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Multiple Primary Malignancies – A Unique And Challenging Clinical Entity.

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Abstract:
Introduction: *Multiple primary malignancies are rare clinical entity seen in 2 to 17% cases. The incidence is on the rise due to improved diagnostic and therapeutic strategies. Most of the available data till now is in the form of case reports. Hence this study was undertaken to know the prevalence of MPM in a tertiary care setup.*
Study design: *It was a single institute retrospective study conducted over a period of 6 months based on the information from past medical records in patients attending medical oncology OPD. Age at presentation, disease free interval , risk factors and survival from onset of second primary were analysed.*
Results: *30 cases of MPM were identified. The median age of study population was 60 years with a female predominance. The most common 1st primary was ca breast and most common second primary was ca lung . The median disease free interval was 24 months. The possible risk factors include smoking, family history, past chemotherapy, past radiotherapy and post menopausal status. 90% of pts were alive at the end of study period.*
Conclusion: *The incidence of MPMs is on the rise. So clinicians should be vigilant to the possibility that patients are at continued risk of new and separate malignancies even after an initial diagnosis. There is no universal protocol for the treatment of multiple malignancies. Each case must be managed individually by a multidisciplinary team.*

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I. Introduction:

Multiple primary cancers are usually defined as primary malignant tumors of different histological origins in one person. The frequency of multiple primaries ranges between 2 and 17%.[1] The risk of developing a second primary malignancy varies from site to site and is reported in a range from 1% in liver malignancies up to 16% in bladder malignancies .[2]

There has been a spike in the number of patients diagnosed with multiple primary cancers in recent times. As per International Agency for Research on Cancer, the global cancer burden in 2012 was 14.1 million new cases and 8.2 million cancer deaths and it is estimated to increase to 21.7 million new cases and 13 million deaths by 2030. With the sheer increase in the number of malignancies alone, the number of patients with multiple primaries will grow significantly.[3]

With recent treatment modalities, cancer patients are surviving longer to be able to develop metachronous new primary. With the recently improved diagnostic modalities such as Positron Emission Tomography (PET), that amount of picking up indolent tumors have increased contributing, further to the obvious increase of multiple primary malignancies incidence.

Majority of multiple primary cancers arise as a result of random chance. Different mechanisms for their occurrence have been proposed like the family history, immunologic and genetic defects, prolonged exposure to carcinogens, radiation and chemotherapy for the primary cancer, and field cancerization.

Double primary malignancies can be divided into synchronous and metachronous, depending on the interval between tumor diagnoses. Synchronous malignancies were those second tumors that have occurred either simultaneously, or within 6 months after the first malignancy was diagnosed , while metachronous malignancies were secondary tumors that have developed after 6 months, or even more than that from the first malignancy.[4]

Warren and Gates Criteria for Diagnosis of Double Primary Malignancies[5] include histological confirmation of malignancy in both the index and secondary tumors, there should be at least 2 cm of normal mucosa between the tumors, if the tumors are in the same location, then they should be separated in time by at least five years and the probability of one being the metastasis of the other must be excluded.

II. Material and methods:

It is a retrospective observational study done at tertiary cancer care center in Andhra Pradesh over a period of 6 months i.e., from July 2022 to December 2022. All patients attending the medical oncology outpatient department with histologically proven malignancy were included in the study. Previous hospital records were verified to assess metachronous disease in all the cases. Any suspicious lesions during routine staging were analysed for possible synchronous disease. All histologically proven multiple primaries were included in the study. Age at presentation, disease free interval , risk factors and survival from onset of second primary were analysed. The collected data was noted in a predesigned study proforma and analysed with IBM SPSS Statistics for Windows, Version 23.0.

III. Results :

A total of 2200 patients attended the medical oncology outpatient department during the study period. Of them 30 patients were identified to have multiple primary malignancies and were included in the study. The prevalence of multiple primary malignancies in our study population was 1.36%.

The predominant sex was female with a female to male ratio was 2:1. Metachronous and synchronous malignancies constituted 56.7% (17) and 43.3%(13) of the study population respectively.

The median age of first primary was 60yrs and 80% of patients were above 50 yrs of age.

Age distribution at diagnosis of Ist Primary		
	frequency	Percent
31 - 40 yrs	1	3.3
41 - 50 yrs	5	16.7
51 - 60 yrs	10	33.3
61 - 70 yrs	9	30.0
71 - 80 yrs	4	13.3
Above 80 yrs	1	3.3
Total	30	100.0

Disease free interval: The median disease free interval for metachronous patients was 24 months and the maximum DFI was 15 yrs.

DISEASE FREE INTERVAL	**NUMBER**	**PERCENTAGE**
≤ 6 MONTHS	**13**	**43.3**
6 - 12 MONTHS	**4**	**13.3**
12 - 18 MONTHS	**2**	**6.6**
18 - 24 MONTHS	**4**	**13.3**
24 - 36 MONTHS	**2**	**6.6**
36 - 48 MONTHS	**0**	**0**
48 - 60 MONTHS	**2**	**6.6**
> 60 MONTHS	**3**	**10**

Possible risk factors: Among the study subjects 6 were smokers, 14 of the 20 women were post menopausal, 10 had history of radiation exposure and 8 had history of chemotherapy infusion. Only one case had family history of malignancy.

Risk factor	**Number**	**Percentage**
Post menopausal	14	70
Smoking	6	20
H/o chemotherapy	8	26.7
H/o radiation	10	33.3

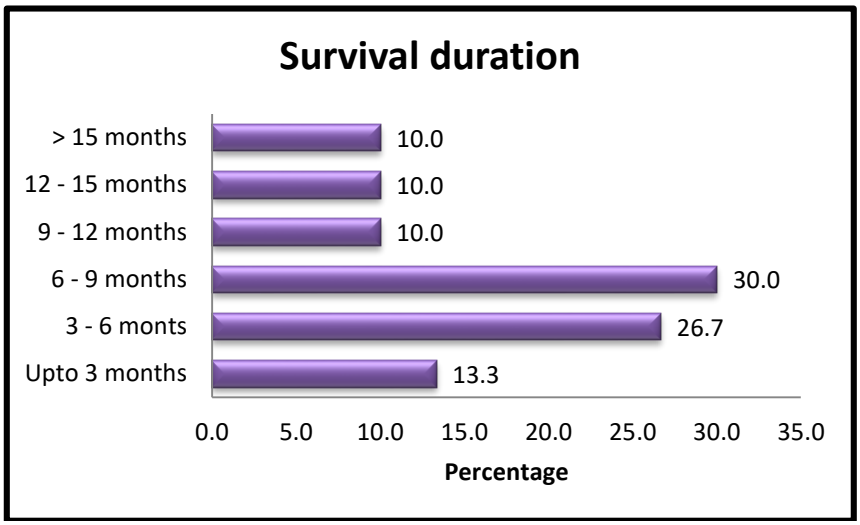
Family h/o cancer	1	3.33

Site of primaries:
The most common 1st primary was carcinoma breast followed by head and neck malignancy. The most common 2nd primary was carcinoma lung followed by breast and head and neck. 13.3%(4) had a 3rd primary malignancy

S.NO	AGE	SEX	TYPE OF 2ND PRIMARY	SITE OF 1ST PRIMARY	SITE OF 2ND PRIMARY	SITE OF 3RD PRIMARY
1	78	F	SYNCHRONOUS	CA COLON	CA OVARY	NA
2	62	F	METACHRONOUS	CA BREAST	CA RECTUM	NA
3	66	F	SYNCHRONOUS	CA BREAST	NHL	NA
4	35	F	METACHRONOUS	CA OVARY	CA COLON	NA
5	45	M	METACHRONOUS	CA TONGUE	CA BUCCAL MUCOSA	CA ALVEOLUS
6	84	F	SYNCHRONOUS	CA COLON	CA GALL BLADDER	NA
7	57	F	METACHRONOUS	CA BREAST	CA BREAST	NA
8	61	M	SYNCHRONOUS	CA STOMACH	RCC	NA
9	68	F	METACHRONOUS	CA CERVIX	CA BREAST	NA
10	53	F	SYNCHRONOUS	CA STOMACH	CA LUNG	NA
11	68	M	METACHRONOUS	CA BUCCAL MUCOSA	CA LUNG	NA
12	51	F	SYNCHRONOUS	CA BREAST	CA OVARY	NA
13	64	F	METACHRONOUS	CA BREAST	CA THYROID	NA
14	49	F	SYNCHRONOUS	CA BREAST	CA THYROID	NA
15	48	F	METACHRONOUS	CA LUNG	CA CERVIX	NA
16	71	M	SYNCHRONOUS	CA GE JUNCTION	CA STOMACH	NA
17	51	M	METACHRONOUS	CA BUCCAL MUCOSA	CA LUNG	NA
18	46	F	SYNCHRONOUS	CA BREAST	CA BREAST	NA
19	55	M	SYNCHRONOUS	CA BLADDER	CA LUNG	NA
20	64	M	SYNCHRONOUS	CA ESOPHAGUS	CA LUNG	NA
21	43	F	METACHRONOUS	CA BREAST	CA BREAST	NA
22	55	F	METACHRONOUS	CA BREAST	CA BREAST	NA
23	72	F	SYNCHRONOUS	CA ESOPHAGUS	CA BREAST	CA HYPOPHARYNX
24	60	M	METACHRONOUS	CA TONGUE	CA LUNG	NA
25	52	F	METACHRONOUS	CA BREAST	AML	NA
26	70	M	METACHRONOUS	CA PENIS	CA ALVEOLUS	CA BLADDER
27	71	F	METACHRONOUS	CA CERVIX	CA COLON	NA
28	60	F	METACHRONOUS	CA OVARY	CA VAULT	NA
29	63	M	SYNCHRONOUS	FIBROSARCOMA ARM	CA LUNG	CA PANCREAS
30	60	F	METACHRONOUS	CA BREAST	CA BUCCAL MUCOSA	NA

Etiology: Possible etiological associations could be field cancerization in 5 cases (16.6%), therapy related in one case(3.3%), known genetic cause in 10 cases(33.3%).

Survival duration: It was measured from the onset of 2nd primary till the date of study conclusion. 90% pts were alive and 10% pts succumbed to disease during the study period.



IV. Discussion :

In a retrospective study by Skelton et al a total of 56 patients with MPMs were identified, 38 (68%) simultaneously diagnosed and 18 (32%) with sequential diagnoses. Forty-seven patients (84%) were male, 48 (86%) were white, and 43 (77%) were active or former smokers. Malignancies of the head and neck region (n=11, 19.6%) and gastrointestinal (GI) tract (n=9, 16.1%) were the most common sites where first malignancies were found, and these same two tumor sites were the most common sites for secondary malignancies.[6] There were wide differences noted in this study compared to our study. These differences may be attributable to the geographical variations of cancer distribution and selection criteria of 60days for synchronous malignancies in their study.

In this retrospective study, over a five year period, total thirteen cases of multiple malignancies diagnosed histopathologically were retrieved from the archives of department of surgical oncology.There was female predominance with age range being 43-68 years. Majority of the cases were in 7th decade. The most common organ involved was breast, followed by cervix.[7] This study findings are in line with our results where there was female preponderance and most common malignancy identified was carcinoma breast.

The majority of the data available regarding multiple primaries is in the form of case reports. Hence the risk factors, possible etiological associations, survival outcomes are not well established. Our study also has these limitations because of small sample size. Multicenter large volume retrospective hospital based analysis may give proper insights into this rare but ever increasing clinical entity.

The possibility of existence of multiple primary malignancies should always be considered during pre treatment evaluation. When a patient is diagnosed with two active malignancies at the same time, the challenge is to find an appropriate curative strategy that covers both cancer types without increasing the toxicity and without any impact on the overall outcome. Long-term survival with multiple primaries is influenced by the cancer type, stage at diagnosis, comorbidities and the performance status of the individual.[8]

The possibility of second primary should be suspected when there is atypical metastatic spread of primary tumour, high tumour burden relative to tumour marker load, new metastatic spread several years after a primary cancer diagnosis, single new metastatic lesion after a primary cancer diagnosis, recurrence in patients with exposure to environmental carcinogens like smoking, haematological malignancy after prior chemotherapy, secondary malignancy in patients with prior radiation therapy, suspicious lesion on imaging detected at staging or in follow-up, differential standard uptake value (SUV) of suspected lesions on PET-CT.[9]

In case of a suspected secondary primary, a histological confirmation is mandatory. The reporting pathologist should be aware of the primary cancer diagnosis and the primary tissue should be available for comparison. The presence of dysplastic changes in the second primary site favours the diagnosis of a new primary.

In case of synchronous primaries, the management decisions are based on the intent of treatment (curative versus palliative), timing of therapy (simultaneous versus sequential), treatment modality (local versus systemic). In case of advanced malignancies, a common treatment regimen which is active against both diagnoses, if feasible should be chosen keeping in mind the drug interactions and toxicity profiles. Genetic testing to identify a common targeted therapy for both tumors can be contemplated.[10]

In case of metachronous disease the major management decision is whether the second primary can be treated with a curative approach or not. The drugs used during the previous episode should be reviewed and new management strategy should be designed accordingly. With the advances and wider availability of genetic

testing, patients diagnosed with multiple primaries should be investigated for an underlying cancer predisposition.[10]

V. Conclusion :

The incidence of MPMs is on the rise. So clinicians should be vigilant to the possibility that patients are at continued risk of new and separate malignancies even after an initial diagnosis. More studies are needed to further elucidate the incidence of MPMs and to investigate risk factors. There is no universal protocol for the treatment of multiple malignancies. Each case must be managed individually by a multidisciplinary team.

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