Original Article

Clinicopathological Characteristics of Multiple Primary Malignancies Involving Female Genital Tract at a Tertiary Cancer Institute of Northeast India

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Abstract

Background: The term "Multiple Primary Malignant Neoplasms (MPMNs)" refers to two or more unrelated primary malignant neoplasms that originate from single or different organs and occur in one patient. MPMNs have been divided into synchronous and metachronous based on time duration after first malignancy. **Materials and Methods:** This was a hospital-based retrospective study conducted at a tertiary cancer institute in Northeast India. Clinicopathological factors of patients with multiple primary malignancies with at least one female genital tract malignancy attending the gynecological oncology outpatient department were observed. Those with ambiguous status of primary malignancy and incomplete treatment of first primary malignancy were excluded from the study. **Results:** A total of 57 patients with MPMN, including one case of triple primary malignancy, were included in the study. 59.18% of cases had metachronous, and 40.81% had synchronous malignancies. The median time to the development of second primary malignancy was 60 months. Among the first diagnosed malignancies, cervix was the most common site (26.5%), followed by endometrium (20.4%) and ovary (14.28%), whereas ovarian malignancy was more commonly diagnosed second malignancy (38.77%), followed by endometrium (14.28%) and cervix (10.2%). In an analysis of synchronous malignancies, the most common genital tract involvement was seen with endometrium and ovary, with a predominance of low-grade endometrioid histology in 75% of cases. **Conclusions:** As the cancer survivor population continues to increase in future, these patients must be comprehensively evaluated on follow-up, and a cognizance of prior treatment taken should be kept. In addition, it is vital that the clinicians keep a lookout for high-risk population in which genetic testing may be beneficial.

Keywords: *Hereditary breast and ovarian cancer, metachronous malignancy, multiple primary malignancies, synchronous malignancy*

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Introduction

The term multiple primary malignant neoplasms (MPMNs) refers to two or more unrelated primary malignant neoplasms that originate from single or different organs and occur in one patient. The credit for description of the term multiple primary malignant tumor goes to Billroth, who described it for the first time in 1869, whereas in 1932, Warren and Gates first published and described patients with MPMN. A varied pathoetiology for the development of these tumors has been postulated. These include the field cancerization effect, an underlying genetic imbalance common to both the tumors, and the effects of therapeutic interventions such as radiation, topoisomerase inhibitors, and alkylating agents. Other implicated causes are

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environmental agents such as tobacco and alcohol consumption.[1]

MPMNs have been classified into synchronous and metachronous based on the time duration elapsed between the two tumors. These have been variably described by the NCI's Surveillance, Epidemiology, and End Results (SEER) Program and the International Agency for Research on Cancer (IARC). While the former labels metachronous malignancies as those that occur within 3 months of each other, the later agency classifies those occurring within 6 months of each other as metachronous.[2] Double MPMNs are relatively common, but triple and quadruple MPMNs are rare. A diagnostic dilemma may arise in distinguishing between the MPMNs and metastasis from previous index cancer.

In patients with preexisting cancer, the incidence of new tumors arising is approximately up to 16%, which is much higher than that of normal population.[3,4] As the cancer treatments improve and the number of survivors increase, the incidence of multiple primary neoplasms will continue to be on a rise.[5] This proportion of cancer patients is usually excluded from clinical trials, and there is a lack of prospective evidence to tailor treatments in them.[6] In addition, there is scant literature on MPMNs involving female genital tract malignancies.

Materials and Methods

This was a hospital-based retrospective study at a tertiary cancer referral institute in Northeast India. The study duration included 4 years from January 2017 to December 2021 and was approved by the institutional ethics committee. The study included patients with at least one genital tract malignancy presenting to gynecological oncology outpatient department (OPD). Patients who had ambiguous origin of primary malignancy were excluded from the study. In addition, patients who were incompletely treated for the index malignancy, those with synchronous malignancies but no immunohistochemistry (IHC) to conclusively differentiate metastasis from synchronous origin were also excluded.

The aim of the present study was to estimate the clinicopathological factors of multiple primary malignancy patients attending the gynecologic oncology OPD at our institute. Details about cases were retrieved from the electronic medical records of the hospital. All the data pertaining to the cases were recorded in the standard pro forma. This included clinical details such as age of onset of first and second malignancies, organ/tissue involvement, relevant medical history, personal history, family history, treatment taken for each malignancy, specific location of malignancy, time period between onset of first and second malignancies, and stage at the time of diagnosis. The pathological details sought were histology of each neoplasm, grade, and differentiation of tumors, whether IHC had to be done for confirmation. The study was done according to the STROBE checklist for observational studies.

If the time elapsing before the diagnosis of second neoplasm was shorter than 6 months, the condition was defined according to the IARC criteria as synchronous MPMN (sMPMN). Alternatively, it was defined as metachronous MPMN (mMPMN).

For patients with sMPMN, the survival time was calculated according to the diagnosis of the first tumor, whereas for patients with mMPMN, survival time was calculated from the diagnosis of the latter tumor.

Statistical analysis

Descriptive statistics were computed for all baseline characteristics. Characteristics of patients were described by mean and standard deviation (SD) (if normally distributed) or median and percentiles (if distribution is skewed) for continuous variables and frequencies and percentages for categorical variables. Associations between continuous variables were tested using an independent sample *t*-test (normal distribution), whereas categorical variables were compared using the Chi-square test. $P < 0.05$ was considered to be statistically significant. The analysis was done on RStudio IDE Version 1.2.1335 (developer: by Posit, PBC, Vienna, Austria) for Mac IOS.

Ethical approval

The study was approved by the institutional ethics committee. Ethical principles according to the Helsinki Declaration were considered during the study. The investigators ensured strict confidentiality of all patients' information and de-identified any data that may link to the patient's identity.

Results

A total of 57 patients were included in this study; however, careful evaluation of the records excluded 8 patients with ambiguous primary sites and metastasis. Of the 49 patients evaluated, the incidence of metachronous and synchronous malignancies was 59.18% ($n = 29$) and 40.81% ($n = 20$), respectively [Figure 1]. The median age of the onset of first malignancy was 47 years (range: 23–74) as compared to 52 years (range: 30–77) for the second malignancy (SD: 9.828, $P < 0.001$). The median age for the development of genital malignancies was still lower at 44 years.

Among the index primary malignancies, cervix was the most common site (26.5%), followed by endometrium (20.4%) and ovary (14.28%), whereas

ovarian malignancy was more commonly diagnosed second malignancy (38.77%), followed by endometrium (14.28%) and cervix (10.2%) [Table 1]. One case of triple primary malignancy was seen, in which adenocarcinoma of the colon preceded the development of synchronous malignancies of the endometrium and breast by 5 years. The patient underwent staging laparotomy with modified radical mastectomy in the same setting [Figure 2]. The median time interval to the development of second malignancy was 48 months (range: 24–336 months).

On a detailed analysis of the metachronous malignancies occurring in cervical cancer survivors (n = 9), ovary (22%), colon, and anal canal (33%) were the most frequently encountered sites of second primary malignancy. All these cervical cancer patients received concurrent chemoradiation as the treatment modality of choice, and 88.89% of the second malignancy sites were located within the pelvis [Figure 3a]. In the subgroup of patients with second primary as ovary, breast cancer was the most common first primary (50%) followed by cervix (20%) [Figure 3b]. Evaluation of etiological factors for the development of second malignancies showed that only 6.12% of patients presented with a positive family history of malignancy, whereas the same embryological origin was seen in 24.4% of patients, and a common human papillomavirus-associated origin was seen in 8.16% of cases. In all the first malignancies, 55.1% of cases received chemotherapy, 28.6% of patients received radiation, whereas surgery was performed in 63.3% of cases. Adenocarcinoma was the most common histology seen across all malignancies and sites, followed by squamous cell carcinoma and infiltrating ductal carcinoma [Figure 4].

In an analysis of synchronous malignancies, the most common genital tract involvement was seen with endometrium and ovary [Table 2]. In seven out of eight

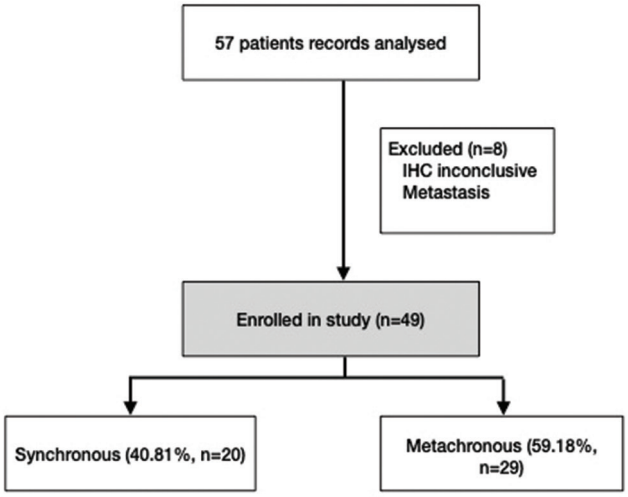

Figure 1: Flow diagram of patient selection

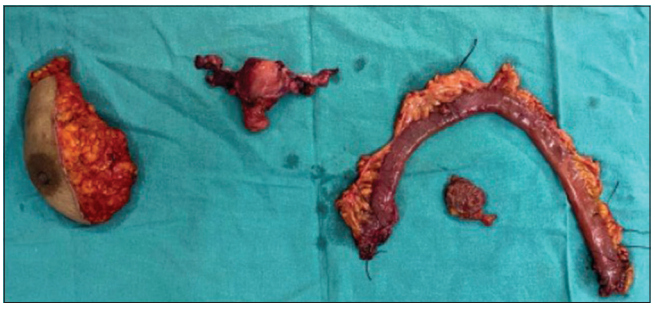

Figure 2: Surgical specimen-triple primary malignancy of colon, endometrium, and breast. Staging laparotomy and modified radical mastectomy were done. The loop of the small bowel with dense adhesions to the previous hemicolectomy incision had to be excised

Table 1: Distribution of primary sites of first and second malignancies

First primary	*n* (%)	χ^2	*P*	Second primary	*n* (%)	χ^2	*P*
Cervix	13 (26.5)	48.714	<0.001	Ovary	19 (38.77)	95.796	<0.001
Endometrium	10 (20.40)			Endometrium*	7 (14.28)		
Ovary	7 (14.28)			Cervix	5 (10.20)		
Breast	9 (18.36)			Breast	4 (8.16)		
Gallbladder	3 (6.12)			Colon	3 (6.12)		
Colon	2 (4.08)			Gallbladder	2 (4.08)		
Buccal mucosa	1 (2.04)			Anal canal and rectum	2 (4.08)		
Appendix	1 (2.04)			Vagina	1 (2.04)		
Esophagus	1 (2.04)			Vulva	1 (2.04)		
GTN	1 (2.04)			Uterus	1 (2.04)		
Bone	1 (2.04)			Pancreas	1 (2.04)		
				Kidney	1 (2.04)		
				Thyroid	1 (2.04)		
				Lung	1 (2.04)		
Total	49				49		

*One case of triple primary malignancy had colon as first malignancy and synchronous malignancy of endometrium and breast.
GTN: Gestational trophoblastic neoplasia

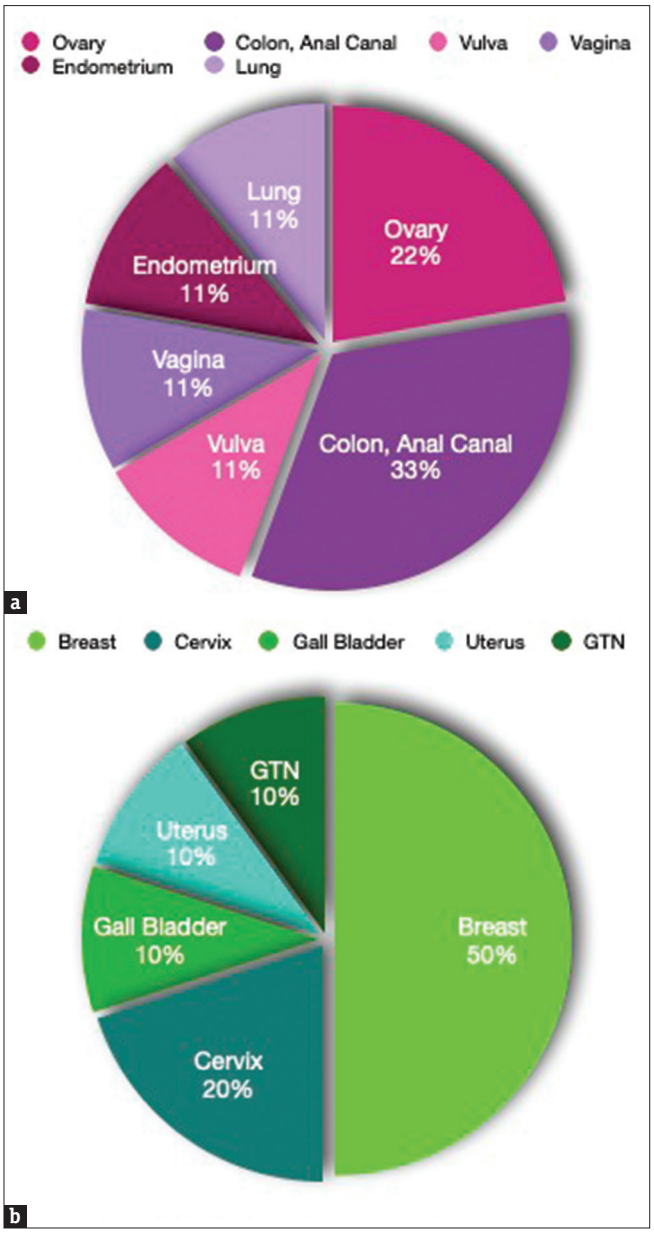

Figure 3: (a) Distribution of malignancies after first cervical malignancy, (b) Distribution of malignancies preceding second primary in ovary

Table 2: Distribution of synchronous malignancy sites

Synchronous sites	*n*
Endometrium and ovary	8
Endometrium and breast	2
Ovary and breast	2
Endometrium and appendix	1
Cervix and ovary	1
Cervix and gallbladder	1
Cervix and pancreas	1
Endometrium and thyroid	1
Endometrium and rectum	1
Ovary and appendix	1
Ovary and gallbladder	1

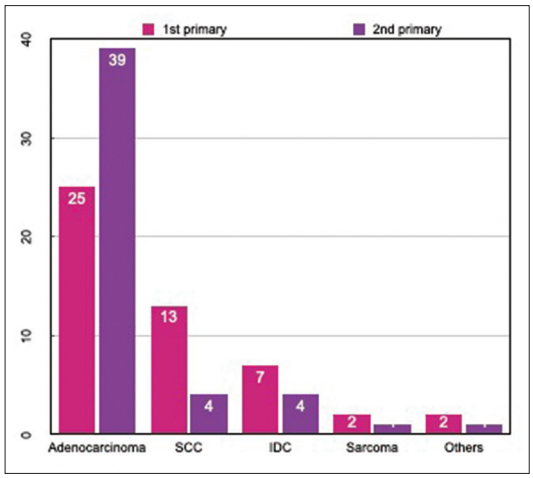

Figure 4: Distribution of histology across first and second primary malignancies

cases, the histology was endometrioid, with low-grade histology predominating in 75% of cases.

A multiple regression model was used to assess the impact of independent factors on survival statistics, only history of chemotherapy had a significant impact on disease-free interval after second malignancy. A total of 42.8% of patients had recurred by the end of the study and the overall survival at 1 year was 42.85%.

Discussion

The incidence of cancers in the population of Northeast India is characteristically higher than the rest of the country.[7] Another striking feature of this population is the earlier onset of malignancies, which is reflected in our study group, being lower than the median age of similar studies reported in the literature.[8] This has a bearing on the larger disease-free life span and incidences of developing a second malignancy thereafter.

Our study concurs with the literature regarding the higher incidence of second malignancies in cervical and breast cancer survivors;[9] however, a higher population sample will have to be examined to elucidate whether it is attributable to the treatment received, underlying genetic factors, or a matter of chance due higher individual incidences of these malignancies.

Among the malignancies that followed cervical cancers, all of which had received concurrent Chemoradiation in the primary setting, 88.89% of second malignancies occurred within the pelvis. Wu *et al*.[10] presented SEER data from 1975 to 2011 and reported a higher (hazard ratio: 1.43, $P = 0.01$) than usual risk of developing a malignancy post radiotherapy in colon, rectum, anus, uterus, as well as bladder. Radiation exposure has been implicated in the development of second primary

malignancies,[11] and these must be kept in mind when following up a patient who has received prior radiation.

The incidence of metachronous malignancies has been reported by Aydiner *et al*.[12] to be 66% versus 34% for synchronous malignancies. Our study also showed a higher incidence of metachronous versus synchronous malignancies (59.18% vs. 40.81%). A study by Dong and Hemminki[13] looking at the development of second malignancies has reported a three times higher incidence of malignancies within 9 years of the first primary, thus suggesting a bias introduced by higher surveillance in the period following the treatment of first malignancy, which may explain the median time period of 5 years to the development of second malignancy in our study.

Among the synchronous malignancies, endometrium and ovary were the most common sites observed, with a predominance of low-grade endometrioid histology. These findings are in concordance with a GOG's study[14] of 74 synchronous ovarian and endometrioid tumors and a predominance of low-grade endometrioid histology seen in their population subset. Similarly, Tong *et al*.[15] also presented a maximum preponderance of synchronous malignancies of endometrium and ovary in their study. The high incidence of synchronous tumors warrants a comprehensive evaluation of organs with similar embryonal and hormone receptor status. Hormonal adjuvant treatment in breast cancer has bearing on the risk for endometrial, gastric, colon, and ovarian cancers, with an increase in endometrial cancer specifically seen with tamoxifen use.[16] While the carcinogenic effects of certain chemotherapeutic drugs and radiation are well known, there is a scope of more research in this regard in future.

In addition, the confluence of ovarian cancers developing after breast cancers points toward underlying genetic mutation, most commonly pathogenic mutations of BRCA 1 and 2 genes, which can confer a risk of up to 39% for developing ovarian cancer, which is much higher than the general population's risk of 1%–12%.[17] While NCCN mandates genetic testing for selective breast cancers fulfilling high-risk criteria, genetic testing is recommended in all cases of epithelial ovarian cancer.[18,19] Thus, a significant gap exists in developing country like ours with regard to access for genetic testing in these patients.

On initial evaluation of patients suspected with multiple primary malignancies, eight patients were excluded after IHC proved the second site to be a metastasis. The majority of sites involved metastasis from cervix to sites such as stomach, gallbladder, lung, and ovary. The presence of uncommon and high-grade histology such as adenosquamous histology has a higher likelihood of being metastatic than conventional ones and carries a worse prognosis.

According to the published SEER data,[20] the incidence rates for MPMNs in females have risen from 1979 to 2003. This is a cause for concern for health care providers following up and managing increasing number of survivor population. Such comprehensive data are not available from our population subset. Another study has reported outcomes in the MPMN group in the Indian subcontinent; however, our study is the first to address this diverse yet unrepresented group of gynecological patients specifically.[21]

A drawback of our study is the sampling of patients from the outpatient cohort, which may induce an inherent bias in the observations. More prospective studies are needed to study the presented risk factors to better understand the disease etiology and populations at a higher risk of second malignancy.

Conclusions

As the cancer survivor population will continue to increase in future, these patients must be comprehensively evaluated on follow-up, and a cognizance of prior treatment taken must be kept. In addition, it is vital that the clinicians keep a lookout for high-risk population in which genetic testing may be beneficial.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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