DOI: 10.4149/BLL_2019_106

Bratisl Med J 2019; 120 (9)
641 – 645

CLINICAL STUDY

Extremely rare synchronous primary neoplasms in testicular cancer patients

Mrinakova B[1,2], Ondrusova M[3], Lehotska V[4], Ondrus D[1]

1st Department of Oncology, Comenius University, Faculty of Medicine & St. Elisabeth Cancer Institute, Bratislava, Slovakia. **dalibor.ondrus@ousa.sk**

ABSTRACT

OBJECTIVES**:** This study analyzes the incidence of multiple primary malignant neoplasms (MPN) in patients with testicular cancer (TC), the results are compared with literature findings and assess the rarest subgroup of patients with MPN.

PATIENTS AND METHODS**:** Clinical data of 1870 patients with TC treated or followed up in a single center in the period of 5/1970–12/2018 were collected and analyzed retrospectively in focus of the occurrence of MPN.

RESULTS: The overall incidence of MPN was 150 (8.02 %). There were 89 cases of bilateral TC (59.3 %), of these 8 cases were synchronous (diagnosed within three months period from the primary diagnosis) and 81 metachronous (9 % and 91 % respectively). Non-testicular other primary malignancies (OPM) occurred in 61 cases (40.7 %), of which 59 cases were metachronous (96.7 %) and two cases were synchronous (3.3 %). Metachronous malignancies included mainly prostate cancer (n = 17 patients), kidney cancer (n = 13 patients) and colorectal cancer (n = 12 patients). Synchronous OPM was found in two patients.

CONCLUSION: In our study we registered two cases of synchronous OPM, both histologically clear cell renal cancer. We have analyzed clinical characteristics, diagnosis and treatment strategies of synchronous OPM, in order to improve its diagnosis and therapy *(Fig. 3, Ref. 22).* Text in PDF *www.elis.sk.*

KEY WORDS: Synchronous primary neoplasms, metachronous primary neoplasm, testicular cancer, renal cancer, duplex cancer.

Introduction

The multiple primary malignant neoplasms (MPN) are defined as two or more unrelated primary malignant tumors that are histologically different and originate from different organs (1). The fact that patients may have MPN was already described by Billroth in 1869 (2). Since then numerous papers were dedicated to the subject with different definitions of MPN by authors. The frequency of multiple tumors in epidemiological studies is reported to range between 2–17 % (3, 4, 5, 6). Better diagnostic techniques, prolonged life span and increased survival of the cancer patients contributes in a gradual increase of incidence of the MPN.

For the purposes of this article we divide the MPN into two categories according to the tumor diagnosis interval: synchronous, when tumors arise simultaneously or within three months period from the primary diagnosis and metachronous with the interval time between diagnoses of more than three months. Metachronous neoplasms are more frequent than synchronous with a ratio of 2.7: 1 (7). Diagnosis of more than two primary tumors is rare (3).

The tendency of developing multiple tumors (synchronous or metachronous) may be explained either by an individual genetic predisposition or by the action of carcinogenic factors acting on different organs at different times. The combined action of genetic and environmental factors facilitates the onset of a tumor. Consequently, the patients who have already developed one invasive neoplasm usually possess higher risk of new primary cancer in the same or different organ. Scientific data describe significantly higher risk of new primary cancer in the same or different organs compared with general population (8, 9). Improvement of the effectivity of anti-neoplastic therapy has led to a significant improvement in patients' survival, but also to a greater risk of therapy-related complications. Toxicity of the treatment modalities, particularly chemotherapy and radiotherapy may lead to secondary malignancies. Added to a combined action of the genetic and environmental factors this may explain the development of metachronous tumors (3). On contrary, it is difficult to explain the origin of synchronous tumors. Their onset seems to be more time depending and questions the sequence of the predisposing factors. Synchronous tumors represent an important diagnostic and therapeutic challenge. Radiologists and clinicians should be aware about different patterns and clinical presentation of tumors. Particularly important is that metastatic lesions among these tumors must be excluded.

[1]1st Department of Oncology, Comenius University, Faculty of Medicine & St. Elisabeth Cancer Institute, Bratislava, Slovakia, [2]Department of Medical Oncology, St. Elisabeth Cancer Institute, Bratislava, Slovak Republic, [3]Pharm-In, Ltd., Bratislava, Slovakia, and [4]2nd Department of Radiology, Comenius University, Faculty of Medicine & St. Elisabeth Cancer Institute, Bratislava, Slovakia

Address for correspondence: D. Ondrus, MD, DSc, 1st Department of Oncology, Comenius University Faculty of Medicine, St. Elisabeth Cancer Institute, Heydukova 10, SK-812 50 Bratislava, Slovakia.

Testicular cancer (TC) represents one of the most curable solid tumors, with a 10-year survival rate of more than 95 %. It is most common in males between 15–40 years and comprises of approximately 50 % seminomas and 50 % non-seminomas (10, 11). Given the young average age at diagnosis, it is estimated that effective treatment approaches, have resulted in a gain of decades of life. The incidence of both unilateral and bilateral testicular cancer (BTC) appears to be increasing, while the age at which it develops seems to be decreasing (10, 12).

The reported incidence of BTC is between 1 and 5 % of TC cases with the majority of metachronous tumors (65–75 %) (10, 13). Synchronous BTC are rare, representing about one third of BTC and only 0.5–1 % of all TC cases. They have worse prognosis with a lower 5-year overall survival than metachronous tumors (10, 14). Risk factors for BTC are the same as for unilateral TC: atrophy of the testis, a history of cryptorchidism or undescended testis (testicular dysgenesis syndrome), infertility, Klinefelter's syndrome, and family history of testicular cancer. This risk significantly increases in presence of two or more factors (14). The majority of synchronous BTC present with the same histologic type, usually as seminoma (14, 15). Treatment decisions for patients with synchronous tumors should be formulated on the basis of risk stratification, as defined by the International Germ Cell Consensus Classification (IGCCCG) (16).

Other primary malignancies (OPM) in patients diagnosed with TC and cardiovascular diseases are important causes of premature death in long-term TC survivors (17). Increased risks of contralateral TC, solid tumors, and leukemia have been reported in TC patients (14, 17, 18, 19). The majority of OPM represent metachronous neoplasms with significantly elevated risks observed for solid tumors compared with general population, including cancers of the stomach, small intestine, colon, rectum, pancreas, prostate, kidney, bladder, thyroid, and connective tissue as well as malignant melanoma. The risk of all metachronous OPM, 25 and 30 years after the diagnosis of TC is 15.7 % and 22.6 %, respectively and seems to be similar following seminomas or non-seminomatous TC (20). The known and well-studied risk factors are the use of single agent and combination chemotherapy regimens and the effect of radiotherapy with significant relationship between radiation dose and the occurrence of metachronous tumors (20).

Although, there were many studies addressing the incidence and risk factors of BTC and metachronous OPM, little is known about the minor subgroup of TC patients with synchronous OPM.

Patients and methods

Patients from a single center database, who were diagnosed with a first primary TC in the period of May/1970 – December/2018, and who survived at least 6 months after the date of diagnosis (until June 30, 2019) were included in the study (n = 1,870 patients). Patients with extra-gonadal germ cell tumors were not included in this study.

All patients were under the continuing care of an onco-urologist. Under the conditions of the baseline staging procedures and control examinations, healthcare was aimed at the eventuality of an incidence of MPN including the diagnosis of TC. All detected cases were confirmed histologically.

The MPN occurred in 150 patients (8.02 %) with primary TC. The most frequent type was contralateral TC, which appeared in 89 patients (59.3 %). Eight cases of BTC occurred simultaneously (BTC was considered to be synchronous, when the interval between the occurrence of the first and second TC was ≤ three months). Metachronous bilateral TC (with the diagnosis interval > three months) occurred in 81 patients (91 %).

When analyzing non-testicular OPM in the study group which occurred in 61 patients (40.7 %) by topographic site high occur-

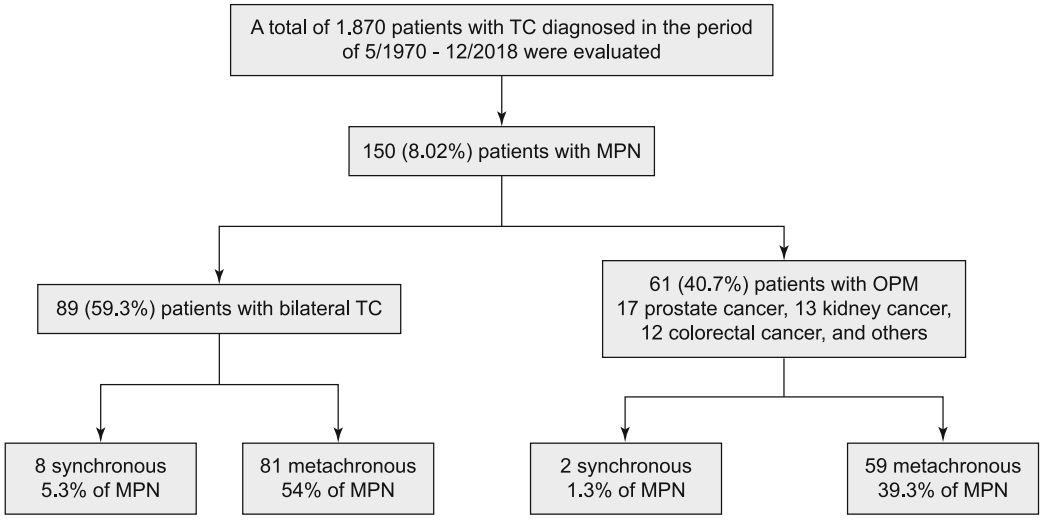

Fig. 1. Method of selection of patient group. TC = testicular cancer, MPN = multiple primary neoplasm, OPM = other primary malignancy.

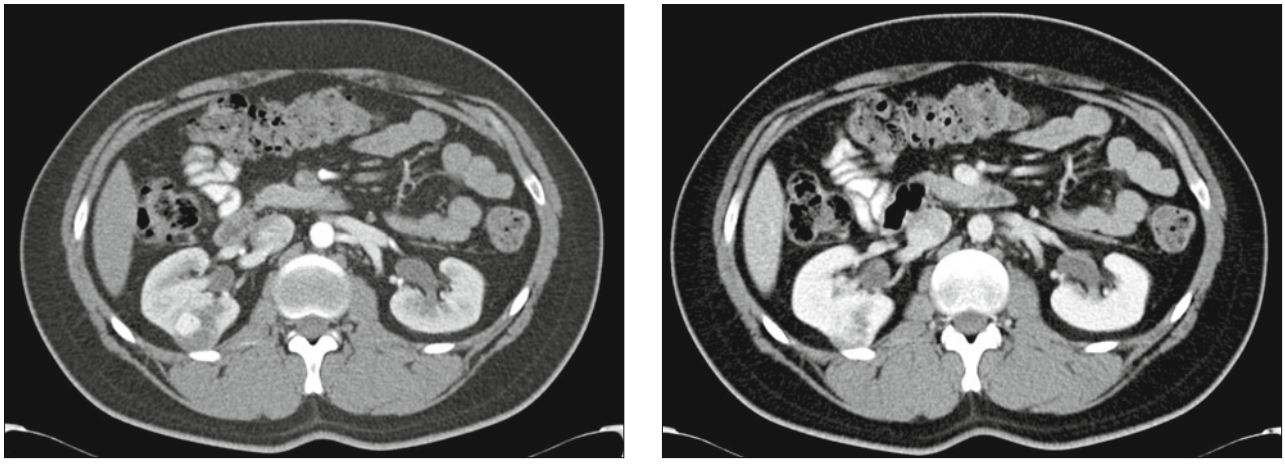

Fig. 2. Renal cell carcinoma in 29y old male with history of right sided testicular teratoma and embryonal carcinoma. Postcontrast (80 ml iodine contrast agent) abdominal CT scan – arterial phase. Postcontrast (80 ml iodine contrast agent) abdominal CT scan – venous phase. Note: Solid tumor of the right kidney with inhomogenous postcontrast enhancement. Circumaortal course of the left renal vein.

rence was registered mainly in prostate cancer (n = 17 patients), kidney cancer (n = 13 patients) and colorectal cancer (n = 12 patients).

The aim of this study was to select the rarest subgroup of patients with MPN which was identified as synchronous OPM category and analyze the cases (Fig. 1).

Results

In our study group, we have identified two cases of synchronous primary TC and OPM representing 1.3 % of MPN and 0.1 % of all TC patients treated in the center. Both patients had primary TC and kidney cancer, diagnosed within the defined period of three months. We aimed to evaluate the clinical and demographic features and treatment strategy and compared it to the literature findings.

46-year old patient with 9 months history of back pain, 2–3 weeks of abdominal pain in epigastrium and right lumbar region. After deterioration of pain in October 2017 the patient visits an emergency department, where contrast enhanced computed tomography (CT) scan reveals an irregular, lobulated tumorous expansion of 69 x 48 x 56 mm in the right kidney located predominantly in its ventral part, extending centrally into the kidney hilum. Despite the tumor extension signs of thrombosis in the renal vein were not present. Displacement of the left kidney laterally due an extensive retroperitoneal lymphadenopathy 93 x 84 x 165 mm was present, causing blockade of urine drainage. Dislocation of renal vessels was also noted (Fig. 2). Patient was referred to a department of urology on 20th of October 2017 for surgical resection of the tumor. During the preoperative investigation a urologist found tumor resistance of the left testicle. Radical orchiectomy was performed on 30th of October 2017 with the histological finding of a pure seminoma of testis, stage IIC (pT2N3M0, S0), good prognosis. Due to CT finding of hydronephrosis caused by an external compression of ureter by retroperitoneal mass, patient required implantation of JJ ureteral stent. After reconvalescence the patient was referred to the department of medical oncology, where he underwent three cycles of the induction combination chemotherapy Bleomycin, Etoposide, Cisplatin (BEP) with the effect of regression of the retroperitoneal lymphadenopathy. A positron emission tomography (PET) scan confirmed complete remission of the disease with persistence of the tumorous expansion of the right kidney. After the termination of the systemic treatment, the patient underwent nephrectomy of the right kidney on 26.03.2018. Histology confirmed clear cell renal carcinoma pT1bN0M0, stage I, histopathological grade 1. PET performed on 14th of May 2018 resulted in no apparent hypermetabolic lesions characteristic for the presence of the viable tumor tissue. Afterwards, the patient is followed up by an onco-urologist in complete remission of both of the tumors with actual disease-free survival (DFS) of 15 months.

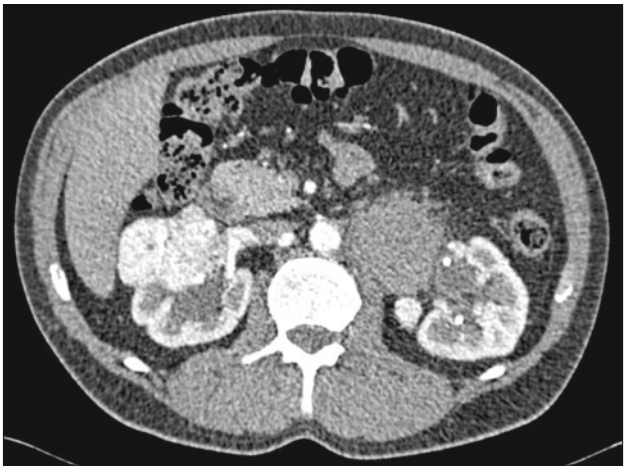

Fig. 3. Clear-cell renal carcinoma in 46y old male with history of left sided testicular seminoma. Tumour of the right kidney extending into the central/hilar region and a pathological lymphadenopathy on the left.

28-year old patient had discovered a small resistance in his right testicle and visited urologist within a week. On 15th of June 2015 he had radical orchiectomy with finding of small tumor (20 x 10 mm). Histology revealed teratoma and embryonal carcinoma, pT1N0M0, serum tumor markers negative. Contrast enhanced CT was performed as a part of standard staging procedures after surgery. On the dorsal contour of the right kidney there was a solid non-homogeneously enhancing lesion 28 x 33 x 29 mm with a sharp outer margin. The tumor lifted the posterior sheet of Gerot's fascia and had a direct contact with the XII. rib on the right side, without its osteodestruction (Fig. 3). Active surveillance was indicated based on the current guidelines. Patient was referred to a department of urology, where they performed laparoscopic nephrectomy of the right kidney. Histology had confirmed clear cell renal carcinoma pT1aN0M0, histopathological grade 2. Consecutive CT confirms complete remission of both malignancies and the patient is followed up by an experienced onco-urologist with actual DFS of 48 months.

Discussion

Testicular cancer represents 1–1.5 % of malignant tumors in males and about 5 % of urologic tumors in general. The reported incidence of BTC is 1–5 %, incidence of synchronous tumors is 1–2.8 %, while of metachronous tumors represent 2.4–5.2 % In our study group the incidence of BTC was 4.7 % (89 patients), of these 8 cases were synchronous (0.43 %) and 81 metachronous tumors (4.33 %). The majority of synchronous BTC present with the same histologic type, usually as seminoma (14, 15).

Because of scarcity of OPM in germ cell cancer patients, most of the publications are in the form of case reports or small-scale studies. Moreover, synchronous non-testicular OPM represent the rarest variation of duplex malignancies in patients with TC. In the present study of 1,870 patients with germ cell tumors, we have detected two cases of synchronous OPM. Interestingly, both patients were diagnosed with clear cell renal carcinoma. To the best of our knowledge, no systemic scientific research data addresses the synchronous incidence of these types of malignant tumors arising from urogenital origin with only one published case study of this combination of tumors (21). This fact restricts the scope of debates on treatment strategies. However, herein analyzed patients were primarily treated for TC and later after completion of therapy underwent definitive surgical treatment of the renal cancer. Both of studied patients have achieved a complete remission of both OPM confirmed by imagining studies (CT and PET). Currently, they have reached the DFS of 15 and 48 months. Interestingly, epidemiological history of both patients was negative for the known risk factors of testicular and renal cancer.

We would like to highlight the fact, that in case of primary diagnosis presumable advanced renal cancer, the experienced urologist has diagnosed a palpable lesion in testis and preferred orchiectomy as the first step of the treatment. The possibility of metastatic spread of renal cancer to the testes is uncommon, but possible. From published meta-analyses an estimated incidence rate represents 0.3–3.6 % (22). In case of palpable mass in scrotum, orchiectomy causes a minimal delay in planned definitive treatment. However, histological examination can unambiguously define the origin of tumor. In case of doubts in indication of orchiectomy, serum tumor marker examination is highly advisable.

In conclusion, this retrospective study of 1,870 patients with TC have led to identification of the rarest subgroup of patients with MPN. With so far single published case of synchronous TC and renal cancer, we bring interesting insight and more data regarding the diagnosis and treatment of this combination of cancers. Nevertheless, our results provide a reasonable estimate of the overall risk of OPM in TC patients, both metachronous (3.2% of overall TC patients, 39.3% of MPN in TC patients) and synchronous (0.1% of overall TC patients, 1.3% of MPN in TC patients). Since little is known regarding the etiology and the increasing incidence of TC, the study of multiple cancers can bring important insights into shared etiologic influences as well as into therapy related and diagnostic factors. However, approximately one third of the cases of MPN are diagnosed as synchronous, the other two thirds are diagnosed as metachronous tumors. Therefore, we recommend that both baseline staging and follow-up clinical examinations should focus on the eventuality of MPN. Patient-oriented approach with focus on identification and possibly histological verification of MPN enables more accurate multidisciplinary decisions. In conclusion, our experience also indicates the advantage of long-term follow up of TC patients within a specialized center by experienced onco-urologist.

References

1. Zhai C, Cai Y, Lou F et al. Multiple primary malignant tumors – A clinical analysis of 15,321 patients with malignancies at a single center in China. J Cancer. 2018; 16; 9 (16): 2795–2801.

2. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and statistical study. Am J Cancer 1932; 16:1358–1414.

3. Xu LL, and Gu KS. Clinical retrospective analysis of cases with multiple primary malignant neoplasms. Gen Mol Res 2014; 13 (4): 9271–9284.

4. Coyte A, Morrison DS, McLoone P. Second primary cancer risk – the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer. 2014; 18; 14: 272.

5. Rosso S, De Angelis R, Ciccolallo L et al. Multiple tumours in survival estimates. Eur J Cancer 2009; 45 (6): 1080–1094.

6. Vogt A, Schmid S, Heinimann K et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open 2017; 2 (2): e000172.

7. Testori A, Cioffi U, De Simone M et al. Multiple primary synchronous malignant tumors. BMC Res Notes. 2015; 27; 8:730.

8. Jena A, Patnayak R, Lakshmi AY, Manilal B, Reddy MK. Multiple primary cancers: An enigma. South Asian J Cancer 2016; 5 (1): 29–32.

9. Nielsen SF, Nordestgaard BG, Bojesen SE. Associations between first and second primary cancers: a population-based study. CMAJ 2012; 184 (1): E57–E69.

10. Watson RA, Morgan RD, Joseph J et al. Bilateral testicular germ cell tumors: A case-series from a UK- based tertiary referral center over 19 years. Clin Genitourin Cancer. 2018; 16 (3): e513–e516.

11. Oldenburg J, Fosså SD, Nuver J et al. Testicular seminoma and non-seminoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24:vi125–vi132.

12. Kopp RP, Chevinsky M, Bernstein M et al. Bilateral testicular germ cell tumors in the era of multimodal therapy. Urology 2017; 103: 154–160.

13. Klatte T, de Martino M, Arensmeier K, Reiher F, Allhoff EP, Klatte D. Management and outcome of bilateral testicular germ cell tumors: A 25-year single center experience. Int J Urol 2008; 15: 821–826.

14. Campobasso D, Ferretti S, Frattini A. Synchronous bilateral testis cancer: clinical and oncological management. Contemp Oncol (Pozn) 2017; 21 (1): 70–76.

15. Ondrus D, Hornak M, Matoska J. Bilateral testicular germ-cell tumors – a single centre long-term experience. Int Urol Nephrol 2001; 33 (3): 521–524.

16. International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997; 15 (2): 594–603.

17. Van den Belt-Dusebout AW, de Wit R, Gietema JA et al. Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 2007; 25 (28): 4370–4378.

18. Travis LB, Fossa SD, Schonfeld SJ et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 2005; 97 (18): 1354–1365.

19. Travis LB, Beard C, Allan JM et al. Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst 2010; 102 (15): 1114–1130.

20. Travis LB, Curtis RE, Storm H et al. Risk of second malignant neoplasms among long-term survivors of testicular cancer. J Natl Cancer Inst. 1997; 89 (19): 1429–1439.

21. Deshmukh S, Fulare S, Chowksey S, Soitkar A, Nagre A, Mundle A. Synchronous mixed germ cell tumor of testis and renal cell carcinoma: A rare presentation. Int J Surg Case Rep. 2019; 16; 60: 123–125.

22. Marzouk K, Alyami F, Merrimen J, Bagnell S. Metastatic renal cell carcinoma to the testis: A case report and review of the literature. Can Urol Assoc J 2014; 8 (11–12): E924–E927.

Received June 18, 2019.
Accepted July 9, 2019.