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AN ANALYSIS OF OCCURRENCE OF SYNCHRONOUS MULTIPLE PRIMARY MALIGNANT NEOPLASMS (MPMN)

Oncology

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ABSTRACT

Introduction: Multiple primary malignant neoplasms is the term used to define malignancies arising from two different organs with different histology and having no relation which each other. Incidences of such cases—both metachronous and synchronous have been reported to be around 0.73 to 11.18% of all cancers. Synchronous cancer is defined as malignancy occurring either simultaneously or within 6 months of primary malignancy. Synchronous cancer occurrence is less frequent as compared to metachronous ones. We describe an interesting series of synchronous multiple primary malignant neoplasms (SPMN).

Materials and methods: We prospectively collected data of patients who were newly diagnosed as synchronous multiple primary neoplasms (SPMN) and retrospective data of patients diagnosed with de novo SPMN during the period of January 2015 to January 2017 in the Surgical Oncology Department, King George Medical University, Lucknow, UP. We have analyzed the records of 22 patients. Warren and Gates criterion was used to include patients. Clinical Details such age, sex, site, histopathology and treatment were recorded.

Results: In our analysis, 13 out of 22 (59%) patients were females. The mean age at the primary malignancy diagnosis for male was 48.5 years (range 30-70 years). Mean age for female was 52 years (range 22-84). The most common primary presenting neoplasm was of oral cavity cancer followed by breast. The most common second malignancy found with oral cavity cancer was a second primary in the oral cavity. Synchronous breast malignancies followed the suit.

Conclusion: With increasing life expectancy and improvement in imaging and investigations there is a rise of reporting of Multiple Primary Malignant Neoplasms. SPMN are quite uncommon. This case series illustrates the challenges in the management of these malignancies

KEYWORDS

Multiple primary malignant neoplasms, synchronous malignancy, metachronous malignancy

INTRODUCTION

wo or more cancers occurring in the same patient without any relation between them is termed as multiple primary malignant neoplasms (MPMN).

As new lesions in different parts of body are anticipated as part of metastatic spread, patients presenting with synchronous cancers may be confused with recurrence or metastasis from primary tumours To avoid such confusion, Warren established following criteria for diagnosis of MPMN which were updated by Liu Fusheng's added standard[1,2,3]

1. Each tumour must be malignant,
2. Each tumour must have its own pathological features
3. Tumours must occur in different parts or organs which are not continuous with each other
4. Each tumour must have its own metastatic pathway and the diagnosis of metastatic or recurrent tumours should be excluded.

The occurrence of such cases is gradually on the rise. Literature suggests the occurrence of MPMN to be around 0.73% to 11.7%[3,4] This may due to the earlier diagnosis or new therapies which allow longer survival of patients. These patients may develop subsequent new primary cancers. Another reason believed for the rise of incidence is the development of better diagnostic tools which may be able to detect occult primaries.[4,5,6,7]

Such cases can be classified into two groups depending on time interval of diagnosis of second malignancy into synchronous or metachronous cancers. Synchronous cancers are those cases in which the second malignancy developed simultaneously or within six months of diagnosis of the first malignancy, whereas metachronous ones are those in whom second malignancy was diagnosed six months or later after the first malignancy.

Synchronous cancer occurrence is less frequent as compared to metachronous ones.[3,4] In this paper We describe a series synchronous cancers seen in our institution.

Materials and methods:

We prospectively collected data of newly diagnosed patients with multiple primary cancer and retrospective data of patients diagnosed with de novo second cancer during the period January 2015 to January 2017 in Oncology department, King George Medical University, Lucknow, UP.

Warren and Gates criterion was used as an inclusion criteria and to define multiple primaries. Synchronous cancer was defined as occurring either simultaneously or within 6 months of primary malignancy. Histopathological confirmation was required for both the malignancies. Clinical details such as age, sex, site, histopathology and treatment were recorded.

Patients with atleast two neoplasms at two distinct locations with distinct histopathology at the the two locations were included. Patients without a clear histopathological confirmation were excluded. Patients in whom the second tumor was suspected to be metastasis of the primary tumor were also excluded.

Results:

During the period of study from 2015 to 2017, 7,141 cancer patients were treated. Synchronous Multiple Primary Malignant Neoplasms were seen in 22 cases (0.30%) In our analysis 13 out 22 (59%) patients were females. The mean age at the primary malignancy diagnosis for males was 48.5 years (range 30-70 years). Mean and median age for females was 52 years (range 22-84). Males get malignancies at an early age whereas females get malignancies later in age Most common histology was squamous cell carcinoma occurring in 20 out of 44 histologies. Out of 22 total cases of synchronous tumours, most common site of presentation was oral cavity (9/22) followed by breast (6/22). Among patients with oral cancer having synchronous cancers, most common second site was oral cavity (8/9). Among patients with breast cancer too, the most common second site was breast (3/6). Other second sites seen in breast cancer patients were GIT malignancy (2/6) followed by oral cavity (1/6).

replacements were 0%, 10 %, 20% and30%by weight of fine aggregate. Tests were performed for compressive strength or all replacement levels of crumb rubber at different curing periods (7-days & 28-days).

Table 1 Detailed Description of patients

S. No.	Age	Primary Site	Histopathology	Treatment	Second Site	HPE	T/t
1	45/F	Cervix	SCC	Palliative Chemotherapy	Gall Bladder	Adeno Ca	Palliative Chemotherapy
2	84/F	Forefoot	Sarcomatoid Carcinoma	Sx	Thigh	Malignant Melanoma	Sx
3	22/F	Rt. Eyelid	Squamous Cell Ca.	Sx	Lt. Eyelid	Squamous Ca.	Sx
4	50/F	Breast	IDC	Palliative chemotherapy Therapy	Gall Bladder	Adeno Carcinoma	Palliative Chemotherapy
5	60/F	Ovary	Adenocarcinoma	Sx + Adj CT	Vault	Squamous Cell Ca.	NACT/RT
6	60/F	Right Breast	IDC (- / - / 3+)	Palliative CT	Left Breast	IDC (- / - / -)	Palliative Chemotherapy
7	40/M	Brain	Astrocytoma	Surgery	Mandible	Osteosarcoma	NACT/Sx/Adj CT
8	52/F	Breast	IDC	Chemotherapy	Gall Bladder	Adeno Carcinoma	Palliative Chemotherapy
9	45/F	Ovary	Adenocarcinoma	NACT/Sx	Breast	IDC (- / - / -)	NACT/Sx
10	56/M	Tongue Rt. LB	Squamous Cell Ca.	Sx	Lt. Lateral Border	Squamous Cell Ca.	Sx
11.	55/M	Right lower alveolus	Squamous cell carcinoma	Sx	Left upper lip	Squamous cell carcinoma	Sx
12	45/M	Left lower alveolus	Squamous cell carcinoma	Sx+ PORT	Rt Retromolar trigone	Squamous cell carcinoma	Sx
13	55/M	Mid oesophagus	Squamous cell carcinoma	Pallative CT	Periampullary carcinoma	Adenocarcinoma	Pallative CT
14	60/F	Endometrium	Endometroid carcinoma	Sx+PORT	Ovary	Papillary serous adenocarcinoma	Sx+ Adj CT
15	30/M	Right lower alveolus	Sarcomatoid carcinoma	Sx	Hard palate	Squamous cell carcinoma	Sx
16	70/M	Left maxilla	Squamous cell carcinoma	Sx	Left lower Alveoulus	Squamous cell carcinoma	Sx
17	41/M	Right buccal mucosa	Squamous cell carcinoma	Pallative chemotherapy	Dorsum tongue	Squamous cell carcinoma	Pallative chemotherapy
18.	36/F	Rt Breast	IDC(+/+/+)	NACT+Sx+Adj CT/RT	LT breast	IDC(+/-/+)	NACT+Sx+Adj CT/RT
19.	60/F	Lt breast	IDC(+/+/-)	NACT+Sx+ AdjCT/RT	Ovary	Papillary serous adenocarcinoma	NACT+Sx+Adj CT
20.	45/F	Rt Breast	IDC(-/-/-)	NACT+Sx+AdjC T/RT	Lt Breast	IDC(-/-/+)	NACT+Sx+AdjC T/RT
21	55/F	Left Buccal mucosa	Squamous Cell Carcinoma	Sx	Right Lateral Border Tongue	Squamous cell carcinoma	Sx
22	40/M	Right lower alveolous	Squamous cell carcinoma	Sx+PORT	Right lateral Border tongue	Squamous cell carcinoma	Sx+PORT

n 15/20 patients, definitive treatment was possible in 15/20 patients and patients were cured of both malignancies. Three patients presented with irresectable disease of either primary. In two patients, diseases of either malignancy were surgically treatable but presence of another malignancy did not allow so. One such patient was having malignancy of mid one third oesophagus along with Periampullary cancer. Due to extensive procedure required and poor performance status of patient, patient was shifted to palliative chemotherapy.

Another patient developed dorsum of tongue cancer while he was being planned up for surgery of right buccal mucosa malignancy. Disease grew aggressively and involved the whole of tongue. Due to extensive resection and comorbid conditions of patients, patient was planned up for palliative chemotherapy.

The third patient was having synchronous adenocarcinoma gall bladder and squamous cell cancer cervix. Gall bladder cancer required extensive surgery with a possibility of multi-organ resection whereas management of cervical cancer required concurrent chemoradiotherapy. Due to poor performance status of the patient and extensive treatment required patient was decided to be managed by palliative chemotherapy.

Discussion:

With the increasing life expectancy and better imaging modalities, available incidence of cases with two or more primaries is on the rise. Spratt and Hoag found that the reported prevalence varies from 0.7% to 11.7% and concluded that, empirically, persons living to extreme age are more likely to have multiple cancers.[3]

Incidence of such neoplasms is seen mostly in 5th to 6th decade with slight female predispostion[1,2]. The favourable site of MPMNs may vary according to geographic distribution of cancer in a particular region. In the study by L.L Xu the primary tumor sites were most commonly observed in the digestive system, followed by the breast, respiratory system, reproductive system, and head and neck[3]. Also in the same study the occurrence of malignancy in different organ system was more likely to metachronous than synchronous. In a study, index location was breast and genital maligancy[3]. In an another study conducted in India, head and neck cancers were the most common first cancer and breast most common second location .[4]

There was female predisposition seen in our patients too with most common malignancies belonging to head and neck region. As breast cancer represents one of the most common cancer of our region, it was also the second most frequent synchronous cancer. Thus site of occurrence of MPMN in our study was according to the distribution of cancers in our geographic region.

The most frequently occurring histology was squamous cell carcinoma closely followed by adenocarcinoma and infiltrating ductal carcinoma. Sarcomatoid carcinomas, melanoma, osteosarcoma, astrocytoma were

the other histopathologies seen. The analysis of MPMN done by Kilciksiz et al[5] reported similar findings with adenocarcinoma and squamous histologies to be most frequent ones.

The proportion of patients presenting with primary and second malignancy in the same organ system was very high. Kilcikisiz also reported the findings suggesting the same. Most of such patients presented with both malignancies in oral cavity.[5] Liu et al analysed the presence of multiple primary malignancies in their cancer registry and found 51 synchronous primaries among 15398 patients. Head and neck cancers and urinary bladder cancer were four time frequent than the other organ system.[6]

This might be explained by the field cancerization theory which supports that carcinogenesis occurs in larger histological areas exposed to the same carcinogen in multistep pathological sequence.

Detailed clinical and radiological attention avoids misdiagnosis and missed diagnosis. Care should be taken to establish the difference between metastasis and recurrence of carcinomas and MPMN.

There has been increased use of whole-body 18F-FDG PET scan as workup tool for various cancers. The scan not only detects metastasis at known drainage areas but also at unusual sites. The scan also enables to detect otherwise undetectable second primaries in patients. Ishimori et al evaluated retrospectively the detection of unexpected second primaries after whole-body 18F-FDG PET/CT in patients with known or suspected malignancies. He found PET-positive lesions suggestive of new primary malignant tumours in 79 (4.1%) of 1,912 patients out of which 22 (1.2%) were pathologically proven to be malignant.[6]

Agress and Cooper et al in their recent study reported the rate of detection of unexpected second malignant primaries in patients with known or suspected malignancies to be at least 1.7% using whole-body 18F-FDG PET screening[7] .But due to affordability issues in our patients we could not use this diagnostic tool which we believe would have increased detection rate.

Synchronous cancers not only just poses a dilemma in diagnosis but the unique challenge lies in its management. In management of such cases, the treatment of each tumour should be done according to its stage irrespective of the other tumour.[9-12]

But the stage of disease of one cancer may alter the management of the other cancer. This might be even truer in case which require two different modalities for treatment of primaries. Also the poor performance status caused by the burden of both malignancies may lead us more towards palliative options, where in isolation definitive treatment could have been possible for either primary. In a study by Lee et al the intention of treatment of cancer was altered after detection of second primary in about 2/3rd of patients, with management going in lines of palliative treatment.[8]

In our analysis 13 patients could undergo definitive treatment which was potentially curative. One patient defaulted from treatment. 3 patients presented in metastatic stage of either primary and hence were kept on palliative treatment. Management was altered in 3 of patients due to presence of second malignancy. One patient had advanced cervical malignancy which required definitive chemoradiation as well as radical surgery for carcinoma gall bladder. Due to extensive procedures required, the patient was given palliative chemotherapy. Similarly, another patient required extensive surgery for his two primaries which were mid one third oesophagus and periampullary area but this was not possible due to poor performance status of the patient. In a patient, rapidly progressing second malignancy could not be operated and was hence shifted to palliative chemotherapy.

Due to shorter period of follow-up, we could not come up with survival data of our patients.

As more data keeps on gathering about such cases certainly in future management may be different and yet more effective to deal with the phenomena of Multiple Primary Malignant Neoplasms..

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