International Journal of Research in Medical Sciences
Nandennavar MI et al. Int J Res Med Sci. 2019 Dec;7(12):4449-4454
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20195163

Original Research Article

Double malignancies: a clinicopathological and outcomes retrospective analysis from a tertiary cancer referral centre in South India

Manjunath I. Nandennavar, Veerendra Angadi*, Shashidhar V. Karpurmath, Roshan Jacob

Department of Medical Oncology, Vydehi Institute of Medical Sciences and Research Centre, EPIP Area, Whitefield, Bengaluru, Karnataka, India

Received: 14 October 2019
Revised: 18 October 2019
Accepted: 24 October 2019

***Correspondence:**
Dr. Veerendra Angadi,
E-mail: angadi_veerendra@yahoo.com

ABSTRACT

Background: The presence of second synchronous or metachronous primary malignancies in a cancer patient is not a rare phenomenon. Our study is an endeavour to present data on the frequency, types, and outcomes of double primary malignancies in Indian cancer patients.
Methods: This was a retrospective study conducted in 28 cancer patients diagnosed with histologically confirmed double malignancy. Retrospective data of the cancer site, patient's age at the presentation, gender, type of cancer (synchronous/metachronous), treatment, and outcome were recorded from patients presented with double malignancies from January 2012 to January 2019.
Results: Among 28 patients (18 females; 10 males) with multiple primary malignancies, 10 (35.7%) and 18 patients (64.3%), respectively, had synchronous and metachronous primary malignancies. Overall, breast, gynecological, head, and neck cancer were the most common primary malignancies. Gastrointestinal tract, breast, and lung cancer emerged to be the most common second primary malignancy sites. Squamous cell carcinoma (SCC) and invasive ductal carcinoma (IDC) were the most common histopathological types of double malignancies. The majority of the patients received appropriate treatment for both the malignancies.
Conclusions: Data from the present study clearly suggest that the occurrence of second primary malignancy is not rare in Indian cancer patients. The double malignancies can occur at any stage and for any type of cancer. Hence, we wish to highlight that the clinician should always be aware of the possibility of developing second malignancy either during evaluation or in follow up of a patient with malignancy.

Keywords: Double primary malignancy**,** Metachronous, Survival, Synchronous, Treatment

INTRODUCTION

According to the GLOBOCAN 2018 report, the incidence and mortality rates of cancer are growing at an epidemic proportion both worldwide and in India.[1] A patient may have multiple primary tumors, i.e. with >1 tumor arising in different organ sites and/or are of a different histology or morphology subtype. According to recent estimates the incidence of multiple primary malignancies ranges from 2% to 17%.[2]

The risks of second primary malignancies are further increased due to the interplay of environmental, lifestyle, and genetic risk factors and the long-term side effects of the applied cancer treatment. Evidence over the years suggests increased risk of second primary malignancies

in cancer survivors.[2,3] According to the Surveillance Epidemiology and End Results (SEER) project, multiple primary malignancies can be synchronous and metachronous.

Synchronous refers to malignancies diagnosed within 2 months of the original diagnosis of cancer; whereas metachronous refers to the multiple lesions that occur >2 months from the initial diagnosis (SEER).[4]

However, the duration changes to six months instead of two months as per the definition laid down by the International Association of Cancer Registries and the International Agency for Research on Cancer (IACR/IARC). With the advent of more sophisticated imaging methods, such as positron-emission tomography computed tomography (PET-CT) and magnetic resonance imaging (MRI), it is not uncommon to find lesions that might have been missed on standard CT and/or bone scintigraphy.[2]

Though many case reports and retrospective studies are present on the pattern and outcome of double malignancies at both global and Indian scenarios, however, they are limited either due to short study duration, small sample size or focus upon specific cancer type.[5-8]

Hence, in endeavor to enhance the knowledge of the practicing oncologist in India with the various latest trends of double malignancies, and further emphasize the importance of follow-up diagnosis, we reviewed the records of patients presenting with double malignancies. The analysis was not restricted to any particular cancer type, hence provided a comprehensive picture of the trend to the clinicians.

METHODS

Inclusion criteria

The study included data from 28, male and female patients presenting with histologically confirmed synchronous or metachronous double primary malignancies, between January 2012- January 2019 was the study period. Patients with at least two neoplastic sites, confirmed by histopathological examination and with distinct histopathology in the two unique sites were included in the study. Time interval used to differentiate between synchronous and metachronous malignancy was 6 months.

Exclusion criteria

Patients without a clear histopathological confirmation of each malignancy, or patients for whom the second tumor was suspected to be a metastasis of the first site were excluded from the trial.

The study design was duly approved by the regional institutional review board. All the patient related- data was anonymized; to preserve patient's identity.

Objectives and study methodology

The main objective of the study was to record data of the patients diagnosed with double malignancies: age at the time of presentation, gender, type of cancer (synchronous or metachronous), site of primary origin, histological subtype, clinical stage of cancer, and the treatment regimen. The diagnosis of malignancy at the primary site was proven by histopathological examination.

Study group

This single-center retrospective study collated and analyzed data from the case records of patients diagnosed with double malignancies in tertiary cancer referral center in South India from January 2012-Jan 2019.

Statistical analysis

As this was a retrospective data collection study, with no hypothesis testing, formal calculation of sample size and statistical power was not performed.

RESULTS

A total of 28 patients with double malignancies were observed. Among the 28 cases, 10 (35.7%) and 18 (64.3%) cases, respectively, were synchronous and metachronous primary malignancies. Out of 28 patients, 18 (64.3%) were females and 10 (35.7%) were males. The mean ages for primary diagnosis of synchronous and metachronous malignancies were 58.9 and 50.56 years, respectively (Table 1).

Six months was considered the maximum duration for the occurrence of synchronous malignancy. The occurrence interval of metachronous malignancies ranged from 2 to 30 years, with an average of 6.47 years.

Table 1: Demographic summary of patients with double malignancies.

Variable	Synchronous (N=10)	Metachronous (N=18)
Gender: Number (percentage [%])		
Male	5 (50)	5 (27.78)
Female	5 (50)	13 (72.22)
Age of diagnosis: Mean (standard deviation)	58.9 (11.56)	50.56 (19.15)

The most common site of primary malignancy was the breast (11 cases; 39.28%), followed by gynecological cancers (6 cases; 21.4%). Among the second malignancies, the most common site of malignancy was

the gastrointestinal tract (7 cases; 25%) followed by the breast (4 cases 14.2%). Furthermore, the majority of the second site tumors were advanced-stage malignancies (stage III and IV) (Table 2).

The most common histopathological cancer sub-types for primary site were squamous cell carcinoma (SCC) type (8 cases; 28.5%) and invasive ductal carcinoma (IDC) (7 cases; 25%). Among the second malignancies too, the most common histopathological cancer sub-types were SCC (5 cases; 17.8%) and IDC (5 cases; 17.8%) (Table 3).The majority of the cancer patients (85.7%) were under an appropriate treatment regimen (surgical, chemoradiotherapy, cytotoxic, supportive, and palliative care) for the primary and second site malignancy according to the type and stage of cancer. A total of three patients lost to follow-up in the study and nine deaths were recorded in the study (Table 4).

Table 2: Summary of synchronous double malignancies.

Age at primary malignancy (years)	Gender	Primary Site	Histopathology	Treatment	Second malignancy site	Histopathology	Treatment
49	F	Cervix	Squamous cell carcinoma (SCC)	Chemotherapy	Urinary Bladder	Transitional cell carcinoma	Chemotherapy
66	M	Blood	Lymphocytic Leukemia	No indication	Head and neck	Basal cell carcinoma	Surgical
60	M	Vallecula	SCC	Chemo radiotherapy	Mid-thoracic esophagus	Moderately differentiated SCC	Chemo radiotherapy
65	M	Rectum	Adenocarcinoma	Chemo radiotherapy	Left ureter	Papillary carcinoma	Adjuvant Chemotherapy
67	M	Neck	poorly differentiated cancer	Chemo radiotherapy	Esophagus mid 1/3rd	moderately differentiated SCC	Chemo radiotherapy
41	F	Right Breast	Invasive ductal carcinoma	Surgery chemotherapy	Left Lung	Large cell carcinoma	Surgical
45	F	Bile duct	Adeno carcinoma	Supportive care	Stomach with ovary	Adenocarcinoma	Supportive care
78	M	Vocal cord	SCC	Chemotherapy	Lung	Adenocarcinoma	Chemotherapy
53	F	Cervix	Modified differentiated adenocarcinoma	Chemotherapy	Ovary	Adenocarcinoma	Chemo radiotherapy
65	F	Lung alveolus	Modified differentiated SCC	Chemo radiotherapy	Ampulla of vater	Adenocarcinoma	Surgical

Table 4: Summary of follow-up for patients with double malignancies.

Status of Patient	Synchronous (N=10) number (%)	Metachronous (N=18) number (%)
Dead	5 (50)	4 (22.2)
Lost to follow-up	-	3 (16.6)
Alive and on follow-up	5 (50)	11 (61.1)

DISCUSSION

Cancer is found to exert a significant economic burden in Indian cancer patients, and evidence indicates its highest prevalence in the elderly and in females in the reproductive age group. Hence, early screening and regular follow-up can not only improve patient survival but also reduce the economic burden implications.[5]

Experience around the globe for various types of cancer, indicate synchronous and metachronous malignancies are not uncommon and unanimously echo the recommendation of long-term diagnostic follow up after resection of the primary cancer in patients.[6,7] In a single center experience spanning up to 15 years; in 892 patients with lung cancer, a total of 41 and 12 patients developed metachronous and synchronous malignancy post treatment of the primary lung malignancy.[6]

In another retrospective study involving 120 patients with a history of head and neck cancer, 42% of the patients developed a metachronous dual malignancy >5 years post diagnosis of the primary malignancy. The study also reported a significantly lower survival rate for the synchronous malignancies (mean survival duration= 18 months) with a 5-year survival rate of 11.9%.[8]

Table 3: Summary of metachronous double malignancies.

Age at primary malignancy (years)	Gender	Primary site	Histopathology	Treatment	Second malignancy site	Histopathology	Treatment
52	F	Left breast	Invasive ductal carcinoma (IDC)	Chemotherapy	Left lung	Adenocarcinoma	Chemotherapy
65	F	Cervix	Squamous cell carcinoma (SCC)	Chemo radiotherapy	Right lung	SCC	
45	F	Left breast	IDC	Surgical	Right breast	IDC	Chemotherapy
9	M	Lymph nodes	Non-Hodgkin lymphoma	Chemotherapy	Brain	Pleomorphic xanthoastrocytoma with anaplastic features	Surgical Chemotherapy
56	F	cervix	SCC	Chemo radiotherapy	Stomach	Adenocarcinoma	Radiotherapy
48	F	Breast	IDC	Surgery chemotherapy	Esophagus	SCC	Chemotherapy
50	F	Breast	IDC	Surgery chemotherapy	Right breast	IDC	Chemo radiotherapy
62	F	Breast	Tubular carcinoma	Surgery chemotherapy	Lymph nodes	CLL	Chemotherapy
55	F	Breast	IDC	Chemo radiotherapy	Larynx	SCC	No indication
53	F	Breast	IDC	Surgery chemotherapy	Left breast	IDC	Radiotherapy
62	F	Cervix	SCC	Chemo radiotherapy	Vulva	Modified differentiated carcinoma	Surgical Chemotherapy
95	M	Thyroid	Papillary carcinoma	Surgical	Esophagus	SCC	Chemotherapy
33	F	Left Ovary	Adeno-carcinoma	Chemotherapy	Left breast	IDC	Palliative care
36	F	Breast	IDC	Chemo radiotherapy	Left breast	IDC	Chemotherapy
65	F	Breast	IDC	Chemotherapy	Nasopharynx	Poorly differentiated malignancy	Chemo radiotherapy
16	M	Brain	Cranio-pharyngioma	Surgical	Brain	Primitive Neuroectodermal tumor	Chemotherapy
57	M	Breast	IDC	Surgical Chemotherapy	Esophagus	SCC	Radiotherapy
51	M	Lung	SCC	Chemo radiotherapy	Kidney	Clear cell carcinoma	Surgical

Another study with 39 patients diagnosed with head and neck cancer; 14 and 25 patients, respectively had synchronous and metachronous malignancies. Although the overall median survival time was comparatively higher than the reported literature; the study highlighted

the presence of synchronous and metachronous to be a huge management challenge for the oncologists.[9]

Retrospective study, analyzing records of 150 patients for presence of synchronous and metachronous malignancy for colorectal cancer which is the second most common cause of malignancy death in western world; revealed 2.67% and 0.67% of synchronous and metachronous malignancies respectively.[10]

In another retrospective hospital based 2-year study; analyzing malignancies for patients with prostate cancer; reported 6 patients with multiple malignancies (synchronous) alongside prostate cancer. The study highlighted the impact of co-existing malignancies on the survival of the patient and supported the surveillance for improved outcome in such patient.[11]

In a recent retrospective analysis by Adeel et al, in 221 patients who underwent surgical intervention for head and neck cancer; second primary malignancy occurred in 8.14% with highest incidence in oral cavity followed by lungs. Nearly half of the patients had stage IV disease followed by stage II disease. In line with other global evidences the study too, emphasized that long-term follow up of patients with head and neck cancer cannot be overlooked and early diagnosis is one of key measure for efficient management of the patient.[12]

Evidence generated over the years from various regions of India also indicate that the occurrence of second primary malignancies is not rare.[13-16] This study was in line with respect to the distribution of synchronous vs. metachronous malignancies as reported in the literature.[16-18] The available retrospective studies from various regions of India suggest higher percentage of metachronous malignancies compared to synchronous malignancy.[18,19]

The distribution of synchronous and metachronous malignancies across various retrospective analyses is presented in (Table 5). Study further highlighted the predominance of breast, gynecological, and head and neck as the primary malignancies, which was in sync with the data generated from previous retrospective Indian analyses (Table 5).[16,19,20]

Table 5: Percentage distribution of double malignancies across various Indian retrospective studies.[13-20]

Factors	Bagri et al	Balasankar et al	Bansal et al	Chaudhary et al	Hulikal et al	Naik et al	Sharma et al	Jena et al
Synchronous	19.51	19.23	33	5.6	35	19.6	26	84.7
Metachronous	80.49	80.7	67	94.4	65	80.4	74	15.3

Among the second malignancies, the most common sites in this study were the gastrointestinal tract, breasts, and lungs. The results were consistent with the result reported by Baghri et al, where the distribution of second malignancy site was breast (21.95%), gastrointestinal tract (21.95%), lung (17.07%) and gynecological cancers (12.2%), respectively.[13]

Furthermore, in line with the data from Balasankar et al, where SCC represented the most frequent histopathological type of cancer in primary and second malignancies (53.84%), the majority of the SCC histopathological subtype cases in both the double malignancy sites.[14] According to existing literature the median/mean age of primary malignancy diagnosis in this study was comparable to the age reported across various studies (>50 years).[17,18]

The potential occurrence of multiple primary malignancies should always be considered during diagnostic evaluation. While screening procedures will help detect any early-stage tumors, regular follow-up strategies will help in reducing the mortality burden from second primary malignancies. This study contributed by the addition of data on the trends of double primary malignancies in the Indian context to the existing literature. The data can, thus, serve to encourage the practicing oncologists in the country to pursue rigorous follow-up diagnosis/screening evaluation during the management of cancer patients.

CONCLUSION

The data from the study concludes that the presence of second primary malignancies is not rare in Indian cancer patients. The double malignancies can occur at any stage and for any type of cancer. Hence, regular monitoring and evaluation workup, by the treating clinicians can lead to early detection of the malignancy followed by its appropriate treatment.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018:

GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2018;68:394-424.
2. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open. 2017 May 1;2(2):e000172.
3. Coyte A, Morrison DS, McLoone P. Second primary cancer risk-the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer. 2014 Dec;14(1):272.
4. THE SEER PROGRAM. Available at: https://seer.cancer.gov/archive/manuals/2004Revision1/SPM_2004_maindoc.r1.pdf. Accessed on: 28 April 2019.
5. Mukhopadhyay A, Mohanti BK, Sharma K, Das S, Dash S. The economic burden of cancer. Economic and Political Weekly.2011; 43:112-7.
6. Aziz TM, Saad RA, Glasser J, Jilaihawi AN, Prakash D. The management of second primary lung cancers. A single centre experience in 15 years. Euro J Cardio-Thoracic Surg. 2002 Mar 1;21(3):527-33.
7. Hujala K, Sipilä J, Grenman R. Panendoscopy and synchronous second primary tumors in head and neck cancer patients. Euro Archi Oto-Rhino-Laryngol Head Neck. 2005 Jan 1;262(1):17-20.
8. Di Martino E, Sellhaus B, Hausmann R, Minkenberg R, Lohmann M, et al. Survival in second primary malignancies of patients with head and neck cancer. J Laryngol Otol. 2002;116:831-8.
9. Dequanter D, Shahla M, Lardinois I, Gilbert O, Hanquet O, Tragas G, et al. Second primary lung malignancy in head and neck cancer patients. Eur Ann Otorhinolaryngol Head Neck Dis. 2011;128:11-3.
10. Brambilla E, Sgarioni AC, Finger G, Sartori G, Cimarosti MJ. Incidence and epidemiological features of synchronous and metachronous colorectal cancer. J Coloproctol (Rio J). 2013;33:58-61.
11. Popoola AA, Abiola OO, Buhari T, Ushie AF, Olanipekun HB, Arogundade AK. Multiple primary cancers: Simultaneously occurring prostate cancer and other primary tumors-our experience and literature search. Niger J Clin Pract. 2017;20:278-82.
12. Adeel M, Siddiqi MI. Metachronous second primary malignancy in head and neck cancer patients: is five years of follow-up sufficient? J Korean Assoc Oral Maxillofac Surg. 2018;44:220-4.
13. Bagri PK, Singh D, Singhal MK, Singh G, Mathur G, Jakhar SL, et al. Double Primary Malignancies: A Clinical and Pathological Analysis Report from a Regional Cancer Institute in India. Iran J Cancer Prev 2014;7:66-72.
14. R. Balasankar, B. Nehru. A Retrospective Study on Second Primary Malignancies Incidence in Regional Cancer Institute. J Evolution Med Dent Sci. 2015;4;4066-75.
15. Bansal S, Gupta M, Nautiyal V, Agrawal C, Pruthi D, Chauhan N, et al. Second Primary Neoplasms: A Clinico-Pathological Analysis from a Sub Himalayan Cancer Centre in India. J Integr Oncol. 2017;6:188.
16. Chaudhary P, Gupta S, Leekha N, Tandon R, Nandy M, De S. Pattern of occurrence and treatment outcome of second primary malignancies: A single center experience. South Asian J Cancer 2017;6:137-8.
17. Hulikal N, Ray S, Thomas J, Fernandes DJ. Second Primary Malignant Neoplasms: A Clinicopathological Analysis from a Cancer Centre in India. Asian Pac J Cancer Prev. 2012;13:6087-91.
18. Naik A, Bhandari V, Saadvik RY, Gupta KL, Kausar M, Batra M, et al. Incidence of second primary malignant neoplasm in Malwa region of central India. J Can Res Ther. 2018;14:999-1004.
19. Sharma D, Singh G, Kakkar N, Raj S. Second primary malignancy: A retrospective analysis report from a tertiary cancer center of North India. Indian J Cancer. 2017:53;595-9.
20. Jena A, Patnayak R, Lakshmi AY, Manilal B, Reddy MK. Multiple primary cancers: An enigma. South Asian J Cancer. 2016;5:29-32.

Cite this article as: Nandennavar MI, Angadi V, Karpurmath SV, Jacob R. Double malignancies: a clinicopathological and outcomes retrospective analysis from a tertiary cancer referral centre in South India. Int J Res Med Sci 2019;7:4449-54.