

## Radiation Therapy for Cervical Cancer: An ASTRO Clinical Practice Guideline

**Junzo Chino, MD,<sup>a,\*</sup> Christina M. Annunziata, MD, PhD,<sup>b</sup> Sushil Beriwal, MD, MBA<sup>c</sup> Lisa Bradfield, BA,<sup>d</sup> Beth A. Erickson, MD,<sup>e</sup> Emma C. Fields, MD,<sup>f</sup> KathrynJane Fitch, PhD,<sup>g</sup> Matthew M. Harkenrider, MD,<sup>h,i</sup> Christine H. Holschneider, MD,<sup>j</sup> Mitchell Kamrava, MD,<sup>k</sup> Eric Leung, MD,<sup>l</sup> Lilie L. Lin, MD,<sup>m</sup> Jyoti S. Mayadev, MD,<sup>n</sup> Marc Morcos, MS,<sup>o</sup> Chika Nwachukwu, MD, PhD,<sup>p</sup> Daniel Petereit, MD,<sup>q</sup> and Akila N. Viswanathan, MD, MPH<sup>r</sup>**

- a. Duke University Cancer Center, Durham, NC, Department of Radiation Oncology and Guideline Vice-Chair*
- b. National Cancer Institute, Bethesda, MD, Women's Malignancies Branch*
- c. UPMC, Hillman Cancer Center, Pittsburgh, PA, Department of Radiation Oncology*
- d. American Society for Radiation Oncology, Arlington, VA*
- e. Medical College of Wisconsin, Milwaukee, WI, Department of Radiation Oncology*
- f. Virginia Commonwealth University, Richmond, VA, Department of Radiation Oncology*
- g. Patient Representative, Charlotte, NC*
- h. Loyola University Chicago, Chicago, IL, Department of Radiation Oncology*
- i. Edward Hines Jr. VA Hospital, Hines, IL, Department of Radiation Oncology*
- j. Olive View/UCLA Medical Center, Sylmar, CA, Department of Obstetrics and Gynecology*
- k. Cedars-Sinai Medical Center, Los Angeles, CA, Department of Radiation Oncology*
- l. Sunnybrook Health Sciences Centre, Odette Cancer Centre, University of Toronto, Toronto, Ontario, Department of Radiation Oncology*
- m. MD Anderson Cancer Center, Houston, TX, Department of Radiation Oncology and Guideline Subcommittee Representative*
- n. University of California, San Diego, CA, Department of Radiation Medicine and Applied Sciences*
- o. Johns Hopkins Medicine, Baltimore, MD, Department of Radiation Oncology and Molecular Radiation Sciences*
- p. UT Southwestern Medical Center, Dallas, TX, Department of Radiation Oncology*
- q. Rapid City Regional Health, Rapid City, SD, Department of Radiation Oncology*
- r. Johns Hopkins University, Baltimore, MD, Department of Radiation Oncology and Molecular Radiation Sciences and Guideline Chair*

\* **Corresponding author:** Junzo Chino, MD; E-mail: [junzo.chino@duke.edu](mailto:junzo.chino@duke.edu)

Sources of support: This work was funded by the American Society for Radiation Oncology.

## Task Force Members' Disclosure Statements

All task force members' disclosure statements were rigorously reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this report. Where potential conflicts were detected, remedial measures to address them were taken.

**Christina Annunziata (American Society of Clinical Oncology representative):** MaxCyte, Medivir, and Precision Biologics (research), Horizon Pharma and Merck (provided drugs for clinical trial), *BMC Cancer and Frontiers in Oncology* (editor); **Sushil Beriwal:** American Board of Radiology (board examiner), *Brachy Journal* and *IJROBP* (editorial board); Eisai, Institute of Education, and Via Oncology (honoraria), *International Journal of Radiation Oncology, Biology, Physics* (senior editor); Varian (consultant), XOFT (DSMB); **Junzo Chino (Vice Chair):** American Board of Radiology (board examiner); NanoScint (stock); *International Journal of Radiation Oncology, Biology, Physics* (editorial board); **Matthew Harkenrider:** ACR (program director and trustee), AstraZeneca (advisory board [ended]), *International Journal of Radiation Oncology, Biology, Physics* (editorial board); Varian (advisory board [ended]); **Christine Holschneider (Society of Gynecologic Oncology representative):** NRG-GOG and GOG Foundation (research), National Institutes of Health grants (research-family member), UpToDate (honoraria); **Mitchell Kamrava:** American Board of Radiology (board examiner), Augmenix (speaker's bureau), *Brachytherapy* and *International Journal of Radiation Oncology, Biology, Physics* (editorial board); **Lilie Lin:** American Board of Radiology (board examiner); AstraZeneca (research); **Jyoti Mayadev:** AstraZeneca (consultant), NRG GOG Foundation (member), NRG Oncology Cervical Board (co-chair), Varian (advisory board); **Marc Morcos:** Elekta (travel); **Daniel Petereit (American Brachytherapy Society representative and President):** American Board of Radiology (board examiner), BMS Foundation (research and salary support), Irving A Hansen Memorial Foundation (patient funding), Ralph Lauren Pink Pony Foundation (board member); **Akila Viswanathan (Chair):** NCI Uterine Task force (co-chair), American Board of Radiology (board examiner), *Brachytherapy* and *Gynecologic Oncology Journal* (editorial board), Springer textbook (chapter editor); **Beth Erickson:** American Brachytherapy Society (CME co-chair); ASTRO (MOC-CME co-chair); *Brachytherapy* and *International Journal of Radiation Oncology, Biology, Physics* (editorial board), Elekta (research and travel), Springer textbook (chapter editor). **Emma Fields, KathrynJane Fitch (patient representative), Eric Leung, and Chika Nwachukwu** reported no disclosures.

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Adherence to this guideline does not ensure successful treatment in every situation. This guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods reasonably directed to obtaining the same results. The physician must make the ultimate judgment regarding therapy considering all circumstances presented by the patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. This guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials. This guideline is based on information available at the time the task force conducted its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to revisit and update the guideline.

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## Preamble

As the leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

**Disclosure Policy** — ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures go through a rigorous review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. The complete disclosure policy for Formal Papers is [online](#).

**Selection of Task Force Members** — The Guideline Subcommittee strives to avoid bias by selecting a multidisciplinary group of experts with variation in geographic region, gender, ethnicity, race, practice setting, and areas of expertise. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

**Methodology** — The task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards. The evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system.

**Consensus Development** — Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of  $\geq 75\%$  ( $\geq 90\%$  for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

**Annual Evaluation and Updates** — Guidelines are evaluated annually beginning 2 years after publication for new potentially practice-changing studies that could result in a guideline update. In addition, the Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

**Table 1.** ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE, individual study quality, and panel consensus, all of which inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.			
Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	<ul style="list-style-type: none"> <li>Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits.</li> <li>All or almost all informed people would make the recommended choice.</li> </ul>	Any (usually high, moderate, or expert opinion)	"Recommend/Should"
Conditional	<ul style="list-style-type: none"> <li>Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks.</li> <li>Most informed people would choose the recommended course of action, but a substantial number would not.</li> <li>A shared decision-making approach regarding patient values and preferences is particularly important.</li> </ul>	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"
Overall QoE Grade	Type/Quality of Study	Evidence Interpretation	
High	<ul style="list-style-type: none"> <li>2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.</li> </ul>	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.	
Moderate	<ul style="list-style-type: none"> <li>1 well-conducted and highly generalizable RCT or a meta-analysis of such trials <b>OR</b></li> <li>2 or more RCTs with some weaknesses of procedure or generalizability <b>OR</b></li> <li>2 or more strong observational studies with consistent findings.</li> </ul>	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.	
Low	<ul style="list-style-type: none"> <li>1 RCT with some weaknesses of procedure or generalizability <b>OR</b></li> <li>1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes <b>OR</b></li> <li>2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.</li> </ul>	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.	
Expert Opinion*	<ul style="list-style-type: none"> <li>Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.</li> </ul>	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.	

**Abbreviations:** ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

\*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

# 1. Introduction

Despite improvements in screening and prevention, cervical cancer remains a significant cause of morbidity and mortality. In the United States, over 13,000 new cases are expected annually, resulting in more than 4250 deaths,<sup>1</sup> and there is a much greater global burden of disease with over 600,000 new cases and 260,000 deaths.<sup>2</sup> Effective treatment is often challenging owing to the disease's propensity for local spread within the pelvis, in close proximity to critical normal tissues.

In the last 2 decades there have been notable advances in surgical procedures, external radiation therapy (RT), brachytherapy techniques, and chemotherapy. Some of these new approaches have a high-quality evidence base; others have been adopted with more limited evidence. This guideline was commissioned by ASTRO to provide evidence-based recommendations for 5 clinical key questions (KQs) that arise when considering curative management in women with cervical cancer. This guideline, however, does not replace careful consideration and discussion of cases in a multidisciplinary manner. Of note, the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system is used in these recommendations, and any discrepancy with the prior staging system is noted in the text.<sup>3</sup>

## 2. Methods

### 2.1. Task Force Composition

The task force consisted of a multidisciplinary team of radiation oncologists; a gynecologic oncologist, medical oncologist, radiation oncology resident, and medical physicist; and a patient representative. This guideline was developed in collaboration with the American Brachytherapy Society, American Society of Clinical Oncology and the Society of Gynecologic Oncology, who provided representatives and peer reviewers.

### 2.2. Document Review and Approval

The guideline was reviewed by 20 official peer reviewers and revised accordingly. The modified guideline was posted on the ASTRO website for public comment in November 2019. The final guideline was approved by the ASTRO Board of Directors and endorsed by the American Brachytherapy Society, Canadian Association of Radiation Oncology, European Society for Radiotherapy and Oncology, Royal Australian and New Zealand College of Radiologists, and the Society of Gynecologic Oncology.

### 2.3. Evidence Review

A systematic search of human subject studies retrieved from the database Ovid MEDLINE was conducted. The inclusion criteria required research to involve adult women (age  $\geq 18$  years), with a diagnosis of cervical cancer, published in English, from January 1993 through October 2018, and RT delivered with curative intent. The literature review excluded studies with  $\leq 50$  participants; those focused on diagnostic methods; preclinical studies, health economics and cost analyses, comments and editorials; those focused on metastatic disease or recurrent disease; or were otherwise not relevant to the scope of the guideline. Because different qualities of evidence were available for each KQ, inclusion criteria were further refined as follows: KQ1 was

limited to meta-analyses and randomized controlled trials (RCTs); KQ2 to meta-analyses, RCTs, and prospective nonrandomized trials; and KQs 3, 4, and 5 to meta-analyses, RCTs, prospective nonrandomized trials, and retrospective studies ( $N \geq 100$ ). For subquestions with limited data, retrospective study results and expert opinion were relied on to support recommendations as reflected in the low-to-moderate quality of evidence cited in these cases.

The following concepts common to all KQs were searched using Medical Subject Heading (MeSH) terms and key search terms were used: *uterine cervical cancer, radiotherapy, radiation therapy, radiation dosage, brachytherapy, intensity modulated radiation therapy, survival, survival analysis, metastasis, adverse events, toxicity, and treatment outcome*. Additional concepts and terms specific to the KQs and hand searches supplemented the electronic searches.

The data used by the task force to formulate recommendations are summarized in evidence tables available in the [supplementary materials](#). References selected and published in this document are representative and not all-inclusive. The outcomes of interest differ per KQ and are listed in Table 2. Additional ancillary references are included in the text but were not used to support the recommendations.

See Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded and included in the evidence review; [Appendix 1](#) (peer reviewer's disclosure information); [Appendix 2](#) (list of abbreviations) and [Appendix 3](#) (literature search strategy).

## 2.4. Scope of the Guideline

This guideline covers only the subjects specified in the KQs (Table 2). The scope is limited to curative management of invasive carcinomas of the uterine cervix, which include squamous cell carcinomas and adenocarcinomas. It focuses on management of cervical cancer with RT and its indications, techniques, and outcomes. It additionally covers other therapies that modify the efficacy of RT when used concurrently or in sequence (eg, chemotherapy or surgery).

Outside the scope of this guideline are several related topics, including rarer histologies (eg, small cell carcinoma), noninvasive and nonmalignant diseases, and palliative treatment. It also does not address interventions of a purely investigational nature. Although these novel therapeutics (eg, triapine, combinations of radiation with immunotherapy, and treatment of oligometastatic disease) may become part of the standard of care, data concerning the relative efficacy is too early for a reasonable recommendation at this time. Lastly, it does not comment on questions of surgery or chemotherapy used outside of RT, except when considered as an alternative to radiation.

**Table 2.** KQs in Population, Intervention, Comparator, Outcome (PICO) format

KQ	Population	Intervention	Comparator	Outcomes
1	Following primary surgery for cervical cancer, when is it appropriate to deliver postoperative RT with and without systemic therapy?			
	Adult women with cervical cancer treated with initial hysterectomy	RT or RT in combination with chemotherapy	Observation or RT without chemotherapy	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Local control</li> <li>• Regional control</li> <li>• Distant metastases</li> </ul>

<b>2</b>	When is it appropriate to deliver definitive RT with and without systemic therapy and with or without hysterectomy after RT for cervical cancer?			
	Adult women with cervical cancer	RT alone or RT with concurrent chemotherapy	Hysterectomy, RT alone	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-free survival</li> <li>• Local control</li> <li>• Regional control</li> </ul>
<b>3</b>	For patients receiving definitive or postoperative RT for cervical cancer, when is it appropriate to deliver IMRT?			
	Adult women with cervical cancer receiving definitive or postoperative RT	Pelvic IMRT with or without para-aortic RT with or without chemotherapy	2-D/3-D whole pelvic radiation with or without para-aortic RT with or without chemotherapy	<ul style="list-style-type: none"> <li>• Toxicity</li> <li>• Patient-reported side effects</li> <li>• Quality of life</li> </ul>
<b>4</b>	For patients receiving definitive or postoperative RT for cervical cancer, when is brachytherapy indicated?			
	Adult women with cervical cancer receiving definitive or postoperative RT	Brachytherapy boost (after whole pelvic RT)	IMRT, 3-D, or SBRT boost to the cervix (after whole pelvic RT)	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Local control</li> <li>• Toxicity</li> </ul>
<b>5</b>	For patients receiving definitive RT for cervical cancer, what is the optimal dose/fractionation schedule, imaging, and technique for the delivery of brachytherapy?			
	Adult women with cervical cancer	Brachytherapy (LDR, PDR, HDR), CT and MRI based planning, differing treatment schedules, total dose, dose-to-target and dose-to-OARs, interstitial and hybrid techniques	Brachytherapy (LDR, PDR, HDR), film-based planning, differing treatment schedules, intracavitary technique	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Toxicity</li> <li>• Local control</li> </ul>

*Abbreviations:* 2-D = 2-dimensional; 3-D = 3-dimensional; CT = computed tomography; HDR = high-dose-rate; IMRT = intensity modulated radiation therapy; LDR = low-dose-rate; MRI = magnetic resonance imaging; N/A = not applicable; OARs = organs at risk; PDR = pulsed dose-rate; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

### 3. Key Questions and Recommendations

#### 3.1. Key Question 1: Postoperative RT With and Without Systemic Therapy (Table 3)

See evidence tables in [supplementary materials](#) for the data supporting the recommendations for KQ1.

**Following primary surgery for cervical cancer, when is it appropriate to deliver postoperative RT with or without systemic therapy?**

**Table 3.** Recommendations for postoperative RT with or without systemic therapy

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For women undergoing surgery for cervical cancer who have high surgicopathologic risk factors, adjuvant EBRT and concurrent platinum-based chemotherapy is recommended.	Strong	High 4-7



<p><u>Implementation remark:</u> High-risk factors include positive margin(s) or positive lymph node(s) or extension into the parametrial tissue.</p>		
<p>2. For women with cervical cancer and intermediate-risk factors, adjuvant EBRT is recommended to decrease locoregional recurrence.</p> <p><u>Implementation remark:</u> Intermediate-risk factors include*:</p> <ul style="list-style-type: none"> <li>• LVSI plus deep one-third cervical stromal invasion with any tumor size</li> <li>• LVSI plus middle one-third stromal invasion and tumor size <math>\geq 2</math> cm</li> <li>• LVSI plus superficial one-third stromal invasion and tumor size <math>\geq 5</math> cm</li> <li>• No LVSI but deep or middle one-third stromal invasion plus tumor size <math>\geq 4</math> cm</li> </ul>	Strong	High 8-10

*Abbreviations:* EBRT = external beam radiation therapy; LVSI = lymphovascular space involvement; RT = radiation therapy.

\*The original Gynecologic Oncology Group (GOG) 92 protocol estimated tumor size based on palpation; however, estimation based on pathologic or magnetic resonance imaging findings are an acceptable substitute.

Radical hysterectomy with lymphadenectomy provides definitive therapy and excellent prognosis for most patients with early cervical cancer. Whether adjuvant RT with or without the addition of concurrent chemotherapy is recommended depends on the final surgicopathologic findings.

### High-risk surgicopathologic findings

There is strong evidence that adjuvant concurrent cisplatin-based chemoradiation improves overall survival and progression-free survival for patients with cervical cancer who have high-risk pathologic features after surgery (eg, positive margins or positive lymph nodes or extension into the parametrial tissue).<sup>4</sup> This corresponds to an absolute benefit in overall survival of 12% and in progression-free survival of 16%.<sup>7</sup> There is an increase in acute grade 4 toxicities with the addition of chemotherapy (17% chemoradiation versus 4% RT), largely hematologic in nature.<sup>7</sup> The benefit of chemoradiation compared with RT alone is similar to the benefit observed for locally advanced patients with cervical cancer who undergo definitive chemoradiation compared with RT alone.<sup>11</sup>

The benefit of concurrent chemotherapy must be assessed individually as increased acute grade 3 and 4 toxicities may result in radiation treatment prolongation.<sup>12</sup> Although the Gynecology Oncology Group (GOG) 109<sup>4</sup> included additional chemotherapy after concurrent chemoradiation, the role of additional cycles of adjuvant chemotherapy is unclear in this population given insufficient randomized trial evidence. An ongoing phase III randomized study (RTOG 0724) is testing if there is an improvement in survival in patients receiving systemic chemotherapy (carboplatin AUC5 and paclitaxel 135 mg/m<sup>2</sup> every 21 days x 4 cycles) after concurrent postoperative chemoradiation (NCT00980954). Therefore, while the use of concurrent chemotherapy is recommended for patients undergoing adjuvant RT for high surgicopathologic risk factors, additional adjuvant chemotherapy following chemoradiation is not indicated at this time.

For cases meeting these *high-risk* criteria, whole pelvic RT can be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40 mg/m<sup>2</sup>).

### Intermediate-risk surgicopathologic findings

Intermediate-risk criteria, frequently referred to as Sedlis criteria, are defined by a combination of lymphovascular space involvement (LVSI), depth of stromal invasion, and tumor size.<sup>8</sup> The specific intermediate-risk factors are summarized in Table 4.

**Table 4.** Intermediate-risk factors for cervical cancer

Lymphovascular space involvement	Stromal invasion	Tumor size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2 cm
Positive	Superficial 1/3	≥5 cm
Negative	Deep or middle 1/3	≥4 cm

Adapted from Sedlis et al.<sup>8</sup>

These criteria were developed based on prospective GOG data (GOG 49) from 575 patients with squamous cell carcinoma of the cervix treated with radical hysterectomy and pelvic lymphadenectomy, where these factors increased the probability of cancer recurrence at 3 years from 2% to 31%.<sup>8,13</sup> The GOG subsequently conducted an RCT (GOG 92) of 277 patients with cervical cancer (including both squamous cell and adenocarcinomas) treated by radical hysterectomy and intermediate-risk Sedlis criteria who were randomized to no further treatment versus adjuvant pelvic RT.<sup>13</sup> Adjuvant radiation was associated with a 47% reduction in recurrence (a 12.6% absolute reduction) with acceptable morbidity and a 6% versus 2% grade 3 or 4 adverse event rate.<sup>8</sup> On long-term follow-up, patients treated with postoperative RT had a continued decrease in risk of recurrence, with no significant impact on survival. However, this study was not powered for a survival endpoint. The benefits of adjuvant RT in the reduction of recurrence were most pronounced in patients with adenocarcinoma and adenosquamous carcinoma.<sup>10</sup> A 2012 meta-analysis, which included data from GOG 92, further supports the benefit of adjuvant RT for those with intermediate-risk factors, with a significantly lower risk of disease progression at 5 years.<sup>9</sup>

There is no strong evidence to support the use of concurrent chemotherapy in patients with intermediate-risk factors. Limited retrospective data suggests that patients with multiple intermediate-risk factors might derive benefit from concurrent chemotherapy.<sup>14</sup> To investigate this further, the GOG/NRG is conducting an RCT (GOG 263) of adjuvant pelvic RT alone versus adjuvant concurrent chemoradiation in patients with intermediate-risk, early-stage cervical cancer following radical hysterectomy and staging lymphadenectomy (NCT 01101451). Until this trial concludes, no definitive recommendation can be made regarding the role of concurrent chemotherapy in this setting. Novel agents such as immunotherapy have not been tested in the postoperative setting.

For cases meeting these *intermediate-risk* criteria, whole pelvic RT can be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy per fraction or 4000 to 4400 cGy in 200 cGy per fraction.<sup>8</sup>

### Occult cervical cancer after total hysterectomy

For women who are found to have an occult invasive cervical cancer after total hysterectomy (either for benign disease or uterine cancer), further treatment is needed for stages greater than or equal to IA2, because a radical hysterectomy with lymph node dissection is required for curative surgery in these cases.<sup>15</sup> Options would be additional surgery (a parametrectomy, upper vaginectomy, and lymph node dissection) or RT. In practice, if additional surgery is expected to be technically difficult and/or potentially morbid, RT or chemoradiation may be offered as an alternative, particularly if RT is already indicated from surgicopathologic findings. Computed tomography (CT) or fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging may help to determine if there is significant residual disease, particularly in nodal basins.

Although prospective evidence is lacking, pelvic RT to 4500 to 5040 cGy, followed by a boost to the sites at high risk of additional occult disease (either with vaginal brachytherapy or external beam radiation therapy [EBRT] depending on location) is a reasonable approach. Concurrent chemotherapy may also be considered depending on factors described earlier in this section.

## 3.2. Key Question 2: Definitive RT With and Without Systemic Therapy; Hysterectomy After RT (Table 5)

See evidence tables in [supplementary materials](#) for the data supporting the recommendations for KQ2 and [Figure 2](#) for a visual representation of the cervical cancer recommendations.

**When is it appropriate to deliver definitive RT with and without systemic therapy? When is it appropriate to perform a hysterectomy after RT for cervical cancer?**

**Table 5.** Recommendations for definitive RT with and without systemic therapy and hysterectomy after RT

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For women with FIGO stage IB3-IVA* squamous cell or adenocarcinoma of the cervix, RT with concurrent platinum-based chemotherapy is recommended for definitive treatment.  <u>Implementation remark:</u> Recommended dose for cisplatin is 40 mg/m <sup>2</sup> weekly for 5 to 6 cycles.	Strong	High 11,16-23
2. For women with FIGO stage IB3-IVA cervical cancer, a planned adjuvant hysterectomy after RT or chemoradiation is not recommended.†	Strong	High 18,24-26
3. In women with FIGO stage IA1-IB2 that are deemed medically inoperable, RT with or without chemotherapy is conditionally recommended.	Conditional	Expert Opinion

*Abbreviations:* International Federation of Gynecology and Obstetrics (FIGO); RT = radiation therapy.

\*Stage IIA1 cancers may be managed with radical hysterectomy in well-selected (eg, non-bulky, with limited vaginal involvement) cases.

†In the setting of biopsy-proven gross residual disease after point-A–based dose specification for brachytherapy, surgery may be an option.

### Integration of chemotherapy with radiation

In 1999, the National Cancer Institute issued a clinical announcement recommending that providers add concurrent chemotherapy to RT after multiple RCTs demonstrated an approximately 10% survival benefit at 5 years for radiation with concurrent platinum-based chemotherapy compared with RT alone for women with stage IB3-IVA cervical cancer.<sup>11</sup> Because of the significant benefit in survival and lack of significant increase in late toxicities, concurrent platinum-based chemotherapy has been adopted as the standard of care for this patient population.

Generally, cisplatin is given weekly (40 mg/m<sup>2</sup>) with pelvic RT for women with locally advanced cervical cancer. Several studies have compared weekly versus tri-weekly cisplatin, however, patient numbers in these trials are small, and definitive high-quality evidence is currently being pursued in the Tri-weekly Cisplatin Based Chemoradiation in Locally Advanced Cervical Cancer (TACO) trial.<sup>27-29</sup> Pending new evidence, the panel recommends weekly cisplatin (40 mg/m<sup>2</sup>) or every 3 weekly cisplatin and fluorouracil (5FU), though the cisplatin-5FU cycles 2 and 3 usually extends beyond the concurrent phase.<sup>11,16-23</sup> For women who cannot receive cisplatin-based chemotherapy for various reasons (eg, renal insufficiency), other radiation sensitizing agents have been evaluated. Both single agent carboplatin and combined weekly paclitaxel and carboplatin have been used.<sup>30,31</sup> Several small prospective and retrospective studies evaluating carboplatin-based regimens have shown similar rates of pelvic control and survival outcomes compared to cisplatin-based regimens.<sup>32-34</sup> However, a meta-analysis showed a trend towards lower progression-free and overall survival at 3 years with carboplatin when compared to cisplatin.<sup>32</sup> Therefore, cisplatin-based regimens are preferred if tolerable for patients receiving treatment to the pelvis or to both the pelvis and para-aortic nodal chain. If treatment of the extended field is indicated, concurrent chemotherapy with cisplatin is administered with appropriate symptom management, consideration of intensity modulated radiation therapy (IMRT; refer to KQ3) to spare bowel; close monitoring of laboratory tests with special attention to assess neutropenia, anemia, and thrombocytopenia; and a potential need to stop chemotherapy before the completion of 5 cycles.<sup>35,36</sup>

Since the 1999 clinical announcement, several other systemic regimens have attempted to improve upon the outcomes seen with platinum-based chemotherapy. The only study to show superior outcomes to cisplatin and RT studied the combination of gemcitabine and cisplatin concurrent with RT followed by 2 additional cycles of gemcitabine and cisplatin, finding significant improvement in both progression free and overall survival at 3 years, particularly for patients with stage III-IVA disease.<sup>37</sup> However, the study design does not permit an analysis of whether the improved survival outcomes were related to the addition of the concurrent gemcitabine, the 2 cycles of adjuvant therapy after chemoradiation, or both. To clarify this question, a study randomized women with locally-advanced cervical cancer to either cisplatin with concurrent radiation or to cisplatin plus gemcitabine with concurrent radiation, but no additional chemotherapy was given after radiation.<sup>38</sup> This trial was stopped early due to an observed lack of benefit at 40% of its accrual goal (68 evaluable patients). The OUTBACK trial (NCT01414608) is currently studying adjuvant carboplatin and paclitaxel after conventional concurrent chemoradiation. Novel agents and immunotherapy are also being tested in ongoing clinical trials.

## Definitive radiation dose and chemotherapy regimen

For definitive RT, whole pelvic RT or extended field RT can be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40 mg/m<sup>2</sup>). Additional nodal boosts may be included (described in KQ3). This is followed by brachytherapy (described in KQ4 and KQ5), with a goal to limit the total treatment time to ≤7 to 8 weeks.

The use of a sidewall boost to address parametria or sidewall involvement has declined significantly in the past decade due to the increase use of image guided brachytherapy (IGBT) to cover these regions.<sup>39,40</sup> In addition, with concurrent chemotherapy, the disease may respond rapidly, resulting in adequate parametrial coverage with high-dose-rate brachytherapy applicators. Women with residual parametrial disease after external beam may also be adequately treated with brachytherapy, with use of MRI and supplemental interstitial needles. Specific recommendations from the task force on sidewall boosts, however, are not provided due to the lack of sufficient data.

## Hysterectomy or radiation

Women with earlier stage cervical cancer (FIGO 2018 Stages IA, IB1, IB2, and IIA1) are eligible for either a radical hysterectomy or definitive RT alone without chemotherapy. One randomized study in stages IB1-IIA2 showed no difference in overall survival or disease-free survival between the 2 approaches.<sup>41,42</sup> Postoperative RT was delivered to women in the surgical arm for high-risk pathologic findings, including parametrial invasion, close or positive margins, or positive lymph nodes. Despite the early-stage population, adjuvant radiation was required for 84% of women with tumors >4 cm and to a total of 64% of the surgical cohort. Those that received both surgery and RT experienced significantly increased toxicity, particularly urological complications, with rates of long-term grade 2-3 toxicity of 29% in the combined modality group.<sup>41</sup> Since this trial was conducted, however, improvements in surgical and radiation techniques may theoretically have lowered this risk. Certain patient factors may influence the decision as to whether surgery or primary radiation is most appropriate. In younger patients, preservation of ovarian function may be achieved with ovarian transposition if primary RT is the recommendation, though reported success rates are highly variable.<sup>43</sup> In surgical patients, the ovaries may be left in-situ, although a low risk of ovarian metastases should be considered particularly for patients diagnosed with adenocarcinoma histology. When evaluating the patient for primary surgical treatment, careful clinical examination should be performed. In addition, magnetic resonance imaging (MRI) may be used to screen for occult parametrial invasion and/or PET/CT may detect involved nodes, which indicates definitive chemoradiation rather than surgery. Multidisciplinary discussion of these cases is paramount to minimize the toxicity of combined radical hysterectomy with postoperative RT.

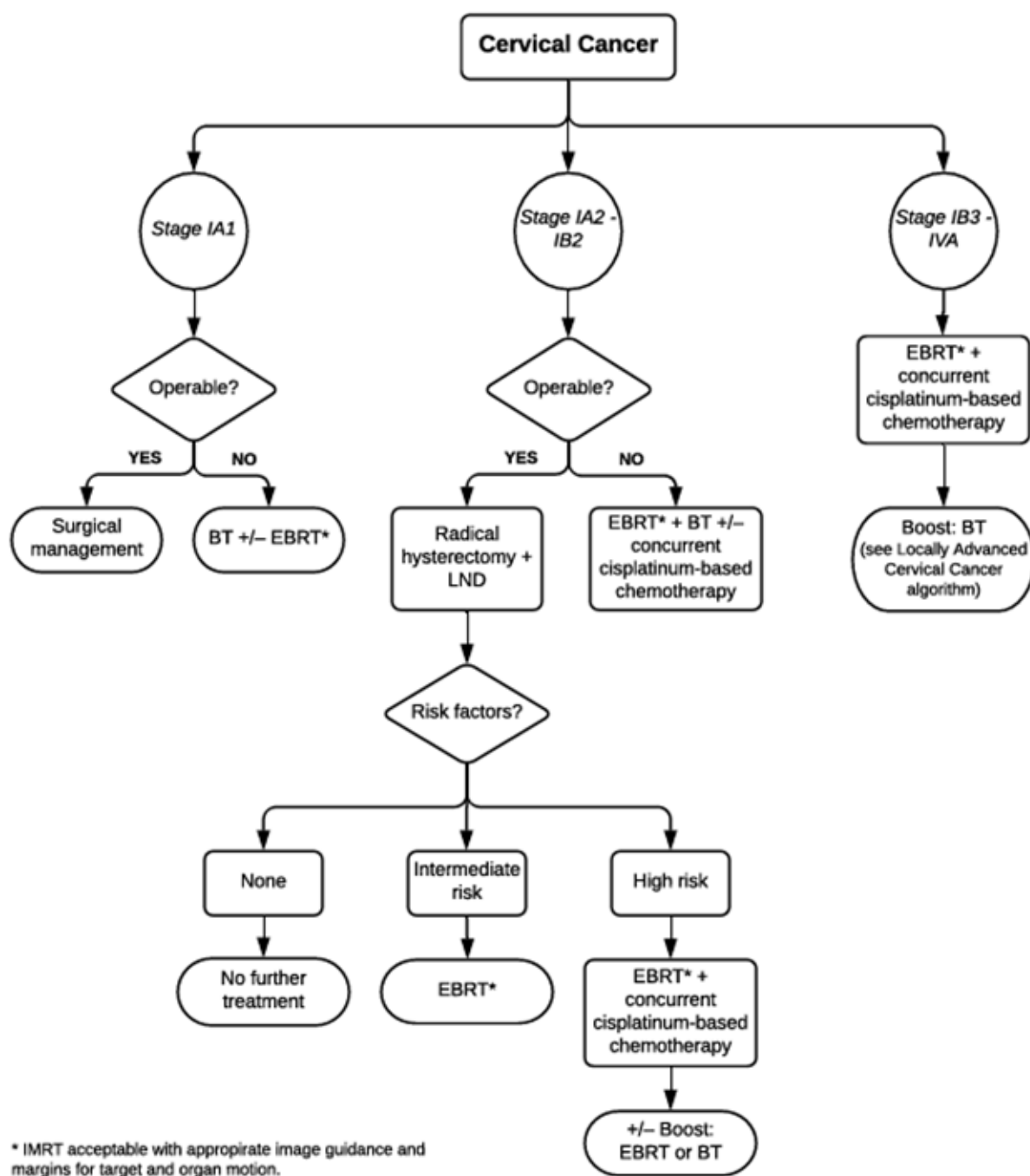
RT should also be considered for women with otherwise early-stage disease who are inoperable due to medical comorbidities, or who refuse a hysterectomy. Though often administered as an extrapolation from the randomized trials with more advanced stage patients, the use of concurrent chemotherapy is untested in stage IA node negative intact cervical cancer.<sup>11,16-23</sup> Many medically-inoperable patients may not be candidates for chemotherapy, and receive EBRT and brachytherapy alone.

Neoadjuvant chemotherapy followed by hysterectomy has been studied as an alternative to definitive chemoradiation in locally advanced (stage ≥IB3) cervical cancer. However, an RCT of this approach found superior disease-free survival with chemoradiation.<sup>44</sup> Therefore, neoadjuvant chemotherapy followed by hysterectomy is not recommended.

### Hysterectomy after radiation

In the era of combined chemoradiation and IGBT, pelvic control is very high even for women with bulky stage IB3-IIIB cervical cancer. Therefore, adjuvant hysterectomy after RT is not routinely recommended, particularly when IGBT is available. When lower dose brachytherapy is given and IGBT is not available, hysterectomy may be considered, especially in the presence of cervix-confined residual disease. GOG 71 randomized women with stage IB3 cervical cancers to radiation alone or radiation to a lower total dose followed by an extrafascial hysterectomy and showed no difference in overall survival.<sup>18</sup> A multi-institutional phase 3 trial, GYNECO 02, conducted by the Federation Nationale des Centres de Lutte Contre le Cancer randomized women with stage IB3-II cervical cancer (FIGO 2018) after completion of chemoradiation with complete clinical and radiological response to either hysterectomy or observation.<sup>45</sup> Accrual was slow and the study was closed early, but in 61 evaluable women, there was a nonsignificant improvement in event free survival and overall survival at 3 years without hysterectomy. Following this publication, a large cohort study of women treated with or without hysterectomy after chemoradiation and IGBT confirmed that an adjuvant hysterectomy did not improve survival outcomes and was associated with increased toxicity, particularly to the bladder.<sup>46</sup> Therefore, a hysterectomy after chemoradiation is not recommended in the setting of IGBT.

Despite high rates of local control, a small percentage of cancers do not respond well to chemoradiation and have evidence of residual disease after treatment. Time should be allowed for delayed response, with consideration of positron emission tomography imaging approximately 3 months after treatment completion.<sup>47</sup> However, if recurrence and/or persistence of disease is confirmed by biopsy as early as 8 to 12 weeks after therapy, there may be a role for salvage hysterectomy or exenteration, if feasible, to improve local control and survival, at the risk of significant morbidity.<sup>48</sup> Prognostic factors such as nodal spread at the time of diagnosis and extent of residual disease may be helpful in determining the benefit prior to proceeding with salvage surgery.<sup>49</sup>

**Figure 2.** Cervical cancer algorithm

**Abbreviations:** BT = brachytherapy; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; LND = lymph node dissection; RT = radiation therapy.

### 3.3. Key Question 3: Intensity Modulated Radiation Therapy (Table 6)

See evidence tables in [supplementary materials](#) for the data supporting the recommendations for KQ3.

**For patients receiving definitive or postoperative RT for cervical cancer, when is it appropriate to deliver IMRT?**

**Table 6.** Recommendations for IMRT

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. In women with cervical cancer treated with postoperative RT with or without chemotherapy, IMRT is recommended to decrease acute and chronic toxicity.	Strong	Moderate (acute) 50,51
		Low (chronic) 50,52
2. In women with cervical cancer treated with definitive RT with or without chemotherapy, IMRT is conditionally recommended to decrease acute and chronic toxicity.	Conditional	Moderate (acute) 53-58
		Moderate (chronic) 53,55,59-62

*Abbreviations:* IMRT = intensity modulated radiation therapy; RT = radiation therapy.

Historically, 2-dimensional (2-D) treatment planning on plain film x-rays was performed in the postoperative and definitive treatment of cervical cancer with anteroposterior/posteroanterior or 4-field techniques. In the era of CT treatment planning, 3-dimensional (3-D) conformal radiation therapy allows for delineation of target volumes and organs at risk (OARs) and a greater ability to protect normal tissues through more precise blocking while using standard beam configurations. IMRT uses the delineation of target volumes and OARs for inverse planning, with modulation of multiple treatment fields or arcs for optimal coverage of the target volume(s) with sparing of OARs. IMRT has been adopted in the treatment of many malignancies due to its ability to spare OARs, improve dose conformity, and deliver a higher dose. In the treatment of postoperative and definitive cervical cancer, dosimetric studies demonstrated decreased volumes of the bladder, rectum, bowel, and bone marrow receiving clinically significant doses of RT.<sup>50,53,55,57</sup>

Retrospective comparisons additionally found decreased acute and chronic toxicity with use of IMRT, compared to 2-D and 3-D RT.<sup>50,52</sup> Single and multi-institution series of postoperative RT have demonstrated a favorable toxicity profile with the use of IMRT.<sup>56,63</sup> RTOG 1203 (TIME-C) is the only published phase III RCT of 3-D RT versus IMRT in the postoperative treatment of patients with early-stage endometrial or cervical cancer.<sup>51</sup> This study demonstrated significantly improved acute patient-reported gastrointestinal (primary endpoint) and urinary outcomes, thus supporting the use of IMRT, when available, in these populations.<sup>51</sup>

Similarly, retrospective comparisons of 2-D and 3-D RT to IMRT found decreased acute and chronic toxicities with use of IMRT during the pelvic/para-aortic phase of definitive RT.<sup>53,54,60,62</sup> Single and multi-institution series of definitive RT with IMRT combined with chemotherapy revealed low rates of acute and chronic toxicity relative to historical controls with favorable disease-specific outcomes.<sup>56,64-68</sup> Three prospective randomized trials and one meta-analysis demonstrated decreased acute gastrointestinal and urinary toxicities with IMRT compared with 3-D RT.<sup>55,57,58,62</sup> One randomized trial<sup>55</sup> and the meta-analysis<sup>61</sup> also showed lower risk of late gastrointestinal and urinary toxicities. The inclusion of para-aortic nodal irradiation in these studies of



definitive RT varies; however, given the additional OARs (eg, duodenum, kidney, liver, and increased volumes of bone marrow and small bowel), IMRT for irradiation of the para-aortic nodal chain is likely to decrease risk of toxicities compared with 2-D and 3-D RT while allowing dose escalation to intact positive nodes, especially for patients receiving concurrent chemotherapy.<sup>35,36,69-74</sup> There are, however, no data that IMRT improves disease-specific survival or overall survival over 2-D/3-D techniques.

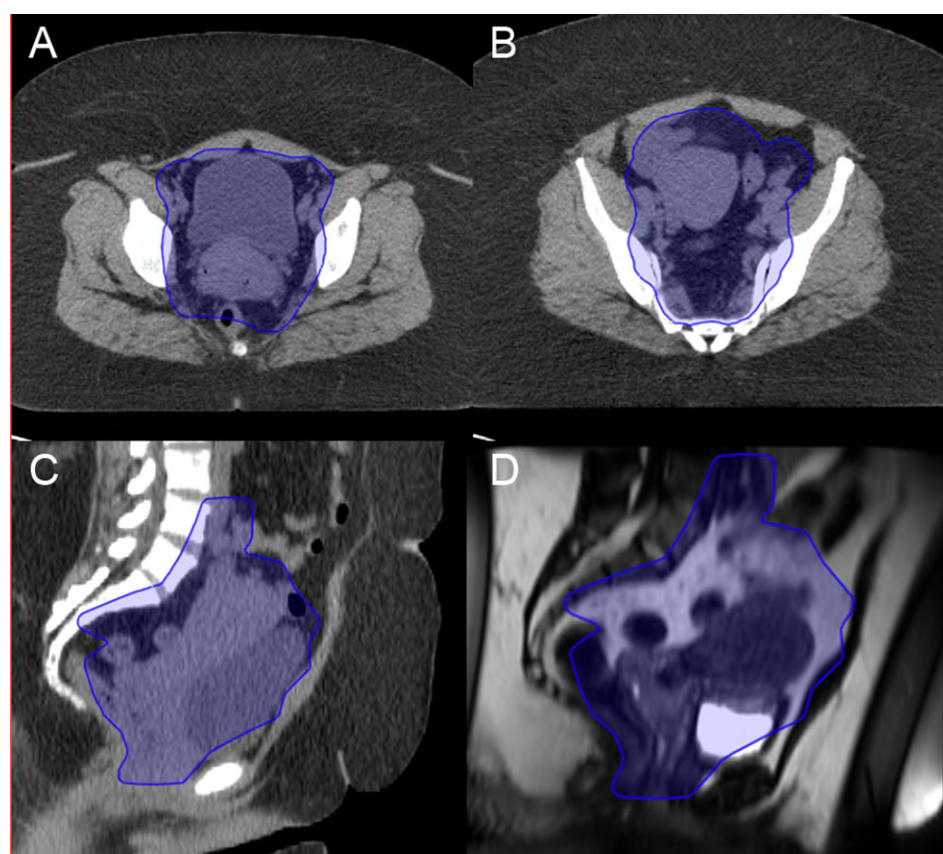
Despite the aforementioned indications for IMRT in the treatment of postoperative and definitive cervical cancer, 3-D RT is acceptable in scenarios in which there are uncertainties with the target volume, lack of provider experience, or lack of facility resources to provide IMRT. Image guided radiation therapy (IGRT) with availability of orthogonal kilovoltage images and routine volumetric imaging (eg, cone beam CT) at the time of treatment is essential to ensure accurate delivery of treatment on a daily basis. The phase II International Evaluation of Radiotherapy Technology Effectiveness in Cervical Cancer (INTERTECC) study of IMRT and IGRT demonstrated improved hematologic and clinically meaningful gastrointestinal toxicity with the use of IGRT in postoperative and definitive RT for cervical cancer in the group undergoing daily IGRT.<sup>56</sup> When kilovoltage imaging is performed, cone beam CT can be utilized during the course of treatment to ensure that the postoperative target (proximal vagina, residual parametria, +/- residual uterosacral ligaments and nodal regions) and definitive target (uterus, cervix, parametria, proximal vagina and nodal regions) are within the corresponding planning target volume given the variation in bladder and rectum filling.<sup>75</sup> The entire excursion of all targets should be incorporated into an internal target volume that is generated from all available imaging including bladder full and bladder empty CT-simulation scans and all available diagnostic imaging. Creation of an internal target volume is also imperative when using definitive RT for intact cervical cancer, given the often-dramatic daily variation in position of the uterus and cervix ([Figure 3](#)). The primary risk of IMRT for intact cervical cancer is the potential to miss the target if careful target delineation with appropriate margins and IGRT are not applied. Particular care is needed during treatment planning to avoid excessive rectal sparing, as the target of treatment is directly apposed to the anterior rectal surface; the ideal planning target volume will extend into the rectal contour significantly. Referral to the available contouring atlases for target delineation in postoperative and definitive scenarios is indicated.<sup>76-81</sup>

IMRT may also be used to boost selective sites of nodal involvement. The dose required is dependent on the size of the grossly involved node. Generally, between 5500 to 6500 cGy is delivered to involved nodes based on size, location, contribution from brachytherapy, and dose per fraction.<sup>82</sup> This may be performed with either sequential or an integrated boost technique as long as normal tissue constraints are met, especially for small bowel and duodenum. Particular care is needed given to spare normal tissues, including small bowel in proximity to any boost volume.<sup>83</sup> A sequential technique allows for replanning to a smaller nodal volume after 4500 cGy for the boost and homogeneity of dose across the node; a simultaneous integrated boost results in heterogeneity of dose across the node, and is therefore better suited for small nodes that will not change in shape or size dramatically over the course of treatment.

In this example case of stage IIB cervical cancer, a final PTV for 45Gy can be seen in the blue shaded contour. The PTV includes the primary CTV of the cervix and uterus, proximal vagina, paracervical tissue, parametrial tissue including uterosacral ligaments, and pelvic nodal basins with additional margins for daily setup variation and internal target motion. The PA nodes are not included in this case because of the absence of any concerning nodes in the pelvis or PA chain on PET imaging; thus, the superior border is set at the level of the aortic bifurcation (approximately L4-5) and inferiorly into the vagina, to 4 cm distal to extent of disease. At the level of the acetabulum (A), note the anterior extension of the PTV well into the bladder as a result of significant

variation in uterine position. Also note posterior extension of the PTV in the rectum to allow for coverage of the uterosacral ligaments and motion of the cervix and the presacral lymph nodes; coverage of the mesorectum may be required in some cases with rectal invasion or posterior uterosacral ligament involvement. At the level of S3 (B), note the extension of the PTV posteriorly to allow for coverage of the uterosacral ligaments. Mid-sagittal CT (C) and MRI (D) obtained on the same day show significant motion of the uterus with partial bladder emptying. The PTV encompasses this entire excursion of the uterine body (may be several centimeters), with additional margin for daily setup. The use of regular image guidance at the time of treatment is necessary to ensure all targets remain within the PTV, and replanning may be necessary if the PTV margin is found to be too small. This is provided as an example of a large PTV rather than a recommended volume for all cases; reference to the appropriate contouring atlases is indicated for each individual considered for IMRT.

**Figure 3.** Example of IMRT PTV definition for intact cervical cancer



A and B axial CT images; C sagittal CT images; and D sagittal MRI images, showing uterine motion; refer to the full-text guideline for a detailed description of PTV definitions. *Abbreviations:* CT = computed tomography; IMRT = intensity modulated radiation therapy; MRI = magnetic resonance imaging; PTV = planning target volume.

### 3.4. Key Question 4: Brachytherapy (Table 7)

See evidence tables in [supplementary materials](#) for the data supporting the recommendations for KQ4.

**For patients receiving definitive or postoperative RT for cervical cancer, when is brachytherapy indicated?**

**Table 7.** Recommendations for brachytherapy

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For women receiving definitive RT for intact cervical cancer, brachytherapy is recommended.	Strong	Moderate 84-88
2. For women with cervical cancer receiving postoperative whole pelvis radiation, a brachytherapy boost is conditionally recommended in the presence of positive margin(s).  <u>Implementation remark:</u> The brachytherapy technique selected is based on the location and volume of the positive margin(s).	Conditional	Low 89

Abbreviation: RT = radiation therapy.

Brachytherapy is an integral component of definitive treatment for patients with locally advanced cervical cancer. The steep dose gradient allows for the delivery of highly conformal doses of radiation to the central pelvis, minimizing toxicities and maximizing tumor control. Although there is no randomized data to compare patients treated with or without brachytherapy, nonrandomized reports from national databases have consistently found improved outcomes using brachytherapy.<sup>84,85</sup> In multiple large national retrospective data sets, the use of brachytherapy in women with cervical cancer declined between 2003 to 2011, whereas use of IMRT or SBRT instead increased during this period.<sup>84,85</sup> The use of brachytherapy has been consistently associated with improved survival compared with IMRT or SBRT as a boost. The omission of brachytherapy has a stronger negative effect on survival than the exclusion of chemotherapy.<sup>85</sup> Other smaller retrospective studies show similar results with improved survival in patients treated with brachytherapy compared with non-brachytherapy cohorts.<sup>86-88</sup> Therefore neither SBRT nor IMRT are a suitable substitute for brachytherapy and should only be considered for those ineligible because of complex medical factors. Referral to tertiary centers for brachytherapy is necessary if the originating facility has a limited capacity to support a patient with complex comorbidities. Previous 2-D prospective cohort studies found high control rates and acceptable toxicities, though these have improved further with 3-D IGBT techniques.<sup>11,16-19,22,23,90-102</sup> Prospective and retrospective cohort data of 3-D–based planning for brachytherapy indicates high rates of cervical control and decreased toxicity, so it is emerging as standard practice in many centers.<sup>93,95,97,99,100,103</sup>

Adjuvant radiation or chemoradiation following surgery for cervical cancer results in high local control and survival rates in the presence of certain clinical and pathological characteristics as noted in KQ2. There is a lack of data evaluating the routine role of brachytherapy in the adjuvant radiation setting after a hysterectomy, and no specific recommendations are made. Brachytherapy may be considered in the postoperative setting in the presence of a positive vaginal mucosal margin. This allows for a localized boost of radiation dose to the positive margin using simple intracavitary techniques. Small retrospective studies reveal that brachytherapy may lead to improved outcomes.<sup>104</sup> A large National Cancer Database analysis of women treated with brachytherapy in addition to EBRT for positive postsurgical margins found a survival advantage with the use of brachytherapy 79.4% versus 71.9%,  $P<0.001$ .<sup>89</sup> The study could not however determine the location of the positive margins (vaginal mucosa/ectocervix versus parametria/paracervical). Given these findings, brachytherapy in addition to

pelvic radiation or chemoradiation in the setting of a positive margin may be offered to deliver additional dose to the localized area at risk. Most commonly, a standard single channel intracavitary technique is effective for delivering a boost dose to the positive vaginal mucosal margin. For positive margins beyond the vaginal mucosa surface (ie, parametrial, paravaginal) or positive macroscopic margins, an advanced brachytherapy technique (eg, an intracavitary multichannel cylinder), or interstitial needles may be required to adequately deliver conformal doses to the areas at risk. For regions at risk not amenable to brachytherapy, a targeted external beam boost may be considered.

### 3.5. Key Question 5: Brachytherapy Technique (Table 8)

See evidence tables in [supplementary materials](#) for the data supporting the recommendations for KQ5, and see [Figure 4](#) for a visual representation of the recommendations for locally advanced cervical cancer.

**For patients receiving definitive RT for cervical cancer, what is the optimal dose/fractionation schedule, imaging, and technique for the delivery of brachytherapy?**

**Table 8.** Recommendations for brachytherapy technique

KQ5 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
<b>Optimal imaging and technique for the delivery of brachytherapy</b>		
1. For women receiving brachytherapy for cervical cancer, intra-procedure imaging is recommended if available.	Strong	Low 105
2. For women receiving brachytherapy for cervical cancer, MRI or CT-based planning to a volume-based prescription is recommended.	Strong	Moderate 65,93,99,100,106-109
3. For women receiving brachytherapy for cervical cancer, if volume-based planning cannot be performed, then 2-D/point-based planning is recommended.	Strong	Moderate 11,16-18,110
<b>Optimal dose/fractionation schedule for the delivery of brachytherapy</b>		
4. For women treated with definitive RT for cervical cancer, the total EQD <sub>2,10</sub> of EBRT and brachytherapy should be $\geq 8000$ cGy. (Table 9)	Strong	Moderate 93,111
5. For women with cervical cancer receiving volume-based brachytherapy, HR-CTV D90 greater than or equal to prescription dose ( $\geq 8000$ cGy) is conditionally recommended, with careful consideration of normal tissue constraints. (Table 10)  <u>Implementation remark:</u> <ul style="list-style-type: none"> <li>For patients with poor response or large-volume (<math>&gt;4</math> cm) disease, D90 <math>\geq 8500</math> cGy is reasonable.</li> <li>Utilization of a hybrid intracavitary/interstitial technique can help improve the dose distribution when not achieving</li> </ul>	Conditional	Moderate 94,112-114

appropriate target and/or OAR dose constraints with an intracavitary alone approach.		
<b>Optimal OAR constraints of brachytherapy</b>		
6. In women treated with brachytherapy for intact cervical cancer, volumetric contouring of the OARs and use of appropriate dose constraints are recommended.	Strong	Moderate 46,100,109,114-116
7. If volumetric planning is not available for women treated with brachytherapy for intact cervical cancer, 2-D/point-based dose constraints should be applied.	Strong	Moderate 11,16-18

*Abbreviations:* 2-D = 2-dimensional; CT = computed tomography; EBRT = external beam radiation therapy; EQD<sub>2</sub><sub>10</sub> = dose calculation to an equivalent dose of 2 Gy with an  $\alpha$ -to- $\beta$  ratio of 10; HR-CTV = high-risk clinical target volume; MRI = magnetic resonance imaging; OARs = organs at risk; RT = radiation therapy.

**Table 9.** Common brachytherapy regimens given in combination with 4500 cGy EBRT

Dose per fraction (cGy)	# of fractions	Total dose (EBRT+BT) EQD <sub>2</sub> <sub>10</sub> * (cGy)
500	6	8180
550	5	7980 <sup>†</sup>
600	5	8430
700	4	8390
800	3	8030

*Abbreviations:* BT = brachytherapy; EBRT = external beam radiation therapy; EQD<sub>2</sub><sub>10</sub> = dose calculation to an equivalent dose of 2 Gy with an  $\alpha$ -to- $\beta$  ratio of 10; HR-CTV = high-risk clinical target volume.

\*Note that the prescription for brachytherapy is made to the 100% isodose line, which may not fully overlap with the HR-CTV. As such the cumulative HR-CTV D90 dose (EQD<sub>2</sub><sub>10</sub>) will differ from the prescription dose due to fraction to fraction variation, and should be tracked over the treatment course to ensure that the goals of therapy are met. This may be calculated and summed by the following worksheet available on the ABS website [https://www.americanbrachytherapy.org/ABS/document-server/?cfp=ABS/assets/file/public/consensus-statements/LQ\\_spreadsheet.xls](https://www.americanbrachytherapy.org/ABS/document-server/?cfp=ABS/assets/file/public/consensus-statements/LQ_spreadsheet.xls).

<sup>†</sup>Although this regimen is technically below the recommended 8000 cGy for prescription, the panel agreed that this regimen is acceptable.

**Table 10.** Dose constraints

Organ at risk	Ideal dose Constraint (cGy) (EQD <sub>2</sub> )	Maximum* dose constraint (cGy) (EQD <sub>2</sub> )	ICRU point (cGy) (EQD <sub>2</sub> )	References
Rectum	<6500 D2cc	<7500 D2cc	<7500 point dose	95,102,115,117,118
Bladder	<8000 D2cc	<9000 D2cc	<9000 point dose	115,117-120
Vagina (recto-vaginal point) <sup>†</sup>	<6500 point dose	<7500 point dose	---	96,116
Sigmoid <sup>†</sup>	<7000 D2cc	<7500 D2cc	---	120
Bowel <sup>†</sup>	<7000 D2cc	<7500 D2cc <sup>†</sup>	---	120,121

*Abbreviations:* ICRU = International Commission of Radiation Units and Measurements; EQD<sub>2</sub> = dose calculation to an equivalent dose of 2 Gy with an  $\alpha$ -to- $\beta$  ratio of 3. D2cc is the minimal dose to the 2 cm<sup>3</sup> (2 mL) of the organ at risk receiving the maximal dose.

\*There will be occasions when exceeding these maximum constraints is necessary to adequately treat the targets of therapy, according to the clinical judgment of the treating physician.

<sup>†</sup>The recto-vaginal point is defined 5 mm posterior to the vaginal mucosa from the center of the vaginal sources.



‡Dose constraints for sigmoid and bowel are based largely on expert opinion, because there is minimal evidence of a dose response.

A 2014 survey of American Brachytherapy Society members reported about 50% of respondents utilize volume-based dose delineation compared with 15% in 2007.<sup>122</sup> Definitions for volume-based targets were established by the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) in 2005.<sup>123</sup> These include the gross tumor volume, HR-CTV (high-risk clinical target volume), and intermediate-risk clinical target volume (Table 11). Validation of these target concepts comes from multiple retrospective and prospective series. One of the largest of these studies, retroEMBRACE, found that women treated with IGBT had improved local control, reduced toxicity, and an altered pattern of relapse relative to 2-D brachytherapy series with the predominant pattern of failure now being systemic rather than local.<sup>93,99,101,103,109,124</sup> Aside from improved local control rates, there is also prospective data from the Soutien aux Techniques Innovantes et Couteuses (STIC) trial indicating significantly reduced grade 3 to 4 toxicities in 3-D versus 2-D planned patients treated with chemoradiation for locally advanced disease (2.6% versus 22.7%,  $P < .002$ ).<sup>100</sup> Taken together these studies support improved outcomes and reduced toxicities when using an image-based brachytherapy approach.

**Table 11.** Target volume definitions for image guided brachytherapy<sup>118</sup>

Volume	Components	Dose Goals
GTV	Gross tumor at the time of brachytherapy, determined by imaging or examination	At a minimum, dose should be $\geq 8000$ cGy
HR-CTV	GTV, the entire cervix, and regions of indeterminate T2-weighted MRI signal (ie, gray zones)	D90 $\geq 8000$ cGy, with consideration of escalation for advanced disease or poor response to initial therapy
IR-CTV	HR-CTV with an asymmetrical expansion,* not extending into OARs, and including sites of initial disease involvement	Optional: D90 $\geq 6000$ cGy, with consideration of escalation for advanced disease

**Abbreviations:** GTV = gross tumor volume; HR-CTV = high-risk target volume; IR-CTV = intermediate-risk target volume; MRI = magnetic resonance imaging; OARs = organs at risk.

\*The IR-CTV expansion is 0.5-1.0 cm globally with an additional 0.5 cm superiorly into the uterus, inferiorly into the vagina, and laterally in bilateral para-cervical tissues.

Transitioning from 2-D to 3-D planning requires a standardized approach. A pelvic MRI prior to brachytherapy either as a diagnostic scan or on an MR simulator to assess the extent of residual disease may aid in planning the brachytherapy approach. The applicator insertion process requires consideration of the extent of residual disease at the time of brachytherapy and the patient's anatomy. Standard tandem and ovoid/ring/mold applicators may not always adequately cover the residual extent of disease after EBRT or allow for optimal sparing of the surrounding OARs. Newer "hybrid" applicators allow for the insertion of interstitial needles through predrilled holes in modifications of the standard tandem and ovoid or tandem and ring applicators. If one does not have access to one of these newer applicators, a perineal template-based or freehand technique for needle placement may also be utilized. The addition of needles can help optimize dose distributions by allowing higher doses to targets, while still meeting normal OAR constraints.<sup>125</sup>

Intraoperative imaging to evaluate the applicator placement should be performed. Real-time guidance with either transabdominal or transrectal ultrasound is easy to obtain and can reduce the risk of uterine

perforation.<sup>105</sup> Alternatively, other imaging modalities (eg, CT, MRI, or plain films) may be utilized during the procedure, with the caveat that plain films cannot always visualize a perforation.

Regarding the imaging modality used for simulation and treatment planning, either MR or CT imaging are standard. An advantage of MRI is that it provides superior soft tissue definition, making it easier to visualize the cervix and residual disease compared with CT imaging. A disadvantage is that scan time is longer than CT and may not be as easily accessible given the small number of MR simulators in radiation oncology. Comparisons of MRI versus CT-based planning reveal similar OAR dose volume histograms, but CT may overestimate the tumor width compared with MRI, particularly in advanced disease.<sup>107,126</sup> This is especially true in women with parametrial disease extension at diagnosis that subsequently regresses during EBRT.<sup>127</sup> If possible, an MRI at or around the time of brachytherapy is very helpful, even if it is just fused with the CT used for dosimetric planning, as it can help inform CT-based contours.

The combined prescription EQD2<sub>10</sub> of EBRT and brachytherapy should be  $\geq 8000$  to 8500 cGy, with doses  $\geq 8500$  cGy for tumors with poor response to EBRT or adenocarcinoma histology or for stage III disease at presentation. Suggested brachytherapy doses in combination with EBRT are listed in Table 9. In the United States, the most common high-dose-rate intracavitary fractionation utilizes a total of 5 fractions while in Europe it is 4 fractions.<sup>128</sup> A multi-institutional retrospective analysis found a correlation between D90  $\geq 8500$  cGy to the HR-CTV and local control outcomes.<sup>112</sup> Another analysis showed a significant correlation between the D90 and the probability of achieving local control, with a D90 of 8140 cGy associated with a 90% probability of achieving local control.<sup>114</sup> Therefore, the D90 to the HR-CTV correlates best with local control outcomes. Further research is indicated for more detailed guidance on HR-CTV dosing given the lack of prospective clinical trials assessing various brachytherapy dose levels.

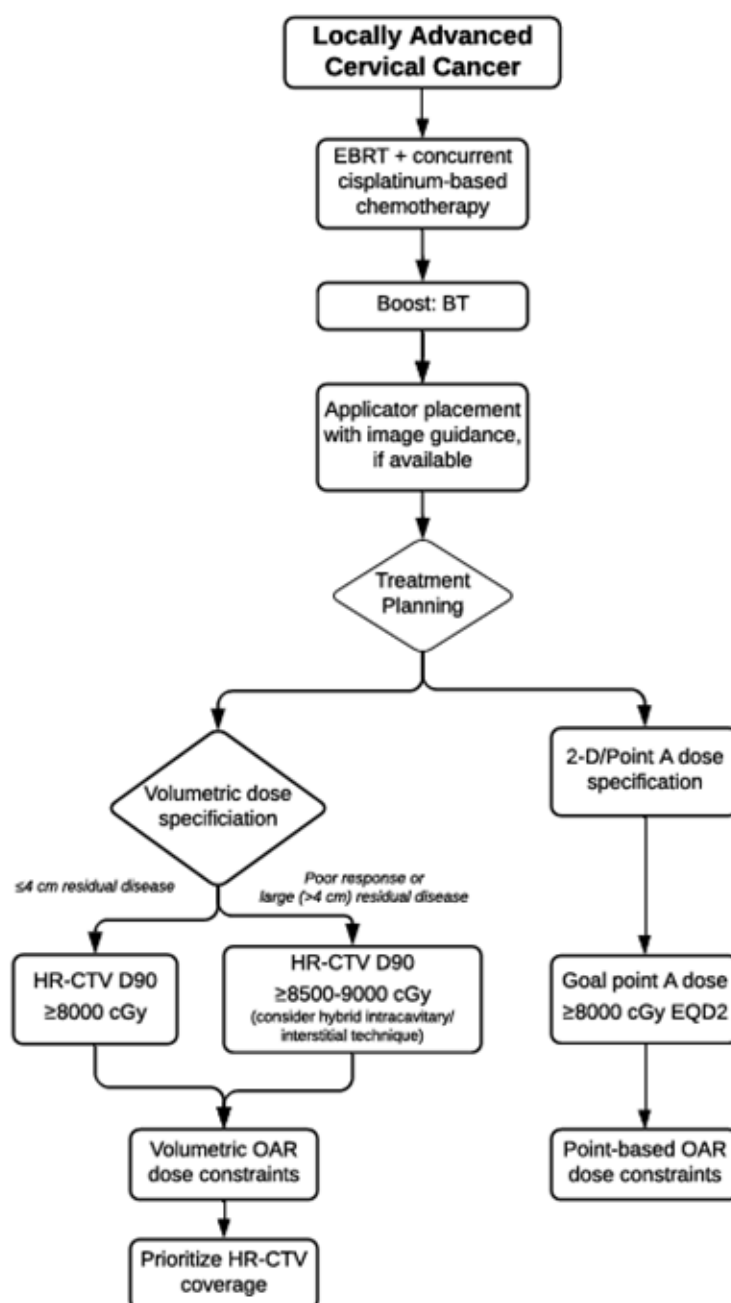
In situations where 3-D planning is not possible, it is recommended that standard 2-D imaging with dose specification to point A be performed. The prescription should conform to the suggested summed prescription EQD2<sub>10</sub>. Prior trials where high-quality point-A–based brachytherapy was consistently performed showed a local control rate  $>80\%$ , and point A-based planning remains an option when volume-based planning is not available.<sup>11</sup> Nevertheless, all efforts to obtain 3-D imaging should be pursued (CT and/or MRI), due to the expected improvements in pelvic control and reduction in toxicity.

For cervical cancer brachytherapy, the most important OARs are the bladder, rectum, sigmoid/bowel, and vagina. The dose volume-effect relationships for predicting late rectal morbidity indicate a threshold rectal D2cc be kept to  $\leq 6500$  cGy.<sup>95</sup> In regards to high-grade toxicity, the fistula risk was 12.5% at 3 years for patients who received a D2cc dose  $\geq 7500$  cGy compared with 0 to 2.7% for patients receiving lower doses. Single institution data suggest limiting the bladder D2cc to  $\leq 8000$  cGy.<sup>119</sup> The EMBRACE study also shows that vaginal stenosis is correlated with the combined EBRT and brachytherapy dose to the rectovaginal point (20% at 6500 cGy, 27% at 7500 cGy, and 34% at 8500 cGy) and propose that this point be kept to  $\leq 6500$  cGy.<sup>96,116</sup> Finally, ongoing work is needed to define optimal constraints to the sigmoid/bowel; the current recommendation is based primarily on expert opinion. Although OAR sparing is expected to improve quality of life for many women, control of the cervical tumor continues to be of primary importance. In situations in which OAR constraints cannot be met despite best efforts, tumor coverage may be prioritized after careful discussion with the patient.

The dose goals for brachytherapy can be achieved with either low-dose-rate, pulsed-dose-rate, or high-dose-rate technique. For high-dose-rate and low-dose-rate, dose conversions occur using the EQD2 formula for dose conversion. Low-dose-rate, however, has a more limited ability to adapt to achieve the goals of therapy,

due to the need for larger physical sources, lack computerized dose optimization and limited inventory in many clinical situations. In general, high-dose-rate and pulsed-dose-rate are more flexible means of delivering dose due to optimization, but the task force makes no specific recommendation for any dose rate, other than the dosimetric goals defined in Table 10.

**Figure 4.** Locally advanced cervical cancer algorithm



**Abbreviations:** 2-D = 2-dimensional; BT = brachytherapy; EBRT = external beam radiation therapy; EQD2 = equivalent dose at 2 Gy per fraction; HR-CTV = high-risk clinical target volume; OAR = organ at risk.



## 4. Conclusions/Emerging Science

Radiation is an integral part of the management of locally advanced disease, either as an adjuvant treatment after surgery in the presence of risk factors or as a primary curative treatment, used in combination with chemotherapy and a brachytherapy boost to the primary site. IMRT and IGBT are effective at reducing normal tissue toxicity and allow for dose escalation to residual disease in the central pelvis (in the case of brachytherapy), or positive nodes (in the case of IMRT). All these factors have resulted in safer and more effective treatment for women with this disease.

Despite advances in the past 2 decades on the use of concurrent chemotherapy and IGBT, many patients still recur distantly, suggesting that further development and integration of systemic or novel therapy is warranted. Results of several ongoing trials may affect these recommendations: the OUTBACK trial (NCT01414608) is examining additional cycles of systemic therapy after completion of chemoradiation and NRG-006 is examining a novel agent, triapine, which has shown promising phase II results. Postoperatively, the GOG 263 trial is examining the potential utility of concurrent cisplatin in those with intermediate-risk factors (“Sedlis Criteria”) and RTOG 0724 is doing the same for additional cycles of systemic therapy after concurrent chemoradiation for high-risk disease. Induction chemotherapy followed by concurrent chemoradiation is being studied in the phase III Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer (INTERLACE) trial (NCT01566240). Immunotherapy, particularly PD-1 and PD-L1 inhibitors, has shown activity in the metastatic setting, and is being evaluated in women with node positive disease, such as the ongoing NRG GY017 study examining the use of atezolizumab concurrently or as a primer with chemoradiation.

In regard to IMRT for intact cervix, results from several ongoing studies are awaited. EMBRACE 2 is a prospective, multi-institution study evaluating use of IMRT and IGRT with an integrated boost to involved lymph nodes and risk-based inclusion of the extended field, with MRI-based brachytherapy for locally advanced cervical cancer. This study is also looking to increase the HR-CTV D90 to  $\geq 9000$  cGy. Though single arm, the results will help to determine how feasible, safe, and effective this approach may be, compared with historical results, in addition to determine appropriate OAR dose limitation when using integrated boosts. Similarly, the aforementioned NRG GY006 trial allows IMRT and is looking at the value of knowledge-based planning and impact of bone marrow sparing for advanced cervical cancer. Long-term follow-up of the TIME-C and PARCER studies will quantify the potential benefit of IMRT in reducing late effects in the postoperative setting. Incorporation of molecular and radiographic or functional imaging biomarkers may provide additional data on use of IMRT for dose adaptation to the cervical primary disease and involved lymph nodes, given an evolving understanding of the molecular heterogeneity of cervical cancer.

There is an opportunity to better risk stratify women with cervical cancer. Tumor gene expression,<sup>129</sup> HPV subtype,<sup>130</sup> and circulating tumor markers<sup>131</sup> may identify women who would benefit from more intensive therapy. Imaging (eg, FDG PET and diffusion weighted MRI)<sup>132</sup> before, during, and after treatment may aid in predicting the eventual response to treatment, in turn allowing early interventions to improve outcomes. Conversely, these factors may also identify women who would benefit from treatment deintensification and a reduced risk of normal tissue toxicity.

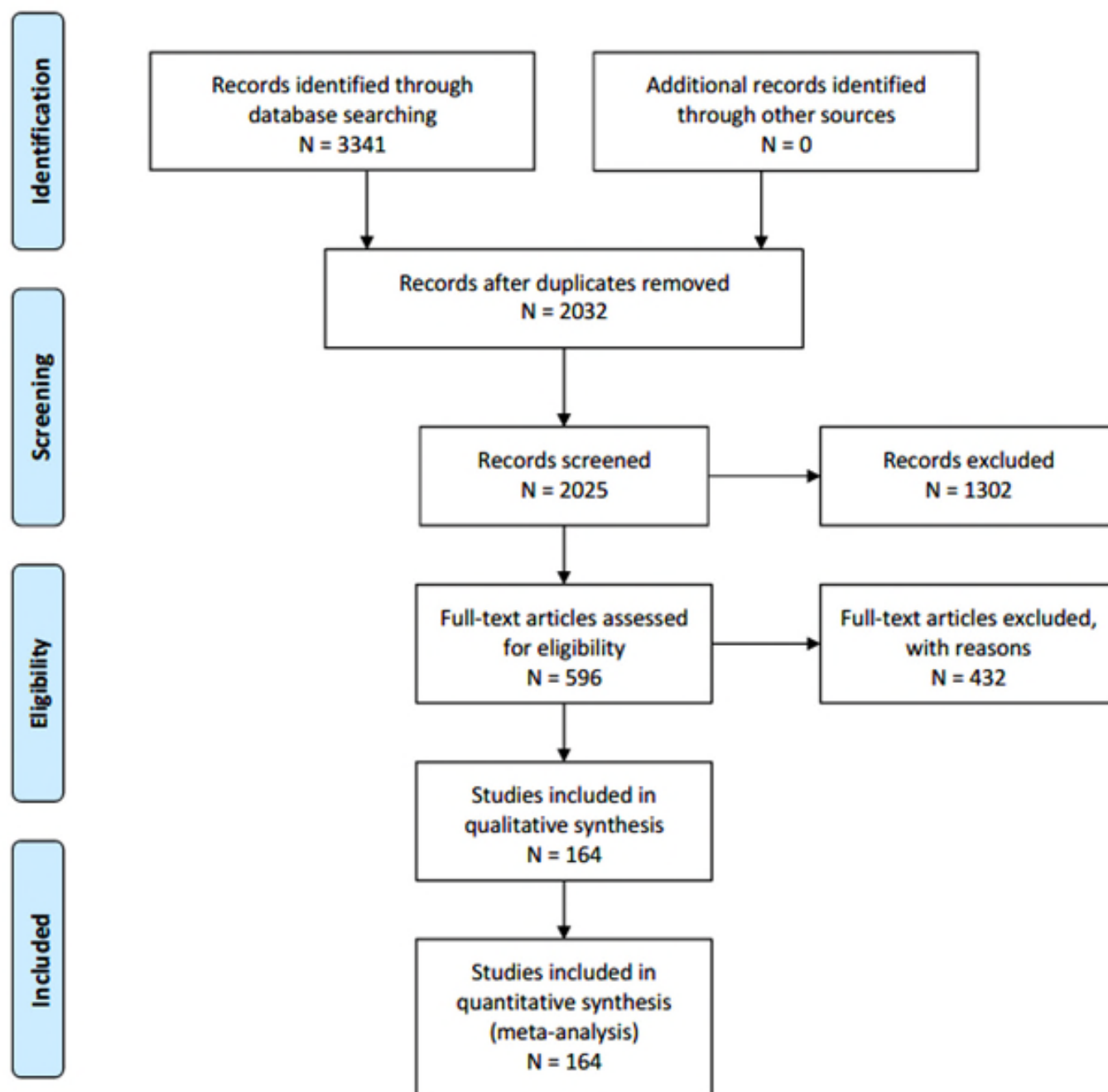
The cost-effectiveness and relative value of these interventions is worthy of further study. Although excluded from the scope of these guidelines, the financial burden of cancer treatment on both the individual and the healthcare system is high.

There also may be a role for aggressive local therapy in the setting of limited metastatic disease. Retrospective series show that RT to the primary site is associated with improved overall survival, even in women with metastatic disease,<sup>133</sup> though this must be confirmed in a prospective manner. In other solid tumors, surgical resection or ablative RT to sites of limited metastatic disease have also been associated with improved outcomes in selected cases; there is an opportunity to explore these techniques in cervical cancer.<sup>134</sup> ASTRO will continue to evaluate the need to update this guideline in the future as potentially practice-changing data, treatment approaches, or technologies emerge.

## 5. Acknowledgements

We are grateful to Yimin Geng, MSLIS, MS, the University of Texas MD Anderson research medical librarian, for her assistance with creating the search strategy for this guideline. The task force also thanks Elisha Fredman, MD, Sarah Hazell, MD, Blair Murphy, MD, Steven Seyedin, MD, Sarah Stephens, MD, and Michael Stolten, MD, for literature review assistance.

The task force thanks the peer reviewers for their comments and time spent reviewing the guideline. See [Appendix 1](#) for their names and disclosures.

**Figure 1.** PRISMA diagram, based on Moher D, et al.<sup>135</sup>

Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## Appendix 1. Peer Reviewers and Disclosures (Comprehensive)

Name	Employment	Disclosure Company/ Organization	Disclosure Category
Kevin Albuquerque, MD (Content Reviewer)	UT Southwestern – Professor, Radiation Oncology	<ul style="list-style-type: none"> <li>• Association of Radiologic Technologists</li> <li>• American Board of Radiology</li> <li>• ACR</li> </ul>	<ul style="list-style-type: none"> <li>• Travel expense</li> <li>• Honoraria and travel</li> </ul>
Kristin Bradley, MD (ABS Reviewer)	University of Wisconsin School of Medicine & Public Health – Professor, Department of Human Oncology	<ul style="list-style-type: none"> <li>• ABS</li> <li>• NCCN</li> <li>• UpToDate</li> </ul>	<ul style="list-style-type: none"> <li>• Board member</li> <li>• Gynecologic section member</li> <li>• Other – Authorship royalty</li> </ul>
William Burke, MD (SGO Reviewer)	Stony Brook University Medical Center – Associate Professor	<ul style="list-style-type: none"> <li>• Titan Medical</li> </ul>	<ul style="list-style-type: none"> <li>• Consultant</li> </ul>
Patricia Eifel, MD (Content Reviewer)	MD Anderson Cancer Center – Professor of Radiation Oncology	None	N/A
Gini Fleming, MD (ASCO Reviewer)	The University of Chicago – Professor of Medicine and Medical Oncology Director	<ul style="list-style-type: none"> <li>• 47inc</li> <li>• Abbvie</li> <li>• Astex</li> <li>• Compugen</li> <li>• Corcept</li> <li>• Hoffman LaRoche</li> <li>• Incyte</li> <li>• Leap Therapeutics</li> <li>• Lovance</li> <li>• Merck</li> <li>• Roche/Genentech</li> <li>• Sanofi</li> <li>• Sermonix</li> <li>• Syndax</li> <li>• Tesaro (now GlaxoSmithKline)</li> </ul>	<ul style="list-style-type: none"> <li>• Research – Local PI</li> <li>• Advisory board meeting</li> </ul>
David Gaffney, MD, PhD (Content Reviewer)	University of Utah – Professor, Department of Radiation Oncology; Huntsman Cancer Institute – Senior Director for Clinical Research	<ul style="list-style-type: none"> <li>• NCI Gynecology Steering Committee</li> <li>• NCI U10 LAPS grant</li> </ul>	<ul style="list-style-type: none"> <li>• Consultant</li> <li>• Research – PI</li> </ul>
Lara Hathout, MD (Guideline Subcommittee Lead Reviewer)	Rutgers Cancer Institute of New Jersey – Assistant Professor of Radiation Oncology	None	N/A
John Hays, MD (ASCO Reviewer)	The Ohio State University James Cancer Hospital – Associate Professor	<ul style="list-style-type: none"> <li>• NCI</li> </ul>	<ul style="list-style-type: none"> <li>• Committee member</li> </ul>

Peter Hoskin (ESTRO Reviewer)	Mount Vernon Hospital – Professor	<ul style="list-style-type: none"> <li>• ESTRO</li> <li>• NICE</li> <li>• Radiotherapy &amp; Oncology</li> <li>• Varian</li> </ul>	<ul style="list-style-type: none"> <li>• Board member &amp; travel expense</li> <li>• Board member</li> <li>• Editor</li> <li>• Research</li> </ul>
Krishna Howell, MD, PhD (Content Reviewer)	Fox Chase Cancer Center – Assistant Professor	<ul style="list-style-type: none"> <li>• Medtronic</li> <li>• Covidien/Medtronic</li> </ul>	<ul style="list-style-type: none"> <li>• Equity Award (Spouse-Employee)</li> <li>• Stock (Spouse)</li> </ul>
Elizabeth Kidd, MD (Content Reviewer)	Stanford University – Associate Professor	None	N/A
Remi Nout, MD, PhD (ESTRO Reviewer)	Erasmus Medical Center Rotterdam – Radiation Oncologist, Professor and Chairman Department of Radiation Oncology	None	N/A
Melanie Powell, MD (Content Reviewer)	Barts Health NHS Trust – Consultant Clinical Oncologist	None	N/A
William Small, Jr., MD (Content Reviewer)	Stritch School of Medicine Loyola University Chicago, Radiation Oncology – Professor and Chairman; Cardinal Bernardin Cancer Center – Director	<ul style="list-style-type: none"> <li>• Zeiss</li> </ul>	<ul style="list-style-type: none"> <li>• Honoraria and research funding</li> </ul>
Sarah Temkin, MD (SGO Reviewer)	Anne Arundel Medical Center – Director, Gynecologic Oncology	<ul style="list-style-type: none"> <li>• Cancer Expert Now</li> </ul>	<ul style="list-style-type: none"> <li>• Consultant</li> </ul>
Stephen Thompson, MBBS, PhD (RANZCR Reviewer)	Prince of Wales Hospital – Senior Staff Specialist, Department of Radiation Oncology; University of New South Wales – Conjoint Senior Lecturer	<ul style="list-style-type: none"> <li>• ANZSA Scientific Advisory Committee</li> <li>• GOROC RANZCR</li> <li>• Cancer Institute New South Wales</li> </ul>	<ul style="list-style-type: none"> <li>• Committee member</li> </ul>
Sujay Vora, MD (Content Reviewer)	Mayo Clinic Arizona – Assistant Professor	None	N/A
Catheryn Yashar, MD (ABS Reviewer)	University of California San Diego – Chief of Staff and Professor and Assistant Vice-Chair, Clinical Affairs of Radiation Medicine and Applied Sciences	<ul style="list-style-type: none"> <li>• ABS</li> <li>• ACR Oncology</li> <li>• NCCN</li> </ul>	<ul style="list-style-type: none"> <li>• Board Chairman &amp; member</li> <li>• Gynecology section co-chair</li> </ul>
Bassem Zaki, MD (Guideline Subcommittee Lead Reviewer)	Dartmouth-Hitchcock Norris Cotton Cancer Center – Associate Professor and Interim Chief, Section of Radiation Oncology	None	N/A
Kristine Zanotti, MD (Content Reviewer)	University Cleveland Medical Center – Associate Professor of Gynecologic Oncology	None	N/A

**Abbreviations:** ABS = American Brachytherapy Society; ACR = American College of Radiology; ANZSA = Australia and New Zealand Sarcoma Association; ASCO = American Society for Clinical Oncology; ESTRO = European Society for Radiotherapy & Oncology; N/A = not applicable; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute; PI = principle investigator; RANZCR = Royal Australian and New Zealand College of Radiologists; SGO = Society of Gynecologic Oncology.

This table represents the reviewers reported disclosures at the time this document was under review (August 2019); not necessarily their disclosures at the time of publication.

## Appendix 2. Abbreviations

2-D = 2-dimensional

3-D = 3-dimensional

3D-CRT = 3-dimensional conformal radiation therapy

cGy = centigray

CT = computed tomography

EBRT = external beam radiation therapy

EQD2<sub>10</sub> = dose calculation to an equivalent dose of 2 Gy with an  $\alpha$ -to- $\beta$  ratio of 10.

GOG = Gynecology Oncology Group

HR-CTV = high-risk clinical target volume

IGBT = image guided brachytherapy

IGRT = image guided radiation therapy

IMRT = intensity modulated radiation therapy

KQ = key question

LVSI = lymphovascular space involvement

MRI = magnetic resonance imaging

OAR(s) = organ(s) at risk

PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework

RCT = randomized controlled trial

RT = radiation therapy

SBRT = stereotactic body radiation therapy

## Appendix 3. Literature Search Strategy

### Literature search method:

A systematic search of the literature using database Ovid MEDLINE was performed for publications in English language, from January 1993 through October 2018 and in human subjects. The following concepts common to all KQs were searched using subject headings (MeSH terms) and keywords as needed, “uterine cervical cancer”, “radiotherapy”, “radiation therapy”, “radiation dosage”, “brachytherapy”, “intensity-modulated radiation therapy”, “survival”, “survival analysis”, “metastasis”, “adverse events”, “toxicity” and “treatment outcome”. Additional concepts and terms specific to the KQs include “postoperative”, “hysterectomy”, “definitive radiotherapy”, and “post-radiotherapy”. The search terms were combined by “or” if they represented similar concepts, and by “and” if they represented different concepts. The literature search excluded the majority of case reports and hand searches supplemented the electronic database searches. MEDLINE search strategy is detailed below.

Search Strategy: Database(s): Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations 1946 to October 25, 2018 (Search performed 10.29.18 – articles older than January 1993 were removed)

#	Searches
1	Uterine Cervical Neoplasms/
2	((cervix or cervical) adj3 (Neoplasm* or cancer or carcinoma*)).ti,ab,kf.
3	1 or 2
4	(cervix or cervical).ti,kf.
5	*Uterine Cervical Neoplasms/ and (cervix or cervical).ab. /freq=2
6	4 or 5
7	3 and 6
8	limit 7 to (english language and yr="1993 -Current")
9	(animals not (humans and animals)).sh.
10	8 not 9
11	((child or children or adolescent or pediatric* or paediatric*) not childhood).ti.
12	10 not 11
13	(esophageal or oesophageal or esophagus or oesophagus or prostate or "head and neck").ti.
14	12 not 13
15	case reports.pt. not (exp clinical study/ or comparative study/ or evaluation studies/ or meta-analysis/ or multicenter study/ or validation studies/ or letter.pt.)
16	case report*.ti,jn.
17	15 or 16
18	14 not 17 [remove case reports]
19	exp Radiotherapy/
20	(radiotherap* or irradiat* or radiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or RT or "intensity modulated" or IMRT or EBRT or brachytherapy).ti,kf.

21	(radiotherap* or irradiat* or radiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or RT or "intensity modulated" or IMRT or EBRT or brachytherapy).ab. /freq=2
22	exp Radiotherapy Planning, Computer-Assisted/
23	exp Radiation Oncology/
24	or/19-23
25	18 and 24 [radiotherapy for uterine cervical cancer]
26	POSTOPERATIVE PERIOD/
27	(postoperative or postop or "post op" or "post operative" or postsurg* or posthysterectom*).ti,ab,kf.
28	((follow* or after or post*) adj5 (surger* or surgical or excision* or operation or resect* or Hysterectom* or Trachelectom* or "cone biopsy" or Conization)).ti,kf.
29	((follow* or after or post*) adj (surger* or surgical or excision* or operation or resect* or Hysterectom* or Trachelectom* or "cone biopsy" or Conization)).ab. /freq=2
30	or/26-29
31	25 and 30 [cervical cancer postoperative RT]
32	exp Hysterectomy/
33	(Hysterectom* or Trachelectom* or "pelvic lymphadenectomy").ti,ab,kf.
34	("cone biopsy" or Conization).ti,ab,kf.
35	(surger* or surgical or excision* or operation or resect* or dissection).ti,kf.
36	(surger* or surgical or excision* or operation or resect* or dissection).ab. /freq=2
37	or/32-36 [cervical cancer with surgery and radiotherapy treatment]
38	25 and 37 [cervical cancer with surgery with radiotherapy treatment]
39	exp TREATMENT OUTCOME/
40	SURVIVAL/
41	exp SURVIVAL ANALYSIS/
42	Survival Rate/
43	Kaplan-Meier.ab.
44	survival.ti,kf.
45	survival.ab. /freq=2
46	exp Neoplasm Recurrence, Local/
47	Recurrence*.ti,ab,kf.
48	exp Neoplasm Metastasis/
49	(Metastasis or Metastases).ti,kf.
50	exp RADIOTHERAPY/ae, co [Adverse Effects, Complications]
51	RADIATION/ae, co [Adverse Effects, Complications]
52	exp Radiation Dosage/ae [Adverse Effects]
53	((radiotherap* or radio-therap* or (radiation adj3 therap*) or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or irradiat*) and (adverse* or toxic* or "side effect*" or safety or injur* or abnormal* or induced)).ti,kf.



54	((radiotherap* or radio-therap* or (radiation adj3 therap*) or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or irradiat*) adj5 (adverse* or toxic* or "side effect*" or safety or injur* or induced)).ab.
55	CTCAE.ti,ab,kw.
56	("common terminology criteria" adj3 "adverse events").ti,ab,kw.
57	or/39-56 [treatment outcome: primary and secondary]
58	38 and 57 [cervical cancer with surgery and radiotherapy treatment with outcomes]
59	(RT or radiotherap* or irradiat* or radiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or brachytherapy or IMRT or EBRT).ti,kf.
60	58 and 59 [cervical cancer with surgery and radiotherapy treatment with outcomes: further restricted by radiotherapy]
61	31 or 60 [KQ1 Postoperative RT]
62	32 or 33 or 34 or 35 or 36 [surgical treatment]
63	18 and 62 [surgical treatment for cervical cancer]
64	occult.ti,ab,kf.
65	61 and 64 [KQ1 Postoperative RT for occult carcinoma]
66	((definitive or primary or alternative or alternate or curative* or remission) adj15 (radiotherap* or radiat* or irradiat* or RT or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or brachytherapy or IMRT or EBRT or therap* or treatment)).ti,ab,kf.
67	((single or only or monotherapy or alone) adj3 (radiotherap* or radiat* or irradiat* or RT or IMRT or brachytherapy or EBRT or chemoradi* or radiochemo* or chemo-radi* or radio-chemo*)).ti,ab,kf.
68	66 or 67
69	25 and 68 [definitive radiotherapy for cervical cancer]
70	((unsuitable or "not") adj3 (operable or resectable or surgery or surgical)).ti,ab,kf.
71	(inoperable or unresectable or non-surgical or nonsurgical or "locally advanced").ti,ab,kf.
72	70 or 71
73	69 and 72 [KQ1 part1: definitive radiotherapy for unresectable or locally advanced cervical cancer]
74	((definitive or primary or alternative or alternate or curative* or remission) adj6 (radiotherap* or radiat* or irradiat* or RT or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or brachytherapy or IMRT or therap* or treatment)).ti,kf.
75	25 and 74
76	73 or 75 [KQ2 part1: definitive radiotherapy for all cervical cancer]
77	((follow* or after or post*) adj5 (radiotherapy or RT radiotherap* or irradiat* or radiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or brachytherapy or IMRT or EBRT)).ti,kf.
78	((follow* or after or post*) adj (radiotherapy or RT radiotherap* or irradiat* or radiat* or chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or brachytherapy or IMRT or EBRT)).ab.
79	(postradiat* or postradiotherap* or postirradiat* or postchemoradiat*).ti,ab,kf.
80	77 or 78 or 79
81	63 and 80 [KQ2 part 2: hysterectomy after RT]
82	(IMRT or "intensity modulated").ti,ab,kf.

83	exp Radiotherapy, Intensity-Modulated/
84	(tomotherap* adj3 helical).ti,ab,kf.
85	82 or 83 or 84
86	25 and 85 [KQ3: intensity modulated radiation therapy]
87	exp BRACHYTHERAPY/
88	brachytherapy.ti,kf.
89	brachytherapy.ab. /freq=2
90	((implant or internal or intracavitary) adj (radiation or radiotherapy)).ti,kf.
91	87 or 88 or 89 or 90
92	25 and 91
93	57 and 92 [KQ4 Brachytherapy , restricted by treatment outcome]
94	brachytherapy.ti,kf. or exp *BRACHYTHERAPY/
95	93 and 94 [KQ4 Brachytherapy and treatment outcome; further restricted]

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