Multiple Primary Malignant Neoplasms – A Single Institutional Audit from Eastern India

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ABSTRACT

Introduction: Various inherited, environmental, iatrogenic factors and improved survival predispose a cancer patient to another de novo malignancy during lifetime. Our study describes the experience of dealing with multiple primary malignant neoplasms in a tertiary care center in Eastern India. Aim of the study is to analyze the clinicodemographic nuances and review of relevant literature of such cases in our setting.

Material and methods: A single institutional retrospective audit of hospital records of patients over 10 years(2010-2019) was done. Patients with histologically proven synchronous or metachronous multiple primary malignancies were included. Various parameters like age at the time of diagnosis, sex, time interval between two diagnoses, sites of tumors, stages at presentation and treatment details were analyzed.

Results: Among 70 analyzed patients, 24(34.3%) had synchronous and 46(65.7%) had metachronous tumors. Of all patients 65.7% were female. Family history was more commonly found in patients with synchronous malignancies(25% compared to 13% in metachronous cohort). Positive addiction history was found in 25.7% cases. Breast cancer was the most common first primary both in the synchronous(29.16%) and metachronous(28.26%) cohorts. Upfront palliative treatment was required in 50% patients of synchronous cohort and in 30.4% patients for second primaries in metachronous cohort. Median overall survival was more in patients with metachronous tumors (125 months versus 45 months, *P*=0.014).

Conclusions: Multiple Primary Malignancies in a cancer patient is no longer rare. Concerted effort in awareness build-up among physicians and stringent surveillance may result in early diagnosis and appropriate management of such cases.

Keywords: Dual Primary Malignancy, Second Primary Malignancy, Synchronous, Metachronous.

INTRODUCTION

More than 150 years have passed since Bilroth first alluded to the concept of Multiple Primary Malignant Neoplasms (MPMN) in 1869.[1] Although apparently Renaud[2] and Rokitansky[3], in 1847 and 1855 respectively, reported the first patients with this clinical entity, it was Bilroth who is credited with initial proper documentation on this subject.[4] However since then, the presence of two or more primary malignancies of different histological origins in the same individual has been gradually relegated from a clinical curiosity to a rather common medical enigma.

Warren and Gates in 1932[5] reviewed a thousand postmortem reports to arrive at an incidence of 3.7%. Bugher[6] analyzed cases of double primary malignancies autopsied at the University of Michigan Hospital from 1896 to 1932, to find an incidence of 3.1%. In an even larger series Warren and Ehrenreich[7] have reported an incidence of 6.8% in 1944.

Traditionally according to Warren and Gates, the diagnosis of MPMN should follow certain specific criteria[4-5] as follows-

1. Each of the tumors must present a definite picture of malignancy
2. Each must be distinct
3. The probability of one being a metastasis of the other must be excluded

In 1964, Moertel et al[8] further refined these criteria and categorized MPMN into two distinct types. Synchronous multicentric lesions are those that develop within 6 months of each other and are distinctly separated by normal tissue. Non-synchronous or Metachronous lesions are those that have been diagnosed at least 6 months apart.[9] Although it is not the only definition of these two types and other researchers have used 12 months and other varying time intervals to define the temporal relation between the lesions of MPMNs.[10]

Throughout history, there have been multiple attempts at classifying MPMNs[4], most meaningful of these are perhaps the one proposed by Lund et al in 1933.[11] Moertel et al[8-9] later expanded this classification as follows-

1. Multiple primary malignant neoplasms of multicentric origin
   a) Of the same tissue and organ
   b) Of common, contiguous tissue shared by different organs
   c) Of bilaterally paired organs
2. Multiple primary malignant neoplasms of different tissues or organs
3. Multiple primary malignant neoplasms of multicentric origin plus a lesion or lesions of a different tissue or organ

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Recently the International Agency for Research on Cancer (IARC) definition is being used more commonly for international comparisons of MPMNs.[12] The rules mentioned here are for defining MPMNs during cancer registrations so that after the data on cancer incidence and survival is reported, cancer risk and outcome are comparable between different populations.[13]

However, Asian population is grossly under-represented in all these studies and such observation applies even more for Indian diasporas. Though few retrospective studies and case series were published from other parts of India, data of MPMN is really sparse from Eastern part of the country which caters to a different ethnic population with unique distribution of common malignancies. Hence, we planned this study to review the cancer registry of a tertiary care centre of Eastern India throughout a period of 10 years to provide a detailed analysis of our experience with the entity called MPMN.

MATERIAL AND METHODS

A retrospective audit was planned to analyze 10 years' (2010-2019) records of the patients who suffered from Multiple Primary Malignant Neoplasm (MPMN) and were treated at Dept. of Radiation Oncology in a tertiary care institute in Kolkata, India.

MPMN was diagnosed as per Warren and Gates criteria[5] and following Moertel's criteria[8], the patients were divided into two broad groups- Synchronous and Metachronous malignancies. Two primary malignancies were labeled as synchronous if they were diagnosed within 6 months of each other; whereas if the time interval between their diagnoses was more than 6 months, the second neoplasm was categorized as a metachronous tumor. Among synchronous tumors, the one that was diagnosed earlier was deemed to be the first primary and the one detected subsequently was classified as the second primary.

From the hospital registry database, various demographic details such as patient's age at the time of each tumor diagnoses, sex, any relevant family history, and history of substance abuse were recorded. Similarly, disease related details such as site of tumor, histology, stage at presentation, time interval between the two diagnoses were noted along with treatment details and disease status at last follow up.

Only patients who could be followed up physically or via telecommunication were included in this study. However patients suffering from hematological malignancies were consciously excluded as they are referred to and treated at Department of Hematology as per institutional policy.

STATISTICAL ANALYSIS

The data was collected in Microsoft Office and Excel 2007. Statistical analysis was done by SPSS version 16 (IBM Inc, Armonk, New York, USA). Descriptive statistics were analyzed using Chi square test for categorical data and Independent Student t test for non categorical data. Mantel-Cox log rank test with DOF=1 was used to compare the survival between two broad groups of patients with synchronous and metachronous malignancies.

RESULTS

Baseline demographic profiles

Data of total 70 patients was analyzed, among which 24 (34.3%) patients were having synchronous malignancy while the rest developed metachronous tumors. The median time interval between the diagnoses of the two lesions for metachronous malignancies was approximately 1451days (4 years), with the maximum being 19 years. For synchronous malignancies, the median time interval between two diagnoses was found to be 3 days.

The mean age at presentation of the first primary was 52.10 (SD +/- 13.18) years, the maximum being 81 and the minimum being 19 years. Among the patients, there was a clear female preponderance with 65.7% of the sample being represented by women. Among the patients with metachronous lesions, only 13.04% were having any first or second degree relatives diagnosed with cancer, while interestingly family history of cancer was present in 25% in those with synchronous malignancies. [Table 1, Table 2, Table 3]

Disease distribution

Among patients with synchronous malignancies Breast Cancer was the most common first primary (29.16%) followed by Head and Neck Cancer (16.67%) with Cancer Cervix and Ovarian Cancer contributing 12.5% cases each and Prostate Cancer, Kidney Cancer, Bladder Cancer, Skin Cancer and CUP 4.16% each . Breast cancer and Lung cancer were the most common second primaries in these patients (20.83% each) followed by Colorectal Cancer (16.67%), Uterine Cancer 12.5%, Prostate Cancer 10.4% and Ovarian Cancer, NHL and Head-Neck Cancer 4.16% each. [Table 4,

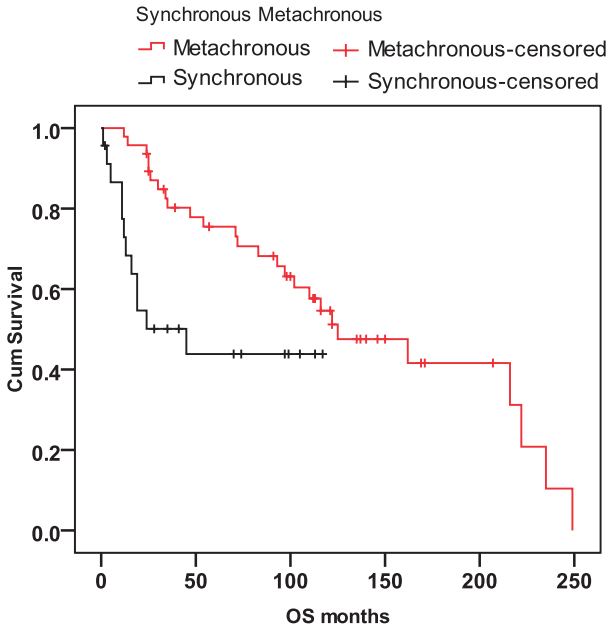

Figure-1: Kaplan Meier Survival Analysis comparing overall survival (in months) between metachronous and synchronous patients : 125 months versus 45 months P = 0.014

		Synchronous (N=24)	Metachronous (N=46)
Age	Median (Range)	53 (19-81)	54(26-77)
Sex	Female	14 (58.33%)	32 (69.57%)
	Male	9 (37.5%)	15 (32.6%)
Family History	Present	6 (25%)	6 (13.04%)
	Absent	17(70.83%)	41(89.13%)
Addiction	Tobacco (T) only	6 (25%)	11 (23.91%)
	Alcohol (A) only	0 (0%)	0 (0%)
	Both (T&A)	1(4.17%)	0(0%)
	Betel nut + Zarda	1(4.17%)	0(0%)
	None	16(66.67%)	35(76.08%)

Table-1: Demographic Profiles

1st Primary in Patient	2nd Primary in Patient	Patients age at diagnosis	Addiction History	Family History
Right Breast	Left Breast	27	None	Maternal Aunt died of Ovarian Cancer
Left Breast	Right Breast	25	None	Mother died of Breast Cancer
Cervix	Ovary	38	None	Father died of Oral Cancer
Cervix	Rectum	47	None	Father died of Colon Cancer
Ovary	Endometrium	51	None	Sister died of Ovarian Cancer
Stomach	Colon	60	Betel Nut+Zarda	Brother died of HCC

Table-2: Family History in patients with Synchronous Malignancy

1st Primary in Patient	2nd Primary in Patient	Patients age at diagnosis	Addiction History	Family History
Tongue	Parotid	64	Tobacco	Sister died of Breast Cancer
Right Breast	Left Breast	57	None	Sister died of Ovarian Cancer
Uterus	Right Kidney	67		Mother died of HCC
Endometrium	Squamous Cell Carcinoma Skin	52	None	Mother died of Gall Bladder Cancer
Left Breast	Right Breast	35	None	Sister died of Breast Cancer
Left Breast	Right Breast	47	None	Mother died of Breast Cancer

Table-3: Family History in patients with Metachronous Malignancy

	1st Primary No (%)	2nd Primary No (%)
Stage I	3 (12.5%)	3(12.5%)
Stage II	6 (25%)	5(20.83%)
Stage III	12(50%)	6(25%)
Stage IV	3(12.5%)	10(41.66%)

Table-4: Stage-wise distribution of Synchronous Malignancies

1st Primary	2nd Primary	
Breast	Breast	4
	Lung	2
	Cervix	1
	Rectum	1
Ovary	Endometrium	2
	Cervix	1
	Rectum	1

Table-5: Site-wise distribution of primaries in patients with Synchronous Malignancy

	1st Primary No (%)	2nd Primary No (%)
Stage I	7 (15.21%)	8(17.39%)
Stage II	16 (34.78%)	13(28.26%)
Stage III	22(47.82%)	11(23.91%)
Stage IV	1(2.17%)	14(30.43%)

Table-6: Stage-wise distribution of Metachronous Malignancies

1st Primary	2nd Primary	No
Breast	Breast	6
	Lung	4
	Uterus	2
HNC	Other HNC	4
	Lung	2
Cervix	Lung	2
	Stomach	1

Table-7: Site-wise distribution of primaries in patients with Metachronous Malignancy

Table 5]

While for patients with metachronous malignancies, most common first primary was again Breast Cancer (28.26%) followed by Head and neck Cancers (23.9% patients), Uterine cancer (8.69%), GI malignancy (6.52%), HPB cancer (6.52%) and Ovarian Cancer (4.34%). In these cohort 21.73% of second primary malignancy are Lung Cancers, followed by Breast Cancer (17.39%), GI Cancers (10.86%). [Table 6, Table 7]

Treatment modality(s)	1st Primary	2nd Primary
Surgery f/b Adjuvant therapy (with or without neoadjuvant therapy)	31(67.4%)	17(36.9%)
Definitive Surgery only	5(10.86%)	8(17.4%)
Definitive Chemoradiation only	6(13.04%)	1(2.17%)
Definitive Chemotherapy only	2(4.35%)	5(10.9%)
Definitive RT only	2(4.35%)	1(2.17%)
Upfront palliative treatment	0%	14(30.43%)

Table-8: Treatment Options for Metachronous Malignancies

Treatment details

In synchronous malignancy cohort, 50% patients required upfront palliative treatment for either or both of the malignancies.

For metachronous malignancies, first primary was treated by upfront curative therapy in all cases whereas second primary was treated with upfront curative therapy in 69.57% cases. [Table 8]

Survival

Disease progression or death experienced by patients with synchronous and metachronous malignancies were 13(54.16%) and 24(52.17%) respectively. In patients with metachronous malignancies median overall survival (mOS) was 125 months (SE= 26.9 with 95% CI 72.3-177.7) compared to 45 months (SE= 16.0 with 95% CI 13.6-76.4) in synchronous malignancy cohort (*P* value of 0.014). [Figure 1]

DISCUSSION

With increased number of cancer survivors, better diagnostic modalities and strict surveillance protocols; numbers of multiple malignant primaries are increasing rapidly with a prevalence of 2 to 17% in various populations.[13] Second cancers can be a result of multiple attributes like cancer predisposition syndromes, environmental exposures and therapy related late effects.[13]

Second primary malignancy(SPM) can be diagnosed at any age, but it shows a predisposition towards elderly population compared to a first malignancy diagnosed de novo. Our study also is showing the median age at diagnosis of second malignancy being 53 years for Synchronous SPMs and 54 years for Metachronous SPMs, which is consistent with the published reports of mean age of developing SPMs at 50 years or above.[14-16] Though male predominance has been reported often[17-19], a SEER database analysis showed a higher prevalence of SPMs among female population.[20] In our study 58% of patients with Synchronous SPMs and 69% of patients with Metachronous SPMs were female may be as a result of breast cancer being the commonest cancer in both the groups.

The average time interval between diagnoses of two primaries in metachronous cohort of our study was 1451days (4yrs). However almost 39% of such patients developed second malignancy beyond 5yrs from the diagnosis of their first cancer and 30.4% of second primaries in them presented at advanced stage. Therefore it implies that stringent long term follow-up is very much needed to detect second primary malignancies at early stage in cancer survivors. However optimal screening modalitites for patients at risk of second primary malignancy are yet to be defined for most tumor sites.[22]

Various attributes postulated to cause SPMs are late sequelae of previous treatment, lifestyle, environmental exposures, genetic predisposition and immune response. Among them genetic susceptibility plays a significant role and often expressed as positive family history and/or different hereditary syndromes. Such common syndromes include Li-Fraumeni syndrome, Lynch Syndrome, Hereditary breast and ovarian cancer syndrome (HBOC), Multiple endocrine neoplasia(MEN1 and MEN2) and Von Hippel-Lindau disease.[21] In our series, 6 patients each were found to have positive family history in both cohorts. Among those patients in synchronous malignancy group, 2 patients had CA Breast-CA Breast and another patient had CA Ovary-CA Endometrium combination and their 1st or 2nd degree relatives died either from breast or ovarian cancer. Similarly in metachronous malignancy group, 3 patients developed CA Breast-CA Breast and their 1st degree relatives died of either breast or ovarian cancer. None of these patients had any addiction history. This typical family history may be suggestive of some genetic susceptibility like BRCA1/BRCA2 mutation and needs to be investigated in such cases. Another known pathophysiology of development of SPMs is 'Field cancerization' due to continuous exposure of aerodigestive tract mucosa or transitional cell mucosa to carcinogens like tobacco and alcohol. In present study 19(27.14%) patients had addiction to tobacco (smoke or smokeless) and or alcohol and 12(63%) of them had some malignancy known to be caused by tobacco or alcohol.

As per prevailing literature the common primaries seen in patients with multiple primary cancers are cancers of the breast, prostate, lung, colorectal, and urinary system, whereas second primary malignancies arise most commonly from respiratory, gastrointestinal, and genitourinary systems.[21] In the present study also breast malignancy was most common followed by lung cancer and head-neck cancer among patients with synchronous multiple primaries. While among patients with metachronous diseases most common first primary was again breast cancer followed by head-neck cancer but most common second primary was lung cancer followed by breast cancer. This distribution is comparable to the present cancer-statistics of our country.[23] As such most common combination of two primaries found in our literature review were CA Prostate–CA Lung in males and CA Breast–CA Breast in females.[23] In our study also most common pair was CA Breast-CA Breast among females (9 out of 46) and CA Head & Neck-CA Lung among males (5

out of 24).

Approximately 30% second primaries of patients with metachronous diseases were not eligible for upfront curative therapy probably because in this particular setting disease presented mostly in locally advanced (23.9%) or metastatic stage (30.4%). Whereas almost 45% patients of synchronous malignancy cohort had metastatic disease and 50% patients required upfront palliative therapy.

Survival data of patients with multiple malignancies are sparse and it depends upon several coexisting factors like age, performance status, type of malignancies, stage at diagnosis, treatment response, co-morbidities and not just related to the presence of multiple malignancies itself. However published long-term experience shows significantly higher overall survival in female patients of sMPMN and all groups of mMPMN.[20] In this present study also, median overall survival of patients with metachronous SPMs was significantly higher compared to patients with synchronous malignancies(125months Vs 45months, *P*=0.014) and that may be attributed to the more advanced stage of disease in synchronous malignancy cohort (almost 79% patients were diagnosed with either locally advanced or metastatic disease).

The limitations of this study were its retrospective nature and exclusion of hematological malignancies resulting in a sample size not large enough for robust statistical exploration.

CONCLUSION

It is the need of the hour to have stringent surveillance system for long term cancer survivors to diagnose second primary malignancies, which is not that uncommon. Similarly, search for second primary cancers should be a routine practice in patients suffering from cancer to optimize the treatment strategy considering the dismal prognosis in presence of synchronous malignancies. Moreover, during follow-up cancer patients may also be encouraged to use cancer screening modalities. As the clinicodemographic as well as survival data is limited for multiple primary malignancies especially in Indian scenario, our study might help to sensitize the practicing physicians in this regard and guide them in their clinical decision making.

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