

Congresses - Kongresse - Congrès

III. Monographic Course on Tumors of the Bladder

Madrid, October 26 – 31, 1970

From the 26th to 31st October, 1970, the 3rd Monographic Course of Urology for Postgraduates dealing with 'bladder tumors' was held in Madrid at the 'Ciudad Sanitaria de La Paz' (La Paz Health Center), Urological Department, under the direction of Dr. J. A. MARTINEZ PIÑEIRO, Head of the Department.

Several foreign and Spanish professors took active part, both in the surgical demonstrations as well as the lectures.

Prof. M. M. MELICOW (Department of Uropathology, College of Physicians and Surgeons, Columbia Presbyterian Medical Center), spoke on Pathology and Natural History of Bladder Tumors. After thanking Prof. MARTINEZ PIÑEIRO for his kind invitation, he mentioned some of the great figures in Spanish medicine such as MARAÑÓN, JIMENEZ DIAZ, OCHOA, CAJAL, and the important men in urology today. He pointed out that bladder tumors are not a single disease, but form a family of neoplasias which arise from the same epithelium, which has been mis-named transitional. What does the term transitional mean? It means something in transit, in change. But, from what is the urinary epithelium in transit?, and if so where to? No it is not in transit, the urinary epithelium is, however, unique; it differs from skin and mucous membrane in appearance and function and deserves its own descriptive label, which the term 'urothelium', he believes, adequately fulfills. Therefore, he has proposed the word urothelium since the year 1945. He said also that it is essential for all pathologists to define exactly what is meant by grades and stages, and urged the universal adoption of a common definition to obtain better knowledge of bladder cancer. 'All tumors have a beginning and, in the beginning, every cancer can be cured.' Evaluation of the efficacy of any method of treatment must take into consideration the histological type, grade, stage, age of the patient, sex, localization, number, spread and other details, which will inform us of their exact value.

Prof. BOYLAND (Emeritus Professor of Biochemistry, University of London, Consultant to the International Agency of Research of Cancer, France) spoke on 'Etiology of Bladder Cancer'. He began his lecture by pointing out that there are certain elements known to produce human cancer, the most fundamental being physical agents or radiations, which represent less than 5%, biological agents (virus), also representing less than 5%, and

chemical agents representing 90%. Among the chemical compounds that cause cancer in man, he mentioned: 2-naphthylamines, 2-naphthylamine-bis (2-chlorethyl) amine (erysan), 4-4 diamino-biphenyl (benzidine), 4-amino-biphenyl (xenylamine).

Later he discussed the so-called bladder tumors of occupational origin, commenting Rehn's observations in 1895, about aniline. Today it is generally considered that pure aniline does not produce cancer either in animals or man. This is possibly due to the fact that today it does not contain impurities, which used to cause cancer of the bladder. Nevertheless, we know that 2-naphthylamine and benzidine increase the risk of developing bladder cancer. He pointed out later the greater incidence of the disease among rubber workers by a chemical not yet identified, and in workers in the electric cable industry, possibly for the same reason, as rubber is used as insulating material. He then mentioned alphanaphthylthiourea, used as rat poison, which contains small amounts of 2-Naphthylamine, and should be banned. The small amounts of 2-naphthylamine measured in cigarette smoke, are probably produced by tobacco pyrolysis, and is probably responsible for the increased incidence of bladder cancer among smokers. He then remarked upon bladder cancer caused by medical products among which are cyclophosphamide, erysan and some nitrofuryl derivatives.

Lastly, he pointed out the endogenous factors, excreted in the urine, as producing bladder cancer; among them, orthoamino-phenols derived from tryptophan metabolism. It has been proved that these metabolites are present in a larger degree in the urine of subjects suffering from bladder cancer.

'Cancer of the urinary apparatus certainly has its causes, some of which are known and can be avoided. There is, therefore, hope that the incidence of disease will decrease in the near future if further steps are taken to identify the causes and then to remove them'.

Prof. CIFUENTES DELATTE (Fundacion Jimenez Diaz, Madrid, Spain) spoke on 'Codification of bladder tumors'. He showed a statistic of 1,000 cases of bladder tumors investigated at the Jimenez Diaz Foundation, Urology Department, Madrid, and the 'Hospital de la Beneficiencia', Madrid. He employed AECC codification, the Spanish Anti-Cancer Association, cards being processed in an IBM 360 computer. Apart from the statistic of the US Forces Pathologic Institute, which includes data from many urologists, there are only 3 papers dealing with results of over 1,000 cases, and he referred to MARSHALL's 1,000 cases, WALLACE and collaborator's 1,420 cases, the Bristol Registry of 1,500 cases. The system employed includes information relative to age, sex, employment, relationship to tobacco,

time of onset and first symptoms, number of neoplasias, endoscopic aspects, localization, degree of malignancy, structural type, stage of infiltration, bimanual palpation, status of upper urinary tract, state of lymphatics and evidence of metastasis, form of therapy, complications, mortality and final outcome.

With reference to the results obtained, his crude 5-year survival amounts to 45.6 %.

CORRAL and RODRIGUEZ CUADRADO, assistant doctors at 'La Paz' Health Center, Madrid, Urology Department, analyzed clinical symptoms of bladder tumors. After detailed study of the various symptoms, they come to the following conclusions:

(1) The age and habits of the patient have no influence on the presenting symptoms.

(2) There are no specific signs, symptoms or syndromes, but very often, in about 87 % cases, bladder tumors present with hematuria.

(3) The hematuria shows no pathognomonic characteristics.

(4) The intensity and frequency of bleeding holds an inverse relation to grade of malignancy, that is, its greater intensity speaks in favour of low grade papillary carcinoma.

(5) In second place they present the syndrome of cystitis, which directly relates to the degree of malignancy and stage of infiltration.

(6) In men over 50, the symptoms of prostatism should lead to suspicion of bladder cancer.

(7) The appearance of other symptoms, like renoureteral colic, uremia etc. is directly related to the localization and/or infiltration of the ureters. In other cases the first symptom may be due to metastasis either lymphatic or parenchymatous.

ESCUDERO, HERNANDEZ ARMERO and SAN MARTIN, assistant doctors from the Urological and Radiology Department 'La Paz' Health Center, Madrid, spoke on 'Radiological diagnosis of bladder tumors'. They made a detailed study of the use of i.v. urography, retrograde cystography with double contrast (barium and gas), vesical arteriography and celiacography. 'We believe IVP not only supplies information of tumor repercussion on the upper urinary tract, but is very useful in diagnosing small tumors, indicating in certain cases the degree of invasion of the vesical wall'. Cystography with barium does not supply new data, they feel. With regard to vesical arteriography, there are keen supporters who believe that it is possible to determine exactly the spread of the tumor, which is the most important factor to have available when choosing the form of treatment. With respect to the technique, they believe it should be carried out bilaterally by means of selective cath-

eterising of both hypogastric arteries. They think the possibility exists also, of distinguishing tumoral from inflammatory new-formed vessel dilatations, caused by radiotherapy.

F. AROCENA LANZ and M. GONZALEZ MARTIN, assistant doctors, Urological Department of 'La Paz' Health Center, Madrid, spoke on the usefulness of vesical biopsy, beginning their lecture by stating that vesical biopsy is the only means of ascertaining histology, grade of malignancy and, to some extent, the stage of spread, either superficial or in depth, of a bladder tumor. As for the method used, they do not consider Lowsley or Riches forceps suitable, and they systematically employ the endoscopic resectoscope trying to assess the stage of invasion in depth, performing a total biopsy, which in a great majority of cases is possible. Afterwards they made a comparative study between the staging according to the biopsy and that of the operative specimen. In O, A, and B₁ stages there was only a 20 % error, which increased in B₂ and C stages to reach 80 %.

GONZALEZ MARTIN presented a report on cytological research with fluorescence in bladder cancer. He pointed out the increase in nucleic acids as the fundamental characteristic of neoplastic cells, which can be dyed with acridine orange. In this way the cytoplasm appears stained in bright orange or red and the nucleus in greenish-yellow. This noticeable fluorescence represents a danger signal, easily detectable under microscopic study. Slides were shown with this lecture, depicting patients suffering from vesical neoplasias. The value of this method is, by far, greater than that of Papanicolaou's stain.

MARTINEZ PIÑEIRO (Head of Urology Department 'Residencia General La Paz', Madrid, Spain – 'La Paz' Health Center), spoke on endoscopic treatment and chemotherapy of bladder tumors. During his lecture, with regard to 'Endoscopy of Bladder Tumors', he began by saying that it is essential to carry out routinely a urethroscopy, since the incidence of urethral invasion is higher than suspected (3–10 %) and imposes changes in the treatment to be followed. By means of the panendoscope the urologist should ascertain details concerning the position, number, size and type of tumor; necrosis, ulceration or incrustation constitute undeniable signs of malignancy. He pointed out later that it is absolutely essential to know details relating to the mucosa, both near and far from the tumor.

'Ultraviolet light endoscopy represents a great hope for early diagnosis of bladder cancer.' He has employed both acridine orange and tetracycline as fluorochromatic agents, being able to demonstrate *in situ* carcinomas not visible under normal light. He has employed this method 32 times, having reached the following conclusions: (1) acute or chronic inflammations show

fluorescence if there is a deposit of calcium salts; (2) the non-malignant papillomas do not show fluorescence, and (3) malignant tumors do show fluorescence, and to a greater degree according to the grade of malignancy.

He concluded by saying 'our results are not as brilliant as those of WITHMORE and BUSCH, who reported, in 1968, 100 % positives in bladder cancers, but neither are they so poor as to justify giving up the method. Provided you realise its limitations, it can be of great assistance in choosing the area to be biopsied and, in the end, forms part of the mosaic of exploratory means available for getting the true picture of the tumor'.

In his lecture on 'Endoscopic Treatment of Bladder Tumors' he mentioned that 'a urologist is first and foremost an endoscopist'. He pointed out the various methods of aspiration with which he does not agree, cryosurgery, of which he has no experience, and electrocoagulation or fulguration. He specially stressed the importance of transurethral resection of bladder tumors, as it avoids tumor dissemination on the abdominal scar and the bladder vault, and it can be repeated again and again. Moreover, it is possible to perform very deep resections for infiltrating tumors, that can be compared to open partial cystectomies. The main drawback of TUR are the technical difficulties, and the possibility of vascular and lymphatic dissemination during surgery. Therefore, use of thio-tepa or some other form of chemotherapy is recommended after resection has taken place. He has not observed tumor implantation in the prostatic lodge after resection of a bladder tumor and a prostatic adenoma in the same stage.

Later he analysed indications of transurethral resection as to histological type, infiltrative stage, size of tumor, multiplicity and localization. To conclude, he pointed out: (1) transurethral resection is indicated for urothelial differentiated carcinomas grades I, II, III, BRODERS, and stage O, A, B₁ of JEWETT and MARSHALL'S classification, and (2) as for results, his experience of 172 TUR in 3 years show a crude survival of 60 %, and 29.5 % without relapse. This percentage is very similar to those recorded by other authors.

Lastly Dr. M. PIÑERO spoke on *chemotherapy*. He began by saying that to the 2 classic anticancer weapons, surgery and irradiation, a new one has been added in the last decade, still imperfect, but in full development: chemotherapy. The results are still uncertain and toxicity is great, 'but in the light of our actual knowledge it is evident that they should not be neglected when treating a patient for cancer'.

He also pointed out the different groups of chemotherapeutics basically alkylating agents, antimetabolites, antibiotics, alkaloids, hormones and miscellaneous.

His experience with thio-tepa is based on 120 patients. The 3-year crude survival rate is 44 %; 8 % are living with recurrences and another 36 % survived without recurrence. Its utilization is recommended fundamentally in low grade, low stage tumors as curative choice.

Afterwards he stressed the prophylactic value of thiotepa, based on 3 reasons: (1) destruction of tumor cells loosened during surgery; (2) destruction of carcinomas *in situ*, and (3) possibility of arresting the action of carcinogenic agents in the urine.

Later he mentioned that differentiated transitional cell carcinomas are sensitive in half of the cases. Nevertheless, according to his findings, epidermoid or undifferentiated epitheliomas are always insensitive. There is no relation between the Broders grade (I, II, III) and sensitivity to therapy; there is close relationship between the invasive stage and an adverse therapeutic reaction.

He spoke later of his experience with 5 fluoro-uracil in association with external irradiation referring to 15 cases, of which 5 died, 5 are not under control, 3 are alive with tumors and 2 are alive, tumorfree, for a year. He believes, nevertheless, that this chemotherapy has been applied to terminal cases, in many instances unsuitable for any kind of treatment.

Prof. G. MAYOR (Director of the Urological Clinic, Zurich University), spoke on 'Conservative Open Surgery'. He began his lecture by saying it is essential to ascertain certain facts about the tumor before applying any surgical technique.

- (1) Exact position of the lesion.
- (2) Size of the base of the tumor.
- (3) Extent of the tumor permeation in the wall of bladder.
- (4) Involvement of the ureter.
- (5) State of the perivesical lymphatic system.
- (6) Existence, or not, of metastasis.
- (7) Histology of the tumor.

The most important means of staging a bladder tumor are urography, bimanual palpation under anaesthesia, cystoscopy and biopsy, and vesical arteriography.

'Total cystectomy is an excellent operation, providing it is carried out only in cases where the bladder is destroyed by previous irradiation or in those instances when functional recuperation would be impossible'.

He spoke later of partial surgery, feeling inclined to elect it if and when it is carried out together with pre or post-operative radiotherapy, according to the extent of tumor permeation and condition of regional lymphatics.

He also spoke of various surgical details in connection with partial cystectomy, submitting statistics of 12 cases of 'inferior transversal cystectomy' as a variation from Couvelaire's trigonal cystectomy, with the advantage of reestablishing urinary tract continuity in the same stage, and avoiding the use of a suprapubic catheter.

Prof. WALLACE (Royal Marsden Hospital and Institute of Urology, London) spoke on 'Radical Surgery for Cancer of the Bladder'. He believed it essential to speak in the first place of multifocal tumors, which cannot be considered as localized neoplasias but as a urothelium disease. According to his experience, which coincides with that of other authors, 10% of the neoplasias of the bladder present dissemination in the urethra as demonstrated by GOWING. In such cases he advises total urethrectomy, because urethral electrocoagulations favour infiltrations of the corpus spongiosum and the possibility of hematogenous metastasis. When the tumor only infiltrates the prostatic glands, total urethrectomy and radical cystectomy in 1 stage may save a patient in 50% of the cases; however, when the prostatic stroma is invaded the prognosis is very serious. Later on, he cited having observed 12% invasions in the lower ureter. Association of vesical tumors with tumors of the renal pelvis and lumbar ureter is a common occurrence. In these cases he proposed, as the only method offering some hope of survival, bilateral nephro-urethrectomy, and cysto-urethrectomy, followed by kidney transplantation or chronic dialysis.

In the second place, he spoke on the problem of localized anaplastic lesions, with invasion of the vesical wall and lymphatics. 'Bladder cancer is curable if and when it is diagnosed in time'. Pre-operative radiotherapy at 4,000 rad level is advisable, by which means he has obtained partial regression of tumors, and their complete disappearance from time to time. Urethrectomy in the same stage as radical cystectomy and lymphadenectomy with an ileal bladder is advisable in men with urethral invasion; in women it is always indicated. He then spoke of chemotherapy, which, in the long run, is the logical and least mutilating treatment, according to his words. He believes that conservative surgery may encourage lymphatic dissemination.

PETREMENT (Head of the Radiology and Physical Therapy Department of 'La Paz' Health Center, Madrid, Spain), spoke on 'External Irradiation in Bladder Tumors'. He defined 'external irradiation as all radiotherapeutic methods, whose point of emission of energy are located outside the body, and whose therapeutic action develops through the cutaneous barrier'. He mentioned the 3 principal weapons at our disposal at present, namely telecobalt, photons and electrons produced by linear accelerators.

Afterwards he analyzed the advantages and disadvantages of said methods, arriving at the conclusion that high energy, either γ , roentgen, ultrahard or rapid electrons, constitute the best means of treatment for bladder tumors in association with surgery. He mentioned the different techniques which depend on localization of the tumor and possible lymphatic metastasis, advising a 4,500 rad dose for total pelvic irradiation technique and a 6,000 – to 6,500 rad dose for irradiation of the tumor only. He concluded his lecture by analyzing complications and pointing out what great help radiotherapy, combined with other forms of treatment, should afford in cases of bladder tumors.

Prof. PIERQUIN (Head of the Department of Radiotherapy, Hopital Henri Mondor, Paris) spoke about 'Interstitial irradiation', stressing the value of radium implantation associated with preoperative telecobalt as B. VAN DER WERF MESSING has pointed out. This association prevents scar recurrences, either in the bladder or in the abdominal wall, and lessens the frequency of lymphatic and visceral metastases. His experience is very limited in this field, but VAN DER WERF MESSING's 5-year survivals of 80 % for T₁ stage tumors, 67 % for T₂ and 47 % for T₃ are outstanding.

With respect to the use of radioactive isotopes, he favours the implantation of removable tantalum or cobalt wires and considers that the intracavitary isotopes are very dangerous, both to the patient and to the staff.

M. CAMEY (Hospital Foch, Suresne, Paris) showed a very interesting film about 'Radical cystectomy with construction of a colonic-functioning bladder', and presented his outstanding results in the treatment of infiltrating carcinomas of the bladder base, with the association of pre- and post-operative telecobalt. The average survival of all his patients is of 3 ½ years, with a very low mortality (7 %) and morbidity. The most important points of his policy are a very careful surgical technique and post-operative attention in the Intensive Care Unit.

MARTINEZ-PINEIRO showed a film, also about the technique of 'Radical cystectomy', which he performs in 2 stages: first stage uretero-sigmoidostomy or ileal conduit, second stage cystectomy. With this staging the operative mortality is very low (0 in the last 20 cases), in contrast to 20 % plus with the 1-stage operation.

A Round Table on 'Choice of Treatment' was held on the last day of the meeting. CAMEY, CIFUENTES, MARTINEZ-PINEIRO, MAYOR, PETREMENT, PIERQUIN, USON, and WALLACE were the panelists and R. GOSALBEZ from the Health Center F. Franco, Barcelona, the moderator. Several points were stressed during the discussion:

(1) Necessity of uniform systems of classification: the most widely used being TNM and JEWETT-MARSHALL'S.

(2) Exact preoperative staging of the tumor, based on cystoscopy, bimanual palpation, IVP, arteriography and biopsy.

(3) For low grade, superficial stage tumors the best method is endoscopic resection, followed by prophylactic chemotherapy (thio-tepa, Epodyl). Multiple, fast recurring, papillary carcinomas should be treated with total cystectomy.

(4) Infiltrating carcinomas, in the muscular stage, should be irradiated first with high energy sources (betatron), the election of the surgical technique depending on its localization and bladder capacity. Tumors of the vault are suitable for partial cystectomy; tumors of the base are best dealt with radical cystectomy. A bladder capacity of 100 ml or less is a contraindication for conservative surgery.

(5) Tumors in the perivesical stage (C, D, T₃, T₄) are mostly suitable for deviation (ileal conduit) and external irradiation. Sometimes, a palliative cystectomy is indicated.

(6) World-wide cooperation between all the centers interested in bladder cancer is a necessity.