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Series Title: Developments in Gynecologic Oncology

OVARIAN CANCER

Edited by
Malte Renz

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Ovarian Cancer

This volume is the first of a new series dedicated to the historical developments in topics that are central to gynecological cancers. The six essays on ovarian cancer included here provide context from the perspective of experts in the field, illustrating what is required for the development and realization of medical innovation: (i) time consuming, decades-long basic research of the tumor genome and cancer cell biology, which may then set the basis for dramatic accelerations of recent therapeutic options; and (ii) the diligent assessment and fine-tuning of surgical techniques and concepts of patient prehabilitation and rehabilitation.

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Preface

> Two things are necessary for our work: tireless perseverance and the willingness to throw away something you have put a lot of time and effort into.
>
> Albert Einstein (1879–1955)

With this preface to *Ovarian Cancer* – Volume 1 in a series on developments in cancers from CRC Press – I am delighted to introduce an entirely new series of essays dedicated to the historical developments of topics that are central to gynecological cancers. We start the book series with six essays on ovarian cancer. These essays are intended to shed light on historic developments and provide context to central topics in ovarian cancer from the perspective of experts in the field. Beyond historical developments in medicine, this first collection of essays illustrates what is required for the development and realization of medical innovation: (i) time consuming, decades-long basic research of the tumor genome and cancer cell biology which may then set the basis for dramatic accelerations of recent therapeutic options; and (ii) the diligent assessment and fine-tuning of surgical techniques and concepts of patient prehabilitation and rehabilitation.

The essays collected here address the following aspects of ovarian cancer: screening, surgical treatment, prehabilitation and rehabilitation, genetic predisposition, targeted therapy exemplified by PARP inhibitors, and immunotherapy. Robert Bast et al. describe the efforts to establish efficient screening programs for ovarian cancer since the discovery of the tumor marker Ca125 by Dr. Bast. Robert Bristow et al. provide the available evidence for cytoreductive or debulking surgeries in ovarian cancer. Susan Domchek et al. give an account of the historical developments of hereditary breast and ovarian cancer syndrome. Jonathan Berek et al. recount breakthroughs and limitations in targeted therapy leading to PARP-inhibitor use. Oliver Dorigo et al. outline recent immunotherapy developments. Finally, Jalid Sehouli and co-workers lay out plans for prehabilitation and rehabilitation programs that include and expand existing ERAS programs.

I hope that these essays provide pearls of knowledge and context for those who aim to continuously study gynecologic oncology. These essays are synopses of the developments over time in a specific field, just like short monographs. This essay series is meant for those who study gynecologic oncology,

clinical fellows and experienced physicians as well as clinical and basic researchers. They may provide an improved understanding and give a glimpse into the temporary and at times provisional nature of medical knowledge and its constant flux. And maybe the insights provided here, including the insights into the temporality of research and clinical achievements, will inspire new avenues and developments in ovarian cancer.

Malte Renz

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1 Early Detection of Ovarian Cancer

An Update

Chae Young Han, Zhen Lu, Karen H. Lu, Jacob S. Bedia, Anna Lokshin, Karen S. Anderson, Charles W. Drescher, Steven Skates, and Robert C. Bast Jr.

1.1 BACKGROUND

This year in the United States 19,710 women will develop ovarian cancer and 13,270 will die from the disease (1). Worldwide, more than 300,000 women are afflicted annually (2). Poor outcomes for women with ovarian cancer relate to detection of the disease at a late stage (III, IV) in more than 70% of cases and to the persistence of drug-resistant cancer cells after primary surgery and chemotherapy, often in a dormant state on the surface of the peritoneal cavity. Earlier detection of ovarian cancer could improve clinical outcomes. When limited to the ovaries at diagnosis (Stage I), 93% of ovarian cancer patients survive 5 years (3). Even when disease has spread to the pelvis (Stage II),

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5-year survival exceeds 70%. By contrast, when cancer has metastasized to the abdominal cavity (Stage III) or into the parenchyma of the liver or above the diaphragm (Stage IV), 5-year survival slips to 31%. At present less than 30% of ovarian cancers are diagnosed in early stage (I–II). Computer models indicate that mortality could be reduced by 10–30% if a greater fraction of ovarian cancers were diagnosed in early stage (4), provided that a stage shift is associated with decreased mortality. As the prevalence of ovarian cancer is 1 in 2,500 for postmenopausal women at average risk for the disease, a successful screening strategy must have both high sensitivity and very high specificity. To achieve an adequate positive predictive value (PPV) of 10% with no more than 10 operations per ovarian cancer detected requires a sensitivity of ≥ 75% for asymptomatic disease and a specificity > 99.6% (5). This performance level of such a high specificity is difficult to achieve, particularly with a single screening modality.

1.2 DISCOVERY AND DEVELOPMENT OF CA125

Attempts to detect ovarian cancer at an earlier stage have used transvaginal ultrasound (TVS) and the blood biomarker CA125. The discovery of CA125 is a study in serendipity. In the early 1970's, the tuberculosis vaccine *Bacillus calmette* Guerin (BCG), an attenuated strain of bovine tubercle bacillus, was used to treat patients with melanoma, where intratumoral injection of BCG produced intense granulomatous inflammation and regression of cutaneous melanoma metastases (6, 7). In some patients, non-injected lesions regressed consistent with the induction of systemic immunity. Rapp and Zbar obtained formal evidence for the immune adjuvant activity of BCG using a guinea pig hepatoma model where intratumoral injection of BCG cured subcutaneous transplants and lymph node metastases, rendering animals specifically immune to re-challenge (8). Clinical application of BCG was extended to intravesical administration to treat superficial bladder cancers (6, 7).

As ovarian cancer grows on the peritoneal surface, intraperitoneal administration of BCG might eliminate small volumes of residual disease that remained after cytoreductive surgery and combination chemotherapy. Risk of progressive infection, however, discouraged use of living BCG for intraperitoneal therapy. Heat-killed *Corynebacterium parvum* provided similar antitumor activity after intraperitoneal injection without the risk of infection. Knapp and colleagues developed a syngeneic murine ovarian cancer transplant model, where cancer cells could grow intraperitoneally, block diaphragmatic

lymphatics and produce ascites, resembling human ovarian cancer (9). Treatment with rabbit antibodies against the murine ovarian cancer prolonged survival. Addition of *C. parvum* proved synergistic, enhancing median survival and producing long term survivors (9). The synergistic effect of antibody and *C. parvum* related to antibody dependent cell mediated cytotoxicity (ADCC) where the *C. parvum* attracted and activated immune effectors that could bind to and kill antibody-coated cancer cells (10).

Translating this model to the clinic, intraperitoneal administration of *C. parvum* through a dialysis catheter produced a 32% objective response rate in patients with small volumes of recurrent ovarian cancer with two CR's lasting 5 and 12 months (11). Importantly, intraperitoneal *C. Parvum* attracted and activated effectors for ADCC, paralleling results in the murine model.

To prepare adequate amounts of specific antibody, the then new technology developed by Kohler and Milstein was used to develop the first monoclonal antibodies reactive with human ovarian cancer. The 125th promising clone (OC125) bound to ovarian cancer cell lines, but not to a B lymphocyte cell line from the same patient (12).

The antigen recognized by OC125, designated Cancer Antigen 125 (CA125), was expressed by 80% of ovarian cancers, suggesting that a large fraction of patients might benefit from OC125 treatment. CA125 was, however, shed from the cancer cell surface. Shed antigen could neutralize the effect of the OC125 antibody before it bound to ovarian cancer cells, preventing enhanced immunotherapy with *C. parvum*. Shed antigen might provide a biomarker for disease burden.

CA125 was found to be a mucin (MUC16) ranging in molecular weight to 5 million Daltons (13). For ovarian cancers that express CA125, up to a million copies are found on the surface of each cancer cell. CA125 is cleaved and shed from the cancer cell surface by proteolysis and finds its way to the bloodstream. The presence of > 60 identical 40 KD tandem repeats on CA125's extracellular domain facilitated the development of a homologous double determinant immunoassay using the OC125 antibody. Given multiple identical epitopes on each CA125 molecule, the same OC125 antibody could be used to trap antigen on a bead and to detect antigen that had been trapped (14). O'Brian subsequently developed the M11 antibody against a distinct epitope on MUC16, permitting the development of a heterologous double determinant assay with less day-to-day variation using this assay (15), CA125 levels are elevated in more than 80% of ovarian cancers. CA125 tracks response to treatment and recurrence in more than 70% of patients, rising 4 months before signs and symptoms of recurrent disease (16). In 1987 CA125 was approved by the US FDA for detection of persistent disease after primary surgery and chemotherapy. In addition to monitoring response to treatment and detecting persistent or recurrent disease, CA125 has been incorporated into the ROMA and