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Multiple Primary Malignancies: A Clinicopathological Profile of Patients at a Tertiary Center of North India—A Retrospective Hospital-Based Observational Study

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Abstract

Introduction The incidence, prevalence, as well as survival of cancer patients, is increasing day by day due to the use of screening and improved diagnostic modalities. Simultaneously, the development of multiple primary malignancies (MPMs) in cancer survivors is not uncommon in recent years, because of an improved understanding of biology and effective management of cancer in the form of local (i.e., surgery/radiotherapy) and systemic (chemotherapy/targeted therapy) treatment, leading to improved survival and subsequent development of more malignancies. The study was conducted to describe the clinicopathological profile of patients diagnosed with MPMs.

Objective To study the clinicopathological profile of MPMs and to look for treatment patterns of these patients.

Materials and Methods This was a retrospective hospital-based observational study. Medical records of 73 patients with MPMs, who were registered in the department of medical and surgical oncology between January 2016 and December 2018, were enrolled in the study. The statistical analysis was done by using IBM SPSS Statistics for Windows from IBM Corp. Categorical data were expressed in the form of frequencies and percentages.

Results Out of the total 73 patients, 2 patients were diagnosed to have triple malignancies and were excluded from the study for discussion purposes. Among 71 patients with double malignancies, 19 patients had synchronous and 52 had metachronous malignancies with synchronous to metachronous ratio of 1:2.73. The study included 39 men and 32 women with a male to female ratio of 1.21:1. Gastrointestinal system was the most common system involved in first primary as well as in second primary malignancy. Squamous cell carcinoma and adenocarcinoma equally were the

Keywords
- malignancy
- synchronous
- metachronous

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most common histologies seen in primary, whereas adenocarcinoma was the most common histology seen in second primary malignancy.
Conclusions The phenomenon of MPMs is not an uncommon presentation due to longer survival and side effects of treatment (radiotherapy/chemotherapy). It should always be kept in consideration in any cancer survivor during surveillance in order to detect it and treat at the earliest.

Background

Multiple primary malignancies (MPMs) in cancer patients are not very rare because of prolonged survival due to advances made in the treatment of cancer patients. The probability of recurrence or a secondary from the initial malignancy may delay treatment and impact the overall prognosis and survival, making the diagnosis of MPMs complicated. The most common presentation of MPMs is double malignancies.[1,2] MPMs were first described by Billroth[3] in 1889 and reported in a detailed study by Warren and Gates[4] in 1932. The criteria for diagnoses of MPM, as proposed by Warren and Gates, include: (1) histological confirmation of malignancy in both the index and second primary tumors; (2) there should be at least 2 cm of normal mucosa between the tumors; if the tumors are in the same location, then they should be separated in time by at least 5 years; (3) probability of one being the metastasis of the other must be excluded.

Double primary malignancies could be divided into two categories, depending upon the interval between tumor diagnoses. Synchronous malignancies are defined where second tumor develops simultaneously or within 6 months after the diagnosis of first malignancy, whereas in metachronous malignancies, second tumor develops after 6 months or more after the diagnosis of the first malignancy.[5]

The aim of our study was to assess the clinical and pathological profile of patients diagnosed with MPMs in our region.

Material and Methods

This was a retrospective hospital-based observational study. Medical records of 73 patients with MPMs who were registered in the department of medical and surgical oncology between January 2016 to December 2018 were enrolled in the study. The patient's details were entered in a set proforma, which include age, sex, family history, smoking and drinking history, histology of synchronous and metachronous lesions, and treatment received.

Inclusion Criteria

Patients with two or more lesions at different sites with different histology or those with two lesions at different sites with similar histology but with different immunohistochemistry markers were included in the study. The tumors were divided into synchronous and metachronous lesions depending upon the time interval between the occurrence of two lesions. Synchronous tumors developed simultaneously or within 6 months of each other, whereas metachronous lesion occurred more than 6 months apart from each other.

Exclusion Criteria

Patients with malignancy at different sites but with same immunohistochemistry or disease at same site within 5 years of first malignancy were excluded from the study.

Sample Size

Sample size was calculated by using the Cochran's formula $n = (1.96)^2 p(1\text{-}P)/d^2$, $p = 0.73\%$, $d = 0.10\%$, and thus, the calculated sample size is 76. Case records of three patients were incomplete and were excluded from the study, so the final sample size of our study was 73 patients having 85% power of study.

Primary Outcome

To study the clinicopathological profile of MPMs.

Secondary Outcome

To study the treatment patterns of MPM patients.

Statistical Analysis

The data analysis was done on a computer running Microsoft Windows. The data were initially entered into a Microsoft Excel spreadsheet to be checked for mistakes. The IBM Corp.'s IBM SPSS Statistics for Windows was used for the statistical analysis (released 2020, Version 27.0. Armonk, New York, USA). The frequency and percentage representations of categorical variables were displayed.

Results

Out of 13,852 newly diagnosed cancer cases, 73 patients were diagnosed to have MPMs comprising of 0.51% of the total cases enrolled during the study. Two patients had triple malignancies, whereas 71 patients had double malignancies. In the two patients with triple malignancy, one had non-Hodgkin's lymphoma and developed metachronous squamous cell carcinoma of esophagus and adenocarcinoma of sigmoid colon. In another patient with index squamous cell carcinoma of skin (thigh), developed two metachronous malignancies, i.e., renal cell carcinoma and adenocarcinoma stomach. For rest of discussion purposes, we will exclude triple malignancies. Of the 71 cases of double malignancy, 39

(54.92%) were men and 32 (45.07%) were women with a male to female ratio of 1.21:1. Median age of our patients was 55 (30–80) with median time to diagnosis of second cancer of 36 months (12–228).

Among the 71 patients with MPMs, 52 patients harbored metachronous double malignancies, whereas 19 patients harbored synchronous double malignancies with metachronous to synchronous malignancy ratio of 2.73:1. The most common systems involved in primary cancer were gastrointestinal system (GI; 22; 30.99%), breast (8; 11.27%), reproductive (8; 11.27%), urinary tract (8; 11.27%), and head and neck (7; 9.86%), whereas in second primary cancer most common systems involved were GI (28; 39.43%), lung (12; 16.9%), reproductive (8; 11.27%), head and neck (8; 11.27%), and breast (4; 5.63%), with esophagus (8; 11.26%), stomach (7; 9.85%), and breast (7; 9.85%) being the most common organs involved in primary cancers, whereas lung (12; 16.90%), colorectal (9; 12.67%), and stomach (8; 11.26%) being the most common organs involved in second primary cancers (►**Table 1**, ►**Fig. 1**). Squamous and adenocarcinoma were equally distributed (16 cases each; 22.53%), the most common histologies involved in primary cancers, whereas adenocarcinoma (22; 30.99%) followed by squamous cell carcinoma (18; 25.35%) were as the most common histologies in second primary cancers (►**Supplementary Fig. S1**, available in the online version). Of the 71 patients with MPMs, 20 (28.17%) were treated with surgery, 14 (19.71%) with surgery + chemotherapy, 10 (14.08%) with chemotherapy + radiotherapy, whereas in second primary malignancy, 15 (21.12%) underwent surgery; 13 (18.30%) chemotherapy + radiotherapy, and 10 (14.08%) patients received surgery + chemotherapy (►**Tables 2** and **3**, ►**Supplementary Fig. S2** [available in the online version])

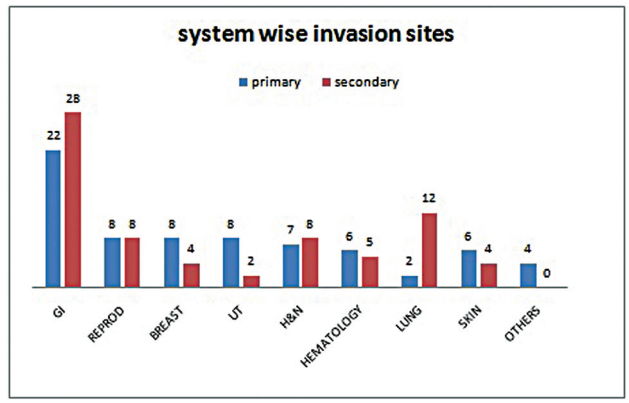

Fig. 1 System wise invasion sites.

Discussion

Recently, there has been a sharp increase in the prevalence of MPMs, ranging from 0.7 to 11.7% among various populations.[6] This can be due to multitude of reasons including the improved survival of cancer patients due to improved treatment modalities, better diagnostic modalities, and more stringent surveillance of cancer survivors.[7] The prevalence of MPMs in the studied group was 0.51%.

MPMs are a special phenomenon in the tumorigenesis. A number of studies have been conducted worldwide leading to better understanding of this phenomenon. The etiopathogenesis of MPMs can be attributed to genetic events or the common environmental risk factors.[8] Various other mechanisms like aging, an unhealthy lifestyle, cancer treatments, or interactions between any of these factors are also believed to contribute to the development of MPMs.[9] The increased risk of MPMs can be attributed to field carcinogenesis due to exposure to tobacco, smoking, and alcohol consumption.[10] In our study population, 32% patients had smoking history, and none had history of alcohol consumption.

The treatment of primary malignancy by chemotherapy and/or radiotherapy may contribute to increased risk of second malignancy as both ionizing radiation and cytotoxic agents (etoposide, cyclophosphamide, and Adriamycin etc.) can cause DNA damage leading to carcinogenesis. The harmful effects of these treatments as well as of the tumor microenvironment on the patient's immune system may be an important contributing factor allowing future renegade mutant cancer cells from

Table 1 System wise invasion sites

Site	Primary	%	95% CI		Second primary	%	95% CI	
			Lower	Upper			Lower	Upper
Gastrointestinal	22	30.99	20.00	43.00	28	39.44	28.00	51.00
Reproductive	8	11.27	4.00	21.00	8	11.27	4.00	21.00
Breast	8	11.27	4.00	21.00	4	5.63	1.00	13.00
Urinary tract	8	11.27	4.00	21.00	2	2.82	0.30	9.00
Head and neck	7	9.86	4.00	19.00	8	11.27	4.00	21.00
Hematology	6	8.45	3.00	17.00	5	7.04	2.00	15.00
Lung	2	2.82	0.30	9.00	12	16.90	9.00	27.00
Skin	6	8.45	3.00	17.00	4	5.63	1.00	13.00
Others	4	5.63	1.00	13.00	0	0.00	–	–

Abbreviation: CI, confidence interval.

Table 2 Summary of synchronous primary malignancies

S No.	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment
1	48	F	Esophagus (20 cm)	SCC	CT-RT	Esophagus (34-37 cm)	SCC	CT-RT
2	80	M	Prostate	Adenoca	GnRH analogues	Thyroid	Papillary carcinoma	Total thyroidectomy
3	36	M	Prostate	Adenoca	Local R/T	Bladder	Malignant paraganglioma	Radiotherapy
4	40	F	Ovary	Endometriod carcinoma	TAH + BSO (OCR) +Chemo	Uterus	Endometrial carcinoma	TAH/BSO done as part of ca ovarian staging
5	41	F	Breast	IDC	BCS + ALND + radiotherapy + chemo	Thyroid	Papillary carcinoma	Total Thyroidectomy
6	60	M	Tongue	SCC	WLE + radiotherapy	Gall bladder	Adenoca	Radical cholecystectomy
7	60	M	Esophagus	SCC	CT-RT	Lung	Adenoca	CT-RT
8	60	M	Urinary Bladder	TCC	TURBT	Lung	Adenoca	CT-RT
9	65	M	Oral cavity	SCC	WLE	Thyroid	PTC	Total thyroidectomy
10	55	M	Stomach	Adenoca	Palliative care	Liver	Hepatocellular carcinoma	Palliative care
11	75	M	Cervical node	NHL	CT + RT	Esophagus	SCC	CT-RT
12	67	M	Esophagus	SCC	CT-RT	Lung	SCC	CT-RT
13	65	M	Stomach	Adenoca	NACT + surgery + adjuvant chemo	Colon	Adenoca	Left hemicolectomy
14	60	M	Esophagus	SCC	CT-RT	Lung	SCC	CT-RT
15	30	F	Ovary	HGS Ca	Surgery/optimal cytoreduction + chemo	Endometrium (1b)	Endometrial Ca	EBRT
16	46	F	Endometriod Ca of ovary	TAH + BSO (OCR)	Observation	Endometrium	Endometrial Adenoca (1A)	Observation (sx already done)
17	50	M	GE junction	Adenoca	Palliative chemo	Larynx	SCC	Palliation
18	50	M	RCC	Clear cell	Immunotherapy	Lung	Adeno	Immuno + chemo
19	55	F	Breast	IDC	Chemo	Ovary	HGS Ca	Chemo

Abbreviations: Adeno, adenocarcinoma; ALND, axillary lymph node dissection; BCS, breast conservative surgery; Chemo, chemotherapy; CLL, chronic lymphocytic leukemia; CT-RT, chemoradiation; DLBCL, diffuse large B cell lymphoma; HGS, Ca-high-grade serous carcinoma; IDC, infiltrating duct ca; NACT, neoadjuvant chemotherapy; NHL, non-Hodgkin's lymphoma; OCR, optimal cytoreduction; PSC, papillary serous adenocarcinoma; PTC, papillary thyroid carcinoma; RAIA, radioactive iodine ablation; RT, radiation therapy; SCC, squamous cell ca; Sx., surgery; TAH, total abdominal hysterectomy with salpingo-oopherectomy; TCC, transitional cell carcinoma; TURBT, transurethral resection of bladder tumor; WLE, wide local excion.

escaping the body's defense mechanisms. Children and young adults may be especially prone to such iatrogenically induced cancers.[11] This was also seen in our patient population, as around 40% of the patients in total and 51.71% patient in metachronous group had received either chemotherapy/radiotherapy or both as treatment for their primary cancers.

In the present study, the incidence of multiple primaries was more common in men as compared with women with a male to female ratio of 1.21:1. Although MPMs can occur at any age, there are several studies that show that incidence is more in older patient population.[12–16] The median age in our study was 55 years (range 30–80 years). Etiz et al in their study had male to female ratio of 1.19:1 with a median age of 59 years (range 29–80 years),[17] consistent with our study. The interval between index primary and second primary in our study was 12 to 228 months (median 36 months), which is consistent with other studies[9,18] (comparison between different studies given in ►**Table 4**).

The ratio of synchronous to metachronous malignancies varies in different studies.[19–22] In a study by Aydiner et al,[14] synchronous malignancies constituted 34%, whereas metachronous malignancies constituted 66%, consistent with our study with synchronous and metachronous malignancy of 27 and 73%, respectively. The most common system involved in first primary as well as second primary malignancy in our study was GI (30.99 and 39.44%) with lung being the most

Table 3 Summary of metachronous double malignancies

S.no	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment	Time interval (mo)
1	51	F	Thyroid	Follicular carcinoma	Total thyroidectomy + RAIA	Blood	CLL	Chemotherapy + targeted therapy	84
2	60	F	Kidney	Clear cell carcinoma	Right radical nephrectomy	Left kidney	Clear cell carcinoma	Sunitinib	24
3	40	F	Skin	Mycosis fungoids	Phototherapy	Ovary	PSCa	Surgery (OCR) + chemotherapy	60
4	70	M	Lymph node	NHL(DLBCL)	Chemotherapy + targeted	Esophagus	SCC	Chemoradiation	24
5	55	M	Lymph node	NHL (small cell type)	Chemotherapy	Blood	CLL	Chemotherapy	12
6	50	F	Colon	Malignant carcinoid	Right hemicolectomy + chemotherapy	Cheek (skin)	Basal cell carcinoma	WLE	12
7	55	F	Cervix	SCC	CT-RT	Labia majora (skin)	SCC	WLE	48
8	41	F	Lung	Adenoca	CT-RT	Choroid	Melanoma	Enucleation of eyeball	24
9	55	M	Urinary bladder	Papillary carcinoma	TURBT + chemotherapy	Colon	Adenoca	Hemicolectomy + chemotherapy	60
10	55	F	Uterus	Adenoca	TAH + BSO	Rectum	Adenoca	Chemoradiation	12
11	35	M	Right kidney	Chromo-phobe carcinoma	Radical nephrectomy	Thyroid	PTC	Total thyroidectomy	12
12	58	F	Skin	SCC	WLE	Stomach	Adenoca	Supportive care	60
13	50	F	Colon	Adenoca	Left hemicolectomy	Uterus	Endometrial carcinoma	TAH + BSO	72
14	67	F	Ovary	Papillary carcinoma	NACT + surgery	Breast	IDC	MRM	24
15	55	F	Uterus	Adenoca	TAH + BSO	Gall bladder	Adenoca	Chemotherapy	24
16	65	M	Skin	SCC	WLE	Esophagus	SCC	CT-RT	12
17	51	F	Thyroid	Follicular ca	Total thyroidectomy	Blood	CLL	Chemotherapy + targeted	84
18	40	F	Rectum	Adenoca	Anterior resection + CT-RT	Uterus	Adenoca	TAH + BSO + radiotherapy	192
19	52	M	Esophagus	SCC	CT-RT	Lung	SCC	Chemotherapy	36
20	55	F	Eyelid	Merkel cell carcinoma	WLE	Breast	IDC	MRM + chemotherapy	12

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Table 3 (*Continued*)

S.no	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment	Time interval (mo)
21	48	F	Breast	IDC	MRM + chemotherapy	Colon	Adenoca	Hemicolectomy + chemotherapy + radiotherapy	48
22	70	M	Colon	Adenoca	Hemicolectomy + chemotherapy	Lung	SCC	Chemotherapy	36
23	60	M	Lung	SCC	CT-RT	Skin	SCC	WLE	36
24	50	F	Gall bladder	Adenoca	Radical cholecystectomy	Stomach	Adenoca	Distal gastrectomy + chemotherapy	24
25	68	M	Esophagus	SCC	Surgery + chemotherapy	Lung	SCC	CT-RT	192
26	55	M	Bladder	TCC	TURBT	Stomach	Adenoca	Distal gastrectomy + CT-RT	36
27	76	M	Bladder	TCC	TURBT + intravesical BCG	GE junction	SCC	Chemotherapy	180
28	40	F	Breast	IDC	MRM + Chemo + RT	Ovary	HGS Ca	Surgery (OCR) + Chemo	84
29	50	M	Esophagus	SCC	Surgery + radiotherapy	Stomach	Neuroendocrine tumor (G1)	Distal gastrectomy	96
30	75	M	Lymph node	NHL	Chemotherapy	Stomach	Adenoca	Defaulted	36
31	56	M	Blood	CLL	Chemotherapy	Lip	Merkel cell carcinoma	WLE + radiotherapy	228
32	60	M	Skin	SCC	WLE + chemotherapy	Lung	SCC	CT-RT	12
33	65	F	Lymph node	NHL	Chemotherapy	Rectum	Adenoca	CT-RT	48
34	50	M	Stomach	Adenoca	NACT with distal gastrectomy + adjuvant chemotherapy	Blood	DLBCL	Supportive care	36
35	70	M	Skin	SCC	WLE	Esophagus	SCC	Radiotherapy	36
36	65	M	Skin	Basal cell carcinoma	WLE	Lung	SCC	Radiotherapy	36
37	55	M	Colon	Adenoca	Hemicolectomy with chemotherapy	Esophagus	Adenoca	Chemotherapy	36
38	40	F	Breast	IDC	MRM	Brain	Meningioma	Observation	12
39	62	M	Spinal cord	Ependymoma	Laminectomy with excision	Blood	CML	Imatinib	60

(*Continued*)

Table 3 (*Continued*)

S.no	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment	Time interval (mo)
40	70	M	Stomach	Adenoca	NACT + total gastrectomy + adjuvant chemotherapy	Rectum	Adenoca	Palliative care	36
41	51	F	Breast	IDC	MRM + chemo + RT	Esophagus	SCC	CT-RT	96
42	55	F	Esophagus	SCC	CT-RT	Stomach	SCC	Palliative care	24
43	55	M	Stomach	Adenoca	Chemo + surgery	Colon	Adenoca	Sx + chemo	20
44	60	F	Breast	IDC	Sx + chemo + RT + hormones	Gallbladder	adeno	Surgery	60
45	65	M	Gastric	GIST	Sx + imatinib	Stomach	Adeno	Sx + chemo	12
46	75	M	Bone marrow	Multiple myeloma	Chemo + immuno	Colon	Adeno	Sx + chemo	36
47	80	M	Colon	Adenocarcinoma	Sx + chemo	Lung	Adeno	Chemo	96
48	56	F	Breast (right)	IDC	Sx + chemo + hormones	Breast (Left)	IDC	Sx + chemo + hormones	108
49	75	F	Thyroid	Papillary carcinoma	Sx + RAIA	Breast	IDC	Sx + chemo + radiotherapy	204
50	45	F	Uterus	Endometrial ca	Surgery (1A)	Periampullary ca	Adenoca	Surgery	48
51	53	M	Kidney	Clear cell ca	Surgery (1B)	Lung	Squamous cell	Chemo	84
52	47	F	Thyroid	Papillary carcinoma	Surgery	Lung	Adeno	TKI	96

Abbreviations: Adeno, adenocarcinoma; ALND, axillary lymph node dissection; BCS, breast conservative surgery; Chemo, chemotherapy; CLL, chronic lymphocytic leukemia; CT-RT, chemoradiation; DLBCL, diffuse large B cell lymphoma; HGS, Ca-high-grade serous carcinoma; IDC, infiltrating duct ca; NACT, neoadjuvant chemotherapy; NHL, non-Hodgkin's lymphoma; OCR, optimal cytoreduction; PSC, papillary serous adenocarcinoma; PTC, papillary thyroid carcinoma; RAIA, radioactive iodine ablation; RT, radiation therapy; SCC, squamous cell ca; Sx., surgery; TAH, total abdominal hysterectomy with salpingo-oopherectomy; TCC, transitional cell carcinoma; TURBT, transurethral resection of bladder tumor; WLE, wide local excion.

Table 4 Multiple primary malignancies: comparison of different studies

Study (ref. No)	Total no. of patients	No. of patients with multiple primary malignancies		Synchronous/ metachronous	Male/ female	Median age (metachronous group)		Common site		Median interval between index and second primary (mo)
		No.	%			Index primary	Second primary	Index primary	Second primary	
Vadgaonkar et al[18]	16,461	44	0.26	7/37	13/31	48	56	Gynecological	Gynecological	38
								Breast	Gastrointestinal	
								Head and neck	–	
Etiz et al[17]	9,772	122	1.2	36/86	67/55	56	62	Lung	Lung	–
								Gastrointestinal	Gastrointestinal	
								Genitourinary	Genitourinary	
Zhai et al[9]	15,321	167	1.09	98/69	117/50	62	64	Gastrointestinal	Gastrointestinal	31.15
								lung	lung	
								Head and neck	Head and neck	
Bisht et al[7]	3,879	29	0.74	8/21	10//19	54	56	Breast	Gastrointestinal	–
								Head and neck	Head and neck	
								Lung	Lung	
Irimie et al[8]	–	63	–	24/41	34/29	58.2 y in entire group		Genital	Breast	–
								Breast	Gastrointestinal	
								Gastrointestinal	Lung	
Present study	13,852	71	0.51	19/52	39/32	55 y in entire group		Gastrointestinal	Gastrointestinal	36
								Breast	Lung	
								Reproductive	Reproductive	

common second primary malignancy after GI (16.9%). In a retrospective study, Zhai et al[9] found that the most common pairs were digestive–digestive (25.75%) followed by digestive–lung pairs (19.16%), which coincides with our findings. In another study conducted by Etiz et al, the most common second primary malignancies were GI (22%) and lung (19%), similar to present study.[17] There is high prevalence of GI malignancies in this region of country, which is presumed due to geographic, dietary, and cultural reasons. In a study from the region by Khan et al,[23] which included 22,180 patients, cancer of esophagus, stomach, and colon were second, third, and sixth most common causes of cancer incidence. This could explain the reason for GI tract being the most common site in both synchronous and metachronous groups.

The possibility of existence of MPMs must always be considered during pretreatment evaluation. There is some evidence that screening will improve outcomes among patients who may develop second malignancies, although the data are limited. The optimal screening modalities and strategies to reduce mortality from second malignancies remain to be defined for most tumor sites.[21] With careful monitoring, second primary tumors can be detected early, and with appropriate intervention might be better managed, without compromising survival.

A sizable prospective study needs to be conducted to better understand the profile and outcome of MPMs in order to better develop the various strategies for screening and early identification of second primary malignancies and to enhance outcomes.

Limitations

The small sample size and retrospective nature of our study are its primary limitations.

Conclusion

In conclusion, second primary malignancies are not rare. They can be synchronous or metachronous. Improvements in diagnostic and staging modalities and improved survival after management of primary cancers have increased the detection of second primary malignancies. A strong clinical suspicion and thorough evaluation would be beneficial in the management of these tumors. A regular follow-up in a patient diagnosed and treated for primary malignancy would help not only to detect recurrence but also could detect most of the metachronous second primary malignancies at an early stage.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the guidelines of the Institutional Ethics Committee (IEC) and approved on January 31, 2022 vide IEC SKIMS No: 2022-34 of the Sheri Kashmir Institute of Medical Sciences (SKIMS), Srinagar. This

study was conducted in accordance with the Declaration of Helsinki. As this was a retrospective audit of the hospital records, the full consent of the patients was waived by Institutional Ethics Committee, SKIMS, Srinagar.

Consent for Publication
Not Applicable.

Authors' Contributions
A.W.M., S.P., and S.N. designed the study and oversaw the research. A.W.M., S.N., I.A., S.N., and N.A.D. developed the concept and drafted the manuscript. S.N. and N.A.D. prepared the tables and figures. A.W.M., S.N., I.A., N.S., S.P., M.H., and N.A. check data for accuracy, contributed to data preparation and analysis. A.W.M., S.N., I.A., N.S., S.P., M.M.H., and N.A. reviewed the results. A.W.M., S.N., I.A., N.S., S.P., M.M.H., and N.A.D. reviewed all versions of the manuscript. A.W.M., S.N., I.A., N.S., S.P., M.M.H., and N.A.D. finalized the manuscript. All authors reviewed the finalized manuscript. The author(s) read and approved the final manuscript.

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Conflict of Interest
None declared.

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