

Double Malignancies: A Rare Entity

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Abbreviations: MPM: Multiple Primary Malignancies; SEER: Surveillance Epidemiology and End Results Programme; SPT: Second Primary Tumor; TT: Third Tumor; QT: Quadrant Tumor; SPM: Second Primary Malignancies; NAACCR: North American Association of Central Cancer Registries

Introduction

Patients which have diagnosed with a cancer, have a life time risk for developing another de novo malignancy depending on various inherited environmental and iatrogenic risk factors. Cancer victims could survive longer due to settling treatment modalities, and then would likely develop a new metachronous malignancy [1]. The incidence of multiple primary malignancies has not been rare at all. Screening procedures have especially been useful for the early detection of associated tumors, whereas careful monitoring of patients has treated for primary cancer, and then a good communication between patients and medical care team would certify not only an early detection for secondary tumors, but only finally & subsequently, an appropriate management [2]. Differentiation between multiple primary and multicentric cancers was addressed in the classification by Moertel CG [3]:

- I. MPMNs of Multicentric Origin
 - a) The same tissue and organ.
 - b) A common, contiguous tissue shared by different organs.
 - c) The same tissue in bilaterally paired organs.
- II. MPMNs of Different Tissues or Organs
- III. MPMNs of Multicentric Origin Plus a Lesion (s) of a Different Tissue or Organ

In 2002, However in 'A review of the definition for multiple primary cancers in the United States' classified the association of different cancers in two categories depending on the timing of their discovery [4];

- a) Synchronous in which the cancers occur at the same time or within two months and
- b) Metachronous in which the cancers follow in sequence of more than two months apart.

Vaamonde [5]. reckoned the time factor as six months. In 2005, International Agency for Research on Cancer working Group has come out with International Rules for Multiple Primary Cancers [6].

Although the mechanism involved in the development of multiple primary cancers has not been clarified, some factors such as heredity, constitution, environmental and immunological factors, oncogenic viruses, radiological and chemical treatments have been implicated. Hereditary susceptibility explains only a small proportion of all second cancers though many hereditary cancer syndromes have been described. MPMNs can occur at any age. However, from the reviewed series, patients with MPMNs tend to be older than those with a single primary malignant neoplasm. In many autopsy series and clinical reports, the median age of 50-94% of MPMN patients was over 50 years [7]. Multiple Primary Malignancies (MPM) were first described in 1879 by Billroth [8]. The neoplasms may be limited to a single organ or may involve multiple separate anatomical organs. The North American Association of Central Cancer Registries (NAACCR) classifies MPM into two categories:

- a) Synchronous, in which the cancers occur at the same time (The Surveillance Epidemiology and End Results Programme (SEER) definition is within two months) and
- b) Metachronous, in which the cancers follow in sequence, that is, more than six months apart [9].

According to Warren Gates criteria a diagnosis of MPM require the following criterias to be fulfilled

- a) Each tumor should present a definite picture of malignancy
- b) Each tumor should be histologically distinct
- c) The possibility that one is metastasis of the other must be excluded [10].

Meta-analyses show the frequency of Second Primary Tumor (SPT) as 3-5%, Third Tumor (TT) as 0.5%, and fourth tumor, that is, Quadrant Tumor (QT), as 0.3%, in different organs and of different histogenesis. Metachronous primary malignancies are becoming increasingly common because of an increase in the number of elderly cancer survivors, greater awareness and improved diagnostic modalities [1]. The exact pathophysiology for MPM remains unknown. However certain factors have been postulated which includes the common carcinogen induced multiple cancers in a exposed epithelial surface, called as "Field-Cancerization" as seen in head-neck tumors. In addition other causative factors includes ionizing radiation, increased use of organ transplant, and the increasing use of newer treatment modalities like hormonal manipulation, target therapies, genetic manipulation, and immunomodulators [2]. In a study conducted by Chakrabarti [11] it has been reported that the over a period of 2 years, 12 cases of MPM were detected against a total of 1255 cases. Of these, five cases were synchronous malignancies and seven cases were metachronous. Head and neck was the commonest site of index malignancies with seven cases followed by the breast cancer with three cases and next gynaecological malignancies with two cases. Most common sites for Second Primary Malignancies (SPM) were head and neck with (four cases).

Male to Female ratio was 1:1.5 in the synchronous primary group and 1:1.3 in the metachronous group. Median age of presentation of the primary tumour was 52 years and 6 months. The age range for the SPM was 17-72 years with the highest incidence in the 6th decade of life. Studies have reported that that the relative risks of SPM ranges from 1.08 to 1.3. SPM are often missed during follow-up and are detected accidentally. According to various series, the onset of SPTs decreases the 5-year survival by 18-30% as compared to those with only a single tumor. The controversy between the lateral spread of clones vs multiple foci of independent alterations does not currently affect the surgical and medical management of theses premalignant and malignant lesions. In the future, the presence of altered clones at mucosal margins may be an indication for aggressive therapy, including chemoprevention or radiotherapy to treat altered clonal patches that are unable to be detected grossly and are beyond the initial scope of surgical excision [3]. The issue of whether those with an extensive visible mucosal field defect is more likely to benefit from chemotherapy, radiotherapy or chemoprevention is a complex one. Current management is often site specific: Recurrent oral

pre-malignant disease is often treated by surgical excision, whereas diffuse high grade pre-malignant changes in the laryngeal mucosa are frequently treated with radiotherapy. Determination of the role for these and other treatment modalities for clinically occult, clonally altered patches of epithelium is likely to be a difficult issue, since treatment of mucosa with widespread visible alteration is already challenging [4]. The paucity of awareness about SPM has also prevented the formulation of population-based screening protocol. Multiple tumors that have been pathologically confirmed at the time of presentation should be evaluated and staged as independent tumors. The treatment plan should be decided after staging of both the primary and secondary tumors in view to attain maximum clinical response. Proper counselling and patient's understanding of magnitude of the disease is paramount. Operable synchronous SPM can be operated in a single setting with minimal morbidity with better survival and is less taxing on the patient and his/her relative both psychologically and financially. A regular follow-up on the patient by the clinician increases the chances of early detection of metachronous SPM and the formulation of the treatment plan at the earliest with better overall survival

Conclusion

MPMNs are still elusive for want of proper guidelines regarding correct terminology and classification encompassing varying presentations of chronological, aetiological, clinical and histopathological combinations. Our case adds up to literature for further research. The possibility of occurrence of synchronous multiple primary malignancies should be considered during workup for any malignant condition to institute early intervention to achieve good outcome [12]. The possibility of multiple primary malignancies existence should always be considered during pretreatment evaluation. Screening procedures were especially useful for the early detection of associated tumors, preferably before clinical manifestations occurrence [12]. There were some evidences that screening would improve outcomes among patients who might develop second malignancies, although the data were limited. The optimal screening modalities and strategies for reducing mortality from second malignancies remained to be defined for most tumor sites [13]. The early diagnosis of secondary malignancies should not be neglected in patients treated for a primary malignancy, especially when the long clinical period before the diagnosis of subsequent tumors has been taken for management. With careful monitoring, secondary tumors could be detected earlier, and, with appropriate intervention, might be better managed, without compromising survival. Our data could guide oncologists towards a closer follow-up strategy in the management of patients treated for common tumors. Availability of data regarding incidence of MPM, particularly those from developing countries is very limited and hence further studies are needed. SEER is working in this direction with an aim to define and develop appropriate and reliable criteria's for synchronous and metachronous cancers. It is imperative that patient with a primary malignant tumors should be thoroughly,

closely, and regularly followed. Genetic counselling, risk estimation, cancer screening and chemoprevention must be emphasized. Appropriate cancer prevention strategy in with proper emphasis on synchronous and metachronous cancer needs to be designed and incorporated in the National Control Programme as multiple primary cancers have unique, biological behaviour requiring specific diagnostic and therapeutic interpretation [14].

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