Multiple Primary Malignancies- Synchronous and Metachronous-
Experience at a Tertiary Care Center in South India

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ABSTRACT

BACKGROUND
Patients diagnosed with cancer have a lifetime risk of developing another denovo malignancy depending on various inherited, environmental and iatrogenic risk factors. However, in recent years multiple primary malignancies have been reported with increasing frequency. The occurrence of second malignancy in a different organ in a known patient with malignancy is known as dual malignancy. There is increase in prevalence of both synchronous and metachronous second primary malignancy, among the cancer patients. The aim of the study was to report our observation of increasing incidence of multiple primary malignancies and analyse metachronous and synchronous types at MNJ Institute of Oncology and Regional Cancer Centre which is a tertiary care and referral center in south India.

METHODS
The study was done in MNJIO & RCC over a period of 4 years (June 2015 to June 2019). All the patients diagnosed with a histologically proven second malignancy as per Waren and Gates criteria were included. Various details regarding sex, age at presentation, synchronous or metachronous were recorded.

RESULTS
Among the total number of cases studied from June 2015 to June 2019, there were 14838 malignancies. The common malignancies noted are from cervix, head and neck, breast. Out of these cases we came across total 12 cases of dual primary malignancies and one triple malignancy.

CONCLUSIONS
There is no reliable clinical means of distinguishing a second primary malignancy from metastasis. The diagnosis must be made only by exploration and biopsy which should be confirmed by IHC when necessary. Therefore, in cancer patients any suspicious lesion not responding to treatment, in contrast to other areas of the disease should be biopsied, as the presence of different pathology and second primary malignancy should always be considered. Second primary malignancy in this era is a double edge sword as a result of multi-modality treatment.

KEYWORDS
Multiple Primary Malignancy, Second Malignancy, Metachronous, Synchronous
BACKGROUND

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Over the past decade of data, the cancer incidence rate (2006-2015) was stable in women and declined by approximately 2% per year in men, whereas the cancer death rate (2007-2016) declined annually by 1.4% and 1.8%, respectively. As a result of screening programmes and improvement in diagnostic procedures, cancer can be detected at an earlier stage. Significant progress has been made in the prevention, diagnosis and treatment of malignant tumours. Significant treatment advances have led to increased overall survival in patients with advanced cancer. This allows more patients with cancer to survive long enough to develop multiple primary malignant tumours (MPMTs).

MPMTs were first described by Billroth in 1889 and reported in a detailed study by Warren and Gates in 1932. Based on criteria proposed by Warren and Gates, diagnosis of MPMTs was dependent on each tumour must have clear evidence of malignancy on histologic examination. International rules for MPMTs are more detailed, and tumours arising in an organ or a pair of organs or a tissue are usually considered to be 1 tumour. However, there are 2 exceptions to this rule: systemic cancers potentially involving many different organs should only be counted once in any individual, and cancers with different histology should be regarded as multiple cancers, even if they are diagnosed simultaneously at the same site. The incidence of MPMTs has been reported to range from 0.52% to 11.7% in various studies from different countries. In different geographical regions, the incidence, characteristics, and survival rates associated with MPMTs have been found to be diverse. Multiple primary malignant tumours are classified into synchronous and metachronous tumours based on international association of cancer registries and international agency for research on cancer (iarc/iarc) guidelines. Second primary malignancy is diagnosed within 6 months of the primary tumour called as Synchronous and more than 6 months after the diagnosis of the primary tumour called as metachronous tumours.

METHODS

The present study is a retrospective study done at MNJ Institute of Oncology and Regional Cancer Centre which is a tertiary care and referral center of malignancies in the two Telugu states and also has referral from many south Indian states. This made the center an ideal center to take up the present study over a period of four years (June 2015–June 2019). Between 2015 and 2019, 14838 patients were diagnosed with malignancy at our institute.

Of these, 12 (0.0008%) patients presented with MPMTs. We collected Clinicopathological data of these patients from the medical records. We defined synchronous cancers as those occurring within 6 months of the first primary cancer, while metachronous cancers were defined as those occurring more than 6 months later. All the patients diagnosed with a histologically proven second primary malignancy as per Warren and Gates criteria were included. The specimens were fixed in 10% neutral buffered formalin. They were examined grossly according to the standard guidelines, with special emphasis on the tumour size and lymph node status of the lesion. The specimens were grossed, and sections were taken from representative sites. These sections were then processed in tissue processor and embedded in paraffin wax. Four to five-micron thickness sections were prepared from the corresponding paraffin blocks, one on albumin coated slide for Haematoxylin and Eosin (H & E) staining. Panel of ihc markers were used.

Inclusion Criteria

Multiple primary malignant tumours.

Exclusion Criteria

Metastatic tumours, benign tumours, inflammatory lesions.

RESULTS

The study was conducted over a period of 4 years from 2015 to 2019 at MNJ Institute of Oncology and Regional Cancer Centre Hyderabad, Telangana state. Between 2015 and 2019, 14838 patients were diagnosed with malignancy at our institute. Of these, 12 (0.0008%) patients presented with MPMTs. Out of 12 cases of MPMTs 11 cases (91%) were dual malignancies and one case (9%) was triple malignancy. The age group ranged from second (2nd) decade to seventh (7th) decade. Youngest patient was a female aged 26 years diagnosed of Infiltrating duct cell carcinoma of breast. Oldest patient was female aged 70 years diagnosed of Infiltrating duct cell carcinoma of breast. There was a marked female preponderance with more than 90% of patients were females accounting for 11 out of 12 cases. The most common site of primary tumour was breast with 7 out of 12 cases (51%) followed by cervix in 2 cases (16%). And time interval between primary tumours in our study was more than 6 months, all tumours were belonging to metachronous type (12/12 -100).

Total 12 cases were diagnosed as multiple primary malignant tumours out of these 11 patients had dual malignancy, 1 case had triple malignancy based on histological features. In our study most common primary tumour was breast-infiltrating duct cell carcinoma. And all patients underwent surgery, chemotherapy and radiotherapy. These patients presented with second primary tumour after taking treatment. This tumour had different histomorphological features from first primary tumour. All cases presented after 6 months of initial primary tumour with an average period of 4.2 years. Second primary tumours were endometrial adenocarcinoma, ovarian serous cystadenocarcinoma, mucinous cystadenocarcinoma,
ovarian sex cord stromal tumour, soft tissue sarcoma and acute myeloid leukemia (AML).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female: Male - 11:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td>26-70 years</td>
</tr>
<tr>
<td>Most Common Site of Primary Tumour</td>
<td>Breast (7 cases), Cervix (2 cases)</td>
</tr>
<tr>
<td>Metachronous Tumours</td>
<td>12 cases</td>
</tr>
<tr>
<td>Simultaneous Tumours</td>
<td>0</td>
</tr>
<tr>
<td>Dual Malignancy</td>
<td>11 cases</td>
</tr>
<tr>
<td>Triple Malignancy</td>
<td>1 case</td>
</tr>
</tbody>
</table>

**Table 1. Clinical Details of the Patients**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Age/ Sex</th>
<th>Primary Site and Histology</th>
<th>Treatment of Primary Tumour</th>
<th>Secondary Site and Histology</th>
<th>Time Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>70 yrs./f</td>
<td>Infiltrating duct cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Endometrium Adenocarcinoma well differentiated</td>
<td>5 years</td>
</tr>
<tr>
<td>2.</td>
<td>50 yrs./f</td>
<td>Infiltrating duct cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Ovary-mucinous cystadenocarcinoma</td>
<td>8 years</td>
</tr>
<tr>
<td>3.</td>
<td>50 yrs./f</td>
<td>Infiltrating duct cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Ovary-serous cystadenocarcinoma</td>
<td>5 years</td>
</tr>
<tr>
<td>4.</td>
<td>40 yrs./f</td>
<td>Infiltrating duct cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Ovary- Sex cord stromal tumour</td>
<td>3 years</td>
</tr>
<tr>
<td>5.</td>
<td>25 yrs./f</td>
<td>Infiltrating duct cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Upper Limb- Soft tissue sarcoma</td>
<td>4 years</td>
</tr>
<tr>
<td>6.</td>
<td>50 yrs./f</td>
<td>Infiltrating duct cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>AML</td>
<td>4 years</td>
</tr>
<tr>
<td>7.</td>
<td>50 yrs./f</td>
<td>Cervix - squamous cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Non-Hodgkin's Lymphoma</td>
<td>3 years</td>
</tr>
<tr>
<td>8.</td>
<td>45 yrs./f</td>
<td>Cervix - squamous cell carcinoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Lung- carcinoma Non- small cell carcinoma</td>
<td>2.5 years</td>
</tr>
<tr>
<td>9.</td>
<td>60 yrs./f</td>
<td>Lymphoma</td>
<td>Surgery Chemotherapy Radiotherapy</td>
<td>Kidney- Renal cell carcinoma</td>
<td>4 years</td>
</tr>
<tr>
<td>10.</td>
<td>68 yrs./f</td>
<td>Rectum- adenocarcinoma</td>
<td>Surgery Radiotherapy</td>
<td>Kidney-NHL</td>
<td>3 years</td>
</tr>
<tr>
<td>11.</td>
<td>63 yrs./f</td>
<td>Buccal mucosa - Squamous cell carcinoma</td>
<td>Surgery Radiotherapy</td>
<td>Cervical lymph node- NHL-DLBCL</td>
<td>5 years</td>
</tr>
</tbody>
</table>

**Table 2. Histology and Treatment of Multiple Primary Malignant Tumours**

In endometrial adenocarcinoma GCDFP was done to rule out metastatic deposits from breast infiltrating duct cell carcinoma and GCDFP was negative. In ovarian sex cord tumour inhibin and calretinin done to confirm ovarian origin of tumour both are positive confirmed ovarian origin.

In our study we had 2 cases of carcinoma cervix was second most common site for first primary tumour with histological features of squamous cell carcinoma. Patients underwent chemotherapy, radiotherapy and presented with Non-Hodgkin’s Lymphoma and Lung Non-small cell carcinoma.

60 years male presented with lymphoma underwent chemotherapy and radiotherapy and within 4 years period presented with kidney-renal cell carcinoma. 68 years female presented with rectal adenocarcinoma underwent surgery and radiotherapy within 3 years presented with kidney-Non-Hodgkin Lymphoma. 63-year female patient with buccal mucosa-squamous cell carcinoma underwent surgery and radiotherapy with in 5 years’ time period presented with cervical lymph node - Non Hodgkin Lymphoma Diffuse Large B Cell Lymphoma. Most of our patients received radiotherapy and chemotherapy with alkylating agents like chlorambucil, cyclophosphamide, cisplatin and triazines.

In our study Interestingly One case was presented with triple malignancy. A 50 years female presented with breast lump 10 years back and underwent surgery, chemotherapy and radiotherapy. Histological diagnosis of Breast was Infiltrating duct cell carcinoma -NST. Within 5 years’ time interval patient was diagnosed with cervix squamous cell carcinoma and again underwent chemotherapy and radiotherapy. After 3 years of second primary tumour the same patient presented with ovarian mass and underwent surgery and to be diagnosed of ovarian mucinous cyst adenocarcinoma.

**DISCUSSION**

The mechanisms responsible for the appearance of multiple primary carcinomas have not been fully explained. Most frequent factors involved are the Genetic susceptibility, Immune system of patients and Intensive exposure to carcinogens including chemotherapy and radiotherapy. Genetic vulnerability associated with specific genes may play a role in the development of Multiple primary malignancies. Microsatellite instability (MSI) has been noticed to occur more frequently in cases of multiple primary malignancies than in sporadic cancers.13 Carcinogenic environmental factors may induce multiple neoplasms of independent organs that were exposed to same carcinogens. For example, field concretionization effect, which is associated with an increased risk of multiple cancers in aero digestive organs after prolonged exposure to cigarette smoking.14 Modalities used in the treatment of the index cancer may also induce secondary cancers. For example, a relationship has been reported between combined therapy with radiotherapy and alkylating agents and an increased risk of gastric and colon cancer in survivors of Hodgkin’s lymphoma. Treatment used for first malignancy has resulted in damage to specific regions of DNA with chromosome re arrangement or loss, responsible for tumourigenesis.

Nyqvist et al15 reported a case of an 81-year-old woman who had been treated for 5 different primary malignancies during a 16-year period. The patient was diagnosed with her first malignancy in 1997 at the age of 61 an endometrium adenocarcinoma without lymph node metastasis. She underwent hysterectomy and bilateral salpingo oophorectomy. In 2002, an invasive, moderately differentiated adenocarcinoma colon was detected with no lymph node metastasis. In 2013, 3 different malignancies were detected, including a malignant melanoma of the left leg at the pretrial region, a pleomorphic spindle cell sarcoma in the left muscular biceps, and a 17-mm large invasive mucinous carcinoma in her right breast. All these primary tumours were well differentiated. Genetic analysis of the patient’s blood sample using DNA sequencing revealed no mutations in genes associated with hereditary cancer syndromes, TP53 or BRCA mutations. These findings

are understandable, as her first malignant tumour was detected after the age of 60 and indicates a low penetrance. Furthermore, none of the 5 tumours were therapy-related malignancies, such as neoplasms that develop after radiation or chemotherapy administration.

Our triple malignancy case was also an elderly female presenting with one malignancy after the other. We could not do a genetic analysis done to limited resources. However, in our study also most common primary site was breast and patients underwent for surgery, chemotherapy and radiotherapy with few years gap presented with second primary tumour with well differentiated histological features without nodal metastasis following primary treatment.

Caterina et al16 studied Incidence of Acute Myeloid Leukemia after breast cancer patients treated with adjuvant chemotherapy regimens, commonly including alkylating agents and anthracyclines, are at increased risk of developing leukemia, further enhanced by the use of radiotherapy. In the last few years also the use of growth factors seems to increase the risk of secondary leukemia. Several studies have reported an increased acute myeloid leukemia (AML) after treatment of Breast cancer, with evidence of a dose-intensity relationship. It is estimated that 1 every 20 patients will develop a secondary non-breast cancer after 10 years, which corresponds to a 22% increase of relative risk, particularly for secondary AML and myelodysplastic syndromes (MDS). In our study also one breast cancer patient presented with acute myeloid leukemia after taking chemotherapy and radiotherapy.

Anil K. Chaturvedi et al17 studied increased risk developing second primary lung cancers in cervical cancer patient survivors. They explained additional cofactors like chemotherapy and radiotherapy. In our study also one case of cervical cancer who took treatment of chemotherapy and radiotherapy presented lung cancer after two and half years diagnosis of primary cervical cancer squamous cell carcinoma type.

Primary renal lymphoma (PRL) is a rare malignancy due to the absence of lymphatic tissues in the kidney, and patients with PRL have been reported to have a poor prognosis due to its rapid invasiveness and limited treatment strategies. Colon cancer is the third most common cancer and has a high mortality rate. Both malignant diseases predominantly affected elderly men. Though the 2 malignancies shared similarities in gender and age, without findings of common genetic features, concomitant occurrence is an exceptional event and rarely reported. Ji Li, MM et al18 reported a case of concomitant PRL and colon cancer in 78 years old male patient. This patient having a family history of colon cancer. Though colon cancers with high microsatellite instability (MSI) demonstrate the characteristics of synchronous occurrence with additional tumours.

In our study also 68 years a female presented with carcinoma rectum and after 3 years of diagnosis of primary rectal carcinoma presented with non-Hodgkin lymphoma of kidney.

There is no reliable clinical means of distinguishing a second primary malignancy from metastasis. The diagnosis must be made only by exploration and Histopathological Examination which should be confirmed by IHC wherever necessary. Therefore, in cancer patients any suspicious lesion not responding to treatment, in contrast to other areas of the disease should be biopsied, as the presence of different pathology and second primary malignancy should always be considered. Second primary malignancy in this era is a double edge sword as a result of multi-modality treatment.

REFERENCES


