

Frontiers of urooncology

Synopsis of PhD thesis

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Introduction

The practical urology has undergone significant changes due to the exponential growth of the lexical material of medicine and the revolution of technical innovations. It is difficult to know all fields of the urology, including surgery, urodynamics, plastic surgery, renal stone treatments, endoscopic interventions and laparoscopy. We have established an Uroncology Center at the Urology Clinic of Semmelweis University, which is unique in Hungary, where patients undergoing surgical treatment and medical care. Summarizing the practices of the last 20 years, we could also gain extensive experience in the treatment and management of metastatic lesions in the urogenital system, and the determination of related urological treatments, which required direct urologic intervention, but the oncological treatment of the primary tumors could not be ignored. In this doctoral work, we compared our experiences to the international and Hungarian literature, collaborating with other specialist areas in clinical oncology and the lexical and practical knowledge of radiation therapy. I was surprised, that the number of relevant publications and comprehensive guidelines were lacking, therefore during my work, I aimed to collect and summarize the uniform principles of urological and oncological treatment. In most cases, the urologist does not have sufficient knowledge of the rare oncology cases, however, the urological consequences and complications of non-urogenital tumors go beyond the urological aspect. On the other hand, oncologists – in the absence of practical urological experience – have to cooperate with urologists as well.

Frequently, after extensive pelvic surgeries due to urologic tumors, as patients with radical cystectomy, urinary and fecal incontinence may apply. Our clinic focuses particularly on the potential side effects of extensive pelvic surgeries. One of the most important part of the examination is the determination of sphincter function, regarding the functional analysis of pelvic floor muscle. Anal sphincterometry is a crucial part, which, due to its simplicity, is a valuable screening tool for predicting post-operative urinary loss.

Our department has participated in several clinical drug trials related to the treatment of various cancer types. Nowadays an increasing number of drug treatments are available for the therapy of urological cancers. Furthermore, it is well known, that tumors with similar histological appearance, often have very different responses to the same therapy treatment. Thus, the consequence of the expansion of therapeutic options, there is an increasing need for a further method that can more accurately predict tumor behavior and therapeutic sensitivity. Through an understanding of the molecular background of tumors, we have the opportunity to identify several prognostic and predictive biomarkers that may influence future individualized therapies.

Aims

- 1.) Investigation of metastases in the urinary system (renal, urinary tract, male reproductive system), assessment of the caused complications, and evaluation of the treatment options.
- 2.) Study and summarize the indirect and direct propagation of non-urological cancers into the urinary system, and their urological complications.
- 3.) Based on the experiences of our Centre of Urooncology, I aim to propose recommendations and guidelines, regarding the diagnosis and treatment of the primary malignancy for the collaborative team of urologists and oncologists.
- 4.) Summarize and publishing our experience and insights into managing tumors of the urological organs, and their complications (including radiotherapy, surgical and medical treatment).
- 5.) Use of the molecular properties of urologic tumors responding to clinical problems.
 - A.) Analysis of MMP-7 levels in serum for the prediction of post-operative progression of renal cancer.
 - B.) Analysis of serum and plasma chromogranin A level for the risk of post-operative prostate cancer progression.

Methods

Summary of urologic tumors as metastases of non-urogenital derived tumors: In this doctoral work, I researched the metastases of non-urological tumors into urological organs and their complications, which case provides a comprehensive summary of the incidence and therapeutic potential of metastases to primary and secondary urological organs. Between 1999 and 2013 thousands of patients attended the Centre of Urooncology, Semmelweis University and the Urological Department of National Institute of Oncology. I have compared the experience of the last 15 years to the literature.

Continence assessment after surgery Mainz Pouch II type: we used Mainz pouch II urinary diversion due to radical cystectomy for muscle-invasive bladder cancer. We analyzed the anal sphincter function and quality of life in pre- and postoperative period in continental and

incontinent patients. The anal sphincter examination was evaluated by resting anal sphincter pressure (RASP), maximum anal closure pressure (MACP), and rectoanal inhibitory reflex (RAIR), which were measured using a rectal manometer.

Analysis of MMP-7 Serum concentration in renal cancer patients: The serum concentration of MMP-7 level was examined of 77 patients diagnosed with renal cell carcinoma and 97 healthy person using the MMP-7 KRYPTOR fluorescent immunoassay (Thermo Scientific B.R.A.H.M.S GmbH, Henningsdorf / Berlin, Germany). The samples were collected at the Urology Clinic of the University of Duisburg-Essen between 1990 and 1994. Blood samples were collected before surgery and centrifuged at 1500 rpm for 15 minutes and stored at -80 ° C until use.

Analysis of serum concentration of Chromogranin A (CGA) in prostate cancer patients: CGA concentration was measured in serum and plasma samples of prostate cancer patients using the CGA KRYPTOR fluorescent immunoassay (Thermo Scientific B.R.A.H.M.S GmbH, Henningsdorf / Berlin, Germany). We examined the CGA levels of patients who underwent radical prostate surgery and palliative transurethral resection. The patient cohort was divided into two groups. The first group (n = 127) contains serum samples from patients treated at the Urology Clinic of the University of Duisburg-Essen between 1990 and 1994. For the second group (n = 110), plasma samples were also available, which were also collected at the Urology Clinic of the University of Duisburg-Essen between 2003 and 2004. After collection and centrifugation, serum and plasma samples were stored at -80 ° C until use.

Statistics: Continence experiments data were analyzed using a two-pattern t-probe. Any p value <0.05 was considered statistically significant. All statistical analyses were performed with NCSS 2000 software for Windows (NCSS statistical software, Kaysville, UT, USA). In the case of serum biomarker measurements, Mann-Whitney U test was used to compare individual marker concentrations with clinicopathological data. To determine and illustrate the survival analyses univariable overall survival, disease-specific survival and metastasis-free survival analyses were done using both Kaplan–Meier log-rank test and univariable Cox analysis. For further multivariable analysis Cox proportional hazards regression model was used. To determine the correlation between the serum biomarker levels Spearman’s analysis was performed measured. To determine the optimal cut-off value with the highest sensitivity and specificity for the detection of PCA and metastasis, we used the nonparametric receiver operating characteristics (ROC) were generated. P-values are to be understood as strictly

descriptive. Statistical analyses were performed using the SPSS 21.0 (Chicago, IL) and SAS 9.4 (Cary, NC) softwares.

Results

We treated a large number of patients in our clinic due to a complication of gynecologic cancer. Mostly we treated patients diagnosed with cervical cancer as a result of urological complications. Before the radical surgery 50 patients cystoscopic examination was carried out to exclude the direct propagation per year. In addition, 90 of advanced cervical tumor patients underwent urinary diversion and ureter stent placement. We performed 8 urological endoscopic procedures due to bleeding or fistula formation. Uterine tumors occur also often. In our practice, we performed urinary diversion 46 times in the last 15 years, most often by percutaneous nephrostoma insertion was investigated. During our 15 years of practice, we treated 16 patients for complications of ovarian cancer by spreading of the tumor, which affects the urological organs, most often the ureter and bladder. For almost all of the 16 patients we treated, due to ovarian cancer, we had to apply percutan urinary diversion, indicated by worsening renal function or fever in 5 cases. Vulvar cancer is an uncommon tumor, but in advanced stage it may often cause urological complications. Radical surgical treatment can be the only way for recovery. Epicystostomy may be the only solution for haemorrhage, fistule development, incontinence, urinary retention. At our Department, we had to carry out epicystostomy for 5 women treated with advanced vulvar cancer because of bleeding and incontinence of urine.

In the last 15 years, we performed several urological examinations because of colorectal tumors, including 16 stomachs, 6 appendages, 12 colon, 18 sigma, 266 rectal tumors. During our practice, we can often detect rectal cancers for digital prostate rectal examination.

Various haematopietic malignancies may also cause urological metastases. In our practice, we have found 119 cases of urological manifestation of haematological malignancy. The most frequently urological diseases occurred due to Hodgkin and non-Hodgkin lymphoma (NHL).

In the retrospective study of incontinence, two groups were distinguished based on the rectal status of patients. Among patients who participated in the research, a high proportion of females were present. In the post-operative period changes in the frequency of stool and urine excretion were also detected. Based on the results numerous patients were unable to distinguish liquid as well as solid faces and the dejection of flatus. Therefore, patients who were otherwise not incontinent wore sanitary pads. Another important observation is the increasing number of daily defecation and urination. Examination of rectal function by manometry during the postoperative state resulted no significant changes in the resting anal sphincter pressure (RASP)

values between the continent and incontinent patients. On the other hand, we found significantly higher maximal anal closure pressure (MACP) values in the case of continent patients. In the prospective study, we observed a significant decrease in RASP values after surgery. We also observed decreases in MACP values after 6 months in the post-operative period. No differences were found between the pre- and postoperative measurements in the rectoanal inhibitory reflex (RAIR).

During the biomarker studies, we found a significant correlation between renal tumor stage and pre-operative MMP-7 concentration, namely elevated MMP-7 concentration associated with higher tumor stage (T3-T4). We also detected significantly higher concentrations of MMP-7 due to the occurrence of lymph node and distant metastases. Besides, we assumed, that the high concentrations of MMP-7 could be a significant risk factor for overall survival, disease-dependent survival, and metastasis-free survival. Moreover, lower tumor differentiation rates were associated with significantly shorter survival. We detected significantly elevated CGA concentrations in serum and plasma samples of patients diagnosed with prostate cancer and distant metastasis. We compared the CGA concentration to disease-dependent survival data, and we found in all prostate cancer cases, that low CGA protein level was associated with significantly better disease-dependent survival in both serum and plasma samples. Overall, patients undergoing radical prostatectomy had significantly lower CGA levels compared to patients undergoing transurethral resection. In addition, we measured the CGA and PSA levels for patient survival. In the case of serum measurements, we found a significantly shorter survival in patients with high CGA or PSA levels, both in the case of all patient cohort and clinically localized prostate cancer cohort.

Conclusion

- 1.) The surgical and medical treatment in the same oncology cancer center is useful regarding the follow-up of the patients and the evaluation of the Cancer.
- 2.) The management of urological manifestations and complications of various tumors requires an interdisciplinary approach. The therapies should be individualized in every case of malignancies of various origins including urological organs.

3.) We have to take into consideration the appropriate treatment of advanced malignancies when the metastasis results an unusual appearance in the urogenital organs. Mostly, instead of urological surgery focus on the treatment of primer tumors is more necessary.

4.) Based on the results the Mainz pouch type II operations for urine diversion after cystectomy should only be carried out only in selected cases, namely the radical cystectomy decreased the anal sphincter function and mostly causes urinary incontinence. Therefore, this surgical solution for urinary deviation can be recommended in patients with adequate sphincter function.

5.) Tissue and serum biomarkers could be used as important prognostic factors of cancer progression and metastases, besides may have predictive values for therapy resistance. According to our results, serum CGA levels are elevated in the case of prostate cancer and pre-operative serum MMP-7 concentrations are also increased in patients diagnosed with renal cancer.

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