

Consensus meeting and update on existing guidelines for management of cervical cancer with special emphasis on the practice in developing countries, including India: The expert panel at the 8th annual women's cancer initiative Tata Memorial Hospital Conference 2010-11

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A B S T R A C T

Background: Cervical cancer is one of the most common cancers seen in developing countries, especially in India. Recent years have seen many new developments in various modalities used in the management of cervical cancer. Although it is important to remain abreast with these advancements, the availability of resources and challenges in practices across the country cannot be ignored. **Materials and Methods:** This is a conference update aiming at reviewing all major advancements with their due merit, which can influence the evidence in daily practice of treatment for cervical cancer in the developing nations. Pre-formulated guidelines questions developed by the scientific committee were discussed and voted by national and international faculty as well as delegates in the light of current evidence and available resources in developing countries for practice. **Results:** The results of these discussions and voting were compiled and are presented as guidelines for practice. **Conclusion:** These recommendations are aimed to help centers in developing countries to deliver and improve best care with available recourses to cervical cancer patients.

Key words: Cervical cancer, developing countries, guidelines

INTRODUCTION

A number of international guidelines exist for management of carcinoma cervix.^[1-5] These guidelines have been developed in the context of evidence and clinical practice in the Western world. There is a little representation from the developing countries, if any, in the expert panels who formulate these guidelines. Clinical practice in developing countries, however, continues to be largely guided by these guidelines since they are based on high-quality evidence

with expert appraisal. Many of these guidelines are not literally applicable to developing countries because of constraints on resources or expertise and, at times, both.

The Women's Cancer Initiative is a nongovernmental organization focused on the cause of women's cancers. Women's Cancer Initiative–Tata Memorial Hospital (WCI-TMH) has organized focused theme-based Annual Breast and Gynaecological Cancers Conferences for the past eight years. This Conference invites and receives participation from national and international experts and academic and community oncologists from all disciplines. The Steering Committee of WCI-TMH decided, in view of the paucity of relevant guidelines, to dedicate the 2010 Annual Conference to the development of guidelines for the management of primary breast and cervical cancers, in the express context of current scenario in India and other developing countries. We report here the results of

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the expert panel for the development of guidelines for loco-regional therapy in primary cervical cancer.

MATERIALS AND METHODS

The scientific committee of the Conference met over several sessions in the early part of 2010. Various methodologies for the development of these guidelines and important issues to be discussed were finalized. A series of questions on each topic and subtopic in the surgical, radiation, and systemic management of cervical cancer were formulated. The majority of questions could be answered in the form of multiple choice answers, with the chosen answer amenable to formulation as a guideline, called the guideline questions.

It was decided that the best existing evidence on each question would be appraised in the Conference prior to the actual formulation of guidelines. It was decided to invite national and international experts to deliver focused talks that will appraise the relevant evidence in the context of the previously decided questions. The final development of the guidelines was done through an expert panel that electronically voted on each guideline question after all talks had been delivered and audience opinion elicited. Although the majority of the panel time was to be allocated to voting, members of the panel would be allowed to make dissenting or consenting comments.

RESULTS

The guideline questions were developed and sent to the invited experts many months in advance of the Conference that was held during October 22-24, 2010.

The experts were repeatedly reminded about the context of developing countries while preparing their presentations. The experts delivered talks that directly appraised the relevant evidence with respect to each question, preceded by audience voting on each of them. The expert panel convened and voted on the guideline questions on October 22, 2010, after completion of expert presentations and audience vote. Following are the subheadings under which the consensus and expert recommendations have been summarized.

Pre-treatment work-up

In the line of recent changes in the International Federation of Gynecology and Obstetrics (FIGO) guidelines for carcinoma cervix investigation work up, pre-treatment investigation recommendations were discussed. Other than routine blood test, chest X-ray, and histopathological confirmation, the radiological investigation of choice was discussed and following points emerged as consensus:

1. It was realized that in a minimum set-up situation (rural/basic centers), at least an abdomino-pelvic ultrasound should be done for assessment of kidneys, additional primary tumor characteristics, if any, and documentation of presence of gross pelvic and para-aortic nodes
2. Magnetic Resonance Imaging (MRI) pelvis was thought to be advantageous in pre-surgery investigation for operable cervical cancer, especially if a choice of fertility preserving surgery was to be offered. Additional information such as depth of invasion, early parametrial invasion, and abnormal anatomical features may assist the physician to offer single-modality treatment
3. For advanced stages, both Computed Tomography (CT) and MRI were seen to be equivalent to identify the nodal involvement. Recording and reporting on the utility of new imaging modalities such as PET, CT-PET findings should be encouraged, especially from better equipped centers under research settings only.

Treatment: This was discussed and compiled according to the FIGO staging.

FIGO stage IA: All patients are diagnosed on cone biopsy, which remains the standard treatment. Further treatment either type II/III hysterectomy with/without pelvic lymph node dissection or radical radiotherapy in the form of brachytherapy remains the widely accepted treatment of choice considering the patient's desire, age, and physician specialty and expertise. It was also realized that trachelectomy as a competent option should be practiced in young women at specialty centers, who have a desire to increase their fertility. When required, such patients should be encouraged to undergo treatment at these centers, and less specialized centers should aim for developing required skills for fertility-conserving surgeries such as trachelectomy.

FIGO stage IB-IIA: Radical surgery and radical radiotherapy both have been considered as treatment of choice and viable options by various groups. There is ample evidence in literature regarding the suitability of each modality in the form of retrospective series and a landmark randomized study. There was a well represented debate between surgery and radiation in which the apt winner was 'the patient'. The aim of treatment for this group should be to offer single-modality treatment, and additional effort by the physician was encouraged to triage this group and offer optimum treatment. Patients should be made aware of the advantages and disadvantages of each treatment modality and, more importantly, offer the treatment option for which local expertise is available or referral to higher level centers.

The radical surgery was defined as “Radical hysterectomy (type III) and bilateral pelvic lymph node dissection (LND)”, which includes removal of the entire uterus, upper third vagina, bilateral parametria, uterosacral, utero-vesical ligaments, and bilateral pelvic lymph nodes; moreover, bilateral salpingo-oophorectomy was termed as discretionary.

The radical surgery can be a definitive option for Stages IB₁ and IIA₁, but the choice of treatment would depend on the age of patient, desire to preserve the ovarian function, comorbid conditions hampering fitness for surgery, available expertise, and patients’ wish. The laparoscopic surgery was taken to be an evolving concept requiring further evaluation including laparoscopic radical hysterectomy with pelvic LND. The radical radiation was described to be a combination of external beam radiotherapy with brachytherapy to a total dose of 80-85 Gy EQD₂ at point A in 6-8 weeks.

For stages IB₂ and IIA₂, the options are similar but caution for surgery was expressed as there are more chances of requirement of postoperative radiotherapy due to risk factors, a situation that should be avoided. Also radical radiotherapy alone (concomitant chemo-radiation with cisplatin) may be an equally better option.

The postoperative risk management remains standard as high, intermediate, and low-risk stratification depending on adverse histopathological factors and adequate surgery. The High-Risk category is defined as the presence of lymph node metastases or positive surgical margins or positive parametrial extension (any one) where adjuvant chemo-radiation with external pelvic radiation therapy with concurrent weekly cisplatin chemotherapy is recommended.

The Intermediate-Risk category is defined as with absence of high-risk features and presence of any two features including deep invasion of cervical stroma, lymphovascular space invasion, or tumor size >4 cm, where adjuvant radiation alone is recommended. The Low-Risk patients are defined as absence of both high- and intermediate-risk features requiring no further adjuvant treatment after adequate radical surgery.

Also, the recent Cochrane meta-analysis for neo-adjuvant chemotherapy (NACT) followed by surgery in early stage showing improved disease-free survival and a trend for improvement of overall survival was discussed.^[6] It was felt that these practices should be taken with caution and can be considered under institutional research protocols only for wider recommendations.

Ovarian transposition/hormone replacement therapy prior to radiotherapy

In the house, although the need for ovarian transposition in young patients (<45 years) undergoing radical radiotherapy was felt by almost all delegates, a large lacunae was seen in the expertise available. If expertise is not available, more generally applicable solution will be hormone replacement therapy (HRT). Bone health and the hormone withdrawal symptoms should be considered when HRT is not being given for some medical reasons. The minimal risk of second malignancy associated with HRT should be discussed with patients. At present, the literature does not show any untoward trend for increasing second malignancies in post radiotherapy cervical cancer-treated patients. HRT can be started in younger patients with age less than 45 years and severe premature post-menopausal syndrome. This is widely applicable for squamous carcinoma histology only and its use in adenocarcinoma should be discouraged.

FIGO stage II-IIIb: The standard treatment remains radical radiotherapy including radical external beam radiotherapy (EBRT) with concurrent chemotherapy and brachytherapy. The EBRT doses are in the range 45-50 Gy with 1.8-2 Gy per fraction with conventional four fields using Co-60 or LA 6-15 MV appropriately according to patient characteristics and infrastructure availability. Higher centers can incorporate more IMRT-based treatment plans with image-guided radiation therapy (IGRT) protocols using MRI and positron emission tomography (PET)-CT information, while radiation planning under research protocols settings only to develop dosimetric and clinical data regarding, bowel and rectal doses, bladder filling and doses, boost to pelvic nodes Simultaneous Integrated Boost- Intensity Modulated Radiotherapy (SIB-IMRT), Internal Target Volume (ITV) and Planning Target Volume PTV margins and bone marrow sparing.

Concurrent chemotherapy: There is a large evidence to suggest the routine and safe practice of concurrent chemotherapy and benefits in all radically treated patients with radiotherapy. The robust data show better benefit if early-stage disease both in radical and post-operative settings; however, in locally advanced disease it is less defined and further larger trials need to be carried out including testing newer drugs and regimens in these patients. The weekly cisplatin 40 mg/m² is the most widely acceptable schedule of concurrent chemotherapy. Considering the logistics it was stressed that cisplatin infusion should be given at least prior to radiotherapy that same day for optimal radiosensitization. At the same time, concern regarding the poor general condition, more prevalence of malnutrition, anemia, and compromised socioeconomic conditions in Indian women leading to

decreased tolerance to intensive treatments was expressed. Also in most of the international trials regarding chemo-radiation, acute toxicity was seen to rise by threefold. Hence, it was recommended that judicious use for addition of chemotherapy to radiation should be considered with primary aim being to give adequate doses of radiation without unprecedented gaps due to increased toxicities associated with addition of chemotherapy.

Brachytherapy: Brachytherapy (low, medium, pulse, and high dose rate) is an integral part of the radiation treatment and is considered vital for high local control and cure rates. Any dose rate with equivalent doses [although high dose rate (HDR) brachytherapy has become increasingly popular] can be practised. For HDR, any dose fractionation is allowed from 9 Gy X 2 fractions to 6 Gy X 3-6 fractions as per the stage such that optimum doses to microscopic disease, gross disease, and cervix are achieved. Brachytherapy can be combined with EBRT as soon as the patient is clinically suitable for it. The timing and fractionation of brachytherapy should be such that the overall treatment time should be within 8 weeks without any major treatment interruptions. The doses should be equated in the form of total EQD₂ calculated as total EBRT, and brachytherapy doses to target volume should be >80-85 Gy₁₀ EQD₂, with rectum and sigmoid 2cc <75 Gy₃ EQD₂, bladder 2cc <90 Gy₃ EQD₂. Doses should be reported as per both International Commission on Radiation Units (ICRU) and Groupe Européen de Curiothérapie and the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendation with clinical toxicity correlation.

With the recent emerging evidence of use of MRI for conformal brachytherapy, it was realized that more and more centers should acquire the required skill and expertise. MRI-based brachytherapy needs to be validated extensively in a research environment at higher centers only.

FIGO stage IV: Patients without para-aortic lymph node involvement or distant metastasis should be treated radically as stage IIIB depending on the patient's general condition and tolerance. In the presence of para-aortic lymph nodes, the patients can be subdivided into two groups of less than 5 cm and more than 5 cm. In the patients with para-aortic lymph nodes less than 5 cm should be primarily treated with extended field radical radiotherapy followed by brachytherapy. The choice of addition of concurrent chemotherapy should be done considering the general condition and tolerance of the patient without compromising radiation treatment. It was felt that the addition of neo-adjuvant chemotherapy in this group of patients does not add to the advantage, but can be detrimental for future extended field radiotherapy,

which is important for long-term local control and symptom relief.

In patients with >5 cm para-aortic lymph nodes or distant metastasis, Neo-adjuvant chemotherapy (NACT) followed by concurrent chemo-radiation with extended fields if there is good response to chemotherapy is offered. However in patients with poor general condition and severe renal dysfunction, reasonable palliation can be achieved using palliative radiation and/or best supportive care.

Follow-up: Routine follow-up with clinical examination was recommended at 2-3 months in the first 2 years, at 3-6 months for 3-5 years, and yearly after that. The need for investigations at follow-up was also discussed. The PAP smear or biopsy was recommended only when clinically local recurrence was suspected. The routine use of pelvic CT or MRI or PET was not advised. These investigations can be done aptly in particular situation of suspected recurrence and planned for salvage surgery.

Specific situations

1. Stage IB2–IIA with pelvic lymph nodes (largest measuring < 3 cm): Options of concomitant chemoradiation (with/without prior lymph nodal dissection) or radical surgery + adjuvant radiation are acceptable options with NACT followed by surgery and adjuvant radiation with or without chemotherapy being still investigational. The evidence to differentiate to best out of these modalities is not available. But there is definite need for additional effort to address these nodes than routine radical radiotherapy or surgery alone. The choice depends on treating physician and the expertise available
2. Residual pelvic nodes after definitive chemoradiation in locally advanced carcinoma cervix: The house and the moderators were divided due to the absence of evidence. The practice of chemotherapy in these patients is not recommended as routine. The intent with chemotherapy is palliative in such cases. Also post-chemoradiation, surgery was seen to be difficult and with palliative intent. It was suggested that prior to radical chemoradiation, the surgical nodal dissection should be promoted. If newer radiation techniques are available, additional radiation doses to the residual nodes with caution may be used
3. Parametrium and lymph nodal boost: House was unanimous for the application of pelvic parametrial boost after EBRT 50 Gy in patients with locally advanced disease to a dose of at least 10 Gy in five fractions or equivalent. The validity of nodal and parametrial boost should be promoted in light of wider availability of more conformal techniques such as IMRT and IGRT.

DISCUSSION

Unresolved/controversial issues: There have been certain deficiencies in this consensus, as there are still many pertinent questions that cannot be answered adequately at present due to lack of evidence in literature. This conference tried to bridge the gap between the minimum standards of care and the highest centers, but still in some areas this was inevitable for the following situations:

1. Lack of wide availability of newer imaging technology
2. Lack of widespread surgical expertise in areas such as fertility preserving surgeries and ovarian transposition
3. Lack of modern radiotherapy facilities across the country
4. The number of trained doctors in all specialties is not equally distributed in various corners of the country.

This calls for a proper referral system (tier system) for patients and the training of staff at specialized centers should be viewed seriously.

Strengths of this consensus panel meeting

1. This was for the first time that centers from all over the country shared their practice guidelines at a common platform
2. The variation of thought and the concept that looked so wide apart across the country before this conference evolved in a mature manner to a common consensus of acceptance to all
3. Both national and international faculty was considerate toward the needs of different centers in different settings
4. There was ample space and opportunity for interaction between delegates, faculty, and students
5. Most of the decisions or recommendations were made after thorough discussions and uniform acceptance.

Drawbacks

1. It was realized that meetings should be conducted more frequently at the national level to raise general awareness regarding current evidence in literature
2. There was a universal lacuna of good indigenous data on various management related issues (eg, chemoradiation, early-stage surgery versus radiation, neo-adjuvant chemotherapy, and various modern techniques in surgery and radiation)
3. The pre-conference meetings for framing the questions and issues for discussions were not framed with participation of all centers.

Possible solutions

1. The pre-conference meeting or interaction through feedback forms by mails or emails can be done to collect the issues felt by various centers to be discussed. These can be later sorted by national and international faculty for discussion at the meeting

2. The introduction of post-conference meeting to frame newer questions to be answered by multicentric national level randomized trials can be done
3. The introduction of telemedicine or interactive courses with live demonstrations of newer techniques of surgeries and radiotherapy practices for less skilled professionals or students
4. The improvement of public, private and non-governmental organization (NGO) relations for futures integration of different centers in a three-tier referral system and upliftment of existing set-up at various centers.

CONCLUSION

The development of guidelines for management of cervical cancer in developing countries is very important as it is a major burden of cancer in these countries. These recommendations bridge the gap for optimizing the efficacy of available recourses and expertise in these countries with the currently available best evidence. This will allow centers to improve care and develop trials through collaboration which will answer important questions relevant in their practice. Further such meetings to address the drawbacks of this effort as benchmark are warranted.

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REFERENCES

1. Available from: <http://www.asccp.org/ConsensusGuidelines/tabid/7436/Default.aspx>. [Last accessed on 2012 Jan].
2. Available from: <http://www.sign.ac.uk/guidelines/fulltext/99/index.html>. [Last accessed on 2012 Jan].
3. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. [Last accessed on 2012 Jan].
4. Available from: <http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer>. [Last accessed on 2012 Jan].
5. Available from: <http://icmr.nic.in/guide/cancer/CcMG.pdf> [Last accessed on 2012 Jan].
6. Available from: <http://www2.cochrane.org/reviews/en/ab007406.html>. [Last accessed on 2012 Jan].

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