*National Imaging Associates, Inc.	
Clinical guidelines **ENDOMETRIAL CANCER**	**Original Date: June 2013**
Radiation Oncology	**Last Revised Date: May 2023**
Guideline Number: NIA_CG_129	**Implementation Date: January 2024**

GENERAL INFORMATION

- *It is an expectation that all patients receive care/services from a licensed clinician. All appropriate supporting documentation, including recent pertinent office visit notes, laboratory data, and results of any special testing must be provided. If applicable: All prior relevant imaging results and the reason that alternative imaging cannot be performed must be included in the documentation submitted.*
- *Where a specific clinical indication is not directly addressed in this guideline, medical necessity determination will be made based on widely accepted standard of care criteria. These criteria are supported by evidence-based or peer-reviewed sources such as medical literature, societal guidelines and state/national recommendations.*

INDICATIONS FOR RADIATION THERAPY AND TREATMENT OPTIONS

- Intermediate-risk factors include age ≥ 60 years, and focal LVSI
- High-risk factors include substantial LVSI, especially without surgical nodal staging
- High-risk histologies include serous carcinoma, clear cell carcinoma, carcinosarcoma, mixed histology carcinoma, dedifferentiated carcinoma, or undifferentiated carcinoma
- For patients with FIGO stage IA grade 1 or 2 endometrioid carcinoma without intermediate- or high-risk factors, adjuvant RT is not recommended
- For patients who have undergone hysterectomy and pelvic nodal assessment with isolated tumor cells present, it is conditionally recommended that uterine risk factors be used to guide adjuvant therapy[1]
- For patients who have undergone hysterectomy and pelvic nodal assessment with nodal micrometastases or macrometastases (FIGO stage IIIC), adjuvant therapy is recommended[1]
- For patients with endometrial cancer considering adjuvant therapy, molecular testing is recommended[1]
    - Implementation remarks:
        - Immunohistochemistry is needed to assess for mutations in mismatch repair and TP53 genes
        - POLE sequencing can be used to identify hypermutated tumors

- **Molecular classification unknown[2]**
    - Low Risk group: no adjuvant treatment is recommended
        - Stage IA endometrioid + low-grade + LVSI negative or focal
    - Intermediate Risk group: Adjuvant brachytherapy can be recommended, Omission of adjuvant brachytherapy can be considered (III, C), especially for patients aged < 60
        - Stage IB endometrioid + low-grade + LVSI negative or focal
        - Stage IA endometrioid + high-grade + LVSI negative or focal
        - Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
    - High–intermediate Risk group: pN0 after lymph node staging adjuvant brachytherapy can be recommended, EBRT can be considered for substantial LVSI and for stage II cN0/pNx (lymph node staging not performed), adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II, adjuvant brachytherapy alone can be considered for high-grade LVSI negative and for stage II grade 1 endometrioid carcinomas (II, B)
        - Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion
        - Stage IB endometrioid high-grade regardless of LVSI status
        - Stage II
    - High Risk group: EBRT with concurrent and adjuvant chemotherapy (I, A) or alternatively sequential chemotherapy and radiotherapy is recommended, Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas)
        - Stage III–IVA with no residual disease
        - Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease
    - Advanced metastatic: Advanced metastatic: Unresectable primary tumor due to local extent of disease: EBRT should be delivered to pelvis and para-aortic nodes with dose escalation to involved nodes using an integrated or sequential boost, residual pelvic disease (positive resection margin, vaginal disease, pelvic side wall disease): an individualized approach with either radiotherapy or chemotherapy or a combination of both modalities should be considered by a multi-disciplinary team
        - Stage III–IVA with residual disease
        - Stage IVB
- **Molecular classification known[2]:**
    - Low Risk group: no adjuvant treatment is recommended
        - Stage I–II POLEmut endometrial carcinoma, no residual disease
        - Stage IA MMRd/NSMP endometrioid carcinoma + low-grade‡ + LVSI negative or focal

- Intermediate Risk group: Adjuvant brachytherapy can be recommended, Omission of adjuvant brachytherapy can be considered (III, C), especially for patients aged < 60
    - Stage IB MMRd/NSMP endometrioid carcinoma + low-grade + LVSI negative or focal
    - Stage IA MMRd/NSMP endometrioid carcinoma + high-grade + LVSI negative or focal
    - Stage IA p53abn and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
- High–intermediate Risk group: pN0 after lymph node staging adjuvant brachytherapy can be recommended, EBRT can be considered for substantial LVSI and for stage II cN0/pNx (lymph node staging not performed), adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II, adjuvant brachytherapy alone can be considered for high-grade LVSI negative and for stage II grade 1 endometrioid carcinomas (II, B)
    - Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion
    - Stage IB MMRd/NSMP endometrioid carcinoma high-grade‡ regardless of LVSI status
    - Stage II MMRd/NSMP endometrioid carcinoma
- High Risk group: EBRT with concurrent and adjuvant chemotherapy (I, A) or alternatively sequential chemotherapy and radiotherapy is recommended, Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas)
    - Stage III–IVA MMRd/NSMP endometrioid carcinoma with no residual disease
    - Stage I–IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease
    - Stage I–IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
- Advanced metastatic: Unresectable primary tumor due to local extent of disease: EBRT should be delivered to pelvis and para-aortic nodes with dose escalation to involved nodes using an integrated or sequential boost, Residual pelvic disease (positive resection margin, vaginal disease, pelvic side wall disease): an individualized approach with either radiotherapy or chemotherapy or a combination of both modalities should be considered by a multi-disciplinary team
    - Stage III–IVA with residual disease of any molecular type
    - Stage IVB of any molecular type

- **Locally Advanced[2]:** Per GOG 2058 study, routine pelvic radiotherapy for locally advanced endometrial cancer, has no benefit in disease-free survival when chemoradiation was compared to chemotherapy alone. Therefore, it is reasonable to offer HDR alone[3]

Post-operative[4,1]

- Brachytherapy Only (HDR or LDR, 6fx maximum[5]
  - Stage IA – with adverse risk factors
  - Stage IA – without risk factors (Grade 3)
  - Stage IB (Grades 1, and 2)
- External Beam Radiation Therapy Only (2D, 3D-CRT, 45-50.4 Gy, 28fx maximum) including no pelvic nodal assessment[1]
  - Stage IA – with adverse risk factors (Grades G2, 3)
  - Stage IB – without adverse risk factors (Grade G3)
  - Stage IB – with risk factors
  - Stage II (Grades G1, 2, 3)
  - Stage III
  - Stage IVA
- External Beam (2D, 3D-CRT, 45-50.4 Gy, 28fx maximum) and Brachytherapy (HDR or LDR, 6fx maximum[5] including positive surgical margins[1]
  - Stage IA – with adverse risk factors (Grades G2, 3)
  - Stage IB – without risk factors (Grade G3)
  - Stage IB – with risk factors
  - Stage II – (Grades G1, 2, 3)
  - Stage IIIA & IIIB & IIIC (Grades G1, 2, 3)

Medically Inoperable/ Pre-Operative

- Brachytherapy Only (HDR or LDR, 6fx maximum[5]
  - Stage I & II
- External Beam Radiation Therapy Only (2D, 3D-CRT, 45-50 Gy, 28fx maximum)
  - All Stages
- External Beam (2D, 3D-CRT, 45-50.4 Gy) and Brachytherapy (HDR or LDR, 6fx maximum[5]
  - All Stages

Note:

- *Unless otherwise indicated, standard radiation fractionation consists of 1.8 Gy to 2.0 Gy per day.*
- *For gross nodal disease, consider boost to 60–65 Gy while respecting normal tissue constraints.*

Palliative

- Up to 10fx

- Hypofractionated Two Week Short-Course Radiotherapy vs. Monthly Single Fraction Palliative Pelvic Radiation in Advanced Gynecologic Cancers, add this fractionation as an option

TREATMENT OPTIONS REQUIRING ADDITIONAL CLINICAL REVIEW

Intensity Modulated Radiation Therapy (IMRT)

IMRT is not indicated as a standard treatment option and should not be used routinely for the delivery of radiation therapy for endometrial cancer.[4] IMRT is strictly defined by the utilization of inverse planning modulation techniques. IMRT may be appropriate for limited circumstances in which radiation therapy is indicated and 3D conformal radiation therapy (3D-CRT) techniques cannot adequately deliver the radiation prescription without exceeding normal tissue radiation tolerance, the delivery is anticipated to contribute to potential late toxicity or tumor volume dose heterogeneity is such that unacceptable hot or cold spots are created.

Clinical rationale and documentation for performing IMRT rather than 2D or 3D-CRT treatment planning and delivery will need to:

- Demonstrate how 3D-CRT isodose planning cannot produce a satisfactory treatment plan (as stated above) via the use of a patient-specific dose volume histograms and isodose plans.
- Provide tissue constraints for both the target and affected critical structures.

Post-Operative IMRT[1]

- IMRT for post-operative radiation therapy is approvable. If there is gross residual disease and the area(s) can be sufficiently utilized, a boost can be added to a total dose of 60-70Gy, respecting normal tissue sensitivity. This is supported by a randomized phase III study (NRG Oncology's RTOG 1203)[6]. For gross nodal disease, consider boost to 60-65Gy while respecting normal tissue constraints.[4]
- When para-aortic nodes are being treated

Stereotactic Body Radiation Therapy (SBRT)

Stereotactic Body Radiation Therapy is not a standard treatment option for the treatment of endometrial cancer.

Proton Beam Radiation Therapy

Proton beam is not an approved treatment option for endometrial cancer. Proton beam has not been proven superior treatment to conventional radiation therapy.[4]

THE FOLLOWING APPLIES TO CMS (MEDICARE) MEMBERS ONLY

For Proton Beam and Stereotactic Radiotherapy, refer to Local Coverage Determination (LCD), if applicable.

BACKGROUND

Most endometrial cancers are adenocarcinomas, with uterine sarcomas accounting for <10%. This clinical guideline will focus primarily on adenocarcinoma of the endometrium.

After a diagnosis of endometrial cancer is made, it is followed by a staging evaluation to determine extent of disease (local, regional, or metastatic) and prognostic findings. For patients in whom cancers of the uterus are suspected, an endometrial biopsy is typically performed.[4] A review of the pathology will determine whether the tumors are of epithelial origin (endometrioid, papillary cirrus, clear cell, or carcinosarcoma) or stromal/mesenchymal carcinoma (stromal sarcoma or leiomyosarcoma). Most endometrial cancers, however, are adenocarcinomas with tumor typically confined to the uterus. Thus, this disease is often localized with an excellent prognosis. Current workup, including a complete surgical assessment, includes a histological grade, depth of myometrial invasion, and extent of extrauterine involvement. Prognostic factors are based on a pathologic assessment and include the percent of myometrial invasion, myometrial thickness, tumor size and location (upper fundus or lower uterine cervical), cervix involvement, and lymphovascular space involvement. Most patients are treated surgically with radiation reserved for patients who are deemed at a high risk of recurrence or for those deemed medically inoperable.[7]

This guideline outlines several methods suitable for the employment of radiation therapy. This includes the use of 3-dimensional conformal radiation therapy and/or internal radiation (brachytherapy). IMRT is not indicated as a standard treatment option for uterine cancer. External beam treatments are typically delivered using a high-energy linear accelerator. Brachytherapy is generally delivered using temporary HDR sources such as iridium-192. The purpose of this guideline is to outline the most efficient, comparatively effective, diagnostic and treatment pathway. Treatment is typically broken down into patients in whom disease is limited to the uterus, cervical involvement (either suspected or confirmed), or extrauterine disease.[8]

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POLICY HISTORY

Date	Summary
May 2023	• Updated/Clarified: INDICATIONS FOR RADIATION THERAPY AND TREATMENT OPTIONS • Updated/Clarified post-operative, inoperable/preoperative, palliative • Added *Note:* ○ *For gross nodal disease, consider boost to 60–65 Gy while respecting normal tissue constraints.* • Deleted additional resources
January 2022	• Under Post-operative, changed external beam to 50.4 Gy for combination external beam and brachytherapy • Added Post-Operative IMRT under Treatment Options Requiring Additional Clinical Review

Reviewed / Approved by NIA Clinical Guideline Committee

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