

DOUBLE PRIMARY – THE PATTERN OF CARE, AND EPIDEMIOLOGY: EXPERIENCE FROM A TERTIARY CANCER CARE CENTER

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ABSTRACT

Objectives: The importance and relevance of double primary are increasing with time as the increasing use of advanced diagnostic investigation and an increasing number of cancer survivors lead to an increase in double primary malignancy.

Methods: We have collected data retrospectively from our own departmental patient's record section from January 2011 to December 2021. All the details such as histopathology of both the malignancy, site of primary and secondary cancer, the time gap between the two cancer, clinical stage, and treatment received, along with demographic details have been recorded. Patients are divided into two categories either synchronous or metachronous when a second tumor develops either simultaneously or within 6 months of the diagnosis of the first tumor or 6 months after the diagnosis of the primary malignancy, respectively.

Results: The total number of registered cases in one decade at our institute was 25,638 and among them were 41 double primary cases (0.16%). Twenty-two cases were metachronous (59%) and 19 cases (41%) were synchronous double primary. The most common site of double primary site was the head and neck region (38 %) followed by the lung, and esophagus (13% each), and the least common site was the colon (<1%). In the case of metachronous double primary, the mean time interval (the time gap between two cancer devolvement) was 7.4 years with a range of 2–19 years. The majority of the patients are treated with curative intention.

Conclusions: The incidence of double primary is increasing over time. The management of double primary should be supervised by a multidisciplinary tumor board and more research is needed in the areas of epidemiology and treatment.

Keywords: Synchronous, Metachronous, Double primary.

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INTRODUCTION

In the past decades, the survival of cancer patients increasing day by day due to recent advances in cancer management [1]. Increasing use of advanced diagnostic investigation and increasing cancer survivors leads to an increase of double primary malignancy [1]. Way back in the year 1932 Warren and Gates defined three criteria for the diagnosis of the double primary malignancy [2]. Three criteria were (1) histological confirmation of malignancy of both primary (index) and second tumor, (2) there should be at least 2 cm of intervening normal tissue in between the tumor, and they should be separated in time gap for at least 5 years if the tumor is in the same location; and last (3) probability of being metastasis of the other (from the primary tumor) must be excluded from the study. The presence of precancerous lesions, such as dysplasia or carcinoma *in situ* in the second tumor histology, strongly suggests a new primary tumor rather than metastasis or recurrent disease (Fig 1).

Over time and from one study to another, the definition of double primary or multiple cancer may differ. Rules according to International Agency for research on cancer, the time interval of 6 months between the diagnosis of two tumors, divide the second primary malignancy into two categories – synchronous and metachronous. The synchronous second primary may be defined when a second tumor develops either simultaneously or within 6 months of the diagnosis of the first tumor and the metachronous tumor develops 6 months after the diagnosis of the primary malignancy [3,4]. However, according to the Surveillance Epidemiology End Results (SEER) database, 2 months period is used to distinguish synchronous and metachronous double primary [1]. Using different guidelines, the number of actual cases will differ. There are several factors such as field cancerization, genetic susceptibility,

exposure to radiotherapy, chemotherapy, and continuing smoking and drinking (depicted in detail in the Table 1) that may influence the development of the second primary cancer [5,6]. Our retrospective analysis reports synchronous and metachronous double primary in known cancer patients from our institute over the last decade.

METHODS

We have collected data retrospectively from our own departmental patient's record section from January 2011 to December 2021. All the details such as histopathology of both the malignancy, site of the primary and secondary cancer, the time gap between the two cancer, clinical stage, and treatment received, along with demographic details have been recorded. According to Warren and Gates, as previously stated, only patients fulfilling the criteria of second primary cancer were included in our study. We follow ICAR rules for categorization of double primary and accordingly, patients were divided into two categories either synchronous or metachronous when a second tumor develops either simultaneously or within 6 months of the diagnosis of the first tumor or 6 months after the diagnosis of the primary malignancy, respectively. All the data were collected from the record section of the department of radiotherapy and before collection of data, we have taken the informed consent of the patient and/or patients relatives, stating the nature of this study and no herm and no financial burden would occur, and that further management of the patients would not be hampered.

RESULTS

The total number of registered cases in one decade at our institute was 25,638 and among them were 41 double primary cases (0.16%).

Demographic profiles of patients have depicted in Tables 2 and 3. Twenty-two cases were metachronous (59%) and 19 cases (41%) were synchronous double primary. Almost 60% of patients were male. The most common site of double primary site head and neck region (38 %) followed by the lung, and esophagus (13% each), and the least common site was the colon (<1%). The median age of patients at the time of primary diagnosis and second malignancy was 55 years and with a range of 16–70 years. In the case of metachronous double primary, the mean time interval (the time gap between two cancer development) was 7.4 years with a range of 2–19 years. All treatment details are depicted in Tables 1 and 2. Most patients' curative intention small proportion of patients offered palliative therapy.

DISCUSSION

The existence of synchronous double primary especially at the site where field cancerization does occur such as head and neck, lung, and genitourinary primary, should be searched by detailed clinical examination and investigation such as CT scan MRI and FDG PET CT scan. Similarly, patients such as survivors of breast and head and neck malignancy who are prone to develop metachronous double primary may be searched for the same. The overall incidence in reported literature, depending on definition (SEER or IACR), ranges from 2.4% to 17% and is depicted in detail in Table 4. In our study, the overall incidence of the second primary is 0.15%.

Table 1: Some risk factors for second malignancy

Lifestyle factors/personal habits	Tobacco smoking/chewing, Alcohol Obesity	Risk factors for multiple cancers- prone to developing >1 of these cancer types, Field cancerization.
Environmental factors	Pathogen-virus	HPV, EBV
Occupational	Asbestosis exposure	Pleural Mesothelioma and lung malignancy
Genetic/Heredity/cancer-predisposing syndrome	BRACA1, BRACA2 P53	Breast, ovary; breast, and prostate in men Breast, brain, colon, sarcoma, and adrenocortical tumor
	FAP	Colon, duodenal cancer, and multiple polyps
	MEN1	Pituitary, parathyroid, and pancreas
	MEN2	MTC and pheochromocytoma
	HPNCC	Endometrium, colon, ovary, stomach, and small bowel
Host factors	Radiotherapy Chemotherapy	Post RT thyroid, breast carcinoma, and bone sarcoma
	Prior cancer diagnosis	Etoposide – secondary Leukemia

Table 2: Metachronous double primary

S. No	Age at 1 st Tumor	Sex	1 st site	Treatment	Histology	2 nd site	Histology	Time gap (Years)	Treatment
1	48	F	Left breast	CCT, RT, Letrozole	IDC	Esophagus	SCC	12	CRT
2	31	F	Thyroid	Thyroidectomy, I ¹³¹ ablation	Papillary ca. thyroid	Left Breast	IDC (Triple Positive)	4	BCS, local RT, CCT, Letrozole
3	52	M	Glottis	Local RT	SCC	Base of tongue	SCC	9	Local RT
4	47	M	Right breast	CCT RT, Tamoxifen	IDC	Esophagus	SCC	10	CRT
5	36	F	CML	Imatinib	CML	Left breast	IDC	7	BCS, local RT, CCT, Letrozole
6	56	M	Right Lung	CRT	Adenocarcinoma	Oral tongue		7	CRT
7	16	M	Hodgkin's lymphoma	CCT, IFRT	Mixed cellularity	Esophagus	SCC	15	CRT
8	49	M	Oral tongue	WLE+SOND+RT	SCC	Stomach	Adeno Ca	7	Gastrectomy +CCT
9	32	M	Mandible	CCT	Osteosarcoma	Maxilla	SCC	14	Local RT
10	47	M	Base of tongue	CRT	SCC	Right Lung	Adenocarcinoma	8	CCT, RT
11	61	F	Buccal mucosa	Surgery, RT	SCC	Glottis	SCC	6	Local RT
12	55	M	Lung	CRT	Adenocarcinoma	Floor of mouth	SCC	5	Local RT
13	54	F	Right breast	BCS, RT, CCT, Letrozole	IDC	Left Breast	IDC	8	TMAC, CCT, Letrozole
14	62	M	Base of tongue	CRT	SCC	Hard palate	SCC	6	RT
15	70	M	Urinary bladder	TURBT, BCG therapy	TCC	Left Lung	SCC	9	CCT
15	54	M	Lower alveolus	WLE+segmental madibulectomy+SOND	SCC	Buccal mucosa	SCC	6	WLE+ reconstruction
16	46	F	Left breast	MRM	IDC	Right breast	IDC	3	MRM
17	44	M	Right tonsil	CRT	SCC	Right Lung	Adenocarcinoma	19	CCT, RT
18	51	M	Left Kidney	radical nephrectomy	RCC (clear cell carcinoma)	Left lower alveolus	SCC	2	WLE+ neck dissection
19	46	F	Cervix	CRT	SCC	Breast	IDC	6	MRM+CCT+RT
20	56	M	Left Lung	CRT	Adeno Ca	larynx	SCC	4	CRT
21	61	F	Left Breast	MRM+CCT+RT+HT	IDC	Colon	Adeno Ca	6	Hemicolecotomy +CCT
22	63	M	Urinary bladder	Radical cystectomy	TCC	Left renal pelvis	Urothelial Ca	4	Radical nephrectomy

CCT: Combination chemotherapy, CRT: Concurrent Chemo-Radiotherapy, RT: radiotherapy, SCC: Squamous Cell Carcinoma, IDC: Infiltrating ductal carcinoma, BCS: Breast-conserving surgery, IFRT: Involved field radiotherapy, TMAC: Total mastectomy with axillary clearance, MRM: Modified radical mastectomy, TURBT: Transurethral resection of bladder tumor; TCC: Transitional cell carcinoma, WLE: Wide local excision, SOND: Supra omohyoid neck dissection, and RCC: Renal cell carcinoma

Table 3: Synchronous double primary

S. No	SEX	1 site	Age	Treatment	Histology	2 nd site	Histology	Treatment
1.	M	Esophagus	67	Local RT	SCC	Great toe	Malignant Melanoma	Palliative chemotherapy
2.	M	Oral tongue	58	Local RT	SCC	Pyriform sinus	SCC	Local RT
3.	M	Base of tongue	62	Local RT	SCC	Right Lung	Adenocarcinoma	Palliative CCT
4.	M	Stomach (antrum)	54	Gastrectomy	Mucinous adenocarcinoma	Esophagus (Mid. 1/3)	SCC	Palliative RT
5.	M	Prostate	66	Hormone (ADT)	Adenocarcinoma	Multiple myeloma	Multiple myeloma	Chemotherapy
6.	F	Urinary bladder	58	CRT	TCC	Renal pelvis	Urothelial Ca	nephrectomy
7.	M	Buccal mucosa	61	WLE+SOND	SCC	Oral Tongue	SCC	WLE+SOND
8.	F	PFS	60	CRT	SCC	Esophagus	SCC	CRT
9.	M	Lower alveolus	48	WLE (Segmental mandibullectomy+SOND	SCC	Maxilla	SCC	Maxillectomy +SOND
10.	F	Esophagus	54	CRT	SCC	Tonsil	SCC	CRT
11.	M	Base of tongue	62	CRT	SCC	Lung	adenocarcinoma	CCT
12.	F	Urinary bladder	61	CRT	TCC	Ureter	TCC	Nephroureterectomy
13.	M	Stomach	62	CCT	Adeno ca	Cervicalesophagus	SCC	RT
14.	F	Base of tongue	66	CRT	SCC	PFS	SCC	CRT
15.	F	Lower (GBS)	48	WLE+SOND	SCC	Lung	Adeno Ca	CCT

CCT: Combination chemotherapy, CRT: Concurrent chemo-radiotherapy, RT: Radiotherapy. SCC: Squamous cell carcinoma, IDC: Infiltrating ductal carcinoma, BCS: Breast-conserving surgery, IFRT: Involved field radiotherapy, ADT: Androgen deprivation therapy, GBS: Gingiva buccal sulcus, TMAC: Total mastectomy with axillary clearance, MRM: Modified radical mastectomy, TURBT: Transurethral resection of bladder tumor, TCC: Transitional cell carcinoma, WLE: Wide local excision, SOND: Supra omohyoid neck dissection, and RCC: Renal cell carcinoma

Table 4: Double primary incidence

Reference	The definition used double primary (SEER/IACR)	Mean follow-up (years)	Incidence (%)	Geographic region	Number of patients evaluated
Hauben et al. [7]	NA	NA	7	Netherland	938
Rosso et al. [8]	IACR	NA	6.3	22 European country	2919023
Buiatti et al. [9]	IACR	2.5	2.4	Italy	19252
Coyte et al. [10]	IACR	5	5	West of Scotland	57393
Amer et al. [4]	SEER	5 10 15 20	7.3 11.4 13.3 14.4	USA	1873
Vogt et al. [1]	IACR	6.6	8.17	Switzerland	82671
Present study	SEER	7	0.16	West Bengal, India	28652

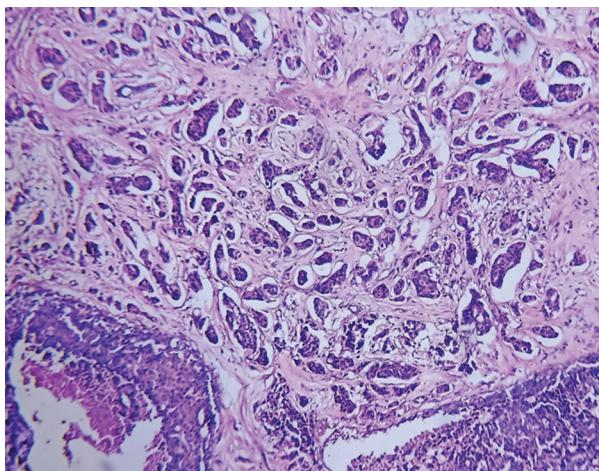


Fig. 1: H & E stain, 100 x magnification, showing DCIS with an invasive component in breast carcinoma (2nd primary)

In the head and neck, the risk of the second primary in the non-primary tumor-bearing site, that is, other head and neck regions reaches up to 40% of long-term survivors [11]. This high risk may be because, in addition to exposure to radiation during treatment, the whole upper aerodigestive tract is exposed to common carcinogens (field cancerization) such as smoking, alcohol intake, and tobacco chewing exposure [12]. In our study, head and neck region most common site of the second primary tumor (37%) and is comparable with reported literature. Manthri et al., from India, reported the second primary in breast cancer survivors is not very rare, and on follow-up, a PET CT scan of any new FDG avid metabolically active lesion in an unlikely site of metastasis, especially in the contralateral breast should raise suspicion of metachronous second malignancy [13]. The author also concluded that an appropriate and early management may be facilitated by early detection of a second primary tumor with the help of an ¹⁸F FDG PET-CT scan. Optimal screening strategies and modalities to detect in early stage and reduce mortality from the second primary tumors are yet to be defined [14]. The effect of prior therapy on toxicity, survival, prognosis, and appropriate management of metachronous or synchronous double primary is yet to be well established, and more studies are required [1].

Patients with synchronous double primary pose a therapeutic dilemma; management is very challenging and should be managed by a multidisciplinary team. The localized disease may be managed by surgery, chemotherapy, RT, and CRT including both malignancies [15,16]. However, in cases of advanced disease at presentation, usually managed by an anticancer regimen and treatment modality with palliative RT and CCT to which both cancers are most likely to respond.

Patients with metachronous double primary are equally challenging, especially in cases with 1st primary is not cured and is still in the advanced stage. Prior chemotherapy regimen and dose received, type of surgery, radiotherapy dose, and volume of RT; toxicity from prior therapy should be taken into consideration while taking the therapeutic decision.

CONCLUSIONS

The management of double primary should be supervised by a multidisciplinary tumor board and more research is needed in the areas of epidemiology and treatment.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to this article including data collection, writing, and reviewing the manuscript.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest for the publication of this article.

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