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RESEARCH ARTICLE

Spectrum, Management Strategies, and Early Outcomes of Dual Primary Malignancies: A Single Tertiary-Center Experience

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Abstract

Objective: The occurrence of a second primary malignancy in a patient with a known cancer is referred to as a dual primary malignancy, which may be synchronous or metachronous. The incidence of dual malignancies is increasing worldwide (2–17%). This study aimed to document the incidence of dual primary malignancies, factors influencing treatment decision-making, and short-term outcomes at a single tertiary care center. **Methods and Analysis:** This retrospective cross-sectional study included patients diagnosed with dual primary malignancies between February 2023 and February 2025. All patients met the Warren and Gates criteria and had histologically confirmed malignancies. Demographic characteristics, tumor details, treatment strategies, and outcomes were collected and analyzed. **Results:** Among 42 cases of dual primary malignancies, 17 were synchronous and 25 were metachronous. Nineteen patients were male and 23 were female, with a mean age of 63 years. Breast cancer was the most common primary tumor site (n=11). The disease-free interval between metachronous primaries ranged from 1 to 26 years. Seventy-five percent of patients received treatment with curative intent using multimodality therapy. **Conclusion:** The rising incidence of dual primary malignancies underscores the importance of vigilant follow-up and multidisciplinary evaluation for early detection and optimal management. Treatment decisions guided by a multidisciplinary tumor board are essential for achieving favorable outcomes.

Keywords: Dual malignancy- Synchronous tumors- Metachronous tumors- Multidisciplinary Tumour Board

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Introduction

According to 2022 global statistics, approximately 19–20 million new cancer cases are diagnosed annually worldwide, and this incidence continues to rise [1]. Due to advancements in diagnostic and therapeutic techniques and also due to better knowledge about cancer in the general public, the mortality rate has declined in both sexes and in all countries [2]. These advancements have also led to an increased detection of dual primary malignancies, and the incidence of dual malignancies is between 2% and 17% [3, 4].

Patients with multiple tumors are at risk of developing a second primary malignancy and can develop synchronous and metachronous malignancy, however, well-defined guidelines for the diagnosis and treatment planning of dual primary malignancies are lacking [5].

Multiple hurdles are faced in the diagnosis of dual malignancy, like the suspicion of the other lesion being a metastatic deposit in the case of synchronous malignancy and the suspicion of recurrence in the case of metachronous malignancy. Establishing an accurate diagnosis is often time-consuming, which may result in delays in treatment initiation, and it affects the overall survival adversely. Multiple factors go into deciding the right treatment, and there is a lack of clear guidelines and literature to back up the decision. Only on further research will there be clarity on the pattern of occurrence, and then a protocol can be formulated for diagnosis, treatment, and prevention of dual malignancy. Our study is one such attempt, and we aim to report the incidences of dual malignancy, the factors considered in treatment decision-making, and their outcomes.

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Materials and Methods

After approval from the institutional ethics committee, this descriptive cross-sectional study was conducted using a hospital-based database of patients who have been diagnosed with dual malignancy from February 2023 to February 2025. All patients included in this study fulfilled the Warren and Gates criteria [6] and had histologically proven synchronous or metachronous malignancies. Patients with defaulted work-ups were excluded from the study.

The Warren and Gates criteria, which were used in this study, are as follows:

1. The tumor must demonstrate definitive histopathological features of malignancy.

2. The tumor must be anatomically separate and distinct from the index tumor.

3. The possibility that the tumor represents a metastasis from the index tumor must be excluded.

Demographic details such as the patient's age, sex, and history of consumption of tobacco were recorded. Disease factors such as site, AJCC TNM stage, histology of tumor at presentation, and time interval between the two diagnoses were also noted. Tumors were classified as synchronous or metachronous according to International Agency for Research on Cancer (IARC) guidelines, which state that more than one primary tumor diagnosed within 6 months is synchronous and more than 6 months apart diagnosed tumors are metachronous. Among synchronous tumors, the one that was diagnosed earlier was deemed to be the first primary, and the one detected subsequently was classified as the second primary.

Treatment information obtained from the tumor board form includes the multi-disciplinary board decision regarding the treatment opted for, the modality chosen and its details (surgery or radiotherapy or systemic therapy), the reasoning for the decision, and the sequence of therapy. Patients follow-up data with clinical examination and imaging studies impressions were collected.

In this cross-sectional study of 2 years of data, we aim to report the incidences of dual malignancy; demographic, patient, and tumor details; the factors considered in treatment decision-making; and their outcomes.

Statistical analysis

Descriptive data were summarized using mean, median, and range. All the collected data were organized in a tabular form, and the patterns of demographic, disease, and treatment variables were reported. Fisher's exact test was used to compare survival with tobacco intake. The interval between two malignancies in metachronous malignancy was analyzed for normality, and it was found to be skewed. The Mann-Whitney test was used to compare the interval and survival as the data demonstrated a skewed distribution.

Results

A total of 5696 patients were treated at our institute during the study period, out of which 42 cases of dual malignancies were reported. These cases represented 0.73% of all patients treated at the institute during the two-year study period. The mean age at presentation of synchronous malignancy or the first malignancy in a metachronous variant was 63.2 years (range 41-79 years). The mean disease-free interval between metachronous malignancies was 9 years (range of 1-26 years) between the two metachronous tumors. The men-to women ratio was 0.82, with 19 men and 23 women patients. Addiction to tobacco was observed in 45% of the patients, and at 6-month follow-up, survival rates were 36.8% among tobacco users and 13% among non-users; however, this difference was not statistically significant ($p = 0.14$), but there was no statistically significant association between tobacco intake and survival ($p = 0.14$).

Breast was the most common site of cancer in this study, with eleven cases, followed by head and neck (oropharynx, larynx, and hypopharynx) and rectal cancers. Among 42 dual malignancy cases, 17 (40%) were synchronous and 25 (59%) were metachronous, and all three modalities in combination were used for their treatment. Seven synchronous and five second primaries of a metachronous malignancy were treated with palliative intent, and the rest, 75%, received therapy with radical intent. Out of the 12 patients who received palliative treatment, 58% are surviving 6 months post treatment. On analysis, the mean interval between metachronous malignancies was longer in patients surviving at 6 months in comparison to those who succumbed to disease (2.5 months), but this association was not statistically significant ($p = 0.059$) (Table 1) (Figure 1).

Discussion

Globally, approximately one in five individuals will develop cancer during their lifetime, and patients surviving a primary malignancy are at 17%–19% risk of developing a second malignancy [3]. The incidence of cancer is increasing worldwide, and so is the increase in multiple primary malignancies (MPMs), which is defined as more than one synchronous or metachronous malignancy in the

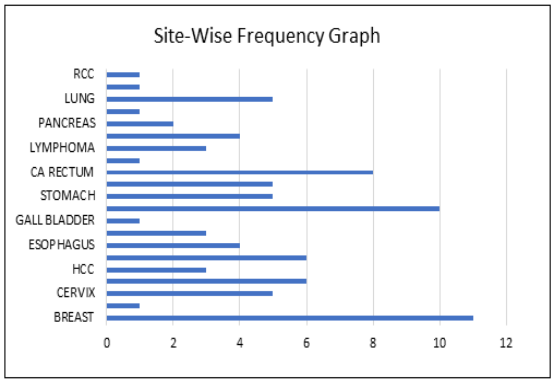

Figure 1. Shows the Site Wise Distribution of Dual Malignancy

Table 1. Shows the Site Distribution of Dual Malignancies

Malignancies	Number	Percentage (%)
Breast	11	13
Vagina	1	1.2
Cervix	5	5.81
Endometrium	6	6.97
HCC	3	3.48
Urinary Bladder	6	6.97
Esophagus	4	4.65
Colon	3	3.48
Gall Bladder	1	1.2
Head and Neck Cancers	10	11.62
Stomach	5	5.81
CA Prostate	5	5.81
CA Rectum	8	9.3
Small Bowel	1	1.2
Lymphoma	3	3.48
Ovary	4	4.65
Pancreas	2	2.32
Skin	1	1.2
Lung	5	5.81
Sarcoma	1	1.2
RCC	1	1.2

same individual. It also encompasses the subject topic dealt with by this study, the dual malignancies.

In the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, it was observed that the proportion of dual malignancies had doubled in the last three decades from 9% in 1975–1979 to 19% in 2005–2009 [3]. Another literature review of 1,104,269 cancer patients concluded that the prevalence of dual malignancies was between 0.70% and 11.7%, and various other epidemiological studies state the incidence is between 2-17% [4]. During the study period of two years, the incidence of dual malignancy was 0.73% in our institute, which is more in comparison to the four years of Indian data by Bisht et al. published in 2021 (0.74%) [5]. The observed increase in dual primary malignancies may reflect a true rise in incidence, improved diagnostic capabilities, or increased clinical awareness or increased awareness about multiple malignancies.

The first patient of multiple malignancies was reported by Billroth in 1860, after which multiple guidelines were developed, like the Warren and Gates guidelines and the International Agency for Research on Cancer (IARC) guidelines, for the diagnosis of dual malignancies. Warren and Gates guidelines were followed in this study for patient accrual due to their simplicity [6-9].

The dual malignancies are classified as synchronous (more than one primary tumor within 6 months) or metachronous (more than 6 months) by IARC and Morton et al [9, 10]; though this classification is the most commonly used, it is not the only one, and other researchers have used 2 months and other varying intervals to differentiate dual malignancies based on the duration between the diagnosis [4].

The pathophysiology behind a new second primary in all cases is unknown, but certain factors found to be responsible are genetic predisposition, for example, breast and ovarian cancers in BRCA gene-positive patients; carcinogen exposure, which can induce cancer at multiple sites by the development of an abnormal area of epithelium known as field cancerization, which is mostly seen with head and neck cancers and bladder cancer [11-13]. Studies have clearly shown that anti-cancer treatment like hormonal, target therapies, genetic and immunomodulatory therapies, and radiation therapy has the potential to induce new primary (second) malignancies [14].

In our study, the most patients were above 60 years (69%) with a mean of 63.2 years (41-79 years), which were similar to results by Chaudhary et al. and Etiz et al. in which more than one third of patients were above 60 years of age [14, 15]. None of the collected data belonged to the pediatric age group patient. Just as most of the malignancies are common in older individuals, so is the incidence of dual malignancies. The cancers known to have genetic predisposition also occurred in the 5th decade in this study.

Men to women ratio was 0.82; 19 were men and 23 were women, with predominantly women patients in our study, and this result was contradictory to the results of Zhai et al. and Bisht et al. in which the incidence of dual malignancy in men was more than in women [5, 11]. Addiction to tobacco was observed in 45% of the patients, and the majority (80%) of them belonged to the synchronous malignancy group. The common cancer observed in them was head and neck cancer, followed by urinary bladder cancer, both having tobacco as a known risk factor.

A study by Bisht et al. [5] reported that the most common dual primary is breast cancers detected in women, and in our study too it was observed that breast cancer was the common cancer, followed by head and neck cancer. Genetic predisposition and carcinogen exposure, respectively, may be the cause for the common occurrence of these malignancies as dual malignancies. Our study is the first step, and further studies in the direction of identifying causes at the molecular level for dual malignancies should follow.

On cross-sectional analysis at 6 months post-treatment, 32 (76%) patients are having a disease-free survival, out of which 13 belong to the synchronous type and 19 belong to the metachronous type of dual malignancy. Among those with metachronous tumors, the mean disease-free time interval between the two tumors was 9 years and ranged between 1 year and 26 years. There was no statistically significant correlation between survival at the 6^{th} month post-treatment and the DF interval between two metachronous cancers ($p=0.059$), unlike in the study by Skelton et al [16], where there was a qualitative difference in mortality between tumors that occurs within or after 60 days.

Factors considered in the therapy of dual malignancies

Curative-intent treatment decisions in patients with dual primary malignancies are clinically challenging, and many factors have to be considered; hence it is best to arrive at a unanimous treatment decision in a multidisciplinary board.

Firstly, informed consent from the patient is a fundamental prerequisite before initiating treatment. in the treatment of dual malignancy, and the patient's performance status (PS) and co-morbidities are to be taken into consideration as treatment is associated with higher toxicities.

In a metachronous malignancy, prior treatment given should be considered:

- Details of surgery done previously are of utmost importance.

- In systemic therapy, what drug was given, and its toxicities have to be considered, and the present drug's pharmacokinetic profile and toxicity profile shouldn't overlap the previous drug's profile?

- Previous irradiation details, including the technique, Dose Volume Histogram (DVH), and the dose range, including the low-dose regions, have to be identified. For the second time irradiating patients, care should be taken to use a more conformal technique, and limiting the dose to a minimum to the previously irradiated area takes priority over the PTV coverage. The time gap between the two malignancies also plays an important role in deciding RT dose and constraints, especially when both treatment fields are in close proximity. Serial structures dose has to be considered before deciding on treating second primary, and it takes top priority during planning and evaluation.

The synchronous malignancies fare poorly and are more complicated to deal with in comparison to metachronous ones, and all aspects have to be thought of before the start of treatment [16].

The prognosis of the patients with synchronous malignancies depends on the more aggressive tumor and the higher-staged tumor of the two; hence that tumorhas to be addressed first by any one of the modalities, if not simultaneously with the other tumor.

- If both tumors in a synchronous malignancy are amenable to surgical resection, both the malignancies may be dealt with at the same sitting.

- In systemic therapy it is ideal to choose the chemotherapeutic agent/agents that can address both the malignancies, but this is not possible in various cases; hence the agent that will target the aggressive tumor is selected.

- RT can be administered to both tumors simultaneously, provided the patient's PS is good and the toxicities predicted are minimal. Immobilization and simulation are to be done such that there is none to minimal change in the position of the patient while irradiating both tumors. In radiotherapy, the appropriate radiation dose, tight margins, conformal technique, and regular image guidance are the pillars for the ideal therapeutic index for both the tumors. Normal tissue constraints for serial structures should be the top priority in planning, followed by prescription dose coverage. Patients must be on weekly follow-up during the radiation for assessment of toxicity and tumor status.

For palliation of symptoms, a single best modality has to be chosen whenever possible. Sequencing and timing of different treatments is based on the patient's symptom development and progression of tumor. Best supportive care must be given as an option, in very advanced cases, as part of informed consent.

The limitations of this study are the shorter study period, leading to a smaller sample size and shorter follow-up. Further follow-up of these patients with assessment of molecular profile is warranted in the future.

In conclusion, the rising trend in incidence of dual malignancy validates frequent follow-up and close observations of oncology patients for early detection of second malignancy. Multidisciplinary tumor board decisions regarding treatment are crucial.

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Declarations

Clinical trial registration

Not applicable.

Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding authors per reasonable request.

Code availability

The custom code was not used.

Authors' contributions

Dr Surabi Chandel contributed to the data collection, primary drafting of the manuscript. Dr Lithika Lavanya M contributed conception, design, supervised the study and final drafting of the manuscript. All authors approved the final version for submission.

Ethics approval

This study was approved by Ethics Committee of the Ramaiah University of Applied Sciences.

Consent to participate

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Declaration on generative AI and AI-assisted technologies in the writing process:

Not applicable.

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