

## REVIEW ARTICLE

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# The impact of multiple primary neoplasms in daily practice- a systematic review of the literature

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## Summary

*Multiple primary neoplasms (MPN) represent particular entities with growing impact in our daily practice due to their increasing incidence and implications in the treatment and outcome of oncological patients. MPN have a specific definition and can be classified as synchronous or metachronous depending on the time of diagnosis of the first and latter malignancies. We review in this article the possible risk factors involved in the etiology of MPN, the most*

*frequent cancer associations, the incidence of synchronous and metachronous tumors, the stage at diagnosis, the treatment administered to the patients with MPN and the survival of patients with MPN.*

**Key words:** metachronous tumors, multiple neoplasms, multiple tumors, synchronous tumors

## Introduction

Multiple primary neoplasms (MPN) represent particular entities with an increasing incidence that nowadays affect a remarkable number of cancer survivors. Since the 1890, when they have been described for the first time, MPN have been a matter of controversy and there is a growing interest in studying MPNs, the most frequent associations, possible risk factors and implications of multiple cancers in the outcome of a patient.

The incidence of MPN increased significantly from their first mentions in the literature when they were described as sporadic cases. Today their incidence ranges between 0.7% and 11.7% [1-3] with continuous increase. The increasing incidence of MPN can be explained by the increase in cancer incidence and also by the increase in life expectancy and improved survival of cancer pa-

tients due to the breakthroughs in cancer patients treatment in the last few years [4-7]. The diagnosis in early cancer stages due to rigorous screening of cancer patients and the technological innovations in terms of diagnostic imaging also contributed to the increase in the incidence of MPNs [5,6].

## Definition

Multiple primary neoplasms (MPN) are defined as two or more primary neoplasms diagnosed in the same patient simultaneously or at a certain time and that do not represent the progression, relapse or metastasis of the first neoplasm [8,9].

The definition of MPN has evolved during the years. The most recent definition is the one elaborated by Warren and Gates in 1932 and refined

later by different authors. The criteria on which two or more neoplasms diagnosed in the same patient can be classified as MPN are the following: 1. each cancer must be malignant according to the histopathology report; 2. the cancers must be geographically separate and histologically different; 3. the possibility of metastases among the cancers must be excluded [10-13].

## Classification

MPN can be classified as synchronous or metachronous depending on the time of diagnosis of the first and latter malignancies. Synchronous is the neoplasm diagnosed within 6 months from the diagnosis of the first neoplasm and metachronous is the neoplasm diagnosed in more than 6 months after the diagnosis of the first, respectively [14,15]. Metachronous neoplasms can be further classified in metachronous <5 years and metachronous >5 years. Furthermore multiple neoplasms diagnosed during the initial workup of one cancer can be classified as simultaneous [8].

## Possible risk factors

The causes implicated in the development of MPN include genetic, immunological, environmental and iatrogenic (chemotherapy and ionizing radiation) factors, although, there are only a few studies that have addressed this issue [5,10,16].

Genetic alterations can be implicated in the development of MPN either as genetic susceptibility or as hereditary cancer syndromes. Patients that have positive family history of cancer, but with cancers that can not be classified as hereditary cancer syndromes seem to be involved in only a small proportion of MPN. On the contrary MPN are described in many hereditary cancer syndromes, especially in the ones associated with DNA microsatellite instability such as hereditary nonpolyposis colorectal syndromes (Lynch I and II syndromes), Li Fraumeni syndrome, neurofibromatosis, familial adenomatous polyposis, hereditary breast and ovarian cancer and multiple endocrine neoplasia syndromes [7,13,17].

The most important environmental factors implicated in the development of MPN are smoking and alcohol consumption involved in the etiology of head and neck, lung, esophagus, pancreas, urinary system and cervical cancer. The occurrence of MPN in heavy smoker and alcohol consumption patients can be explained by the field cancerization theory [13,18]. Approximately 35% of cancer survivals who continue to smoke will develop a second malignancy [19]. Other en-

vironmental factors that can be incriminated in the occurrence of MPN are hormonal factors (endogenous and exogenous estrogen exposure) and dietary factors ( fat intake and low fiber intake) for breast, gynecological, prostate and colorectal cancer [7,8,13,20-22]. Obesity and physical inactivity have been incriminated in the development of primary or second primary cancer of the breast, uterine body and colorectum [7,8,23-27].

Chemotherapy and ionizing radiation can be involved in the development of MPN especially after 5-15 years from the treatment of the primary neoplasm. Chemotherapeutic agents such as alkylating agents, topoisomerase II inhibitors and anthracyclines can cause acute myeloid leukemia, sarcomas, bladder cancer or lung cancer after few months up to 9 years from their administration [18,19,28-33]. In a study on 377 patients with MPN, Babacan et al. showed that 66.7% of the 138 patients who received chemotherapy received topoisomerase II inhibitors and anthracyclines. Curtis et al. found a higher risk of developing leukemia in women with breast cancer treated with alkylating agents (relative risk 10.0), especially in patients treated with melphalan alone (relative risk 31.4), but also with cyclophosphamide (relative risk 3.1) [33]. Radiation therapy can induce second malignancies after 5-10 years in the radiation fields. The risk of rectal and urinary bladder cancer, bone and soft tissue sarcomas was found to be increased in patients receiving radiation therapy in the pelvis [19,34]. Babacan et al. reported that 4.6% of the patients who received radiation therapy for their primary tumor developed second malignancies in the radiotherapy field [18]. On a series of 38 patients with MPN Hulikal et al. showed that 12 out of 38 patients included in the study had second tumors in the radiation field [13].

## Frequent cancer associations

Several studies published in the literature reported head and neck, breast, prostate, colorectal and gynecological cancers as the most common initial primary neoplasms and head and neck, breast, lung, colorectal and gynecological cancers as the most common subsequent neoplasms [8,13,18,35-37].

Babacan et al. reported on a series of 377 patients with MPN that in women breast, gynecological and colorectal tumors were the most frequent primary tumor types and breast, gynecological and colorectal tumors were the most frequent second primary tumor types. In men head and neck tumors, bladder cancer and prostate cancer were the most frequent primary tumor types

and lung cancer, colorectal tumors and renal cell carcinoma were the most frequent second primary tumor types [18].

Only few published studies analyzed the most frequent associations between the first and the second malignancy. One of them reported in women the following associations: breast-gynecological tumors, colorectal tumors-breast cancer, breast cancer-colorectal tumors. In men the most frequent associations reported were head and neck tumors-lung cancer, bladder cancer-lung cancer and bladder cancer-prostate cancer. Sixty-three percent of the patients included in this study were smokers, with a median body mass index of 25. Chemotherapy (including topoisomerase II inhibitors and/or anthracyclines) was administered to 36.6% of the patients, while 15.1% of the patients received radiotherapy for their primary tumor, out of which 4.6% developed second tumors in the previous radiotherapy field [18]. Powell et al. showed that the most frequent pairing was prostate cancer-bladder/ureter cancer in a study on 506 patients with MPN [36].

### **Synchronous vs. metachronous tumors**

Data published in the literature show that approximately 60% of patients with MPN present with metachronous tumors, with respect to the different number of patients included in studies on MPN, with a median time between the diagnosis of the two tumors ranging from 15 to 76.5 months. Most tumors are diagnosed within the first 5 years from the initial primary, with fewer tumors being diagnosed after 5 years [8,13,18,35-38]. In a retrospective study on 322 patients with MPN 7.1% of patients were identified with synchronous tumors, 27.3% with metachronous tumors <5 years and 24.2% with metachronous tumors > 5 years. Among the patients with synchronous tumors 7.5% of patients present with simultaneous tumors as reported by Amer [8].

### **Stage of primary/subsequent tumors**

Studies that have analyzed the stage of the tumors in patients with MPN reported conflicting data, the majority though report that patients with MPN present in early stage regarding the primary tumor (stage 0-II) and in advanced stage regarding subsequent tumor (stage III-IV) [8, 19,39-41].

Amer showed on a series of 322 patients with MPN that 3.7% of patients present with an initial stage 0 tumor, 43.5% with an initial stage I tumor, 31.7% with an initial stage II tumor, 11.2% with a stage III tumor and 9.9% with an initial stage IV

tumor. The authors showed that patients present with more advanced second primary tumor. 5.9% of patients present with a stage 0 tumor, 30.4% with a stage I tumor, 22.4% with a stage II tumor, 14.9% with a stage III tumor and 36.4% with a stage IV, respectively [8]. When compared to patients with single primary tumors, these data revealed that patients with single primary tumors present more often with advanced stage disease (2.6% stage 0, 21.7% stage I, 26.6% stage II, 21.5% stage III and 27.6% stage IV). This study also revealed that patients with synchronous tumors present with advanced stage tumors compared to patients with metachronous tumors (2.1% vs. 4.0% stage 0, 23.4% vs. 46.9% stage I, 17% vs. 34.2% stage II, 23.4% vs. 9.1% stage III and 34% vs. 5.8% stage IV) [8].

In contrast with Amer's study, Irimie et al. reported on a series of 63 patients with MPN that 66.5% of patients presented with stage III and IV primary tumors. Regarding the stage of the second tumor the authors showed that 52.3% of the patients also presented with stage III and IV tumors, concluding that this might be due to either a low compliance to follow-up or to neglecting the initial symptoms [35].

### **Treatment**

Treatment of patients with MPN might be challenging, In terms of choosing the chemotherapy regimen or the correct sequence of treatment for synchronous tumors, metachronous tumors' therapeutic approach is also challenging because the treatment of the initial neoplasm might influence the treatment of subsequent neoplasms. Studies that have analyzed the treatment of patients with MPN reported that patients underwent surgery with or without adjuvant chemotherapy or radiation therapy, chemotherapy alone or radiation therapy alone for their primary tumor and surgery with or without adjuvant chemotherapy or radiation therapy for their subsequent tumors [8,13,18,35]. Out of the 22 patients with synchronous tumors included in a study on 63 patients with MPN, 40.9% of patients underwent surgery alone for their primary tumor and 59.1% underwent surgery and adjuvant therapy for their primary tumor, while only 30% of those patients underwent surgery alone for their second tumor and 70% underwent surgery and adjuvant therapy for their second tumor. Most patients with metachronous tumors underwent surgery and adjuvant therapy (55% of the 41 patients with metachronous tumors), the remaining underwent surgery alone (10%) [35]. These studies also showed that

especially patients with metachronous tumors sometimes refuse treatment for the second tumor [8,13,18,35]. Hulikal et al. reported that 5 out of 25 patients with metachronous tumors refused treatment for their second tumor [13].

## Survival

The survival of patients with MPN was not uniformly analyzed by the studies published in the literature due to either the small number of patients included or to the immature data at the moment of the publication of the study. Amer concluded that patients with MPN had better survival than patients with single primary. This difference was more obvious in patients with metachronous tumors (95% five years survival rate for patients with metachronous tumors vs. 59% for patients with single primary). Patients with synchronous tumors had similar survival with patients with single primary tumors [8]. In a study on 72 Chinese patients with MPN, Jiao et al. reported a median survival of 3.8 years for patients with synchronous tumors vs. 17.3 years for patients with metachronous tumors [38]. It should be noted that the survival of patients with MPN depends on the site of the primary and subsequent tumors. The best survival rate has been reported in patients with breast cancer that have been diagnosed with

metachronous contralateral breast cancer (breast cancer was both the primary and the second primary tumor in this study) (5-year survival rate of 100% and 10 years survival rate of 96%), in contrast with patients diagnosed with hepatocellular carcinoma as primary or second primary tumor who had the worse survival (5-year survival rate of 51.8%) [42,43].

## Conclusion

Multiple primary neoplasms represent entities for which there is an increasing interest. The studies published in the literature are not only few but also not uniform in evaluating the different aspects that MPN involve. Also the number of patients included in studies with MPN varies from several tens to several hundreds, which might influence the statistical power of the results. All these make it difficult to draw clear conclusions on the possible risk factors involved in the occurrence of MPNs. The most frequent cancer associations maybe can lead us on developing clear protocols for the follow-up of patients at risk for developing multiple neoplasms.

## Conflict of interests

The authors declare no conflict of interests.

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