

## Multiple primary cancers: An enigma

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## Abstract

**Background:** Incidence of multiple primary cancers though uncommon, is being frequently reported now-a-days owing to better diagnostic techniques, the prolonged life span and the increased incidence of long-term survival of cancer patients. **Materials and Methods:** This is a retrospective study. Cases of multiple malignancies diagnosed histopathologically were retrieved from the archives of department of surgical oncology. Clinical data were obtained from the medical records. They were categorized as synchronous malignancies if the interval between them was less or equal to 6 months and metachronous, if the interval was more than 6 months. **Results:** A total of 13 cases were encountered in the 5 year study period. Out of them two were in the metachronous category and the rest were synchronous as the 2<sup>nd</sup> malignancy was detected mostly during clinical evaluation of the patients for the primary malignancy. There was female predominance with age range being 43-68 years. Majority of the cases were in the 7<sup>th</sup> decade. The most common organ involved was breast, followed by cervix. Apart from bilateral breast malignancies, there were combinations like breast with uterine endometrial carcinoma, cervical carcinoma and even papillary thyroid carcinoma. **Conclusion:** Detection of multiple primary malignancies is becoming increasingly common in day-to-day practice. Greater awareness of this is required among both cancer patients and their treating clinicians.

**Key words:** Dual malignancies, metachronous malignancy, multiple primary cancers, synchronous malignancy

## Introduction

Multiple primary cancers are usually defined as primary malignant tumors of different histological origins in one person. Recently, there has been an increase in the number of patients diagnosed with multiple primary cancers. This trend can be attributed to improved diagnostic techniques, prolonged life span and the increased incidence of long-term survival of patients with malignancy. Most multiple primary cancers are double primary cancers.<sup>[1,2]</sup>

Definitions and classifications for multiple primary cancers and multi-centric cancers, proposed by Moertel way back in 1977 hold true even today.<sup>[2,3]</sup> Accordingly, group I includes, multiple primary cancers occurring in organs with the same histology, group II includes multiple primary cancers that originate from different tissues and group III consists of cancers from different tissues and organs that concurrently exist with group I cancers, and they form multiple primary cancer of three or more cancers. Group I is further subdivided into group A, which includes cancers that occur in the same tissue and organ, group B, which includes cancers that are from the same tissue and different organs, and group C, which includes cancers that occur in bilateral organs. Multiple primary cancers are again classified as synchronous and metachronous. Those malignancies that are observed at the same time or within 6 months are termed as synchronous multiple primary cancers, and those cancers that develop at more than a 6-month interval are termed as metachronous multiple primary cancers.<sup>[4]</sup> On the other hand, many studies have defined 1 year as the dividing time of these two types of multiple cancers.<sup>[5]</sup>

In Indian literature, scant data is available regarding multiple primaries, most of them being case reports, including two from our institute.<sup>[6-13]</sup> In this retrospective study, we have analyzed the multiple cancers encountered in the department of surgical oncology of a single institute over a 5 year study period.

## Materials and Methods

In this retrospective study, from May 2007 to May 2012, total thirteen cases of multiple malignancies diagnosed

histopathologically were retrieved from the archives of department of surgical oncology. Clinical data were obtained from the medical records. We did not include leukemia as 2<sup>nd</sup> malignancy. Furthermore, autopsy data was not included. We have not included those cases where the possibility of the 2<sup>nd</sup> malignancy being a metastatic deposit was not completely excluded. We have categorized the malignancies as synchronous if the interval between development of them was less or equal to 6 months and if it was more than 6 months we have termed it as metachronous. Positron Emission Tomography- Computed Tomography (PET-CT) was not done in any of these cases due to financial constraints.

In this retrospective study, the patients and their relatives have given consent to utilize the information for publication purpose as noted from the standard case sheet record obtained from the medical records department. As the study had no intervention other than standard care, we have not obtained permission from the institutional review board.

## Results

We retrieved a total of thirteen cases in the 5 year study period. Out of them, two were in the metachronous category owing to interval between detection of primary and 2<sup>nd</sup> malignancy being more than 6 months. The synchronous ones were detected simultaneously either at the time of clinical examination or reported in histopathological examination of the surgical specimen.

There was female predominance with age range being 43-68 years. Majority of the cases were in 7<sup>th</sup> decade. The most common organ involved was breast, followed by cervix.

In the metachronous category, there were two cases. In the first case, the first primary was (IDCC (nos)) Infiltrating duct cell carcinoma (not otherwise specified) of breast and the 2<sup>nd</sup> malignancy was endometrial adenocarcinoma. This patient was diagnosed as a case of IDCC (nos) after lumpectomy which was carried out in an outside center. After that the patient did not receive any chemo or radiotherapy. She presented to our institute after a gap of 39 months with fine needle aspiration (FNA) findings suggestive of recurrence of IDCC (nos). At that time she complained of bleeding per vaginum for which she was evaluated and ultrasonography showed thickened endometrium. The patient underwent right modified radical mastectomy (MRM) for recurrence of IDCC and was advised chemotherapy and hormonal therapy. She also underwent radical hysterectomy and the final histopathological impression was endometrial adenocarcinoma.

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The 2<sup>nd</sup> metachronous case was a 37-year-old male patient in whom the first primary was detected as squamous cell carcinoma of penis. This patient was treated with emasculation, bilateral ilioinguinal block dissection and was referred to radiotherapy. However, the patient was lost to follow-up and presented again after a gap of 22 months. At that time, the routine chest X-ray showed a cavitory lesion in the left upper zone of lung. FNA of the lesion in the lung was proved to be adenocarcinoma of lung.

In the synchronous category, there were eleven cases. Out of them, four were bilateral carcinomas of breast. One bilateral carcinoma of breast revealed a histology of infiltrating lobular carcinoma and the rest that of IDCC (nos). These patients underwent bilateral MRM and received chemotherapy and hormonal therapy (Adriamycin + Cyclophosphamide for 6 cycles and Tamoxifen).

One case of bilateral carcinoma breast was detected simultaneously with endometrial adenocarcinoma of uterus.

In one case of IDCC breast, at the time of routine examination, cervical growth was detected. This patient underwent right MRM and radical hysterectomy. She also received chemo and hormonal therapy.

A breast lump was detected on the routine examination of a case of papillary carcinoma of thyroid, which later on proved to be IDCC (nos). She underwent total thyroidectomy and right MRM followed by chemotherapy.

In another case, the cervical biopsy distinctly showed adenocarcinoma of endocervix and cervical intraepithelial neoplasia (CIN-III) of ectocervix. This patient was advised radical hysterectomy but subsequently she was lost to follow-up.

Again in another case of squamous cell carcinoma of buccal mucosa, cervical growth (stage III B) was detected. This patient was referred for chemoradiotherapy.

Other cases, which were included in the synchronous variant from the department of surgical oncology were cervix showing changes of CIN-III and sertoli and leydig cell tumor of ovary and another case of squamous cell carcinoma of esophagus and mixed epithelial tumor of ovary, previously reported from our institute.<sup>[7,8]</sup>

Follow-up data was available for various patients ranging from 6 to 42 months [Table 1].

## Discussion

Though, multiple primary cancers are not common, yet it is believed that the incidence is increasing. Since in patients with multiple cancers, the focus is mainly on the primary disease, there is a higher likelihood of missing incidental co-existence of another primary malignant lesion. Therefore, it is important to make an early diagnosis and administer prompt therapy in case of multiple cancers.<sup>[2]</sup>

The theory regarding the origin of majority of multiple primary cancers is that they arise as a result of random chance, but different mechanisms have been suggested to be involved in multiple primary cancers, such as the family history, immunologic and genetic defects, prolonged exposure to carcinogens, radiation and chemotherapy for the primary cancer, and field cancerization.<sup>[1,6,14,15]</sup> Previously reported

cases of multiple primary cancers are mainly described in the respiratory, gastrointestinal, and genitourinary systems.<sup>[16]</sup> One autopsy series has reported prostate cancer as one of the most common malignancies in patients with multiple primary cancers and also as a frequent incidental autopsy finding in elderly men.<sup>[17]</sup>

In our study, we have encountered two cases of malignancies in the metachronous category, where the primary was carcinoma breast in one case followed by endometrial carcinoma and the other one was carcinoma penis followed by adenocarcinoma of lung.

Breast cancer patients often develop a 2<sup>nd</sup> primary malignant tumor; common sites being opposite breast, endometrium and ovary with rare primary cancer of cervix.<sup>[9]</sup>

We have noted eight cases of carcinoma breast, out of them four being bilateral. According to the classification by Moertel, they fall under the Group IC category.<sup>[3]</sup> However, Tan *et al.* did not include bilateral carcinoma breast in their study stating that they are fairly common.<sup>[18]</sup>

In our study, there was one case of synchronous bilateral breast carcinoma and endometrial adenocarcinoma.

There were also three cases of carcinoma breast and endometrial adenocarcinoma. One of the cases was metachronous and the other two were synchronous in nature. One of the synchronous cases had bilateral IDCC (nos) breast and endometrial adenocarcinoma. However, in one case, the patient did not give any history of treatment after excision of breast lump and subsequently had endometrial carcinoma. We could not find an association between tamoxifen use for breast carcinoma and subsequent development of endometrial adenocarcinoma, though in literature it is described that tamoxifen use of at least 60 months is associated with high risk uterine histological subtypes when compared to no tamoxifen use.<sup>[19]</sup>

We also had a synchronous case of breast carcinoma and cervical carcinoma.

Goto, *et al.* in their article have described a case of synchronous invasive squamous cell carcinoma and clear cell adenocarcinoma of endocervix. They also detected Human papillomavirus (HPV) 18 in the squamous cell carcinoma; but not in the clear cell adenocarcinoma.<sup>[20]</sup> In our case the cervical biopsy showed adenocarcinoma of endocervix and CIN-III of ectocervix, but the patient was lost to follow-up prior to complete evaluation.

There was also an unusual case of synchronous papillary carcinoma of thyroid and breast IDCC.

The numbers of patients with multiple cancers have recently been increasing. In the present scenario, the possibility of a 2<sup>nd</sup> or 3<sup>rd</sup> malignant lesion should be considered for patients with primary cancer. Furthermore, the importance of screening procedures should be emphasized for the early detection of malignancy before the appearance of clinical symptoms.

In our study though, we have encountered a good number of multiple cancers in a relatively short period, most of them being synchronous, still a larger multi-institutional study with longer follow-up is required to arrive at a definite conclusion regarding the true incidence of multiple primaries.

**Table 1: Patient characteristics**

Case	Age/ sex	Type	First primary and histology	Treatment	Time interval	Second primary and histology	Treatment	Follow-up
1	59/F	Meta	Breast, IDCC (nos)	Right lumpectomy No RT, no CT	39 months	Uterus Endometrial adenocarcinoma	A. Right MRM for recurrence, CT, Letrozolepatient refused RT B. Radical hysterectomy	5 months
2	37/M	Meta	Penis, SCC	Emasulation, B/L IIBD referred to RT, lost for follow-up	22 months	Lung, primary adenocarcinoma	Advised palliative chemotherapy. Again LFU	-
3	64/F	Syn	B/L cabreast ILC	-	-	-	B/L MRM	12 months
4	68/F	Syn	B/L breast IDCC	-	-	-	Neoadjuvant CT-4 cycles. Bilateral MRM, Completion CT, HTx	39 months, No recurrence
5	68/F	Syn	B/L Ca breast rt. after 4 month left, IDCC (nos)	-	-	-	CT-AC4 cycles B/L MRM, Completion CT	42 months No recurrence
6	45/F	Syn	A. B/L ca breast, IDCC (nos) B. Uterus Endometrial adenocarcinoma	-	-	-	A. B/L MRM, CT (8 cycles) B. Radical hysterectomy	10 months No recurrence
7	40/F	Syn	A. Breast, IDCC (nos) B. Uterus Endometrial adenocarcinoma	-	-	-	A. Left MRM, CT (6 cycles+HTx) B. Radical hysterectomy	9 months
8	66/F	Syn	A. Thyroid, PTC B. Breast, IDCC (nos)	-	-	-	A. Total thyroidectomy B. Right MRM CT (AC 6 cycles+ HTx)	12 months
9	43/F	Syn	A. Breast, IDCC (nos) B. Cervix, SCC	-	-	-	A. Right MRM+CT (FAC 6 cycle)+Tamoxifen B. Radical hysterectomy	29 months No recurrence
10	66/F	Syn	Cervix-Carcinoma- <i>in situ</i> (ectocervix) Adenocarcinoma (endocervix)	-	-	-	Advised radical hysterectomy	-
11	65/F	Syn	A. Buccalmucosa, SCC B. Cervix, SCC	-	-	-	ChemoRT	8 months
12	45/F	Syn	A. Cervix-Carcinoma- <i>in situ</i> (CIN-III) B. Ovary–sertoli and leydig cell tumor	-	-	-	Radical hysterectomy Planned for CT and RT	7 months
13	50/F	Syn	A. Esophagus-SCC B. Ovary, mixed epithelial tumor	-	-	-	A. Palliative jejunostomy followed by radiotherapy B. Excision of ovarian cyst	

MRM=Modified radical mastectomy, CT=Chemotherapy, RT=Radiotherapy, IDCC (nos)=Infiltrating duct cell carcinoma (not otherwise specified), SCC=Squamous cell carcinoma, PTC=Papillary carcinoma of thyroid, AC=Adriamycin+cyclophosphamide, FAC=5-Fluorouracil+adriamycin+cyclophosphamide, IIBD=Ilio inguinal block dissection, Meta=metachronous, Syn=synchronous, B/L=bilateral, HTx=harmonal treatment

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