

Multiple Primary Malignant Tumours

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Abstract: Two or more histologically distinct malignancies in one individual are termed as multiple primary malignant tumours (MPMT). The incidence of these cases has been rising over the past few decades, primarily due to improved methods for cancer screening, diagnosis, treatment, and follow-up. They can show up as metachronous lesions later on or synchronously with the index malignancy. The precise aetiology is still unknown; however, a number of epidemiological variables have been proposed as potential risk factors. Modern imaging techniques are very helpful in the diagnosing process. Physician awareness is essential in order to raise suspicions about the potential for MPMT and to conduct appropriate investigations. There are currently no universal protocols based on evidence; instead, management is empirical and dependent on the judgments made by interdisciplinary teams.

Keywords: Multiple primary malignant tumours, synchronous, metachronous, prognosis, survival, hormones.

INTRODUCTION

Cancer patients now have access to more sophisticated diagnostic and therapeutic options than they had a few decades ago, which has improved disease management, raised survival rates, and allowed for earlier cancer discovery. The number of long-term surviving patients has increased, and this has led to an increasing burden of a condition for which Billroth T., as early as 1889, coined the term "multiple primary malignant tumours" [1]. Since then, the phrase "multiple primary malignant tumours (MPMT)" has been widely used to describe two or more distinct primary malignancies that develop concurrently or successively at various sites in the same person, provided that none of the tumours is a metastasis, extension, or recurrence of the others [2,3].

METHODS

A literature review was carried out using the keywords "multiple primary malignant tumours"; "Multiple primary malignant neoplasms"; "multiple primary cancers"; "synchronous"; "metachronous" in electronic databases like PubMed, PubMed Central, ResearchGate, Google Scholar, Semantic Scholar, and

Scopus. Individual keywords were used in the search together with a Boolean logic (AND) combination. The rationale behind the review was to gain insight into the definition, epidemiology, clinical presentation, management, and prognosis of MPMT in the light of the recent studies. Though no time limits were set but the articles that have been published in the English language between 2003 and 2023 were given preference due to their recency. Cross-references from earlier literature were used, if they had some academic or historical merit.

DEFINITION

Warren and Gates [4] first described this condition in detail in 1932, and they established the diagnostic criteria for it. A cancer must meet three requirements in order to be classified as an MPMT: it must be (1) distinct histologically, (2) definitively malignant, and (3) the possibility of metastasis must be ruled out. Warren and Gates [4] have categorized MPMTs as synchronous or metachronous based on their appearance timeline. The terms "synchronous" or "contemporaneous" refer to a second primary cancer diagnosed within six months of the index cancer, and "metachronous" refers to a second primary cancer identified six months or more subsequently. Only in the absence of any past records of invasive malignancy is a cancer considered index cancer [5]. The International Agency for Research on Cancer (IACR) recognizes six

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months as the cut-off point, but the Surveillance Epidemiology and End Results (SEER) database suggests using a two-month timeframe to distinguish between synchronous and metachronous multiple primaries [6]. In the situation of triple MPMTs, various possible scenarios are: metachronous-metachronous, metachronous-synchronous, synchronous-metachronous, or synchronous-synchronous malignant neoplasms. Like this, there may be more options for the infrequent cases with quadruple primary tumours like synchronous-synchronous-metachronous, synchronous-metachronous-metachronous, and so on.

INCIDENCE

According to reports from various regions of the world, the incidence of MPMT varies from 0.4% to 21% within 20 years of follow-up [7–8]. A second primary malignant lesion develops in 1 in 6 (16%) patients who had a primary cancer, and the incidence of metachronous MPMT is higher than that of synchronous MPMT, with a ratio of 2.7:1 [9]. The chance of acquiring a second primary malignancy varies depending on the cancer site [10] and can range from 1% (primary liver malignancy) to 16% (primary bladder cancer). Multiple primaries occurred in 16.9% of colon cancer patients and 19.9% of lung cancer patients, according to research by Weir *et al.* [11]. Amer [6] discovered nearly identical rates of multiple primaries in colon cancer patients; in contrast, he documented only 5.6% of multiple primaries in lung cancer patients. 25% of MPMT survivors are women whose breast cancer was their first primary, and 15% of men and women had colorectal cancer as their first primary [12].

RISK FACTORS

The exact aetiology is still unknown, but many epidemiological risk variables (Figure 1) have been proposed in the literature, which acting in combinations may lead to MPMTs [13].

Host Factors

Age has been proposed as a major risk factor. Patients between the ages of 50 and 64 have a 5%–12% prevalence of MPMT; for those over 80, that figure rises to 12%–26% [14]. Genetic predisposition is another significant factor that has been proposed [15]. It is primarily caused by mutations in about 100 identified genes, as well as an undetermined number of genes that have not been identified yet. These mutations can cause abnormal activation or silencing of

oncogenes, epigenetic changes, microsatellite instability (MSI), and defective repair of DNA damage [15]. According to a "multicentric origin" theory, several primary tumours in the same host may result from distinct mutation patterns in different genes. On the other hand, multi-site cancers may be predisposed by a mutation in a single gene. For example, germline mutations in the tumour protein p53 (TP53) gene cause a unique group of early-onset malignant tumours at various sites, such as soft tissue sarcoma, breast cancer, brain tumours, leukaemia, and adrenal carcinoma, in patients with Li-Fraumeni syndrome [17]. Similarly, germline mutations in the MEN1 gene in Multiple Endocrine Neoplasia (MEN) 1 syndrome predispose a carrier to pancreatic islet cell tumours, pituitary adenomas, and parathyroid adenomas, while in MEN2 syndrome, a germline RET-proto-oncogene mutation results in pheochromocytoma and medullary thyroid cancer [18,19]. Germline mutations in the BRCA1 and BRCA2 genes [20] predispose to breast, ovarian, and prostate tumours in hereditary breast and ovarian cancer syndrome (HBOC). The majority of cancers have an excess of familial clustering, and almost all malignancies that are inherited have an early age of beginning and a greater incidence of multiple primaries. Familial clustering seen with certain malignancies has been linked to aberrant genes or gene variants that predispose people to cancer, such as BRCA1, BRCA2, and p16/CDKN2A [21]. According to a study by Amer [6], patients with multiple primaries, and particularly Caucasians, had a strong family history of cancer, indicating a strong possibility of inherited cancer predisposition gene mutations. In contrast to the 7% incidence in the controls, Morita *et al.* [22] found that 27% of patients with MPMT had a family history of lung cancer or upper aerodigestive tract (UADT) cancer.

Endogenous and exogenous reproductive hormones drive cell proliferation, which tends to create opportunities for the accumulation of random genetic errors [23]. Hormonal therapy of breast cancers with agents like Tamoxifen, have been shown to increase the risk for subsequent development of endometrial, gastric, colon and ovarian cancers [24]. The co-occurrence of breast and colorectal cancers in women, but not in males, suggests that reproductive hormone variables are important in the development of both cancers in women [25].

Lifestyle

The odds of both cancer recurrence and the emergence of at least 11 new primary cancers are

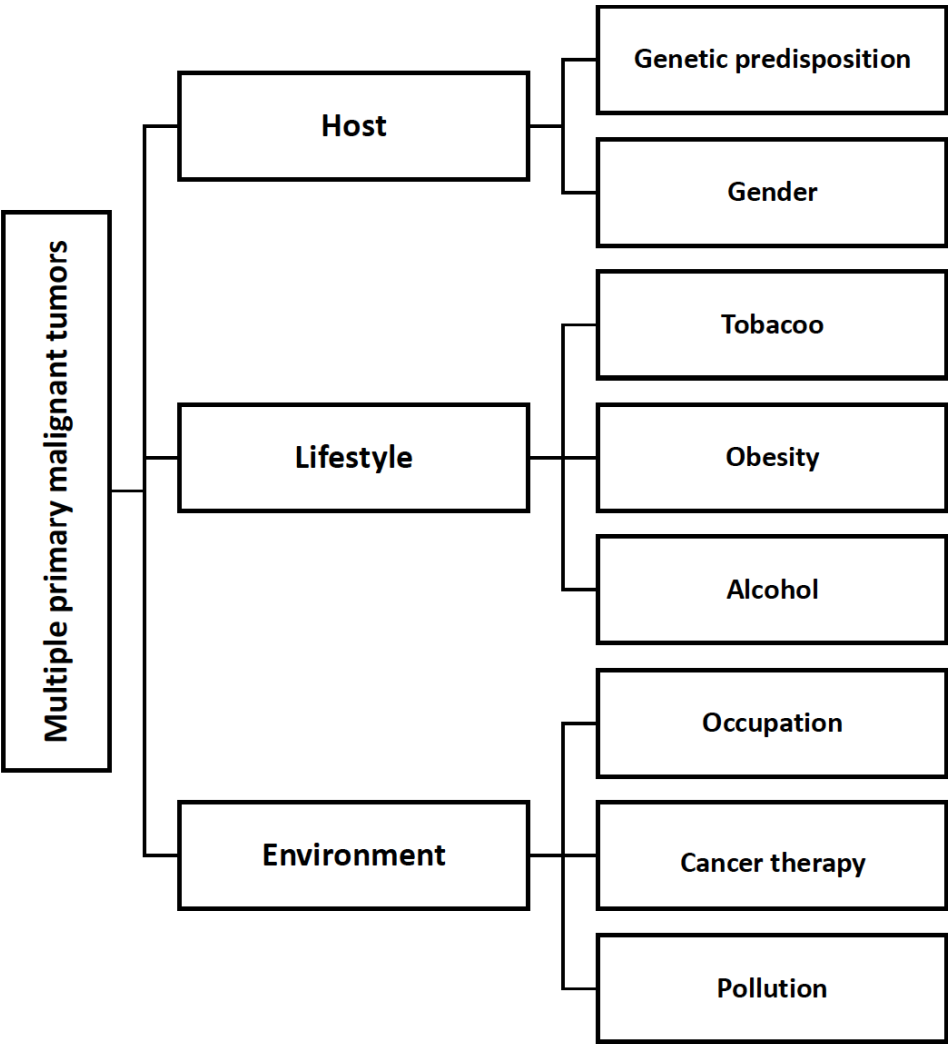


Figure 1: Epidemiological risk factors for multiple primary malignant tumours.

increased by active tobacco use [26]. Additionally, smoking shortens the survival period for cancer patients, and quitting smoking (SC) improves outcomes [27-29]. Following a retrospective analysis of 111 individuals with multiple primary malignancies, Romaszko-Wojtowicz *et al.* [28] reported that the incidence of multiple primary malignancies in cancer patients reached about 15%. Cancer patients who stopped smoking had an interval of 11.55 years (SD 7.24) between their index cancer and second tumour; those who did not quit had an interval of 6.10 years (SD 8.62) ($p = 0.005$). Furthermore, a longer survival time was observed in patients who had stopped smoking following the index cancer diagnosis compared to those who had not ($p = 0.027$). Similar to tobacco use, alcoholism has been linked to a higher chance of developing second primary cancers among survivors of upper aerodigestive tract tumours [30]. Accordingly, research indicates that abstinence from alcohol and tobacco use is the best strategy to lower

the chance of developing additional primary aerodigestive tract cancers [30-32].

Cancer in the population at large has been shown to be related to obesity, especially in relation to cancers of the breast, female reproductive organs, thyroid, and gastrointestinal system. Research has indicated a positive association between an individual's body mass index (BMI) prior to the diagnosis of the index primary cancer and their likelihood of developing secondary primary cancers [33-35]. A low-grade chronic inflammatory state or elevated levels of circulating oestrogen, other circulating hormones, or growth factors are some of the hypothesized pathways by which obesity increases one's risk of developing multiple cancers [36].

Environment

Carcinogenic substances found in environmental contamination have implications. Radon is a major

environmental source of ionizing radiation and long-term exposure to radon and its decay products can induce oxidative damage to DNA. Although there is clear evidence linking radon exposure to lung cancer, patients may also get primary cancers of the stomach [37], skin [38], kidneys, and central nervous system (CNS).

A substantial amount of literature has been generated about the causal role that cancer therapy plays in the occurrence of subsequent primary malignancies [39]. While there is a longer latency

period of 5–10 years after radiation therapy or hormone treatment, subsequent primaries following chemotherapy for index cancer may occur within a few months to a few years [14]. Lacouture *et al.* showed that using vemurafenib, an inhibitor of RAF (rapidly accelerated fibrosarcoma), induced the development of secondary cutaneous squamous cell carcinoma [40]. Olaparib, a Poly (ADP-ribose) polymerases (PARPs) inhibitor, has been associated with myelodysplastic syndromes and acute myeloid leukaemia [41]. The well-established adverse effects of asbestos exposure

Table 1: Examples of clinical cases of patients with synchronous advanced multiple primary tumours. Source: Vogt A, et al. ESMO Open 2017;2: e000172. doi:10.1136/esmoopen-2017-000172; reused in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license. <https://creativecommons.org/licenses/by-nc/4.0/deed.en>

Patient characteristics	Malignancy 1	Malignancy 2	Therapeutic dilemma	Current management strategy
60-year-old man, former smoker	Small cell lung cancer (SCLC) Progression: after 6 cycles of cisplatin/etoposide	Aplastic anaemia Diagnosed 4 months after completion of cisplatin/etoposide	Chemotherapy at progression of SCLC not possible due to grade 4 neutropenia and thrombocytopenia in the setting of aplastic anaemia Immunosuppressive therapy for aplastic anaemia with possible negative impact on SCLC	Supportive treatment with eltrombopag for thrombocytopenia In case of stabilisation of pancytopenia, evaluation of second line therapy for SCLC
71-year-old man, hereditary haemochromatosis	Castration-resistant prostate cancer with bone and lymph node metastases	Renal cell carcinoma with lung metastases	Drugs active in for CRPC different than agents in RCC TKI used for RCC endocrine drugs (abiraterone/enzalutamide) used for CRPC: combinations not tested, no safety data, possible drug–drug interactions, expensive combinations	Alternating treatment for the two malignancies: for example, TKI for 3–4 months for mRCC, then interruption and treatment for mCRPC for 3–4 months depending on the most significant tumour
64-year-old man, former smoker	Non-small cell lung cancer (NSCLC) stage IIIB	Rectal cancer stage I	Chemotherapy regimens active in NSCLC generally not active in rectal cancer NSCLC stage IIIB prognosis-defining, but untreated rectal cancer bears high risk of local complications (eg, bowel obstruction)	Curative resection of rectal cancer (node-negative) with protective colostomy Chemoradiation with curative intent for NSCLC (IIIB)
65-year-old woman, former smoker	NSCLC, metastatic to lymph nodes and bone, KRAS proto-oncogene (KRAS)-mutated, programmed death receptor ligand (PD-L1) expression 0%	Acute myeloid leukaemia (AML) Diagnosed simultaneously with NSCLC	Chemotherapy for NSCLC not possible due to grade 4 neutropenia in the setting of AML State-of-the art treatment for AML in the setting of metastatic NSCLC	Treatment with azacitidin for AML In case of stabilisation of AML, evaluation of treatment for NSCLC (checkpoint inhibitor rather than chemotherapy due to limited bone marrow reserve)

at work include malignant mesothelioma and cancers of the lungs, upper aerodigestive tract, colon, pancreas, and breast, among other primary tumours [42-44].

MANAGEMENT

There are no well-defined evidence-based treatment protocols that may fit all situations, and the management approach adopted for each patient is based upon individual decisions taken by multidisciplinary teams (MDT) [13]. Typically, the plan entails radiation/chemoradiation therapy and surgery or else palliation in highly advanced cancers (Table 1). There may be situations where synchronous multiple primaries, may be responsive to the same antitumour regimen [13].

PROGNOSIS

The prognosis of MPMT patients varies greatly, depending on a number of factors such as age, comorbidities, lifestyle, behavioural influences, the amount of time that passes between the index and subsequent primaries, the type of cancer, the location and stage of the disease at diagnosis [13]. Compared to patients with a single primary, those with MPMT have generally been shown to have a higher survival rate [6,45]. The patients who had three or more primaries in the study by Amer [6] had the greatest survival rate, which was roughly comparable to the expected life expectancy of the general US population that was age- and sex-matched. Patients with metachronous primaries do better than those with synchronous primaries [6, 46]. There was a 5-year survival rate of 44% for metachronous primary lung cancer and 10% for synchronous primary lung cancer in patients who had lung cancer as a second primary after having index breast cancer [47]. The longer the interval between the index cancer and the subsequent tumours, the better the prognosis [46].

SCENARIOS THAT DEMAND MORE CAREFUL CONSIDERATION

It is emphasized that a physician should constantly be cognizant of the possibility of a second, distinct primary tumour, either synchronous or metachronous, and that the following clinical scenarios ought to urge them to provide the patient a more comprehensive assessment [13].

- a. Atypical nature of metastatic spread of the identified primary tumour (e.g., sclerotic bone

lesions on imaging studies of papillary thyroid carcinoma).

- b. Disproportional tumour burden with respect to tumour marker titre (e.g., low prostate-specific antigen level in prostate cancer with extensive liver metastases on imaging studies).
- c. Appearance of new or chronologically atypical metastases many years after an index cancer management.
- d. Recurrence in patients with exposure to environmental carcinogens (e.g., smoking, Radon, asbestos).
- e. Features of new malignancy after prior chemotherapy or radiation therapy for malignancy.
- f. During initial staging or at follow-up of index tumour, suspicious lesion on imaging (e.g., lesions on Positron emission tomography-computed tomography (PET-CT) with difference in standard uptake value). Ishimori *et al.* [48] discovered that in a large series of 1912 patients who had undergone whole-body (18)F-FDG PET/CT scans for known or suspected malignant lesions, new, unexpected (18)F-FDG-avid primary malignant tumours were found in 22 (1.2%) cases, and the origin was from the thyroid, colon, breast, oesophagus, bile duct, and head and neck regions. In 17% of patients, synchronous multiple primary tumours were found in the stomach, colon, lungs, head, and neck regions during PET-CT staging of oesophageal cancer, as reported by Miyazaki *et al.* [49].

CONCLUSION

When evaluating and monitoring a patient with cancer, it is important to consider the possibility of multiple primary malignant tumours (MPMT). Newer techniques for imaging such as PET scans can now identify cancers that would not otherwise be detectable by clinical examination and traditional imaging modalities. Clinicians need to be well-versed on different scenarios that increase the probability of having multiple primary malignant tumours.

ABBREVIATIONS

MPMT = multiple primary malignant tumours

PET-CT = Positron emission tomography–computed tomography

RAF = Rapidly accelerated fibrosarcoma

UADT = Upper aerodigestive tract

PARP = Poly (ADP-ribose) polymerases

IACR = International Agency for Research on Cancer

MDT = Multidisciplinary teams

AUTHOR CONTRIBUTIONS

The authors have participated in conceptualization of the article, review of the literature, drafting of the manuscript and illustrations; and all have approved the final draft of the manuscript.

SUPPORTIVE FOUNDATIONS

None.

CONFLICT-OF-INTEREST

None.

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