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# LEGENDS IN UROLOGY

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I was really surprised and happy when I was asked by *The Canadian Journal of Urology* to be included among a 'legendary' group of colleagues who have been leaders in the field of Urology. I do not feel like a legend but this invitation makes me proud of all my accomplishments in the field of urological practice and research.

As a medical student I planned to become a cardiac surgeon. By chance I became involved in Urology. When I was in my 4<sup>th</sup> year of medicine I met a gynecologist, Dr. Renato Grossi who advised me to present myself at the Department of Urology at AUSL of Modena, where Professor Palladini, the director, was looking for help. The next day I was introduced to him and started working in Urology. It was 1974 and since then I never left Urology and have been always committed to it. Since the beginning tumors were my main field of interest.

In 1977, I graduated from the University of Modena with a thesis on "Cryotherapy in BPH and Prostate Cancer". At that time cryotherapy was experimental and very few centers were using it. Professor Umberto Musiani, an international recognized urologist and Chairman of the Department of Urology in Reggio Emilia supervised my first publication on patients with urinary symptoms and negative biopsies and patients with prostate cancer treated in the urological centers of Modena and Reggio Emilia.

I completed my residency program in Urology at the University of Bologna under the leadership of Professor Aldo Martelli with a thesis on Cryotherapy in Prostate Cancer which was subsequently published. Later on I also specialized in Medical Oncology and General Surgery writing two theses on "Nephro-Ureterectomy in transitional cell carcinoma of upper urinary tract" and on "Surgical treatment of renal cell carcinoma", respectively. I always remember my first database created on paper for prostate cancer patients treated with cryotherapy. Only years later, when computerized era arrived, did I realize the importance of manual collection of data.

In 1978, I started working as urologist at the Department of Urology of the S. Maria Nuova Hospital, Reggio Emilia. The Chairman was Professor Musiani, a famous urologist and a great minimally invasive surgeon. The posterior access to the kidney using mini-skin incision was his main contribution. In those days, the leading European urologists were French, Rene Kuss and Spanish, Gil-Vernet and Solè-Bacell who were good friends of Professor Musiani. During that period I visited the Department of Urology of Salpêtrière University in Paris, chaired by Professor Kuss. The scientific organization of his department and oncologic surgery were the main topics I studied.

In 1979, I returned to the AUSL of Modena as an assistant urologist. In 1980, I came to Columbia University in New York where I worked in the pathology laboratory with the Chairman, Professor Tannenbaum. My basic research was on the role of PSMA in prostate cancer. Professor Lattimer, the Chairman of the Department of Urology invited me to participate in departmental activities. It was an incredible experience that helped me learn the real value of basic science which can be translated from bench to bedside.

In 1981, I spent two months in the Department of Urology at the University of Miami, chaired by Professor Victor Politano. I learned his famous anti-reflux technique, the Teflon injection for male and female incontinence, and

the semi-rigid prosthesis implant for erectile dysfunction developed by Professor Carrion. This experience was important for improving my surgical skills.

In 1981, my mentor, Professor Pavone Macaluso, introduced me to the European Organization for Research and Treatment of Cancer (EORTC) GU Group that was based in Brussels. I learned how to design clinical trials and the rigorousness of clinical research. I recruited patients with bladder and prostate cancer for phase II and III studies. The EORTC-GU group was comprised of urologists like Boccon-Gibod, Schroder, Kurth, Studer, Debruyne, and medical oncologists, like Peter deMulder, Stoter, De Wit, Sternberg, and radiation oncologists such as Bolla. The Chairman was Professor Louis Denis and Richard Sylvester was our statistician. Ideas for new studies were discussed during the general assembly in a multidisciplinary way and this was for me a unique opportunity to experience high quality teaching and to discuss my ideas with the European masters of urologic oncology. I thought I could not miss that opportunity and I put all my efforts in working with them. I recruited many patients in superficial bladder cancer, prostate and renal cancer protocols. After 1 year I became an active member of the EORTC-GU Group. I was deeply involved with the Group for many years and still am.

In June 1985, I met Mark Soloway in Sicily during an international meeting and I was impressed by his research work on bladder cancer. I asked to join him in Memphis for a period of 6 months in 1986. I was based in the lab but was also seeing patients with him in the clinic and the OR. The research on chemotherapy using platinum in mice and rats was our main field of interest. We used the cell line MBT-2 and MBT-3 to test different drugs in mice. It was impressive to see how mice could tolerate high dose of cisplatin without side effects and that this was not true for humans. The combination of drugs MVAC were also tested, together with many other combinations. I returned to Memphis in 1988 bringing with me a new chemotherapeutic drug to test: Peptichemio which I was going to utilize in humans with TCC of the bladder as prophylaxis in my department in Modena. The mice with MBT-2 could tolerate Peptichemio well with a good response rate. Since then Peptichemio became our standard drug for prophylaxis of NMIBC. The time spent in Memphis with Mark Soloway was scientifically very productive. I published six research articles: animal studies on the use of chemotherapy in murine bladder cancer, a review of clinical studies in muscle invasive bladder cancer, and radiotherapy of prostate cancer (the role of lymphadenectomy and the complication rate of radiotherapy in these patients).

In 1994, I became Chairman of the EORTC Quality Control Committee. This committee was conceived by the EORTC to oversee high quality research. All the GU Centers participating in clinical trials were evaluated by a commission of two members. This activity gave me the opportunity to visit many Italian and European centers and to evaluate the organization and quality of different health care systems in different countries. In those times the EORTC-GU was one of the strongest research group in the world, especially in superficial bladder cancer. This was due to the capability of the group to randomize many patients and follow them for long periods of time. Our protocols recruited more than 2500 patients with low, intermediate and high risk superficial bladder tumors. The results of these trials changed the standards of care in the urologic community and were crucial for the EAU Guidelines compilation. One trial showed that a single instillation of a chemotherapeutic agent after TUR could reduce the long term recurrence rate by 20%. I was co-PI of a trial (30911) which demonstrated that BCG was better than chemotherapy for the treatment of intermediate and high risk patients and that isoniazid was not useful in reducing BCG side effects. Finally another trial (30962) which I coordinated as PI, was designed to evaluate if we could reduce the dose of BCG while maintaining the same efficacy and learn for how long should BCG be administered. The study recruited more than 1300 patients and is the largest study in NMIBC ever done in the world. The results showed that reducing the BCG dose was not sufficient, and that the best results in reducing recurrence and progression in high risk patients was for BCG to be given for 3 years. In intermediate risk patients, BCG given for 1 year was the best option. My abstract of trial 30962 won third prize for the best oncological paper at the EAU.

In 1995, as a full EORTC-GU member I was elected national coordinator for Italy and in 1996 Chairman of the Superficial Bladder Subcommittee where I remained for 5 years. In the same year I was appointed Professor of Urology at the University of Sassari.

In 1997, I moved to the Department of Urology at San Raffaele Hospital in Milan, as a coordinator of uro-oncology and EORTC Clinical Research. The San Raffaele Institute was a real stimulating and high quality institution. An enormous research building was close to the central building where the urology ward was located. Immunotherapy was the

main field of research. I was involved in the bladder cancer protocols using tumor vaccines. The 3 year period spent there helped me also in improving my surgical skills. The volume in oncological surgery was very impressive with complex cases like renal cancer with caval and atrium thrombi performed with cardiac surgeons, difficult re-operation cases and almost 100 cases of radical cystectomies with extended lymphadenectomy and orthotopic neobladder done each year. In 1999, the department had performed more than 3000 radical prostatectomies. Laparoscopic surgery was started for adrenal and kidney tumors. At that time robotic surgery was initiated at San Raffaele by cardiac surgeons but was soon abandoned. After 2000 our department started to use the robot for radical prostatectomies. Soon robotic radical prostatectomy became the standard. Clinical research in prostate and kidney cancer within EORTC was carried on with good patient recruitment. In the Bolla study of adjuvant radiotherapy after radical prostatectomy, more than 70 patients were randomized and our department was one of the largest contributors to the trial.

I liked very much the years in Milan which were full of science, research and major surgery. It was at that time that the EAU executive proposed to form a Uro-Oncology Society (ESOU). I was part of the task force organizing this society. It was a big honor and a great opportunity for me to continue to work at an international level. The board was composed of eight colleagues and the Chairman was my good friend, Vincent Ravery from Paris. That period was really full of commitments, very demanding, but wonderful.

In 1999, the position of Chairman at the Department of Urology in Modena became available. Modena is the second largest city of Emilia-Romagna, a region in northern Italy. The province, with about 1 million people, has many industries (fashion, tiles, car makers like Ferrari, Maserati, Lamborghini, Bugatti) and is very active with international commerce. In March 2000, I was appointed Urologist-in-Chief of the Department of Urology in Modena and six other urological centers were included in my department. More than 80 beds of urology were activated. The staff consisted of 17 well-trained and experienced urologists. My challenge, coming from Milan, was to transition a department focused on pure clinical urology into a scientific research center focused on uro-oncology. The department had a large patient base and all the subspecialties were represented, but the equipment and technology was outdated. In our region kidney stone disease is very frequent and this induced me to create a stone center. I was able to replace an obsolete ESWL machine with a modern one, to have new semi-rigid and flexible ureteroscopes and new PCNL equipment. A holmium laser with 100 watts was donated to the department by a local bank. Three specialized urologists were put in charge of the stone center. Each year we treated more than 1000 patients.

Oncology was the main focus of our department. About 70% of our operations were done for cancer. Prostate cancer was the most frequent urological cancer seen. The incidence increased steadily after I came to Modena. We increased the number of biopsy cores from 6 to 10-12 cores. This change came from my experience at San Raffaele Institute where we showed that increasing the number of biopsies from the classical 6 to 8 or 12, the number of cancers diagnosed is significantly higher. I applied this in Modena and after 3 months the number of radical prostatectomies performed at our department tripled. I organized a prostate cancer center. My idea was to have basic research and institute new approaches to prevention, watchful waiting (WW), active surveillance (AS), focal therapy and radiotherapy, including brachytherapy. We performed radical prostatectomies open, laparoscopically, and robotically.

I started a collaboration with two internationally reknown basic scientists, Professor Corti and Professor Bettuzzi who were working on the genetics of prostate cancer at the University of Modena. This was a unique opportunity to work as part of a multidisciplinary research team. The downregulation of clusterin, (SGP-2, ApoJ), a new gene found by Professor Bettuzzi, was identified as one of the important genes involved in prostate cancer carcinogenesis (Int J Cancer 2004). We found that the combination of eight different genes (clusterin included) together with clinical (age, familiar history, PSA, volume,) and pathological data (Gleason score, stage), could predict prostate cancer recurrence in 96% of patients (Cancer Research 2003). We used these results in clinical practice to select patients who needed aggressive treatment after radical prostatectomy.

In 2002, the group started to study the chemoprevention of prostate cancer. Polyphenols are substances found in nature with an important anti-oxidant effect. Green tea in particular, contains a large amount of polyphenols. We showed that both Green Tea Catechin (GTC) and EGCG possess anti-tumor activity in vitro, as well as in vivo in the TRAMP mouse model. We suggested that administration of GTCs might be beneficial in the early stages of cell transformation. We performed a prospective placebo controlled trial in 60 volunteers bearing high grade

prostatic intraepithelial neoplasia. Volunteers consumed 600 mg/day GTC or placebo for 1 year and received saturation biopsies at 6 months and 1 year. Treatment with GTCs led to almost 80% reduction in prostate cancer diagnosis from 53% to 11%. These results, published in 2006 in cancer research, were confirmed also after 2 years of follow up (Eur Urol 2008). This long lasting chemoprevention in high risk patients would fulfill a significant therapeutic and social need, opening a new scenario for a novel and effective clinical approach for prostate cancer.

Watchful waiting (WW) was an approach adopted many years ago by my former Chairman, Professor Palladini in patients with incidental prostate cancer. Having a database of the patients I was able to follow them for more than 15-20 years. A long term report was presented at the AUA in 2009 showing that WW may be a valid option for elderly patients 75 years or older. The study also showed that patients 65-year-old or less should be treated more aggressively. The screening program in our province resulted in many patients diagnosed with small or minimal cancers, who did not need surgery. The idea of treating a small focus of solitary cancer (index lesions) with freezing or heat was reported for breast and kidney cancers. Perhaps this could also work for prostate cancer. Cryotherapy was already used in our department. However at Stanford University in the USA, a technique called irreversible electroporation (IRE) (electricity passing from a point to another using special needles) was proposed by researchers. IRE was available from a new company located in Carpi (Modena), my native town. A new technology (machine) delivering heat in a controlled manner through different needles was created. My department was chosen to test the system in a phase I-II studies. Patients with low risk prostate cancer in only one area of a prostatic lobe were selected after template guided biopsy. This method was very precise and allowed us to reach the cancer (index lesion) with the IRE needles. The areas treated were evaluated with biopsy at 3 and 6 months. The results showed that the treated areas were fibrotic and cancer free. The results of this phase I-II study were reported during the 2009 EAU and published in *European Urology*. Our center was the first center in Europe to adopt and use IRE for the treatment of prostate cancer. We now use multiparametric MRI for localization and focal therapy with HIFU in patients at intermediate risk (GS 3+4) according to the international focal therapy recommendations. I strongly believe that focal therapy will expand in the future.

Bladder cancer has always been my preferred field. Since the beginning of my career as a urologist, I had the chance to perform many endoscopic procedures. TUR of bladder tumors was one of the most frequent operations I was performing. Under the guidance and suggestion of Mark Soloway who has been my mentor in this field, I started to collect my own experience in a database and check the quality of my work. The first small survey I did in the department was a comparison of the results, the 3 months recurrence rate, between different urologists. We were six surgeons performing the same operation. I compared the 3 month recurrence, complication rate and the rate of diagnosis of carcinoma-in-situ (CIS). I discovered big differences between all of us. The 3 month recurrence varied from 8% to 31% and the CIS diagnosis also, 5% to 15%. Complication rates were not different. I reported and discussed these results in a meeting of the EORTC, in the superficial bladder cancer subcommittee chaired by Adrian van der Meijden and it was decided to start a European survey including all the European centers involved in EORTC superficial bladder cancer protocols. They were all expert tertiary centers performing more than 200 procedures per year. I suggested to design a form per each bladder cancer patient describing meticulously the surgical characteristics of the procedure (type of instrument used, time in the OR, cross control yes or no and others) and the type of follow up, done: cytology yes or no, flexible or rigid cystoscope and who performed the surgery, resident, staff members or chief to test if the experience of the operator was important. The 3 month recurrence and progression according to surgery in patients with the same characteristics, participating in prospective randomized trials, were the first objectives. The results of this survey was astonishing. We found a big difference between centers in the 3 month recurrence rate, from 4% to 46%. With the help of our statistician, Richard Sylvester, we analyzed also tumor characteristics and we found that the difference observed was due to the surgical quality, the surgeon. These finding became an article which was published in *European Urology* in 2002 and resulted as one of the most read article by urologists. It was one of the first well conceived, large and organized work dealing with the QUALITY of SURGERY. The statement we proposed within the EORTC was: "The surgeon is a prognostic factor in patients with superficial bladder cancer".

One of my first activities as Chairman was to create a brand new bladder center with all the newest technologies available for diagnosis and treatment. A multidisciplinary group of medical oncologists, radiologists, and pathologists worked together. An out-patient department for bladder instillations and patient follow up was organized. All the patients were divided in low, intermediate and high risk and recruited in EORTC protocols and others according to their risk of recurrence and progression. BCG, Epirubicin, MMC, Gemcitabine, EMDA and Hypertermia were

available. GE company proposed to me PDD as soon as I arrived in Modena. This together with accurate TUR the use of cytology and Cellvizio (confocal laser endomicroscopy by AB Medica, Italy) allowed me to diagnose CIS and bladder dysplasia without histology which was studied in a phase 2 prospective study.

Our treatment of choice for muscle invasive tumors was radical cystectomy with extended lymphadenectomy. Orthotopic neobladder, prostate-seminal sparing in men and gynecologic sparing in women were performed routinely. I started performing radical cystectomy in elderly patients, 80 year-old or more with MIBC, since these patients were previously managed with repeated TURs with complications such as hematuria. I adopted a mini-invasive approach, extraperitoneal with ureterocutaneostomy as diversion, to minimize complications. The results were satisfactory with only 2% of re-operation rate. We reported one of the largest single-institutional series in the world, 170 patients, at EAU and AUA meetings. Robotic radical cystectomy was also initiated in 2016.

In renal cancer, we conducted AS protocols, focal therapy with radiofrequency ablation (phase II study performed in 2001), laparoscopy, robotics and open surgery. The preservation of renal function was the primary objective of my surgery. I am a strong believer of warm and zero ischemia which were always adopted. A prospective study comparing AS to focal therapy to open surgery was performed. A second study with laparoscopic sutureless tumor resection of small renal masses was conducted. Finally the cases of large renal masses involving the vena cava and the right atrium were performed with cardiac surgeons via open surgery.

In 2010, I was elected Chairman of ESOU, one of the most important sections of the EAU. The ESOU stand alone meeting was held annually and during my chairmanship new activities, like hands on training in laparoscopy and robotics, STEPS program for the young European urologists and also meeting of the European Schools of Urology (ESU) were proposed. In those years the ESOU meeting became an annual event for all the urologists, European and international, interested in uro-oncology. An average of 1100 urologists attended the meetings. Young European urologists were involved in ESOU activities, and it gave me great satisfaction and joy to promote many of them for lecturing and moderating sessions during ESOU meetings. It was a great experience and success.

In the meantime I was involved also in the activities of the Italian Society of Urology (SIU). I was elected Chairman of the bladder cancer group who was dealing with guidelines, courses and scientific work. In 2014 I was elected President of the SIU. My proposed program was based on the constitution of Multidisciplinary Teams in Uro-Oncology (MDT) in all the Italian regions and this involved all the Italian Societies of medical oncology and radiation oncology. The final achievement was a very detailed document which was signed by all the societies and proposed to the Italian Ministry of Health.

The surgical volume of the department was impressive. More than 3500 cases were performed each year, especially in uro-oncology and this was important for the training of Italian and foreign residents and fellows. A visiting professor program was instituted in 2001: two visiting professors, one from Italy and one from Europe have been invited early to our center, including Montorsi, Ravery, Zlotta, Alberts, Mafezzini, Heidenreich, Janeshekt, Palou and others. In recent years the department of Urology of AUSL of Modena became a nationally and internationally recognized center for oncology and technology.

In conclusion my urological career started very early, was very intense and partly conducted abroad. Basic and clinical research had a great impact on my career. Living in the US I learned that quality and dedication must be always present when important achievements are the objective. Organizing and growing a department of urology and raising it to a prominent level requires great effort, experience, collaboration with co-workers and nursing staff personnel. Skillful work with hospital administrators is required to gain their support of your ideas if drastic changes, good results and eventually excellence are our goals.

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