Profesional paper

SYNCHRONOUS AND METACHRONOUS PRIMARY MALIGNANT NEOPLASM OF THE UROGENITAL ORGANS - OUR RECENT EXPERIENCE

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INTRODUCTION

Synchronous malignant infections occur in two or more primary neoplasms that occur continuously or at different intervals in the same patient.

According to the time of occurrence, they can be divided into so-called simultaneous multiple so-called synchronous small neoplasms that occur within 6 months, and multiple hetero small neoplasms that occur at an interval of more than 6 months (1). According to the studies published so far, synchronous small neoplasms of different generation of origin can be considered the same between organs or controls of different or different organ systems. The most common reasons for their occurrence include: increasingly advanced screening diagnostic methods, genetic defects, reduced immunity due to receiving oncological therapy, the influence of one of the malignant processes, congenital or acquired diabetes, chronic renal failure, environmental influences, etc. (2). The prevalence rate of such two or more synchronous primary neoplasms is estimated at 4.5% to 11.7%. In most cases, over 75% of diagnosed patients belong to the population group older than 50 years. Men are more affected than women in terms of synchronous and metachronous neoplastic phenomena (3).

The treatment is most often multimodal, which simultaneously includes surgical, oncological and radiological treatment approaches.

MATERIAL AND METHODS

The study includes an analysis of 19 rare cases of surgically treated patients, in whom the presence of two or more histological different malignant tumors from the same or different organ system was diagnosed simultaneously or at different time intervals, at the urology department of the City General Hospital "8th September" - Skopje, in the last five years.

The data related to the type of malignant neoplasm, etiology, accompanying comorbidities, used diagnostic procedures and treatment methods, in the study are statistically processed and presented through percentage representation, mean value, tabular and graphical display.

OBJECTIVE OF THE STUDY

-Determination of the most common malignant neoplasm associated with malignant tumors of the urogenital organs in the studied group.

-Determination of the etiological relationship for the simultaneous occurrence of two different malignant entities in the same patient with other diseases or

conditions, as induction factors for the occurrence of malignant tumors.

-Determination of the most adequate approach in the treatment of synchronous malignant tumors, depending on the type of malignant process, the type of affected organs or tissues, the age and general health status of the patient, based on our clinical experience to date.

Results

Out of a total of 19 patients with pathohistologically verified primary neoplastic tumor, operated on at the urology department of the "8th September" General Hospital in Skopje, in the last 2,5 years, in 8 patients or 42.1%, simultaneous carcinoma of two organs of the urogenital tract (UGT) was diagnosed preoperatively (table no. 1). Primary neoplastic tumor of two different organs of the UGT, diagnosed and operated on in different time intervals, was determined in 5 patients or 26.31% (table no. 2).

Table No. 1 - Simultaneous finding of primary carcinomas of two organs of the urogenital tract, operated on in the last five years (Synchronous neoplasm).

Types of synchronous primary malignant neoplasms among organs of the urogenital tract in the last 2,5 years	Number of patients
Renal cell carcinoma (RCC) of both kidneys	1
RCC of the right kidney and Adrenocortical carcinoma of the left adrenal gland	1
Prostate adenocarcinoma and transitional cell carcinoma of the bladder	2
Adenocarcinoma of the prostate and Carcinoma of the penis	1
Sarcomatoid urothelial carcinoma of the bladder and adenocarcinoma of the prostate	1
Invasive (High Grade) Urothelial Bladder Cancer and Prostate Adenocarcinoma	2
Total	8

Table No. 2 - Finding of primary carcinoma of UGT organs and organs of other organ systems in different time intervals (heterochronous-metachronous neoplasm).

Types of metachronous (heterochronous) primary malignant neoplasms among organs of the urogenital tract in the last 2,5 years	Number of patients
Renal cell carcinoma of both kidneys	1
Prostate adenocarcinoma and transitional cell carcinoma of the bladder	3
Renal cell carcinoma of the right kidney and Adrenocortical carcinoma of the left adrenal gland	1
Total	5

In 4 patients or 21.05%, primary neoplasm of UGT organs were diagnosed simultaneously with organs of other organ systems (table no. 3), while in 2 patients or 10.52%, primary neoplasm between UGT organs and organs of other organ systems were diagnosed at different time intervals (heterochronous neoplasm) (table no. 4).

Table No. 3 - Patients with simultaneous malignant neoplasm of UGT organ and organ of another organ system, operated on in the last 2,5 years at the Urology Department of the "8th September" General Hospital - Skopje.

Synchronous primary malignant neoplasms of organs of the urogenital tract with organs of other organ systems, in the last five years	Number of patient
Prostate adenocarcinoma with high-grade gastric adenocarcinoma	1
Papillary renal cell carcinoma of the left kidney with basal cell carcinoma of the skin of the nose and face	1
Uroepithelial carcinoma of the bladder with basal cell carcinoma of the skin of the nose	1
Prostate adenocarcinoma with basal cell carcinoma of the skin of the nose	1
Total	4

Table No. 4 - Patients with malignant neoplasm of an organ of the UGT with an organ from another organ system diagnosed and operated on in different time intervals (Heterochronous neoplasm).

Metachronous (heterochronous) primary malignant neoplasms of urogenital organs with organs of other organ systems, in the last 2,5 years	Number of patients
Prostate adenocarcinoma and sigmoid carcinoma	1
Breast adenocarcinoma with ovarian adenocarcinoma and sigmoid adenocarcinoma	1
Total	2

Of total of 19 patients with synchronous and metachronous malignant neoplasm, 16 patients or 84.21% are men and only 2 (10.52%) are women. The average age of the patients is 67.46 years.

The analysis of biochemical parameters in patients with synchronous and heterochronous multiple primary malignant neoplasm (MPMN) in most cases showed elevated values of the hepatic enzymes SGOT (Aspartate Aminotransferase) SGPT (Alanine Aminotransferase), Creatine kinase SK, CRP (C-reactive protein), pancreatic enzymes Amylase and Lipase in patients with prostate cancer PSA (Prostate Specific Antigen) and moderately elevated blood glucose values. In contrast to these values in most cases, the blood analysis showed reduced values of urea and albumin (table no. 5).

Table 5. Characteristic changes in the biochemical analysis of blood in patients with multiple primary malignant neoplasm in the study group.

Biochemical blood parameters in patients with MPMN	Elevated values	Low values
SGOT (Aspartate Aminotransferase)	<91 U/L	
SGPT(Alanine Aminotransferase)	<118 U/L	
Creatin kinase CK	<174 U/L	
CRP (C-reactive protein)	28-72mg/l	
PSA (Prostate Specific Antigen) in patients with Prostate Cancer	>15,1 ng/ml	
Amylase	>114 U/L	
Lipase	>96 U/L	
Glucosis	<7,7 mmol/l	
Urea		< 2,3 mmol/L
Albumin	<32,4 g/l	

Characteristically for most patients with MPMN in the study group, urine analysis showed elevated values of erythrocytes, leukocytes, glucose and urobilinogen (table no. 6).

Table No. 6 - Elevated biochemical parameters in urine in patients with multiple primary malignant neoplasm in the study group.

Biochemical parameters in urine in patients with MPMN	Elevated values	Normal values
Erythrocytes	>25 Er/ml	
Leukocytes	>15 Le/ml	
Glucose	>5,5 mmol/l	
Urobilinogen	>16 umol/l	
Proteins		>0,3 g/l

DISCUSSION

Malignant primary multiple neoplasm (MPMN) represent the simultaneous presence of two or more primary malignant neoplasm in the same patient. If they are diagnosed at the same time, we are talking about the so-called synchronous malignant neoplasm, and if they are diagnosed at different time intervals, we are talking about the so-called heterochronous or metachronous malignant neoplasm.

The etiology of multiple cancers in the same patient is quite complex and still not sufficiently explained. In the published studies so far, the following etiological factors for their occurrence are included: genetic predisposition, environmental factors, reduced immunity due to an already present cancer, radiological and chemotherapy, autoimmune diseases or a combination of some of them (6,7,8).

-The genetic predisposition for the occurrence of MPMN, especially in some autosomal dominant hereditary syndromes such as Von Hippel-Lindau (VHL) syndrome, Lynch syndrome, Cowden syndrome, Bird Hogg Dube Syndrome and others is based on mutations in the gene located in chromosome 3, which is a tumor suppressor. When this gene mutates, tumors develop in various parts of the body as a result of the production of abnormal and non-functional proteins that lead to uncontrolled cell growth and the formation of tumors or cysts (8). Genetic hereditary syndromes such as: Von Hippel Lindau (VHL) syndrome and Birt Hogg Dube Syndrome, which are characterized by the diagnosis of a kidney tumor in combination with malignant tumors of the skin, lungs

or some gastrointestinal organ, were also diagnosed and treated in our study group.

- Environmental factors such as long-term exposure to carcinogenic agents (chemical agents, drugs containing acetaminophen), smoking and alcohol, can cause MPMN, especially involving the organs of the urogenital tract.

In the majority of studies published so far regarding MPMN, the most common cases described are the simultaneous occurrence of lung or breast cancer in combination with ovarian cancer, colon cancer or squamous cell carcinoma of the skin (9,10,11,12).

In this study, an attempt was made to determine the most common types of MPMN in which neoplasm is present in two or more urogenital organs or in a urogenital organ in combination with an organ from another organ system in the same patient. The latest published study shows that organs of the urogenital tract are represented in multiple primary malignant neoplasm in 0.9% of cases, and in relation to the total number of treated urological cancers, they are represented by about 9%. In this case, malignant urological tumors were most often combined with cancer of the stomach, small and large intestine and with tumors of the nervous system. 76% of all MPMN in which cancer of a urogenital organ is included belong to the so-called metachronous malignant neoplasm, with the second tumors being diagnosed within five years of the diagnosis of the first cancer (13,14).

In the period from 01.01.2023 to 15.08.2025 in the surgical departments of the General Hospital "8th September" in Skopje, out of a total of 1352 cases of malignant neoplasm operated on, 19 (1.4%) patients with multiple primary malignant neoplasm in which at least one urogenital organ was affected were operated on (diagram no. 1). In relation to the total number of 677 urological operations for malignant neoplasm for the same time period, the percentage of occurrence of synchronous and metachronous malignant tumors of two or more urogenital organs is 2.3% (diagram no. 2). In this, a total of 66 operations for kidney cancer were performed, and of these, two patients or 3.03% were diagnosed with renal cell carcinoma simultaneously in both kidneys. It is characteristic that in both cases, in addition to bilateral renal carcinoma, skin (fibrofolliculomatous) changes were also present, characteristic of Birt Hogg Dube syndrome.

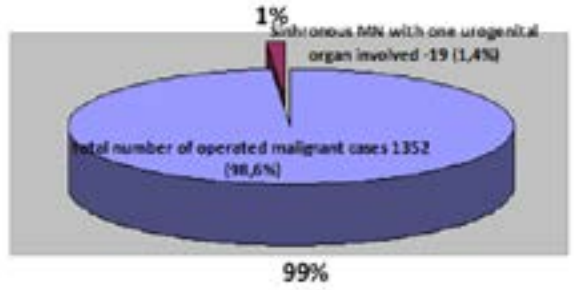

Diagram No. 1 - Percentage of Multiple Primary Malignant Neoplasm where at least one urogenital organ was affected, in relation to the total number of operated malignant diseases for a period of 2.5 years in the General Hospital "8th of September" - Skopje.

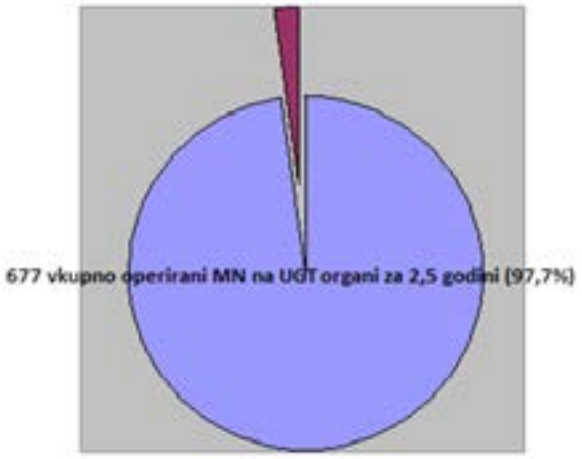

Diagram No. 2 - Percentage prevalence of synchronous and metachronous malignant tumors of two or more urogenital organs for a period of 2.5 years in the "8th of September" General Hospital - Skopje

The treatment of patients was based on the principle of an individual approach to treatment, taking into account: the type of malignant neoplasm, the stage of the disease, the patient's age, the present comorbidities and the expected five-year survival period of the patient (life expectancy).

Patients with multiple primary malignant neoplasm in which the urogenital organs were affected with organs of other systems (intestinal carcinomas, lung carcinoma, ovarian carcinoma and skin carcinoma), were treated multidisciplinary.

The patient with simultaneous diagnosis of renal cell carcinoma on both sides (by percutaneous biopsy), with frequent spontaneous pneumothorax due to cystic changes in the lungs and characteristic fibrofolliculomatous benign skin change on the neck (Birt Hogg Dube Syndrome), was surgically treated with radical

nephrectomy on the left side and a radical nephrectomy on the right side was proposed, due to the finding of three biopsy-confirmed tumorous malignant changes (RCC) in the same kidney (Figure 1).

Figure 1. A 64-year-old patient with synchronous malignant neoplasm of both kidneys, frequent spontaneous pneumothorax due to cystic changes in the lungs and characteristic skin changes on the neck (Birt Hogg Dube Syndrome), operated on at the General Hospital "8 September" - Skopje, North Macedonia.

The patient was advised that after the right nephrectomy he would undergo chronic hemodialysis. Due to his refusal to undergo this, he was referred for oncological therapy.

In the second patient, cancer of the left kidney was diagnosed four years after a right nephrectomy, also performed due to massive renal cell carcinoma (Figure 2).

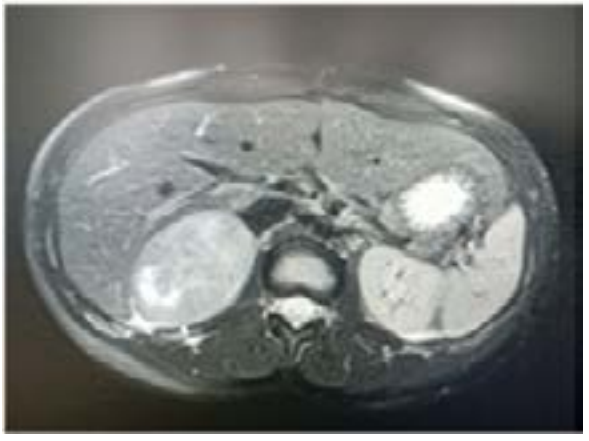

Figure 2. Patient 77 years old with diagnosed massive tumor (RCC) of the right kidney. Radical nephrectomy performed in GOB "8mi Septemvri", Skopje.

After four years, due to his age (81 years) and previous abdominal aortic aneurysm surgery and iliac blood vessel grafts, the patient did not agree to the proposed partial nephrectomy of the left kidney or oncological therapy and is undergoing active surveillance (Figure 3,4).

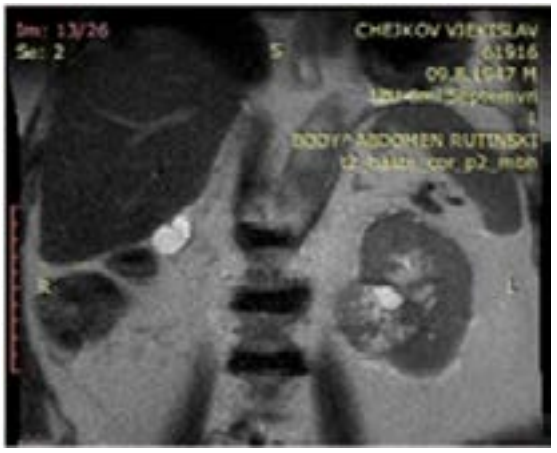

Figure 3.4. - Metachronous renal cell carcinoma, diagnosed four years after right nephrectomy performed due to massive carcinoma in an 81-year-old patient operated on at the "8th September" General Hospital - Skopje, North Macedonia.

CONCLUSION

Multiple primary malignant neoplasm represent a constant challenge in terms of timely diagnosis and adequate treatment. Out of a total of 1352 cases of malignant neoplasm operated on in the surgical departments of the General Hospital "8th September" in Skopje, in two and a half years, 19 or 1.4% were patients with multiple primary malignant neoplasm in which at least one urogenital organ was affected. In relation to the total number of 677 urological operations on malignant neoplasm for the same time period, the percentage of occurrence of synchronous and metachronous malignant

tumors of two or more urogenital organs is 2.3%. Out of a total of 66 operations on kidney cancer, two patients or 3.03% were diagnosed with renal cell carcinoma simultaneously in both kidneys. It is characteristic that in both cases, in addition to bilateral renal carcinoma, cystic changes in the lungs with frequent spontaneous pneumothorax and fibrofolliculomatous skin changes, characteristic of Birt Hogg Dube syndrome, were present.

The most common factors for the occurrence of synchronous and metachronous malignant neoplasm, in our practice so far, were determined to be: the familial factor, i.e. genetic predisposition, given that they were diagnosed in patients with autosomal hereditary genetic syndromes such as Von Hippel Lindau Syndrome and Birt Hogg Dube Syndrome, reduced immunity as a result of radiological or hematological therapy, and autoimmune diseases such as: Diabetes Mellitus, Myasthenia Gravis and Sclerosis multiplex.

The incidence of Multiple Primary Malignant Neoplasm in the studied group is significantly higher in men than in women in the ratio of 84.21% to 10.52%. Therefore, timely screening diagnostics in men over 50 years of age is the main prevention for their occurrence.

The analysis of each individual case in the studied group indicates the need for a so-called individual approach to the treatment of these patients, based on the principle of multimodal and multidisciplinary treatment, given that there is still no standard protocol for the treatment of synchronous and heterochronous primary malignant neoplasm.

Keywords: Synchronous primary malignancies, renal carcinoma, prostate carcinoma, bladder carcinoma, oncological treatment of malignant neoplasm, incidental diagnosis.

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