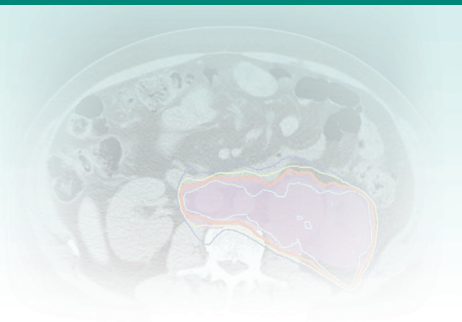

Overview

Gillian M. Thomas

This overview provides an introduction to the chapters on specific gynecologic tumors that follow, including discussions of cancer of the cervix, uterine corpus, vulva and vagina, and ovary. It highlights important clinical issues and areas of controversy. The etiologic and epidemiologic differences among these tumors are addressed in the relevant chapters. Progress toward improving outcomes is slow but where gains in the therapeutic ratio have resulted they are addressed for each tumor site.

Gynecologic cancers continue to be staged using the FIGO staging system. In 2009 the FIGO staging system was modified from the previous version of 1988. Each sites specific chapter will note the differences. Caution needs to be taken because changes in the FIGO staging system may not allow direct comparisons of outcomes by stage between the new and the old systems.

Conformal radiotherapy techniques including intensity-modulated radiation therapy (IMRT) and image-guided brachytherapy (IGBT) appear in some situations to have improved the therapeutic ratio of radiation principally by decreasing dose received by normal tissues and therefore an expectation for decreasing incidence of acute and late complications. Its implementation for gynecologic cancers has lagged behind that in other tumor sites for a variety of valid reasons. Caution around the possibility of geographic miss of tumor because of imposed dose constraints for normal tissues must be exercised; for cervical cancer close margins in tumor may result in underdosage if internal organ motion and changing tumor configurations are not taken into account.[1] Consistent guidelines for the use of IMRT at least in the postoperative adjuvant setting for endometrial and cervical cancer are published and are undergoing revision. This has facilitated wide uptake.[2] It is critical to deliver acceptable radiation volumes and dose, that strict measures of quality assurance for physics, dosimetry, and tumor volume delineation be practiced.

Promising novel therapies are currently being investigated in Phase I, Phase II, and some Phase III studies in cervical, ovarian, and endometrial cancers. These therapies are based on the identification of specific pathways of tumor progression that can be targeted for interruption (e.g., angiogenesis and the identification of "druggable" molecular targets).

In addition to this direction of development are the multiple progressive steps made in novel imaging techniques. It is anticipated with optimism that techniques such as positron emission tomography–computed tomography (PET-CT) scanning, magnetic resonance diffusion imaging, and spectroscopy will enable a conjunction of anatomic and functional imaging to more accurately define tumor volumes and that these techniques will act as both predictive and response biomarkers as has been observed in cervical cancer.[3,4]

Disseminated metastatic disease remains a problem but the utility of standard chemotherapeutic agents in various combinations, doses, and strategies has leveled out and is far from optimal. Thus, the identification of new biomarkers and targeted molecular therapies to these markers constitutes a rational new research direction for the management of disseminated disease. The ultimate anticipation from these advances is that individual patients or small groups of patients expressing specific biomarkers may be treated with a targeted therapy most suited to those individuals and their respective tumors. It is hoped that cancer research will lead to an era of "personalized" medicine. The splitting of population into smaller groups however, makes the conduct of Phase III trials extremely difficult.

CERVICAL CANCER

In cervical cancer, hypoxia and angiogenesis form part of a common pathway to cancer development and progression. The antiangiogenic agent, bevacizumab, was recently reported in a Phase III trial in recurrent, persistent or metastatic disease to improve overall survival (OS) in a selected population by 3.7 months compared to standard chemotherapy (median OS 17.0 versus 13.3 months, $p = 0.004$).[5]

Although Phase II data have demonstrated the tolerability of combining bevacizumab with definitive pelvic irradiation and concurrent cisplatin, recent discussions with the National Cancer Institute (NCI) and the pharmaceutical producers of bevacizumab suggest that these data will not be used to proceed to a larger randomized Phase II or Phase III trial with this agent.[6] Currently a randomized Phase II trial is proceeding with the agent triapine (ribonucleotide reductase inhibitor that inhibits radiation damage repair) added to chemoradiation.[7] The paucity of patients with cervical cancer in the developed world means that future trials to advance outcomes in locally advanced cervix cancer will of necessity be international in scope. At the present time, the international "outback trial" is proceeding, which examines the role of adjuvant chemotherapy after standard chemoradiation to the pelvis.[8] It is unlikely that further large-scale trials in locally advanced cervical cancer will be conducted until this trial completes accrual.

Although IMRT is being used widely in adjuvant treatment of cervical cancer, its role in the intact cervix is still not widely accepted given the necessity for strict quality assurance measures to ensure tumor coverage of the mobile target of the cervix and uterus.

ENDOMETRIAL CANCER

In endometrial cancer in addition to similar exploration of angiogenesis inhibitors and tyrosine kinase inhibitors is the exploration of MTOR inhibitors including temsirolimus, everolimus, and deforolimus. Forty to 80% of women with type I endometrial carcinoma have a mutation in PTEN, which up regulates MTOR activity making its inhibition a rational target. Significant response rates have been reported in patients who are chemotherapy naïve with advanced or recurrent endometrial cancer although response in this study is not correlated with PTEN status.[9] Various combinations of these MTOR inhibitors with chemotherapy or with other biologic agents are being conducted.

The relative roles of adjuvant chemotherapy and radiation in locally advanced disease remain unclear. The pending results of completed randomized Phase III trials should clarify this considerably.

VULVAR AND VAGINAL CARCINOMA

Vaginal carcinoma treatment continues to be based on extrapolations of information from cervical cancer with its similar herpes papillomavirus (HPV) etiology. Refinements in the delivery of irradiation using conformal methods such as IMRT, at least for boosting locally advanced disease where brachytherapy is inappropriate, may help to decrease potential toxicities of radiation therapy.

The major advance in the treatment of vulvar cancer with definitive or neoadjuvant chemoradiation has been the ability also to use more conformal radiation techniques. Vulvar cancers are often difficult to image on magnetic resonance imaging (MRI) so the importance of merging planning information from scans as well as the clinical appearance of the tumor is vital. It continues to be widely important to encompass the entire tumor rather than compromising tumor volume coverage to further spare some adjacent normal tissues. Unfortunately, no level-1 evidence is available to clearly define tumoricidal doses for definitive chemoradiation. In this highly radiosensitive tumor, application of basic principles with regard to delivering the irradiation component of treatment must apply.

OVARIAN CANCER

In heritable ovarian cancer, those with *BRCAI* or *BRCAII* mutations, poly ADP ribose polymerase (PARP inhibitors), may specifically target tumor cells that are deficient in their ability to repair DNA double-stranded breaks. Several PARP inhibitors are currently under investigation in *BRCA*-deficient cancers. Early results from Phase II trials are encouraging.

In advanced ovarian cancer results of two Phase III studies were recently reported.[10,11] The combination of bevacizumab and chemotherapy followed by maintenance bevacizumab alone modestly increased the progression-free survival by 3.8 months and 1.7 months compared to the use of chemotherapy alone or with concurrent bevacizumab. This finding has major societal implications not only for patients with ovarian cancer but also for future implementation of widespread use of expensive targeting agents, which may provide some advantage in progression-free survival, not as yet in overall survival but may not be affordable for general use.

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