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Baltasar Llopis Mínguez (1934-1990). A pioneer in research of bladder cancer and introduction of computing in Urology

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ABSTRACT

Objective: To recall the figure of a great Valencian urologist, to emphasize his great personality and humanity, and to draw particular attention to his significant contribution to the study of prognostic factors in urology and estimation of individual oncological risk, as well as to introduction of computing in urology.

Method: His work, the testimony of colleagues who treated him, and data obtained from his close relatives, as well as our own personal knowledge, are reviewed.

Result: Baltasar Llopis was born in Valencia, and obtained his degree and doctorate in Medicine at the Valencia University. He specialized in urology with Dr. Tramoyeres Cases, for whom he acted as assistant surgeon and with whom he shared work at La Fe Hospital, where he carried out his complete urological activity, since its inception. Dr. Llopis opted for oncological research, with a special focus on urothelial tumors. He pioneered diagnosis of these tumors using tumor markers and the study of prognostic factors to assess the individual risk of relapse and to implement a specific chemotherapeutic treatment, which he introduced in clinical practice at La Fe Hospital. He thus demonstrated the two essential components of his personality, his investigative and human sides.

Conclusion: A multi-faceted person with great skills and intelligence, Dr. Llopis eagerly devoted himself to research aimed at understanding the biological behavior of cancer, particularly urothelial tumors. In the early 80s he pioneered worldwide the development of specific markers, estimations of individual oncological risk, and prognostic factors useful for planning treatment. He was 20 years ahead of the era of predictive nomograms and their clinical introduction. In addition to being a forerunner of computing applications in Urology, he designed a database for registration of superficial bladder tumors, which allowed him to perform statistical and multivariate analyses using multiple regression models to predict the risk of relapse.

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Baltasar Llopis Mínguez (1934-1990). Pionero en la investigación del cáncer vesical y en la introducción de la informática en Urología

RESUMEN

Palabras clave:
Historia de la Urología
Oncología urológica
Factores pronóstico tumorales
Semblanzas urológicas
Baltasar Llopis Mínguez

Objetivo: rememorar la figura de un gran urólogo valenciano, destacar su gran personalidad y humanidad, además de resaltar su importante aportación urológica en el estudio de los factores pronósticos y del cálculo del riesgo oncológico individual, así como introductor de la informática en Urología.

Método: repasamos sus trabajos, el testimonio de los compañeros que lo trataron y datos obtenidos de sus familiares directos, además de nuestro conocimiento personal.

Resultado: valenciano de nacimiento, licenciado y doctor en Medicina por su Universidad, formado en la especialidad con el Dr. Tramoyeres Cases, de quien fue su ayudante quirúrgico y a quien acompañó en el Hospital de La Fe desde su creación, donde desarrolló toda su actividad urológica. Se decantó por la investigación oncológica, especialmente por el tumor urotelial, en el que fue pionero en el diagnóstico mediante marcadores tumorales, y en el estudio de los factores pronósticos para evaluar el riesgo individual de recidiva y para llevar a cabo un tratamiento quimioterápico específico, los cuales introdujo en la práctica clínica en el Hospital La Fe. Con ello puso de manifiesto las dos vertientes esenciales de su personalidad: la investigadora y la humana.

Conclusión: persona polifacética, dotado de grandes aptitudes y una elevada inteligencia, se dedicó con ahínco a la investigación del cáncer para entender su comportamiento biológico, especialmente el del urotelio; pionero mundialmente a principios de los ochenta en el desarrollo de marcadores específicos, de estimaciones de riesgo oncológico individual y de los factores pronósticos para llevar a cabo su tratamiento. Se adelantó en 20 años a la era de los nomogramas predictivos y a su introducción clínica, además de ser un precursor de la aplicación informática en Urología, diseñó una base de datos para el registro del tumor vesical superficial, que le permitió realizar análisis estadísticos y multivariantes con modelos de regresión múltiple para vaticinar el riesgo de recidiva.

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"I am the happiest man in the world, because I get up in the mornings to go and work on my hobby".

Baltasar Llopis Mínguez

Objective

We look back at the work of a great Valencian doctor to highlight his important urological contribution as a world pioneer in the study of prognostic factors, in the calculation of individual cancer risk, and in the introduction of computer science to the field of urology, and moreover underscore his great humaneness and personality.

Method

A review has been made of all the works of Dr. Baltasar Llopis-Minguez, and we have selected those dedicated to tumor disease, particularly urothelial lesions, which is the field to which this investigator was fully dedicated. We have looked at the work he carried out in the area of oncology in La Fe University Hospital (Valencia, Spain), based on his colleagues' testimonies and on biographical details from his immediate family, as well as on the personal relationship we had with him.

Result

Baltasar Llopis-Minguez was born to a working class family in Valencia (Spain) on 4 July 1934. His father was the owner of a tooling workshop. He received his primary education in the Trafalgar school, secondary education in Castellanos, and graduated from high school in 1952. At the age of fourteen, his brother and he began music lessons with a local music teacher. He showed great musical aptitude: he played the piano, the guitar, the lute, the mandolin, and other string instruments. He was part of El Cabañal street band, playing a special seven-string concert guitar, which he hugely enjoyed. Thanks to his skill and talent, the bandmaster gave him the job of turning concert scores into band music.

Baltasar started his medical studies in his home city of Valencia, during the course of 1956-1957 (Fig. 1), at the same time his passion for nature put him in touch with the Faculty of Biology in Valencia, where he participated in practical classes. In his first two years at the University, he was a member of the student music group. He enjoyed composing music and even made a record. Fed up with his son's low grades due to



Figure 1 - Dr. Llopis in 1955.



Figure 2 - Dr. Llopis before the microscope in 1958.

so much extracurricular activity, Llopis's father refused to continue covering his university fees and stopped providing his allowance; at the same time, a lecturer told him that with his faculties, he'd better start hitting the books or he wouldn't let him come to class anymore. He also barred him from the Anatomy hall, the subject he liked most and the most interest he had in learning. All this made him think. On one hand, he began to take his textbooks seriously, while on the other he was determined to find a way to cover his university fees and personal expenses, so he looked after patients at night and taught natural science at the German school in Valencia.

Baltazar completed his medical studies in 1962 with a good record and entered as physician on duty in the clinic of Dr. Carbonell, with the wish to practice surgery. Thanks to his excellent work and curriculum, he received a continued study grant in the Hospital of Turin, in Italy. On his return in 1964, he went back to the Faculty of Biology, where he was appointed assistant lecturer in practical sessions. He worked in the

Figure 3 – Contribution to the knowledge of ichneumonides in Spain.

laboratory and in entomological classification with Professor Ignacio Docavo-Alberti, whose personality impressed him and from whom he learned about methodology and who instilled his interest in research (Fig. 2). With his dedication and great capacity for work, Baltasar described a great number of insects, and was able to discover and catalog a new species of mosquito in the Albufera lake in Valencia, belonging to the genus *Chaenusa*, which he termed *Llopisi*. This finding was made known in his publication, *Contribución al conocimiento de los icneumónidos de España*¹ (Fig. 3). For this work he received a scholarship from the Fundación Juan March in 1966, allowing him to marry María del Carmen Pérez-Hernández de Alba, a neighbor living on his same street (Fig. 4). The couple were to have four daughters and a son.

In the Department he also met a colleague, Dr. Lorca-García, a specialist in Urology, as well as Dr. Tramoyeres-Cases, with whom he worked as Social Security surgical assistant. After 6 years in training, Dr. Tramoyeres returned to his home province of Murcia, and offered Baltasar the possibility of replacing him in his post. Baltasar accepted, and thus, in 1964, he came into contact with Urology for the first time. Enthralled by this surgical specialty, Baltazar became fully dedicated to its learning.

Not long after meeting him, Dr. Tramoyeres found Baltasar to be a person of great natural intelligence, a very fast and eager learner, who made good use of what he had been taught and who carried out his tasks properly. This led Dr. Tramoyeres, upon his appointment as head of department at the new La Fe Hospital in Valencia, to take Baltasar with him as an assistant in 1971. There Baltasar threw himself body and soul into his work at the hospital. In a short time he was appointed section chief, and spent his entire career in that center.

He prepared his doctoral Thesis in the Department of Medical History in the Faculty of Medicine of Valencia, under the title: Las publicaciones sobre venereología en la España isabelina (1834-1868) y su posición internacional. The Thesis was read in May 1990, and was directed by Dr. López Piñero – receiving the qualification of Cum Laude. This work catalogued 6198 articles on Venereology published in the journals Boletín de Medicina, Cirugía y Farmacia, Gaceta Médica and El Siglo Médico (all printed in Madrid).

He was involved in writing articles published in Spanish and in foreign journals since his time as a student ², particularly in relation to all kinds of urological tumours³⁻⁷. His main interest



Figure 4 - Dr. Llopis with his wife.

Figure 5 – Guided chemotherapy. Actas Urol Esp 1989²⁰.

lay in urothelial cancer - the disease his father had suffered, and which also caused his own death. In 1969 Baltasar began his study on primary ureteral tumors⁸ and upper urothelial tumors^{9,10}. This was followed by other papers and works on bladder tumors, describing the physio- and chemotherapy of bladder tumors¹¹, pursuing their different types and varieties to which he brought his clinical and therapeutic expertise¹²⁻¹⁶.

Of all his facets, his interest in computer science stood out: he knew about the evolution that microprocessors had undergone since their introduction in the 1970s and, with his enthusiasm for software that found its way into medical practice, he began with a small Macintosh, later moving on to a PC with a 186 kb processor with progressive versions of the Dbase program. His tireless preoccupation and dedication in this area is notable, as in the early 1980s programs like BMDP and SPSS were in their very early stages. As they were developed in the USA with the DOS operating system, they were very hard to obtain in Spain, and were extremely difficult to use as there were no instruction manuals. To export, manage and process the information it was necessary to invent a whole host of commands, each written in a specific language to be learnt. It took an entire night to execute a command which today would take barely a thousandth of a second.

These tools and his mathematical and statistical know-how enabled him to process information, design a database to register bladder cancer patients and, in this way, turn the Service of Urology of La Fe University Hospital into one of the first hospitals in Spain to keep a registry on this disease. Dr. Llopis continued processing information and, more importantly, began statistical studies which he gradually elaborated enabling him to make multivariate calculations. To do this he had the help and expertise of his friend and colleague Dr. Miguel Sanz, head of the Service of Hematology of La Fe University Hospital, and the professional stimulation, total freedom and scientific atmosphere that Dr. Jiménez-Cruz provided on his arrival in the Service of Urology in 1982.

Based on the model created, he mainly performed Cox multiple regressions, developing calculations for individual risk of superficial bladder cancer recurrence. If this achievement in

itself was important, since in the international literature the results of prognostic factors by way of multivariate analysis had barely begun to be outlined, Baltasar went further and introduced it to clinical practice. Using his own mathematical models as a starting point, he designed software for guided and individualized chemotherapy for each patient according to the tumor reproduction group involved. The system incorporates as predicative variables the number of tumors (1 vs 2-3), size (< 2 cm vs > 3 cm), grade (1 vs 2-3), and whether the lesion is primary or secondary. Once the characteristics of each patient's tumor have been entered, the program's mathematical model resolves and calculates the personalized relative risk of new neoplasms - classifying them into groups of low, medium or high risk of relapse, with the definition of a concrete chemotherapeutic regimen. He published the results after applying his prophylaxis protocol referred to treatment with local cytostatic agents¹⁷⁻²² (Fig. 5).

This method of assigning targeted therapy standards was put into practice at La Fe University Hospital in 1985 and has remained in use until today. More than three thousand treatments have been carried out to prevent bladder tumor recurrence (translational research, a concept described by Claude Lenfant in 2003, in the New England Journal of Medicine). As an extension of the individual tumor reproduction risk calculation, Dr. Llopis established a new follow-up protocol adapted to each group - adjusting the frequency of follow-up controls and the number of complementary tests (cystoscopy, ultrasound and cytology) to each patient's recurrence risk (before clinical management became an important part of our medical practice).

In 1985 he published an article in European Urology²³ that in turn was expanded the next year in Actas Urológicas Españolas²⁴ (Fig. In this article Dr. Llopis analyzed the capacity of urinary lipids to act as tumor markers. He determined the phospholipid/fatty acid ratio using thin-layer chromatography (TLC) in the first urine of the morning in patients with bladder cancer, with the purpose of evaluating whether this can detect the presence of a tumor by way of the semiquantitative determination of these lipids and their ratios. He found the phospholipid / fatty acid ratio to be the most significant marker, explained by the increase in tumor cell anaerobic metabolism, giving rise to an

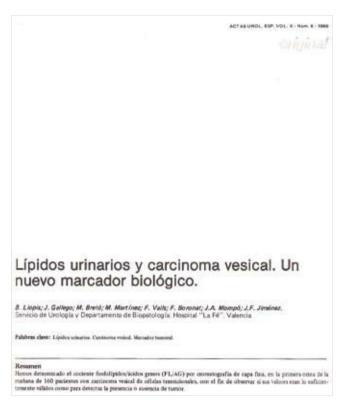


Figure 6 - Urinary lipids. Actas Urol Esp. 1986;X(6)²⁴.



Figure 7 – Computer science in Urology. LVI National Urology Conference. Lanzarote; 1991.

increase in fatty acids and a decrease in phospholipids. Based on these data, Dr. Llopis devised a patient control protocol using the lipidogram as a marker to be monitored together with cytology and transabdominal ultrasound as additional tests, of use in determining whether cystoscopy is necessary or not.

The program defined, and all of his expertise in this field, was presented under the heading *Informática en Urología*, on occasion of the LVI National Urology Conference held in Lanzarote in May 1991, where he presented version 1.02 of the UROMEDI program for a computer with a 640 kb memory working under the operating system MSDOS 3.2 ²⁵ (Fig. 7).

Dr. Llopis was a member of the Spanish Urology Association, in which he was appointed first member between 1983 and 1987. He participated as a guest speaker at symposia, conferences and various urological meetings (Fig. 8). Baltasar developed bladder cancer, which was his main reason for study, and was operated upon in his own Service in La Fe University Hospital in Valencia. He finally left us as a result of the disease, loved and admired by all of his colleagues, on 28 December 1990.

Discussion

The scientific contribution of Dr. Llopis to Oncological Urology merits special consideration. He was a pioneer in the analysis of prognostic factors and, by extension, of the estimation of individualized disease relapse risk. Through the former he showed his investigative nature by demonstrating his interest and curiosity in learning in-depth how tumors behave biologically, while with the latter he expressed his more humane side - his sincere concern for the patient as a person and an individual with dignity.

In order to appreciate the importance and dimension of the research work of Dr. Llopis, two aspects must be taken into account: the period in which it was done, and the bases upon which it was fundamented. He was a pioneer and a leader in both areas, as he pre-empted in predicting and applying concepts that would subsequently be imposed, such as translational research, clinical management and individual risk estimation. The study of tumor markers for superficial bladder cancer was conducted in the early 1980s, i.e., 10 years before molecular biology techniques began to be developed, and 15 years before the application of knowledge obtained in this area to discover the efficacy of new molecular markers in the diagnosis and follow-up of superficial bladder cancer.

The evaluation of prognostic factors and the calculation of individual risk were also conducted in the early 1980s, which proves even more remarkable, since they predated diffusion of the famous tables of Alan W. Partin for prostate cancer²⁶. Although a different type of tumor was involved, the concept and objective are identical, and comparisons can be made. Five years before Partin began presenting his prognostic factors based on mathematical models derived from multivariate analysis²⁷, Dr. Llopis had already introduced them into clinical practice. When Partin presented his predictive model, on which the mentioned tables were based²⁸, Dr. Llopis and Dr. Vera-



Figure 8 – Group of speakers in a course of the Fundación Puigvert. From left to right, Dr.s (second) Allende, Tramoyeres-Celma (behind), Ponce de León, Firstater, Escrivá, Llopis and Jardi.

Donoso had already published three years before the results of the application of chemoprophylaxis according to multifactor analysis²⁹, and the modification of bladder cancer follow-up adjusted to the relapse risk group³⁰ (Fig. 9). When in 1992 Partin reported on nuclear morphometry associated to the Gleason score³¹, Dr. Llopis had already created a line of research in the same direction, and from which a number of Doctoral Theses and international studies were produced during the 1990s. Finally, it may be mentioned that he preempted by 20 years the era of predictive nomograms or of bladder tumor markers, since the first bladder cancer nomogram appeared in 2005³², and that advocated by the EORTC was presented one year later³³. Even today these nomograms are in wait of being introduced in routine clinical practice, despite the fact that Dr. Llopis already took this step in 1985.

Conclusions

A relevant personality in Valencian Urology, the professional and humane dimension of Dr. Baltasar Llopis-Minguez was immense. A man of great aptitudes and intelligence, he was a self-taught innovator, and a tireless worker - characteristics which he also showed in his hobbies: music, nature, computer science and mathematical calculations. However, he above all dedicated himself with intensity to oncological research, working to understand the biological behavior of tumors particularly those of urothelial origin. In the early 1980s ha did world pioneering work in the investigation of a specific tumor marker, and in estimating individualized oncological risk and prognostic factors with a view to defining chemotherapeutic management of the disease. He predated by 20 years the era of predictive nomograms and their inclusion in clinical practice, and was also a forerunner to the introduction of computer science in Medicine.

Figure 9 – Vera-Donoso CD et al.³⁰.

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