



Clinical Commentary

The ASTRO clinical practice guidelines in cervical cancer: Optimizing radiation therapy for improved outcomes

Junzo Chino^{a,*}, Christina M. Annunziata^b, Sushil Beriwal^c, Lisa Bradfield^d, Beth A. Erickson^e, Emma C. Fields^f, Jane Fitch^g, Matthew M. Harkenrider^{h,r}, Christine H. Holschneiderⁱ, Mitchell Kamrava^j, Eric Leung^k, Lilie L. Lin^l, Jyoti S. Mayadev^m, Marc Morcosⁿ, Chika Nwachukwu^o, Daniel Petereit^p, Akila N. Viswanathan^q

^a Duke University Cancer Center, Department of Radiation Oncology and Guideline Task Force Vice Chair, Durham, NC, United States of America

^b National Cancer Institute, Women's Malignancies Branch, Bethesda, MD, United States of America

^c UPMC, Hillman Cancer Center, Department of Radiation Oncology, Pittsburgh, PA, United States of America

^d American Society for Radiation Oncology, Arlington, VA, United States of America

^e Medical College of Wisconsin, Department of Radiation Oncology, Radiation Oncology Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226, United States of America

^f Virginia Commonwealth University VCU, School of Medicine, Department of Radiation Oncology, 401 College St., Richmond, VA 23298, United States of America

^g Patient Representative, United States of America

^h Loyola University Chicago, Chicago, IL, United States of America

ⁱ Olive View/UCLA Medical Center, Department of Obstetrics and Gynecology, 14445 Olive View Dr, Sylmar, CA 91342, United States of America

^j Cedars-Sinai Medical Center, Department of Radiation Oncology, Los Angeles, CA, United States of America

^k Sunnybrook Health Sciences Centre, Odette Cancer Centre, University of Toronto, Department of Radiation Oncology, Toronto, Ontario, United States of America

^l MD Anderson Cancer Center, Department of Radiation Oncology and Guideline Subcommittee Representative, Houston, TX, United States of America

^m University of California, Department of Radiation Medicine and Applied Sciences, San Diego, CA, United States of America

ⁿ Johns Hopkins Medicine, Department of Radiation Oncology and Molecular Radiation Sciences, Baltimore, MD, United States of America

^o UT Southwestern Medical Center, Department of Radiation Oncology, Dallas, TX, United States of America

^p Rapid City Regional Health, Department of Radiation Oncology, Rapid City, SD, United States of America

^q Johns Hopkins University, Department of Radiation Oncology and Molecular Radiation Sciences and Guideline Task Force Chair, Baltimore, MD, United States of America

^r Edward Hines Jr. VA Hospital, Department of Radiation Oncology, Hines, IL, United States of America

Cervical cancer continues to be a significant source of morbidity and mortality. While great strides have been made in preventative measures, over 13,000 new cases this year are expected in US, and 600,000 worldwide [1,2]. Radiation therapy (RT) has been a key part of multi-modality treatment for women with locally advanced disease who are not best served with a primary surgical approach, as well as for those with risk factors for local recurrence after surgery.

Much has changed in radiation therapy in the past two decades, both in the realm of external beam treatments (EBRT) to the pelvis, and in the practice of brachytherapy (BT). The American Society for Radiation Oncology (ASTRO) has released the first Clinical Practice Guideline in Radiation Therapy for Cervical Cancer in order to aid modern clinical decision making for the optimal care of women with this disease [3]. The guideline was centered around five key questions (KQ). These were addressed by a multidisciplinary task force, utilizing a robust literature search and review process to provide answers, as well as a measure of the quality of evidence. This led to the following peer and publicly reviewed recommendations (Table 1).

We strongly recommend that readers refer to the published executive summary [3] as well as the full document online [4] for a much more detailed description of these recommendations, and an in-depth discussion of the rationale, level of evidence and appropriate implementation of these recommendations.

The recommendations for KQ 1 and KQ 2 are based on several pivotal randomized trials released in the last two decades. The recommendation for postoperative RT for intermediate risk criteria is based on the GOG 92 study due to the significant decrease in disease recurrence in women meeting such criteria [5]. The recommendation for cisplatin based concurrent chemotherapy, for locally advanced disease, and for high risk factors after hysterectomy, are based on the improvements in overall survival in multiple randomized trials published at the turn of the century [6–8]. The recommendations for KQ 2 also emphasize that for women with FIGO stage IB3 disease (i.e. cervical lesions >4 cm), concurrent chemo-radiation, followed by brachytherapy is the optimal treatment in many cases.

It is also worthy to note that, with the development of the new FIGO staging system in 2018, women with involved nodal disease detected by imaging, are now included in stage IIIC, with the implication that these women are best treated by concurrent chemo-radiation therapy (as stated in the recommendations for KQ 2). The use of nodal dissection to debulk nodes prior to treatment however is not specifically commented on in the guideline, due to the lack of high-quality published data.

Intensity modulated radiation therapy (IMRT), as a means of more rationally designing and delivering external beam radiation therapy is recommended as a part of KQ 3 due to a randomized trial in the post-operative setting, and multiple prospective and retrospective experiences in the intact setting, finding decreased toxicity rates, without compromising disease control [9–11]. IMRT, however, can only be

* Corresponding author.

E-mail address: junzo.chino@duke.edu (J. Chino).

Table 1
ASTRO clinical practice guidelines in cervical cancer.

Recommendations	Strength of Recommendation	Quality of Evidence
<p>KQ1. Following primary surgery for cervical cancer, when is it appropriate to deliver postoperative RT with or without systemic therapy?</p> <p>For women undergoing surgery for cervical cancer who have high surgicopathologic risk factors, adjuvant EBRT and concurrent platinum-based chemotherapy is recommended.</p> <p>Implementation remark: High-risk factors include positive margin(s) or positive lymph node(s) or extension into the parametrial tissue.</p> <p>For women with cervical cancer and intermediate-risk factors, adjuvant EBRT is recommended to decrease locoregional recurrence.</p> <p>Implementation remark: Intermediate-risk factors include#:</p> <ul style="list-style-type: none"> • LVSI plus deep one-third cervical stromal invasion with any tumor size • LVSI plus middle one-third stromal invasion and tumor size ≥ 2 cm • LVSI plus superficial one-third stromal invasion and tumor size ≥ 5 cm • No LVSI but deep or middle one-third stromal invasion plus tumor size ≥ 4 cm 	Strong	High
<p>KQ2. 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?</p> <p>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.</p> <p>Implementation remark: Recommended dose for cisplatin is 40 mg/m² weekly for 5 to 6 cycles.</p> <p>For women with FIGO stage IB3-IVA cervical cancer, a planned adjuvant hysterectomy after RT or chemoradiation is not recommended.†</p> <p>In women with FIGO stage IA1-IB2 that are deemed medically inoperable, RT with or without chemotherapy is conditionally recommended.</p>	Strong	High
<p>KQ3. For patients receiving definitive or postoperative RT for cervical cancer, when is it appropriate to deliver IMRT?</p> <p>In women with cervical cancer treated with postoperative RT with or without chemotherapy, IMRT is recommended to decrease acute and chronic toxicity.</p> <p>In women with cervical cancer treated with definitive RT with or without chemotherapy, IMRT is conditionally recommended to decrease acute and chronic toxicity.</p>	Strong	Moderate (acute) Low (chronic)
<p>KQ4. For patients receiving definitive or postoperative RT for cervical cancer, when is brachytherapy indicated?</p> <p>For women receiving definitive RT for intact cervical cancer, brachytherapy is recommended.</p> <p>For women with cervical cancer receiving postoperative whole pelvis radiation, a brachytherapy boost is conditionally recommended in the presence of positive margin(s).</p> <p>Implementation remark: The brachytherapy technique selected is based on the location and volume of the positive margin(s).</p>	Strong Conditional	Moderate Low
<p>KQ5. For patients receiving definitive RT for cervical cancer, what is the optimal dose/fractionation schedule, imaging, and technique for the delivery of brachytherapy?</p> <p>Optimal imaging and technique for the delivery of brachytherapy</p> <p>For women receiving brachytherapy for cervical cancer, intra-procedure imaging is recommended if available.</p> <p>For women receiving brachytherapy for cervical cancer, MRI or CT-based planning to a volume-based prescription is recommended.</p> <p>For women receiving brachytherapy for cervical cancer, if volume-based planning cannot be performed, then 2-D/point-based planning is recommended.</p> <p>Optimal dose/fractionation schedule for the delivery of brachytherapy</p> <p>For women treated with definitive RT for cervical cancer, the total EQD2₁₀ of EBRT and brachytherapy should be ≥ 8000 cGy. (Table 9)</p> <p>For women with cervical cancer receiving volume-based brachytherapy, HR-CTV D90 greater than or equal to prescription dose (≥ 8000 cGy) is conditionally recommended, with careful consideration of normal tissue constraints. (Table 10)</p> <p>Implementation remark:</p> <ul style="list-style-type: none"> • For patients with poor response or large-volume (>4 cm) disease, D90 ≥ 8500 cGy is reasonable. • Utilization of a hybrid intracavitary/interstitial technique can help improve the dose distribution when not achieving appropriate target and/or OAR dose constraints with an intracavitary alone approach. <p>Optimal OAR constraints of brachytherapy</p> <p>In women treated with brachytherapy for intact cervical cancer, volumetric contouring of the OARs and use of appropriate dose constraints are recommended.</p> <p>If volumetric planning is not available for women treated with brachytherapy for intact cervical cancer, 2-D/point-based dose constraints should be applied.</p>	Strong Strong Strong Strong Strong Conditional	Low Moderate Moderate Moderate

Abbreviations: 2-D = 2-dimensional; CT = computed tomography; EBRT = external beam radiation therapy; EQD2₁₀ = dose calculation to an equivalent dose of 2 Gy with an α -to- β ratio of 10; International Federation of Gynecology and Obstetrics (FIGO); HR-CTV = high-risk clinical target volume; LVSI = lymphovascular space involvement; MRI = magnetic resonance imaging; OARs = organs at risk; RT = radiation therapy; IMRT = intensity modulated 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.

*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.

Taken from: Chino, J., Annunziata, C.M., Beriwal, S. et al.; Radiation Therapy for Cervical Cancer: Executive Summary of an ASTRO Clinical Practice Guideline; Practical Radiation Oncology, Vol. 10, Issue 4, p220–234, July 12, 2020; DOI: <https://doi.org/10.1016/j.prro.2020.04.002>

recommended if there is sufficient ability to ensure that the contoured targets of treatment are consistently in the irradiated volume, necessitating intra-treatment imaging to ensure that patient setup variation, organ motion, or tumor response do not result in a therapeutic miss.

Fortunately, this technology is commonly available in many centers within the US and developed regions, however, 3D conformal treatment continues to be an effective treatment where such online imaging techniques are not available.

Brachytherapy as a means of boosting the central disease continues to be a critical component of the curative management of locally advanced cervical cancer, as indicated by the response to KQ 4. However in the last decade, the use of brachytherapy had declined, a trend associated with a dramatic decrease in overall survival. Thus, despite the recommendation for IMRT in the pelvic phase of radiation treatment in KQ3, IMRT and stereotactic body radiotherapy (SBRT) are *not* recommended for boosting the cervix and central disease, both due to concerns of toxicity [12] and inferior survival [13,14].

Brachytherapy techniques have also evolved, with implementation of volumetric target definition and treatment planning, aided by procedural CT and/or MRI, the transition to high dose rate (HDR, Ir192) from low dose rate (LDR, Cs137), and the availability of hybrid intracavitary/interstitial applicators. These techniques have resulted in methods to improve coverage of residual disease at the time of implantation, in turn associated with improved pelvic control. Simultaneously, the ability to define and appropriately limit dose to the adjacent organs at risk is associated with a concordant decrease in chronic toxicity compared with point-based brachytherapy paradigms. Nonetheless, in settings where volumetric brachytherapy planning is not feasible, point-based brachytherapy remains effective for many cases.

There are several limitations to the guidelines, not the least of which is the relative paucity of randomized data to guide the task force in regards to KQ3, KQ4 and KQ5. We must be mindful that not all technical advancements result in improved outcomes; one does not have to look far to find the cautionary tale of minimally invasive radical hysterectomy for a prominent contrary example [15]. While there is no signal in the data reviewed of worse outcomes with any of the discussed techniques, efforts for current or future randomized trials should not be abandoned. The guideline also did not consider the cost effectiveness of any intervention when making recommendations, though this is a critical issue for both the individual and for public health in general.

There are also many emerging therapeutic approaches that may result in improved outcomes that are not yet incorporated into the current guideline. The addition of concurrent cisplatin to postoperative adjuvant pelvic RT in patients with intermediate-risk, early-stage cervical cancer is currently being studied (GOG-0263/NCT01101451). The utility of chemotherapy after concurrent chemo-radiotherapy (CTRT) is of particular interest, pending the results of the OUTBACK trial (GOG-0274/ NCT01414608, intact disease) and RTOG-0724 (NCT00980954/high risk disease postoperatively). Novel therapeutics such as triapine (NRG-GY006/ NCT02595879) and immune therapies (NRG-G017/ NCT03738228, CALLA/NCT03830866, ATOMICC/ NCT03833479, ENGOT-cx11/NCT04221945) have shown promise in initial experiences when combined with CTRT. ASTRO has committed to review its content annually after 2022 and re-affirm or revise the guideline in the future.

There have been many advances in the methods by which radiation therapy can be delivered, however the core principals remain intact – whole pelvic radiation therapy with concurrent cisplatin-based chemotherapy followed by high quality brachytherapy results in the best outcomes for locally advanced disease. Earlier stages are best treated with optimal surgery, with postoperative risk adapted radiation therapy offered when indicated. In the end, however, no guideline is a replacement for discussion and co-management of all cases by a dedicated multidisciplinary team.

Author contributions (CRediT statement)

Conceptualization	Junzo Chino, Akila Viswanathan, Christine Holschneider
Methodology	N/A
Software	N/A

Validation	N/A
Formal analysis	N/A
Investigation	N/A
Resources	N/A
Data Curation	N/A
Writing - Original Draft	Junzo Chino, Akila Viswanathan, Christine Holschneider
Writing - Review & Editing	Junzo Chino, Christina Annunziata, Sushil Beriwal, Lisa Bradfield, Beth Erickson, Emma Fields, Jane Fitch, Matthew Harkenrider, Christine Holschneider, Mitchell Kamrava, Eric Leung, Lilie Lin, Jyoti Mayadev, Marc Morcos, Chika Nwachukwu, Daniel Petereit, Akila Viswanathan
Visualization	N/A
Supervision	Junzo Chino, Akila Viswanathan
Project administration	Lisa Bradfield
Funding acquisition	N/A

Declaration of Competing Interest

Christina Annunziata (American Society of Clinical Oncology representative): MaxCyte, Medivir, and Precision Biologics (research), Horizon Pharma and Merck (provided drugs for clinical trial); Sushil Beriwal: Eisai, Institute of Education, and Via Oncology (honoraria), Varian (consultant), XOFT (DSMB); Matthew Harkenrider: AstraZeneca (advisory board [ended]), Varian (advisory board [ended]); Christine Holschneider (Society of Gynecologic Oncology representative): UpToDate (honoraria); Mitchell Kamrava: Augmenix (speakers bureau); Lilie Lin: AstraZeneca (research); Jyoti Mayadev: AstraZeneca (consultant), Varian (advisory board); Marc Morcos: Elekta (travel); Daniel Petereit: (American Brachytherapy Society representative and president): BMS Foundation (research and salary support), Irving A Hansen Memorial Foundation (patient funding), Ralph Lauren Pink Pony Foundation (board member); Beth Erickson: Elekta (research and travel); and Junzo Chino, Akila Viswanathan, Emma Fields, Jane Fitch (patient representative), Eric Leung, and Chika Nwachukwu reported no disclosures.

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