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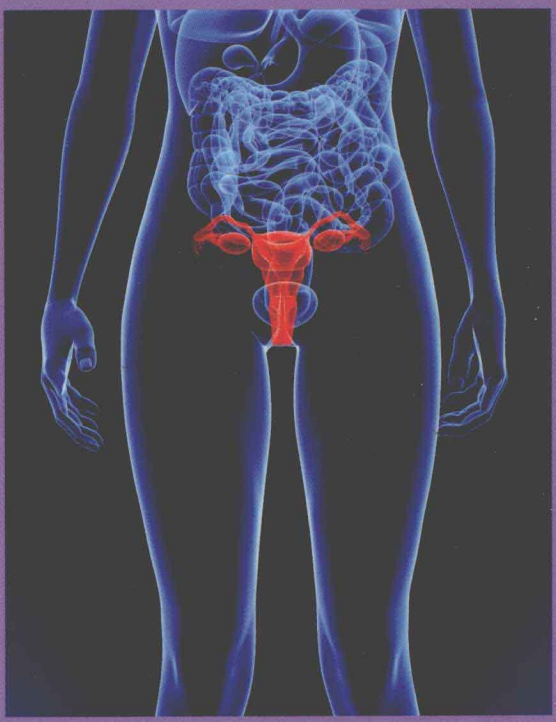
Dx/Rx

Dx/Rx: Gynecologic Cancer

Don S. Dizon, MD, FACP and
Susana M. Campos, MD, MPH



Series Editor: Manish A. Shah

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Gynecologic Cancer

Don S. Dizon, MD, FACP
Women & Infants' Hospital
The Warren Alpert Medical School of
Brown University
Providence, Rhode Island

Susana M. Campos, MD, MPH
Dana Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

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Dedications

I am grateful to Susana for agreeing to undertake this huge endeavor and to the folks at Jones and Bartlett (especially Chris Davis) for this opportunity. Once more, I am indebted to my parents, Mody and Inday Dizon, for their love and encouragement. I dedicate this book to my family: my sisters, Michelle, Mae, Precy, and Marie; my spouse, Henry; and our kids, Isabelle, Harrison, and Sophia. I also dedicate this book to my mother-in-law, Marilyn, who helps run our hectic household and allowed me to finish this book, and to Nick Hemond, who I hope, as an intern in women's oncology, will find inspiration and promise in what he witnesses to help him realize that we can always do more. Finally, it is dedicated to the women, cancer survivors all, who have allowed me to participate in their care and welcomed me into their lives, amidst some of the most trying times. I hope I have served you well, because you have always been the source of my continued passion as we strive for a cure to these tumors.
Don S. Dizon, MD, FACP

I dedicate this book to my parents, Maria and Humberto Campos, who had the wisdom to understand that the future lies in the education of the young and old. As immigrants to this country, their focus was one that centered on hard work and commitment to education. In addition, this book is dedicated to the patients who continue to educate their healthcare providers on the need for better therapeutics that effectively balance treatment with quality of life. I am indebted to my colleague Don Dizon who continues to share with me innovative projects aimed at moving the field of gynecological cancers forward. It is our goal that this text will ignite the same passion in others pursuing the ultimate goal: a cure for patients with gynecological malignancies.
Susana M. Campos, MD, MPH

Foreword

The tides have changed. In the past several years there has been considerable interest, and hence, progress in the prevention, diagnosis, surgical management, and treatment of gynecological malignancies. Basic diagnostic tools and therapeutics have been replaced by provocative and innovative measures that allow a personalized approach to patient management.

An understanding of cellular signaling pathways involved in carcinogenesis and tumor growth have allowed the development of prevention strategies and the development of targeted cancer drugs. To this end, various targeted therapeutics have been recently explored in the management of gynecological cancers. These include monoclonal antibodies to epidermal growth factor receptors (EGFR), small molecule tyrosine kinase inhibitors, monoclonal antibodies directed at the vascular endothelial growth factor (bevacizumab), and the small tyrosine kinase inhibitors that target the vascular endothelial growth factor receptor. In addition, several other agents have come forth as potential therapeutic agents in the management of ovarian cancer. These include monoclonal antibodies to the folate receptor, triple angiokinase inhibitors, PARP inhibitors, aurora kinase inhibitors, inhibitors of the Hedgehog pathway, folate receptor antagonists, and MTOR inhibitors.

The introduction of novel therapeutics has been paralleled by successes in other disciplines involved in the treatment of gynecologic cancers. Continuing with a movement towards minimally invasive procedures, robotic surgical systems are finding a place in the standard armamentarium for the surgical gynecologic oncologist. Data is already available indicating it is not only comparable to both laparoscopic and open surgery, but also allows for less postoperative

complications and potential morbidity. Likewise, the utility of intensity modulated radiation therapy continues to develop in the management of certain gynecological malignancies.

At the forefront is research centered on the prevention of gynecological cancers. Advances in the understanding of the epidemiology of cervical cancer coupled with innovative tools have produced the HPV vaccine, a therapeutic capable of the prevention of significant morbidity and mortality in women. It is hopeful that novel approaches, potentially relying on genomics and proteomics, may lead to the development and validation of a protein-based signature for the detection of ovarian cancer.

This volume brings together an emphasis in the multidisciplinary focus that is required to effectively manage these diseases. Experts in the field of gynecologic cancer have collaborated in this text in order to increase the understanding of new treatment paradigms in women's pelvic malignancies, and to increase knowledge of new technologies and procedures to stimulate interest in and improve care of women with gynecologic cancers.

Our continued success lies in our commitment to the development and participation in clinical trials. Only then will we walk forward...

Susana M. Campos, MD, MPH
Don Dizon, MD, FACP

Editor's Preface

I would like to welcome you to the DX/RX Oncology Series, and in particular to this volume, DX/RX: Gynecologic Cancer, which focuses on the diagnosis and management of a large and diverse group of malignancies including ovarian epithelial cancers, germ cell tumors, endrometrial cancer, cervival cancer, and many more. The management of these diseases encompasses coordinated efforts from gynecological surgical oncology, radiation oncology, and medical oncology. As with all volumes in this series, this comprehensive handbook is organized and presented in an easy-to-read, succinct bulleted format with summary tables. The management is organized practically into early and advanced disease settings, with discussion of novel targeted therapies as well. Drs. Dizon and Campos have put together a remarkably easy to grasp, comprehensive overview of the management of gynecologic malignancies. You will not be disappointed—there truly is "something for everyone" in this volume of the DX/RX Oncology Series.

Manish A. Shah, MD

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SECTION 1

Cancers of the Ovary

CHAPTER 1

Epithelial Ovarian Cancer

Epidemiology[1]

- Accounts for nearly 3% of all cancers among women
- Over 20,000 new cases are diagnosed each year in the United States
  - Of all the gynecologic neoplasms, it is associated with the highest mortality rate of any gynecologic cancer: Over 5,000 women die of this disease annually.
- Risk increases with age and peaks in the late 70s
- Approximately 81% of cases are diagnosed with advanced (stage III/IV) disease
- Incidence higher among the Caucasian population (17.9/100,000) versus African American population (11.9/100,000)
- Distinct geographic variations with the highest incidence in industrialized countries; Japan a notable exception (3.0/100,000)
- Overall 5-year survival rate is 45%
- 30% in patients with distant disease at diagnosis

Ovarian Cancer Risk Factors

- Factors associated with an increased risk:
  - Advanced age
  - Family history
  - Nulliparity
  - Estrogen replacement
  - Talc powder
  - Pelvic inflammatory disease
  - Living in industrialized Western countries
  - Being of Jewish descent

- Factors associated with a decreased risk:
  - Lactation
  - Oral contraceptives
  - Parity
  - Reproductive surgery (tubal ligation, oophorectomy/hysterectomy)
  - Diet high in carotene
  - Low alcohol use
  - Low lactose intake

Hereditary Ovarian Cancer

- Only 5% to 10% of cases
- Hereditary breast/ovarian cancer syndrome
  - BRCA1 and BRCA2 mutations
  - BRCA1 and BRCA2 classified as tumor suppressor genes that play a role in repair of oxidative damage to DNA
  - BRCA1 and BRCA2 located on chromosomes 17 and 13, respectively
  - Inheritance of these mutations confers an increased lifetime risk for ovarian cancer:
    - BRCA 1 = 20% to 60%
    - BRCA 2 = 10% to 35%

Signs and Symptoms

- Abdominal bloating
- Increased abdominal size
- Urinary symptoms
- Early satiety
- Changes in bowel habits
- Pelvic pain
- Nausea
- Shortness of breath
- Vaginal bleeding
- Abdominal nodules

Screening

- PLCO study (Prostate, Lung, Colorectal, and Ovarian Trial) examined the impact of screening patients with serum CA-125 levels and transvaginal ultrasound (TVUS)[2]
  - Among 34,000 women screened, the compliance was 83% at time 0 and 83% after the third round of screening
  - Transvaginal ultrasound screens that were positive declined during screening from 4.6 to 2.9 to 3.4; screening rates for cancer antigen 125 (CA-125) positivity remained constant
  - Of 80 ovarian cancers detected during four rounds of screening, 60 discovered during screening for a positive predictive value range between 1% and 1.3%
  - Majority of screened cases still advanced at diagnosis
  - Combining CA-125 to ultrasound: positive predictive value still only 23.5%
  - Not deemed an effective strategy for use in the general population
  - No technique is specific as a screening tool but continued research on serum proteomics is ongoing
- The United Kingdom Trial in Ovarian Cancer Screening (UK-TOCS) enrolled over 200,000 women between 2001 and 2005, who were randomized to no screening versus screening by CA-125 and transvaginal ultrasound (combined screening) versus transvaginal ultrasound alone.[3]
  - Compliance was improved with combined screening as compared to ultrasound alone, 99% versus 95%, respectively; combined screening was also associated with a lower chance that women would need to undergo a more intensive evaluation compared to screening by ultrasound alone (0.3% versus 3.9%, respectively)
  - Among women undergoing screening: 0.2% undergoing combined screening underwent surgery; 1.8% who underwent ultrasound alone had surgery

- Surgery picked up 87 primary cancers with 42 detected among women undergoing combined screening and 45 among those undergoing ultrasound alone; invasive ovarian cancer picked up by combined screening more often than on ultrasound with 33 and 25 cancers discovered, respectively. However, a significant number of cases were advanced at diagnosis.
- Still too early to determine if screening also improved survival in women ultimately diagnosed with ovarian cancer

Diagnosis

- Early diagnosis remains difficult as symptoms are nonspecific; however, a study from the University of California at Davis compared the symptoms of women over 65 who were ultimately diagnosed with ovarian cancer to symptoms in a matched cohort with breast cancer and a third group without a diagnosis of cancer.[4] The following were more common in women with ovarian cancer, and were present 1–3 months before diagnosis:
  - Abdominal pain (odds ratio [OR], 6.0; 95% confidence interval [CI], 5.1–6.9)
  - Gastrointestinal symptoms (OR 2.3; 95% CI, 1.8–3.0)
  - Pelvic pain (OR 4.3; 95% CI, 2.8–6.7)
- Consider these target symptoms—if persistent require workup to rule out this diagnosis
- Workup requires: physical and pelvic examination, CA-125, and pelvic imaging, including pelvic ultrasound or CT scan

Pathology

- Approximately 90% of all ovarian malignancies are of epithelial origin. Histologic subtypes include:
  - Papillary serous carcinoma
  - Clear cell
  - Mucinous carcinoma
  - Endometroid carcinoma
  - Carcinosarcoma