SUPPLEMENTAL MATERIAL

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An Analysis of Appropriate Delivery of Post-Operative Radiation Therapy for Endometrial Cancer Using the RAND/UCLA Appropriateness Method

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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.

Conflict of Interest Disclosure Statement

Before initiation of this analysis, all members of the working group and multidisciplinary panel were required to complete disclosure statements. These statements are maintained at the ASTRO headquarters in Fairfax, VA and pertinent disclosures are published with the report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. Where a potential conflict is detected, remedial measures to address any potential conflict are taken and will be noted in the disclosure statement.

Working Group

Sushil Beriwal, MD is a consultant for Varian and receives honoraria from Xoft for participation in a data safety monitoring board for a clinical trial. Jeff Michalski, MD, MBA and Ivy Petersen, MD, are co-chairs of the Radiation Oncology Committee for NRG Oncology. Dr. Michalski is also a board member for the National Children's Cancer Society. Arno Mundt, MD received honoraria from UpToDate and from the American College of Radiation Oncology, where he is President and on the Board of Chancellors. Lorraine Portelance, MD, is a member of the Radiation Therapy Oncology Group Gynecology Working Group. The working group chairs reviewed these disclosures and determined that they do not present a conflict with respect to these members' work on this analysis.

Multidisciplinary Panel

Brett Cox, MD served on the Bayer Radium-223 speaker bureau. Sunil Krishnan, MD received royalties from Taylor and Francis Group. D. Scott McMeekin, MD was a member of the National Cancer Institute Gynecologic Cancer Steering Committee's Uterine Corpus Cancer Task Force and served on the Gynecologic Oncology Group (GOG) Board of Directors. He was also site chair for the GOG phase II endometrial program and a member of the GOG Corpus Committee, Developmental Therapeutics Committee, and Phase I Subcommittee. David Mutch, MD was a member of the GOG Corpus Committee. Stanley Benedict, PhD received honoraria from Elekta and the Focus Ultrasound Surgery Foundation. Endometrial cancer trials led by multidisciplinary panelists during their panel participation are listed in the Supplemental Materials.

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Legend

ACP	American College of Physicians
AP	doxorubicin-cisplatin
ASTEC	A Study in the Treatment of Endometrial Cancer
ASTRO	American Society for Radiation Oncology
BSO	bilateral salpingo-oophorectomy
CGCRG	Cochrane Gynaecological Cancer Review Group
DFS	disease-free survival
DSRFS	disease-specific recurrence-free survival
DSS	disease-specific survival
CI	confidence interval
CIR	cumulative incidence of recurrence
CSS	cancer-specific survival
CT	chemotherapy
EBRT	external beam radiation therapy
EORTC	European Organisation for Research and Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
GI	gastrointestinal
GOG	Gynecologic Oncology Group
HDR	high-dose-rate
HR	hazard ratio
IMRT	intensity modulated radiation therapy
IOM	Institute of Medicine
JGOG	Japanese Gynecologic Oncology Group
KQ	key question
LDR	low-dose-rate
LVSI	lymphovascular space invasion
MaNGO	Gynaecologic Oncology group at the Mario Negri Institute
MI	myometrial invasion
NAT	no additional treatment
NS	not significant
NSGO	Nordic Society for Gynaecologic Oncology
OS	overall survival
PA	para-aortic
PAN	para-aortic nodes
PFS	progression-free survival
PICO	population, interventions, comparators, and outcomes
PORTEC	Postoperative Radiation Therapy in Endometrial Carcinoma
RCT	randomized, controlled trial
RFS	recurrence-free survival
RH	relative hazard
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology, and End Results
TAH	total abdominal hysterectomy
VBT	vaginal brachytherapy
VCB	vaginal cuff boost
WAI	whole abdominal irradiation

Introduction

Scope and purpose of this RAND/UCLA analysis

Endometrial cancer is a common disease with increasing incidence and yet considerable controversy exists regarding optimal therapy. Although randomized trials address many important questions regarding use of radiation in this disease site, ambiguity remains due to patient and disease heterogeneity and the availability of a multitude of treatment strategies. This ASTRO analysis is designed to define appropriate use of radiation oncology treatments using a structured process, the RAND/University of California-Los Angeles (UCLA) Appropriateness Methodology, to evaluate existing literature and multidisciplinary expert opinion and provide guidance for optimal patient care. This analysis sought to address adjuvant radiation therapy among a cohort of women with stage I to IVA, operable endometrial cancer.

This process provides a formalized way to combine the best available scientific evidence with the judgment of experts to guide clinical decision making. The methodology employs a multidisciplinary panel to benefit from collective expertise and to mitigate the tendency of physicians performing a procedure to rate it higher than those who do not. The process relies on the ratings of the ten members of the multidisciplinary panel to identify scenarios in which a treatment is rated Appropriate (median ratings 7-9), Inappropriate (median ratings 1-3) or Uncertain (median ratings 4-6).

The ASTRO Guidelines Subcommittee has also recently published on the role of adjuvant radiation for endometrial cancer.[1] These two projects were designed to parallel one another and spotlight the different processes utilized in evaluating the available literature and providing guidance to clinicians. While the Guideline panel comprised predominately gynecologic-specialized

radiation oncologists, the RAND/UCLA analysis used a multidisciplinary panel to rate the scenarios. In addition, a Guideline is strictly evidence-based, following the Institute of Medicine (IOM) criteria and relies on available literature to determine recommendations. The RAND/UCLA Method intentionally combines the best evidence with collective expert judgment. Many scenarios in this analysis are not addressed by current literature and thus panelists used their best judgment to reach conclusions.

Endometrial cancer was chosen by ASTRO for this analysis due to its common nature and increasing incidence, accompanied by substantial controversy regarding optimal treatment and interpretation of findings from randomized trials. The fine distinctions of various pathologic features and myriad options for combining radiation therapy with systemic therapy also contribute to this ambiguity. Given the substantial controversy in this area, it is not surprising that many scenarios were rated as 4-6, reflecting the uncertainty in the field.

Overview of the clinical landscape

Surgical management is the mainstay of initial treatment for endometrial cancer, and since the 1980s, the staging system has evolved from a clinical to a surgically staged cancer. For this project, the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system is used.[2] Adjuvant therapy including chemotherapy, radiation therapy (RT), and combinations of the two has been used, depending on the stage, pathologic features, and patient factors.

In early-stage patients, the goal of cure is readily attainable, but the nuanced risks and benefits of further adjuvant therapy have been the subject of large multi-institutional phase III trials. In general, the most favorable stage I patients are cured with surgery alone. For higher risk early-stage patients, for additional local therapy, either vaginal brachytherapy (VB) or external beam radiation therapy (EBRT) may be considered to improve local control. Options for systemic therapy can potentially address the risk for occult distant metastasis in these higher risk patients.

For advanced stage patients, the optimal regimen has yet to be determined and includes the options of chemotherapy and radiation therapy (vaginal brachytherapy and EBRT). In addition, when advanced stage patients receive both radiation and chemotherapy, the sequencing and combination of these modalities has been studied in a variety of permutations. As a general principle, the treatment goal for early-stage patients is to cure with minimal morbidity and, for more advanced stage patients, to improve survival with optimal locoregional control and eradicate potential distant disease.

Methods and Materials

Process

The American Society of Radiation Oncology (ASTRO) Board of Directors approved the creation of an analysis using the RAND/UCLA Method on how to appropriately deliver radiotherapy for post-operative endometrial cancer in February 2012. The Best Practices Subcommittee recruited a working group of radiation oncologists with expertise in gynecological cancers and/or the methodology. The working group and ASTRO staff developed the literature review, scenarios, and definitions through a series of discussions by conference call and electronic mail. A multidisciplinary panel was assembled to evaluate the literature and rate the scenarios in two rounds, first prior to an in-person meeting and again after face-to-face discussion of the first-round results. Next, the working group reconvened to interpret the rating results and write the final document. The document was reviewed by the multidisciplinary panel, the writing panel of the ASTRO endometrial Guideline, the Best Practices Subcommittee, and the Clinical Affairs and Quality Committee. The final draft was approved by the Board of Directors in January 2015.

Brief background on the RAND/UCLA Method

The RAND/UCLA Appropriateness Method was developed in the 1980s in an attempt to determine whether procedures were being used appropriately, despite the paucity of randomized controlled trials and other high-level evidence for many important clinical questions. The process provides 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 at the level of patient-specific symptoms, medical history and test results."[3] Because it uses a multidisciplinary panel, the RAND/UCLA approach counters the tendency of physicians who provide a therapy to rate it higher than those who do not.[4,5] This method results in a rating of Appropriate, Uncertain, or Inappropriate for a wide range of common clinical scenarios. An Appropriate rating signifies that the predicted benefit for the patient is sufficiently greater than the anticipated risks to make it valuable to apply the intervention. However, it is not intended to indicate that the treatment must be used in all patients who fit the scenario described. Similarly, an Inappropriate rating is not meant to be interpreted as an indication that the treatment should never be used under the circumstances in the scenario but rather that

the projected risks may outweigh the expected benefits. The Uncertain rating reflects inconclusive evidence and/or a lack of consensus regarding the benefits and risks of the therapy. The RAND/UCLA process has been used internationally in many medical fields. Previous oncology topics include renal cell, colorectal, carcinoid tumors, melanoma, and acute myelogenous leukemia.[6-10]

Literature review

A comprehensive literature search was conducted during September and October 2012 on the appropriate role of radiation therapy in endometrial cancer. We included studies evaluating women age 18 years or older with stage I to IVA endometrial cancer of any histology, other than sarcoma, who received radiotherapy or combined chemoradiation. A search of MEDLINE PubMed and Trip Databases for English-language articles published between January 1970 and September 2012 yielded 427 citations. The electronic searches were supplemented with references identified by the working group and by hand-searching bibliographies of pertinent articles including systematic reviews. After eliminating articles that fit the exclusion criteria (case report, inoperable patients, primary or neoadjuvant radiotherapy, non-English language, recurrent or metastatic disease, sarcoma, and whole abdominal radiation), a total of 238 full-text articles were selected for inclusion and data abstraction. Evidence tables and literature summaries were developed.

Clinical scenarios and definitions of terms

The working group generated a list of factors likely to impact clinicians' decisions about which treatment is appropriate. These factors included stage, histology, lymph node dissection and status, and risk classification, which combined age, presence of myometrial and/or lymphovascular space invasion, and grade. Tumor size was not one of the factors included. Next these factors were used to develop scenarios representing patients who might be encountered in practice and potential treatments. Endometrioid adenocarcinoma, papillary serous, and clear cell histologies were included and sarcoma was excluded. Adjuvant treatment regimens evaluated included vaginal brachytherapy, external beam pelvic radiation therapy (with or without para-aortic radiation) delivered via 3D versus intensity-modulated radiation therapy (IMRT), or combined chemoradiation. Although the scenarios were intended to address the role of radiation specifically, the treatment options covered radiation alone and multimodal therapy incorporating chemotherapy. Given that practicing radiation oncologists are often tasked with making radiation therapy decisions in the context of other treatment decisions having already been made, the scenarios were designed to determine the role of radiation in the context of chemotherapy versus no chemotherapy. The working group defined three chemotherapy options to represent the most common combinations: (1) concurrent chemoradiation or concurrent plus adjuvant chemotherapy, (2) chemotherapy before or adjuvant to radiation, and (3) sandwich chemotherapy, with radiation therapy in-between chemotherapy cycles. In retrospect, offering this detail for the chemotherapy provided the multidisciplinary panel with the opportunity to rate detailed nuances of the chemotherapy options, which was not an intended part of the process.

There were 1038 total initial scenarios, which were divided into four "chapters" for stages I, II, III, and IV. There were also two separate questions on IMRT. Due to the small amount of clinical literature on IMRT, stand-alone questions were used rather than including IMRT as a treatment option for all of the scenarios. A definition list was also produced to ensure common understanding of terms among panelists.

Multidisciplinary Panel

The panel was responsible for rating the scenarios based on the literature review and definitions developed by the working group. Panel composition reflected representatives from radiation oncology, medical oncology, gynecologic oncology, medical physics, gynecology, internal medicine, and health services research to achieve an objective perspective. This multidisciplinary composition is inherent to the process and was recommended by RAND/UCLA methodology experts. It is intended to achieve an objective perspective. Also based on discussion with RAND/UCLA methodology experts, most radiation oncologists selected were non-gynecologic specialists, which again aimed to make the panel broad in scope and potentially decrease bias. Prospective panelists were identified through nominations from ASTRO committees and external outreach to other medical specialty societies. Invited panelists were selected by the Best Practices Subcommittee based on specialty, geographic region, practice setting, and availability for the in-person meeting. They were screened for potential conflicts and bias. Although the goal was to include all desired specialties, the gynecologist invited was ultimately unable to participate. The final ten-member panel (Table 1) was made up of nine physicians and one medical physicist from eight states. One panelist worked in private practice and the others worked in an academic setting. There has been significant discussion of how the panel composition may have impacted the ratings, which will be addressed further in the Discussion.

Table 1. *Multidisciplinary Panel Members*

Specialty	*Name*	*Institution*
Radiation oncology	Brett Cox	North Shore-Long Island Jewish Health System, New Hyde Park, NY
	Mitchell Kamrava	University of California, Los Angeles, CA
	Sunil Krishnan	The University of Texas, M.D. Anderson Cancer Center, Houston, TX
	Joshua Lawson	Lexington Medical Center, West Columbia, SC
Medical oncology	Vicky Makker	Memorial Sloan Kettering Cancer Center, New York, NY
Gynecologic oncology	D. Scott McMeekin	University of Oklahoma, Oklahoma City, OK
	David Mutch	Washington University, St. Louis, MO
Internal medicine	Craig Nielsen	Cleveland Clinic, Cleveland, OH
Internal medicine/ health services research	Kimberly Peairs	Johns Hopkins University, Baltimore, MD
Medical physics	Stanley Benedict	University of California, Davis, Sacramento, CA
Moderator	Michael Broder	Partnership for Health Analytic Research, LLC, Beverly Hills, CA (also a board-certified Obstetrician-Gynecologist)

Rating process and panel meeting

For each scenario, the multidisciplinary panel rated the appropriateness of the treatment from 1 to 9. 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. Additionally, panelists were instructed to envision an "average patient" treated by an "average physician" in an "average facility" and not to consider cost or cost-effectiveness.

Prior to rating, an orientation to the rating procedure and the materials, which included instructions, the literature tables and summaries, and the definitions list, was held to ensure consistency in how panel members approached this portion of the process. The panel rated the scenarios iteratively in two rounds. The initial rating was done remotely and independently via an online survey during March and April 2013.

The panel met face-to-face from May 4 to 5, 2013 in Virginia; the meeting was overseen and moderated by a methodologist experienced in the RAND/UCLA process. Each panelist received an individualized form showing their rating per indication and the median and mean distance from the median for the entire panel. During the meeting, the panelists discussed the scenarios and then re-rated them individually using the same survey and process. Panelists were not forced to reach agreement.

Statistical analyses

Ratings were analyzed by a statistician using SAS statistical software. For both rounds, the median and the mean distance from the median were calculated for each scenario. The median was used to measure central tendency because the responses were ordinal and the distance between points on the scale was not fixed. Average distance from the median was used to measure dispersion. Treatments were rated Inappropriate when the median was 1 to 3 without disagreement, Uncertain when it was 4 to 6 or there was disagreement, and Appropriate when it was 7 to 9 without disagreement. Disagreement was defined as ≥3 ratings from 1 to 3 and ≥3 from 7 to 9 on the same item. Statistics summarizing the appropriateness ratings and agreement by chapter and section, as well as changes in the ratings between rounds, were also calculated.

Results

The multidisciplinary panel rated a total of 1038 scenarios in the first round and 698 in the second. The scenarios were divided into four chapters and the two additional questions on IMRT. During the initial rating, 14.3% (148 scenarios) were rated Appropriate; 62.7% (651 scenarios) were rated Uncertain; and 23.0% (239 scenarios) were rated Inappropriate. There was disagreement on 10.9% (113 scenarios). Following the in-person meeting, 18.3% (128 scenarios) were rated Appropriate; 44.4% (310 scenarios) were rated Uncertain; and 37.3% (260 scenarios) were rated

Inappropriate. There was disagreement on 6.3% (44 scenarios). All but one scenario that had disagreement were already Uncertain based on the median rating.

The color-coded tables show the median rating for each scenario. The treatments that were rated are displayed in the tables along the top as column headers and the factors impacting treatment decisions, such as extent of nodal dissection and receipt of chemotherapy are displayed in the tables along the left as rows. The colors of the cells denote the appropriateness of the scenario based on the median rating. Red shows scenarios that were rated Inappropriate (median 1-3 without disagreement) and green displays scenarios that were rated Appropriate (median 7-9 without disagreement). Indications that were rated Uncertain (median 4-6) without disagreement are colored yellow, and grey cells present scenarios that met the definition of disagreement (≥3 ratings from 1 to 3 and ≥3 from 7 to 9 on the same item), regardless of median.

Subsequent to the multidisciplinary panel ratings, several decisions were made regarding how best to display the results. A consensus decision was made to not display the ratings in this manuscript for sandwich chemotherapy. The panel never rated available radiation modalities as Appropriate in the setting of sandwich chemotherapy, and we feel the ratings to be reflective of panelists' view of sandwich chemotherapy rather than of the queried radiation modalities. So as not to potentially mislead the reader attempting to make a radiation decision in the setting of sandwich chemotherapy, we have elected not to include the results in this setting.

Scenarios were designed and panelists were instructed to rate the appropriateness of radiation in the context of chemotherapy (administered concurrently, adjuvantly, sequentially, or sandwich) versus no chemotherapy. This was intended to reflect the presumed reality that practicing radiation oncologists are most often tasked with making radiation therapy decisions in the context of chemotherapy decisions having already been made.

Stage I

The first chapter comprised 117 scenarios in both rounds and assessed the impact of nodal dissection, histology, and risk classification on the appropriateness of potential therapies. Low risk was defined as grade 1 or 2, <50% myometrial invasion (MI), and no lymphovascular space invasion (LVSI) present. Low intermediate risk was any grade and ≥50% MI but not meeting the criteria for high intermediate risk. High intermediate included patients ≥70 years with one risk factor (grade 2 or 3, outer-third MI, or LVSI), ≥50 years old with two risk factors, or any age with three risk factors. These definitions were adapted from the Gynecologic Oncology Group (GOG) 99 trial.[11] Risk classification was not included in scenarios for serous/clear cell tumors. Three treatments were rated with or without chemotherapy: vaginal brachytherapy, pelvic RT, and both brachytherapy and pelvic RT.

In the first round, 11.1% (13 scenarios) were rated Appropriate; 63.2% (74 scenarios) were rated Uncertain; and 25.6% (30 scenarios) were rated Inappropriate. There was disagreement on 17.1% (20 scenarios). In the second round, 13.6% (16 scenarios) were rated Appropriate; 49.6% (58 scenarios) were rated Uncertain; and 36.8% (43 scenarios) were rated Inappropriate, with disagreement on 5.1% (6 scenarios).

Stage I (Endometrioid Histology)

Table 2. ***Stage I Scenario Group A:*** Stage I (endometrioid histology, low risk)

	VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	**3**	**2**	**1**
<10 nodes dissected			
≥10 nodes dissected			

Key: red = Inappropriate (median 1–3 without disagreement).

For patients with low risk stage I disease, the panel rated the use of adjuvant radiation therapy, including vaginal brachytherapy, pelvic RT, or brachytherapy and pelvic RT as Inappropriate. Adjuvant radiation therapy was not rated Appropriate for any subset of patients within the low risk category, regardless of the extent of nodal dissection.

Table 3. ***Stage I Scenario Group B:*** Stage I (endometrioid histology, low intermediate risk)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	No chemotherapy	5	2	2
	Concurrent or concurrent + adjuvant chemotherapy	1	1	1
	Chemotherapy before or adjuvant to RT	2		
<10 nodes dissected	No chemotherapy	4	3	2
	Concurrent or concurrent + adjuvant chemotherapy	2	1	1
	Chemotherapy before or adjuvant to RT			
≥10 nodes dissected	No chemotherapy	7	3	2
	Concurrent or concurrent + adjuvant chemotherapy	5	2	
	Chemotherapy before or adjuvant to RT			

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

In the low intermediate risk category, the use of pelvic RT with or without vaginal brachytherapy was rated Inappropriate in all scenarios, regardless of extent of node dissection or use of chemotherapy. The role of vaginal brachytherapy in the low intermediate risk category was less certain. Panelists rated vaginal brachytherapy as Inappropriate, Uncertain, or Appropriate, depending on extent of nodal dissection and receipt of chemotherapy. In the subset of patients with no nodal assessment or fewer than 10 nodes dissected, in the absence of chemotherapy, adjuvant vaginal brachytherapy was rated Uncertain, although there was disagreement in the panel for patients with fewer than 10 nodes dissected. In those with an extensive nodal dissection (≥10 nodes), in the absence of chemotherapy, vaginal brachytherapy was rated Appropriate. When concurrent or sequential chemotherapy was used, vaginal brachytherapy was rated Uncertain in patients with extensive dissection and Inappropriate in those with none or fewer than 10 nodes. These data differ with the ASTRO endometrial Guideline by Klopp et al. in terms of use of pelvic RT and chemotherapy and the influence of node dissection.

Table 4. ***Stage I Scenario Group C:*** Stage I (endometrioid histology, high intermediate risk)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	No chemotherapy	7	7	5
	Concurrent or concurrent + adjuvant chemotherapy	6	5	
	Chemotherapy before or adjuvant to RT	7	6	
<10 nodes dissected	No chemotherapy	7	6	7
	Concurrent or concurrent + adjuvant chemotherapy	6	5	5
	Chemotherapy before or adjuvant to RT			
≥10 nodes dissected	No chemotherapy	8	6	6
	Concurrent or concurrent + adjuvant chemotherapy	7	4	5
	Chemotherapy before or adjuvant to RT			

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

For high intermediate risk, stage I disease, there was a significant amount of uncertainty. Vaginal brachytherapy alone was rated Appropriate for patients not treated with chemotherapy, independent of nodal count. Vaginal brachytherapy was also rated Appropriate for patients with high intermediate risk disease and extensive nodal dissection when treated with concurrent or sequential chemotherapy. There was more uncertainty about the use of brachytherapy and concurrent or sequential chemotherapy in the setting of a low nodal count or absence of a nodal dissection. The panel also expressed uncertainty about the use of adjuvant pelvic RT, with or without vaginal brachytherapy, for high intermediate risk disease. However, it was rated Appropriate, particularly in the absence of chemotherapy with no or low nodal count. There is limited prospective data currently regarding the utility of chemotherapy in this setting and no prospective data to support the use of both external beam and brachytherapy in this group of patients, as was discussed in the endometrial Guideline.

Stage I (Serous and Clear cell Histology)

Table 5. ***Stage I Scenario Group D:*** Stage I (serous/clear cell)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	No chemotherapy	5	6	6
	Concurrent or concurrent + adjuvant chemotherapy	7	5	5
	Chemotherapy before or adjuvant to RT			6
<10 nodes dissected	No chemotherapy	7	4	6
	Concurrent or concurrent + adjuvant chemotherapy			5
	Chemotherapy before or adjuvant to RT		5	6
≥10 nodes dissected	No chemotherapy	6	6	6
	Concurrent or concurrent + adjuvant chemotherapy	7	5	5
	Chemotherapy before or adjuvant to RT			6

Key: green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement

For stage I, serous/clear cell carcinomas, there was a significant amount of uncertainty. The sole area of agreement among the panel on the appropriateness of radiation was with the use of vaginal brachytherapy alone when adjuvant chemotherapy was given. There was uncertainty regarding the role of vaginal brachytherapy in the absence of chemotherapy. The panel rated pelvic radiation with or without vaginal brachytherapy Uncertain regardless of whether chemotherapy was utilized and regardless of extent of nodal dissection. This uncertainty regarding the management of early-stage serous/clear cell carcinomas did not change significantly between the first and second round evaluations with only one scenario moving from the Uncertain to the Appropriate category.

Stage I Summary

The scenario ratings among the panelists for stage I endometrial cancer largely support observation or the use of adjuvant vaginal brachytherapy based on risk classification and histologic subtype. For patients with high intermediate risk disease or serous/clear cell histology, there was considerable uncertainty about the use of pelvic radiotherapy, independent of chemotherapy use and extent of nodal dissection. The consensus that adjuvant radiotherapy was rated Inappropriate for patients with low risk disease of endometrioid histology is supported by high-quality evidence and the published literature that demonstrates an absolute risk of vaginal recurrence of less than 5% with observation.[12] The risk of nodal involvement is similarly low in this setting, and the extent of nodal dissection did not influence the panel's rating against adjuvant RT.

For intermediate risk disease, the use of adjuvant radiation therapy has been extensively evaluated in prospective randomized trials.[11,13-15] Although the eligibility criteria varied between the studies, pelvic radiotherapy was shown to reduce the risk of local-regional recurrence when compared to observation, although there was no overall survival benefit. These studies also provided details on the site(s) of relapse, which was predominately vaginal in the observation arm, and led to further risk stratification into low and high intermediate risk categories based on age and pathologic risk factors such as high tumor grade, presence of lymphovascular invasion and deep myometrial invasion. The Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-2 trial compared vaginal brachytherapy and pelvic radiotherapy in patients with high intermediate risk disease.[16] The published findings of equivalence for vaginal relapse and overall survival between the treatment arms have led to great enthusiasm for vaginal brachytherapy given its more favorable side effect profile.

In this context, the panelists rated pelvic RT as Inappropriate for patients with low intermediate risk disease, and its use was rated Uncertain for high intermediate risk patients. Pelvic RT was rated Appropriate in the scenario of no or low nodal count for high intermediate risk disease when chemotherapy was not delivered. As the PORTEC study did not allow nodal dissection, many practitioners will advocate for the use of pelvic RT if the estimated risk of nodal involvement is clinically significant. The panel supported the use of vaginal brachytherapy for low and high intermediate risk patients with extensive nodal dissection and no chemotherapy. When concurrent or sequential chemotherapy was given, the use of brachytherapy was rated Inappropriate or Uncertain for low intermediate risk patients, and Uncertain or Appropriate for the high intermediate risk group, which varied by the extent of nodal assessment. The GOG 249 trial attempted to address some of the unanswered questions regarding adjuvant therapy by comparing pelvic RT to vaginal brachytherapy with sequential chemotherapy in a high risk subset of patients, including those with deeply invasive, high grade disease, and results were recently presented in abstract form.[17]

The high risk histologic subtypes, uterine papillary serous (UPSC) and clear cell (CC) carcinoma, are rare, accounting for 10–15% of all endometrial cancers.[18] When complete surgical staging is performed, these cancers more frequently present at more advanced stages. Their behavior is known to be more aggressive with increased rates of local and distant relapse compared to the similarly staged endometrioid cancers. Both UPSC and CC subtypes were excluded from GOG 99 and PORTEC-2, and patients with UPSC and CC cancers represented less than 1% of patients treated on PORTEC-1.[11,13,16] Due to the lack of evidence from randomized trials, there is significant variation in clinical practice for adjuvant treatment for early-stage UPSC and CC. It is not surprising that our ratings reflect this variation, with nearly all of the treatment approaches being rated as Uncertain, particularly the use of adjuvant pelvic external beam radiotherapy either alone or combined with vaginal brachytherapy. At the in-person meeting, many panelists expressed the belief that papillary serous and clear cell carcinomas are best treated with chemotherapy with the role of radiation, in general, being less certain.

Retrospective data does support the use of pelvic radiotherapy to decrease locoregional recurrence after surgery for stage I UPSC and CC cancers.[19,20] Several recent retrospective studies report excellent rates of local control with the combination of complete surgical staging (including a complete pelvic lymph node dissection) and high dose rate vaginal brachytherapy with or without use of chemotherapy.[21-23]

Despite the potential risk of metastases in stage I serous and clear cell uterine tumors, the role of chemotherapy in the adjuvant setting is still an open question with respect to the survival advantage. The panel rated vaginal brachytherapy alone as Appropriate for adjuvant treatment for stage I UPSC and CC cancer when this treatment is combined with chemotherapy. The GOG 249 study allowed inclusion of these high risk histologies and results of this study were reported in abstract form earlier this year.[17]

Stage II

The same clinical factors and treatments as in the stage I chapter were used for stage II. It was likewise made up of 117 scenarios during both rounds. The first round ratings resulted in 22.2% (26 scenarios) being rated Appropriate, 74.4% (87 scenarios) rated Uncertain, and 3.4% (4 scenarios) rated Inappropriate. Disagreement was seen on 29.1% (34 scenarios). During the second round, 35.9% (42 scenarios) were rated Appropriate, 1.7% (2 scenarios) rated Uncertain, and 62.4% (73 scenarios) rated Inappropriate. Disagreement occurred on 8.6% (10 scenarios).

In the stage II, low risk endometrioid cohort, the panel rated pelvic radiation plus brachytherapy Appropriate (rating of 7) regardless of extent of nodal dissection. The panel also rated vaginal brachytherapy alone Appropriate in the setting of ≥10 nodes dissected. There was uncertainty regarding the role of vaginal brachytherapy alone in the setting of no or limited node dissection. There was similar uncertainty regarding the role of pelvic radiation alone, regardless of extent of nodal dissection.

Table 6. ***Stage II Scenario Group A:*** Stage II (endometrioid histology, low risk)

	VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	5	6	7
<10 nodes dissected	6		
≥10 nodes dissected	7		

Key: green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement

Table 7. ***Stage II Scenario Group B:*** Stage II (endometrioid histology, low intermediate risk)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	No chemotherapy	5	6	8
	Concurrent or concurrent + adjuvant chemotherapy	6	5	7
	Chemotherapy before or adjuvant to RT			8
<10 nodes dissected	No chemotherapy	7	6	6
	Concurrent or concurrent + adjuvant chemotherapy	6	5	6
	Chemotherapy before or adjuvant to RT	7	5	
≥10 nodes dissected	No chemotherapy	7	7	7
	Concurrent or concurrent + adjuvant chemotherapy	6	6	
	Chemotherapy before or adjuvant to RT		5	

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

In the stage II, low intermediate risk, endometrioid cohort, the panel favored the combination of vaginal brachytherapy and pelvic radiation. The panelists rated pelvic radiation plus brachytherapy Appropriate in the absence of chemotherapy, regardless of extent of nodal dissection. There was less certainty regarding the role of vaginal brachytherapy or pelvic radiation alone in this group. In the setting of no chemotherapy, vaginal brachytherapy alone was rated as Appropriate if node dissection was performed but was rated Uncertain in the setting of no node dissection. Pelvic radiation alone was rated Appropriate if ≥10 nodes were dissected but was rated Uncertain in the setting of no or <10 nodes dissected. With concurrent chemotherapy, there was general agreement that combined vaginal brachytherapy and pelvic radiation was preferred, with uncertainty regarding the role of either radiation modality alone combined with chemotherapy.

Table 8. ***Stage II Scenario Group C:*** Stage II (endometrioid histology, high intermediate risk)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	No chemotherapy	4	6	8
	Concurrent or concurrent + adjuvant chemotherapy	5	5	7
	Chemotherapy before or adjuvant to RT		6	
<10 nodes dissected	No chemotherapy	5	6	8
	Concurrent or concurrent + adjuvant chemotherapy	6	5	
	Chemotherapy before or adjuvant to RT		6	
≥10 nodes dissected	No chemotherapy	5	7	8
	Concurrent or concurrent + adjuvant chemotherapy	6	6	7
	Chemotherapy before or adjuvant to RT			

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

In the stage II, high intermediate risk, endometrioid cohort, the panel again favored the combination of vaginal brachytherapy and pelvic radiation. The panelists rated pelvic radiation plus brachytherapy Appropriate in the presence or absence of chemotherapy, regardless of extent of nodal dissection. The panel also rated pelvic radiation alone Appropriate in the absence of chemotherapy with <10 nodes dissected. Pelvic radiation alone was rated Uncertain in all other scenarios. Vaginal brachytherapy alone was rated Uncertain in all scenarios.

For stage II, papillary serous or clear cell histology, the panel continued to favor the combination of vaginal brachytherapy and pelvic radiation. The panelists rated pelvic radiation plus brachytherapy Appropriate in the presence or absence of chemotherapy, regardless of extent of nodal dissection. There was less certainty regarding the role of vaginal brachytherapy or pelvic radiation alone. In the setting of no chemotherapy, vaginal brachytherapy alone or pelvic radiation alone were rated Uncertain. As was stated previously, many panelists expressed that papillary serous and clear cell represent systemic diseases best treated with chemotherapy, thus potentially influencing the ratings for a "no chemotherapy" category. If concurrent chemotherapy was given, ratings of 6 or 7 were universally bestowed upon vaginal brachytherapy alone or pelvic radiation alone, regardless of extent of node dissection.

Stage II (Serous and Clear cell Histology)

Table 9. ***Stage II Scenario Group D:*** Stage II (serous/clear cell histology)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*
No dissection	No chemotherapy	3	6	8
	Concurrent or concurrent + adjuvant chemotherapy	7	7	
	Chemotherapy before or adjuvant to RT		6	
<10 nodes dissected	No chemotherapy	5	6	8
	Concurrent or concurrent + adjuvant chemotherapy	6		
	Chemotherapy before or adjuvant to RT	7	7	
≥10 nodes dissected	No chemotherapy	5	6	8
	Concurrent or concurrent + adjuvant chemotherapy	7		
	Chemotherapy before or adjuvant to RT		7	

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

Stage II Summary

Despite limited and conflicting data, there was general agreement from the multidisciplinary panel that combined pelvic radiation and vaginal brachytherapy is the preferred approach for stage II disease. In the revised FIGO 2009 staging system, cervical stromal invasion, but not cervical gland invasion, qualifies as stage II. This reflects the negative prognostic effect of invasion of cervical stroma, which is considered a high-risk feature for local recurrence and contributes to the risk of pelvic recurrence since it predicts for both nodal and parametrial spread. In one report, invasion of the outer third of the cervical stroma was an independent predictor of overall survival.[24] However, another report found extent of cervical stromal invasion was not a predictor of survival.[25]

There are no reported randomized trials looking specifically at radiation in patients with stage II endometrial cancer and studies randomizing patients to treatment with and without radiation have included very few with stage II. Patients with cervical stromal invasion were not eligible for PORTEC-1 and <1% of patients on the Adjuvant External Beam Radiotherapy in the Treatment of Endometrial Cancer (ASTEC) study had cervical stromal invasion.[13,26] Most frequently, patients with cervical stromal invasion disease have been treated with pelvic radiation on prospective trials including Radiation Therapy Oncology Group (RTOG) 9708, Nordic Society of Gynecologic Oncology/European Organization for the Research and Treatment of Cancer (NSOG/EORTC), Instituto Mario Negri (MANGO), and Japanese Gynecologic Oncology Group (JGOG).[27-29]

Retrospective series have reported higher rates of survival among patients with cervical involvement who received radiation therapy. In one series of 79 patients with endometrial cancer with cervical stromal invasion, the 49% who received adjuvant RT had higher rates of disease-specific survival (87% vs. 58%; P = 0.023).[30] In a SEER study of 1577 patients with stage II endometrial cancer who underwent lymphadenectomy, patients who did not receive radiation were 48% (HR, 1.48; 95% CI, 1.14-1.93) more likely to die than those who did.[31] The presence of cervical involvement has been cited as a predictor of vaginal recurrence and thus an indication for vaginal brachytherapy after pelvic radiation. However, Greven et al. found no difference in 5 year pelvic disease control with or without brachytherapy after pelvic radiation among stage II patients (93% vs. 90%, p = 0.32)[32] Similarly, Scotti et al noted that there was no difference in vaginal relapse among the patients with cervical involvement who did (136 patients) or did not (93 patients) receive brachytherapy.[33]

The panel ratings reflect generalized support for combined pelvic radiation and vaginal brachytherapy despite limited evidence in the literature to support this approach. This is likely a reflection of the small number of stage II patients, the limited and retrospective nature of available data to demonstrate a local control benefit to the addition of brachytherapy to whole pelvis radiation, significant perceived risk in both the vaginal cuff and pelvis due to cervical involvement, and less concern regarding additive toxicity. In the single institution series looking at stage II patients, there could be an inherent selection bias for which patients received the brachytherapy boost. The conclusions of the panel appropriately reflect the potential concern for greater risk of vaginal failure associated with cervical stromal invasion.

Stage III

The third chapter divided patients by sub-stage, histology, nodal dissection, and nodal involvement. It contained 520 scenarios in the first round and 440 in the second, due to the panel's decision to remove four sets of scenarios deemed not to occur in practice. Five radiation treatments, alone or with chemotherapy, were rated: vaginal brachytherapy, pelvic RT, pelvic RT plus vaginal brachytherapy, pelvic and para-aortic RT, and pelvic and para-aortic RT plus vaginal brachytherapy. As mentioned earlier, a "no radiation" option was not provided. In the first round, 13.3% (36 scenarios) were rated Appropriate, 68.1% (354 scenarios) rated Uncertain, and 18.7% (97 scenarios) rated Inappropriate. Only 7.9% (41 scenarios) had disagreement. The results of the second round rating were 15.0% (66 scenarios) rated Appropriate, 37.1% (163 scenarios) Uncertain, and 48.0% (211 scenarios) rated Inappropriate. Disagreement was observed on 6.4% (44 scenarios).

Among 120 scenarios for stage IIIA in the second round, 8 (6.7%) were rated Appropriate, 60 (50%) Uncertain, and 52 (43.3%) Inappropriate, including 3 that had disagreement. For stage IIIB, 18 of 120 scenarios (15%) were rated Appropriate, 30 (25%) Uncertain, and, 72 (60%) Inappropriate with disagreement on 6. Out of 200 scenarios in stage IIIC, 40 (20%) were rated Appropriate, 73 (36.5%) Uncertain, and 87 (43.5%) Inappropriate. Disagreement occurred on 19 scenarios.

Stage IIIA (Endometrioid Histology)

Table 10. ***Stage III Scenario Group A:*** Stage IIIA (endometrioid histology)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	2	5	7	4	5
	Concurrent or concurrent + adjuvant chemotherapy	5	6		3	3
	Chemotherapy before or adjuvant to RT		7	6		4
<10 nodes dissected	No chemotherapy	2	5	7	3	3
	Concurrent or concurrent + adjuvant chemotherapy	4	6			4
	Chemotherapy before or adjuvant to RT	5		6	4	
≥10 nodes dissected	No chemotherapy	3	4	7	3	3
	Concurrent or concurrent + adjuvant chemotherapy	5	6	6		
	Chemotherapy before or adjuvant to RT	6				

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

There was considerable variation among the adjuvant radiation treatment conclusions for stage IIIA disease. The panel rated the combination of pelvic radiation and vaginal brachytherapy Appropriate for patients with stage IIIA endometrioid histology regardless of extent of lymph node dissection, in the absence of chemotherapy. There was greater uncertainty and disagreement as to the role of combined pelvic radiation and vaginal brachytherapy, and radiation in general, when chemotherapy was given.

The panel rated pelvic radiation alone Appropriate in combination with chemotherapy before or adjuvant to RT if there was no nodal dissection. In the setting of no chemotherapy, vaginal brachytherapy alone was rated Inappropriate, and there was uncertainty in the remaining scenarios including all combinations of pelvic RT and chemotherapy. The addition of para-aortic radiation was rated either Uncertain or Inappropriate.

Stage IIIA (Serous and Clear Cell Histology)

Table 11. ***Stage III Scenario Group B:*** Stage IIIA (serous/clear cell histology)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	2	5	6	4	5
	Concurrent or concurrent + adjuvant chemotherapy	3		7	3	3
	Chemotherapy before or adjuvant to RT		6	6		
<10 nodes dissected	No chemotherapy	2	4	6	4	4
	Concurrent or concurrent + adjuvant chemotherapy	3	5		3	3
	Chemotherapy before or adjuvant to RT		6			
≥10 nodes dissected	No chemotherapy	2	4	6	4	4
	Concurrent or concurrent + adjuvant chemotherapy	3	5	7	3	3
	Chemotherapy before or adjuvant to RT		5	6		

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

The only Appropriate rating bestowed for patients with stage IIIA papillary serous or clear cell histology was for combined pelvic radiation and vaginal brachytherapy for patients receiving concurrent +/- adjuvant chemotherapy regardless of the extent of node dissection. Vaginal brachytherapy alone and para-aortic radiation were consistently rated Inappropriate regardless of extent of node dissection when chemotherapy was given. In the absence of chemotherapy, with the exception of vaginal brachytherapy alone being rated Inappropriate, there was general uncertainty as to the role of all other radiation modalities. When chemotherapy was given, regardless of the extent of node dissection, pelvic radiation alone and pelvic radiation combined with vaginal brachytherapy were rated Uncertain. The Uncertain and Inappropriate ratings in general for radiation in this category are a likely reflection of the panelists' agreement that stage IIIA papillary serous or clear cell disease warrants chemotherapy, with the role of radiation being less certain.

Stage IIIB

Table 12. *Stage III Scenario Group C:* Stage IIIB (endometrioid histology)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	2	4	8	3	3
	Concurrent or concurrent + adjuvant chemotherapy		5		4	4
	Chemotherapy before or adjuvant to RT					
<10 nodes dissected	No chemotherapy	2	4	8	3	3
	Concurrent or concurrent + adjuvant chemotherapy					
	Chemotherapy before or adjuvant to RT					
≥10 nodes dissected	No chemotherapy	2	4	8	3	3
	Concurrent or concurrent + adjuvant chemotherapy		5			
	Chemotherapy before or adjuvant to RT					

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

Table 13. *Stage III Scenario Group D:* Stage IIIB (serous/clear cell histology)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	2	4	8	3	3
	Concurrent or concurrent + adjuvant chemotherapy		5		4	
	Chemotherapy before or adjuvant to RT					
<10 nodes dissected	No chemotherapy	2	4	8	3	3
	Concurrent or concurrent + adjuvant chemotherapy		5			
	Chemotherapy before or adjuvant to RT					
≥10 nodes dissected	No chemotherapy	2	5	8	3	3
	Concurrent or concurrent + adjuvant chemotherapy					
	Chemotherapy before or adjuvant to RT					

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

The panel rated the combination of pelvic radiation and vaginal brachytherapy Appropriate, for all patients with stage IIIB disease regardless of receipt of chemotherapy, extent of lymph node dissection, or histology. Vaginal brachytherapy alone was consistently rated Inappropriate. For endometrioid histology, there was uncertainty as to the role of pelvic radiation alone regardless of receipt of chemotherapy or extent of lymph node dissection. When concurrent chemotherapy was given and no node dissection performed, there was uncertainty as to both the role of pelvic radiation alone and the use of pelvic radiation with para-aortic radiation, with or without vaginal brachytherapy. In scenarios for endometrioid histology where concurrent chemotherapy was given and node dissection performed, pelvic radiation alone was rated Uncertain. The panel felt that PA nodal irradiation was not typically indicated in the setting of IIIB endometrioid histology.

For papillary serous or clear cell histology there was uncertainty as to the role of pelvic radiation alone regardless of receipt of chemotherapy or extent of lymph node dissection. For this rare histologic subset of stage IIIB patients, there may be a locoregional control benefit to radiation, and there would also be strong consideration for adjuvant chemotherapy. Given the overall uncertainty, adjuvant therapy decisions for these patients will need to be developed on an individual basis with an experienced multidisciplinary team.

As stage IIIB is largely indicative of vaginal disease (parametrial extension was also added to stage IIIB in 2009), maximizing the vaginal treatment took priority, regardless of systemic therapy choices. The endometrial Guideline did not specifically endorse vaginal brachytherapy with RT in the case of parametrial extension since an adequate dose from vaginal brachytherapy may not reach the area of concern.

Stage IIIC 1&2 (Endometrioid Histology)

Table 14. ***Stage III Scenario Group E:*** Stage IIIC1 (endometrioid histology, positive pelvic nodes)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	1	6	8	5	5
	Concurrent or concurrent + adjuvant chemotherapy	2				
	Chemotherapy before or adjuvant to RT					
<10 nodes dissected	No chemotherapy	1	6	7	5	5
	Concurrent or concurrent + adjuvant chemotherapy	2	7		4	3
	Chemotherapy before or adjuvant to RT					4
≥10 nodes dissected	No chemotherapy	2	7	7	3	4
	Concurrent or concurrent + adjuvant chemotherapy					3
	Chemotherapy before or adjuvant to RT					

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

The panel consistently rated the combination of pelvic radiation and vaginal brachytherapy Appropriate, for all patients with stage IIIC disease regardless of receipt of chemotherapy or extent of lymph node dissection. The endometrial Guideline did not recommend vaginal brachytherapy with RT in cases of IIIC unless there were risk factors such as cervical stromal invasion or LVSI that could lead to a higher risk of a vaginal recurrence. Vaginal brachytherapy alone was consistently rated Inappropriate. There was uncertainty as to the role of pelvic radiation alone, and pelvic radiation in combination with para-aortic radiation with or without vaginal brachytherapy. The panel did rate pelvic radiation alone Appropriate for stage IIIC disease with a limited node dissection if chemotherapy was used either sequentially or concurrently. In the setting of no or <10 nodes dissected, adding para-aortic radiation was rated Uncertain, however when ≥10 nodes were dissected, the panelists rated para-aortic radiation Inappropriate.

In the presence of para-aortic nodal disease, the panel rated an extended radiation field to encompass the para-aortic nodes Appropriate, with or without vaginal brachytherapy, regardless of chemotherapy. Vaginal brachytherapy or pelvic radiation alone was rated Inappropriate.

Table 15. ***Stage III Scenario Group F:*** Stage IIIC2 (endometrioid histology, positive para-aortic nodes with or without positive pelvic nodes)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	1	3	3	7	8
	Concurrent or concurrent + adjuvant chemotherapy	2		4		7
	Chemotherapy before or adjuvant to RT					
≥10 nodes dissected	No chemotherapy	1	3	3	7	7
	Concurrent or concurrent + adjuvant chemotherapy	2				
	Chemotherapy before or adjuvant to RT					

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

Table 16. ***Stage III Scenario Group D:*** Stage IIIB (serous/clear cell histology)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	2	3	6	5	5
	Concurrent or concurrent + adjuvant chemotherapy	3	6	7		
	Chemotherapy before or adjuvant to RT		6			
<10 nodes dissected	No chemotherapy	2	4	6	5	4
	Concurrent or concurrent + adjuvant chemotherapy	3	6	7	4	
	Chemotherapy before or adjuvant to RT				5	
≥10 nodes dissected	No chemotherapy	2	5	6	4	4
	Concurrent or concurrent + adjuvant chemotherapy		7	7	3	3
	Chemotherapy before or adjuvant to RT					

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

The panel consistently rated the combination of pelvic radiation and vaginal brachytherapy Appropriate for patients with stage IIIC papillary serous or clear cell histology, if chemotherapy was given, regardless of the extent of lymph node dissection. Pelvic radiation combined with vaginal brachytherapy was rated Uncertain in the absence of chemotherapy. Vaginal brachytherapy alone was consistently rated Inappropriate. Aside from consensus that vaginal brachytherapy was Inappropriate in the absence of chemotherapy, there was general uncertainty as to the role of all other radiation modalities without chemotherapy. This uncertainty may have been a reflection of limited data supporting pelvic radiation alone in the absence of chemotherapy, and the panelists' general agreement that stage IIIC papillary serous or clear cell disease warrants chemotherapy.

There was uncertainty as to the role of pelvic radiation alone, and pelvic radiation in combination with para-aortic radiation with or without vaginal brachytherapy. The panel did rate pelvic radiation alone Appropriate for stage IIIC disease with ≥10 nodes dissected if chemotherapy was used either sequentially or concurrently. In the setting of no or <10 nodes dissected, adding para-aortic radiation was rated Uncertain. However, when ≥10 nodes dissected had been performed, the panelists rated para-aortic and pelvic radiation Inappropriate, with or without vaginal brachytherapy.

Table 17. ***Stage III Scenario Group F:*** Stage IIIC2 (endometrioid histology, positive para-aortic nodes with or without positive pelvic nodes)

		VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No dissection	No chemotherapy	1	2	2	7	7
	Concurrent or concurrent + adjuvant chemotherapy	2		3		
	Chemotherapy before or adjuvant to RT	3				
≥10 nodes dissected	No chemotherapy	1	2	3	7	7
	Concurrent or concurrent + adjuvant chemotherapy	2	3		6	6
	Chemotherapy before or adjuvant to RT					

Key: red = inappropriate (median 1–3 without disagreement), green = appropriate (median 7–9 without disagreement), yellow = uncertain due to median 4–6 without disagreement, grey = uncertain due to disagreement, regardless of median.

For stage IIIC2 para-aortic node involvement, the panelists rated all radiation modalities that did not target the para-aortic nodes as Inappropriate. In the absence of chemotherapy, regardless of extent of node dissection, the panelists rated pelvic radiation plus para-aortic radiation with or without vaginal brachytherapy Appropriate. With chemotherapy, the panelists rated pelvic radiation plus para-aortic radiation with or without vaginal brachytherapy Appropriate in the setting of <10 nodes dissected. With chemotherapy, in the setting of ≥10 nodes dissected, the panelists rated pelvic radiation plus para-aortic radiation with or without vaginal brachytherapy Uncertain.

Stage III Summary

The ratings for stage III disease reflect tailoring of the radiation field to perceived risk, as well as the fact that the multidisciplinary panel considered patients with stage III to be highly heterogeneous. The higher ratings for pelvic radiation plus vaginal brachytherapy seen throughout the stage III scenarios may indicate concern regarding potential cervical involvement since the presence or absence of cervical involvement was not specified by the stage definition alone.

For stage IIIA endometrioid histology (i.e. serosal and/or adnexal involvement), pelvic radiation in combination

with vaginal brachytherapy was the preferred approach, regardless of extent of nodal dissection or receipt of chemotherapy. Pelvic radiation alone was rated Uncertain regardless of extent of nodal dissection or receipt of chemotherapy. Vaginal brachytherapy alone was rated Inappropriate across all stage IIIA scenarios reflecting perceived maximal risk in the pelvis. In the setting of node dissection, para-aortic node radiation was Inappropriate but there was some uncertainty regarding para-aortic node directed RT when no nodal dissection was performed.

For women with stage IIIB endometrioid histology (i.e. vaginal and/or parametrial involvement), pelvic radiation in combination with vaginal brachytherapy was the preferred approach in the absence of chemotherapy. When chemotherapy was given, the panelists' voting reflected a greater degree of uncertainty with vaginal brachytherapy alone, pelvic radiation alone, and the combination of vaginal brachytherapy and pelvic radiation all rated Uncertain in the setting of ≥10 nodes dissected. When chemotherapy was given and no or limited node dissection performed, the panel rated combined vaginal brachytherapy and pelvic radiation Appropriate. For stage IIIB in the setting of ≥10 nodes dissected, para-aortic node radiation was Inappropriate but there was some uncertainty regarding para-aortic node directed RT when no or <10 nodes were dissected.

For stage IIIC1 endometrioid histology (i.e. pelvic node involvement), pelvic radiation in combination with vaginal brachytherapy was the preferred approach, regardless of extent of nodal dissection or receipt of chemotherapy. Pelvic radiation alone was rated Uncertain or Appropriate, dependent on extent of nodal dissection or receipt of chemotherapy. Vaginal brachytherapy alone was rated Inappropriate across all stage IIIC scenarios reflecting perceived maximal risk in the pelvis. In the setting of node dissection, para-aortic node radiation was rated Inappropriate but there was some uncertainty regarding para-aortic node directed RT when no nodal dissection was performed.

For stage IIIC2 endometrioid histology (i.e. para-aortic nodal involvement), radiation targeting the pelvic and para-aortic nodes, with or without vaginal brachytherapy, was rated Appropriate. The options of pelvic RT alone and vaginal brachytherapy alone were rated Inappropriate.

For endometrioid histology stage III disease, pelvic radiotherapy with or without vaginal brachytherapy was generally rated Appropriate, with clear agreement that the para-aortic basins should be covered if involved. The ratings also reflected if there was no evidence of para-aortic involvement, the para-aortic nodes should not be covered electively, unless the nodal dissection was considered insufficient to rule out occult involvement. Vaginal brachytherapy alone was consistently rated Inappropriate for stage III disease. The plan for chemotherapy did little to change the radiation ratings of the panel.

The same general themes were reflected in the ratings for stage III papillary serous or clear cell, which supported radiation directed based on perceived risk. Pelvic radiation +/- vaginal brachytherapy received the most favorable ratings in the absence of para-aortic node involvement. Coverage of the para-aortic nodes was favored when pathologically involved. There was a general agreement by the panel that patients with stage III serous/clear cell should be treated with pelvic RT +/- vaginal brachytherapy with chemotherapy. These conclusions were slightly different than for the patients with endometrioid histology in that patients with endometrioid histology could also be treated without chemotherapy. The greater degree of uncertainty in general for radiation reflected across stage III papillary serous or clear cell is likely a reflection of the panelists' agreement that stage III papillary serous or clear cell disease warrants chemotherapy, with the role of radiation being less certain.

Unanswered by this investigation is whether or not radiation therapy should be used at all in women with stage III, as "no radiation" was not an option that was available for selection. In general, systemic chemotherapy is indicated for patients with stage III disease. GOG 122, a trial comparing chemotherapy alone to radiation alone, demonstrated a greater benefit to chemotherapy, and thus established chemotherapy as a mainstay in the adjuvant therapy for stage III.[34] However, there are still substantial risks for locoregional recurrence which could be impacted with the addition of tailored radiation therapy. In stage IIIC specifically, the argument for radiotherapy is the strongest, as the target of pelvic and/or para-aortic treatment is largely the lymph node basins, which has been shown prospectively to improve the control in these regions, compared to chemotherapy alone.[28,34] Likely the results of the ongoing phase III trial GOG 258, randomizing between chemotherapy alone and a combination of concurrent chemoradiotherapy and additional outback chemotherapy, will aid in determining the clinical outcomes and benefit of adding radiation to chemotherapy.[35]

Another question for future exploration is the comparative effectiveness of sequential versus concurrent chemoradiotherapy. The panel did not consistently rate either approach to be superior. Should GOG 258 demonstrate superiority of combined modality treatment over chemotherapy alone, the concurrent and sequential approach it examines will likely become the treatment of choice. It will remain unclear, however, whether there is any role for purely sequential treatment. The biggest question that remains unresolved, as mentioned previously, is whether or not there is any role for radiation therapy in stage III, especially in women with serous carcinoma, where the rate of peritoneal/distant metastasis is high. There is little literature available on the treatment of stage IIIC serous/clear cell endometrial carcinoma due to the rarity of these cell types. Many of the advanced stage trials for endometrial cancer specifically exclude the papillary serous and clear cell histologies because of their different patterns of recurrence, and what literature that is available is retrospective.

However, it remains a fact that these patients do have local failures and that addition of target RT aids in local control. Whether or not it helps in survival in this subgroup of patients may or may not be answered by GOG 258 since these cell types are uncommon.

Stage IVA

The fourth chapter focused on stage IVA and the clinical factors included histology, nodal dissection, and nodal involvement. The same treatments were evaluated as for stage III. This chapter consisted of 280 scenarios in the first round and 20 in the second. It was reduced to a single set of scenarios during the meeting because of a general consensus among panelists that stage IVA was a rare scenario with considerable heterogeneity in patient presentation. Initially, 12.9% (36 scenarios) were rated Appropriate, 48.6% (136 scenarios) rated Uncertain, and 38.6% (108 scenarios) rated Inappropriate. In the second round, no scenarios were rated Appropriate, 80% (16 scenarios) were rated Uncertain, and 20% (4 scenarios) were rated Inappropriate. Disagreement was 6.4% (18 scenarios) in the first round and 0% in the second.

Table 18. ***Stage IVA***

	VB alone	*3D pelvic RT alone*	*3D pelvic RT + VB*	*3D pelvic + PA RT*	*3D pelvic + PA RT + VB*
No chemotherapy	**2**	**6**	**6**	**5**	**5**
Concurrent or concurrent + adjuvant chemotherapy	**3**				
Chemotherapy before or adjuvant to RT					

Key: red = inappropriate (median 1–3 without disagreement), yellow = uncertain due to median 4–6 without disagreement.

Stage IVA endometrial cancer is a rare subset with locally advanced disease invading bladder and/or rectum. We had stipulated that we would restrict our analysis to only operable cases. Given the locally advanced nature of stage IVA disease, the panel commented that most cases are not resectable. It was also noted that the extent of surgery (radical hysterectomy versus pelvic exenteration, etc.) for resectable cases may influence adjuvant radiation conclusions. The management of stage IVA disease is in general very individualized, and requires close multidisciplinary management. The panel rated vaginal brachytherapy Inappropriate, and there was generalized uncertainty regarding the remaining options in this unusual setting.

IMRT

Table 19. *IMRT*

	3D conformal radiation therapy	*Intensity-modulated radiation therapy*
Scenarios in which pelvic RT was rated appropriate	**8**	**8**
Scenarios in which pelvic and PA RT was rated appropriate	**7**	

Key: green = appropriate (median 7–9 without disagreement).

In two questions separate from the scenarios, panelists were asked to rate the appropriateness of IMRT and three-dimensional conformal radiation therapy (3D-CRT) for scenarios for which they believed pelvic and then pelvic and para-aortic RT were Appropriate. For both rounds, both IMRT and 3D-CRT were rated Appropriate.

Discussion

In this era of "personalized medicine," the broadest goal for cancer therapy is both curing the patient and minimizing the risks for late sequelae of treatment. The management of endometrial cancer is an excellent example of this trend. Endometrial cancer is a very heterogeneous disease, and the optimal management relies on thoughtful multidisciplinary collaboration between gynecologic oncologists, medical oncologists, and radiation oncologists. The challenge in this setting, as mirrored in the construction of the case scenarios, is the many nuances of the pathologic features, surgical management, and options for combining radiation therapy with systemic therapy.

The field of radiation oncology has been in the spotlight in recent years, both for tremendous progress in advanced technologies and for high stakes involved in patient safety. However, due to the rarity and heterogeneity of many diseases treated with radiation and the multitude of radiation-specific modalities available, randomized trials often cannot be relied upon to provide much needed data to guide clinical practice. This is reflected in endometrial cancer where, although there is a significant body of literature guiding clinical decision making, there are many remaining questions. In this regard, the RAND/UCLA process is well suited to explore these uncertainties because it incorporates not only the existing high level evidence but also formal multidisciplinary expert opinion. This allowed the analysis to look at a number of issues that lack a strong literature base, such as the effect of histology, the impact of node dissection, the role of chemotherapy in decisions about radiation therapy, and the appropriateness of 3D versus IMRT delivery.

As the results show, ambiguity remains in a number of areas, indicating the need for new research. The ability to specifically focus on questions lacking literature is one of the RAND/UCLA methodology's strengths but the process is not meant primarily to eliminate uncertainty. In some cases, the multidisciplinary panel may reach a conclusion on questions for which there is not sufficient high-level evidence for a Guideline recommendation but ratings of Inappropriate, Uncertain, and Appropriate have equal value.

The effect of histology

The major pathologic feature which most influences treatment decisions is the presence of the uterine papillary serous carcinoma and clear cell variants. While this represents only 10–15% of the total patients who are diagnosed with endometrial cancer, it accounts for approximately half of patients with recurrent disease.[18] There was extensive discussion among the panelists that papillary serous and clear cell variants are at significant risk of systemic spread and thus warrant chemotherapy across all stages. The role of radiation was less certain in these histologies. For stage I papillary serous or clear cell histology, vaginal brachytherapy in addition to chemotherapy was rated Appropriate. For stage II and III papillary serous or clear cell histology, the panel favored the combination of vaginal brachytherapy and pelvic radiation in addition to chemotherapy. Due to lack of evidence from randomized trials, there is considerable uncertainty for this subgroup, and this is an area where renewed focus of clinical trials may yield important progress for optimal management. Based on the rarity of the subtype, this may be best addressed through an international 'rare cancer' cooperative network or serial phase II studies. In the recently completed GOG 249

trial, patients with this high risk histology are eligible, but it remains to be seen whether adequate numbers of patients in this subtype are enrolled.[17,36]

The effect of nodal dissection

Nodal dissection is the major surgical intervention which impacts adjuvant clinical management. This is important in two areas, first in interpreting the literature, and second in the management of an individual patient because there is substantial heterogeneity in lymph node sampling practice. For stage I patients, the multidisciplinary panel had greater confidence in general in the appropriateness of vaginal brachytherapy alone when more extensive nodal dissection was performed. For stage II patients, the panel favored combined pelvic radiation and vaginal brachytherapy regardless of extent of nodal dissection. Among stage III patients, there was a degree of uncertainty regarding adding para-aortic radiation in the setting of no or <10 nodes dissected. When ≥10 nodes were dissected, the panelists rated para-aortic radiation Inappropriate for stage III disease unless the para-aortic nodes were pathologically involved.

The effect of the chemotherapy options

There are several options for how to combine chemotherapy with radiation. There are concurrent or concurrent and adjuvant combinations, as piloted in an RTOG phase II trial[37] and now incorporated into ongoing phase III GOG trials. Chemotherapy can also be given before or after radiation, and the GOG 184 trial compared a 2 vs. 3 drug chemotherapy regimen given after tailored radiation.[38] The sequential "sandwich" chemotherapy regimen adds radiation at the half way point through 6 cycles of chemotherapy. While there is multi-institutional data showing reasonable results with the sandwich approach, there are no prospective randomized data with this strategy, and the current/ongoing randomized trials are using the concurrent and adjuvant approach originally piloted by the RTOG.

The scenarios designed for this endeavor were intended to address the role of radiation specifically. The objective was to have the panelists rate various radiation therapy options in the setting of no chemotherapy and in the setting of commonly used chemotherapy approaches (e.g. concurrent chemotherapy, chemotherapy given pre or post radiation, and sequential/sandwich chemotherapy). Despite this instruction, the panelists commonly voiced preferences that were specific to chemotherapy. For example, panelists commonly argued that papillary serous or clear cell histology warrants chemotherapy, regardless of stage, and they would have liked to rate a chemotherapy only option. Also, panelists in general voiced opposition to the sandwich chemotherapy approach. In the vast majority of stage II–III disease scenarios, the panelists preferred the same radiation modality regardless of the use of chemotherapy. For example, in stage II disease, for low intermediate and high intermediate risk disease, pelvic radiation in combination with vaginal brachytherapy was preferred, regardless of receipt of chemotherapy. Similarly, for stage IIIA, IIIB, and IIIC1, pelvic radiation in combination with vaginal brachytherapy was preferred, regardless of the use of chemotherapy. For stage IIIC2, the combination of pelvic and para-aortic radiation with or without vaginal brachytherapy was preferred, regardless of the use of chemotherapy.

The role of IMRT vs. 3D-CRT

Intensity-modulated radiation therapy use has increased significantly in the management of gynecologic cancers. In one survey study published in 2005, 27% of respondents were using IMRT for gynecological cancers.[39] Dosimetric studies indicate that IMRT significantly reduces dose to critical normal structures including the small bowel, bladder, rectum and bone marrow.[40] However, dosimetric parameters have been criticized as not necessarily translating into meaningful clinical endpoints such as patient or clinician reported reduced toxicity.[41,42] Furthermore, IMRT can result in larger tissue volumes treated to a low dose which could have potential negative consequences.[43] Also, due to the more conformal dose distribution created by IMRT, it has been argued that tumor control could be compromised by an increased risk of compromised target coverage (i.e., missing the target).[41]

Although literature supports dosimetric improvement and the suggestion of improved acute effects, there is promising, albeit limited data on late toxicity and efficacy.[41,44,45] For other disease sites, such as prostate cancer, IMRT has gained widespread adoption and acceptance. RTOG 0418 is a prospective trial in progress which is prospectively evaluating the role of IMRT in women with gynecologic malignancies specifically and does include an assessment of patient reported toxicity and quality of life.[42] The discussion during the panel meeting cited the most common setting for IMRT usage as treatment of the para-aortic lymph node region, where several critical normal organs such as kidneys, small bowel, and spinal cord make sparing of normal tissues particularly important. Furthermore, some clinicians might use a hybrid approach treating the pelvis with a three-dimensional technique, with a non-divergent matched IMRT field to encompass para-aortic nodes. Although not reflected in the ratings,

the panelists further discussed that cost, insurance reimbursement, technical capacity to plan and deliver IMRT, and concurrent chemotherapy influence IMRT specific decision making. Currently, there is a phase III RTOG 1203 trial comparing 3D to IMRT pelvic radiation post-hysterectomy for cervical and endometrial cancer patients, and this trial should provide substantial information on the advantages of IMRT.

The ASTRO RAND/UCLA analysis and Clinical Practice Guideline on endometrial cancer

Reflecting the complexity of treatment decisions for endometrial cancer and the frequently limited or contradictory evidence available to illuminate the most appropriate therapeutic approach, ASTRO has explored this topic in both this analysis and a recent Clinical Practice Guideline. Although both approaches focus on the same disease site, they had different clinical questions to frame the scope of their guidance, different methodologies for assessing the literature, different levels of evidence, and subsequently differences in their conclusions

By utilizing a multidisciplinary panel of experts, and including non-gynecologic specialized radiation oncologists, the RAND/UCLA Method's goal is to remove possible biases from a tendency to support treatments that are delivered by the panelists. However, in some cases, the difference in composition between the endometrial Guideline panel, which was comprised predominately of gynecologic specialized radiation oncologists, and the panel for the RAND/UCLA analysis may account for the discrepancies in conclusions. A Guideline is evidence-based and by definition relies strictly on available literature to reach conclusions and endorse management recommendations. The RAND/UCLA Method by intent provides a formalized way to combine the best available scientific evidence with the collective judgment of experts to guide clinical decision making, especially in areas where evidence may be lacking. A multitude of scenarios depicted in this analysis are not addressed by available literature and thus the panel used their best judgment to reach conclusions. Whereas the Guideline panel may have failed to endorse an approach due to lack of evidence, the panel for the RAND/UCLA analysis may have concluded that absence of evidence does not necessarily mean a treatment option is inappropriate, despite a lack of high quality evidence.

For stage I, both documents are in agreement over the most appropriate treatment of low and low intermediate endometrial cancer. Both documents did not support any adjuvant radiation therapy for patients with low risk endometrial cancer, defined in both as grade 1 or 2 endometrioid cancers with less than 50% MI. Among the high intermediate cohort, there was consensus that vaginal brachytherapy is the most appropriate treatment when chemotherapy was not delivered. Among the low intermediate cohort, defined according to the RAND/UCLA analysis as patients with >50% invasion that did not meet criteria for high intermediate risk, vaginal brachytherapy was Uncertain to Appropriate when chemotherapy was not given. This agrees with the Guideline, which recommended vaginal cuff brachytherapy for patients with deeply invasive grade 1 or 2 cancers or grade 3 tumors with <50% invasion and indicated brachytherapy may be considered for patients with grade 3 cancer without invasion and grade 1 or 2 tumors with <50% invasion but other high risk features. The lack of support expressed for brachytherapy when chemotherapy is delivered is not supported by the literature and likely reflects a concern of the panel about the delivery of chemotherapy, and not the use of brachytherapy. This is in agreement with the Guideline statement, which recommended vaginal cuff brachytherapy for patients with intermediate risk factors, such as deeply invasive grade 1 or 2 cancers. The appropriateness rating of brachytherapy for the RAND/UCLA analysis varies as a function of node dissection, which is not the case for the Guideline. The extent of node dissection would be expected to impact the decision about pelvic radiation due to concerns about increased toxicity but generally would not be expected to impact the decision making about the use of vaginal brachytherapy.

The guidance from the two documents diverges over the use of pelvic radiation in patients with low and high intermediate risk findings. The Guideline statement recommends that: "Patients with grade 1 or 2 tumors with greater than or equal to 50% MI may also benefit from pelvic radiation to reduce pelvic recurrence rates if other risk factors are present such as age greater than 60 years and/or LVSI."1 The rating in the RAND/UCLA analysis for pelvic radiation in this setting is largely "Uncertain" with scores ranging from 4–7. Although these conclusions appear discordant, the divergence reflects a known controversy in the field. The randomized trials supporting pelvic RT have not demonstrated an overall survival advantage and may have been 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. A multitude of factors must be considered when rendering treatment guidance

for this heterogeneous group, and the two documents reflect that the evidence base may support differing conclusions.

To address this issue in the Guideline, a statement was added to highlight the fact that pelvic radiation has not been shown to improve overall survival, although it has been repeatedly shown with high quality evidence to decrease pelvic recurrence. It is also important to note that studies investigating pelvic radiation have not been powered to address overall survival. The treatment rated most appropriate in the RAND/UCLA analysis for patients with high intermediate risk findings is vaginal brachytherapy with or without chemotherapy. The recently completed GOG 249 study, which compared pelvic radiation to brachytherapy with chemotherapy, should provide further insight into this area of controversy.[17]

For patients with stage II endometrial cancer, both the Guideline and the RAND/UCLA analysis support pelvic radiation. However, the most appropriate treatment according to the analysis is a combination of pelvic radiation and brachytherapy. The Guideline statements favor the use of pelvic radiation without brachytherapy, reporting that: "Prospective data is lacking to validate the use of vaginal brachytherapy after pelvic radiation and retrospective studies show little conclusive evidence of a benefit, albeit with small patient numbers."[11] The Guideline statement does note that brachytherapy may be indicated after pelvic radiation in patients with high risk features for vaginal recurrence, which includes cervical involvement.

Stage II is defined as involvement of the cervical stroma and a recurring theme during the moderated face-to-face panel discussion for the RAND/UCLA analysis was tailoring treatment to perceived risk, especially when evidence was lacking. Panelists discussed that vaginal brachytherapy was likely to provide benefit when assessment of cuff recurrence risk was high, pelvic radiation when nodal risk was high, and chemotherapy when systemic failure risk was high. Absent level 1 evidence, panelists likely favored vaginal brachytherapy with pelvic RT due to perceived risk of vaginal cuff recurrence in the setting of cervical involvement. In contrast, the Guideline is strictly evidence-based and thus unable to endorse vaginal brachytherapy. Its recommendation against routine addition of vaginal brachytherapy to external beam is graded as weak and acknowledges prospective data is lacking. Again, what appear to be conflicting conclusions appropriately highlight an area of controversy in the field. Also, although pelvic radiation and brachytherapy were often rated higher in the RAND/UCLA analysis than pelvic radiation alone, the latter was never rated Inappropriate.

For patients with stage III and IV endometrial cancers, both the Guideline and RAND/UCLA analysis support radiation and chemotherapy when there are positive nodes or involved uterine serosa/ovaries/fallopian tubes, vagina, bladder or rectum. The analysis rated highest a combination of external bream radiation and brachytherapy, while the Guideline recommended pelvic radiation alone. In terms of sequencing of chemo and radiation, the best available evidence in the Guideline is for concurrent chemoradiation followed by adjuvant chemotherapy. The analysis rated concurrent chemoradiation as relatively equivalent to sequential. In both documents, there is less enthusiasm for sandwich therapy. Sandwich chemoradiation was never rated Appropriate in the RAND/UCLA analysis and the Guideline noted that this regimen delays radiation, which may reduce local control, and interrupts chemotherapy delivery. In the analysis, patients with stage IIIC disease that had endometrioid histology can also be treated with radiation therapy alone. However, the endometrial Guideline, even though radiation alone was considered an alternative treatment, noted there is low quality evidence for it. In the Guideline, chemotherapy alone had moderate quality evidence; however, this was not evaluated in the analysis.

The RAND/UCLA analysis' ratings for stage III disease reflect the panelists' discussion that Stage III is a very heterogeneous group and the stage definition alone does not indicate presence or absence of cervical involvement for Stage IIIA and IIIC. As for stage II, in no Stage III scenario (other than positive para-aortic nodes) did the analysis rate pelvic radiation Inappropriate. The proclivity for adding vaginal brachytherapy likely reflects panel discussions that cervical involvement warrants brachytherapy. We may have seen less enthusiasm for vaginal brachytherapy if panelists were specifically asked to rate Stage IIIA and IIIC scenarios separately for presence and absence of cervical involvement. Again, the ratings reflect consensus decisions reached in the absence of robust evidence to define adjuvant management of Stage III disease.

Finally, the Guideline does not make any specific recommendations regarding pelvic IMRT but does favor IMRT for extended field radiation targeting the para-aortic nodes. The multidisciplinary panel for this RAND/UCLA analysis rated 3D-CRT or IMRT Appropriate for patients in whom pelvic or pelvic and para-aortic radiation is indicated.

Future Directions

This analysis of management of endometrial cancer utilizing the RAND/UCLA Method is designed to provide a rigorous framework for selecting among the multiple treatment options for endometrial cancer patients. The ratings should not be taken as absolutes, as there may be unique circumstances that guide clinicians and patients in optimal decision making. This project represents ASTRO's first experience with the RAND/UCLA Method and the combined energies of many experts in gynecologic oncology, medical oncology, radiation oncology, and other medical disciplines, as well as in the RAND/UCLA Method. It highlights the investment ASTRO is making in advancement of multidisciplinary care and has yielded important lessons learned about the application of the RAND/UCLA Method to radiation oncology. In the future, results of ongoing trials may help clarify areas of uncertainty, particularly the combination of radiation and systemic therapy for the higher risk patients, and the benefits of IMRT versus three-dimensional pelvic radiation. Meanwhile, this project will serve to highlight areas of uncertainty that may refine the focus of intergroup clinical trialists.

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Appendix 1.
Multidisciplinary panel members who were leads of endometrial cancer clinical trials – January to June 2013

Panelist (specialty)	*Trial name*	*Role in trial*	*Trial phase during panel participation*
Brett Cox (radiation oncology)	None	Not applicable	Not applicable
Mitchell Kamrava (radiation oncology)	Efficacy of multiparametric MRI in endometrial cancer staging – University of California Los Angeles institutional study	Principal Investigator	Patient accrual
Sunil Krishnan (radiation oncology)	None	Not applicable	Not applicable
Joshua Lawson (radiation oncology)	None	Not applicable	Not applicable
Vicky Makker (medical oncology)	GOG0229N – A Phase II evaluation of dalantercept, a novel soluble recombinant activin receptor-like kinase 1 (ALK-1) inhibitor receptor-fusion protein in The Treatment of Recurrent or Persistent Endometrial Cancer	Study Chair and Principal Investigator	Patient accrual
	Phase II trial of GDC-0980 (dual PI3K/mTOR inhibitor) in patients with advanced endometrial carcinoma – sponsored by Genentech	National Principal Investigator	Patient accrual
	Phase II, two-stage, two-arm, PIK3CA mutation stratified trial of MK-2206 in recurrent endometrial cancer.	Principal Investigator for Memorial Sloan Kettering Cancer Center	Patient accrual
	GOG 261 – A Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Ifosfamide Plus Paclitaxel in Chemotherapy-Naive Patients with Newly Diagnosed Stage I-IV Persistent or Recurrent Carcinosarcoma (Mixed Mesodermal Tumors) of the Uterus or Ovary	Co-Principal Investigator	Patient accrual
	GOG248/09-019 – A Randomized Phase II Trial of Temsirolimus or Combination of Hormonal Therapy Plus Temsirolimus on Women with Advanced, Persistent, or Recurrent Endometrial Carcinoma	Principal Investigator for second stage accrual	Data analysis

Panelist (specialty)	*Trial name*	*Role in trial*	*Trial phase during panel participation*
David Mutch (gynecologic oncology)	GOG 229K – Phase II Study of BIBF in persistent recurrent endometrial cancer	Principal Investigator for Washington University	Patient accrual
	GOG 229N – Phase II study of Dalantercept in persistent/recurrent endometrial cancer	Principal Investigator for Washington University	Patient accrual
	GOG 249- A randomized phase III trial of pelvic radiation therapy vs. vaginal cuff brachytherapy with 3 cycles of chemotherapy in patients with high-risk stage I-II endometrial cancer	Principal Investigator for Washington University	Patient accrual
	GOG-258 – Carboplatin and Paclitaxel With or Without Cisplatin and Radiation Therapy in Treating Patients With Stage I, Stage II, Stage III, or Stage IVA Endometrial Cancer	Principal Investigator for Washington University and Co-study chair	Patient accrual
	GOG-9920 – Intraperitoneal Paclitaxel, Doxorubicin Hydrochloride, and Cisplatin in Treating Patients With Stage III-IV Endometrial Cancer	Principal Investigator for Washington University	Patient accrual
D. Scott McMeekin (gynecologic oncology)	GOG 249- A randomized phase III trial of pelvic radiation therapy vs. vaginal cuff brachytherapy with 3 cycles of chemotherapy in patients with high-risk stage I-II endometrial cancer	Study Chair	Patient accrual
	GOG 9920 – Phase I trial of intraperitoneal chemotherapy in patients with high risk endometrial cancer.	Study Chair	Patient accrual
	A Phase II, Single-Arm Study of Orally Administered BKM120 as Second-line Therapy in Patients with Advanced Endometrial Carcinoma – Sarah Cannon Research Institute, sponsored by Novartis Pharmaceuticals	Principal Investigator for University of Oklahoma	Data analysis
	Vaginal Cuff Brachytherapy Followed by Chemotherapy in Patients With Endometrioid Cancer – University of Oklahoma institutional study	Principal Investigator	Data analysis
Craig Nielsen (internal medicine)	None	Not applicable	Not applicable
Kim Peairs (internal medicine)	None	Not applicable	Not applicable
Stanley Benedict (medical physics)	None	Not applicable	Not applicable