ASTRO Guidelines on Radiation Therapy in Endometrial and Lung Cancers

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GUIDELINE FOR POSTOPERATIVE RADIATION THERAPY IN ENDOMETRIAL CANCER

The American Society for Radiation Oncology (ASTRO) evidence-based guideline addressing the role of postoperative radiation therapy in patients with endometrial cancer found that external beam radiation and brachytherapy were relevant treatment options for patients with intermediate- and high-risk disease. Anne H. Klopp, MD, PhD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, presented guidelines on behalf of the ASTRO endometrial cancer guideline task force [Klopp A et al. *Pract Radiat Oncol.* 2014].

In clinical practice, appropriate protocol for the use of radiation as adjuvant treatment in patients with endometrial cancer is unclear. Even though prospective studies have been conducted, many have weaknesses that make deciphering optimal treatment regimens difficult. This guideline aims to offer recommendations for the use of adjuvant radiation in treatment of patients with postoperative endometrial cancer.

An expert panel reviewed 330 articles to develop recommendations, and it categorized evidence quality using the American College of Physicians Strength of Evidence Rating. The panel focused on survival, local and distant recurrence rate, toxicity, and quality-of-life outcomes. Patient population of interest was determined as adult women with stage I to IVA endometrial cancer of any histology who underwent hysterectomy. Treatments investigated included no adjuvant therapy and pelvic radiation and/or vaginal brachytherapy with or without chemotherapy.

The guideline addressed 5 key questions:

1. Which patients with endometrioid endometrial cancer require no additional therapy after hysterectomy?
2. Which patients with endometrioid endometrial cancer should receive vaginal cuff radiation?
3. Which women with early-stage endometrial cancer should receive postoperative external beam radiation? Which women with stage III to IVA endometrial cancer should receive postoperative external beam radiation?
4. When should brachytherapy be used in addition to external beam radiation?
5. How should radiation therapy and chemotherapy be integrated in the management of endometrial cancer?

After hysterectomy in patients with endometrioid endometrial cancer, researchers found that adjuvant radiation is not indicated for all patients. Patients with grade 1 to 2 disease and < 50% myometrial invasion and patients with no residual disease in hysterectomy specimen, despite positive biopsy, may avoid additional radiation treatment. Evidence for patients with grade 1 to 2 disease was high, and strength of recommendation was considered strong, with 100% of reviewers agreeing. Evidence for patients with no residual disease was low due to lack of randomized evidence, but experts considered recommendation strength strong with 94% agreement. Patients with low-risk findings should still be monitored after hysterectomy.

Recurrence of early-stage endometrial cancer often occurs at the vaginal cuff; therefore, vaginal cuff brachytherapy has an important role in postoperative treatment. Vaginal cuff brachytherapy is considered an appropriate treatment option in patients with grade 1 to 2 disease with < 50% myometrial invasion and increase of risk factors, such as older age and high lymphovascular space involvement. In these patients, vaginal cuff brachytherapy is considered a treatment option but not

an absolute necessity. This was considered a strong recommendation, with moderate evidence and 94% agreement. Patients with grade 3 disease and no myometrial invasion may also be candidates for vaginal cuff brachytherapy. Although evidence was low, consensus was high at 94%.

The expert panel recommends that patients with grade 1 to 2 disease and ≥ 50% myometrial invasion and patients with grade 3 and < 50% invasion receive vaginal cuff radiation. This was supported by moderate evidence and 100% consensus. In these patients with intermediate-risk cancer, guidelines strongly recommend that vaginal cuff brachytherapy be considered the preferred treatment choice versus pelvic radiation, especially in patients who underwent comprehensive nodal assessment, even though evidence strength was low.

The advantage of pelvic external beam radiation is that it treats a wide area. It can treat the vagina as well as regional lymphatic; therefore, the consideration for pelvic radiation as a treatment option is associated with pelvic node involvement. In patients with grade 3 disease and ≥ 50% myometrial invasion or cervical stroma and in patients with grade 1 to 2 disease and ≥ 50% invasion with increase of risk factors, pelvic radiation is an appropriate treatment postoperative therapy. Evidence strength supporting this recommendation was high for both patient groups.

Pelvic radiation is also associated with a low rate of vaginal recurrence; therefore, vaginal brachytherapy following pelvic radiation has limited potential for added benefit. Guidelines do not recommend brachytherapy after pelvic radiation as a treatment option. Evidence for this combination therapy is limited to retrospective studies with small patient numbers, and it received only a 77% agreement. Dr Klopp noted that vaginal brachytherapy after pelvic radiation may be considered when appropriate external beam radiation doses cannot be achieved and need to be supplemented with vaginal brachytherapy.

In high-risk patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum, pelvic radiation with chemotherapy is the preferred treatment regimen, with moderate strength of evidence and 100% consensus. Guidelines do not support chemotherapy without radiation, nor do they support radiation without chemotherapy.

When chemotherapy and radiation are used to treat patients with high-risk endometrioid cancer, the strongest recommendation supports the use of concurrent chemotherapy and radiation, followed by adjuvant chemotherapy. This recommendation had moderate strength of evidence and a 77% agreement rate. A total of 82% of experts also found alternative sequencing strategies of external beam radiation with chemotherapy acceptable, but the recommendation was given a weak rating because of low strength of evidence.

In the studies reviewed, toxicity was usually local with vaginal cuff brachytherapy, and it involved vaginal complications and mild urinary side effects. Pelvic radiation, in contrast, had higher rates of gastrointestinal toxicity, mainly diarrhea.

Researchers noted that external beam radiation and vaginal brachytherapy have a significant role in adjuvant treatment for endometrial cancer, and the high-quality evidence used to develop these guidelines supports that pelvic recurrence is reduced by radiation therapy. Patient risk factors should be considered when therapy is chosen, and further knowledge of preferred therapy regimens should be gained from current studies.

GUIDELINE FOR DEFINITIVE AND ADJUVANT RADIOTHERAPY IN LOCALLY ADVANCED NON–SMALL CELL LUNG CANCER

ASTRO is currently assembling recommendations to serve as guidelines for definitive and adjuvant radiotherapy treatment in patients with locally advanced non–small cell lung cancer (LA-NSCLC). George Rodrigues MD, PhD, University of Western Ontario, London, Ontario, Canada, presented current guideline progress on behalf of the ASTRO locally advanced lung cancer practice guideline task force.

Radiotherapy in patients with LA-NSCLC is indicated as palliative treatment in patients with poor performance status and prognosis, as definitive treatment with chemotherapy or alone, and as adjuvant treatment in preoperative and postoperative settings. Guidelines for the use of palliative radiotherapy in patients with lung cancer are available, but despite over 40 years of evidence, guidelines for definitive and adjuvant radiotherapy have not been determined. This guideline aims to provide guidance for definitive and adjuvant radiotherapy in the treatment of patients with LA-NSCLC, and it addresses 5 key questions:

1. What is the ideal external beam dose fractionation for the curative-intent treatment of LA-NSCLC with radiation therapy alone?
2. What is the ideal external beam dose fractionation for the curative-intent treatment of LA-NSCLC with chemotherapy?
3. What is the ideal timing of external beam radiation therapy in relation to systemic chemotherapy for the curative-intent treatment of LA-NSCLC?
4. What are the indications for adjuvant postoperative radiotherapy for the curative-intent treatment of LA-NSCLC?

5. When is neoadjuvant radiotherapy prior to surgery indicated for the curative-intent treatment of LA-NSCLC?

The expert panel found that radiotherapy alone demonstrated superiority when compared with observation strategies or chemotherapy alone and may serve as definitive treatment in patients who cannot receive combined modality therapy. Radiotherapy alone was associated with toxicity—specifically, esophagitis and pneumonitis.

When radiotherapy is used alone, a conventionally fractionated minimum dose of 60 Gy is suggested to improve local control and other clinical outcomes. This recommended dose was based on high-quality evidence and 100% consensus.

When chemotherapy is given concurrently with radiotherapy, a dose of 60 Gy should be administered in 2-Gy once-daily fractions for 6 weeks for patients receiving standard thoracic radiotherapy. Investigators found that increasing the dose higher than 60 Gy had no association with clinical benefit. Moderate-quality evidence supported both recommendations. Other findings also supported the use of conventional fractionated therapy when no benefit was seen with hyperfractionated radiotherapy that did not accelerate treatment course.

In sequential chemotherapy, ideal radiotherapy dose and schedule have not been determined. Phase 3 trials have found that using accelerated hyperfractionated therapy to increase the biologically equivalent dose may offer better outcomes when following chemotherapy. Accelerated radiotherapy needs additional evaluation to determine optimal therapeutic ratio of treatment in advanced imaging radiotherapy planning and delivery of treatment.

Concurrent chemoradiation had better response rate, overall survival, and local control than chemotherapy followed by radiation, according to phase 3 data, and the most common chemotherapy regimens were cisplatin with etoposide and carboplatin with paclitaxel, although optimal chemotherapy in concurrent regimen has not been decided. Sequential chemotherapy followed by radical radiation in patients who could not tolerate concurrent therapy was associated with improved overall survival when compared with radiotherapy alone.

Investigators also noted that evidence does not support the use of routine induction chemotherapy before chemoradiotherapy nor consolidation chemotherapy after chemoradiotherapy, but both may be used to manage specific cases. Induction chemotherapy may be an appropriate treatment option when bulky tumors are present, and consolidation chemotherapy may be an appropriate treatment option when full chemotherapy doses were not administered during radiotherapy in the presence of suspected micrometastatic disease.

Phase 3 trials and meta-analyses found that postoperative radiotherapy in patients with resected LA-NSCLC and N2 disease improved local control as compared with observation, but a benefit in overall survival was not found. In patients with resected LA-NSCLC and N0-1 disease, postoperative radiotherapy had worse survival outcomes when compared with observation and is not suggested for treatment in this patient population.

Currently, chemotherapy is the standard of care in patients with resected disease because it has demonstrated a benefit in overall survival; therefore, postoperative radiotherapy should follow chemotherapy to avoid any possible interference. Conventionally fractionated doses administered for adjuvant postoperative radiotherapy range from 50 to 54 Gy. Quality of evidence for this dose range was considered low but received 100% consensus.

Investigators recognize that appropriate doses for postoperative radiotherapy may be different for patient subsets. A conventionally fractionated dose of 54 to 60 Gy may be considered with chemotherapy to improve local control in patients with microscopic residual primary disease and/or microscopic nodal disease, and patients with gross residual primary and/or macroscopic nodal disease may receive a conventionally fractionated dose ≥ 60 Gy with chemotherapy to improve local control.

In patients with resectable stage III NSCLC, level I evidence supporting induction radiotherapy or chemoradiotherapy before resection surgery is nonexistent. When radiotherapy is used preoperatively, doses ≥ 45 Gy should be administered to match previous trials, although no optimal dose has been determined. Acceptable mediastinal clearance rates appeared to be correlated with preoperative conventionally fractionated doses up to 60 Gy, but no evidence of association with overall survival was found.

Investigators found that an increase in treatment benefit was associated with no weight loss, female sex, and only 1 involved nodal station in patients receiving trimodality therapy, but evidence was not sufficient enough to develop patient selection criteria for trimodality treatment. Trimodality therapy was also associated with improved survival when preoperatively planned lobectomy was performed, as compared with pneumonectomy.

By addressing 5 key questions, recommendations offer guidance for definitive and adjuvant radiotherapy in patients with LA-NSCLC. Full guidelines will be published in *Practical Radiation Oncology*.