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ORIGINAL ARTICLE

Synchronous Double Primary Malignancies: Clinical and Pathological Analysis Report From Tertiary Cancer Center

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Abstract

Background: Synchronous double primary malignancy is described as the presence of two histologically different primary tumors that occur either simultaneously or at intervals not exceeding six months. Their prevalence is on the rise because of better methods of diagnosis, early cancer detection, and prolonged survival of cancer patients. Early identification of the second primary malignancy is important to distinguish it from metastatic tumors. **Methods:** The retrospective study involved 18 patients diagnosed with synchronous double primary malignancies from a tertiary cancer referral facility during the period of January 2023 to January 2026. Data regarding demographic characteristics, clinical/pathological factors, and therapy was obtained from hospital records. **Results:** Out of the 18 patients included in the study, 15 (83.3%) were females with a median age of 53.5 years. The most frequent cancer type was breast carcinoma, with ovarian and endometrial cancers coming second. Combination of bilateral breast carcinomas and synchronous ovarian-endometrial carcinomas was the most frequent combination among these tumors. Majority of the cases had positive family history of cancer. All of the patients underwent therapeutic procedures, where 10 patients underwent neoadjuvant therapy with subsequent surgery and 8 underwent surgery alone. **Conclusion:** Synchronous double primary tumors call for timely diagnosis and a multidisciplinary approach for favourable outcomes. Early diagnosis and proper treatment may provide good short-term survival rates, but more studies on this rare disease condition are required.

Keywords: Multiple primary neoplasm, Synchronous Neoplasm, Ovarian neoplasm, Clinicopathological features

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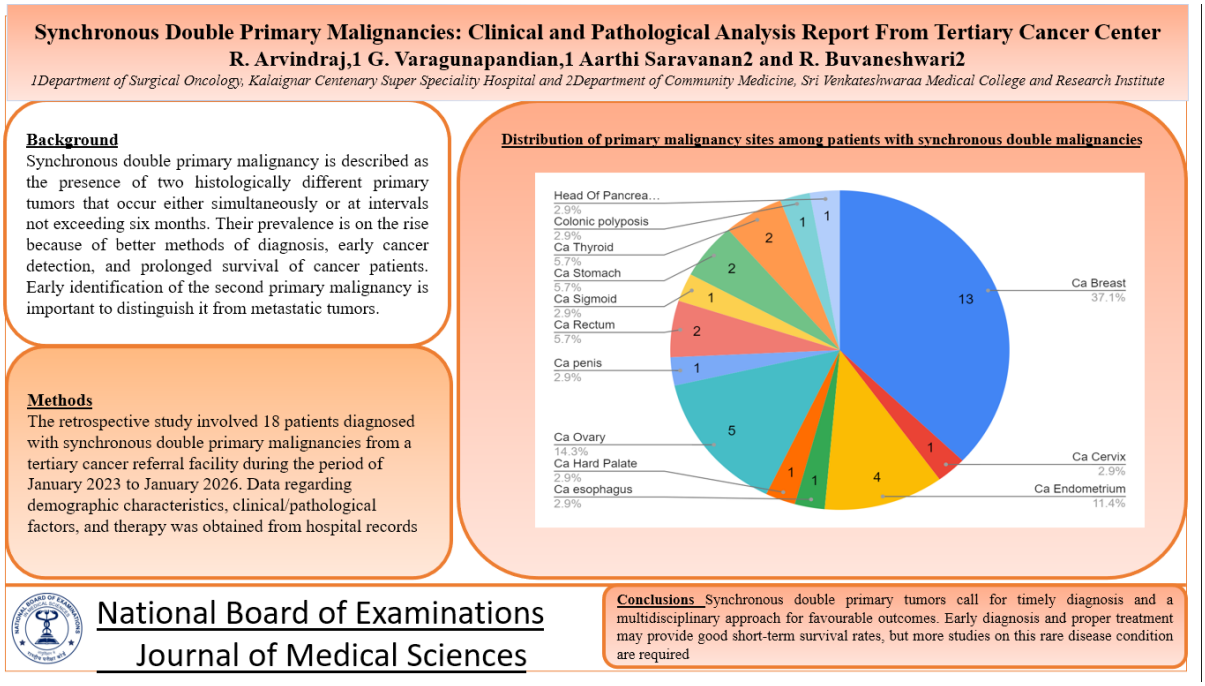
Graphical Abstract



Introduction

Multiples primaries malignancies (MPMs) are characterized by having two or more primary malignant tumors of different origins in the same person. The tumors should be independent of one another without any connection of metastasis from one lesion to another. Diagnostic criteria laid down by Warren and Gates are considered essential and fundamental for determining multiple primaries cancers. In this regard, each cancer should be proven to be malignant, histologically different, and non-metastasized, with each being separated from the other with normal tissue [1].

Classification of MPMs includes synchronic and metachronous depending upon the time interval between two cancer diagnoses. According to the classification, MPMs that occur together or within six months of each other are considered synchronic cancer, whereas those that occur after an interval of more than six months are metachronous cancers [2].

However, there has been an observed rise in the occurrence of multiple primary cancers in recent decades. Cases of double primary cancers have been predominant. Several factors have been attributed to this trend, including advances in diagnostic imaging, endoscopy, pathology, cancer screening programs, prolonged survival after cancer therapy, and increased life expectancy. Also, genetic predisposition, exposure to environmental carcinogens, smoking and alcohol use, lifestyle habits, and therapies like chemotherapy and radiation therapy have played a role in developing multiple primary cancers [2,3].

Synchronous double primary cancers pose a great diagnostic and treatment problem because distinguishing a secondary cancer from metastasis may be very problematic. It is extremely important to differentiate a secondary primary cancer from metastasis because their management differs significantly and affects patients' prognosis differently. Clinical examination,

imaging studies, pathology confirmation, and consultation are necessary for correct management [3,4].

Despite the rising prevalence of multiple primary malignancies globally, the Indian scenario with regard to existing data has been relatively underexplored. There have been mainly case reports and small series of cases available. There have been more studies involving the metachronous type than the synchronous type of multiple primary malignancy. Clinicopathological studies involving synchronous double primary malignancies are very rare [4,5].

The current retrospective study was performed for the purpose of understanding the clinicopathological features of cases with simultaneous double primaries encountered in the Department of Surgical Oncology within a tertiary cancer center during the past three years. The objectives of the study include an evaluation of the demographic features, localization of lesions, pathologic features, and management practices among these patients, thus adding to the scarce Indian data on this important issue.

Materials and Methods

This retrospective observational study was conducted in the Department of Surgical oncology at a tertiary care center and included patients diagnosed with synchronous double primary malignancies between January 2023 and January 2026.After obtaining institutional ethical clearance and waiver of consent from the head of the institution, clinical records of 18 patients were retrieved and reviewed from the institutional database .Patients were included if they had at least two histopathological confirmed primary malignant tumors occurring simultaneously or within six months of each other with each tumor demonstrating distinct histopathological features suggestive of an independent primary origin. Patients without clear histopathological confirmation of both tumors or those in whom the second lesion was suspected to be a metastasis or recurrence of the first primary malignancy were excluded from the study. The diagnosis of synchronous double primary malignancies was established based on clinical evaluation, radiological investigations and histopathological findings after excluding metastatic disease. Data regarding demographic characteristics, including age and sex, anatomical sites of the primary tumors, mode of diagnosis, histopathological subtype, clinical stage at presentation and treatment modalities were collected from the medical records, pathological reports and operative notes.The collected data were entered in Microsoft excel and analyzed using SPSS version 21. Patient confidentiality was maintained throughout the study by anonymizing all identifying information and the study was conducted in accordance with institutional ethical guidelines.

Results

The total number of patients with simultaneous double cancers was 18, which were diagnosed in the period between January 2023 and January 2026. There was a significantly high occurrence of the condition among women, as there were 15 (83.3%) females and only 3 (16.7%) males, making a female/male ratio of 5:1. The ages of the subjects varied from 43 to 77 years, with an average age of 53.5 years.

Breast malignancies were most commonly involved, with nine cases (50%) followed by ovary (four cases, 22.2%) and endometrium (four cases, 22.2%). In

women, carcinoma ovary and endometrium (three patients) and bilateral breast carcinoma (three patients) were more common combinations of the synchronous malignancies. Other combinations included breast with rectal carcinoma, breast with renal cell carcinoma, breast with ovarian carcinoma, breast with endometrial carcinoma, and cervix with ovarian malignancy. The predominant sites of malignancies in males were the gastrointestinal tract, including one case each with carcinoma stomach with carcinoma hard palate and carcinoma penis. One patient had carcinoma rectum and papillary carcinoma thyroid.

A positive familial background for any form of cancer in first- or second-degree relatives was noted among 10 of the 18 participants (55.6%), which may imply hereditary susceptibility to the disease among a considerable number of patients.

Biopsy diagnosis of all primary tumors was successfully confirmed in all patients. Most of the breast cancers were characterized by the histologic subtype of invasive ductal carcinoma of no special type (IDC-NOS), while the ovarian cancers were primarily high-grade serous carcinoma. On the other hand, the endometrial malignancies were primarily endometrioid adenocarcinoma and papillary serous carcinoma, whereas most of the gastrointestinal cancers were adenocarcinomas or squamous cell carcinomas.

The staging of all tumors was done in accordance with the 8th edition of AJCC staging system. All patients were evaluated to undergo curative intent treatment. Out of the total number of patients studied, ten patients, constituting 55.6% of patients, underwent pre-surgical treatments while eight other patients, 44.4% of patients, had surgical resection performed first followed by adjuvant treatments. Definitive histopathological diagnosis was established prior to any form of treatment in all patients except those who had either renal or pancreatic tumors, whose histological diagnosis were confirmed following surgery.

Out of the total number of patients, one patient was documented to have experienced an anastomotic leak following the surgery, which led to his death. The patient had a concurrent carcinoma stomach and carcinoma penis. Thus, there was a postoperative mortality rate of 5.6% in this study. Disease recurrence occurred in four patients during the follow-up period(Figures 1 and 2).

Overall, the present study demonstrates that synchronous double primary malignancies occur predominantly in females with breast and gynaecological cancers constituting the most frequent combinations. Early recognition through comprehensive diagnostic evaluation and multidisciplinary management enabled curative treatment in the majority of patients and resulted in favourable short-term outcomes (Table 1).

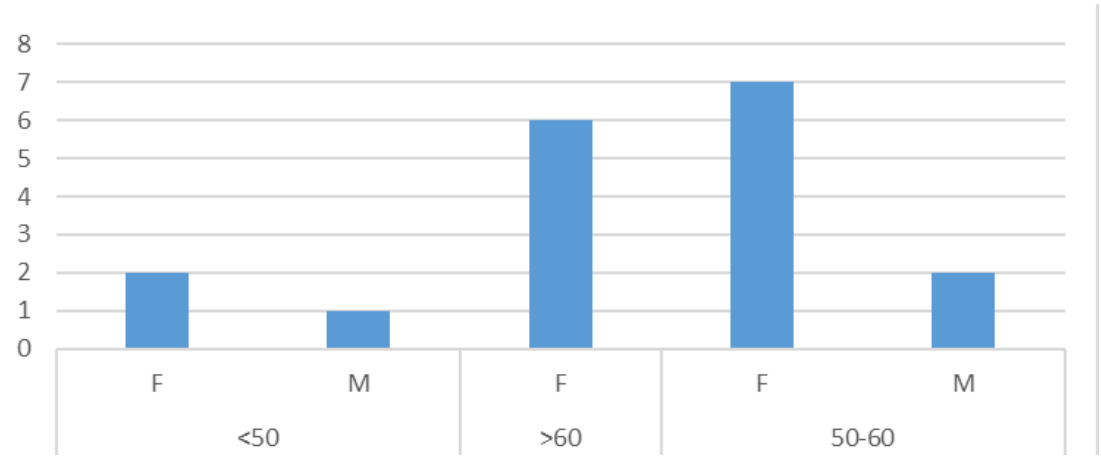


Figure 1. Distribution of synchronous double primary malignancy cases according to age group and gender

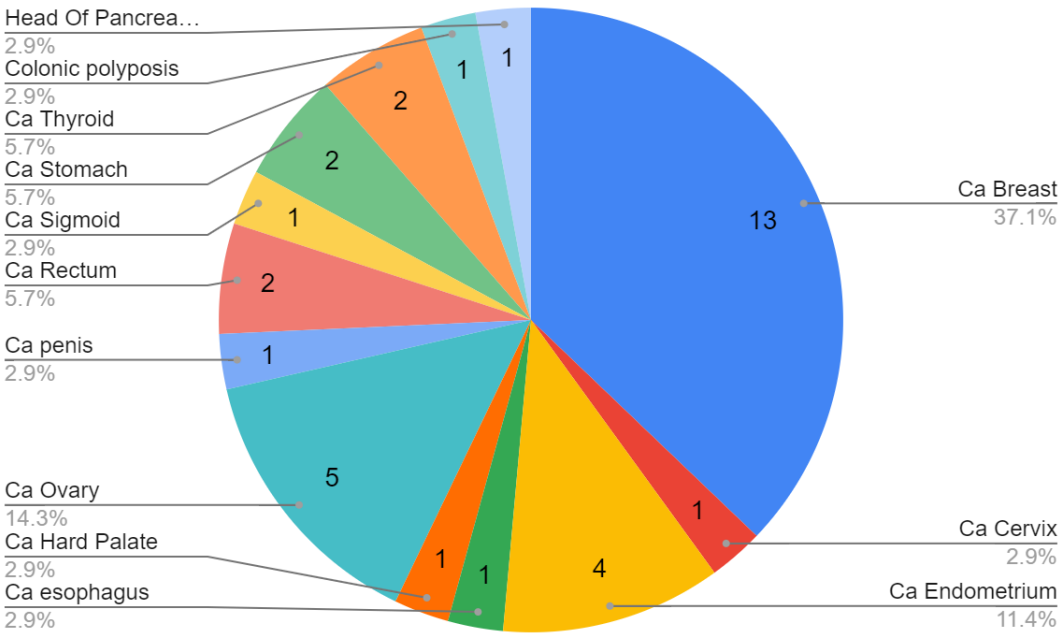


Figure 2. Distribution of primary malignancy sites among patients with synchronous double malignancies

Table 1. Clinicopathological characteristics and treatment details of patients with synchronous double primary malignancies

S. No	Age	Sex	First site	Treatment	HPE	2nd Site	Treatment	HPE
1.	56	F	Ca Cervix-	CCRT + Brachy	MD - Squamous cell carcinoma ((FIGO 2B)	Ca Ovary	NACT f/b Cytoreduction	Adult Granulosa cell tumor (FIGO 3C)
2.	64	F	Ca Ovary -	NACT f/b Cytoreduction	HG pap serous Ca (FIGO 3C)	Ca Endometrium	Cytoreduction	Endometroid Adeno Ca Gr1 (FIGO 1A)
3	48	M	Ca Stomach	D2 Subtotal Gastrectomy f/b adj chemo	Poorly Diff AdenoCa (signet ring type)- pT4N1	Ca Hard Palate	Wide excision	MD SCC - pT2Nx
4	65	F	Ca Breast	MRM f/b Adj. chemo + RT	IDC-NOS G2 - pT2N2	Colonic polyposis	Total Proctocolectomy	Adenomatous polyposis with High Grade dysplasia
5	56	F	Ca Ovary	NACT f/b Cytoreduction	HG pap serous Ca (FIGO 3C)	Ca Endometrium	Cytoreduction	Endometroid Adeno Ca Gr1 (FIGO 1A)
6	53	F	Ca Endometrium	NACT f/b Staging f/b EBRT & brachy	Pap Serous Ca (FIGO 2)	Ca ovary	NACT f/b Staging	Pap serous Ca (FIGO 3C)
7	54	M	Ca stomach	D2 Subtotal Gastrectom	PD adenoCa - pT4aN3b	Ca penis	Partial Penectomy + B/L IBD	MD SCC - pT3N3
8	77	F	Head Of Pancreas Mass	Whipple's procedure	Benign serous Cystadenoma	Ca breast	MRM	HG solid papillary DCIS
9	65	F	Ca R. Breast	NACT f/b MRM f/b Adjuvant	IDC NOS G2 ypT2N0	Ca L. Breast	NACT f/b MRM f/b Adjuvant	IDC NOS G3 ypT4bN3

				chemo + PMRT	(Luminal A)		chemo + PMRT	(TNBC)
10	57	F	Ca R. Breast	MRM	IDC-NOS G3 - pT2N0	R. Renal mass	Partial Nephrectomy	ccRCC-Gr1-pT1aNx
11	43	F	Ca Breast	MRM	IDC NOS Gr2 - pT2N0	Ca endometrium	Surgical Staging	PD adenoCa - FIGO 1A
12	53	M	Ca rectum	NACRT f/b LAR -> chemo	MD-AdenoCa ypT2N0	Ca Thyroid	TT + CCND+ R.FND	Pap Ca (classical) - pT2N1b
13	64	F	Ca Breast	MRM f/b Adj Chemo	IDC - NOS gr1 (Luminal A)	Ca Rectum	NACRT f/b LAR f/b Adj.Chemo	MD infiltrating AdenoCa ypT2N0
14	57	F	Ca Breast	NACT f/b MRM	IDC NOS - Gr2 (TNBC)	Ca Ovary	NACT f/b Cytoreduction	LG serous Ca
15	67	F	Ca esophagus	VATS Esophagectomy	MD - SCC - pT1bN0	Ca thyroid	Total Thyroidectomy + CCND	Invasive Follicular variant of Pap Ca - pT2N0
16	60	F	Ca R breast	MRM	IDC - NOS GR1 (luminal A)	Ca L Breast	MRM	HG-DCIS (Luminal A)
17	52	F	Ca Sigmoid	Anterior Resection	Tubulovillous adenoma with invasive Adenoca - Gr 2	Ca Breast	MRM	IDC - NOs Gr2-pT1N0
18	44	F	Ca R Breast	NACT f/b MRM f/b PMRT	IDC NOS Gr2 - ypT2N1 (Luminal A)	Ca L Breast	NACT f/b MRM f/b PMRT	IDC NOS Gr2 - ypT1N0 (TNBC)

Discussion

Double synchronous primaries are rare, but increasingly recognized entities due to improvement in cancer detection methods, imaging, pathology, and prolonged survival in cases of malignancies. Simultaneous existence of two independent primaries creates considerable diagnostic difficulties and raises issues concerning differential diagnosis between secondary tumor and metastasis. It is important to make the correct diagnosis since there are vast differences in treatment strategies for both these diseases [6].

This study showed a distinct preponderance of females, with over four-fifths of subjects being women. This is mainly due to the prevalence of breast cancer and ovarian cancers seen in the current group of patients. Other institutional studies have shown similar findings in cases wherein there was a synchronous presence of tumors arising from the breast, ovary, and endometrium, the most frequent combination [7].

Breast carcinoma was the most frequent form of malignancy found among the participants, followed by ovarian and endometrial malignancies. Three patients had synchronous bilateral breast carcinomas, and three others had concurrent ovarian and endometrial carcinomas. The simultaneous occurrence of such tumors is known to be related to hereditary cancers, especially those caused by genetic mutations affecting BRCA1/BRCA2 genes and genes responsible for the mismatch repair deficiency syndrome. With the progress made by the use of next-generation sequencing technology, more emphasis should be placed on susceptibility genes among individuals with multiple primary malignancies [8].

The common cancer sites in male patients included those from the gastrointestinal tract, which were linked to malignancies from the penis, thyroid gland, and mouth. This type of combination highlights the importance of synchronous malignancies occurring from different organ systems that could easily go undetected if attention is only focused on the initial site of malignancy. Proper imaging and pathology tests should thus be conducted before surgery [9].

Over 50% of the patients in this current study showed the presence of malignancy in their family history, including their first- and second-degree relatives. This may imply a potential hereditary factor, hence the need for a comprehensive family history among patients with multiple primary tumors. In recent molecular research, changes in the cancer susceptibility gene at a germline level have been shown to play an important role in the etiology of both synchronous and metachronous tumors [10].

Each of our patients was treated for their cancer on a curative basis after multidisciplinary assessment of the situation. Treatment modalities have been chosen depending on the specific stage of the tumor, its histology, as well as behavior. The presence of synchronous tumors may imply that priority of treatment should be given to certain aspects of management by coordinating efforts between surgical, medical, and radiation oncologists, weighing the risk-to-benefit ratio of therapy [11].

Of the studied cases, there was 1 postoperative death and 4 cases of recurrence, while other cases were disease-free at their last follow-up visits. According

to current literature, the prognosis of patients with simultaneous double primary cancers mainly depends on the stage and aggressiveness of each individual cancer and not because of the presence of more cancers in one patient.

Thus, the accurate diagnosis by thorough staging followed by prompt multi-specialty treatment is still the key to effective management [12].

This current research provides relevant information on the clinico-pathological aspects of synchronous double primary cancers in an Indian tertiary cancer institution; however, owing to its retrospective nature and limited sample size, the results obtained are not generalizable. It would be appropriate to conduct a multicentric prospective study with the inclusion of molecular genetic testing in future to elucidate the issues of risk factors, prognosis, and management of this rare but important condition.

Conclusion

Double primary synchronous tumors are relatively uncommon but have been increasingly diagnosed in clinical practice owing to the advancement in diagnosis methods as well as enhanced cancer survivorship. The combination of breast and gynaecologic tumors was the most prevalent type of double primary tumors in the current study population, and they were predominantly observed in females. Timely detection of such tumors through meticulous patient examination, imaging analysis, and biopsy plays a significant role in distinguishing between metastatic disease and synchronous primaries for better management. Curative surgery could be successfully performed in most of our patients who had satisfactory early post-operative results. Prospective multicentre studies with the inclusion of genetic testing are required in the future.

Limitations

This retrospective study is a single cantered study with a small sample size of 18 patients which limits the generalizability of the findings. Additionally, the lack of long term follow up and molecular genetic evaluation restricted assessment of survival outcomes and hereditary cancer predisposition. Larger multicentre prospective studies are needed to validate these findings

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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