

## Scientific Article

# An analysis of appropriate delivery of postoperative radiation therapy for endometrial cancer using the RAND/UCLA Appropriateness Method: Executive summary

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## Abstract

**Purpose:** To summarize the results of American Society for Radiation Oncology (ASTRO)'s analysis of appropriate delivery of postoperative radiation therapy (RT) for endometrial cancer using the RAND/University of California, Los Angeles (UCLA) Appropriateness Method, outline areas of convergence and divergence with the 2014 ASTRO endometrial Guideline, and highlight where this analysis provides new information or perspective.

**Methods and materials:** The RAND/UCLA Appropriateness Method was used to combine available evidence with expert opinion. A comprehensive literature review was conducted and a multidisciplinary panel rated the appropriateness of RT options for different clinical scenarios. Treatments were categorized by the median rating as Appropriate, Uncertain, or Inappropriate.

**Results:** The ASTRO endometrial Guideline and this analysis using the RAND/UCLA Appropriateness Method did not recommend adjuvant RT for early-stage, low-risk endometrioid cancers and largely agree regarding use of vaginal brachytherapy for low-intermediate and high-intermediate risk patients. For more advanced endometrioid cancer, chemotherapy with RT is supported by both documents. The Guideline and the RAND/UCLA analysis diverged regarding use of pelvic radiation. For stages II and III, this analysis rated external beam RT plus vaginal brachytherapy Appropriate, whereas the Guideline preferred external beam alone. In addition, this analysis offers insight on the role of histology, extent of nodal dissection, and para-aortic nodal irradiation; the use of intensity modulated RT; and management of stage IVA.

**Conclusions:** This analysis based on the RAND/UCLA Method shows significant agreement with the 2014 endometrial Guideline. Areas of divergence, often in scenarios with low-level evidence, included use of external beam RT plus vaginal brachytherapy in stages II and III and external beam RT alone in early-stage patients. Furthermore, the analysis explores other important questions regarding management of this disease site.

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## Background

This document was prepared by a working group with expertise in endometrial cancer designated by the American Society for Radiation Oncology (ASTRO). This analysis presents scientific, health, and safety information and may to some extent reflect scientific or medical opinion. It is made available to ASTRO members and to the public for educational and informational purposes only. Any commercial use of any content in this analysis without the prior written consent of ASTRO is strictly prohibited.

Adherence to this analysis will not ensure successful treatment in every situation. Furthermore, this analysis should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all circumstances presented by the individual patient. ASTRO

assumes no liability for the information, conclusions, and findings contained in this analysis. In addition, this analysis cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored.

This RAND/UCLA analysis was prepared on the basis of information available at the time the working group and multidisciplinary panel were conducting their research and discussions on this topic. There may be new developments that are not reflected in this document and, that may, over time, be a basis for ASTRO to consider revisiting and updating this analysis.

## Introduction

Endometrial cancer is a common disease with increasing incidence and yet considerable controversy

regarding optimal therapy. Although randomized trials address many important questions regarding radiation, uncertainty remains because of patient and disease heterogeneity and numerous potential treatment strategies. The most favorable stage I patients are often cured with surgery alone. For higher risk early-stage patients, vaginal brachytherapy or external beam radiation therapy (RT) may be considered to improve local control, and systemic therapy can potentially address occult distant metastasis risk. For advanced-stage patients, the optimal regimen and sequencing has yet to be determined and includes chemotherapy and RT.

Reflecting the complexity of endometrial cancer treatment decisions and ambiguity of available evidence for many questions, ASTRO applied the RAND/University of California at Los Angeles (UCLA) Appropriateness Method to assess clinical scenarios and provide management recommendations. Although this analysis and ASTRO's clinical practice guideline on endometrial cancer<sup>1</sup> focus on the same disease site, they differ in their clinical questions, methodologies for assessing the literature, level of evidence considered, and subsequently their recommendations. This executive summary briefly discusses areas of concordance and divergence between the Guideline and the RAND/UCLA analysis and highlights where the analysis explores issues not covered in the Guideline. The full analysis results are reported in the [Supplemental Materials](#).

## Methods and Materials

### Process

This analysis uses the RAND/UCLA Appropriateness Method, developed in the 1980s to provide a formalized way to “combine the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of performing a procedure.”<sup>2</sup> It has been applied internationally across medical disciplines and uses a multidisciplinary panel to rate wide-ranging clinical scenarios that physicians may encounter in practice based on a comprehensive literature review. The panel includes different clinical specialties potentially involved in the care of the patients represented in the scenarios and is designed to benefit from collective expertise and mitigate the tendency of physicians performing a procedure to rate it higher than those who do not.<sup>3</sup> For this analysis, the panel was composed of members from radiation oncology, medical oncology, gynecologic (GYN) oncology, medical physics, internal medicine, and health services research. Primarily non-GYN-specialized radiation oncologists were used, based on discussion with experts in the RAND/UCLA Method, to potentially reduce bias.

The process results in ratings of Appropriate, Uncertain, or Inappropriate for potential treatments for the clinical scenarios. An Appropriate rating indicates predicted benefits are sufficiently greater than risks to make the intervention worth using. It is not intended to imply the treatment must be used in all patients fitting the scenario. Similarly, an Inappropriate rating shows projected risks may outweigh benefits but does not mean the treatment should never be applied in that scenario. The Uncertain rating reflects inconclusive evidence and/or a lack of consensus regarding benefits and risks.

### Working group

The working group comprised radiation oncologists with expertise in GYN cancers and/or the RAND/UCLA Appropriateness Method. With ASTRO staff, the working group developed the literature review, scenarios, and definitions via conference call and e-mail and later reconvened to interpret the ratings and write the final document.

### Literature review

We searched MEDLINE PubMed and Trip Database for English-language articles published between January 1970 and September 2012 evaluating women age  $\geq 18$  years with stages I to IV endometrial cancer of any nonsarcoma histology who received vaginal brachytherapy, external beam RT, and/or intensity modulated RT (IMRT), with or without chemotherapy. The electronic searches were supplemented by hand searches. In total, 238 articles were included and data abstraction performed. Evidence tables and short literature summaries were developed as resources for the panelists to reference when rating the scenarios.

### Scenarios and definitions

The working group identified factors likely to impact decisions about appropriateness of radiation treatment, from which scenarios were developed representing patients potentially encountered in practice and potential radiotherapeutic options. Although these scenarios were intended to address radiation specifically, the treatments also covered chemoradiation. There were 1038 initial scenarios and 698 second-round scenarios. A definition list was produced to ensure common understanding of terms among panelists.

### Multidisciplinary panel

A multidisciplinary panel, representing radiation oncology, medical oncology, GYN oncology, medical physics, general GYN, internal medicine, and health

**Table 1** Multidisciplinary panel members

Specialty	Name	Institution
Radiation oncology	Brett Cox (specialist in GU and CNS cancers)	North Shore-Long Island Jewish Health System
	Mitchell Kamrava (specialist in GYN cancers, sarcomas, and brachytherapy)	University of California, Los Angeles
	Sunil Krishnan (specialist in GI cancers)	MD Anderson Cancer Center
	Joshua Lawson (general radiation oncologist)	Lexington Medical Center
Medical oncology	Vicky Makker	Memorial Sloan Kettering Cancer Center
Gynecologic oncology	D. Scott McMeekin	University of Oklahoma
	David Mutch	Washington University
Internal medicine	Craig Nielsen	Cleveland Clinic
Internal medicine/health services research	Kimberly Peairs	Johns Hopkins University
Medical physics	Stanley Benedict	University of California
Moderator	Michael Broder	Partnership for Health Analytic Research (board-certified obstetrician-gynecologist)

CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic.

services research was recruited. This multidisciplinary composition is inherent to the process and intended to achieve an objective perspective. As noted earlier, most radiation oncologists selected were non-GYN specialists, which aimed to broaden the panel's scope and potentially decrease bias. Prospective panelists were identified through ASTRO committees and outreach to other medical specialty societies. Despite efforts to include all planned specialties, the general gynecologist was ultimately unable to participate. The final 10-member panel (Table 1) was chosen by the Best Practices Subcommittee and subsequently screened for potential conflicts and bias.

For each scenario, panelists rated the treatment's appropriateness from 1 to 9 based on the literature review, definitions, and their clinical judgment of an "average patient" treated by an "average physician" in an "average facility." A "1" indicated much greater anticipated harms than benefits and a "9" much higher expected benefits than harms. A "5" signified balanced harms and benefits or that the rater felt unable to reach a conclusion. Panelists were instructed not to consider cost or cost-effectiveness. Before rating, panelists received an orientation to the RAND/UCLA Method, the scenarios, and the evidence tables, literature summaries, and definitions provided to inform the rating; this approach enhanced consistency in their methodology. The scenarios were rated iteratively in 2 rounds. The initial rating was conducted remotely and independently via an online survey during March/April 2013. Next, at a face-to-face meeting, each panelist received an individualized form showing the ratings per scenario and the median and mean distance from the median for the entire panel. Panelists discussed the scenarios, moderated by a methodologist experienced in the RAND/UCLA Method, and then individually rerated them using the same survey and process.

Ratings were analyzed using SAS statistical software. Central tendency was measured using median because responses were ordinal and the distance between scale points not fixed. Mean distance from the median measured dispersion. Treatments were rated Inappropriate for medians 1 to 3 (without disagreement), Uncertain for medians 4 to 6 or if there was disagreement, and Appropriate for medians 7 to 9 (without disagreement). Disagreement was defined as  $\geq 3$  ratings from 1 to 3 and  $\geq 3$  from 7 to 9 on the same scenario.

## Results

### Comparison of RAND/UCLA analysis and endometrial guideline

Because ASTRO produced a Guideline on endometrial cancer in 2014 and conducted this analysis within the same time frame, we will briefly summarize where they agree and diverge.

Despite methodological differences, there is significant concordance (Table 2). This is reassuring and reflects the substantial randomized data for some major questions. For stage I endometrioid tumors, both documents recommend against adjuvant RT for low-risk patients, defined in the RAND/UCLA analysis as grade 1 or 2 tumors with  $<50\%$  myometrial invasion (MI), and no lymphovascular space invasion (LVSI). For the high-intermediate cohort, which included patients  $\geq 70$  years with 1 risk factor (grade 2 or 3, outer-third MI, or LVSI),  $\geq 50$  years old with 2 risk factors, or any age with 3 risk factors, there was consensus that vaginal brachytherapy is the most appropriate treatment. Among low-intermediate patients ( $\geq 50\%$  MI but not high-intermediate), vaginal brachytherapy was rated Uncertain to Appropriate. This

**Table 2** Areas of concordance between Guideline and RAND/UCLA analysis<sup>a</sup>

Treatment	Guideline	RAND/UCLA analysis
No adjuvant radiation	Reasonable in patients with: <ol style="list-style-type: none"> <li>1. No residual disease in hysterectomy specimen despite positive biopsy and</li> <li>2. Grade 1 or 2 with no invasion or &lt;50% MI without other high-risk features.</li> </ol>	All radiation options rated Inappropriate for stage I, low-risk patients
Vaginal brachytherapy alone	May be considered in patients with negative node dissection and: <ol style="list-style-type: none"> <li>1. Grade 3 without MI and</li> <li>2. Grade 1 or 2 with &lt;50% MI and higher risk features such as age &gt;60 and/or LVSI</li> </ol> <p>Preferred to pelvic radiation in patients with:</p> <ol style="list-style-type: none"> <li>1. Grade 1 or 2 with ≥50% MI</li> <li>2. Grade 3 with &lt;50% MI</li> </ol>	Rated appropriate for: <ol style="list-style-type: none"> <li>1. Stage I, low-intermediate risk, ≥10 nodes dissected,</li> <li>2. Stage I, high-intermediate risk, regardless of node dissection, and</li> <li>3. Stage II, low risk or low-intermediate risk, ≥10 nodes dissected</li> </ol>
External beam radiation therapy alone (late stage)	Pelvic radiation without concurrent chemotherapy may be considered based on pathologic risk for pelvic recurrence for patients with: <ol style="list-style-type: none"> <li>1. Positive nodes and</li> <li>2. Involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum</li> </ol>	Rated Uncertain or Appropriate in stages IIIA-IIIC1 Pelvic plus para-aortic radiation rated Appropriate for stage IIIC2
Chemoradiation	Concurrent chemoradiation followed by adjuvant chemotherapy indicated for patients with: <ol style="list-style-type: none"> <li>1. Positive nodes and</li> <li>2. Involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum</li> </ol> <p>Alternative sequencing also acceptable.</p>	Although chemoradiation was not specifically rated, VB rated Uncertain or Appropriate with chemotherapy for stage I, high-intermediate risk. Pelvic RT + VB rated Appropriate with chemotherapy for: <ol style="list-style-type: none"> <li>1. Stage II, high-intermediate risk,</li> <li>2. Stage IIIA if &lt;10 nodes dissected and chemo given concurrently, and</li> <li>3. Stages IIIB and IIIC1</li> </ol> <p>Pelvic and para-aortic RT ± VB rated Appropriate for stage IIIC2 with chemotherapy</p>

High-intermediate risk, ≥70 years with 1 risk factor (grade 2 or 3, outer-third MI, or LVSI), ≥50 years old with 2 risk factors, or any age with 3 risk factors; low-intermediate risk, any grade and ≥50% MI but not meeting the criteria for high-intermediate risk; low risk, grade 1 or 2, <50% MI, and no LVSI; LVSI, lymphovascular space invasion; MI, myometrial invasion; RT, radiation therapy; VB, vaginal brachytherapy.

<sup>a</sup> For the purpose of this comparison, histology was limited to endometrioid.

agrees with the Guideline, which recommended brachytherapy for deeply invasive grade 1 or 2 cancers or grade 3 tumors with <50% invasion and indicated brachytherapy may be considered for grade 3 cancer without invasion and grade 1 or 2 tumors with <50% invasion but other high-risk features.

For stage II endometrioid cancers, the RAND/UCLA analysis and Guideline both recommend pelvic RT, although pelvic RT plus brachytherapy received the highest ratings in the RAND/UCLA analysis. For stages III and IV endometrioid tumors, both documents recommend combined chemoradiation when there are positive nodes or involved uterine serosa/ovaries/fallopian tubes, vagina, bladder, or rectum. Both also demonstrate less enthusiasm for sandwich therapy than other chemotherapy and radiation sequences. RT was never rated

Appropriate with sandwich chemotherapy in the RAND/UCLA analysis and the Guideline noted this regimen delays RT, which may reduce local control and interrupts chemotherapy.

There were also areas where the RAND/UCLA analysis and Guideline diverged (Table 3), perhaps reflecting differences in their processes and the composition of the groups determining the recommendations. Although the Guideline panel comprised predominately GYN-specialized radiation oncologists, the RAND/UCLA analysis used a multidisciplinary panel. This was intended to mitigate potential for physicians to rate treatments they deliver as more appropriate. Furthermore, a Guideline is strictly evidence-based and relies on available literature to make recommendations for predetermined “key questions.” The RAND/UCLA Method combines the best

**Table 3** Areas of divergence between Guideline and RAND/UCLA analysis<sup>a</sup>

Treatment	Guideline	RAND/UCLA analysis
External beam radiation alone (early stage)	May benefit patients with: <ol style="list-style-type: none"> <li>Grade 3 with <math>\geq 50\%</math> MI or cervical stroma invasion and</li> <li>Grade 1 or 2 with <math>\geq 50\%</math> MI with other risk factors, such as age <math>&gt;60</math> years and/or LVSI</li> </ol>	Pelvic radiation alone rated Appropriate for: <ol style="list-style-type: none"> <li>Stage I, high-intermediate risk, no node dissection and</li> <li>Stage II, low-intermediate or high-intermediate risk, <math>\geq 10</math> nodes dissected</li> </ol>
External beam radiation therapy plus brachytherapy	Vaginal brachytherapy in patients undergoing pelvic external beam radiation therapy may not generally be warranted, unless risk factors for vaginal recurrence are present	Rated Appropriate for: <ol style="list-style-type: none"> <li>Stage I, high-intermediate risk, <math>&lt;10</math> nodes dissected,</li> <li>Stage II, and</li> <li>Stage III</li> </ol>

High-intermediate risk,  $\geq 70$  years with 1 risk factor (grade 2 or 3, outer-third MI, or LVSI),  $\geq 50$  years old with 2 risk factors, or any age with 3 risk factors; low-intermediate risk, any grade and  $\geq 50\%$  MI but not meeting the criteria for high-intermediate risk; low risk, grade 1 or 2,  $<50\%$  MI, and no LVSI; LVSI, lymphovascular space invasion; MI, myometrial invasion.

<sup>a</sup> For the purpose of this comparison, histology was limited to endometrioid.

evidence with collective expert opinion and addressed many scenarios with limited current literature. Thus panelists used their best judgment to reach conclusions. The ability to focus on questions lacking literature is one of this methodology's strengths. However, the process is not primarily designed to eliminate uncertainty and Inappropriate, Uncertain, and Appropriate ratings have equal value.

One area where the two documents differ is pelvic RT in stage I endometrioid low- and high-intermediate risk patients. The Guideline indicates that “[p]atients with grade 1 or 2 tumors with  $\geq 50\%$  myometrial invasion may also benefit from pelvic RT to reduce pelvic recurrence rates if other risk factors are present such as age  $>60$  years and/or lymphovascular space invasion” based on several randomized clinical trials showing decreased pelvic failure with pelvic RT.<sup>1</sup> The RAND/UCLA analysis rated vaginal brachytherapy Appropriate and pelvic RT Uncertain for most scenarios. Although these recommendations appear discordant, this divergence reflects a known controversy in the field. The randomized trials supporting pelvic RT have not demonstrated an overall survival advantage and perhaps were underpowered to do so. They also had varying inclusion criteria, degrees of surgical staging, and receipt of vaginal brachytherapy. Proponents of vaginal brachytherapy argue it is associated with less toxicity than pelvic RT and the majority of failures for uterine-confined disease are vaginal. Many factors must be considered in treatment recommendations for this heterogeneous group, and the 2 documents reflect that the evidence may support differing conclusions.

For stage II, the RAND/UCLA analysis rated pelvic RT and brachytherapy Appropriate, whereas the Guideline recommended pelvic RT alone because of limited evidence for adding brachytherapy. The Guideline specified brachytherapy may be indicated after pelvic RT in

early-stage patients with high-risk features for vaginal recurrence, such as cervical involvement. Stage II is defined as involvement of cervical stroma and a recurring theme during the moderated face-to-face panel discussion was tailoring treatment to perceived risk, especially when evidence was lacking. Panelists suggested vaginal brachytherapy is likely to provide benefit when assessment of cuff recurrence risk is high, pelvic RT when nodal risk is high, and chemotherapy when systemic failure risk is high. Absent level 1 evidence, panelists rated vaginal brachytherapy with pelvic RT Appropriate because of perceived vaginal cuff recurrence risk given cervical involvement. In contrast, the Guideline is strictly evidence-based and lacked data to support endorsing vaginal brachytherapy. Its recommendation against routine addition of vaginal brachytherapy is graded weak and acknowledges that prospective data are lacking. Again, what appear to be conflicting recommendations highlight an area of controversy in the field. Also, although the RAND/UCLA analysis rated pelvic RT and brachytherapy Appropriate more frequently than pelvic RT alone, the latter was never rated Inappropriate.

For stages III or IV endometrioid tumors, both documents support chemotherapy and RT. Sequencing of the treatments strongly affected the ratings in the RAND/UCLA analysis, a trend not seen in the Guideline. The analysis rated external beam RT and brachytherapy Appropriate, whereas the Guideline recommended external beam RT alone. The analysis' ratings for stage III disease reflect tailoring of radiation to perceived risk. The panelists noted stage III is a very heterogeneous group and the stage definition alone does not indicate presence or absence of cervical involvement for stages IIIA and IIIC. As for stage II, in no scenario (other than positive para-aortic nodes) did the RAND/UCLA analysis rate pelvic RT Inappropriate. The Appropriate ratings for

vaginal brachytherapy and external beam likely reflect panel discussions that cervical involvement warrants consideration of brachytherapy. Less enthusiasm for vaginal brachytherapy may have been seen if panelists had rated stage IIIA and IIIC scenarios separately for presence and absence of cervical involvement. Again, the ratings reflect consensus decisions in the absence of robust evidence.

By using a multidisciplinary panel moderated by a specialist in the RAND/UCLA Method and including non–GYN-specialized radiation oncologists, this analysis was designed to limit biases. However, differences in composition between the Guideline panel and the panel for the RAND/UCLA analysis may account for divergences in recommendations. Panelists for the analysis received a comprehensive literature summary to inform ratings; however, the literature is dense and difficult to navigate for nonspecialists in GYN radiation oncology. This is ASTRO's first analysis using the RAND/UCLA Method, and a lesson learned was that the multidisciplinary panel may benefit from greater disease-site expertise when addressing complex topics such as management of endometrial cancer. It will remain unanswered whether differences in panel composition would have affected the ratings in this analysis.

The Guideline panel was tasked with providing strictly evidence-based recommendations regarding key clinical questions for which existing literature provided a framework. The working group for the RAND/UCLA analysis had a broader mission that may be more reflective of

day-to-day clinical practice and the struggles of making recommendations in the absence of level 1 evidence. However, both methodologies reached similar conclusions overall, particularly where relevant literature was most robust. Areas of divergence reflect places where data are limited and differing conclusions can fairly be reached.

### Areas of new perspective from the RAND/UCLA analysis

There are several areas not addressed in the Guideline where the RAND/UCLA analysis offers new perspective (Table 4). These include the role of histology, para-aortic nodal irradiation, and extent of nodal dissection; IMRT versus 3-dimensional conformal RT (3D-CRT); and management of stage IVA.

#### Effect of histology

The most influential pathologic feature for treatment decisions is presence of uterine papillary serous or clear cell histology, which represent only 10% to 15% of endometrial cancer patients, but approximately half of those with recurrence.<sup>4</sup> There was extensive discussion among panelists, who felt papillary serous and clear cell tumors have significant risk of systemic spread and warrant chemotherapy across all stages, and the role of radiation showed considerable uncertainty. There is

**Table 4** Areas of new perspective from the RAND/UCLA analysis

Papillary serous and clear cell histologies	<ul style="list-style-type: none"> <li>Panelists concluded that these tumors have significant metastasis risk and warrant chemotherapy across all stages. Role of radiation showed uncertainty because of a lack of evidence.</li> <li>For stage I, vaginal brachytherapy with chemotherapy was rated Appropriate for most scenarios.</li> <li>For stages II and III, vaginal brachytherapy plus pelvic radiation was rated Appropriate for the majority of scenarios.</li> </ul>
Para-aortic radiation	<ul style="list-style-type: none"> <li>Ratings indicated positive para-aortic basins should receive radiation, but negative nodes should not be covered unless nodal dissection was insufficient to rule out occult involvement.</li> </ul>
Nodal dissection	<ul style="list-style-type: none"> <li>For stage I, ratings for vaginal brachytherapy alone increased in most scenarios with more extensive nodal dissection.</li> <li>For stage II, pelvic radiation plus vaginal brachytherapy rated highest regardless of extent of nodal dissection.</li> <li>For stage III, uncertainty about para-aortic radiation with no or &lt;10 nodes dissected. After ≥10 nodes dissected, para-aortic radiation rated Inappropriate except for pathologically involved nodes.</li> </ul>
IMRT	<ul style="list-style-type: none"> <li>Both 3D-CRT and IMRT rated Appropriate for scenarios where pelvic or para-aortic radiation is indicated.</li> <li>Panelists cited most common setting for IMRT as treatment of para-aortic nodes.</li> </ul>
Stage IVA	<ul style="list-style-type: none"> <li>Stage IVA is a rare subset with locally advanced disease invading bladder and/or rectum. The Guideline included stage IVA, but did not give specific recommendations.</li> <li>The analysis was restricted to operable patients. Panelists indicated most stage IVA cases are unresectable and that the extent of surgery may influence recommendations.</li> <li>Vaginal brachytherapy rated Inappropriate and remaining options Uncertain.</li> </ul>

3D-CRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy.

currently a paucity of randomized trials addressing radiation and chemotherapy for these histologies. For stage I, vaginal brachytherapy with chemotherapy was rated Appropriate, despite limited evidence. For stages II and III, the panel rated combined pelvic RT and vaginal brachytherapy as Appropriate.

### Para-aortic nodal RT

For stage III endometrioid cancers, pelvic RT with or without vaginal brachytherapy was rated Appropriate for most scenarios. The ratings indicated positive para-aortic nodes should receive radiation but negative para-aortic nodes should not be covered electively, unless nodal dissection was insufficient to rule out occult involvement or postoperative computed tomography abdomen/pelvic imaging reveals gross nodal disease. For stage IIIA and IIIB endometrial cancer, regardless of histology, para-aortic RT was rated Uncertain or Inappropriate, trending toward Inappropriate with more extensive nodal dissection.

For endometrioid stage IIIC1 (pelvic node involvement), pelvic RT plus vaginal brachytherapy was rated Appropriate. Pelvic RT alone was rated Uncertain to Appropriate, depending on extent of nodal dissection or use of chemotherapy. After node dissection, para-aortic node RT was rated Inappropriate, but showed some uncertainty for no dissection. For endometrioid stage IIIC2 (para-aortic nodal involvement), RT targeting pelvic and para-aortic nodes, with or without vaginal brachytherapy, was rated Appropriate, and pelvic RT alone Inappropriate. Across stage IIIC, vaginal brachytherapy alone was rated Inappropriate, reflecting perceived maximal risk in the pelvis. The plan for chemotherapy did little to change the ratings.

The same themes were reflected for stage III papillary serous or clear cell tumors, with RT directed based on perceived risk. There was general agreement that stage III papillary serous/clear cells should receive pelvic RT, with or without vaginal brachytherapy, plus chemotherapy. Coverage of pathologically involved para-aortic nodes was rated Appropriate in stage IIIC. There was generally greater uncertainty for stage III papillary serous/clear cell cancers than for endometrioid tumors.

### Effect of nodal dissection

Nodal dissection is the major surgical intervention affecting adjuvant management. This is important for both interpreting the literature and individual patient management because of substantial heterogeneity in lymph node sampling practice. For stage I, the panel generally had greater confidence in appropriateness of vaginal brachytherapy alone with more extensive

dissection. For stage II, the panel rated pelvic RT and vaginal brachytherapy Appropriate regardless of extent of dissection. Among stage III patients, there was some uncertainty regarding adding para-aortic RT with no or <10 nodes dissected. For  $\geq 10$  nodes dissected, panelists rated para-aortic RT Inappropriate except for pathologically involved para-aortic nodes.

### IMRT versus 3D-CRT

IMRT use has increased significantly for GYN cancers. Dosimetric studies indicate IMRT significantly reduces dose to critical normal structures, including small bowel, bladder, rectum, and bone marrow.<sup>5</sup> However, dosimetric parameters have been criticized as not necessarily translating into meaningful clinical endpoints, and IMRT can result in larger tissue volumes treated to a low dose.<sup>6,7</sup> Furthermore, because IMRT's more conformal dose distribution, tumor control could be threatened by increased risk of compromised target coverage.<sup>6</sup>

Although the literature suggests improved acute effects, data on late toxicity and efficacy are promising but limited.<sup>6,8,9</sup> The panel rated both 3D-CRT and IMRT Appropriate for scenarios where pelvic or para-aortic RT is indicated and cited as the most common setting for IMRT treatment of para-aortic lymph nodes, where several critical structures make normal tissue sparing particularly important. Some clinicians might also use a hybrid approach, treating the pelvis with 3D-CRT and encompassing para-aortic nodes using a nondivergent matched IMRT field. Although not reflected in the ratings, panelists felt cost, insurance reimbursement, technical capacity to plan and deliver IMRT, and concurrent chemotherapy influence decision-making. Ongoing trials evaluating IMRT in GYN malignancies should provide substantial information on its potential advantages.

### Stage IVA

Stage IVA endometrial cancer is a rare subset with locally advanced disease invading bladder and/or rectum. Although the Guideline included stage IVA, it did not give specific recommendations in this setting. The RAND/UCLA analysis was restricted to operable cases and the panel noted most stage IVA is unresectable. They indicated extent of surgery (radical hysterectomy vs pelvic exenteration) may influence adjuvant radiation recommendations. The panel rated vaginal brachytherapy Inappropriate and the remaining options Uncertain in this unusual setting. Management of stage IVA disease is very individualized and requires close multidisciplinary coordination.

## Conclusion

ASTRO produced both a Clinical Practice Guideline and a RAND/UCLA analysis to address optimal management of endometrial cancer, a common and yet controversial disease because of patient and disease heterogeneity and many treatment strategies. Whereas the Guideline relied strictly on available evidence and was developed primarily by GYN-specialized radiation oncologists, this analysis used the RAND/UCLA Method to supplement current literature with collective judgment from a multidisciplinary panel. These different methodologies yielded both concordant conclusions and areas of divergence. Importantly, the analysis also explored several topics not covered by the Guideline. As ASTRO's first analysis based on the RAND/UCLA Method, this project has offered valuable lessons learned about how to best apply this methodology to radiation oncology. It is hoped that these 2 documents will prove valuable for clinicians navigating this area of complicated decision-making and inform future research by identifying evidence gaps.

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## Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.adro.2015.10.001>.

## References

1. Klopp A, Smith B, Alektiar K, et al. The role of post-operative radiation therapy for endometrial cancer: An ASTRO Evidence-Based Guideline. *Pract Radiat Oncol*. 2014;4:137-144.
2. Fitch K, Bernstein S, Aguilar M, et al. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND; 2001.
3. Kahan JP, Park RE, Leape LL, et al. Variations by specialty in physician ratings of the appropriateness and necessity of indications for procedures. *Med Care*. 1996;34:512-523.
4. Acharya S, Hensley ML, Montag AC, Fleming GF. Rare uterine cancers. *Lancet Oncol*. 2005;6:961-971.
5. Yang B, Zhu L, Cheng H, Li Q, Zhang Y, Zhao Y. Dosimetric comparison of intensity modulated radiotherapy and three-dimensional conformal radiotherapy in patients with gynecologic malignancies: A systematic review and meta-analysis. *Radiat Oncol*. 2012;7:197.
6. Wagner A, Jhingran A, Gaffney D. Intensity modulated radiotherapy in gynecologic cancers: Hope, hype or hyperbole? *Gynecol Oncol*. 2013;130:229-236.
7. Zwahlen DR, Ruben JD, Jones P, Gagliardi F, Millar JL, Schneider U. Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys*. 2009;74:539-545.
8. Beriwal S, Jain SK, Heron DE, et al. Clinical outcome with adjuvant treatment of endometrial carcinoma using intensity-modulated radiation therapy. *Gynecol Oncol*. 2006;102:195-199.
9. Shih KK, Milgrom SA, Abu-Rustum NR, et al. Postoperative pelvic intensity-modulated radiotherapy in high risk endometrial cancer. *Gynecol Oncol*. 2013;128:535-539.