Article published online: 2022-02-15

Gynecologic Oncology: On the Shoulders of Giants

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Ind J Med Paediatr Oncol 2022;43:34–39.

Abstract

Gynecologic oncology is considered a new field, but its roots are buried deep in the past. As with other tumors, the earliest progress in modern times started with anesthesia and surgery. This was followed by landmark achievements in pathology, cytology, radiotherapy, chemotherapy, tumor virology, generation of high-quality evidence, and, more recently, genetics and genomics. Some of the most notable progresses in gynecologic cancers have been made by integrating the expertise of various specialties in multimodality management approaches. In this article we review the most important milestones in the history of gynecologic oncology and acknowledge the contributions of pioneers who made these possible.

Keywords
- gynecologic oncology
- history
- treatment

Introduction

Newton once said and we quote, "If I have seen further, it is by standing on the shoulders of giants." The history of gynecologic oncology is fascinating and it is unfortunate that most clinicians know little about it. Hence, we decided to write this article to trace and review the historical aspects of this subject and acknowledge the invaluable legacy of the giants.

Pre-Christian Era

There are very few descriptions of gynecologic cancers, specifically from this era. The scriptures of Hippocrates the father of medicine, mention tumors of uterus only in passing. At that time, in our part of the world, the great sages, Charaka and Sushruta, in their respective treatises (*Samhita*) described benign and malignant tumors as *granthi* and *arbudha*, respectively,[1,2] and elaborated on various treatments for these conditions.

Common Era

The evolution of gynecologic oncology is closely tied to the invention of vaginal speculum. Prior to the invention of this relatively simple but vital instrument, it is said that many women went to their graves with the site of disease undiscovered. The earliest description of a speculum and its use to visualize ulcerating lesions of the uterine cervix has been found in the works of the Greek physician Soranus, dated around 2 CE.[3] The commonly used speculums today, Sim's and Cusco's, were developed in the early nineteenth century.[4,5]

Modern Era

Surgery: Lion's Heart with a Lady's Touch

There were rapid advancements in surgical techniques with the development of anesthesia and after the performance of first successful surgery under anesthesia in 1846.[6] This

DOI https://doi.org/10.1055/s-0042-1742658.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

brought about a paradigm shift in the management of many diseases, including cancer. Sir James Simpson is credited with application of this novel discovery in gynecologic procedures. He performed the first amputation of cervix for a large warty growth on the cervix, assumed to be cervical cancer.[7]

Wilhelm Alexander Freund, in the late nineteenth century, was the first person to report successful removal of cervical cancer by an abdominal hysterectomy. However, in that era, this procedure had a 25 to 30% risk of operative mortality.[8] This mortality was considerably reduced by Schauta's technique of vaginal hysterectomy.[9,10] This technique found resurgence later, when extraperitoneal lymphadenectomy was added to it by Professor Subodh Mitra.[11] The landmark year for gynecologic oncology was 1898, when the Austrian gynecologist Ernst Wertheim introduced the procedure of radical abdominal hysterectomy to the world.[9,12] His eponymous technique further reduced operative mortality, although the long-term survival for cervical cancer patients still remained at only 20 to 30%. However, prior to popularization of the technique by Wertheim, radical hysterectomy had already been performed for the first time in 1895 by an American doctor John Clark, at Johns Hopkins Hospital, who was a resident at the time.[13,14]

This was followed by the brilliant work of Joe Vincent Meigs, an American obstetrician and gynecologist, and Professor of Gynecology at Harvard Medical School, who was a grandson of Captain Joe Vincent Meigs, the inventor of a steam monorail known as the Meigs single-track elevated railroad. Aside from his scholarship and numerous publications, including the famous textbook *Tumors of the Female Pelvic Organs* (1934),[15] and vivid description of the clinical syndrome that goes by his name, he is credited with adding extensive pelvic lymphadenectomy to Wertheim's procedure.[16]

In the 1930s and 1940s, Meigs conceptualized the modern ovarian cancer cytoreductive surgery (CRS) by staunchly advocating for removal of uterus, ovaries, and diseased peritoneum. He is credited with the following statement: "it is a good rule in ovarian cancer, to remove as much tissue as possible, if the patient's condition permits." These principles continue to hold good to this day in the management of this disease.[16,17] It was Griffiths, Meigs' protégé, who used multiple regression analysis (which was relatively new in that era) in his retrospective case series of ovarian cancer patients. He found that survival time was inversely proportional to the size of the largest residual mass. He recommended a cut-off of 1.5 cm for residual disease, which correlated with better survival.[18] Eventually, the goal of CRS has evolved to removal of all macroscopic disease. Following this seminal work, CRS combined with chemotherapy became the standard of care for ovarian cancer.

Meigs is also credited with envisioning the "peritoneoscope" to achieve a diagnosis and for intraperitoneal evaluation—a precursor of modern-day laparoscope.[16] This was perhaps the birth of minimally invasive surgery (MIS), primarily as a diagnostic tool. MIS has subsequently achieved a strong foothold in surgery for benign conditions and has recently made inroads in cancer care. Subsequent to some path-breaking randomized trials in colon and endometrial cancers, which showed superior outcomes of laparoscopic surgery in terms of immediate postoperative morbidity and recovery with noninferior survival rates when compared with open surgeries, there was rapid adoption of MIS in management of gynecologic cancers.[19–21] Robotics-assisted laparoscopic surgery was added to MIS armamentarium in 2005. However, the presentation and publication of multi-institutional, multinational LACC—Laparoscopic Approach to Cervical Cancer—trial in 2018 dealt a huge blow to the use of MIS in cervical cancer.[22] The results of this ground-breaking trial showed nearly a fourfold increase in the chance of recurrence and sixfold increase in the chance of death associated with MIS in cervical cancer. Subsequently, there has been a global decline in the use of MIS for early cervical cancer. However, it remains a standard treatment in early endometrial cancer.

The next theme of debate in gynecologic oncology is secondary CRS in ovarian cancer. The debate is currently without resolution because one well-conducted multicentric randomized controlled trial (RCT) failed to show overall survival benefit with the secondary CRS,[23] while two subsequent studies show progression-free survival benefit (one of them also showing an overall survival benefit) in well-selected cases based on predefined objective criteria.[24,25]

Radiotherapy: Rays Replacing Knives

Concomitant with surgical advances, the field of radiotherapy also progressed rapidly. Marie Curie, a Polish-French physicist, a two-time Nobel Laureate, laid the foundation of radiotherapy by isolating the first known radioactive elements, polonium and radium, in 1898.[26] Later, medical use of radiation was standardized by the selfless work of many scientists like Emil Grubbe, who ultimately succumbed to radiation-induced cancer much like Marie Curie, who died of aplastic anemia induced by repeated high-radiation exposure.[27] Many early advocates of radiotherapy supported the use of radiotherapy source close to tumor, i.e. brachytherapy. At that time, this technique was hazardous due to high-radiation exposure to the treating staff. Hence, it faded away with the advent of teletherapy, which was considerably safer in terms of radiation exposure. Recently, with newer techniques of remote after-loading, brachytherapy has had a second coming as a major mode of treatment in gynecologic cancers. An important milestone in the field of gynecologic radiotherapy was the world's first ever use of Cobalt-60 for the treatment of cervical cancer on October 27, 1951.[28]

The first radiotherapy unit in India was started in Calcutta Medical College Hospital in 1910.[29] Documented reports of brachytherapy for cancer treatment in India have been found as early as 1930.[30] However, a big impetus to radiotherapy was given by Dr. Ramaiah Naidu, a former associate of Marie Curie, who established the first radon plant at Tata Memorial Hospital, Mumbai, in 1941.[31]

Over time, radiotherapy evolved as the standard treatment in patients with locally advanced cervical cancer. The burning question regarding choice of surgery versus radiotherapy in early-stage carcinoma cervix was answered by the well-known Landoni trial in 1997.[32] This study established

that surgery and radiotherapy resulted in equivalent outcomes in early-stage cervical carcinoma in terms of overall and disease-free survival (DFS). However, combination of radical surgery followed by adjuvant radiation therapy led to increased morbidity, especially urinary tract complications. In 1999, multiple studies established the superiority of concurrent chemo-radiation when compared to radiotherapy alone in locally advanced cervical cancer.[33,34] Since then, chemo-radiation has remained the standard of care in management of locally advanced cervical cancer.

Radiation has also been shown to be beneficial in improving DFS when used as adjuvant treatment in high- and intermediate-risk endometrial cancers.[35–37]

Pathology: The Backbone of Oncology

Rudolph Virchow, a German physician, politician, and anthropologist, arguably laid the foundation of modern oncopathology with his description of the framework of cellular pathology. The word "cell", to describe the basic unit of life, had already been coined in 1665 by Robert Hooke. Virchow, who loved the microscope, emphasized that most diseases could be understood in terms of cellular dysfunction. He proposed his famous axiom *Omnis cellula e cellula*—every cell arises from another cell—in 1855. It was only several decades later, in the early twentieth century, that the diagnosis of cervical and other cancers had transitioned from clinical to pathological.[38]

In 1925, a German gynecologist, Hans Hinselmann, constructed a low-power telescope, called the colposcope, which was used to visualize the cervix.[39] Around the same time, in 1928, the novel idea of examining the vaginal smears to detect cervical cancers was put forth by Aurel Babes in Romania and Georges Papanicolaou, a Greek-American, in America. The "Pap smear", named after Papanicolaou, became accepted and implemented widely after Papanicolaou's publication of *Diagnosis of Uterine Cancer by the Vaginal Smear* with Herbert Traut in 1941.[40,41] Medical history has sided with Papanicolaou in the credit for "Pap test" because the method used by Babes (collecting cervical cells by using a platinum loop) was considered to be substantially different. However, Babes also deserves credit for this discovery. He actually described his method one year before Papanicolaou, in 1927, and the test is known as *Methode Babes-Papanicolaou* in Romania.

James Ernst Ayre further refined this procedure and put forth the idea of direct sampling of the cervix with help of a simple easily available wooden spatula in 1949, which was later named after him as the "Ayre spatula." He was granted a patent for this spatula but donated all profits from its sale to the American Cancer Society. A little later, in much the same spirit, Jonas Salk, the discoverer of polio vaccine, would famously say: "Could you patent the Sun?" Ayre is also credited with the first description of "halo" cells or koilocytes in cervical epithelial cells, the microscopic description of perinuclear haloes caused by cytoplasmic vacuolation around a condensed nucleus.[42] Later, this appearance would be linked to the human papilloma virus (HPV) as its characteristic cellular hallmark.[42]

If one does not count the recent discovery of HPV in an Italian renaissance era mummy, the papilloma viruses were first discovered in rabbits in 1934 followed by the HPV in 1956. However, the link between infection with some subtypes of HPV and cervical cancer was worked out by Harald zur Hausen et al in the 1970s and 1980s using cross-hybridization experiments between cervical cancer DNA and that from known papilloma viruses. He was awarded the Nobel Prize for Physiology or Medicine for this work in 2008.[43]

Chemotherapy: The Magic Bullets

One of the important pillars of cancer care is chemotherapy. Early twentieth century marked the birth of this modality when Paul Ehlrich, a German scientist, first coined the term "chemotherapy" for any chemical used to treat diseases.[44] However, it was not until World War II that major developments in cancer chemotherapy began.

World War II was a tumultuous time in human history. It was a great tragedy, but born out of its churning were a flurry of inventions and discoveries. This period marked the discovery of many chemotherapeutic drugs that are commonly used until now, like alkylating agents, antibiotics, and antimetabolites.

The first turning point was the observation of depleted bone marrow and lymph nodes in the troops who were exposed to an accidental spill of sulfur mustards in a bombed ship in Italy. Following this, after years of research and hardship, two prominent Yale pharmacologists, Goodman and Gilman, proved the therapeutic benefit of nitrogen mustard.[45] This set off a cascade of synthesis and testing of several alkylating agents such as cyclophosphamide, which was extensively used in ovarian cancer before the discovery of platinum and taxanes.

World War II also had a nutritional research program, which led to significant insights into folates and their effect on blood cells. This eventually led to the synthesis of antifolates with chemotherapeutic activity, mainly due to the work of Dr. Sydney Farber, considered the "father of modern chemotherapy." A name that is often forgotten, but will remain etched in history, is that of Dr. Yellapragada Subba Rao, an Indian-origin American researcher who is credited with the discovery aminopterin and methotrexate, two antifolate drugs, during his quest for synthesis of crystalline form of folic acid. Methotrexate remains the frontline single agent in treatment of gestational trophoblastic neoplasia (GTN).[46] He also discovered the function of adenosine triphosphate as the cellular energy store. Another important discovery in this period was that of actinomycin D as a result of the intense focus on antibiotic discovery to prevent infection and sepsis among soldiers. This drug also continues to be an important treatment for GTN.[47]

One of the most important and impactful discoveries in the domain of chemotherapy was that of platinum compounds. Cisplatin was first created by the Italian chemist Michelle Peyrone in 1844 but its anticancer property was accidentally discovered in 1965 by biophysical chemist Barnett Rosenberg who was studying the growth of bacteria under electrical currents. He found the strange effect that

bacteria could grow to 300 times in size when platinum electrodes were used. This was due to corrosion of the test solution by the platinum electrodes to produce cisplatin. He published his initial findings, followed 3 years later by the activity of cisplatin against tumors in mice.[48,49] Cisplatin was first licensed for use in testicular cancer in 1978, in which it dramatically increased the cure rates, followed soon by a number of other cancers, including ovarian cancer,[50] in which it became the backbone of combination regimens.[51] Although highly effective, cisplatin is a toxic drug.

Other platinum analogues like carboplatin were subsequently tested and were found to be equivalent in terms of efficacy, while being less toxic, in ovarian cancer. Carboplatin has largely replaced cisplatin in ovarian cancer treatment although cisplatin continues to be the drug of choice in cervical cancer when used as a radiosensitizing agent. The other important chemotherapy drug in gynecologic cancers is paclitaxel. It was discovered by Monroe Wall and Mansukh Wani at Research Triangle Institute in North Carolina in 1971,[52] while its action on microtubule function was discovered by Susan Horwitz in New York in 1979.[53] Its single agent activity was initially demonstrated in advanced ovarian cancer.[54] The landmark trial that established its use as a standard treatment in first-line setting was "GOG 111," which showed that a combination of paclitaxel and cisplatin improved overall survival compared with cyclophosphamide and cisplatin.[55] This treatment, with cisplatin substituted by carboplatin, continues to be the standard first-line treatment of ovarian cancer 25 years later, today. Carboplatin replaced cisplatin as a result of evidence of its equivalent efficacy and lesser toxicity from GOG 158 and AGO trials.[56,57]

Multidisciplinary Approach: United We Win

Most of the initial chemotherapeutic advances were in hematolymphoid malignancies, while solid tumor arena remained dominated by locoregional treatments—surgery and radiotherapy—until the 1960s. However, it began to be noticed that irrespective of the radicality of local treatment, cure rates had plateaued.[58] This led to the hypothesis of presence of micrometastases, early in the natural history of cancers. These thoughts were pioneered by an American breast cancer surgeon, Dr. Bernard Fisher, under whose leadership the National Surgical Adjuvant Breast and Bowel Project conducted a series of landmark clinical trials to show that postsurgical outcomes could be markedly improved with the use of chemotherapy in breast cancer.[59] This brought about the idea of adjuvant, and later neoadjuvant, chemotherapy that resulted in dramatic increase in cure rates of many solid tumors—ovarian cancer being a prime example.

Thomas C. Griffiths continued the legacy of Meigs. He further refined CRS for ovarian cancer and subjected his patients to adjuvant chemotherapy with nitrogen mustard. His 1972 publication, wherein he used nitrogen mustard as adjuvant therapy, showed a doubling of survival time compared to Meigs series.[60]

A longstanding debate in ovarian cancer has been the relative merit of using neoadjuvant chemotherapy followed by surgery versus surgery-first approach. Surprisingly, this question is still being debated, a decade after the publication of the first trial that proved the equivalence of the two approaches.[61] Most clinicians now consider neoadjuvant chemotherapy to be a valid treatment option in patients with advanced-stage disease that is unlikely to be optimally cytoreduced by initial surgery. A similar longstanding debate in cervical cancer has been the use of neoadjuvant chemotherapy followed by surgery versus concomitant chemoradiation (CTRT) in patients with locally advanced disease. This debate was only recently settled with the presentation and publication of an important randomized trial from India, which showed that CTRT results in higher DFS compared with neoadjuvant chemotherapy surgery.[62] These results were confirmed by a very similar trial by the EORTC group, which has been subsequently presented but not yet published.[63]

Evidence-Based Medicine and Clinical Trials: Devil Is in the Data

James Lind, the British naval doctor, has been widely credited with conducting the first clinical trial in 1753, wherein he discovered the cause of scurvy in ailing sailors.[64] The era of evidence-based medicine truly began when the then American President Richard Nixon began his "war on cancer" by passing the National Cancer Act of 1971. In the past few decades, there has been a consensus among medical fraternity and regulatory agencies that the best way to determine optimal treatment protocols is by conducting adequately powered "randomized controlled trials," which are universally acknowledged as the highest level of evidence. The theory and procedure of random assignment of treatments was pioneered by two great scientists, Ronald Aylmer Fisher in the 1920s and 1930s and Austin Bradford Hill in the 1940s and 1950s.[65,66] Modern medicine now stands on a pillar of high-quality evidence thanks, in no small measure, to the ideas pioneered by these giants.

Cancer Biology and Genetics: DNA Holds the Key

No history of cancer can be complete without paying homage to the biologists and other basic scientists who made important contributions that translated into actionable treatments.

An apt example in gynecologic oncology is the discovery of *BRCA* gene by Mary Claire-King, who initially trained to become a mathematician but later shifted to genetics. Years of painstaking research, which involved complex multivariate linkage and segregation analyses, finally yielded fruit when she officially announced the discovery of a locus on chromosome *17q21*, which was very strongly associated with the risk of inherited breast cancer (*BRCA1* gene), in October 1990 at the American Society of Human Genetics meeting.[67] Three years later, in 1994, Wooster et al announced the discovery of *BRCA2* gene.[68]

Others consolidated Claire-King's work and firmly established the role of *BRCA1* and *BRCA2* genes in breast and ovarian cancers.[69] The therapeutic exploitation of *BRCA* mutations, and the resulting homologous recombination deficiency, began with famous publications in *Nature* by two groups in the UK, wherein they showed that cells with

BRCA1 or *BRCA2* mutation were profoundly sensitive to inhibition of the enzyme poly(adenosine diphosphate-ribose) polymerase (PARP), which is involved in another DNA repair mechanism called base excision repair.[70,71] This is now understood in terms of PARP inhibition being synthetically lethal with the presence of either of the *BRCA* mutations. It is interesting to note that PARP itself was discovered in 1963, not too long after the discovery of the double-helical structure of DNA.[72]

The story of PARP inhibition is a lesson, if one was needed, that progress in biology in general and cancer therapeutics in particular is the result of a series of steps that may seem apparently disconnected initially, but form beautiful patterns when eventually linked to each other.

Conclusion

The story of gynecologic oncology has been written by many hands, some unseen, which have helped shape this specialty into the form it has taken today. We conclude by paying our tribute to the pioneers.

Conflict of Interest
None.

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