LEGENDS IN UROLOGY

Eduardo Solsona Narbón, MD, PhD
Former Chairman of Department of Urology, IVO
Former Professor Associated of University of Valencia
Honorary Member of EAU
Member of RAMCV

It is a great honor for me, to have been invited to write an article in this series for the prestigious *CJUI* journal, and I am truly grateful for this opportunity. If my personal experiences from my extensive career in Oncological Urology can be even minimally helpful to young urologists, it would be a rewarding outcome for both my personal efforts and the service I have had the privilege of leading for over 30 years.

I was born in the Valencian Community, Spain, during the challenging years of international blockade, following the end of World War II, due to the political situation. However, this did not hinder me from enjoying a happy childhood surrounded by my family and unforgettable friends from school.

With most of my family members involved in the public health sphere – my father, grandfather, and uncle being veterinarians, another uncle being a pharmacist, and another one a physician, and so on – it was not surprising that both my brother and I chose medicine as our profession. After completing our studies in the University of Valencia, my brother specialized in Pediatric Surgery, while I directed my path towards a medical-surgical specialty, with Urology appearing to be the most comprehensive choice.

It was at the current Hospital General Universitario de Valencia where I received my urological training under the guidance of Professor Felipe Alcalá-Santaella. He instilled in me a love for surgical urology, a passion for patient care, a cherished human relationship between teacher and student, humility in the face of achievements, and a constant drive for progress. Those were incredibly fulfilling years, both in scientific and personal development, during which I had the great fortune of meeting Macu, who would later become my wife – also a physician and subsequently a urologist. After completing my training, I held the position of Assistant and later Associated Physician at the same Department of Urology in this hospital. In 1982, I was hired by the recently established Instituto Valencia de Oncología (IVO) to create the Department of Oncological Urology. It was a challenging and exciting task, undertaken with the collaboration of three colleagues who remained by my side until our retirement. In order to execute this project, Dr. Iborra, a member of the department, completed two extensive training periods at the Memorial Sloan Kettering Cancer Center in New York and the MD Anderson Cancer Center in Houston.

This provided me with the opportunity to make a short stay at the Memorial, where I had the privilege of meeting Professor Willet Whitmore, the father of modern Uro-Oncology and an extraordinary person who, to me, was endearing due to the treatment and teachings he provided. Subsequently, both Dr. Iborra and I completed a stay at the Cleveland Clinic Foundation with Professors Andrew Novick, James Montie, and Edson Pontes in their respective oncological disciplines. Not only did this complement our training, but it also provided us with a systematic approach to work, connections with research laboratories, and planning of clinical sessions, which proved to be extremely valuable for our department.

After enduring challenging initial years establishing the work system, surgical techniques, and fighting to secure certain infrastructure within the department and the hospital, we began to see the first fruits of our work.

BLADDER TUMORS

Given the high incidence of bladder tumors in our country at that time, I focused my attention on this group of tumors.

Non-muscle-invasive bladder tumors (NMIBT). Regarding these tumors, we initiated a line of clinical research in collaboration with the Pathology Department aimed at analyzing: The impact of **extravesical extension** of NMIBT on the prognosis of these patients. After the publication of 8 articles in *J Urol* (2002), *Eur Urol*, and Urology, it was concluded that the **involvement of the prostatic gland** had a variable prognosis depending on the involvement level, the urethral mucosa, ducts, or prostatic stroma, with the latter having the worst prognosis. This led us to recommend a conservative treatment in cases of urethral mucosa involvement, and radical cystectomy in cases of duct or prostatic stroma involvement. These observations were consistent with other publications at that time in the international literature.

We also wanted to assess the impact of **upper urinary tract involvement**, which we observed to occur later than prostatic involvement. Initially, it did not have as negative a prognosis as prostatic involvement if diagnosed early. However, early diagnosis was challenging, needing close and prolonged monitoring.

Based on all the aforementioned, we analyzed **predictive factors** for these two conditions and found that high-risk patients, specifically when associated with carcinoma in situ was the most relevant predictive factor. Therefore, these patients would benefit from close monitoring.

Taking a step further, we assessed **panurothelial involvement**, publishing the first international literature on this topic in *J Urol*, demonstrating the high aggressiveness of this entity, which required extensive surgery involving most of the urothelium and innovative methods of urinary diversion.

Randomized studies. During this period, we designed several phase III trials, including one that aimed to demonstrate that in low-risk NMIBT patients, early instillation of a single dose of Mitomycin C, within 24 hours of transurethral resection, could reduce the recurrence rate. The results were positive and published in *Eur Urol*, subsequently incorporated into two meta-analyses, leading to the consideration of this approach as the standard treatment in international guidelines.

Response to intravesical treatment. After analyzing another randomized study conducted in our department, where response to intravesical treatment in NMIBT could be a prognostic value, we initiated a phase II study to evaluate this factor in high-risk patients. In this study, we observed that non-response to intravesical treatment, as assessed endoscopically at 3 months, with a pathological pattern of G3 or T1 or carcinoma in situ or prostatic involvement, was a predictive factor for disease progression in over 70% of cases. This suggested recommending early radical cystectomy for these patients. This was the first work published in the literature, *J Urol*, regarding this prognostic factor and has subsequently been endorsed by numerous international publications, leading to its incorporation in international guidelines and the current definition of BCG-unresponsive patients.

CUETO Group. Recognizing the need for cooperative studies in the field of Urologic Oncology, we joined CUETO, the Spanish group for clinical research on bladder tumors, where I participated in and designed new randomized studies. When the founder of the group, Prof. Martinez-Piñeiro, retired, I was appointed coordinator for over 8 years. During that period, 8 articles were published, 5 of them in *Eur Urol* and 1 in *J Urol*. Three of these articles were phase III randomized trials, and I was the first author in one of them.

Muscle-invasive Bladder Tumors (MIBT). These tumors were the subject of my doctoral thesis, which involved evaluating prognostic factors. At that time, we used the BMDP package, thanks to the indispensable collaboration of D. Marco López, Professor of Mathematics at the University of Alicante. This resulted in 7 publications, among which a study analyzing the prognostic value of prostatic involvement in MIBT, published in *J Urol*, stands out. It concluded that stromal involvement constitutes the worst prognostic factor, equivalent to tumors classified as cT4b in the TNM system.

Bladder Preservation. Subsequently, we conducted two phase II studies aimed at the possibility of bladder preservation in MIBT. The first study was designed to evaluate whether extensive, fractionated, and complete transurethral resection was sufficient treatment for patients who met strict inclusion criteria. These criteria were primarily based on the absence of tumor in biopsies of the tumor bed or in patients who underwent re-resection transurethral at 4-6

weeks. The results, published in J Urol (2010), were favorable in the medium and long term, with a minimum follow up of 15 years, indicating the possibility of bladder preservation in this select group of patients. Based on these results, another phase II study was initiated, expanding the inclusion criteria to include patients whose complete transurethral resection of the tumor should show positive biopsies in the apparently healthy tumor bed. Patients were offered either radical cystectomy or 3 cycles of cisplatin-based systemic chemotherapy. Approximately half of the patients chose one procedure or the other, with no significant difference in specific survival at 5 and 10 years between the two therapeutic methods. These results were published in *Eur Urol* (2009) and confirmed the possibility of bladder preservation in patients who met the proposed criteria. Both results had a significant international impact, and I was invited to present them at multiple scientific forums, especially in two plenary sessions of the EAU Congress and at the NCI in Bethesda.

Adjuvant Chemotherapy to Cystectomy. In collaboration with the SOGUG group of the Spanish Society of Medical Oncology, I was designated as the principal co-investigator of a phase III study comparing the administration of 3 cycles of chemotherapy versus placebo in high-risk MIBT patients treated with radical cystectomy. The result was a significant prolongation of specific survival in patients who received chemotherapy. This study was included in the publication by Dr. Cora Sternberg in *Eur Urol*.

PENILE CANCER

I paid special attention to this tumor due to its high incidence in our department, as we received patients with this pathology from other hospitals. For the first time, we defined risk groups by associating grade and corpus cavernosum invasion of primary tumor, and this was published in J Urol and subsequently prospectively validated in another publication in the same journal and *Eur Urol* (2015). This classification, along with the incorporation of other prognostic factors, is still valid in the guidelines. As a result, I was appointed the first Chairman of the Penile Cancer group in the EAU Guidelines for 8 years, and I remained in the group for another 8 years when it was coordinated by Professors Pizzocaro and Horenblas. I also participated in international guidelines for the same tumor, leading the topic of local conservative treatment, published in Urology.

TESTICULAR CANCER

Another area I developed was the preservation of neurological structures, during retroperitoneal lymph node dissection aiming to preserve antegrade ejaculation in patients with testicular cancer after chemotherapy. It was the first publication in the literature, *Eur Uro* (1994), and I had the honor of being recognized by Professor John P. Donohue from the University of Indiana in his subsequent publication in *J Urol*.

I have also participated in over 200 publications conducted in our department, focusing on kidney, urinary tract, penis, and especially prostate cancer. These publications were led by different colleagues who progressively joined the department. My participation in international randomized studies resulted in my name appearing in 1 article in the *NEJM* and 2 in the *Lancet*. This activity was rewarded by being appointed as a member of the Scientific Committee of the EAU, led by Professor Boccon-Gibod, and including Urs Studer, Peter Alken, Peter Ekman, Paul van Caugh, Jan Breza, Roger Kirby, and Franz Debruyne. I also participated in the non-muscle-invasive bladder tumors group of the European and International Guidelines, as well as the Prostate and Renal Cancer groups in the latter guidelines.

Recently, I was appointed as honorary member of the *EAU*. I had also been elected a member of the Reial Acadèmia de la Comunitat Valenciana (RAMCV), received the Francisco Diaz Medal, and served as the coordinator of the Spanish Uro-Oncology group. I was also appointed as an honorary professor at Ricardo Palma University in Lima, Peru, and an honorary member of the Romanian, Colombian, Peruvian, and Buenos Aires Urology Societies.

This is the trajectory of a urologist who embarked on the adventure of creating the first Oncological Urology Department in Spain, made possible by my perseverance and, the never sufficiently acknowledged effort, of all the members of the Urology Department at IVO.

Eduardo Solsona Narbón, MD, PhD
Former Chairman of Department of Urology, IVO
Former Professor Associated of University of Valencia
Honorary Member of EAU, Member of RAMCV