special article

National Cancer Grid of India Consensus Guidelines on the Management of Cervical Cancer

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executive summary

Standard guidelines for the management of early and locally advanced cervical cancer are available from various academic consortiums nationally and internationally. However, implementing standard-of-care treatment poses unique challenges within low- and middle-income countries, such as India, where diverse clinical care practices may exist. The National Cancer Grid, a consortium of 108 institutions in India, aims to homogenize care for patients with cervical cancer by achieving consensus on not only imaging and management, but also in addressing potential solutions to prevalent challenges that affect the homogenous implementation of standard-of-care treatment. These guidelines therefore represent a consensus statement of the National Cancer Grid gynecologic cancer expert group and will assist in homogenization of the therapeutic management of patients with cervical cancer in India.

INTRODUCTION AND METHODS

Cervical cancer is the second most common cancer in Indian women.[1] A majority of patients present in the locally advanced stage. In 2016, the Ministry of Health and Family Welfare strengthened the operational framework for the screening and management of common cancers and provided detailed algorithms for the early detection and management of cervical cancer via Indian Council of Medical Research (ICMR) guidelines.[2,3] However, the biggest challenge remains in its systematic execution. The National Cancer Grid (NCG) of India, funded by the Department of Atomic Energy, Government of India, was initiated in 2012 with a mandate of creating uniform standards of health care across cancer institutions to reduce disparities in patient care across various geographic regions.[4] Short-term steps to address this issue include the development and implementation of evidence-based guidelines that have been adapted to address challenges in the delivery of first-line standard of care in India.

The cervical cancer guideline development process was initiated in November 2016. NCG nominated experts from all geographical regions in India to ensure adequate representation from both government-funded and private health care providers. Initial guidelines were prepared by lead representatives (S.C. and A.M.) under the framework of questions that were identified to be clinically relevant by the core group (S.C., A.M., and S.G.). Recommendations were based on comprehensive and objective assessment of evidence searched through the National Library of Medicine database and the Cochrane data base of systematic reviews. In clinical situations in which level I evidence was not available, recommendations were guided by reports from large prospective studies. Where prospective data were not available, retrospective data reviews were used. Special emphasis was placed on published data from India and challenges that were encountered during the implementation of diagnostic and therapeutic services in low- and middle-income countries, such as India. Best practice consensus recommendations were used when there was a lack of structured clinical evidence. The first draft was circulated via e-mail to all experts in January 2017, and feedback was requested before the NCG expert group meeting in February 2017. The core group meeting focused on summarizing the recommendations and discordance between experts. Consensus was achieved through voting by expert members, and recommendations were incorporated in the revised draft. Recommendations were additionally summarized at minimal, optimal, and optional levels of execution. Revised versions were circulated over two rounds of e-mails to the NCG expert group as well as to an external international expert who has experience in working in both high- and low-resource settings

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(S.G.). Recommendations made by all experts were incorporated before submission for publication. Following are recommendations of the expert consensus.

RESULTS

What Is Optimal Radiologic Evaluation for Early and Locally Advanced Cervical Cancer?

The International Federation of Gynecology and Obstetrics recommends ultrasonography for imaging cervical cancer.[5] However, it is also recommended that, whenever magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CECT) is available, they be used to guide management. An American College of Radiology Imaging Network study has reported the superiority of MRI over CECT in identifying tumor size and parametrial invasion, with equivalent performance in identifying nodal disease[6,7]; therefore, CECT should be considered as minimal investigation, if available, and MRI as optimal investigation for imaging early cervical cancer. In select patients with ectocervical tumors < 2 cm, only ultrasonography may be performed before surgery, with MRI reserved for patients who desire fertility-sparing surgery.

In locally advanced cervical cancer (LACC), MRI at baseline and at the time of brachytherapy facilitates image-based brachytherapy[8-10] and has equivalent performance to CECT for identifying nodal disease; therefore, MRI should be considered as optimal investigation and CECT as minimal investigation, if available. For those with suspected bladder or rectal infiltration, additional confirmatory cystoscopy and/or proctosigmoidoscopy should be performed.

A template for synoptic reporting for MRI in cervical cancer is included in the Data Supplement.

Should Patients With Early Cervical Cancer With Equivocal Pelvic Nodes Undergo Positron Emission Tomography-CT or Fine-Needle Aspiration Cytology to Facilitate Therapeutic Decision?

Positron emission tomography (PET) -CT scan does not have incremental specificity over CECT to predict pathologic nodal involvement.[6] Patients with nodes ≥ 10 mm in size should undergo upfront chemoradiation (CRT). In the case of equivocal nodes, fine-needle aspiration cytology (FNAC) should be performed. If the decision is made for upfront surgery, then an intraoperative frozen section should be used. If nodes are positive on pelvic lymph node dissection (PLND), surgery should be abandoned in favor of CRT. Centers that do not have facilities for FNAC or frozen section should consider treatment with CRT.

Should Patients With Equivocal Para-Aortic Nodes Undergo PET-CT, FNAC, or Surgical Staging?

Integration of PET-CT in the imaging algorithm does not affect the overall oncologic outcome.[11] A recent study that compared PET-CT with surgical staging reported negative and positive predictive values of 83% and 71%, respectively.[12] Therefore, confirmatory FNAC should be performed.

A small, randomized study reported increased morbidity after surgical staging.[13] Other studies have demonstrated improved survival after surgical staging[14] as the addition of surgical staging over negative PET-CT detects para-aortic (PA) nodes in an additional 22% of patients[15]; however, a review of the Cochrane database noted a lack of robust data by which to recommend surgical staging.[16] An ongoing phase III randomized study is investigating the effect of surgical staging.[17] Hence, surgical staging is not recommended outside of clinical trials. A summary of imaging recommendations is listed in Table 1.

MANAGEMENT

Early Cervical Cancer (Stages IA1 to IB1 and IIA1)

What is the adequate management for stage IA1 disease? Type I/class A (extrafascial hysterectomy) is recommended for stage IA1 disease. Ovarian preservation should be offered to young patients with squamous histology. Conization may be considered for fertility preservation. If margins are involved, then trachelectomy may be considered. PLND with ovarian transposition should be considered if the specimen demonstrates lymphovascular space invasion (LVSI). Radical brachytherapy (BT) alone to a dose of up to 65 Gy equivalent dose in 2 Gy to point A (that anatomically represents crossing of ureter and uterine artery on either side) should be considered for medically inoperable patients.

What is the adequate management for stage IA2 disease? Type II/class B radical hysterectomy

Table 1. Summary of Imaging and Management Recommendations for Optimal and Minimal Resources Setting

Disease	Optimal	Minimal	Optional	Remarks
Imaging				
Stage				
Early cervical cancer (stage IA1, IA2, IB1, and IIA1)	MRI abdomen and pelvis Chest X-ray	CECT abdomen and pelvis, if available, otherwise USG abdomen and pelvis Chest X-ray For ectocervical tumors < 2 cm, USG may be sufficient		EUA is preferred if there is a discrepancy in clinical staging and MRI findings of parametrial involvement MRI should be considered in patients who desire fertility preservation
Locally advanced cervical cancer (IB2, IIA2-IVA)	MRI abdomen and pelvis	CECT abdomen and pelvis, if available, otherwise USG abdomen and pelvis Chest X-ray	PET-CT	As incidence of lymph node metastasis is high, CECT is preferred over USG
Para-aortic nodes	Nodes identified on CECT and/or MRI should be confirmed with fine-needle aspiration cytology, especially with negative pelvic lymph nodes CT of the thorax should be done for patients with positive PA nodes	Radiologic size criteria is used to diagnose nodal involvement	PET-CT	Adding whole-body PET-CT after CECT of abdomen and pelvis has additional cost implications and is not encouraged
Management				
FIGO stage				
IA1	Type 1/class A extrafascial hysterectomy or Conization or Radical trachelectomy if fertility desired	Conization	Radical BT 60 Gy to point A. Consider ovarian transposition in premenopausal patients	Patients with positive LVSI should be referred for PLND or assessment for the need for adjuvant pelvic RT
IA2	Type 2/class B radical hysterectomy and pelvic lymphadenectomy or Radical trachelectomy and PLND if fertility is desired	Type 2/class B radical hysterectomy and pelvic lymphadenectomy	Radical BT alone 65-70 Gy point A. Consider ovarian transposition in premenopausal patients	Patients with LVSI should be assessed for the presence of other risk factor(s) for recommending adjuvant radiation
IB1-IIA1	Type 3/class C radical hysterectomy with PLND Adjuvant radiation in those with postoperative two or three intermediate risk factors (size > 4 cm, LVSI, deep stromal infiltration). Concurrent chemotherapy to be added in the case of any high-risk features (vaginal cut margins, nodes, or parametria positive). 3DCRT represents the current standard of care for postoperative RT. Additional BT to be used only in patients with insufficient vaginal cuff or vaginal cut margin positive. Patients with adenocarcinoma and > 2 cm in size and an additional risk factor may be considered for adjuvant radiation or Upfront 3DCRT and BT with or without chemotherapy CT/MR-based planning is recommended for BT	Type III/Class C radical hysterectomy with PLVD. Adjuvant radiation in those with postoperative two or three intermediate risk factors (size > 4 cm, LVSI, deep stromal infiltration). Concurrent chemotherapy to be added in the case of any high-risk features (vaginal cut margins, nodes, or parametria positive). 3DCRT represents the current standard of care for postoperative RT. Additional BT to be used only in patients with insufficient vaginal cuff or positive vaginal cut margin. Patients with adenocarcinoma and > 2 cm in size and an additional risk factor may be considered for adjuvant radiation or Upfront 3DCRT and BT with or without chemotherapy 2D BT transition toward CT-based BT is recommended	Para-aortic lymph node assessment. Radical trachelectomy and PLND in suitable cases of stage IB1, if fertility is desired	Preoperative thorough assessment of size, parametrial involvement, and nodal status is recommended to avoid adjuvant treatment. Patients with nodes > 1 cm in size should be offered upfront CTRT. If the decision is made to operate in the presence of equivocal nodes on imaging, then frozen section should be used to assess nodes. Surgery should be abandoned if nodes are positive on frozen section

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Table 1. Summary of Imaging and Management Recommendations for Optimal and Minimal Resources Setting (Continued)

Disease	Optimal	Minimal	Optional	Remarks
IB2	Concurrent pelvic chemoradiation (3DCRT) and 3D CT/MR BT Patients with positive para-aortic nodes should receive extended-field radiation with concurrent chemotherapy, and intensity-modulated radiation is recommended for these patients. Nodal boost may be considered. This should be followed by CT/MR-based BT	Concurrent pelvic chemoradiation (3DCRT) and 2D BT Patients with positive para-aortic nodes should receive extended-field radiation with concurrent chemotherapy, and 3DCRT is recommended for these patients. Sequential nodal boost may be considered. This should preferably be followed by CT/MR-based BT	Radical RT alone (in patients who are unable to tolerate concurrent chemoradiation as a result of low creatinine clearance or advanced age) Patients who are reluctant to undergo RT and with small IB2 tumors with no nodes or deep invasion of the cervix on MRI may be considered for type 3/class C hysterectomy with PLND Ovarian preservation in young patients with squamous histology	Surgery is not the preferred treatment; however, it may be used only in select patients. Such patients should undergo surgery in select centers with access to frozen section facilities for nodal assessment at the time of surgery. Surgery should be abandoned if nodes are positive; in such select patients, ovarian transposition should be performed if patients are premenopausal. Use of Neoadjuvant chemotherapy prior to surgery is not recommended
IIA2-IIIB	Concurrent pelvic chemoradiation (3DCRT) and CT/MR-based BT Patients with positive para-aortic nodes should receive extended-field radiation with concurrent chemotherapy, and intensity-modulated radiation is recommended for these patients; nodal boost may be considered; this should be followed by CT/MR-based BT	Concurrent pelvic chemoradiation (3DCRT) and 2D BT Patients with positive para-aortic nodes should receive extended-field radiation with concurrent chemotherapy, and 3DCRT is recommended for these patients. Sequential nodal boost may be considered. This should preferably be followed by CT/MR-based BT	Radical RT alone (in patients who are unable to tolerate concurrent chemoradiation as a result of low creatinine clearance or advanced age)	Use of neoadjuvant or adjuvant chemotherapy is not recommended. No prophylactic stenting is recommended in patients with IIIB and hydroureteronephrosis. Percutaneous nephrostomy and DJ stenting should be avoided in patients with deranged creatinine > 3 g/dL; such patients should be considered for palliative RT
IVA	If focal bladder/rectal infiltration, then pelvic chemoradiation (3DCRT). This should be followed by cystoscopy/rectosigmoidoscopy, then CT/MR-based BT Patients with focal bladder/rectal infiltration and large para-aortic nodes may be considered for 2-3 cycles of neoadjuvant chemotherapy followed by re-evaluation with cystoscopy and nodal response, then decide on extended-field radiation and concurrent chemotherapy followed by BT *v* palliative RT Patients with frank bladder infiltration may be considered for upfront palliative RT and/or palliative chemotherapy Palliative care reference should be done early on in patients who are planning for palliative treatment	If focal infiltration, then pelvic chemoradiation (3DCRT); this should be followed by cystoscopy, then BT or Radical RT alone (in patients who are unable to tolerate concurrent chemoradiation as a result of low creatinine clearance or advanced age) or Palliative RT alone in the case of extrapelvic disease or frank bladder infiltration or Palliative care reference should be done early on in patients who are planning for palliative treatment	Select patients with IVA disease may be considered for exentration after pelvic RT, depending on treatment response, patient wishes, and the availability of infrastructure and expert	

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Table 1. Summary of Imaging and Management Recommendations for Optimal and Minimal Resources Setting (Continued)

Disease	Optimal	Minimal	Optional	Remarks
IVB	Palliative RT with or without palliative chemotherapy Palliative care consult	Palliative RT with or without palliative chemotherapy or Best supportive care Palliative care consult	Bevacuzimab use is optional and is not advised as a result of the limited benefit and high costs	

Abbreviations: 2D, two-dimensional; 3DCRT, three-dimensional conformal radiation therapy; BT, brachytherapy; CT, computed tomography; CECT, contrast-enhanced computed tomography; DJ, double J stent; EUA, examination under anesthesia; MRI, magnetic resonance imaging; LVSI, lymphovascular space invasion; PET-CT, positron emission tomography-computed tomography; PLND, pelvic lymph node dissection; RT, radiation therapy; USG, ultrasonography.

and PLND with or without bilateral salpingo-ophrectomy is recommended for stage IA2 disease. Conization with extraperitoneal or laparoscopic lymphadenectomy or radical trachelectomy should be considered in those patients who desire fertility preservation. BT alone or external beam radiation therapy (EBRT) and BT to a dose of up to 70 Gy to point A should be considered for medically inoperable patients.

What Is the optimal management of stage IB1 and IIA1 disease? Type III/class C radical hysterectomy with or without bilateral salpingo-ophrectomy with PLND or EBRT and BT has similar outcomes for stage IB1 and IIA1 cervical cancer; however, surgery may be associated with lower long-term vaginal morbidity. Therefore, the choice of treatment depends mainly on the patient and the availability of expertise. Patients with stage IB1 disease who desire fertility preservation can be offered radical trachelectomy, provided that the tumor is small and lymph nodes are negative on PLND. A consultation with a fertility expert can be considered if feasible. Patients who favor radical radiation should be offered a combination of EBRT and BT (75 to 80 Gy to point A). In such patients, ovarian transposition may be considered.

Should minimal access surgery be the standard of care? There is a lack of level I evidence for minimal access surgery in the management of cervical cancer, and, hence, the treatment remains investigational.[18] However, single-institution studies have demonstrated oncologic safety and a reduction in patient morbidity.[19] Minimal access surgery should be performed after adequate training and within a clinical protocol. Institutional audit committees should monitor and report on the rates of conversions and complications.

What should a standard histopathology report contain? Use of standardized templates (Data Supplement) with synoptic pathology reporting, including International Federation of Gynecology and Obstetrics stage, is strongly recommended to harmonize surgical pathology reports within the National Cancer Grid. The gross pathology report should include the description of tumor size, vaginal cuff and parametrial length, and the number of dissected nodes. The microscopic report should include the description of pathologic subtype, grade, vaginal and parametrial margins, the extent of stromal infiltration (< 50% *v* ≥ 50%), and the presence or absence of LVSI. Pathologists should also report nodal yield and nodal involvement.

What are additional measures by which to improve the quality of surgery? Regular surgicopathologic audits should be conducted in all institutions. The NCG expert committee noted an increase in suboptimal surgeries within the community and thus recommends that only gynecologic oncologists or gynecologists with adequate oncology training perform cervical cancer surgery. Suboptimal surgery represents a serious deviation from clinical practice that compromises oncologic outcomes and is strongly discouraged.

Which patients can be observed after surgery and how should such patients be evaluated on follow-up? Patients with tumor size < 4 cm with no adverse risk factors (eg, deep stromal invasion, LVSI, nodal or parametrial positivity, cut margin positivity, or inadequate vaginal cuff removal) should be offered observation. Patients should thereafter be scheduled for follow-up every 4 months for up to 2 years, every 6 months for another 3 years, and yearly thereafter. Cytologic evaluation should be considered optional. Follow-up imaging should be directed by symptoms and is not recommended for all patients.

Which patients need postoperative adjuvant treatment? Patients with two intermediate risk factors

(tumor size > 4 cm, deep stromal invasion, or LVSI) should be offered radiation therapy.[20] Patients with any high-risk features (positive vaginal or parametrial margins or positive pelvic lymph nodes) should be offered CRT.[21] The EBRT dose should be 45 to 46 Gy in 23 to 25 fractions delivered over 5 weeks. Additional BT should be recommended in patients with involved vaginal margins or with suboptimal removal of vaginal cuff (< 2 cm vaginal cuff or tumor-free margin of < 1 cm). The target volume for BT should be the upper one third of residual vagina and in no case > 4 cm in length. High-dose rate BT should be delivered in two fractions of 6 Gy each, prescribed at 5 mm from the vaginal cylinder surface and delivered 1 week apart, keeping the overall treatment time (OTT) within 8 weeks.

These recommendations apply to patients who have undergone recommended surgical procedures for their disease stage. Patients who undergo suboptimal surgery, either in terms of lymph node or parametrium dissection or vaginal cuff removal, should be considered to be at high risk for relapse and should be offered adjuvant CRT and vaginal BT.

In all patients, attempts should be made to initiate EBRT within 6 weeks of treatment initiation. The expert panel acknowledges that there may be delays in referring patients from the community surgeon and that recommendations for treatment initiation may often be violated. The expert panel therefore encourages conducting educational forums to improve the referral practice.

Should intensity-modulated radiation therapy be offered for postoperative radiation therapy? An interim analysis of a phase III trial from India of intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiation (3DCRT) demonstrated reduced incidence of late bowel toxicity with IMRT; however, the difference was not statistically significant.[22] Another phase III trial demonstrated improved patient-reported outcomes at week 5 with IMRT, with no difference reported at 6 weeks after treatment completion.[23] Until additional data become available, 3DCRT should remain the standard of care.

LACC (Stages IB2 and IIA2 to IVA)

What is the optimal treatment for stage IB2 disease? Concurrent CRT is the standard of care for the treatment of stage IB2 disease. Surgery is associated with high use of adjuvant treatment and is not recommended.[24] The expert committee acknowledges that ICMR recommends the use of surgery in patients with stage IB2 disease, and there is unacceptably high use of surgery with or without neoadjuvant chemotherapy (NACT) in India for stage IB2 disease; however, this practice should be replaced with concurrent CRT as new results from phase III Indian trials are now available.[3,25]

In 2017, a phase III randomized trial from India investigated the role of NACT followed by surgery versus concurrent CRT in stage IB2 to IIB disease.[25] The study reported high rates of crossover to CRT (23%) and the need for adjuvant radiation (20%) within the NACT arm. Overall, NACT and surgery arm were associated with reduced 5-year disease-free survival (DFS; 67.5% *v* 72.2%; P = .07); therefore, CRT should represent the standard of care in all patients with stage IB2 disease. For young patients with small IB2 tumors and no adverse factors on imaging, such as nodes or deep stromal invasion on MRI, the surgical option may be discussed; however, patients should be apprised of the potential need for adjuvant radiation as well as the cumulative adverse effects as a result of combination treatment.

What is the optimal treatment for stage IIA2 to IIIB disease? Pelvic CRT and BT constitute the standard of care in LACC.[25-27] The radiation field should encompass the uterus, cervix, vaginal disease extension, ovary, parametrium, and pelvic lymph nodes with adequate margins. Mesorectum should be included in patients with mesorectal nodal involvement or gross uterosacral infiltration. 3DCRT with CT-based planning should be used as two-dimensional planning can underdose the target.[28,29] In radiologically node-negative patients, the upper extent of the field should be the L4 and L5 junction; however, in patients with enlarged nodes, the field should extend to the aortic bifurcation.[28] If nodes are identified at the aortic bifurcation, extending the treatment fields 2 to 3 cm above the gross nodes or up to the renal vein should be considered.[30] Medial inguinal nodal irradiation should be considered in patients with disease that extends to the lower one third of the vagina. Nodal boost should be considered in those patients with enlarged nodes, and doses should be individualized on the basis of the contribution received during BT if CT-/MRI-based BT planning is performed.

Equal efficacy of cisplatin that is administered every week or every 3 weeks has been reported, with lower toxicity with the weekly schedule.[31,32] Prospective studies have demonstrated improved outcomes in patients who received five or more cycles,[33] and careful scheduling of CRT is recommended to improve clinical outcomes. In patients with reduced creatinine clearance (CC), a dose reduction of up to 20% may be used, or carboplatin may be considered.[34,35] If CC is < 40 mL/min, chemotherapy should be omitted.

There is no proven role for NACT[25] or adjuvant chemotherapy in the standard management of LACC. A single randomized study demonstrated a benefit for adjuvant chemotherapy after CRT; however, this approach has not been widely adopted. Patients with LACC (IIB to IVA) who were treated with cisplatin/gemcitabine, both during and after radiation therapy, demonstrated improvement in progression-free survival and overall survival (OS).[36] However, the OUTBACK trial (ClinicalTrials.gov identifier: NCT01414608) is awaited to define clinical use of adjuvant chemotherapy; however, in patients with large pelvic nodes (> 3 to 4 cm) or those with focal bladder infiltration (infiltration > 1 × 1 cm), NACT may be considered with the consensus of a multidisciplinary team. In such cases, patients should receive two to three cycles of paclitaxel 175 mg/m^2 and carboplatin (area under curve, 5), followed by clinical and radiologic nodal reassessment before the initiation of CRT.[37] Patients with bladder infiltration at baseline should undergo cystoscopy after NACT to evaluate their response. Patients who achieve a good response (ie, disappearance of infiltration or minimal residual infiltration) should proceed to CRT. Patients with small-cell cancer of the cervix should receive four cycles of systemic chemotherapy (cisplatin and etoposide) before the initiation of CRT.

There is no role for prophylactic ureteric stenting in patients with hydronephrosis and normal CC. Palliative radiation therapy should be considered in patients who present with obstructive uropathy with serum keratinize > 3 mg/dL, as percutaneous nephrostomy followed by radical radiation or CRT is associated with survival of < 8 months.[38]

BT should be initiated in the last week of EBRT for patients with LACC, and three to four fractions of 7 to 8 Gy (high-dose rate) should be administered with the aim of delivering 80 to 84 Gy to point A within 8 weeks while minimizing the dose to the rectum and bladder to 65 to 68 Gy and 80 to 85 Gy, respectively.[39,40] The expert group acknowledges that many centers may be currently practicing two-dimensional or X-ray–based planning; however, the transition to CT-based planning is recommended as it allows for better assessment of the applicator position in relationship to the target and facilitates accurate dose reporting to organs that are at risk. Combined intracavitory and interstitial BT with magnetic resonance–based treatment planning and delivery should be performed for patients with residual parametrial disease beyond point A. Dose escalation > 84 Gy is recommended in this patient cohort. IMRT or stereotactic radiation are not alternatives for BT and are associated with reduced local control.[41]

Should IMRT be recommended for pelvic radiation in patients undergoing radical CRT? Clinical implementation of pelvic IMRT is challenging and extreme care must be taken with regard to organ motion. The need for large margins may reduce the anticipated benefit of IMRT. A small, randomized trial of 44 patients demonstrated that the use of whole-pelvic IMRT had fewer grade II and III GI toxicities.[42] The recently published results of the INTERTECC trial demonstrate reduced GI and hematologic toxicity; however, the trial did not have a comparator arm.[43] Considering that pelvic IMRT may be associated with significant uncertainties and unconfirmed benefit in large studies, the use of pelvic IMRT should be restricted to clinical trials until additional information becomes available.

Can recommended guidelines for cervical cancer radiation be adequately implemented? A multiinstitutional registry from India (n = 7,336), published in 2015, reported that only 55.5% of patients receive optimal radiation, with only 44.4% receiving CRT. A cumulative cisplatin dose of > 150 mg was associated with improved outcomes but also with increased toxicity.[33] Another study from rural India reported poor compliance, higher grade III toxicity, and treatment breaks.[44] Up to 16% to 20% of patients had treatment gaps as a result of toxicity and received three or fewer cycles, which reduced the cumulative dose to 152 mg/m^2 (80 to 200 mg/m^2) rather than the desired cisplatin dose of 225 to 250 mg/m^2.[33,45] In patients with coexisting HIV infection, potential

interactions between antiretroviral drugs and cancer therapy should be considered, and higher toxicity and poor outcomes[46] may be anticipated. CRT should be cautiously used in patients with CD4 counts of > 200 cells/μL.[47]

The NCG expert panel also noted that academic centers treat significantly higher numbers of patients than their existing infrastructure can support and also accept patient referrals only for BT. An unpublished audit from the lead institute indicated that treatment breaks were often a direct result of toxicity that was incurred during treatment (most often diarrhea) or technical infrastructure-related problems, such as machine breakdown or an imbalance between available infrastructure and the number of patients who required treatment, often increasing OTT to > 8 weeks. An unpublished audit of chemotherapy compliance reported that up to 86% of patients receive more than four cycles of concurrent chemotherapy; however, only 48% proceed to receive five or more cycles of concurrent chemotherapy.

The expert panel therefore recommends that, to improve compliance with the proposed CRT guidelines, all patients should undergo detailed evaluation of performance and nutritional status and renal function at the first consultation and that remedial actions be taken whenever applicable. Patients should also be provided an institutional social worker referral before treatment initiation. For treatment planning, 3DCRT should be considered as a standard treatment to minimize toxicity. To ensure compliance to five or more cycles of concurrent chemotherapy, it is mandatory that patients receive the first chemotherapy cycle by day 2 of radiation initiation. Coordination between medical and radiation oncology is recommended to ensure the delivery of five or more cycles of chemotherapy. Adopting abbreviated equieffective BT fractionation schedules can strengthen compliance to OTT. A final analysis of the International Atomic Energy Agency trial that compared 4x7 Gy with 2x9 Gy demonstrated the superiority of the four-fraction schedule.[48] Therefore, instead of two fractions of 9 Gy, twice weekly BT schedules using 7 Gy per fraction may be considered.

Should prophylactic PA radiation be used in patients with LACC? Prophylactic PA radiation therapy within the RTOG 7920 trial demonstrated an 11% improvement in OS without any improvement in DFS[49]; however, no difference in OS was reported in an European Organisation for Research and Treatment of Cancer trial.[50] In RTOG 90-01 (Pelvic Irradiation With Concurrent Chemotherapy Versus Pelvic and Para-Aortic Irradiation for High-Risk Cervical Cancer: An Update of Radiation Therapy Oncology Group Trial 90-01) pelvic CRT improved OS compared with extended-field radiotherapy (EFRT) alone[51]; therefore, there is no role for prophylactic EFRT.

What should be the optimal management in patients with involved PA nodes? Patients with involved PA nodes should receive EFRT with concurrent weekly cisplatin 40 mg/m^2, followed by BT. High acute (33% to 87%) and late (10% to 40%) toxicity have been reported with conventional techniques.[52-54] IMRT studies report reduced acute (24% to 76%) and late (5%) toxicity[30,55-57]; therefore, wherever feasible, IMRT should be considered for EFRT. Select patients with bulky PA nodes (> 3 to 4 cm in size) may be considered for NACT followed by EFRT and chemotherapy.[38,58]

What is the optimal management of stage IVA cervical cancer? Patients with focal infiltration of the bladder (< 1 × 1 cm) should be considered for upfront CRT. Patients who have a larger area of infiltration should receive palliative radiation therapy. Use of palliative radiation therapy leads to a reduction in symptoms in 40% to 100% of patients, with a median survival of 7 to 8 months.[59-62] Select patients who present with a urinary or rectal fistula without parametrial involvement may be considered for pelvic exentration.[63]

What should be the treatment of choice for metastatic cervical cancer? Platinum-containing combination regimens have demonstrated improved progression-free survival.[64-66] Patients with an isolated visceral metastasis may also be considered for stereotactic radiation and palliative pelvic radiation therapy.

What should be an optimal follow-up strategy for patients with LACC? Follow-up should include per-speculum and bimanual pelvic examination every 4 months for 2 years, then every 6 months thereafter with symptom-directed imaging as indicated.[67] Routine cytologic evaluation is not recommended.

What should be the optimal treatment of postradiation residual disease? In patients who have persistent

residual disease after treatment, options for additional treatment should be considered. The decision to administer salvage surgery should be made no sooner than 5 to 6 months after the completion of treatment to minimize unnecessary surgical intervention.

Patients with isolated central recurrences should be evaluated for salvage hysterectomy. If this is not feasible, re-irradiation (preferably with intracavitary or interstitial BT) should be considered. Outcomes after re-irradiation for local recurrence have been published from the Tata Memorial Centre. Re-irradiation is associated with 44% 2-year local control and 52% OS in carefully selected patients.[68] Patients who are not candidates for surgical or radiation salvage should be considered for systemic chemotherapy and be reassessed for BT or surgery. If local salvage is not feasible, then additional chemotherapy should be considered on the basis of response and the general condition of the patient[69]

What should be the optimal salvage therapy for recurrent disease after surgery? Postsurgical recurrences should be treated with CRT and vaginal intracavitary or interstitial BT.[70,71] A prospective phase II study from India reported local control of 89% and 5-year DFS of 75% at a median follow-up of 42 months.[72]

DISCUSSION

In addition to already available national[2,3] and international cervical cancer management guidelines,[73] resource-stratified guidelines have been published for the management of cervical cancer by ASCO.[74] Although ASCO guidelines intend to provide resource-stratified recommendations, the minimal recommendations are deviations from evidence-based guidelines and are likely to result in suboptimal oncologic outcomes and are not recommended for the treatment of cervical cancer in India. ICMR guidelines provide an evidence-based framework; however, discrepancies in delivery have been reported as a result of the unique challenges within low- and middle-income countries. NCG guidelines therefore make an attempt to address the common challenges encountered in the delivery of standard practice and provide either evidence-based or best practice–based solutions that can lead to the optimal adaptation of standard guidelines, thereby ensuring that cost-effective optimal care is offered to women with cervical cancer.

As with any guideline, the biggest challenge remains in uniform and widespread adaptation, and the NCG provides the framework to ensure this adaptation, as participating institutions and local experts were extensively consulted for the development of recommendations. In addition to agreement on the contents of the recommendations, the expert committee and our coauthors have agreed to audit and report compliance with NCG guidelines within their institutions.

A multi-institutional, two-phased clinical audit would be initiated to report compliance with guidelines and quality indices for the treatment of cervical cancer by NCG member institutions that will further guide cervical cancer care implementation policies in India.

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AUTHOR CONTRIBUTIONS

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