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MULTIPLE PRIMARY NEOPLASMS: PATTERNS, RISK FACTORS, AND OUTCOMES FROM A TERTIARY CARE CENTER

Radiation Oncology

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ABSTRACT

Multiple primary malignancies (MPMs) constitute an increasingly recognized oncological challenge. This retrospective observational study analyzed 16 patients with histologically confirmed dual malignancies managed at a tertiary care oncology center. Seven patients had synchronous malignancies and nine had metachronous malignancies. Breast carcinoma was the predominant index malignancy in both groups. In synchronous cases, breast cancer was commonly associated with gynecological, thyroid, and head-and-neck malignancies. In metachronous cases, contralateral breast carcinoma was the most frequent second malignancy, followed by rectal carcinoma, renal cell carcinoma, nasal cavity malignancy, hypopharyngeal malignancy, chronic myeloid leukemia, and cervical carcinoma. The interval between first and second primary malignancies in metachronous cases ranged from 3 to 10 years. The mean overall survival was 8.67 years and the mean disease-free survival was 7.16 years. The findings underscore the importance of long-term surveillance, careful distinction between second primary tumors and metastatic disease, and multidisciplinary treatment planning. With timely detection and individualized management, favorable long-term outcomes are achievable in patients with dual malignancies.

KEYWORDS

Multiple Primary Malignancies, Dual Malignancy, Synchronous, Metachronous, Breast Cancer, Survival.

INTRODUCTION

Dual malignancies, also referred to as multiple primary malignancies (MPMs), are defined as the occurrence of two or more independent primary malignant tumors in a single individual, arising in the same or different anatomical sites, and not representing metastatic spread. The distinction between multiple primaries and metastasis is crucial, as it has significant implications for diagnosis, staging, treatment planning, and prognosis. Historically, the concept of multiple primary cancers was first described by Billroth, and later refined by Warren and Gates, who proposed diagnostic criteria requiring that each tumor must be histologically malignant, distinct, and that the possibility of one being a metastasis of the other must be excluded. Based on the temporal relationship between tumors, MPMs are broadly classified into synchronous and metachronous types.

Synchronous malignancies are defined as those diagnosed within a short time interval, commonly within six months, whereas metachronous malignancies occur after a longer interval.

The reported incidence of multiple primary malignancies varies widely, ranging from approximately 2% to 17% of all cancers, reflecting differences in population characteristics, diagnostic capabilities, and follow-up duration. Institutional data further indicate that dual malignancies may occur in about 1.6% of cancer patients, with metachronous tumors being more common than synchronous tumors. However, synchronous dual malignancies remain relatively uncommon and present unique diagnostic and therapeutic challenges.
The increasing incidence of dual malignancies in recent decades can be attributed to multiple factors. Advances in diagnostic imaging modalities such as computed tomography and positron emission tomography have enabled earlier and more accurate detection of additional primary tumors. Furthermore, improved cancersurvival due to advances in treatment modalities has increased the likelihood of developing subsequent malignancies. Additional contributing factors include genetic predisposition such as BRCA mutations and tumor suppressor gene alterations, environmental exposures, lifestyle factors such as tobacco and alcohol use, prior chemotherapy and radiotherapy, and the concept of field cancerization, particularly in aerodigestive tract malignancies.

Pathophysiologically, the development of multiple malignancies is thought to result from cumulative genetic hits leading to malignant transformation in different tissues, influenced by host susceptibility and carcinogenic exposure. Certain tumor types and anatomical regions, such as the head and neck, breast, lung, and gastrointestinal tract, are more commonly associated with dual malignancies, reflecting both shared risk factors and underlying biological mechanisms. Clinically, dual malignancies pose significant challenges in diagnosis and management. Distinguishing between a second primary tumor and metastatic disease is often difficult and may require advanced imaging, histopathological evaluation, and immunohistochemistry. Moreover, treatment strategies must be individualized, taking into account the stage, biology, and aggressiveness of each tumor, as well as the patient's overall condition. In some cases, simultaneous treatment of both malignancies is feasible, while in others, prioritization of the more advanced or symptomatic tumor is necessary.

Despite growing recognition of dual malignancies, there remains a paucity of comprehensive data regarding their optimal management and outcomes, particularly in synchronous presentations. This highlights the need for further clinical studies and case-based analyses to improve understanding and guide evidence-based management strategies.

AIMS AND OBJECTIVES

To analyze the clinicopathological characteristics and temporal distribution (synchronous vs. metachronous) of multiple primary malignancies in a tertiary care setting.

Secondary Objectives

- To describe the distribution of primary tumor sites and histological subtypes among patients with multiple primary malignancies.
- To assess the association of demographic, environmental, and treatment-related factors with the occurrence of multiple primary malignancies.
- To compare clinical and pathological characteristics between synchronous and metachronous malignancy groups.
- To estimate overall survival (OS) and compare survival between groups using appropriate survival analysis methods.
- To determine independent predictors of survival outcomes using multivariable regression analysis.

MATERIALS AND METHODS

This retrospective observational study was conducted at a tertiary care oncology center to evaluate the clinical and pathological characteristics of patients diagnosed with multiple primary malignancies. A total of 16 patients with histologically confirmed dual malignancies were identified from institutional records. Among these, 7 cases were classified as synchronous malignancies and 9 as

metachronous malignancies based on the temporal relationship between the two tumors. Synchronous malignancies were defined as two primary cancers diagnosed within six months of each other, whereas metachronous malignancies were defined as malignancies diagnosed after a period exceeding six months.All included cases fulfilled the criteria for multiple primary malignancies, with histopathological confirmation of both tumors and exclusion of metastatic disease. Patients with incomplete records or suspicion of metastatic spread were excluded. Data were collected from medical records, including demographic details, tumor characteristics such as site, histopathology, stage, immunohistochemical profiles, family history, treatment details, follow-up status, and survival outcomes. Only cases with at least one follow-up since 2023 were included in the current study to improve the reliability of outcome assessment.

The primary objectives were to analyze the pattern of occurrence of dual malignancies, identify the most common tumor types and associations, and evaluate survival outcomes, including overall survival and disease- free survival.

RESULTS

In this study, dual malignancies were observed in 16 patients, with metachronous malignancies accounting for 56.3% of cases and synchronous malignancies accounting for 43.7%. Breast carcinoma emerged as the predominant index malignancy in both groups.

Among synchronous cases, breast carcinoma constituted the predominant index tumor in 57.1% of patients, with a substantial proportion showing concomitant gynecological malignancies, particularly carcinoma cervix and endometrial carcinoma. Other synchronous associations included thyroid carcinoma, oral cavity squamous cell carcinoma, esophageal squamous cell carcinoma, and an ovarian granulosa cell tumor with endometrial malignancy. Histopathologically, invasive ductal carcinoma was the dominant breast malignancy. Most breast cancer cases belonged to the Luminal A subtype, while one patient had triple-negative breast cancer, indicating heterogeneity in tumor biology and possible therapeutic implications.

Clinical outcomes in the synchronous group were mixed. One patient subsequently developed liver metastasis three years after diagnosis, one patient died within one year in the ovarian–endometrial case, one patient was lost to follow-up, and the remaining cases were either on active treatment or on follow-up. No family history of cancer was documented in this group, suggesting predominantly sporadic occurrence.

In the metachronous group, the majority of cases had breast carcinoma as the initial primary malignancy. Contralateral breast carcinoma was the most frequent second malignancy, followed by rectal carcinoma, renal cell carcinoma, nasal cavity malignancy, hypopharyngeal malignancy, chronic myeloid leukemia, and cervical carcinoma. The time interval between the first and second malignancy ranged from 3 to 10 years among most breast-index cases, indicating a clinically important latency period requiring prolonged surveillance.

The molecular classification of breast tumors in the metachronous cohort demonstrated a predominance of the triple-negative subtype, with additional cases showing Luminal A, Luminal B, and HER2-positive biology.

The cohort demonstrated a mean overall survival of 8.67 years for breast cancer patients, underscoring sustained long-term disease management and therapeutic success. The mean disease-free survival across evaluable metachronous cases was 7.16 years, reflecting durable oncologic control in several patients.

A notable proportion of patients were unfortunately lost to follow-up, posing challenges to comprehensive longitudinal assessment and survival analysis. However, despite these limitations, the overall pattern suggests that meaningful long-term survival can be achieved in selected patients with dual primary malignancies when the diagnoses are made accurately and managed appropriately.

Table 1. Distribution of synchronous and metachronous malignancies

Category	Number of cases	Percentage
Synchronous	7	43.7%
Metachronous	9	56.3%

Table 2. Clinicopathological profile of synchronous malignancies

Primary malignancy	Stage	Associated malignancy	Stage	IHC	Family history	Follow-up	Survival / outcome
Breast IDCa	IIB	Cervix SCC	IIB	Luminal A	No	On treatment	—
Breast IDCa	IIB	Perineal region SCC in situ	—	Luminal A	No	2025	Now has liver metastases; 3 years
Breast IDCa	III	Thyroid papillary carcinoma + mandible adenoid cystic carcinoma	I	TNBC	No	2023	Lost to follow-up (LOF)
Breast IDCa	IIB	Endometrium endometrioid carcinoma	IIA	Luminal A	No	2024	Lost to follow-up (LOF)
Ovarian granulosa cell tumor	IA	Endometrium endometrioid carcinoma	IA	—	No	2022	Lost to follow-up (LOF; death) at 1 year
Floor of mouth SCC	III	Esophagus SCC	IB	—	No	On follow- up	—
Tongue SCC	IVA	Thyroid follicular carcinoma	—	—	No	On treatment	—

Most breast cancer cases in the synchronous group were of the Luminal A subtype, while one case was triple- negative. Oral cavity squamous cell carcinoma and ovarian granulosa cell tumor were less frequent but notable associations. Survival outcomes were mixed, with one patient developing liver metastasis at 3 years, one patient dying within 1 year, one patient being lost to follow-up, and two patients remaining on active treatment. No family history was recorded in this group.

Table 3. Clinicopathological profile of metachronous malignancies

Primary malignancy	Lost to follow-up	Time interval (years)	Secondary malignancy	Histopathology / IHC	Family history	In follow-up until	OS (years)	DFS (years)
Breast 2014 IIA	2	8	Contralateral breast 2022 IIA	IDCa/IDCb; TNBC/TNBC	Yes	2025*	11	8
Breast 2009 IIB	9	10	Contralateral breast 2019 IIA	Invasive lobular / IDCb; TNBC/TNBC	No	2020 (LOF)	11	10
Breast 2020 IV	*	3	Rectum 2023 IIA	IDCa and poorly differentiated adenocarcinoma; Luminal A	No	2024	4	3
Breast 2020 IIA	1	3	Renal cell carcinoma 2023	IDCa; HER2+	—	2024 (LOF)	5	3
Breast 2014 IIA	*	9	Nasal cavity 2023 IVB	IDCa and SCC; Luminal B	No	2025*	11	9

Breast 2015 IIB	5	10	Hypopharynx 2025 III	IDCa and SCC; TNBC	—	2025*	On treatment	10
Breast 2015 IIA	7	7	CML 2022	IDCa; Luminal A	No	2024 (LOF)	Cannot be reached	7
Ovarian 2013	4	9 then 3	Rectum 2022 III and scalp 2025	NA / moderately differentiated adenocarcinoma / SCC	No	2025*	15	9
CML 2019	1	5	Cervix 2025 IIIC1	SCC	No	2025*	5	5

Molecular classification of breast tumors in the metachronous group identified a predominance of triple-negative breast cancer, which carries important prognostic and therapeutic implications. Family history of cancer was uncommon and was noted in only one breast cancer case. Despite the complexity of these cases, the mean overall survival and disease-free survival values suggest prolonged disease control in several patients.

Table 4. Primary tumor distribution

Primary site	Frequency	Percentage
Breast	11	68.7%
Oral cavity	2	12.5%
Ovary	2	12.5%
Hematologic	1	6.3%

Table 5. Molecular subtypes of breast cancer cases

Subtype	Number of cases	Percentage
Luminal A	4	~36%
TNBC	4	~36%
Luminal B	1	~9%
HER2-positive	1	~9%
Not available / not documented	Remaining	—

Table 6. Time interval between first and second malignancy in metachronous cases

Case	Primary tumor	Interval (years)	Second tumor
1	Breast	8	Contralateral breast
2	Breast	10	Contralateral breast
3	Breast	3	Rectum
4	Breast	3	Renal cell carcinoma
5	Breast	9	Nasal cavity
6	Breast	10	Hypopharynx
7	Breast	7	CML
8	Ovary	9	Rectum + scalp
9	CML	5	Cervix

FIGURES

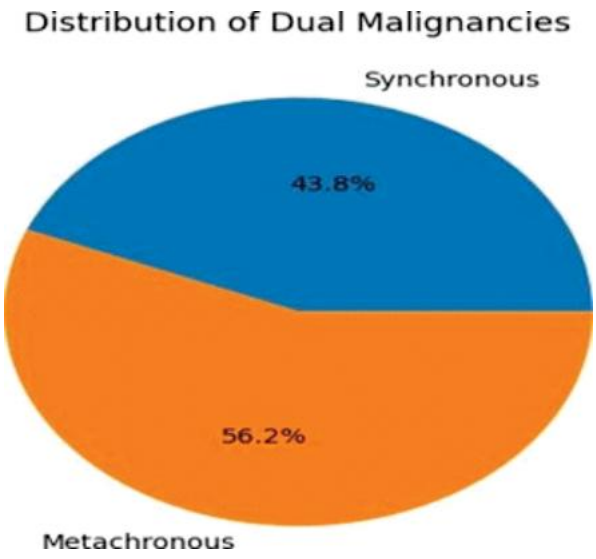

Figure 1. Pie diagram showing the distribution of dual malignancies, with metachronous cases comprising 56.3% and synchronous cases comprising 43.7% of the cohort.

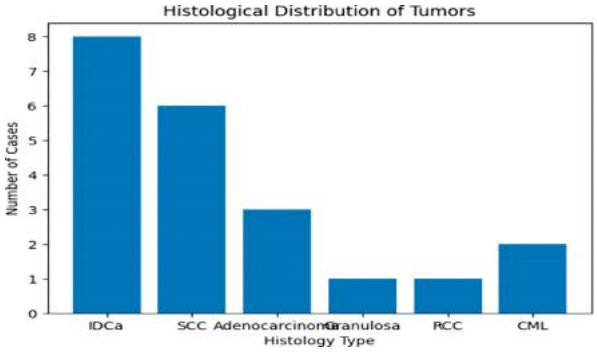

Figure 2. Histogram showing the distribution of histopathological subtypes, with invasive ductal carcinoma and squamous cell carcinoma being the most commonly encountered histologies.

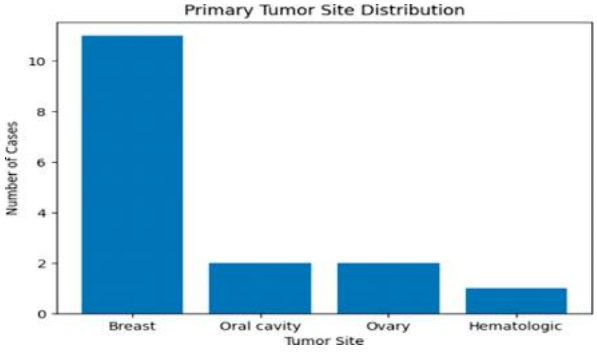

Figure 3. Histogram depicting the distribution of primary tumor sites, highlighting breast cancer as the predominant index malignancy

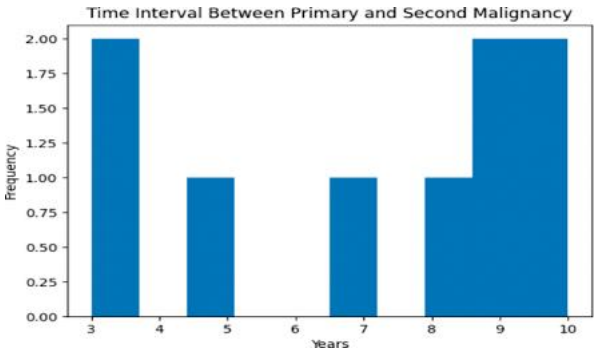

Figure 4. Histogram illustrating the time interval between the first and second malignancy in metachronous cases.

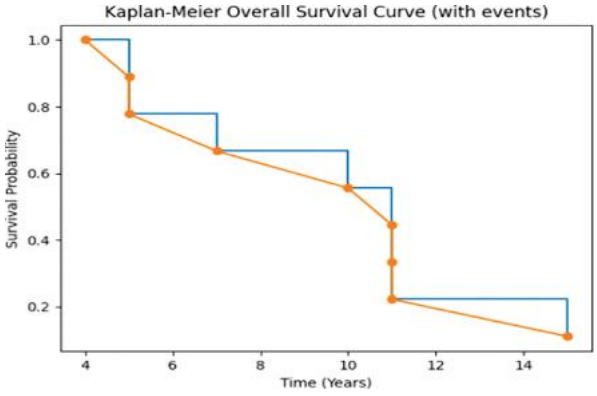

Figure 5. Kaplan-Meier curve demonstrating overall survival in patients with dual malignancies. Circular markers indicate event time points, and the curve reflects favorable long-term survival trends in several patients.

DISCUSSION

Multiple primary malignancies represent a significant and increasingly recognized challenge in modern oncology. In the present study, metachronous malignancies were more common than synchronous malignancies, which is consistent with previously published literature. Several studies have reported a higher prevalence of metachronous tumors due to prolonged survival of cancer patients and improved surveillance strategies, allowing detection of second primary malignancies over time.

Breast carcinoma emerged as the most common index malignancy in both synchronous and metachronous groups in this study. This observation aligns with findings from earlier studies, which have highlighted breast cancer as a frequent primary tumor in patients developing subsequent malignancies. The improved survival rates in breast cancer patients, owing to advancements in early detection and treatment modalities, contribute significantly to the increased likelihood of developing second primary cancers.

The occurrence of contralateral breast cancer as the most common metachronous malignancy in this study is also consistent with existing evidence. Studies suggest that patients with primary breast cancer have an elevated lifetime risk of developing malignancy in the contralateral breast, influenced by genetic predisposition, hormonal factors, and environmental exposures. This emphasizes the importance of long-term surveillance and screening in breast cancer survivors.The association of breast malignancies with gynecological cancers, such as carcinoma cervix and endometrial carcinoma observed in synchronous cases, may be attributed to shared hormonal influences and genetic susceptibility. Similarly, the occurrence of head-and-neck and aerodigestive tract malignancies supports the concept of field cancerization, wherein prolonged exposure to carcinogens such as tobacco and alcohol leads to multiple independent malignant transformations within the same epithelial field.

From a biological perspective, the heterogeneity in molecular subtypes observed in this study, particularly the predominance of triple-negative breast cancer in metachronous cases, suggests an aggressive tumor phenotype. Triple-negative breast cancer is associated with poorer prognosis and higher recurrence rates, which may influence the pattern and outcomes of dual malignancies. The role of molecular profiling is therefore crucial in understanding tumor behavior and guiding treatment decisions.

Despite the complexity associated with dual malignancies, the survival outcomes observed in this study were relatively favorable, with a mean overall survival of 8.67 years and disease-free survival of 7.16 years. These findings are comparable to previous studies, which have demonstrated that early detection and appropriate management of second primary malignancies can significantly improve patient outcomes.

The management of dual malignancies remains challenging and requires a multidisciplinary approach. Treatment strategies must be individualized, taking into account the stage, biological behavior, and aggressiveness of each tumor, as well as patient-related factors. In synchronous cases, simultaneous treatment may be considered, whereas in metachronous cases, sequential management is often employed.

A major diagnostic challenge lies in differentiating a second primary malignancy from metastatic disease. This distinction is critical, as it directly impacts staging and treatment planning. Advanced imaging techniques, histopathological evaluation, and immunohistochemical analysis play a pivotal role in making this differentiation.

Overall, the findings of this study reinforce the need for increased awareness, vigilant follow-up, and comprehensive evaluation in cancer patients to facilitate early detection and effective management of multiple primary malignancies.

CONCLUSION

Dual malignancies are an increasingly encountered clinical entity in the era of improved cancer survival and advanced diagnostic capabilities. This study highlights that breast cancer was the most common index malignancy and that metachronous tumors occurred more frequently than synchronous tumors. The occurrence of second primary malignancies, particularly contralateral breast cancer and tumors of the aerodigestive and genitourinary systems, underscores the importance of long-term surveillance in cancer survivors.

Favorable survival outcomes observed in this study suggest that early detection, accurate differentiation from metastatic disease, and individualized treatment strategies can significantly improve prognosis.

Multidisciplinary management, incorporating oncologists, pathologists, radiologists, and surgeons, is essential for optimizing patient care.

Furthermore, the study emphasizes the need for continued research into the molecular and genetic mechanisms underlying multiple primary malignancies. Identification of high-risk patients through genetic profiling and targeted surveillance strategies may further enhance early detection and improve outcomes.

In conclusion, dual malignancies require a high index of clinical suspicion, comprehensive diagnostic evaluation, and tailored therapeutic approaches to achieve optimal patient outcomes.

LIMITATIONS

The present study has several limitations. The sample size was small, limiting the generalizability of the findings. A notable proportion of patients were lost to follow-up, which reduced the robustness of long-term survival analysis and may have introduced outcome bias.

The study design was retrospective and based on available institutional records, which may have led to incomplete capture of treatment details and follow-up events. Additionally, due to financial constraints, genetic profiling and molecular diagnostics were not performed in most cases, thereby restricting insights into hereditary predisposition and precision-guided therapeutic stratification.

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