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Double Primary Malignancies at a Tertiary Cancer Hospital: Our Experience

ABSTRACT

Background: Patients, who have been detected with cancer, have a life time risk of developing a new second cancer depending on several genetic, environmental and lifestyle risk factors as well as long-term side effects of cancer treatment. They can be detected simultaneously or in the follow-up period. Improved diagnostic techniques, newer treatment modalities, and improved survival in cancer patients can be responsible for this trend. **Aim:** Our aim was to report our observation of incidence, management, and outcome analysis of the second primary malignancies in a tertiary cancer hospital. **Materials and Methods:** A single-center retrospective study collected and analyzed data of patients diagnosed with double primary malignancies in a tertiary cancer hospital. The study was conducted over a 5-year period from 2013 till 2018. All patients satisfying the Warren AND Gates criteria were included in the study. The details such as sex, age at diagnosis, site, synchronous or metachronous, treatment, and outcomes were noted. **Results:** Among the thirty cases of dual primary cancers detected, 14 (46.66%) were synchronous and 16 (53.33%) were metachronous. Out of the 30 patients, 19 were females and 11 were males. The most common sites of primary malignancy were breast (12 cases), followed by head and neck (6 cases). Among the second malignancies, the most common was head and neck followed by breast, gynecological, and lower gastrointestinal tract. The incidence of double primary malignancy was 0.7%. All the patients received the proper treatment for both the malignancies. Median overall survival was 65 months in the synchronous group and 108 months in the metachronous group. There was no significant difference in disease-free survival between the two groups. **Conclusion:** The occurrence of double primary malignancies is not uncommon in Indian cancer patients. They can manifest as synchronous or metachronous. A strong clinical suspicion, thorough assessment, and regular monitoring are a must among clinicians in the management of these tumors. Counseling of patients is a must after treatment of the primary neoplasm.

Key words: Metachronous, Second primary malignancy, Synchronous, Treatment

INTRODUCTION

Advances in the management of cancer care, such as expansion of screening efforts and the improvements in cancer treatment, have substantially allowed cancer patients to live longer.[1-3] According to the reports of National Cancer Institute's Surveillance, Epidemiology, and End Results Program in 2007–2013, among all cancer patients, the 5-year survival rate is now almost 67%. Nearly one in five cancers diagnosed today occur in an individual with a previous diagnosis of cancer, and these "second primary malignancies (SPMs)" are a leading cause of morbidity and mortality among cancer survivors.[4] The entity of SPM is not uncommon. A second or higher order primary malignancy accounts for ~6–10% of all cancer diagnosis and are the fifth most commonly diagnosed cancer in Western countries.[5] This can be attributed to improved diagnostic techniques such as positron emission tomography-computed tomography (PET-CT) which have made possible the detection of synchronous occult malignancy.[6-8] A SPM is a second *de novo* malignant neoplasm with a known cancer. In 1934, Bugher analyzed cases of double primary malignancies and derived an equation for the probability of death during a specified period with a new second malignancy.[9] Warren and Gates were the first, to give the criteria used for the diagnosis of SPM and which further refined later [Table 1].[10-12]

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Table 1: Warren and Gates criteria

1. Histological confirmation of malignancy in both the index and second tumors
2. Each must be geographically separate and distinct and the lesions should be separated by normal mucosa
3. Probability of one being the metastasis of the other must be excluded

On the basis of time interval between malignancy diagnosis, a SPM can be either synchronous or metachronous.[13] Synchronous neoplasms are second primary malignancies occurring simultaneously or within 6 months after the first malignancy, whereas metachronous neoplasms are second primary malignancies that develop after more than 6 months from the first malignancy.[14]

Aim

In this study, we aimed to report our observation of incidence, management, and outcome analysis of the second primary malignancies in a tertiary cancer hospital.

MATERIALS AND METHODS

This was a retrospective study, conducted in the Department of Surgical Oncology in a tertiary care center for a period of 5 years from July 2013 to June 2018. A total of 4200 patients of cancer were analyzed, and all patients satisfying Warren and Gates criteria were included in the study. All the patients underwent a complete diagnostic assessment including PET-CT scan. Details such as age at diagnosis, sex, site, whether synchronous or metachronous, histopathology and radiological imaging, treatment, and outcome were retrieved from electronic database of the hospital. As this was a retrospective data collection study, with no hypothesis testing, formal calculation of sample size and statistical power was not performed. Kaplan–Meier log rank test was used for survival analysis.

RESULTS

We identified total thirty cases of SPM in the entire period of 5 years, of which 14 (46.66%) were synchronous and 16 (53.33%) were satisfying the metachronous criteria. The median age for primary malignancy was 54 years (range: 27–79 years) with the majority of patients developing primary malignancy between 4th and 6th decade of life (63.3%) [Figure 1]. The time interval of the metachronous cancers ranged from 1 to 25 years, with an average of 6.81 years. Out of the total thirty patients, 19 (63.3%) were females and 11 (36.6%) were males [Figure 2].

The most common site of primary malignancy was breast (12 cases, 40%), followed by head and neck (6 cases, 20%). Most common site for second malignancy was head and neck

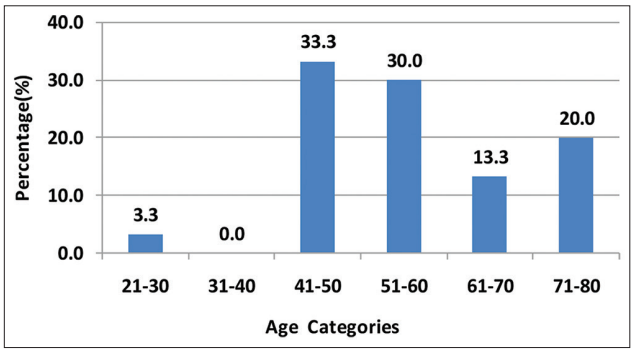

Figure 1: Pattern of age group distribution in primary malignancies

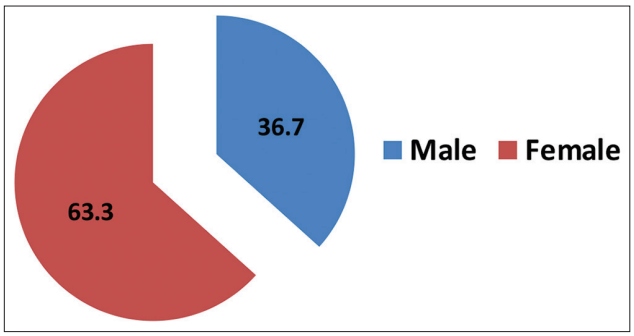

Figure 2: Female-to-male ratio in primary malignancies

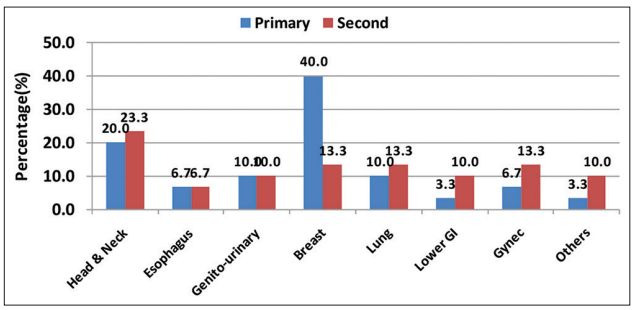

Figure 3: Site distribution of the primary and second malignancy

(7 cases, 23.3%), followed by breast and lower gastrointestinal (4 cases each, 13.3%) [Figure 3].

The most common histopathological cancer for the primary site was infiltrating duct carcinoma (IDC) (10 cases, 33%) and squamous cell carcinoma (SCC) (4 cases, 20%) [Table 2]. Among the second primary cancers, the most common histology was papillary carcinoma (5 cases, 16.6%) and IDC (4 cases, 13.3%) [Table 3]. All the patients underwent a proper treatment regimen (surgery, chemotherapy, radiotherapy, and supportive and palliative care) for the primary and secondary cancers. Median overall survival (OS) was 65 (95% confidence interval [CI]: 56.9–73.1) months and 108 (95% CI: 77.7–138.3) months. General survival graphs of synchronous and metachronous tumors are shown in Figures 4 and 5. A total of 8 patients were lost to follow-up and 9 deaths were recorded in the study.

Table 2: Synchronous SPM

S. No.	Age	Sex	Primary site	Histopathology	Treatment	Secondary site	Histopathology	Treatment	Status
1	50	F	Thyroid	Papillary carcinoma	Surgery, RAI	Lung	Adenocarcinoma	Surgery	Alive, disease free (5 years)
2	71	M	Esophagus	SCC	Chemotherapy, Surgery	Colon	Adenocarcinoma	Chemotherapy, Surgery	Lost to follow up
3	52	M	Vocal cord	SCC	Surgery	Thyroid	Follicular adenoma	Surgery	Alive, disease free (6 years)
4	69	M	Vocal cord	SCC	surgery	Lung	Adenocarcinoma	Surgery, chemotherapy	Alive, disease free (7 years)
5	76	F	Right Breast	IDC	Surgery	Left Kidney	Clear cell RCC	Surgery	Dead, lung metastases (5 years)
6	60	F	Thyroid	FVPTC	Surgery	Lung	adenocarcinoma	Chemotherapy, Surgery	Dead, liver and skeletal metastasis (1 year)
7	66	M	Right Kidney	Clear cell RCC	Surgery	Colon	Adenocarcinoma	Surgery, Chemotherapy	Dead, lung metastasis (2 years)
8	59	F	Right Breast	IDC	Surgery, Hormone Therapy	Right Ovary	Adenocarcinoma	Surgery, Chemotherapy	Alive, disease free- 4 years
9	27	F	B/L Breast	Angiosarcoma	Surgery, chemotherapy	Right Ovary	Angiosarcoma	Surgery, Chemotherapy	Lost to follow up
10	61	M	Right Lung	Adenocarcinoma	Chemotherapy, Surgery	Right Kidney	Papillary RCC	Surgery	Lost to follow up
11	54	F	Right Lung	Adenocarcinoma	Chemotherapy, Surgery	Thyroid	FVPTC	Surgery	Alive, distant metastasis -5 years
12	76	M	Prostate	Adenocarcinoma	Surgery, Chemotherapy	Colon	Adenocarcinoma	Surgery, Chemotherapy	Dead, distant metastasis (2 years)
13	72	M	Colon	Adenocarcinoma	Surgery, Chemotherapy	Thyroid	Follicular adenoma	Surgery	Alive, Disease free- 5 years
14	50	F	Right Breast	IDC	Surgery, Chemotherapy, Radiotherapy	Left breast	IDC	Surgery, Chemotherapy, Radiotherapy	Alive, Disease free- 5 years

M: Male, F: Female, SPM: Second primary malignancy, SCC: Squamous cell carcinoma, IDC: Infiltrating duct carcinoma, FVPTC: Follicular variant of papillary thyroid carcinoma, RCC: Renal cell carcinoma, RAI: Radioactive iodine

DISCUSSION

The SPMs are not very rare. Various population-based studies have reported relative risks of SPM ranging from 1.08 to 1.3.[15-18] SPM can occur at any age but more common in old age.[19] In our study, the median age at the time of second malignancy diagnosis is 54 years (range: 27–79 years) and 93% of patients with SPM were more than 50 years of age.

In the reviewed literature, male/female ratio varies between 0.9 and 3.5, with male predominance. In our series, the male/female ratio was 0.57, with female predominance which may be due to high percentage of primary breast malignancy in the present study.

Cancer survivors may be at increased risk of further primary cancers for mainly three reasons: genetic and behavioral risk factors for the initial cancer may persist, common environmental risk factors, and treatment-related risk factors, particularly radiotherapy and chemotherapy.[20-23] Although genetic susceptibility explains only small percentage of all second malignancies, various syndromes associated with the DNA microsatellite instability such as Lynch I and II syndromes, mutation in multiple tumor suppressor genes such as p16, p53, PTEN, and Rb gene are associated with the development of multiple malignancies in different organs.[24] Head-and-Neck SCC (HNSCC) patients are known to have 36% cumulative life time risk of developing SPM over 20 years[12] and the reported risk of developing SPM in a known case of HNSCC is estimated to be 2–6% per year of follow-up.[25,26] In our study, there are three cases (10%), in which SPM is

Table 3: Metachronous SPM

S. No.	Age	Sex	Primary site	Histopathology	Treatment	Time interval (years)	Secondary site	Histopathology	Treatment	Status
1	50	F	Right Breast	Phyllodes tumor	Surgery	1	Thyroid	Papillary carcinoma	Surgery	Alive, Disease free- 8yrs
2	77	F	Left Buccal Mucosa	SCC	Surgery, Radiation	1	Esophagus	SCC	CTRT, Surgery	Dead- 2 years- Locoregional recurrence- pall chemo
3	54	F	Left Breast	IDC	Surgery, Chemotherapy	3	Thyroid	Papillary carcinoma	Surgery, RIA	Alive, disease free (5 years)
4	41	F	Left Breast	IDC	Chemotherapy, Surgery, Hormone Therapy	3	Right Breast	IDC	Chemotherapy, Surgery	Lost to follow up
5	79	M	Right Lung	Adenocarcinoma	Surgery	4	Colon	Adenocarcinoma	Surgery	Dead- postop complications
6	52	F	Right Breast	IDC	Chemotherapy, Surgery	4	Left Breast	IDC	Chemotherapy, Surgery	Dead, liver metastasis (1 year)
7	56	F	Right Breast	IDC	Surgery, Chemotherapy, Radiotherapy	5	Ovary	Adenocarcinoma	Surgery, Chemotherapy	Alive, disease free (3 years)
8	47	F	Left Breast	IDC	Surgery, Chemotherapy, Radiotherapy, Hormone Therapy	5	Right Breast	IDC	Surgery, Chemotherapy, Radiotherapy	Neck recurrence (1 year), chemotherapy. Alive with disease
9	49	F	Ovary	Adeadenocarcinoma	Chemotherapy, Surgery	5	Stomach	Adenocarcinoma	Chemotherapy, Surgery	Dead, distant metastases (1 year)
10	45	F	Left Breast	IDC	Surgery, Chemotherapy, Radiotherapy,	6	Duodenum	Adenocarcinoma	Surgery	Lost to follow up
11	62	M	Prostate	Adenocarcinoma	Surgery, Radiotherapy	8	Thyroid	Papillary carcinoma	Surgery, RAI	Alive, disease free (5 years)
12	48	M	Tongue	SCC	Surgery	8	Peritoneal mesothelioma	Mesothelioma	Surgery, Chemotherapy	Recurrence (1 year) Lost to follow up
13	56	F	Blood	AML	Chemotherapy	9	Esophagus	SCC	Chemotherapy, Surgery	Lost to follow up
14	69	M	Esophagus	Adenocarcinoma	Chemotherapy, Surgery	11	Buccal mucosa	SCC	Surgery, Radiotherapy	Lost to follow up
15	58	F	Ovary	Adenocarcinoa	Chemotherapy, Surgery	11	Klatskin's tumor	Adenocarcinoma	Palliative chemotherapy	Dead (6 months)
16	67	F	Left Breast	IDC	Surgery, Chemotherapy	25	Kidney	Urothelial carcinoma	Surgery	Alive, disease free (4 years)

M: Male, F: Female, SPM: Second primary malignancy, SCC: Squamous cell carcinoma, IDC: Infiltrating duct carcinoma, RAI: Radioactive iodine, AML: Acute myeloid leukemia, CTRT: Cardiotoxicity of radiation therapy

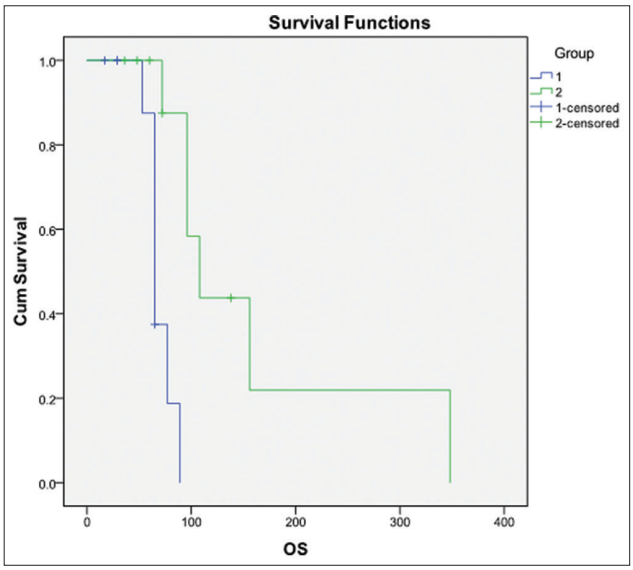

Figure 4: Kaplan–Meier curves for overall survival (months) in synchronous second primary malignancy (SPM) (1) and metachronous SPM (2)

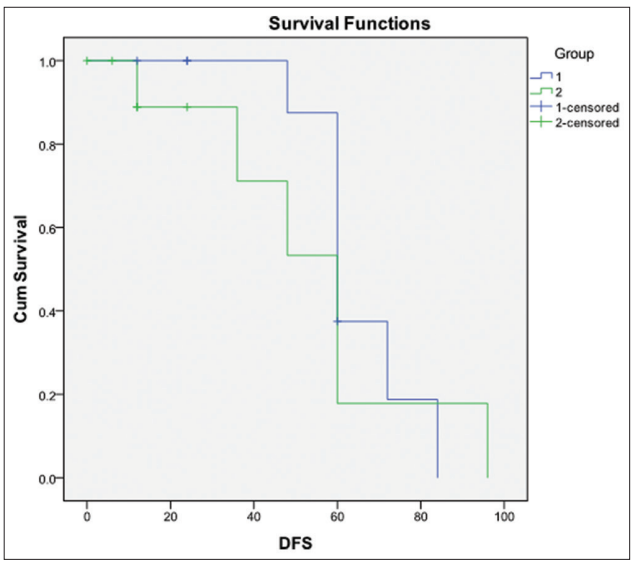

Figure 5: Kaplan–Meier curves for disease-free survival (months) in synchronous second primary malignancy (SPM) (1) and metachronous SPM (2)

attributed to field carcinogenesis. The common environmental risk factors are smoking and the use of alcohol. Tobacco smoking appears related with cancers of the head and neck, esophagus, respiratory system, pancreas, urinary system, and cervix.[27,28] It is a known fact that continued smoking increases the second cancer frequency and quitting decreases the risk.[29] Further, SPM (especially metachronous malignancies) may induced by prior irradiation[30] or chemotherapy,[31-33] and it usually manifests after a latent period of 15–20 years,[34,35] and hence a close clinical follow-up is recommended for long periods to detect SPM at the earliest. Such radiation-induced malignancies arise in the field of radiation. In our study, only one case of metachronous malignancy developed in prior radiation field. Certain chemotherapeutic agents such as alkylating agents and topoisomerase II inhibitors may give rise to SPM.[36] In our study, one case of acute myeloid leukemia treated with chemotherapy developed metachronous malignancy of esophagus.

In the present study, the most common primary malignancies were carcinoma breast, head and neck carcinomas, genitourinary, and lung carcinomas. This is sync with the data generated from previous retrospective Indian analyses.[37] The proportion of synchronous to metachronous malignancies differs in different studies. In the present study, there is 46.66% of synchronous malignancy as compared to 53.33% of metachronous malignancies. The available retrospective studies from various regions of India suggest higher percentage of metachronous cancers compared to synchronous cancers.[37,38]

Besides routine investigations, a baseline PET-CT scan may aid in the diagnosis of the SPM (especially synchronous).[39] In our study, most of the synchronously diagnosed second tumors were incidentally diagnosed. Only three patients had symptoms attributable to their second malignancy.

In terms of prognosis, there is a worse survival time in double primary malignancy cases, especially in synchronous cancers. The cause for this is to confront two cancers in the same period in the synchronous group compared to the metachronous group where the time to development of a second cancer is longer. In our study, the median OS for synchronous cancers was 65 months and 108 months for metachronous cancers. However, there was no significant difference in disease-free survival between the two groups.

In the literature, the incidence of double primary cancers varies between 0.4% and 21%. This rate was 0.7% in our series.

The treatment modalities, depending on the tumor location, can involve curative surgical resection, radiotherapy, and chemotherapy.[40,41] For synchronous neoplasms, each tumor should be evaluated, staged, and treated aggressively with the curative intent depending on their stage. If surgery is needed for both the tumors, it can be done in a single stage.[42] In our study, we have done total thyroidectomy with lobectomy, radical nephrectomy with lung lobectomy, total esophagectomy with left hemicolectomy, and radical nephrectomy with modified radical mastectomy as single-stage procedures. Treatment of the primary tumor should be kept in mind while planning the management of second neoplasm. Prior radiation fields, doses, radiation techniques, and chemotherapy should be taken into account. Appropriate dose constraints have to be assigned to the previously irradiated organs. Previously, re-irradiation was associated with high rates of treatment related toxicity, but emerging data support the safety and feasibility of conformal delivery techniques in cases of re irradiation.

Further, it could be a difficult task to educate patient and his relatives regarding the occurrence of two primary tumors. A considerable proportion of these patients, on detection of the second primary refuse any further treatment, due to psychological distress, socioeconomic, and other reasons. In our study, out of 16 metachronous cases 5 died, 5 were lost to follow-up and 6 are still alive and follow-up. Out of the 14 synchronous patients, 7 are alive and on follow-up, 4 are dead, and 3 are lost to follow-up

As a part of preventive strategy, the patients (particularly with HNSCC) should be encouraged to stop the use of alcohol and tobacco in any form, adopt healthy diet, and exercise regularly. At present, there is no evidence to the recommend use of chemo-preventive agents such as beta carotenoids and antioxidants in the prevention of SPMs.[43] The chances of finding a second primary cancer must always be considered during diagnostic evaluation. While screening tests help to detect early stage cancers, regular follow-up policies will help in reducing the deaths due to second primary cancers.

CONCLUSION

SPMs are not uncommon in Indian cancer patients. It manifests as a synchronous or metachronous malignancy. Early diagnosis of cancer and long survival may be responsible for increased occurrence of double primary cancers. A strong clinical suspicion and thorough evaluation are a must among clinicians in the management of these tumors. Newer diagnostic/staging modalities such as PET CT do aid in the diagnosis of multiple primary malignancies. Each patient must be counseled about the risk of developing second malignancies after the treatment of primary neoplasm and the importance of regular monitoring in the follow-up period.

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