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Meeting Report

Cervical cancer state-of-the-clinical-science meeting on pretreatment evaluation and prognostic factors, September 27–28, 2007: Proceedings and recommendations

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ABSTRACT

Objectives. We choose to review current knowledge focused on pretreatment evaluation and prognostic markers in cervical cancer and make recommendations for future research.

Methods. We convened representatives from 10 of the member groups belonging to the Gynecologic Cancer Intergroup, members of the NCI's Gynecologic Cancer Steering Committee and its Cervical Cancer Task Force, investigators in the fields of imaging, translational research, gynecologic, radiation and medical oncology, patient advocates and NCI program staff for a two-day retreat.

Results. Clinical examination must remain mandatory for staging and evaluation. Measurements of tumor volume should also be mandatory. Magnetic resonance imaging provides the most accurate imaging measure of tumor volume. Identification of lymph node (LN) metastasis needs to remain a high priority. Promising data in FDG-PET warrants multicenter validation. Validated prognostic markers include tumor volume, uterine corpus extension, cervical lymph–vascular space invasion, extent of LN metastasis, current tobacco smoking, hemoglobin levels at time of diagnosis, and HPV-16 associated cancer. No 'high-technology' biomarkers are ready for validation in multicenter trials.

Discussion. Our current specimen collections are inadequate for discovery and validation of biomarkers. Current and future trials should mandate collection of fixed tissues as well as DNA/RNA. Effective cross-group collaboration is necessary to permit timely completion of phase III trials. Centers with appropriate expertise and resources in the developing world should be encouraged to participate in the current clinical trial networks.

Introduction

Cervical cancer remains the leading cause of cancer deaths among women in the developing world [1]. Despite major advances in prevention, screening, and treatment over the last century, each year approximately 250,000 women die of cervical cancer. The development of more effective treatment for women diagnosed with cervical cancer must remain a high priority. The United States National Cancer Institute (NCI), the Gynecologic Cancer Intergroup (GCIG) [2], the American College of Radiology, and the American Society for Radiation Oncology sponsored a cervical cancer "State-of-the-Clinical-Science" meeting September 27–28, 2007 to review current knowledge focused on pretreatment evaluation and prognostic markers in cervical cancer and make recommendations for future research. This manuscript summarizes the proceedings and conclusions of that SOTS meeting. Highlights of the recommendations are listed in Table 1. The participants in this cervical cancer meeting included members of the NCI's Gynecologic Cancer Steering Committee and its Cervical Cancer Task Force, investigators in the fields of imaging, translational research, radiation, gynecologic, and medical oncology, patient advocates, NCI program staff, and representatives of the clinical trials cooperative groups which form the international Gynecologic Cancer Intergroup [see Appendix A for participants, their home institutions and groups].

Pretreatment evaluation

Trial design and eligibility must take into account current standards of pretreatment evaluation of women with cervical cancer across various degrees of resource, as patients come from diverse settings even in the developed world.

Pretreatment evaluation has included physical examination, examination under anesthesia, imaging studies, surgical staging and prognostic markers. The goals of pretreatment evaluation include the accurate identification of local tumor extent, tumor volume, and metastatic spread, particularly to pelvic and para-aortic (PA) lymph nodes, so as to guide subsequent treatment decisions. In theory, prognostic and predictive markers might also provide guidance for treatment decisions. As noted below, to date, no single prognostic marker or combinations of markers has gained widespread acceptance in cervical cancer, nor have we yet identified effective treatment modifications appropriate for cancers found to have adverse prognostic markers.

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Table 1
Highlights of recommendations.

A.	Pretreatment evaluation should capture extent of local disease, tumor volume, and metastatic spread, particularly to pelvic and para-aortic lymph nodes.
B.	Pelvic and para-aortic lymph node dissection in surgical staging should be standardized.
C.	FDG-PET for staging, assessment of response to treatment, and surveillance should undergo multicenter validation and harmonization.
D.	Development and validation of predictive and prognostic biomarkers should be a high priority.
E.	The collection of tumor specimens and DNA/RNA from patients enrolled on clinical trials should be strengthened.
F.	Future phase III trials for women with cervical cancer will require strong intergroup collaboration, as well as inclusion of investigators and centers in the developing world.

In the past, pretreatment evaluation was made on the basis of FIGO staging, a clinical system based on findings at physical examination, chest radiograph, and intravenous pyelogram, as well as optional cystoscopy and/or proctoscopy. These evaluations did not incorporate attempted evaluation of loco-regional lymph nodes although their presence and location significantly alter outcomes. The FIGO Gynecologic Cancer Committee has been reluctant to incorporate more sophisticated imaging into staging for cervical cancer as many sites worldwide do not have routine access to CT, PET/CT, and MRI. Thus, they have relied upon older imaging studies and procedures which are much less expensive and thus more widely available. These older imaging studies and procedures do carry a high risk of under-staging and missing sites of disease, leading to under-treatment. Several recent reports have documented the weaknesses of current FIGO staging for cervical cancer, which does not take into account such strong prognostic factors such as tumor volume and retroperitoneal lymph node (LN) metastases. The clinical trialists participating in this meeting made clear the limitations of using FIGO staging alone for determining clinical trials eligibility. They recommended that investigators developing clinical protocols consider the addition of the appropriate pretreatment evaluation to capture such critical prognostic factors as tumor volume and LN metastases, some of which may be more precisely defined with computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/PET.

Meeting attendees agreed that clinical examination must remain mandatory for staging and evaluation. There was consensus that routine exam under anesthesia added little benefit to clinical examination. They recommended that measurements of tumor volume should be mandatory within the limits of accuracy of the pelvic examination and imaging. Para-aortic and pelvic LN involvement is clearly one of the most important prognostic markers, as well as one of the most important factors to influence treatment decisions. Identification of LN involvement, therefore, needs to remain a high priority in pretreatment evaluation. Additional adverse anatomic prognostic markers include extent of local disease, peritoneal spread, as well as presence of supraclavicular nodes in those with more advanced disease.

Surgical staging

Surgical evaluation of the retroperitoneal lymph nodes has been advocated as the "gold standard" to assess metastasis to pelvic and PA LNs. Laparoscopic extraperitoneal surgical staging (EPSS) has been put forward as the technique with the fewest complications. There was no consensus that surgical staging, while considered the gold standard, should be performed routinely except as part of prospective studies to assess the accuracy of more intensive nodal evaluation. Meeting attendees did advocate for a standardized surgical staging procedure with a clear definition of the extent of LN dissection to be performed routinely.

Sentinel node evaluation

At present, sentinel node evaluation has not been widely accepted in cervical cancer, although it has become common practice in breast cancer and melanoma. Although preliminary studies were promising, the largest prospective multi-institutional cohort study did not find adequate sensitivity to warrant adoption of SN assessment into standard practice [3–5].

Imaging evaluation in clinical trials

As mentioned above, there was reasonable agreement that future trials should routinely collect information on tumor volume and location of extent of nodal involvement. The consensus opinion was that MR provided the most accurate measure of pelvic tumor volume and favored its use, based on the prospective study comparing CT and MRI conducted jointly by the American College of Radiology Imaging Network (ACRIN) and the GOG) [6] (ACRIN 6651/GOG-0183). The promising data upon the ability of fluorodeoxyglucose (FDG) PET imaging to identify women with para-aortic and/or distant metastasis, delineate a metabolic tumor volume, assess tumor glucose metabolism as well as document response to treatment and progression of disease reported from Washington University also warrants validation in multicenter trials [7,8]. In addition, meeting participants concluded that studies to validate outcome of treatment decisions based on imaging modalities are needed.

There was consensus that imaging needs to be standardized across institutions. Clinical protocols must adequately describe the actual methodology of imaging specifications. Basic standards should include whether contrast material is used for CT or MRI, whether the techniques for pretreatment and post-treatment imaging are comparable, who reads the studies, how are the studies analyzed (qualitative versus quantitative), and how the imaging data is collected and analyzed centrally. Furthermore, there is ongoing evaluation of what represents a significant change in the FDG-PET signal for assessing tumor burden or therapeutic response. In this regard, the development of an Imaging Manual by the GCIG or several of its constituent groups would seem a high priority. Meeting participants repeatedly expressed concern about difficulties assuring reimbursement for imaging studies from third-party payers for women with cervical cancer, as well as the inconsistent availability of imaging modalities at treating institutions both between and within cooperative groups.

Currently open clinical trials of imaging among women with cervical cancer are shown in Table 2. As noted above, several of them rely upon surgical staging to determine the accuracy of imaging findings. Several of them are evaluating novel agents; ferumoxtran-10, is a synthetic super-paramagnetic iron oxide composed of dextran-coated iron oxide nanoparticles used as a MRI contrast agent, while 18 F fluoroazomycinarabinofuranoside (18FAZA), 18 F fluoromisoniadazole (FMISO), and copper-labeled diacetyl-bis (N4-methylthiosemicarbazone (CU 64-ATSM) were developed as PET tracers for hypoxia.

Imaging to guide brachytherapy for women with cervical cancer

Groups in the US and Europe have recently proposed recommendations to standardize image-guided cervical brachytherapy (IGBT) dosimetry [9,10]. Together, they have formed a Joint Trans-Atlantic 3-D Image-based Gynecologic Brachytherapy Group and developed two complementary trials. These include the *E*uropean Study on *M*RI-based 3D *bra*chytherapy in locally advanced *ce*rvical cancer (EMBRACE) and the proposed addition of image-guided brachytherapy to the RTOG phase II study of bevacizumab, definitive radiotherapy, and cisplatin in patients with previously untreated locally advanced cervical cancer (RTOG 0417). It appears that MRI is favored

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Table 2
Currently open imaging studies with eligibility restricted to women with cervical cancer.

Protocol IDs title	Cooperative group or institution
ACRIN-6671/GOG-0233/NCT00416455 Phase I/II study of the utility of fluorodeoxyglucose F18 positron emission tomography/CT scanning and ferumoxtran-10 MRI scanning prior to chemoradiotherapy in detecting retroperitoneal lymph node metastasis in patients with locoregionally advanced carcinoma of the cervix	American College of Radiology Imaging Network; Gynecologic Oncology Group
103017/NCT00199680 Interest of PET imagery with 18-FDG in the extension assessment of the cervical cancer	Central Hospital Regional Universitaire de Limoges, France
TMH/205/2004/CX_PET STUDY/NCT00193752 Para-aortic lymph nodal staging and evaluation of treatment outcome by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in advanced cancer cervix	Tata Memorial Hospital, Mumbai, India
EK Nr: 241/2006/NCT00388687 Hypoxia imaging with 18F FAZA. Prognostic impact in cervical cancer	Universitätsklinik für Innere Medizin I, Vienna, Austria
UW-6143/NCI00559377 Phase II study of positron emission tomography using fluoromisonidazole F18 and fluorodeoxyglucose F18 in assessing tumor hypoxia in patients undergoing therapy for newly-diagnosed stage III or IV cervical cancer	University of Washington Medical Center, Seattle, Washington
ACRIN 6682/NCT000794339 Phase II study of Copper CU 64-ATSM PET/CT scan in predicting prognosis and tumor behavior in patients newly-diagnosed with stage IB2-IVA cervical squamous cell carcinoma undergoing standard treatment with radiotherapy and cisplatin	American College of Radiology Imaging Network
2006-0153/NCI00631241 Analysis of parametrial lymph nodes as sentinel nodes in patients with cervical cancer	University of Texas MD Anderson Cancer Center

for assessing pelvic disease extent for IGBT, although MRI is not always available. Currently open trials evaluating imaging to guide brachytherapy are shown in Table 3.

Prognostic markers

Classical prognostic factors for cervical cancer have included stage, tumor grade, tumor size, depth of cervical stromal invasion in early disease, cervical lymph–vascular space invasion, and extent of lymph node metastasis. One recent large retrospective single-institution study showed that tumor volume and the presence or absence of uterine corpus extension, as determined by MRI, were more accurate prognostic factors than two-dimensional tumor size or stage [11]. More recently, current tobacco smoking, hemoglobin levels at time of diagnosis, race other than Caucasian and African-American, and HPV 16 have been identified as adverse prognostic factors [12–16]. Advancing age at time of diagnosis also conveys worsening prognosis.

An older marker, squamous cell carcinoma antigen (SCC), does appear to have prognostic value in cervical cancer [17,18]. To date, however, it has not been well-studied in prospective clinical trials, nor has its use been validated for treatment decisions in the management of women with cervical cancer.

There was consensus that no 'high-technology' biomarkers were ready for validation in multicenter trials. A list of biomarkers appropriate for further evaluation is shown in Table 4. A survey of hypoxia research included presentations on CA9, an endogenous marker for hypoxia , EF5 and 18F-EF5, immunohistochemical and PET-based exogenous hypoxia markers, respectively, and pimonidazole, a immunohistochemical marker of hypoxia [19–21]. After extensive discussion, the participants concluded that hypoxia must be seen as an exceedingly complex biologic factor. While direct measurement of hypoxia with the polarographic O2 probe (Eppendorf) has been considered the clear "gold standard", it cannot be can easily be used to evaluate hypoxia in large, multicentric and multinational clinical trials. In addition, the Eppendorf probe may not capture the important dynamic changing status of tumor and microenvironmental oxygen levels. A valuable prospective study would evaluate three or more different markers for hypoxia, including an endogenous marker, an exogenous marker detected by immunohistochemistry, and one detected by PET imaging. Inclusion of needle electrode studies, although potentially instructive, would likely be impossible to perform due to unavailability of equipment and patient reluctance to undergo placement of needle electrodes. The endpoints of interest would be inter-correlation of each marker to the other and to response to treatment, PFS, and survival, as well as with the other two markers of hypoxia.

Since hypoxia is a common phenomenon in cervical cancer and hypoxia drive angiogenesis as well as resistance to treatment, markers of angiogenesis are important. In a limited number of studies, overexpression of either VEGF or EGFR have been associated with worse survival for women with cervical cancer [22,23]. Both biomarkers deserve further evaluation, and both would seem to be promising therapeutic targets.

Potential biomarkers worthy of exploration include cervical cancer stem cells, circulating tumor cells, microRNAs, mutations predicting for sensitivity to EGFR inhibition, mutations predicting for sensitivity

Table 3
Currently open trials evaluating imaging to guide brachytherapy for women with cervical cancer.

Protocol ID#/acronym title	Cooperative group or institution
MMH-I-S-260/NCT00319462 Localization of point A in cervical cancer	Mackay Memorial Hospital, Taipei, Taiwan
GY-O3-0018/NCT00124423 Megavoltage CT (MVCT) imaging for intracavitary radiation treatment in cervix cancer	Cross Cancer Institute at University of Alberta, Edmonton, Canada
NCI00571415 Image-guided adaptive radiotherapy for cervix cancer; patient image acquisition	Virginia Commonwealth University, Richmond, Virginia, USA
EMBRACE A European study on MRI-guided brachytherapy in locally advanced cervical cancer	Coordinating center: Medical University of Vienna, Vienna, Austria; endorsed by Groupe Européen de Curiethérapie/European Society for Therapeutic Radiology and Oncology

Table 4
Potential biomarkers appropriate for consideration in clinical trials for women with cervical cancer.

Squamous cell carcinoma antigen (SCC)
CA9 (endogenous hypoxia marker)
EF5 (immunohistochemical hypoxia marker)
Vascular endothelial growth factor (VEGF)
Epidermal growth factor receptor (EGFR)
Mutations predicting sensitivity to EGFR inhibition
Mutations predicting sensitivity to cisplatin
Cancer stem cells
Circulating tumor cells
MicroRNAs
Gene expression profiles

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to cisplatin, and validated gene expression profiling based on subsets of gene groupings involved in cancer progression (i.e., proliferation, cell division, apoptosis, etc.). Close collaboration between clinical trials cooperative groups and translational research laboratories is needed to foster development and validation of biomarkers in cervical cancer.

Selection of patients for less radical surgery

One recurrent question was how best to use data from pretreatment studies and intra-operative findings to accurately identify the extent of local disease and other know prognostic factors, such as lymph–vascular space invasion. This should enable selection of patients more appropriate for less radical surgery, including fertility-conserving surgery. A multi-institutional Japanese study, for example, used MRI to identify women with FIGO stage IA1 cervical cancer appropriate for conization [24]. Although the relatively small number of patients potentially appropriate for fertility-conserving surgery precludes randomized phase III trials, novel approaches toward pre-treatment evaluation warrant multi-site phase II feasibility and outcome studies.

Specimen collection

There was consensus that our current specimen collections are inadequate for discovery and validation of biomarkers. The largest tissue collections associated with a clinical trial are those collected with GOG 219, a phase III trial evaluating tirapazamine to standard chemoradiation among women with locally advanced cervical cancer (130 specimens) and RTOG 0128, a phase II trial evaluating celecoxib with chemoradiation among women with locally advanced disease (80 specimens). Current and future trials should mandate collection of formalin-fixed, paraffin-embedded tissues as well as DNA/RNA. Cervical cancer does provide a greater opportunity for specimen collection at time of diagnosis and during chemoradiation or neo-adjuvant chemotherapy than many other solid tumors due to the relative ease of obtaining a biopsy. A virtual biorepository should link information on the tissue collections currently available within the cooperative groups, cancer centers, and SPOREs. In addition, participants noted that stored specimens may not adequately address future questions, requiring prospective specimen collections to address specific questions.

International and intergroup participation

The falling incidence of cervical cancer in the developed world underscores the importance of close intergroup and international participation in cervical cancer treatment trials. Completion of phase III trials in a timely manner requires effective cross-group collaboration. In addition, centers with appropriate expertise and resources in the developing world should be encouraged to participate in the clinical trials networks currently based primarily in the developing world. In order to ensure that treatment advances are translated rapidly into settings with lower resources, we also need to strengthen the current networks of trialists conducting studies in such sites, such as the International Network for Cancer Treatment and Research and the International Atomic Energy Agency. It will also be important to strengthen communication between trialists in high- and low-resource settings, so that trials in both settings are as complementary as possible. Both telemedicine and in-person meetings can facilitate such collaborations.

Statistical considerations

Randomization in phase III trials should minimize potential for selection bias. In the case of cervical cancer, as noted above, access to imaging studies and surgical staging may vary by the resources at site of evaluation, practice patterns and expertise, as well as an individual patient's insurance coverage or lack thereof. One statistical approach which may be helpful in this setting is adaptive stratified randomization, which compares the distribution of stratification factors for patients already in a trial before assigning a patient to a therapeutic arm. Subgroups should be defined beforehand, based on characteristics known at randomization, which may include known biological mechanisms or information derived from evaluation of prognostic factors during trial entry. Statistical designs for establishing the validity and utility of imaging markers remain in early stages of development.

Defining eligibility for trials

The participants wrestled with the issue of how best to define eligibility for multicenter and multinational trials given the diversity of access to imaging resources. Even among centers committed to clinical trials for women with cervical cancer, imaging capabilities vary greatly by institution at any one point in time. Although promising new technologies, such as MRI and PET, do become more widely available over time, expertise at interpreting these scans may well differ between sites with greater or lesser experience using the new technology. In addition, the PET imaging scanners and agents may not be uniformly available for international trials. Similarly, surgical expertise varies by institution. In addition, institutional resources, institutional practice, and third-party payer policies may restrict the availability of certain imaging studies or surgical staging procedures for women with cervical cancer. Trial budgets may need to support the costs of studies or procedures which are not part of the institution's standard of care. As noted above, adaptive stratified randomization may be a helpful strategy to address these issues.

Future cervical cancer intergroup meetings

Subsequent cervical cancer intergroup meetings will focus on issues related to treatment of cervical cancer as well as symptom management and survivorship among women treated for cervical cancer.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Appendix 1

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