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Antonio Mussa

New Technologies in Surgical Oncology

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Antonio Mussa (Ed.)

New Technologies in Surgical Oncology

Foreword by
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New Technologies in Surgical Oncology

Foreword

The Italian Society of Surgery has taken the opportunity to offer its members and the medical community at large an update on new technologies in the detection and treatment of neoplastic pathologies. Progress achieved over the last few decades, especially in the field of oncology, has been unstoppable, necessitating an update on the methods used to examine patients and in turn the therapeutic protocols used in their treatment. Despite concerns over the enormous increase in the cost of healthcare, there is an irresistible drive by physicians and medical institutions to acquire state-of-the-art systems and to apply the most recently developed methods.

The Italian Society of Surgery has entrusted the subject of the Bi-annual, 2009 Report to Antonio Mussa, an internationally famous oncologist and surgeon, Director of the Oncology Department of the "Molinette" Hospital of Torino, and President of the Oncology Commission of Piemonte. Prof. Mussa has addressed many of the innovative scientific advancements in the 350 articles he has published to date and in the many congresses and meetings he has organized. His experience covers a wide range of medical specialties, from breast receptors to radio-immuno-guided surgery of various organs. His organizational skills have led to the creation of the Piemonte Oncological Network, the first and only such structure in Italy.

This volume is a particularly interesting scientific publication, of great significance to today's clinical practice. As President of the Italian Society of Surgery, it is with great pride that I present this work. I sincerely recommend it to surgeons and oncologists as an excellent guide, one that covers all the therapeutic options in the treatment of neoplasms. The book's detailed suggestions and explanations will facilitate the choice of the best treatment for patients, in terms of both cure and preservation of function.

Rome, October 2009

Enrico De Antoni
President
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Preface

I would like to thank the President and Board of Trustees of the Italian Society of Surgery for the opportunity to realize this important task, as well as all those who cooperated in the achievement of this project, particularly Professor Sergio Sandrucci, for his invaluable cooperation and support.

Oncological surgery consists of a moment in the diagnostic-therapeutic course of the patient. The outstanding progress that has taken place in the field of oncology in the last two decades has benefited from the development of new surgical techniques, which have allowed highly specialized oncological surgery and a surgical approach more thoroughly integrated within the context of multidisciplinary oncological treatment. Indeed, it is no longer acceptable that a surgeon care for an oncology patient without having broad therapeutic and diagnostic knowledge of the opportunities offered by other fields of medicine.

After many years of experience in general medicine, and after 20 years as Rector of the Institute of Oncological Specialization, I was eager to leave my own personal mark in the evolution of oncological surgery.

At the Oncological Institute, together with my colleagues, partners, and students, I have developed two post-graduate University Masters programs, one dealing with Palliative Care and the other with Oncological Surgery, which offer much more than the standard surgical knowledge. Undoubtedly, the aim of this collection of techniques, currently the most modern in this field, is to diffuse different types of knowledge and skills to other surgeons, in order to not only improve the lifespan of the oncological patient but also to preserve its quality.

Turin, October 2009

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The Evolution of Surgical Oncology

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A. Mussa, A. Mobiglia

Providing a description of the history of surgery, which is considered the main therapeutic option for a disease once absolutely incurable, is extremely complex. Cancer is the disease which perhaps more than any other summarises man's past and present fears in the face of his own vulnerability – as claimed and described by Cosmacini and Sironi [1] in their book *"Il male del secolo"* ("The disease of the century") which accurately portrays the history of tumor disease.

From the time when the causal suspicion connected with the "black bile disorder" (also known as "choleric upset") was introduced in *De naturalibus facultatibus* by the physician Claudio Galeno (129–200 A.D.), up until the identification of oncogenes at the origin of many neoplastic forms, evolution in the past has entailed a radical revision of etiopathogenetic mechanisms, as well as therapeutic results. The latter, thanks to the development and integration of a number of practices, have changed appreciably both in terms of survival and recovery of the patient to social life. Nonetheless, the inability to totally control the disease still persists, except in the initial phase and with drastically ablative methods, where still today surgery is the most frequently applied option.

In only one hundred years, a mere blink of the eye since the appearance on Earth of Homo sapiens, the whole of medicine gathered the fruits of the scientific fervor sown by the Renaissance and the Enlightenment. At the dawn of the nineteenth century, defined "the century of surgery", it reached its epitome thanks to two discoveries: anesthetics and antiseptics [2].

Prior to 1846, the year the first operation under ether anesthetic was carried out at the Massachusetts General Hospital, it was not at all strange for the surgeon dressed in a frock coat and with bare hands to operate on patients who were awake, horror-stricken and immobilised by the surgeon's assistants. Indeed coldness and temperament were appreciated in those who operated on the sick without anesthesia.

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These were the same requisites asked of those wanting to practise surgery indicated by Celso some 1,500 years earlier as indispensable character traits for the profession.

Important intuitions concerning infection were made by Semmelweis, Lister and Pasteur. Infective agents therefore began to find their nosological setting only a few years later following Robert Koch's discoveries and thanks to the importance demonstrated by microorganisms, made possible by the use of the microscope (moreover invented two centuries earlier). Antiseptic treatment extended rapidly from wounds to surgical instruments, then to the rooms and furnishing used, to clothes and the surgeon's hands, and contributed in a decisive way to limiting the till-then devastating damage of infectious diseases.

From antiseptics the next step was to seek asepsis, with operations being performed in closed environments exclusively dedicated to this activity: the first operating theatres were thus born. The surgeon wore more suitable clothes for this dedicated work: in a few years the use of the white coat spread, followed by hair covering (with Neuber), gloves (with Halsted) and finally masks (with von Mikulicz).

Anesthesia and antiseptics meant that in a few decades the surgeon could tackle increasingly difficult and longer operations. Between the end of the nineteenth and the early twentieth centuries many techniques were invented that were valid enough to still be used today: Billroth honed complex gastric surgical procedures, Kocher dealt with thyroid surgery, and Halsted proposed radical mastectomy extending to the lymphatic stations for breast cancer treatment. However, opening the abdominal or thoracic cavity and tackling the skull still proved risky due to the chance of provoking infections not easy to control, and it was only the discovery made by Sir Alexander Fleming of penicillin which provided the surgeon with an efficacious weapon to combat them.

With the advent of epidemiological studies, research on cancerogenous agents, innovations in diagnostic techniques and radiotherapy, oncology in the early 1900s began to be configured as a multidisciplinary investigational science.

At a conference on tumor immunology in 1908, Paul Ehrlich postulated that malignant cells could frequently form during the course of life and that antigenic structures were found on their plasmalemma against which the host produced an antibody response which in most cases was sufficient to eliminate the neoplastic elements. This was the first insight into the importance of the immune system in controlling neoplastic disease.

On the other hand, it began to be conjectured at the same time that cancer derived from "genetic errors" (in 1914, by studying the eggs of sea urchins, the German zoologist Theodor Boveri postulated that cancer was due to chromosome abnormalities).

From the beginning of the century up to the Second World War there were basically two weapons used against cancer: surgery and radiotherapy. However, some discoveries made in the 1940s showed that cancer was not invulnerable to drugs: this marked the dawn of chemotherapy.

In the meantime diagnostic techniques improved and, against the risk of tumors and metastases, prevention and early diagnosis were recommended. An article had already appeared on this subject in 1913 in the American women's magazine 'Ladies' Home Journal', which described tumor symptoms and transferred the risk of mortal-

ity from the ruthlessness of the disease to its late surgical treatment. To all effects this was the first publicity campaign for prevention!

In 1946 George Papanicolaou perfected the first method for early diagnosis – the Pap-test for cancer of the uterine cervix. At the time cervical cancer was the most serious and common tumor among women, and the test consequently determined the drastic drop in mortality of this disease.

Farber demonstrated the efficacy of a drug (aminopterine) against leukaemia in children, and, during the same period, Goodman and Gilman together with a thoracic surgeon, Gustav Linskog, administered a mustard gas derivative, mustine, to a patient suffering from non-Hodgkin lymphoma, which led to the drastic reduction of the tumor. They were therefore the first clinical researchers to witness the efficacy of a drug in attempting to halt neoplastic growth, at least temporarily. This took place in 1946–1947.

Important studies were also carried out by C. Huggins, who discovered the therapeutic efficacy of estrogens in breast carcinoma (1940), and orchiectomy in prostate carcinoma (1941), thus introducing the concept of "hormonal control" of tumor development.

Almost simultaneously the first large scientific work of an epidemiological and investigational nature was published in the United States on the correlation between smoking and lung cancer. The attempt to identify all the chemical substances which could cause cancer coincided with the growing awareness on the part of the public of environmental problems: talk thus began of a possible link between the increased rate of cancer and pollution.

The ferment of those years led D.A. Karnofsky to seek to organise tumor treatment in a systematic form: in 1949, in his attempt to make single case studies homogeneous and comparable, he formulated the "validity status" of the tumor patient (subsequently, in 1961, he also dictated the criteria for objective evaluation of the response to anti-proliferative drugs).

It was at Cambridge in 1953 that James Dewey Watson and Francis Harry Compton Crick discovered the DNA double helix structure (for which they received the Nobel Prize in Medicine in 1962), thus laying the cornerstone of the modern era of oncology.

To return to the strictly surgical sphere, the outcome of an operation, apart from the technique adopted, remains largely connected with the skill of the operator. But the human factor, among others, poses a practical and ethical problem. In effect it creates categories of merit based on often debatable judgements which engender confusion and doubt in patients towards the surgeon, whom in most cases they have not had the chance to choose and to whom they are entrusting their life. It is therefore not surprising that there have always been attempts to see this aspect in its true light, trying to limit the influence of individual capacities on the outcome of the operation by adopting protocols and codified procedures, preferably mechanical and therefore automatic. It is even less surprising that this reasoning was fundamental for the birth, in Soviet Moscow of the 1950s, of a "Scientific Research Institute of Experimental Surgical Apparatus and Instruments" where work began to study and make instruments for automatic suture that could be used by all surgeons, even in the farthest

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hospital of that immense territory so as to ensure standard treatment for an adequate, homogeneous level of care.

In actual fact the need to create automatic suture mechanisms arose much earlier. The strange, remarkable method thought up by Abulcasis in the tenth century should be recalled, whereby for intestinal suture the jaws of a particular type of ant decapitated after it had bitten into tissue were used; or again that of J.B. Murphy who invented a metallic button for intestinal suture in 1892, which would be taken up again almost a century later in Valtrac's invention, a biodegradable ring used for the same purpose.

However, the mechanical suture method intended as a process capable of automatically placing stitches was born at the beginning of the twentieth century. The fist apparatus, perfected in Budapest by Humer Hultl and presented at the Second Congress of the Hungarian Society for Surgery in 1908, deserves a mention. Used in gastric resection, it was able to apply four rows of metallic stitches which, by hermetically fixing the anterior part of the stomach to the posterior part, enabled removal of a portion with no bleeding or spreading of its contents.

A surgeon with expertise in tumor disease could therefore apply the so-called "no touch" techniques in an almost flawless way, with the help of excluding mechanical staplers – the so-called "cut and sew".

However, research also progressed in terms of the patient's quality of life. In 1973 the first clinical trial was started on quadrantectomy for breast cancer, a new surgical technique developed by Umberto Veronesi. It was the first introduction to a conservative operation, the removal of only the diseased part of the breast, with the purpose of reducing patient mutilation. The trial ended successfully in 1981 but only in 2002 was the technique given full recognition by the international scientific community.

From 1982 to 1985, new means for diagnosing tumors were perfected thanks to the progress of information technology. Diagnostic Imaging, for example, has since been used to increase the ability to visualize the details of organs and tissue: from that moment on it became possible to "see" the tumor – even in its initial phases or in parts of the body not accessible to physical examination.

Increasingly effective, more selective and ever less invasive pharmacological therapies were sought: the concept of "therapeutic targets" was born. Proteins and "wrong" genes giving origin to diseases could be hit by made-to-measure drugs able to distinguish between healthy and diseased tissue.

In 1992 Ira Pastan bound a monoclonal antibody able to distinguish healthy cells from tumor cells to a toxin. The result was a sort of guided "bullet" which destroyed diseased tissue while sparing the healthy tissue surrounding it.

By the end of the 1990s the link between genes and cancer had been established. It was now apparent that the disease arises when a critical number of "genetic errors" accumulate in the DNA. This can be confirmed in studies on familiarity, or when there is the co-presence of more than one form of cancer in the same subject. We began to speak of "genic therapy", whereby the "broken" genes could be substituted with ones that functioned.

The Human Genome Project intended to complete the genome inventory, namely the reading of the complete sequence of nitrogen bases composing our genetic code,

and thanks to the extraordinary progress of information technology this was completed in 2000. The gene inventory had become a reality, with researchers laying the foundations for a great scientific revolution: the post-genomic revolution.

Clinical trials began to deal with a new class of drugs, whose objective was not so much to kill the tumor cell, but to repair or deactivate it. In more recent years research has shifted from observation of the gene to its protein (proteomics), which is actually the molecule which carries out the genetic programme, and then to relations between proteins and metabolic systems of the body (metabolomics). It was thus understood that the tumor alters the entire surrounding environment to its favor, exploiting almost all the body's systems (e.g. neoangiogenesis).

Today's surgeon is certainly more eclectic than in the past and needs to have a wider vision of tumor disease and its problems in order to tackle its treatment with both traditional and more innovative procedures. These include mini-invasive techniques, endoscopy, laparoscopy (which has taken huge steps both in application criteria and oncological radicality), and robotics, with the achievement of tele-guided surgery and multidisciplinary integration with imaging diagnostic options directly usable in the operative field, and performance enhancement of some procedures in day-surgery as well.

Consequently, at the beginning of the new millennium, the figure is increasingly emerging of a surgeon specialized in treating tumors, who is fully up to date in diagnostic practice and aware of the non-surgical therapeutic options, and who is an expert in integrated therapeutic programmes with a multidisciplinary approach.

The oncological surgeon is no longer seen merely as a technical craftsman, but rather as a faithful presence at the different moments of prevention, diagnosis, treatment and palliation of tumor disease, and shall remain so at least until the recent and future scientific acquisitions manage to substitute tumor "removal" with absolutely selective and less invasive methods.

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