Dual primary malignancies with varied histological pattern: A 5-year experience in a single tertiary care urology centre.

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Abstract:

Introduction: Dual primary malignancies, though rare, are increasingly common nowadays. This study aims to highlight our experience in diagnosis and management of patients with multiple primary malignancies either synchronously or metachronously.

Materials and methods: A retrospective observational study was conducted in the Department of Urology and Renal Transplantation in our institute. All patients with histologically proven double primary malignancies were included in the study. Records of several patient details over a period of 5 years between May 2018 and May 2023 were analyzed.

Results: A total of 10 cases of dual malignancies, constituting 1.12% of a total of 895 cancer patients seen over a period of 5 years. There was a clear male predominance with 6 patients (60%) being men. The mean age at presentation of first malignancy was 55 years, while the mean age at presentation of second malignancy being 57 years. In 3 cases (30%), Renal cell carcinoma was the most common urological primary. All three cases were of clear cell histology. Out of 10 cases, synchronous malignancies were found in 6 patients (60%), while 4

(40%) had metachronous malignancies. Colorectal cancer was the most common second primary site of cancer in the study with 5 cases (50%).

Conclusion: A high index of clinical suspicion and knowledge is mandatory during follow up period for identifying multiple malignancies.

Keywords: Dual, Histology, Malignancy, Metachronous, Synchronous.

Introduction:

Multiple primary malignant tumours in a patient is a well-known phenomenon. Factors that contribute to the increased incidence of more than one primary malignancy includes improved life expectancy, increased awareness, and better diagnostic facilities. The proposed reasons for multiple primary malignant tumours is said to be complex, and interlinked, which covers environmental aspects (tobacco, occupation, pollution, ultraviolet radiations), genetic makeup, earlier management (radiotherapy or chemotherapy), gender-related elements, and hormonal imbalances. Our study highlights the experience in diagnosis and management of patients with dual primary malignancies with one primary malignancy being urological in origin occurring either synchronously or metachronously.

Patients and Methods:

A retrospective observational study was conducted in the Department of Urology and Renal Transplantation in our tertiary care centre. Institutional Ethics Committee clearance was obtained. All patients aged above 18 years with histologically proven dual primary malignancies presenting synchronously or metachronously as documented in contrast enhanced helical Computed Tomography (CT) abdomen, CT chest and X-ray Mammogram were included in the study. The sample size was 895 cancer patients, which was obtained for a duration of 5 years from the medical registry department of our centre. Various details of patients like demographic data, origin of the tumor, stage of presentation, histological pattern,

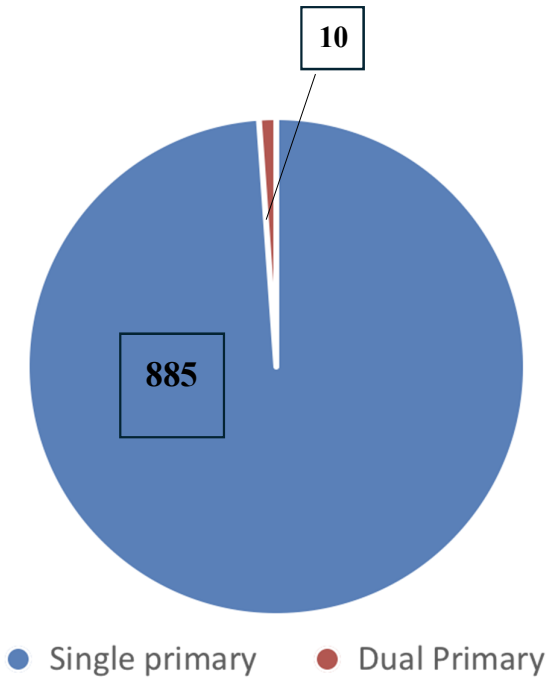
and line of management over a period of 5 years between May 2018 and May 2023 were analyzed. Complete specifics regarding the management including investigations, surgical procedures, radiotherapy, and chemotherapy were recorded.

Patients was followed up for a duration of two years from the diagnosis of the second primary malignancy. They were labelled as synchronous, if the two primary malignancies were diagnosed within 6 months of each other. It is categorized as metachronous, if the time interval between their diagnoses was more than 6 months.

Results:

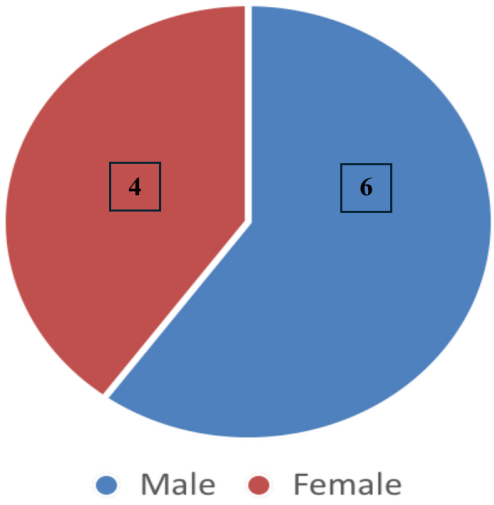
After an observational study done for a period of five years, the findings were formulated and tabulated. A total of 10 cases of dual malignancies, making up 1.12% of a total of 895 cancer patients seen over 5 years, were found in our study (Figure 1).

Fig. 1: Pie chart illustrates dual primary malignancies constituting 1.12% (n - 10) and remaining 98.88% (n - 885) single primary malignancy.



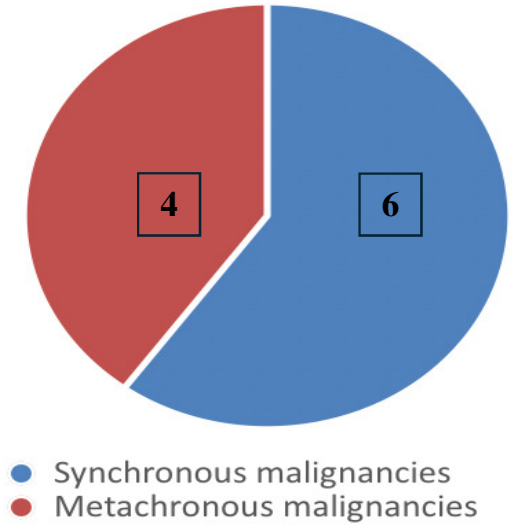
There was a clear male predominance with 6 out of 10 patients (60%) being men and remaining 4 patients (40%) being women (Figure 2).

Fig. 2: Pie chart illustration showing number of males and females with dual primary malignancies.



Out of 10 cases, 6 patients (60%) had synchronous malignancies, and 4 (40%) had metachronous malignancies (Figure 3). In Metachronous malignancies, the mean age at presentation of first primary malignancy was 58 years, while the mean age at presentation of second primary malignancy was 60 years.

Fig. 3: Pie chart illustration showing number of patients having synchronous and metachronous malignancies.



All 10 dual primary malignancies have one primary malignancy of urological origin (kidney, ureter, urinary bladder, and prostate) presenting as either first primary malignancy or second primary, synchronously or metachronously. Only one patient had both first primary malignancy and second primary of urological origin (Table 1 and 2).

Table 1: Synchronous malignancies

S. No	Age at presentation/Sex	1st Primary	2nd primary
1	52/F	Left Renal Cell Carcinoma	Endometrial Carcinoma
2	80/M	Adenocarcinoma - Prostate	Adenocarcinoma - Rectum
3	56/M	Left Renal Cell Carcinoma	Adenocarcinoma - Sigmoid colon
4	48/M	Left Renal Pelvis Urothelial carcinoma	Right Renal Cell Carcinoma
5	56/M	Adenocarcinoma - Left lung	Bladder Urothelial Carcinoma

6	62/F	Primary Bladder adenocarcinoma	Adenocarcinoma - Sigmoid colon

Table 2: Metachronous malignancies

S. No	Age at Presentation/sex	1st Primary	Age at presentation/sex	2nd Primary
1	63/M	Adenocarcinoma - Prostate	64/M	Squamous cell carcinoma - layrnx
2	60/M	Right Renal Cell Carcinoma	63/M	Adenocarcinoma - Rectum
3	56/F	Carcinoma Breast	60/F	Low grade Sarcoma - Left distal ureter
4	53/F	Right upper tract urothelial carcinoma	56/F	Adenocarcinoma - descending colon

We observed 4 cases (40%) of Renal cell carcinoma (RCC), which was the most common urological malignancy, of which 3 cases presented as first primary malignancy, and one case of RCC presented as second primary malignancy, synchronously with transitional cell carcinoma (TCC) being the first primary. All 4 cases of RCC were of clear cell histology. Out of 4 cases, 3 patients were males and all 3 had smoking history, and in this, 2 male patients had colorectal cancer as the second primary malignancy. Colorectal cancer was the most common second primary site of cancer in the study with 5 cases (50%). Other non-urological malignancies presenting as first primary are Breast cancer, and Adenocarcinoma lung and as second primary are Endometrial cancer, and Squamous cell carcinoma larynx. Other than RCC, 2 cases of bladder malignancy (one urothelial type and one adenocarcinoma type), 2 cases of ureteric tumors (one upper ureteric site and one distal ureteric site), and 2 cases of adenocarcinoma prostate were observed.

Two synchronous associations of RCC

1). Figure 4 illustrates Renal Pelvis Urothelial (transitional cell) carcinoma histopathological study with Immunohistochemistry staining. Figure 5 illustrates Clear cell RCC histopathological study with Immunohistochemistry staining. Figure 6 shows contrast enhanced CT abdomen images of Right RCC and Left Renal Pelvis Urothelial (transitional cell) carcinoma.

Fig. 4: A – Renal Pelvis Urothelial carcinoma (H & E 10x). **B –** P63 positivity. **C –** CD10 negativity.

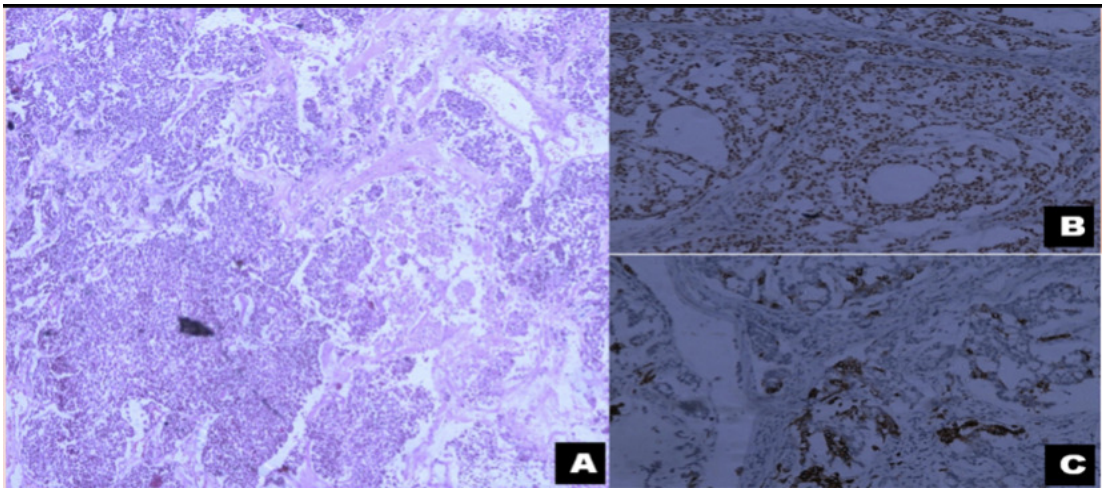
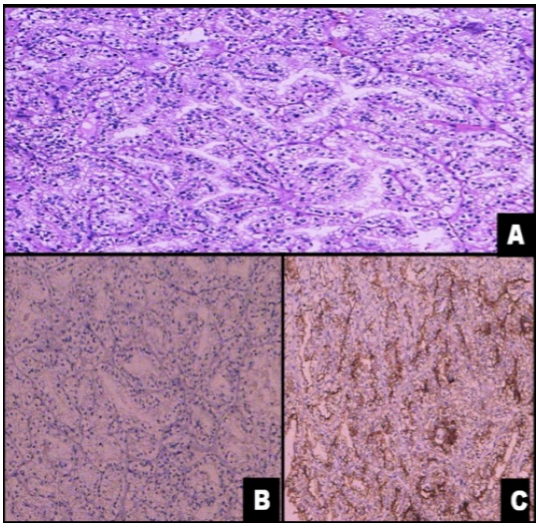
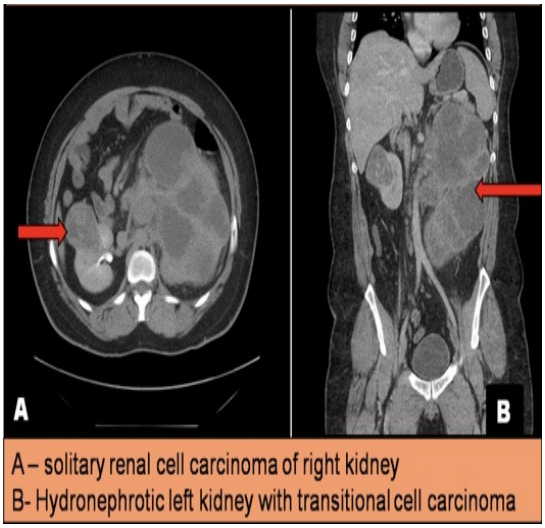


Fig. 5: A – Clear cell Renal cell carcinoma.

Fig. 6: CT abdomen – axial & coronal

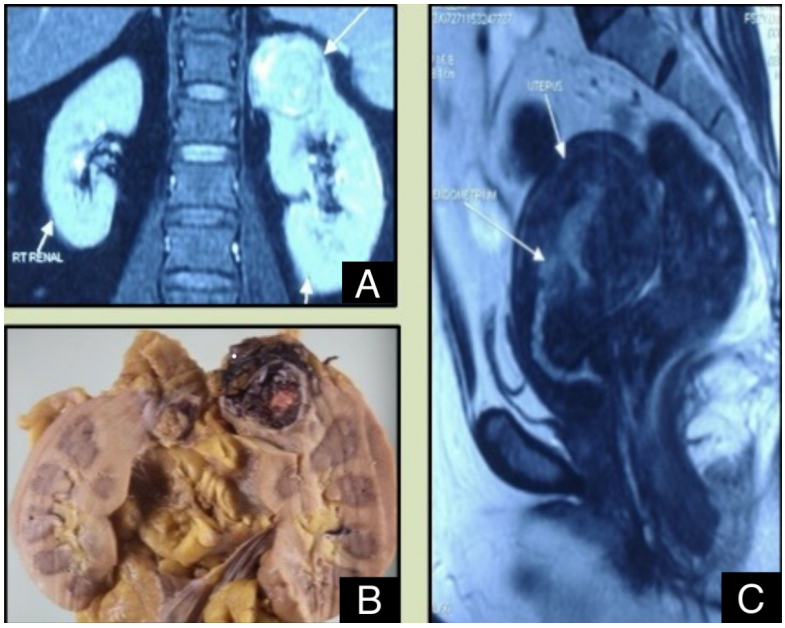
B – CD10 positivity. **C –** P63 negativity. sections. (**A & B**)





2). Figure 7 illustrates CT abdomen showing Left upper pole RCC and its specimen image along with Magnetic Resonance Imaging (MRI) pelvis depicting Endometrial carcinoma.

Fig. 7: A – CT abdomen coronal section showing left upper pole RCC. **B –** Gross specimen of left kidney cut section with tumor. **C –** MRI Pelvis showing Endometrial carcinoma.



Discussion:

The incidence of multiple primary cancers among all cases of malignancy has been reported as 1 to 3% [1]. It is difficult to determine whether the second lesion is actually a primary lesion or reflects metastases [2]. Symptoms of the patients should be completely elucidated to avoid missing major findings. For this, Warren and Gates Guidelines (1932) are used, which puts forth the following salient points,

1.Each tumor should present a definite picture of malignancy.

2.Each tumor should be histologically distinct.

3.The possibility that one is a metastasis of the other must always be excluded.

4.They should be separated by at least 5 years if the malignancies are in the same location [3].

Moertel et al	Simultaneous within 6 months, Metachronous more than 6 months [4].
North American Association of Central Cancer Registries (NAACCR)	Synchronous: The cancers occur at the same time. Metachronous: The cancers follow in sequence, that is, more than two months apart.

Guidelines to define a second primary malignancy were laid down International Agency for Research on Cancer (IARC) which includes,

1.The existence of two or more primary cancers does not depend on time.

2.Both tumors are confined to primary sites, and no direct connections between the tumors exist.

3.One tumor should only be recognized in an organ or a pair of organs or tissue (as defined by the code of the International Classification of Diseases, ICD)

4.Rule 3 does not apply if tumors in an organ are of a different histology

5.Be different in histological form when diagnosis of pathology available [5].

While there is no complete understanding of the processes involved in the development of multiple primary cancers, many factors have been implicated. They include personal factors such as Occupation, Alcohol abuse, tobacco abuse, Gender-specific factors, Environmental factors (pollution), Genetic inclination, Prior treatment with radiotherapy or chemotherapy, Gender-specific factors and hormonal factors [6].

The pathophysiology has also been theorized to be a common carcinogen induced multiple cancers in an exposed surface, called '**field-cancerization**.' Significant dysplastic changes with premalignant and malignant lesions may result from continuous exposure of different mucosa to the same carcinogen [7,8]. With great understanding and enhanced diagnostic modalities, metachronous primary malignancies are becoming increasingly common [9]. In our study, 3 cases of RCC were managed by radical nephrectomy. One case of right RCC was RCC which had synchronous association with left renal pelvis urothelial carcinoma was managed by left radical Nephroureterectomy and bladder cuff excision and right partial nephrectomy. 2 cases of Bladder cancers were managed by neoadjuvant chemotherapy followed by radical cystectomy with urinary diversion and pelvic lymphadenectomy in male patient and anterior exenteration with urethrectomy and urinary diversion in female patient. Proximal and distal ureteric tumors were managed by radical nephroureterectomy with bladder cuff excision. Localised adenocarcinoma prostate cases were managed by radical prostatectomy. Colorectal cancer patients underwent left hemicolectomy and abdominoperineal resection. Modified radical mastectomy was performed for breast cancer.

For endometrial carcinoma, total abdominal hysterectomy was done. Squamous laryngeal carcinoma case underwent total laryngectomy and for adenocarcinoma lung, lobectomy was performed followed by radiotherapy.

Conclusion:

The knowledge of multiple primary malignancies is cardinal for the clinician as it throws light upon etiologic factors such as a common carcinogenic substance such as tobacco and genetic alterations as in the Li-Fraumeni syndrome. A high index of clinical suspicion is mandatory during follow up. The comprehension about multiple primary malignancies helps in crafting follow up studies for screening for the associated neoplasms.

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