

## Multiple Primary Malignant Tumors in Current Oncology Practice. Clinical Case Report

DA Khlanta<sup>1\*</sup> and GP Guens<sup>2</sup>

<sup>1</sup>Resident, Department of Oncology and Radiotherapy, A I. Evdokimov Moscow State University of Medicine and Dentistry, Ministry of Health of Russia

<sup>2</sup>Professor, Head, Department of Oncology and Radiotherapy, A I. Evdokimov Moscow State University of Medicine and Dentistry, Ministry of Health of Russia

**\*Corresponding Author:** DA Khlanta, Resident, Department of Oncology and Radiotherapy, A I. Evdokimov Moscow State University of Medicine and Dentistry, Ministry of Health of Russia.

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### Abstract

Multiple primary malignant tumors (MPMT) or polyneoplasia is one of the challenging and understudied categories in modern clinical oncology. The importance of studying MPMT is caused by such factors as growing cancer morbidity worldwide, increasing incidence of polyneoplasia, the need to make difficult decisions regarding further management strategies. The cause of the growing incidence of MPMT remains unclear. It appears that, in addition to the actual increase of the MPMT share in tumor statistics, improvement of diagnostic means in modern oncology plays a major part. Another important factor is the increasing life expectancy of patients with primary tumors due to improvement of chemotherapy and radiotherapy methods, which is associated with growing rates of detection of "second" tumors. There are also numerous risk factors predisposing to MPMT development (lifestyle, environment, genetic factors, age, antitumor immunity related factors).

This article describes a case of a 78 years old patient I.V. with multiple primary malignancies including malignant tumors of the bladder, ureter, kidney, prostate, stomach diagnosed over 8 years.

**Keywords:** Multiple Primary Malignancies; Polyneoplasia; Kidney Cancer; Bladder Cancer; Ureteral Cancer; Prostate Cancer; Gastric Cancer

### Abbreviations

MPMT: Multiple Primary Malignant Tumors; UC: Urothelial Carcinoma; UUT-UC: Upper Urinary Tract Urothelial Cell Carcinoma; ChRCT: Chromophobe Renal Cell Tumors; MGC: Metachronous Gastric Cancer; EGD: Esophagogastroduodenoscopy; MRI: Magnetic Resonance Imaging; GFR: Glomerular Filtration Rate; CEA: Carcinoembryonic Antigen; AFP: Alpha-Fetoprotein

### Introduction

Multiple primary malignant is a process, where several malignant growth sites occur independently in one or several organs (paired organs, organs of different systems, multiple lesions in one organ) at the same time or one after another.

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The existence of multiple malignancies was discovered by Billroth in 1889 and reported in a detailed study by Warren and Gates in 1932 [1]. Many scientists had speculated on the existence of this pathology long before that. Indeed, Abu Ali Ibn Sina, also known as Avicenna, described a case of a woman with bilateral breast cancer in his writings back in the 10<sup>th</sup> century [2]. Centuries later, as the diagnostic methods improved and the number of risk factors increased, MPMT became a permanent part of cancer statistics worldwide. The causative factors predisposing to MPMT development can be subdivided into several groups: lifestyle factors, environmental factors, genetic factors, patient's age, and prior cancer treatment. Studying the causes of MPMT development, researchers revealed the importance of the impact of various carcinogens on malignancy development. Notably, the "cancer field" theory suggested by R.A. Willis in 1967 stipulates that multiple lesions in the form of a cell or a group of cells of potential tumor growth may occur in the entire volume of tissues affected by carcinogenic alterations [3]. However, many authors believe that MPMT occur due to inflammatory and dystrophic changes in tissues, as well as due to metabolic, hormonal shifts contributing to malignant transformation of cells [4-6].

Improvement of diagnostic means in modern oncology was instrumental in inclusion of MPMTs in the cancer statistics. Improvement of tumor visualization methods [7,8] and advances in genetics [9] facilitated early detection of MPMTs and predisposition thereto. Increasing life expectancy has also contributed to the growing incidence of MPMT cases. This factor is directly related to the improvement of cancer treatment methods and, therefore, makes it possible for the "second" tumor development risk factors to become actualized.

Thus, it can be concluded that the carcinogens in pathogenic mechanisms of MPMT development are identical to those leading to development of solitary tumors. Moreover, as is known, natural antitumor immunity is decreased dramatically by specific antineoplastic treatment of the primary tumor, which could contribute to development of "second" lesions.

One of MPMT classification factors is the time interval of tumor development. There are synchronous tumors found within 6 months following detection of the primary tumor; metachronous tumors found 6 or more months after the primary tumor was diagnosed; concomitant tumors where one patient has three or more tumors (synchronous-metachronous and metachronous-synchronous occurrence types) [10,11].

This article will contain a summary of MPMT epidemiology, main treatment principles, as well as a review of specific high-priority ICD codes the patient was diagnosed with.

### Epidemiology

It is beyond argument that MPMT incidence and survival rates vary between different geographical regions globally. These variations are related to different climate patterns, behavioral and genetic traits characteristic of specific countries [12,13]. The MPMT structure is of interest to numerous researchers. A recent study showed a ratio of MPMT presentation depending on sex, age and location of the malignant process. Among the analyzed MPMT cases, the most common tumor types are adenocarcinoma (49.3%), squamous cell carcinoma (26.1%), malignancies of hematopoietic and lymphoid tissues (8.1%), transitional cell carcinoma (6.2%). The mean age in the synchronous cancer group was 64 years, while in the metachronous cancer group the mean age was 57 years at the time of the diagnosis and 63 years at the point of detection of a second malignancy. There were 39.1% female and 60.9% male patients with MPMT. The three most frequent malignancies in the synchronous group were malignancies of the gastrointestinal (48.7%), genitourinary (21.8%), respiratory (15.4%) systems [14].

According to epidemiological surveys, the current rate of multiple primary neoplasia in Russia is between 7% and 9% [15]. The total incidence of primary malignant tumors globally varies from 2.4% to 17% depending on the specific ICD code [16].

### MPMT management principles

The MPMT treatment principle depends on the stage of each tumor, its histological type, and the physical condition of the patient, presence of comorbidities. For morphological confirmation of MPMTs, each tumor is assessed separately. Generally, the tumor that is the most life-threatening or the most detrimental to the patient's quality of life is treated first. The treatment method (multiple- or single-stage) should be selected considering not only the properties of the tumor and its impact on the organism, but also the overall effect of MPMTs on the patient's physiological state.

In case of medication, when MPMTs are not treatable with one chemotherapy regimen, a more effective regimen is usually chosen designed to treat higher-grade tumors.

Surgical treatment of MPMTs includes a preoperative risk assessment and postoperative monitoring necessary for MPMT patients subjected to resection of vital organs. MPMT treatment post surgery is usually conducted according to the recommendations for the tumor stage.

Radiation therapy used separately or as a part of a combined/complex therapy is an important method of treatment of cancer diseases in various sites. In combination with chemotherapy or surgical intervention, radiotherapy can have an effective contribute to increasing survival of MPMT patients. Various methods of tumor treatment using radiotherapy have been improved over the years [17]. However, despite the major progress in this area, the issue of post-radiation complications is as relevant as ever. These complications must be considered when treating MPMTs [18,19], especially given the tendency towards combination of treatment methods different in their toxicity.

We must not forget that any MPMT treatment is based upon a complex approach, which highlights the importance of cooperation between medical professionals of different specialties.

### Upper urinary tract MPMT

Urothelial carcinomas (UC) are the fourth most common tumors worldwide [13].

Upper urinary tract urothelial cell carcinoma (UUT-UC) is a rare, but aggressive tumor type with an unfavorable prognosis that accounts from 5% to 10% of all UCs. It is known that the gold standard for of upper tract urothelial carcinomas is radical nephroureterectomy [20] and immunotherapy [21].

Due to the radicalization of treatment methods and the subsequent increase of the life expectancy of patients with this condition, oncology is now facing an increasing risk of development of metachronous contralateral cancer of the upper urinary tract. According to a recent study, the 30-year cumulative incidence of metachronous contralateral cancer of the upper urinary tract was 2.6% [22]. Additionally, the study results demonstrate that an older age at the time of the initial diagnosis and a larger tumor size are associated with reduced risk of metachronous contralateral cancer development. However, the researchers specify that the presence of bladder cancer is a very important risk factor for contralateral malignancy development. Furthermore, development of the latter is not associated with a decrease in survival when compared to the patients with unilateral UUT-UC. Statistics show that contralateral cancer development occurs within 5 years after the primary UUT-UC was diagnosed in 70.1% of the patients and within 10 or more years in 10.4% of the patients [22]. These data are needed to develop an appropriate follow-up concept for the patients treated for urothelial carcinoma considering the time frames. There is some evidence that the risk of recurrent bladder tumors remains significant even after a radical surgery [23]. Follow-up of patients after radical nephroureterectomy mainly consists of routine laboratory tests, various imaging methods, and cystoscopy. For this reason, it is necessary to adhere to follow-up programs for the patients subjected to surgical interventions.

### Chromophobe renal cell carcinoma

Chromophobe renal cell tumors (ChRCT) account for 6% to 8% of renal cell cancer cases [13]. This tumor type is characterized by a relatively good prognosis and a low degree of malignancy. Diagnosing these tumors is of interest to many medical community representatives. Chromophobe tumors are often found accidentally as they are usually benign and exhibit no clinical symptoms [24]. This made researchers concentrate their attention on various molecular markers of this tumor type in addition to morphological methods of diagnosis verification. A benign tumor, such as an oncocytoma, can be easily mistaken for ChRCT since they both have similar morphological characteristics and imaging methods sometimes fail to differentiate clearly between them. This resulted in the necessity to study molecular markers allowing for differential diagnosis of these changes. The main tumor markers used in immunohistochemistry to diagnose ChRCT include CD117 (KIT) overexpression of which was reported in cells of different sarcomas, lung cancer, ChRCT and cadherins, in particular, E-cadherin (epithelial cadherin) and N-cadherin (neural cadherin) [25]. In addition, an auxiliary method of fluorescence in situ hybridization (FISH) is used for differential diagnosis of ChRCT and oncocytoma. Loss of chromosomes 2, 6 and 10 is often an indicator of ChRCT, while oncocytomas may exhibit loss of chromosomes 6 and 10, but not 2 [25].

### Gastric cancer

Gastric cancer is a major problem for modern oncology and the third most common cause of death from cancer worldwide [26]. Esophagogastroduodenoscopy (EGD) included in the Japanese gastric cancer screening program has undoubtedly increased the rate of early gastric cancer detection [27]. For example, about one half of all gastric malignancies in Japan are detected at the stage when the tumor is confined to the mucosa and submucosa [28]. The improvement of diagnostic methods was followed by an increase in survival rates in this cohort. This is due to the increasing number of early gastric cancer cases being treated surgically, namely by partial gastrectomy. This surgical technique maintains the gastric function with no significant impact on the patient's quality of life [29]. The disadvantage of partial gastrectomy is the risk of metachronous gastric cancer (MGC) developing in the remaining part of the organ. Studies show that the incidence of MGC post resection varies from 2.7% to 15.6% [30-32]. The main risk factors for this process are old age, history of recurrent early gastric cancer, as well as persistent *Helicobacter pylori* [30].

Routine endoscopic examinations of patients subjected to partial gastrectomy for cancer allow physicians to diagnose MGC at an early stage.

*H. pylori* was officially recognized as a group 1 carcinogen for gastric cancer in 1994. *H. pylori* exhibits its carcinogenic effect by inducing the following changes in gastric mucosa: chronic active gastritis, atrophy, intestinal metaplasia and dysplasia followed by gastric adenocarcinoma [33]. Eradication of *H. pylori* is considered potentially beneficial for prevention of MGC development.

### Case Presentation

In 2007, patient I. born in 1942 presented to a clinic in Ryazan Oblast with frequent urination and aching lumbar pain. The examination resulted in the following diagnosis: chronic prostatitis, benign prostate hyperplasia. During a routine examination in May 2012, the patient was diagnosed with a bladder tumor for which the patient was treated with transurethral resection (TUR) of the bladder followed by chemotherapeutic treatment using Vero-Mitomycin 40 mg at the Hospital of the Ministry of Internal Affairs. Histology showed a non-invasive papillary urothelial tumor. Based on the obtained data, the patient was diagnosed with: Bladder cancer pT1N0M0. In September 2013, the patient presented to the P.A. Hertsen Moscow Oncology Research Institute with increased total PSA of 2.12 ng/mL, free PSA fraction of 17.9%. Pelvic MRI showed: prostate dimensions 4.5 x 3.9 x 4.7 cm with a small, well-defined intravesical growth in the shape of a protrusion up to 0.9 cm, inhomogeneous structure of the gland. A multi-focal prostate biopsy was conducted in the same month. Based on the histology results, the patient was diagnosed with: Small acinar adenocarcinoma of the prostate with a Gleason score of 8 (4+4). A

radical prostatectomy was performed in the Hospital of the Ministry of Internal Affairs in October 2013. Considering the histology data, the patient was diagnosed with: G3, stage II prostate cancer pT1cN0M0. Cystoscopy showed no evidence of bladder cancer.

In May 2014, the patient was treated using Winkelmann's procedure bilaterally for hydrocele. The patient was discharged to be followed up by an oncologist and an urologist in the home area. However, a recurrent hydrocele developed on the right side during the following two weeks. In July 014, the patient was operated on using the Bergmann's technique on the right side.

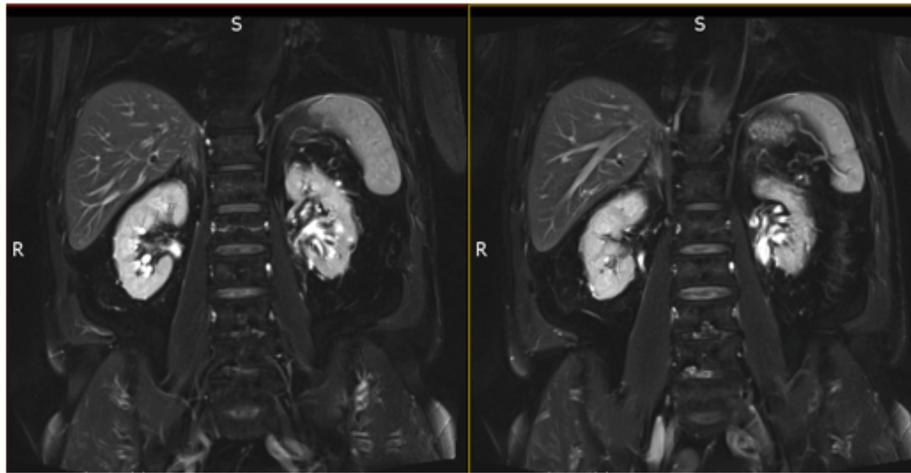
A follow-up examination in November 2014 showed that the patient developed recurrent bladder cancer manifested as a growing non-invasive papillary urothelial tumor with a low degree of anaplasia. On December 1, 2014 the patient had a bladder TUR with laser ablation of the tumor bed with intravesical instillation of 40 mg of Vero-Mitomycin. Eight rounds of intravesical chemotherapy were conducted at the II treatment stage. A follow-up examination in December 2015 showed no evidence of tumor recurrence or progression (PSA was 0.02 ng/mL). However, suture calculus was found in the vesiculo-ureteral anastomosis region. A TUR of the vesiculo-ureteral anastomosis region with the sutures and the calculus was performed in December 2015. Histology showed no tumor growth in the removed tissues. A follow-up examination performed later showed no progression. A follow-up cystoscopy conducted in February 2018 showed a mucosa portion of about 1.0 x 1.0 cm in diameter with villous proliferation in the right section of the neck. Histology showed proliferation of non-invasive papillary urothelial carcinoma (G1). In March 2018, a TUR of the bladder and the 1st round of intravesical chemotherapy with Vero-Mitomycin were conducted. No evidence of progression was observed during the follow-up.

An examination conducted in July 2020 showed a tumor in the left ureter. MRI showed: bilateral hydroureter, left sided hydronephrosis. Excretory urography showed: normal accumulation function, but delayed excretory function of the right kidney; impaired concentration and excretory function of the left kidney. A TUR-biopsy of the tumor was performed in August 2020. Histology showed: papillary urothelial cancer with a microinvasive focus (high-grade). GFR 60 mL/min/1.73m<sup>2</sup>. Tumor markers: CEA 0.537 ng/mL (0 - 3.8); AFP 3.21 IU/mL (0 - 5.8); CA 19-9 2.11 U/mL, PSA (total) 0.11 ng/mL (0 - 4.4); CA 72-4 0.8 U/mL (0 - 6.9). Based on the clinical findings and the results of instrumental method of examination, it was decided to place a catheter stent in the ureter (Figure 1). Follow-up EGD conducted in August 2020 showed a gastric ulcer, a biopsy was performed. Quantification of the IgG class antibodies to Helicobacter pylori showed > 200 U/mL (> 1.1-detected). Histology showed mucinous gastric cancer with ulceration and invasion into the lamina muscularis mucosae.



**Figure 1:** Excretory urography in the postoperative period (nephroureterectomy with laparoscopic resection the wall of the bladder).

At the first stage, considering the severity of the malignancy, it was decided to perform an urological operative intervention followed by making a decision regarding gastrectomy. On September 15, 2020, the patient had a laparoscopic nephroureterectomy with partial cystectomy (Figure 2). Histology findings: high-grade papillary urothelial carcinoma of the ureter with subepithelial invasion, poorly marked peritumoral lymphoid infiltration. A chromophobe tumor in the renal cortex (0.4 cm) with no evidence of vascular or perineural invasion.



**Figure 2:** MRI of bilateral hydronephrosis and stenting of the affected left ureter.

Based on the obtained data, the patient was diagnosed with: Ureteral cancer pT1N0M0 G3Pn0L0. Renal cancer pT1aN0M0 Pn0L0. A near-total distal gastrectomy was performed on October 8, 2020. Histology findings: moderately differentiated adenocarcinoma of the body of stomach in combination with mucinous carcinoma with ulceration (pT1aM0M0 G2 L0V0, Pn0, R0, Lauren classification: mixed type).

Based on the medical history, laboratory and instrumental diagnostics, the patient was diagnosed with: Primary diagnosis: multiple primary malignancies, metachronous-synchronous growth. Gastric body cancer pT1aN0M0 G2 L0V0Pn0 R0, Lauren classification: mixed type, stage I. Surgical treatment (10.2020) by near-total distal gastrectomy. Left ureter cancer pT1N0M0 G3Pn0L0, stage I. Chromophobe tumor in the left kidney pT1N0M0 Pn0L0, stage I. Surgical treatment (09.2020) by nephroureterectomy on the left side. Bladder cancer pT1N0M0, stage I. Combination treatment (2012-2018): Bladder TUR, chemotherapy with Vero-Mitomycin. Process stabilization. Prostate cancer pT1cN0M0, G3, stage II. Surgical treatment (10.2013) by radical prostatectomy. Process stabilization.

Secondary diagnosis: Arteriosclerotic heart disease: Atherosclerotic cardiosclerosis. Stage II, grade 1 arterial hypertension, cardiac risk III. Erosive bulbitis. Axial hiatal hernia. Grade II dyscirculatory encephalopathy. Cerebral atherosclerosis. Spinal osteochondrosis, radiculopathy. Incipient cataracts in both eyes. Retinal angiopathy. Chronic bilateral sensorineural hearing loss. Colonic diverticulosis.

## Discussion

In the clinical observation presented by us, patient I. aged 78 had a number of specific features worthy of a clinical analysis. First, the multiplicity of lesions is of note: malignancies were found in five organs, most of them are urothelial tumors. Second, the clinical picture is not that of a generalized neoplastic process, it is rather obscure, which once again points at the importance of screening programs.

Finally, the existing diagnostic options, including contrast-enhanced MRI, make it possible to assess the lesion very thoroughly, record the effectiveness of the therapy used, which is indicative of the value of this procedure as a widely applied diagnostic method. This clinical observation also demonstrates a case of a chromophobe renal tumor which was found accidentally following radical nephroureterectomy for treatment of a malignancy in the ureter. This example highlights the difficulty of diagnosing tumors of this type even when high-technology diagnostic tests are applied.

### Conclusion

A stable increase of the incidence of multiple primary malignancies in the population is a pressing issue for oncologists, genetic scientists and representatives of many other medical fields.

Better management of such neoplasms requires timely diagnosis and screening of cancer diseases, a certain level of cancer alertness among general practitioners. However, timely detection of a primary tumor at an early stage should not discourage medical professionals from performing further diagnostic tests, especially when risk factors for “second” tumor development or parallel precancerous conditions are present.

Psychological support of the patients, promoting their adherence to therapy and medical recommendations regarding observation intervals during the remission period and follow-up care are essential for improvement of oncology care of patients with such conditions. If these conditions are met, metastatic spread as well as newly developed cancer diseases will be diagnosed timely.

### Conflict of Interest

The authors have no conflicts of interest to declare.

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