JBUON 2020; 25(4): 2117-2122
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Follow-up protocol for oncological patients at risk of developing multiple primary neoplasms

Adina Nemes[1,2], Nicolae Todor[2], Viorica Nagy[1,2]

[1]"Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania. [2]The Oncology Institute "Prof.Dr.Ion Chiricuta" Cluj-Napoca, Romania.

Summary

Purpose: *Multiple primary neoplasms (MPN) have a growing impact in the outcome of oncological patients given the rising incidence of these entities in daily practice. The early diagnosis of secondary tumors could translate into better survival of patients with MPN. The final objective of this study was the elaboration of a follow-up protocol for oncological patients at risk of developing multiple primary neoplasms.*

Methods: *Patients with MPN diagnosed and treated in the Oncology Institute "Prof.Dr.Ion Chiricuta" Cluj-Napoca (OICN) between 2008-2012 were included in this nonrandomized, retrospective study and the clinicopathological characteristics of these patients and the prognostic factors possibly involved in the occurrence of MPN were analyzed.*

Results: *278 patients with MPN were included in this study. The median age at diagnosis was 60 years. The median interval between the diagnosis of the primary and secondary neoplasm was 30.98 months. Smoking and alcohol consumption were the most frequent environmental factors observed in patients with MPN. Patients diagnosed with breast cancers, head and neck cancers, colorectal cancer, prostate cancer, ovarian cancer or uterine body cancer were the patients with the highest risk of developing MPN.*

Conclusion: *This first follow-up protocol for oncological patients at risk of developing multiple primary neoplasms could be implemented in daily practice with further validation of the protocol.*

Key words: *multiple neoplasms, multiple cancers, metachronous tumors, synchronous tumors, second primary*

Introduction

Multiple primary neoplasms (MPN) represent a reality in the daily practice of medical oncologists and radiotherapists with a major impact on the outcome of oncological patients. In the past, MPN were described as sporadic cases but nowadays their incidence ranges between 0.7% and 11.7% with more and more cases being diagnosed every day [1-4]. Diagnosis in early stages of a secondary synchronous or metachronous tumor could have a favorable prognosis for the survival of patients with MPN.

Data in the literature regarding MPN are limited and most of the published studies do not uniformly evaluate the whole complexity of MPN.

The aim of this study was to evaluate the clinicopathological characteristics of patients with MPN and the prognostic and predictive factors for the development of MPN and, based on the results, to elaborate a protocol for the follow-up of cancer patients at risk for the development of a second cancer for the purpose of the early diagnosis of the second, or even third cancer.

Corresponding author: Adina Nemes, MD. "Iuliu Hatieganu" University of Medicine and Pharmacy, Victor Babes Str, no.8, 400012, Cluj-Napoca, Cluj, Romania.
Tel:+40 741922226, Fax:+40 264450477, Email:Adina.Nemes@umfcluj.ro
Received: 29/01/2020; Accepted: 04/03/2020

Methods

This was a retrospective, nonrandomized study that included 278 patients with MPN diagnosed and treated in the Oncology Institute "Prof.Dr.Ion Chiricuta" Cluj-Napoca (OICN) between 2008-2012.

MPN were defined as two or more primary neoplasms diagnosed in the same patient simultaneously or at a certain time and that did not represent the progression, relapse or metastasis of the first neoplasm [5,6]. The criteria used in order to consider a patient as having MPN were the following: 1. each cancer must have been malignant according to the histopathology report; 2. the cancers must have been geographically separate and histologically different; 3. the possibility of metastases among the cancers was excluded [7-10].

From the study were excluded patients with carcinoma *in situ* regardless of localization.

Depending on the time of diagnosis of the first and second malignancies MPN were classified as synchronous and metachronous, respectively; synchronous when the second neoplasm was diagnosed within 6 months from the diagnosis of the first neoplasm and metachronous when the second neoplasm was diagnosed in more than 6 months after the diagnosis of the first neoplasm [11,12]. Metachronous neoplasms were further classified in metachronous < 5 years and metachronous > 5 years [5].

The possible risk factors implicated in the etiology of MPN were recorded and the cases were classified in one of the following categories according to major etiological factors: syndromic cases, iatrogenic neoplasms, neoplasms with common etiologic factors (genetic predisposition or environmental factors) and incidental cases.

The demographic, clinical, pathological and treatment related data of the patients included in the study were collected from the patient's medical records and analyzed. An informed consent has been previously signed by all the patients included in this study. The Ethics Committee of OICN and of the "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca evaluated and approved the study design.

Statistics

A database was created based on the data collected. Descriptive analysis was used for demographic and clinical characteristics of the patients. Kaplan-Meier method and log-rank test were used in plotting survival curves and comparing data. Statistical significance was considered at a p value less than 0.05.

Results

There were 278 patients with MPN diagnosed and treated in OICN between 2008-2012. Out of the 278 patients 120 (43%) presented with synchronous tumors and 158 (57%) presented with metachronous tumors. 260 patients presented with two MPN and 13 patients presented with three MPN. Among the patients with metachronous tumors 92% developed a second neoplasm in the first 5 years after the diagnosis of the primary tumor.

The median age at diagnosis of the first neoplasm was 60 years (26-87). When age was analyzed according to age groups (young 0-14 years, adults 15-64 years and old 65+ years), most patients (197;71%) with MPN were in the age group 15-64 years, with only 81 (29%) patients being in the age group 65+.

The median interval between the diagnosis of the primary and subsequent tumor for metachronous tumors was 30.98 months, ranging between 6.07 months and 85.47 months.

The analysis of the major etiological factors possibly implicated in the etiology of MPN showed that 73 (26%) cases were syndromic cases, 15 (5%) cases were iatrogenic neoplasms, 95 (34%) were neoplasms with common etiologic factors [23 (8%) with genetic predisposition and 72 (26%) with environmental factors] and 95 (34%) were incidental cases. Smoking and alcohol consumption were the most frequent environmental factors observed (in 22% of the cases and 11% of the cases, respectively).

Breast cancer (40 patients, 14%), head and neck (H&N) cancers (36 patients, 13%), colorectal (24 patients, 9%), ovarian (24 patients, 9%), prostate (23 patients, 8%) and uterine body tumors (20 patients, 7%), were the first 6 most frequent initial primary tumors identified and breast (33 patients, 12%), colorectal (31 patients, 11%), uterine body (23 patients, 8%), H&N (21 patients, 8%), lung (20 patients, 7%) and thyroid tumors (20 patients, 7%) were the most frequent secondary tumors.

The most frequently diagnosed 6 tumors in women were breast (74 patients, 24%), uterine body (41 patients, 13%), ovarian (36 patients, 12%), cervix (31 patients, 10%), colorectal (29 patients, 9%) and thyroid tumors (23 patients, 7%) and in men H&N (51 patients, 20%), prostate (42 patients, 16%), lung (32 patients, 12%), colorectal (29 patients, 11%), bladder (20 patients, 8%) and skin tumors (19 patients, 7%).

For patients diagnosed with colorectal cancer with MPN the median interval between the diagnosis of the primary and subsequent tumor was 34.15 months (22.99-45.31), for patients diagnosed with uterine body cancer the interval was 43.5 months (32.26-54.65), for prostate cancer patients 25.3 months (17.15-33.38), for breast cancer patients 33 months (24.94-41.07), for lung cancer patients 26.1 months (14.36-37.89) and for H&N cancers patients 33.3 months (22.94-43.69).

The mean age at diagnosis for patients with breast cancer with MPN was statistically higher compared to patients with breast cancer as a single tumor (59.7 years vs 55.6 years, p=0.011). For patients diagnosed with H&N cancers, uterine body cancer, colorectal, prostate, and lung cancer the

mean age at diagnosis was similar among patients with MPN compared with patients diagnosed with the respective localizations as single neoplasms.

For patients diagnosed with breast cancer with synchronous MPN the most frequent associations were with uterine body cancer (4 cases), cervical cancer (3 cases), ovarian cancer (2 cases) and breast cancer (4 cases). For the patients diagnosed with breast cancer with metachronous MPN the most frequent associations were with renal cancer (3 cases), thyroid (3 cases), uterine body (2 cases), ovarian (2 cases), bladder cancer (4 cases) and non-Hodgkin's lymphoma (4 cases) (Table 1).

The most frequent associations observed in patients diagnosed with synchronous H&N cancers were H&N cancers-H&N (9 cases), H&N cancers-esophageal cancer (4 cases) and H&N cancers-lung cancer (4 cases). For patients diagnosed with metachronous H&N cancers the most frequent associations were H&N cancers-lung cancer (5 cases), H&N cancers-H&N cancers (3 cases), H&N cancers-esophageal cancer (2 cases) and H&N cancers-colorectal cancer (2 cases) (Table 1).

Uterine body cancers with synchronous tumors were most commonly associated with ovarian cancer (12 cases), breast cancer (5 cases), skin cancers (2 cases) and cervical cancer (2 cases). For patients diagnosed with uterine body cancer with metachronous MPN the most frequent associations were uterine body cancer-breast cancer (4 cases) and uterine body cancer-colorectal cancer (2 cases) (Table 1).

The association colorectal cancer-renal cancer was the most frequent association in patients diagnosed with colorectal cancer with synchronous tumors (3 cases), followed by colorectal cancer-cervical cancer (3 cases), colorectal cancer-ovarian cancer (3 cases) and colorectal cancer-colorectal cancer (2 cases). The most frequent associations in patients with metachronous colorectal cancer were colorectal cancer-prostate cancer (4 cases), colorectal cancer-renal cancer (2 cases) and colorectal cancer-breast cancer (2 cases) (Table 1).

For patients diagnosed with prostate cancer who developed synchronous neoplasms the most frequent associations were with bladder cancer (9 cases) and renal cancer (3 cases). For patients diagnosed with prostate cancer with metachronous neoplasms the most frequent associations were with bladder cancer (2 cases), colorectal cancer (2 cases) and lung cancer (2 cases) (Table 1).

The most frequent associations observed in patients with lung cancer with synchronous tumors were lung cancer-H&N cancers (2 cases) and lung cancer-esophageal cancer (2 cases). The association of lung cancer-colorectal cancer was the most frequent association in patients diagnosed with lung cancer with metachronous tumors (3 cases), followed by lung cancer-breast cancer (2 cases) (Table 1).

Table 1. Frequent cancer associations in the main localizations

	Synchronous MPN		*Metachronous MPN*	
Breast cancer	Breast cancer	4 cases	Bladder cancer	4 cases
	Uterine body cancer	4 cases	NHL	4 cases
	Cervical cancer	3 cases	Renal cancer	3 cases
	Ovarian cancer	2 cases	Thyroid cancer	3 cases
Head and neck cancers	H&N cancer	9 cases	Lung cancer	5 cases
	Esophageal cancer	4 cases	H&N cancer	3 cases
	Lung cancer	4 cases	Esophageal cancer	2 cases
	Colorectal cancer	2 cases		
Uterine body cancer	Ovarian cancer	12 cases	Breast cancer	4 cases
	Breast cancer	5 cases	Colorectal cancer	2 cases
	Cervical cancer	2 cases		
	Skin cancer	2 cases		
Colorectal cancer	Renal cancer	3 cases	Prostate cancer	4 cases
	Cervical cancer	3 cases	Renal cancer	2 cases
	Ovarian cancer	3 cases	Breast cancer	2 cases
	Colorectal cancer	2 cases		
Prostate cancer	Bladder cancer	9 cases	Bladder cancer	2 cases
	Renal cancer	3 cases	Colorectal cancer	2 cases
Lung cancer	H&N cancer	2 cases	Colorectal cancer	3 cases
	Esophageal cancer	2 cases	Breast cancer	2 cases

Discussion

A follow-up protocol for oncological patients at risk of developing MPN was elaborated based on the results presented above and to our knowledge this protocol would be the first such protocol developed both nationally and internationally.

Oncological patients should be followed-up for 5 years, and during this interval the evaluation of these patients for the diagnosis of metachronous neoplasms should be considered. The secondary neoplasm could be diagnosed at a median interval of 30.98 months from the diagnosis of the primary neoplasm.

Patients at risk of developing MPN are those aged 60 years at the time of primary tumor diagnosis.

MPN are more frequent in adult patients diagnosed with cancer, under the age of 65, MPN being less common in the elderly patients (over 65 years of age).

Environmental factors, such as alcohol consumption and smoking, and genetic alterations, either in the form of genetic predisposition or syndromic cases, are the main risk factors for the development of MPN, risk factors that need to be identified and detailed in the history of patients diagnosed with cancer.

Patients diagnosed with breast cancers, H&N cancers, colorectal cancer, prostate cancer, ovarian cancer or uterine body cancer are the patients with the highest risk of developing MPN, these patients needing to undergo a rigorous program of follow-up and screening for the early diagnosis of a possible secondary neoplasm.

Patients at risk of developing MPN should be evaluated periodically by history, physical examination and laboratory examinations for suspicion

Table 2. Follow-up protocol for oncological patients at risk of developing multiple primary neoplasms

Localization	*Evaluation during the initial work-up for the primary tumor for the diagnosis of synchronous tumors*	*Evaluation during follow-up for the diagnosis of metachronous tumors*	*Mean diagnostic interval between primary and secondary tumor diagnosis*
Breast cancer	gynecological examination	gynecological examination thyroid ultrasound CT chest+abdomen+pelvis	33.01 months
Head and neck cancers	complete ENT examination gastroscopy CT chest +/- bronchoscopy	complete ENT examination gastroscopy colonoscopy CT chest +/- bronchoscopy	33.32 months
Colorectal cancer	gynecological examination complete colonoscopy CT abdomen	breast examination mammography/breast ultrasound PSA CT chest+abdomen+pelvis	34.15 months
Prostate cancer	serial urinary cytology CT abdomen+pelvis	serial urinary cytology colonoscopy CT chest+abdomen+pelvis	25.26 months
Uterine body cancer	breast examination mammography/breast ultrasound colonoscopy	breast examination mammography/breast ultrasound colonoscopy	43.46 months
Lung cancer	complete ENT examination gastroscopy	breast examination mammography/breast ultrasound colonoscopy	26.12 months
Ovarian cancer	breast examination mammography/breast ultrasound colonoscopy		
Bladder cancer	PSA		
Renal cancer	PSA colonoscopy		
Esophageal cancer	complete ENT examination CT chest +/- bronchoscopy		

and diagnosis of breast cancer, colorectal cancer, uterine cancer, H&N cancers, lung cancer, or secondary thyroid cancer.

Female patients diagnosed with breast cancer, uterine body cancer, ovarian, cervical, colorectal and thyroid cancer are the patients with the highest risk of developing MPN.

Male patients diagnosed with H&N cancers, prostate cancer, lung, colorectal, bladder and skin cancers are the patients with the highest risk of developing MPN.

Patients diagnosed with breast cancer at a mean age of 59.7 years are at increased risk of developing MPN, and the median interval at which secondary neoplasms are diagnosed is 33.01 months.

For patients diagnosed with breast cancer, a gynecological examination is required in order to diagnose a possible secondary synchronous neoplasm of the cervix, uterine body or ovary. Patients diagnosed with gynecological cancers must perform screening examinations for the diagnosis of a possible synchronous breast cancer. During the follow-up of the patients diagnosed with breast cancer, a gynecological examination, a thyroid ultrasound and a computed tomography (CT scan) of the chest, abdomen and pelvis must be performed once a year in order to diagnose a possible secondary metachronous neoplasm in the genital sphere, renal, thyroid, bladder or Hodgkin's lymphoma (Table 2).

From the initial work-up of patients diagnosed with H&N cancers it should not be missing a complete ENT examination, upper digestive endoscopy and a chest CT scan completed in case of suspicion with a bronchoscopy for the diagnosis of a possible synchronous tumor with localization in the esophagus, ENT sphere or lung. Also, patients diagnosed with esophageal cancer or lung cancer should undergo a complete ENT examination. The aforementioned examinations should also be included in the follow-up of patients diagnosed with H&N cancers, at least once a year, for the diagnosis of possible metachronous tumors with these localizations, and in addition a colonoscopy should be recommended for the screening of colorectal tumors. The mean interval at which metachronous tumors are diagnosed in patients with H&N cancers is 33.32 months (Table 2).

Secondary neoplasms are diagnosed at a median time of 34.15 months in patients diagnosed with colorectal cancer. In these patients it is extremely important to perform a complete colonoscopy in order to diagnose possible synchronous colorectal neoplasms, as well as an abdominal CT scan to exclude possible liver metastases and a possible synchronous renal tumor. Patients diagnosed with renal cancer and patients diagnosed with gynecological tumors must undergo a complete colonoscopy for the diagnosis of a possible synchronous colorectal tumor. Patients diagnosed with colorectal cancer should undergo a gynecological examination within the initial work-up, and during the follow-up a breast examination and an annual mammogram. Male patients diagnosed with colorectal cancer should be screened for possible metachronous prostate cancer during follow-up (annual dosing of PSA). Also, patients diagnosed with colorectal cancer should perform at least once a year a CT scan of the chest, abdomen and pelvis, which in addition to possible metastases or relapse may reveal a possible metachronous renal tumor (Table 2).

Patients diagnosed with prostate cancer should undergo a CT scan of the abdomen and pelvis and a serial urinary cytology for the diagnosis of possible renal or bladder neoplasm. Patients diagnosed with bladder cancer and renal cancer should undergo a PSA screening for the diagnosis of a possible synchronous prostate tumor. Also, during the follow-up of patients diagnosed with prostate cancer, serial urinary cytology and CT scan of the abdomen and pelvis should be maintained, and a chest CT scan is recommended for the diagnosis of lung and bladder metachronous neoplasms. During follow-up, patients diagnosed with prostate cancer must undergo a complete colonoscopy annually for the diagnosis of possible metachronous colorectal cancer. The median interval between the first and second neoplasm for patients diagnosed with prostate cancer is 25.26 months (Table 2).

An ENT examination and a gastroscopy should not be absent from the initial work-up of patients diagnosed with lung cancer. Patients diagnosed with H&N cancers or esophageal cancer should have a chest CT scan, coupled in the case of suspicion with a bronchoscopy. Annual colonoscopy should be introduced in the follow-up of patients diagnosed with lung cancer. Female patients diagnosed with lung cancer should perform an annual mammogram for breast cancer screening. The median interval between the first and second neoplasm for patients diagnosed with lung cancer is 26.12 months (Table 2).

Gynecological examination in patients diagnosed with uterine body cancer at the time of diagnosis should also include the careful evaluation of the cervix and annexes. Patients diagnosed with uterine body cancer must undergo a mammogram within the initial work-up, as well as during the follow-up. Also colonoscopy should be included in the follow-up of patients diagnosed with uterine body cancer. The median follow-up for the diagnosis of metachronous neoplasms is 43.46 months (Table 2).

Conclusions

This follow-up protocol for oncological patients at risk of developing MPN could be implemented in the current clinical practice, thus a larger number of patients with MPN could be identified and analyzed with subsequent protocol validation.

Conflict of interests

The authors declare no conflict of interests.

References

1. Mariotto AB, Rowland JH, Ries LA et al. Multiple cancer prevalenece : a growing challange in long-term survivorship. Cancer Epidemiol Biomarkers Prev 2007;16:566-71.
2. Coleman MP. Multiple primary malignant neoplasms in England and Wales, 1971-1981. Yale J Biol Med 1986;59:517-31.
3. Babacan NA, Aksoy A, Cetin B et al. Multiple primary malignant neoplasms: multicenter results from Turkey. JBUON 2012;17:770-5.
4. Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: case report and comprehensive review of the literature. Am J Clin Oncol 2003;26:79-83.
5. Amer HM. Multiple neoplasms, single primaries, and patient survival. Cancer Manag Res 2014; 6:119-34.
6. Takalkar U, Aseganaonkar BN, Kodlikeri P et al. An elderly woman with triple primary metachronous malignancy: a case report and review of literature. Int J Surg Case Rep 2013; 4:593-6.
7. Warren S, Gates O. Multiple primary malignant tumors. A survey of the literature and a statistical study. Am J Cancer 1932;16:1358-414.
8. Moertel CG. Multiple primary malignant neoplasms. Tumors of different tissues or organs. Cancer 1961;14:231-7.
9. Morris LGT, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after the index head and neck cancer:subsite-specific trends in the era of huma papillomavirus-associated oropharyngeal cancer. J Clin Oncol 2010;29:739-46.
10. Hulikal N, Ray S, Thomas J, Fernandes DJ. Second primary malignant neoplasms: a clinicopathological analysis from a cancer center in India. Asian Pac J Cancer Prev 2012;13:6087-91.
11. Moertel CG. Multiple primary malignant neoplasms: historical perspectives. Cancer 1977;40 (Suppl.4):1786-92.
12. Aydiner A, Karadeniz A, Uygun K et al. Multiple primary neoplasms at a single institution: differences between synchronous and metachronous neoplasms. Am J Clin Oncol 2000;23:364-70.