhardt B, Gill B, Glaser S, et al. Image-guided tandem and cylinder brachytherapy as monotherapy for definitive treatment of inoperable endometrial carcinoma. *Gynecol Oncol*. 2017;147(2):302-8.
- Gill BS, Kim H, Houser CJ, et al. MRI-guided high-dose-rate intracavitary brachytherapy for treatment of cervical cancer: the University of Pittsburgh experience. *Int J Radiat Oncol Biol Phys*. 2015;91(3):540-7.
- Watanabe Y, Satou T, Nakai H, et al. Evaluation of parametrial spread in endometrial carcinoma. *Obstet Gynecol*. 2010;116(5):1027-34.
- Harkenrider MM, Martin B, Nieto K, et al. Multi-institutional Analysis of Vaginal Brachytherapy Alone for Women With Stage II Endometrial Carcinoma. *Int J Radiat Oncol Biol Phys*; 2018;101:1069-77.
- Vargo JA, Boisen MM, Comerci JT, et al. Neoadjuvant radiotherapy with or without chemotherapy followed by extrafascial hysterectomy for locally advanced endometrial cancer clinically extending to the cervix or parametria. *Gynecol Oncol* 2014;135:190-5.

Recommendation Two: On pages MS-22 and MS-23, distinction between early stage uterine clear cell carcinoma vs serous carcinoma is missing.

Rational: Clear cell carcinoma has better prognosis (with adjuvant RT) and requires less chemotherapy.

Reference: Zhang M, Yang TJ, Desai NB, et al. Comparison of outcomes in early-stage uterine clear cell carcinoma and serous carcinoma. *Brachytherapy*. 2018;18(1):38-43.

Recommendation Three: On page ENDO-4, EBRT +/- VBT should be recommended for stage IB G3 rather than RT (VBT and/or EBRT).

Rational: Aalders et al. showed a survival benefit in stage IB G3 with EBRT + VBT vs. VBT alone. Additionally, GOG 249 showed VBT + chemo did not improve relapse free survival compared EBRT (standard arm). EBRT was shown to have lesser acute toxicity and fewer nodal failures compared to VBT + chemo.

References:

- Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol*. 1980;56:419-27.
- Randall M, Filiaci V, D. M, et al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. *J Clin Oncol*. 2019, Epub ahead of print.

Recommendation Four: On page ENDO-4, we recommend the additional option of “or Consider EBRT if extensive LVSI and no nodal evaluation with other risk factors” for stages IA G3 with invasion and IB G1-2. Stage IA G3 has option of observation only, which contradicts inclusion of G3 as high risk feature in the rest of the document. On page ENDO-A 1 of 2, lymphovascular invasion should be classified as none, focal, multifocal/extensive.

Rational: Extensive LVSI was shown in a combined analysis of PORTEC 1 & 2 to be a strong predictor of pelvic nodal failure in patients who did not receive EBRT. Extensive LVSI is a very important risk

factor for regional recurrence and the guideline as written does not adequately emphasize this. Other risk factors would include age >60 years and deep myoinvasion. Regarding quantification of LVSI, this 3-tiered system (none, focal, multifocal/extensive) of reporting LVSI is predictive of distant metastases and nodal failure and is increasingly driving the decision-making about adjuvant therapy.

Reference: Bosse T, Peters EE, Creutzberg CL, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 2015;51:1742-50.

Recommendation Five: On page ENDO-10, for locoregional recurrence after EBRT, the options include surgical resection +/- IORT and/or systemic therapy +/- palliative RT. We suggest also including salvage interstitial brachytherapy on both page ENDO-10 and page MS-19.

Rational: Brachytherapy is potentially curable salvage therapy for local failure in patients who received prior EBRT. Despite the lack of consensus on the optimal dose and volume, it is worth considering salvage brachytherapy for low volume disease limited to the vagina and paravaginal tissues. Referring the patient to a GYN brachy expert prior to initiating palliative treatment should be considered.

References:

- Huang K, D'Souza D, Patil N, et al. High-dose-rate interstitial brachytherapy for the treatment of high-volume locally recurrent endometrial carcinoma. Brachytherapy. 2016;15(5):543-8.
- Kamrava M, Beriwal S, Erickson B, et al. American Brachytherapy Society recurrent carcinoma of the endometrium task force patterns of care and review of the literature. Brachytherapy. 2017;16(6):1129-43.
- Lee LJ, Damato AL, Viswanthan AN. Clinical outcomes following 3D image-guided brachytherapy for vaginal recurrence of endometrial cancer. Gynecol Oncol. 2013;131(3):586-92.

Recommendation Six: On page ENDO-11, for patients unsuitable for surgery, guideline should recommend EBRT + Brachytherapy or use "and/or" as is done for endometrioid histology (not EBRT +/- Brachytherapy)

Rational: Brachytherapy is likely as imperative for local tumor control in patients not suitable for surgery with adverse histologies as it is for endometrioid type.

Reference: Schwarz JK, Beriwal S, Esthappan J, et al. Consensus statement for brachytherapy for the treatment of medically inoperable endometrial cancer. Brachytherapy. 2015;14:587-99.

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

Sincerely,



Laura I. Thevenot
Chief Executive Officer
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