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A single centre study from western India to evaluate the frequency of developing second and subsequent multiple primary malignancies among cancer survivors

Anjali Sharma[1], Ajay Sharma[2], Sanjeev Patni[3], Anil Gupta[3], Naresh Ledwani[3], Shashikant Saini[3], Nidhi Patni[4], Ajay Bapna[5], Naresh Somani[5], Mudit Sharma[1], Shubham Verma[6], Gulshan Kumar Sharma[6] and Vandana Nunia[7*]

Abstract

Aim: This study was designed to evaluate the frequency of developing second and subsequent primary cancers among cancer survivors.

Methods: We have retrospectively analyzed 121 multiple primary cancer patients treated at Bhagwan Mahavir Cancer Hospital and Research Centre, Jaipur, Rajasthan, India from the last 20 years. The survival analysis was performed by Kaplan-Meier methodology.

Results: The prevalence of multiple primary malignant tumors (MPMTs) was 1.51% (121/8000), with a male to female ratio of 1:1.42. In males most of the reported MPMTs were synchronous and most common first primary cancer cases were head & neck and lung whereas, in females most of the reported MPMTs were metachronous and most common first primary cancer cases were breast and gynaecological malignancies. Family history was reported in 15 cases. Maximum 33.05% patients received combined treatment of chemotherapy, radiotherapy and 91.73% (111/121) of patients with MPMTs were effectively followed up, 35 (28.92%) patients died and 5-year survival rate of the remaining 86 patients was 68.46%.

Conclusions: In the present observational study the most frequent sites of MPMTs in men were head & neck and lung whereas, in women breast and gynaecological sites were common. Therefore, careful monitoring and follow up are required for these patients.

Keywords: Multiple primary malignant tumors, Clinical characteristics, Treatment, Survival study

Introduction

The presence of a single tumor does not make patient immune against the development of subsequent second, third or additional primary malignant cancers. In fact, frequency of MPMTs in the same individual is high due to exposure to various factors during the life span of cancer survivors (Zhai et al. 2018). The risk of developing a second primary tumor is varying at different cancer sites and is reported in the range from 0.7 to 11.7% (Demandante et al. 2003). Due to extensive screening programs, improved diagnostic procedures and significant treatment advances that contributed to the prolonged overall survival of the cancer patients, the incidences of MPMTs

*Correspondence: vandananunia@gmail.com

[7] Department of Zoology, University of Rajasthan, Jaipur, Rajasthan 302004, India
Full list of author information is available at the end of the article

are increasing. At the same time expanded use of cancer treatments, particularly combined modality of radiotherapy and chemotherapy contribute to the increased incidence of second malignancies among cancer survivors. Various factors can influence the reported numbers of MPMTs like the applied definition, follow-up time and patient population types (Wood et al. 2012).

MPMTs are primary malignant tumors of different histological origin in one person and often misdiagnosed as recurrence or metastasis of the original malignancy. Low incidence and variability in clinical characteristics of MPMTs makes diagnosis and treatment difficult for clinicians (Spratt and Hoag 1966; Lv et al. 2017). There are several factors that may increase the likelihood of a second primary cancer. These factors include intrinsic, extrinsic, genetic and therapeutic factors. Intrinsic factors involve individual patients disease susceptibility, immune status, endocrine and embryonic development. Extrinsic factors include environmental factors and personal lifestyle, occupational diseases, long exposure to ultraviolet rays, industrial pollution and treatment history whereas, genetic factors include mutations in various genes (Spratt and Hoag 1966; Yamamoto et al. 2006).

In some patients vulnerable immune system leads to the development of the first cancer, further it makes them more susceptible for the development of second cancer (Zheng et al. 2020). The risk of developing a second primary tumor varies at different cancer sites. According to few studies "field effect" is observed in some areas of digestive tract, ovaries, breast and others, in which changes were detected in uninvolved tissues. Cells of certain organs are similar to one another therefore, the same changes that made one organ susceptible to cancer may occur in the similar cells of other organ also, causing them at risk for the development of cancer as well (Chai and Brown 2009). In India breast, cervical, ovarian and uterine cancers account for more than 70% of the cancers in females and advanced treatment strategies allowing higher chances of survival on treatment (Mallath et al. 2014). Primary cancers of the breast account for nearly 40% of all cancers diagnosed among female breast cancer survivors with a 5-year relative survival rate of 89%. In males head and neck cancer prevalence is high and 5 year survival among head and neck cancer patients range between 25% for cancer tongue to 74% for lip (Pisani et al. 2002; Wells and King 2017). During this survival time, the patient is subjected to various mechanisms, which act as a triggering agent in the development of second primary cancer. In India, limited studies are available regarding multiple primaries, most of them being case reports (Mohanti et al. 1998; Reddy et al. 2009; Angurana et al. 2010; Kumar et al. 2010; Bishen and Singh 2011; Chowhan et al. 2011; Rajalingam et al. 2012; Bagri et al. 2014). Present study is an attempt to analyse and review 121 patients presenting with multiple primary malignancies to evaluate the frequency of developing second and subsequent cancers at commonly occurring primary cancer sites.

Material and method

This was a retrospective study carried out at Department of Pathology, Bhagwan Mahavir Cancer Hospital and Research Centre, Jaipur, Rajasthan, India during the period of 1999 to 2019. Ethical Committee approval was taken for the present study. Only those patients were included in the study where diagnosis of malignancy was histologically proven in our department as per Warren and Gates criteria. For metachronous contralateral breast cancer, the inclusion criteria consisted of a time gap of 5 years and/or disparity in hormone receptor status without any reported metastasis. Tumors defined in original medical records as either recurrent or metastatic were excluded. The tumor diagnosed first and associated with the cause of the patient's initial visit was defined as the first primary cancer (primary cancer), the second primary cancer (second cancer) was the one diagnosed second and so forth. All of the primary tumors in MPMTs patients diagnosed within 6 months were classified as synchronous multiple primary malignant tumors (SMPMTs), and tumors diagnosed after more than 6 months were deemed metachronous multiple primary malignant tumors (MMPMTs).

Selected 121 patients were analyzed and various clinicopathological parameters were noted like personal details (age, sex, family history, habits and duration of illness), histopathological details (location of tumour, size, microscopic features, extent of spread, stage and grade), treatment details, time interval between each malignancy and follow up. The cases were sub grouped according to the site of tumour as follows: Head and neck (buccal mucosa, tongue, Guillain-Barré syndrome (*GBS*), salivary gland, uvula, tonsil, vallecula, parotid, pyriform fossa (PFF), floor of mouth, oropharynx and larynx), thyroid, breast, lung, reproductive tumor (cervix, uterus and ovary, vagina, testis and prostate), gastrointestinal tract (caecum, colon, oesophagus, gall bladder, jejunum, pancreas, rectum, stomach) urinary tract (urinary bladder and kidney), haematological tumor (leukemia, lymphoma and non-Hodgkin lymphoma) and others (pleural, bone and soft tissue). Hematoxylin and eosin (HE) stains were employed to stain the histological slides.

Statistical analysis

All the data received from hospital-based software and available files, was filled in the excel sheet. Further this numerical data of various parameters was analysed by

calculating mean, and median with the help of Excel functions. For significance, $p < 0.005$ was considered significant. Patients' follow-up was carried out by telephone, electronic medical records and letters. The overall survival of the patients was determined as the interval from diagnosis of MPMTs to the date of death or the last follow-up and patients were followed until January 31, 2020. Kaplan-Meier methodology was employed to analyze survival and line plot was made using matplotlib python library function.

Results

Total 8000 cancer cases were studied at our centre during the period of 1999 to 2019. Out of 8000 cases of cancer, head & neck comprised 1840 (23%), gastrointestinal tract 1120 (14%), breast 1200 (15%), gynecological 720 (9%), lung 1120 (14%), hematological 800 (10%) and others 1200 (15%) cases. Male to female ratio was 1: 1.22. Most of the patients were between the age of 31 and 60 years with peaks at 55 years for males and 50 years for females.

From these 8000 cases 121 cases of MPMTs were reported, of which 114 cases were double primaries and 7 were triple primaries. Out of 121 cases, 24 cases were grouped as synchronous malignant tumors (SMPMTs) and 97 cases as metachronous malignant tumors (MMPMTs) and the ratio of SMPMTs to MMPMTs was 1: 4.041. Out of 121 cases, 50 were males and 71 females (sex ratio M:F = 1:1.42). For SMPMTs cases, 16 were males while 8 were females whereas, for 97 MMPMTs cases, 34 were male and 63 were female patients. The occurrence of multiple primary malignant tumors (MPMTs) in our study was 1.51% (121/8000).

The mean age of the 121 patients was 52 years (range 15–80) at diagnosis of the first primary cancer with most patients being diagnosed with MPMTs at the age of 50 to 59 (33.05%). For second primary cancer mean age at diagnosis was 58.27 (range 24–90) and most patients were diagnosed with MPMTs at the age of 60 to 69 (35.53%). For breast cancer malignancies mean age for first primary malignancy and second primary malignancy was 48.55 and 55.95 years respectively. For third primary cancer the mean age at diagnosis was 71.42 (range 65–86) and most patients were diagnosed with MPMTs at the age of 60–69 and 70–79 age group (42.85% each) (Fig. 1). The youngest case in SMPMTs series was a 15 years old male child who first presented with ewings sarcoma and then after 33 years developed invasive ductal carcinoma of breast at the age of 48 years. While the oldest case was an 80-year-old male who presented with synchronous malignancies of lung adenocarcinoma and stomach gastrointestinal stromal tumor.

Interval between the diagnosis of the first primary and second primary cancer & the first primary and third primary cancer was recorded for all the cases. The minimum

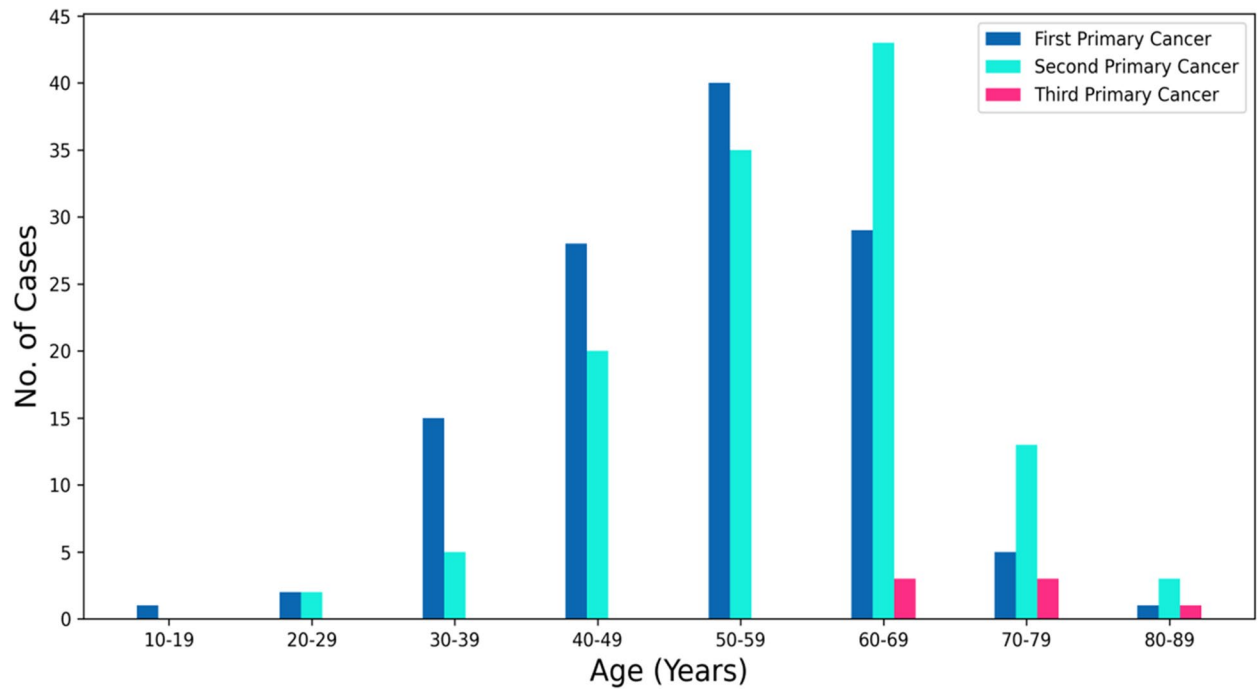

Fig. 1 Graph depicting the age of the first, second and third primary cancer patients at the time of MPMTs diagnosis (MPMTs* multiple primary malignant tumors)

duration was noted in a case of breast - ovary cancer pair (2 days) and maximum duration of illness was noted in a case of ewings sarcoma - breast cancer pair (33 years). Among our 121 patients the mean interval between the diagnosis of the first primary and second primary cancer was 6.204 years and median value was 5 years, and the mean interval between the diagnosis of the first primary and third primary cancer was 10.142 years and median was 8 years (Fig. 2). Mean interval for SMPMTs and MMPMTs was 2.8 months and 7.67 years. Median time interval between cancer diagnosis for synchronous and metachronous cancers was found to be 2 months and 7 years respectively.

In male patients most of the first primary cases were head and neck cancer (44%) followed by lung (22%) and digestive cancers (20%) respectively. In female patients most of the reported first primary cancer cases were breast cancer (60.53%), followed by gynaecological malignancies (21.12%). For second primary malignancies maximum cancer cases for males were lung cancer (24%) followed by digestive malignancies (20%) whereas, in females breast cancer (38.02%), followed by gynaecological malignancies (22.53%) and digestive malignancies (14.08%). Most of the reported first primary and second primary cancer pairs were breast-gynaecological malignancies (18/121) breast-breast (14/121), breast-head & neck (7/121) and head & neck - lung cancer (7/121). Out of 121 cases, 7 cases of third primary malignancy were reported with male to female ratio of 1:2.5.

Most common first primary malignancy site was breast 45 (37.19%) followed by head and neck 24 (19.83%), reproductive tumor 20 (16.52%), digestive tumor 11 (9.09%), hematological 8 (6.611%), lung 5 (4.13%), urinary tract 5 (4.13%), 2 (1.65%) and others 1 (0.82%). While the most common second primary site was also breast 30 (24.79%), followed by reproductive and digestive malignancies 21(17.35%) each, head & neck 12 (9.91%), lung 15 (12.39%), hematological 8 (6.611%), urinary tract 4 (3.30%), thyroid 6 (4.95%) and others 4 (3.30%). For Third primary 28.57% cases included haematological, 28.57% gastrointestinal malignancies and 14.28% each for reproductive, urinary and lung cancer each. The ratio of MPMTs sites in the same system was 18.18% (22/121), and the ratio of MPMTs sites in the different system was 81.81% (99/121) (Fig. 3).

On the basis of histological examination most common tumors were adenocarcinoma, invasive ductal carcinoma (IDC) and squamous cell carcinoma (SCC). 15.70, 24.79, and 42.85% of primary, second and third malignant tumors were adenocarcinomas, respectively. 33.05, 23.96%, IDC cases were reported for first primary and second primary malignancies respectively. 24.79, 17.35 and 14.28% squamous carcinomas cases were reported for first, second and third primary malignancies respectively.

Family history of cancer in first degree relatives was seen in 15 cases (12.39%), out of 15 first primary cases, 7 cases (46.66%) were for breast, 3 cases (20%) for digestive malignancy and 1 case (6.66%) each for larynx, tongue, uterus, bone and urinary bladder. In one case with triple primary malignancies (breast-breast-ovary) the BRCA 2 gene mutation was reported however, the genetic analysis was not performed for the remaining 14 cases.

Clinical stages

Staging of all cases was done except leukemia. Most of the first primary cases 60/118 (50.84%) as well as second primary 52/119 (43.69%) cases were having stage 2 disease at the time of presentation. 10.16% of first malignancies were at stage 4 while there was a considerable rise of

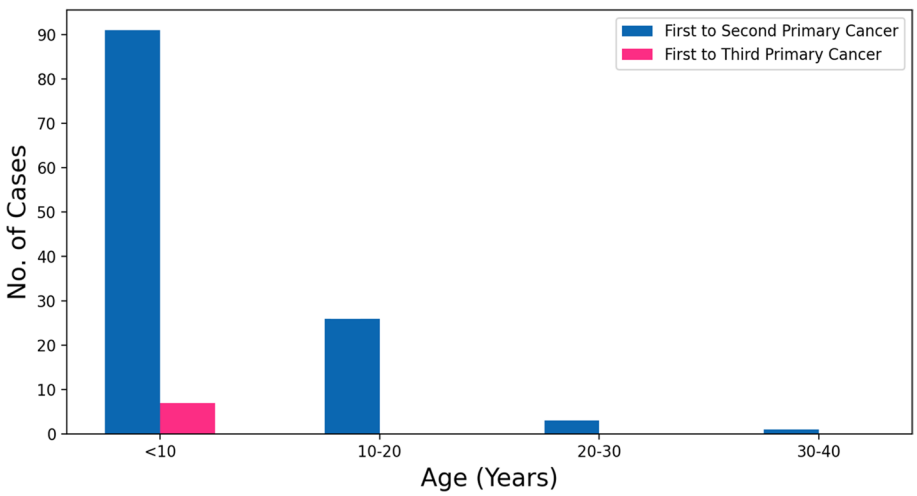

Fig. 2 Graph showing the interval between the diagnosis of the first primary and second primary cancer & first primary and third primary cancer

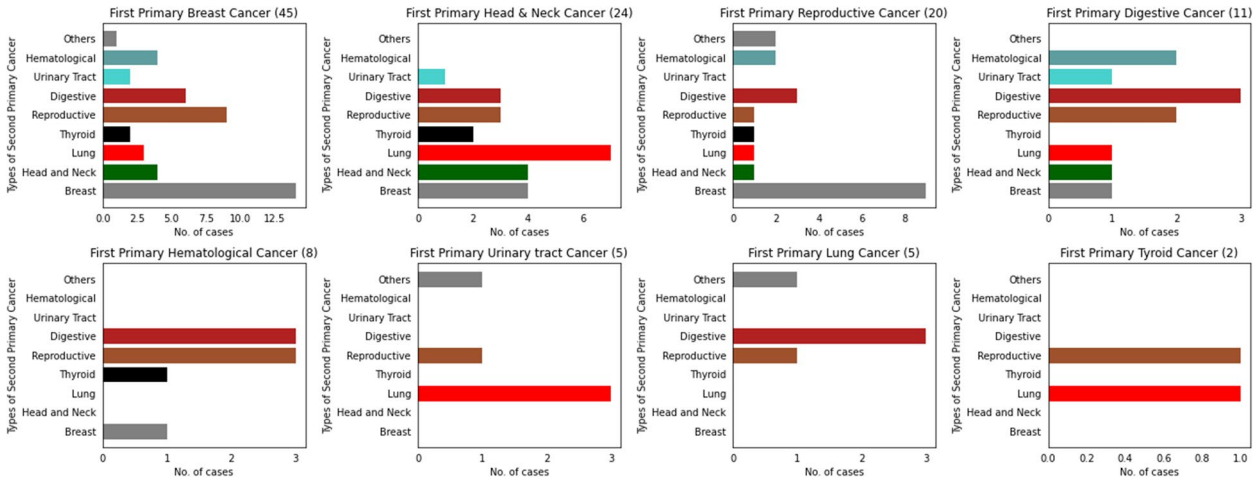

Fig. 3 Graph showing the site-wise distribution of MPMTs in commonly occurring primary cancer sites (*others include bone and soft tissue tumors)

19.8% stage 4 cases in the second primary at the time of presentation ($P < 0.005$) (Fig. 4).

Treatment factors

Treatment modalities were considered and cases were subjected to chemotherapy or radiotherapy or surgery according to the type of tumour and its stage. Of 121 cases, among all primary cancers, 33.05% (40/121) were treated with combined treatment of chemotherapy, radiotherapy and surgery, 17.35% (21/121) were treated with chemotherapy & radiotherapy both, 14.04% received only surgery (17/121) and 11.57% only chemotherapy (14/121), 4.95% radiotherapy & surgery and 1.65% only radiotherapy (2/121). Among all second cancers, 25.61% (31/121) were treated with only chemotherapy, 19.00% (23/121) were treated with only surgery, and 18.18% treated with chemotherapy, radiotherapy & surgery (22/121), 15.70% chemotherapy & radiotherapy, chemotherapy & surgery respectively (19/121), 4.95% radiotherapy and surgery (6/121), 0.82% treated with only radiotherapy (1/121). Among all 3rd primary cancers, 28.57% (2/7) were treated with only chemotherapy, 14.28% (1/7) were treated with only surgery, 14.28% (1/7) chemotherapy & surgery and 42.85% (3/7) with radiotherapy and chemotherapy (Table 1).

Prognosis

A total of 91.73% (111/121) of patients with MPMTs were effectively followed up until January 31, 2020 and 10 patients were lost to follow-up, with a missing rate of

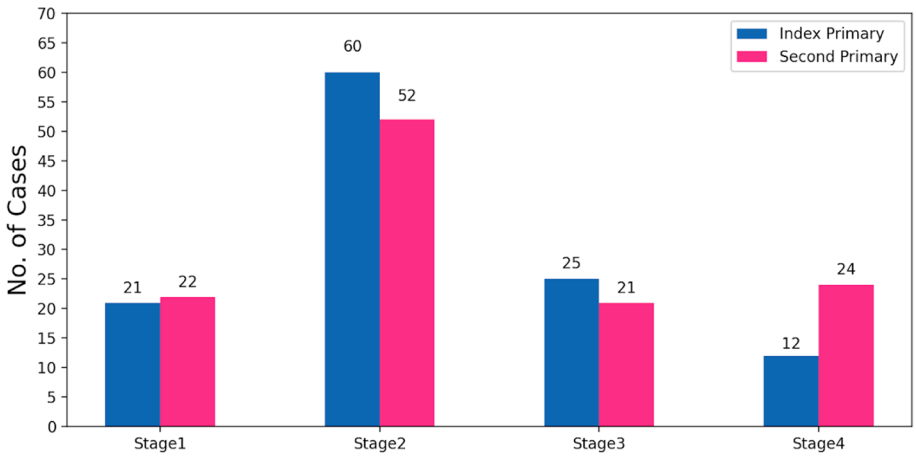

Fig. 4 Graph representing the clinical TNM Staging of first and second primary malignancies

8.26%. Median follow up time was 215 months. Among the 111 patients who were followed up, 31.53% (35/111) have died, and 5-year survival rate of the remaining 86 patients was 68.46%. Of the 31.53% (35/111) who died, cause of death was unknown in 3 cases, 6 patients died of cancer causes and 26 died of cancer (Fig. 5).

Discussion

Present study aimed to analyse the risk of developing second and subsequent multiple primary malignancies at commonly occurring primary cancer sites. Patients with a first primary tumor have almost 10% higher risk of developing second tumor with respect to the general population (AIRTUM working group 2013; Xu and Gu 2014). The prevalence of multiple primary malignant tumors (MPMTs) in our study was 1.51% (121/8000). The reported frequency of MPMTs incidences varies between 0.7 and 11.7% in other countries.

The diverse incidence of MPMTs in different geographical regions might arise due to genetic factors, environmental factors, diagnostic methods, longer analysis duration and inclusion of autopsy series in these studies (Demandante et al. 2003; Lv et al. 2017).

The average age of MPMTs in the present study was 52 years whereas for the breast cancer MPMTs incidences it was 48 years. It is in agreement with the

Table 1 Distribution of various treatment strategies used for first, second and third primary malignancies

	Treatment Strategies						
	CT	**RT**	**Surgery**	**CT RT**	**CT Surgery**	**RT Surgery**	**CT RT Surgery**
Head and neck							
P (24)			3(12.5)	14 (58.33)	1(4.16)	3 (12.5)	3(12.5)
S (12)			5(41.66)	5(41.66)	1(8.33)	1(8.33)	
Breast							
P (45)			4(8.88)		14(31.1)	1(2.22)	26(57.77)
S (30)	3(10)	1(3.33)	4(13.33)	3(10)	3(10)		16(53.33)
Reproductive							
P (20)	1(5)	1(5)	3(15)	3(15)	3(15)	2(10)	7(35)
S (21)	2(9.52)		6(28.57)	3(14.28)	4(19.04)	3(14.28)	3(14.28)
T (1)					1 (100)		
Digestive							
P (11)	1(9.095)		4(36.36)	1(9.09)	3(27.27)		2(18.18)
S (21)	4(19.04)		4(19.04)	5(23.80)	6(28.57)		2(9.52)
T (2)				2 (100)			
Urinary Tract							
P (5)	2(40)	1(20)		1(20)			1(20)
S (4)			1(25)		3(75)		
T (1)			1 (100)				
Haematological							
P (8)	8(100)						
S (8)	8(100)						
T (2)	2 (100)						
Lung							
P (5)	2(40)		1(20)	2(40)			
S (15)	11(73.3)			2(13.33)	2(13.33)		
T (1)				1(100)			
Thyroid							
P (2)			2(100)				
S (6)			3(50)	1(16.66)		1(16.66)	1(16.66)
Others							
P (1)							1(100)
S (4)	3(75)					1(25)	

P First Primary, *S* Second Primary, *T* Third Primary, *CT* Chemotherapy, *RT* Radiotherapy

* Values in the bracket indicates percentage of patients received various therapies

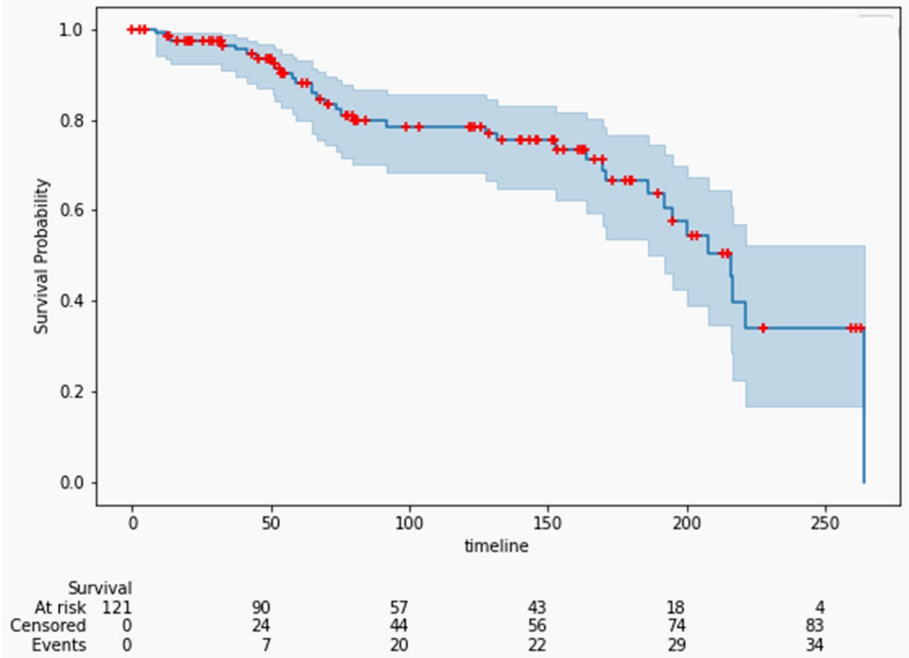

Fig. 5 The Kaplan–Meier survival curve of 121 patients with multiple primary tumors

finding of Motuzyuk et al. 2018, where total 2032 cases were studied and found that the average age of breast cancer MPMTs patients was 46.6 years. In India, maximum cases of breast and ovarian cancer reported in the age group of 45–50 years, which appears to be a decade younger than western countries and this could be due to genetic and environmental factors. We have found the early occurrence of breast cancer as early as 15 years in our study. There is a strong relationship between younger age at diagnosis of the primary breast cancer and risk of a subsequent cancer occurrence (Munker et al. 1996; Spratt and Hoag 1966).

As per our study the ratio of men was found to be higher in SMPMTs group while the numbers of women were greater in MMPMTs group. In India, major sites of cancer occurrence in males are head & neck and lung whereas, in females breast and gynaecological sites are common and same pattern was followed in MPMTs studies. This could be due to higher survival rates for the first primary cancer in these sites rather than unusually high risks for a subsequent cancer (Mallath et al. 2014). We have reported that in females most (97.18%) of the either first primary, second primary and both the malignancies in pairs were breast (20% cases of bilateral breast cancer) and gynaecological malignancies (8.86% breast-cervix, 10.12% breast-ovary and 2.5% breast-uterus cancer pairs). This is in agreement with the finding of various other studies done by Bagri et al. 2014; Jena et al. 2016; Motuzyuk et al. 2018. A strong association between breast cancer and gynaecological tumors exists, as they are (Filippakis et al. 2006; Bălțătescu et al. 2013) influenced by common hormonal risk factors related to menstrual and pregnancy history, use of hormonal medications, as well as genetic susceptibility factors that increases risk for several cancers (Vogt et al. 2017). Age, race and hormone receptor status are risk factors of developing second female genital cancers among breast cancer survivors (Li et al. 2018). In a study done by Xiong et al. 2018 found that younger patients have a high risk of developing contralateral breast cancer.

In the present study 86% of male patients with MPMTs exhibited tumors of the respiratory, lung and digestive systems. The main reason for the high incidence of these MPMTs tumors are use of tobacco and alcohol in men (Priante et al. 2011). Survivors of cancers of the oral cavity and pharynx have high risk of developing a subsequent cancer of oral cavity, pharynx, esophagus, larynx and lung. The risks of subsequent cancers of the lung and oral cavity are especially high among lung cancer survivors who continue to smoke cigarettes (Mallath et al. 2014; Lin et al. 2005; Chuang et al. 2010; Schottenfeld 1996). This indicates that these three sites should be closely monitored by screening in men. Men should also be advised of the risk between tobacco and alcohol consumption and developing MPMTs in future. In the present study the major site of MPMTs in the digestive

system was the esophagus, colon and rectum, followed by stomach. This is in agreement with the previous study of Moertel et al. 1958. We have also reported few familial cases of colon and rectum cancers that may be related to genetic syndromes associated with early onset colon cancer mentioned by *familial adenomatous polyposis* and hereditary nonpolyposis colorectal cancer.

We have reported family history in 15.55% (7/45) first primary breast cancer samples. Several studies have proven that many genes, including BRCA1/BRCA2, ATM, POLD1, PABL2 and SMAD4 played pivotal role in the occurrence and pathogenesis of MPMTs. Mutations in BRCA1 and BRCA 2 genes, contribute to the excess risk of subsequent cancer among women with early-onset breast cancer (Lv et al. 2017; De Luca et al. 2019). In addition to these genes, significant relationship has been observed between the microsatellite instability (MSI) phenotype and MPMTs. Thus, MSI testing might provide an effective tool to detect those patients who are at the higher risk of developing MPMTS (Ohtani et al. 2000; Yun et al. 2009).

The long survival of cancer patients after successful treatment of primary cancers, reports late effects of radiotherapy and chemotherapy and in particular, the occurrence of second primary cancers (Manavoğlu et al. 1996). In our study also maximum breast MPMTs patients received chemotherapy and radiotherapy along with surgery. Association of breast and hematological malignancies was found which may be due to late toxic effects of radiotherapy, chemotherapy and immunosuppression. In addition, thyroid cancer, second malignancies of breast, bone, connective tissue and lung may arise after radiotherapy (Ricceri et al. 2015).

There are no well-established guidelines for the treatment of MPMTs and treatment generally follows management of first primary, second and third primary cancer. Each case varies by type and stage of each tumor, response to treatment and the patient's overall health status (Copur and Manapuram 2019). Treatment strategies for MPMTs aim to cover both first and second primary cancer types without increasing toxicity and negative impact on the overall outcome. Tumor which is more detrimental to the patients survival and quality of life is treated on priority. Treatment of MPMTs should be monitored by a multidisciplinary team of clinicians and interdisciplinary treatment is essential given the diversity of disease combinations and treatment strategies (Williamson et al. 2015). If surgery fits in, tumor removal should be done on priority followed by chemotherapy, radiotherapy and other treatment methods (Gu et al. 2015). In our study patients were offered treatment as per NCCN guidelines according to site and stage of tumor by single/ double / triple modality and chemotherapy & radiotherapy after initial surgery was the most preferred mode of treatment. Total, 91.73% of patients with MPMTs were effectively followed and overall 2- and 5-year survival rate of the remaining 86 patients was 55.29, and 44.71% respectively. This is in agreement with the study of Zhai et al. 2018 who reported overall 2- and 5-year survival rates of the 164 MPMTs patients were 54.3 and 31.4%, respectively.

Our study included retrospective characteristics with a relatively small cohort of hospital-based data (not population-based data in India), the results might be biased and may not represent the trends of general Indian population. Further investigations with larger cohort size or multicentre studies are required to confirm our results.

Conclusion

With the better diagnostic modalities and increase in survival rates of cancer patients the incidence of MPMTs has shown remarkable increase. Furthermore, prolonged follow-up after surgery should be considered with periodical radiological imaging and other relevant examinations. For common occurring multiple primary tumor pairs like in breast cancer cases, second breast, ovarian and uterine cancer needs to be tracked as well, and in head and neck cancer cases, close tracking of head & neck and lung cancer needs to be carried out. Women with hereditary syndromes should undergo regular check-up and if warranted may choose to undergo mastectomy, oophorectomy and salpingectomy to reduce the risk of subsequent invasive breast cancer by 50% and nearly eliminates the risk of ovarian and fallopian tube cancer. To reduce the risk of hereditary multiple colon cancers, recommended treatment is the removal of the entire colon at an early age.

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Authors' contributions
AS involved in study concept, design and clinical studies. SP, AG, LMS, NJ, NL, SS, NP, AB and NS performed clinical studies. MS performed experimental parameters, VN carried out data analysis and manuscript preparation. SV and GKS helped in data analysis. AJS involved in critical evaluation of the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Study was conducted in accordance with declaration of Helsinki and approved by the Ethics Review Committee of Bhagwan Mahavir Cancer Hospital, Jaipur.
Consent to participate was not applicable.

Competing interests
The authors declare that they have no competing interests to disclose.

Author details
[1]Department of Pathology, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan, India. [2]Department of Surgical Gastroenterology, Mahatma Gandhi Medical College, Jaipur, Rajasthan, India. [3]Department of Surgical Oncology, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan, India. [4]Department of Radiation Oncology, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan, India. [5]Department of Medical Oncology, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan, India. [6]Bioinformatics Infrastructure Facility (DBT-BIF), Centre for Converging Technologies, University of Rajasthan, Jaipur, Rajasthan 302004, India. [7]Department of Zoology, University of Rajasthan, Jaipur, Rajasthan 302004, India.

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References

AIRTUM Working Group. Italian cancer figures, report 2013: Multiple tumours. Epidemiol Prev. 2013;37(4–5 Suppl 1):1–152 PMID: 24259384.
Angurana SL, Kapoor R, Kumar P, Khosla D, Kumar N, Sharma SC, et al. Quadruple malignancy in a single patient: a case report and comprehensive review of literature. J Cancer Res Ther. 2010;6:230–2. https://doi.org/10.4103/0973-1482.65237.
Bagri PK, Singh D, Singhal MK, Singh G, Mathur G, Jakhar SL, Beniwal S, Sharma N, Kumar HS, Sharma A, Bardia MR. Double primary malignancies: a clinical & pathological analysis report from a regional cancer institute in India. Iran J Cancer Prev. 2014;7(2):66–72 PMID: 25250152; PMCID: PMC4142942.
Bălţătescu GI, Aşchie M, Sârbu V. Synchronous ovarian dysgerminoma and breast carcinoma in a patient with positive immunostain of BRCA1. Chirurgia (Bucur). 2013;108(2):259–63 PMID: 23618579.
Bishen KA, Singh A. A case of dual malignancy: presenting the necessity for extensive sampling for pathologic examination. J Oral MaxillofacPathol. 2011;15:306–10. https://doi.org/10.4103/0973-029X.86698.
Breast Cancer Facts & Figures 2019–2020 - American Cancer Society n.d. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-andstatistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf.
Chai H, Brown RE. Field effect in cancer-an update. Ann Clin Lab Sci. 2009;39(4):331–7 PMID: 19880759.
Chowhan AK, Jena A, Kinnera SB, Patnayak R, Reddy OM, Reddy KM. Dual malignancy: an interesting concurrent mixed epithelial ovarian tumor with esophageal carcinoma. Indian J Cancer. 2011;48:361–2. https://doi.org/10.4103/0019-509X.84911.
Chuang SC, Scelo G, Tonita JM, Tamaro S, Jonasson JG, Kliewer EV, Hemminki K, Weiderpass E, Pukkala E, Tracey E, Friis S, Pompe-Kirn V, Brewster DH, Martos C, Chia KS, Boffetta P, Brennan P, Hashibe M. Risk of second primary cancer among patients with head and neck cancers: a pooled analysis of 13 cancer registries. Int J Cancer. 2010;129(1):173–9. https://doi.org/10.1002/ijc.25652.
Copur MS, Manapuram S. Multiple primary tumors over a lifetime. Oncology (Williston Park). 2019;33(7):629384 PMID: 31365752.
De Luca A, Frusone F, Vergine M, et al. Breast Cancer and multiple primary malignant tumors: case report and review of the literature. In Vivo. 2019;33(4):1313–24. https://doi.org/10.21873/invivo.11605.
Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. Am J Clin Oncol. 2003;26(1):79–83. https://doi.org/10.1097/00000421-200302000-00015.
Filippakis GM, Lagoudianakis EE, Genetzakis M, Antonakis P, Papadima A, Boussiotou A, Katergiannakis V, Manouras A. Squamous cell carcinoma arising in a mature cystic teratoma of the ovary with synchronous invasive lobular breast cancer: case report. Eur J Gynaecol Oncol. 2006;27(5):537–40 PMID: 17139997.
Gu HL, Zeng SX, Chang YB, et al. Multidisciplinary treatment based on surgery leading to long-term survival of a patient with multiple asynchronous rare primary malignant neoplasms: a case report and literature review. Oncol Lett. 2015;9(3):1135–41. https://doi.org/10.3892/ol.2014.2833.
Jena A, Patnayak R, Lakshmi AY, Manilal B, Reddy MK. Multiple primary cancers: an enigma. South Asian J Cancer. 2016;5(1):29–32. https://doi.org/10.4103/2278-330X.179698.
Kumar V, Singh K, Tatke M, Rathi AK, Shekhar S, Bahadur AK. Synchronous anaplastic oligodendroglioma and carcinoma tongue: a rare association. J Cancer Res Ther. 2010;6(2):227–9. https://doi.org/10.4103/0973-1482.65241.
Li Z, Wu Q, Song J, Zhang Y, Zhu S, Sun S. Risk of second primary female genital malignancies in women with breast Cancer: a SEER analysis. Horm Cancer. 2018;9(3):197–204. https://doi.org/10.1007/s12672-018-0330-0.
Lin K, Patel SG, Chu PY, et al. Second primary malignancy of the aerodigestive tract in patients treated for cancer of the oral cavity and larynx. Head Neck. 2005;27(12):1042–8. https://doi.org/10.1002/hed.20272.
Lv M, Zhang X, Shen Y, Wang F, Yang J, Wang B, Chen Z, Li P, Zhang X, Li S, Yang J. Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. Medicine (Baltimore). 2017;96(17):e6799. https://doi.org/10.1097/MD.0000000000006799 PMID: 28445321; PMCID: PMC5413286.
Mallath MK, Taylor DG, Badwe RA, et al. The growing burden of cancer in India: epidemiology and social context. Lancet Oncol. 2014;15(6):e205–12. https://doi.org/10.1016/S1470-2045(14)70115-9.
Manavoğlu O, Orhan B, Evrensel T, Karabulut Y, Ozkocaman V, Ozyardimci C. Second primary cancer due to radiotherapy and chemotherapy. J Environ Pathol Toxicol Oncol. 1996;15(2–4):275–8 PMID: 9216821.
Moertel CG, Bargen JA, Dockerty MB. Multiple carcinomas of the large intestine: a review of the literature and a study of 261 cases. Gastroenterology. 1958;34(1):85–98 PMID: 13501357.
Mohanti D, Pohare YH, Kumar S, Biswal BM, Kumar L. Breast cancer followed by cervix cancer: a rare form of double malignancy. Indian J Med Paediatr Oncol. 1998;19:90–3.
Motuzyuk I, Sydorchuk O, Kovtun N, Palian Z, Kostiuchenko Y. Analysis of trends and factors in breast multiple primary malignant neoplasms. Breast Cancer (Auckl). 2018;12:1178223418759959. https://doi.org/10.1177/1178223418759959.
Munker R, Hiller E, Melnyk A, Gutjahr P. Second malignancies. Int J Oncol. 1996;9(4):763–76. https://doi.org/10.3892/ijo.9.4.763.
Ohtani H, Yashiro M, Onoda N, Nishioka N, Kato Y, Yamamoto S, Fukushima S, Hirakawa-Ys CK. Synchronous multiple primary gastrointestinal cancer exhibits frequent microsatellite instability. Int J Cancer. 2000;86(5):678–83. https://doi.org/10.1002/(sici)1097-0215(20000601)86:5<678::aid-ijc12>3.0.co;2-o.
Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer. 2002;97(1):72–81. https://doi.org/10.1002/ijc.1571.
Priante AVM, Castilho EC, Kowalski LP. Second primary tumors in patients with head and neck Cancer. Curr Oncol Rep. 2011;13:132–7. https://doi.org/10.1007/s11912-010-0147-7.
Rajalingam R, Javed A, Gondal R, Arora A, Nag HH, Agarwal AK. Non-familial double malignancy of the colon and ampulla of Vater: a case report and review of literature. Saudi J Gastroenterol. 2012;18(2):143–5. https://doi.org/10.4103/1319-3767.93823.
Reddy PA, Harinarayan CV, Suresh V, Jena A, Chandrasekhar SL, Rashmi P, et al. An unusual case of virilizing ovarian tumor associated with carcinoma *in situ* of cervix. Int J Endocrinol Metab. 2009;4:255–8.
Ricceri F, Fasanelli F, Giraudo MT, et al. Risk of second primary malignancies in women with breast cancer: results from the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2015;137:940–8. https://doi.org/10.1002/ijc.29462.
Schottenfeld D. In: Schottenfeld D, Fraumeni JF, editors. Principles and Applications of Cancer Prevention. Cancer Epidemiology and Prevention. Oxford: University Press; 1996. p. 1404.
Spratt JS, Hoag MG. Incidence of multiple primary cancers per man-year of follow up: 20-year review from the Ellis Fischel state Cancer hospital. Ann Surg. 1966;164:775–84. PMID: 5923101. https://doi.org/10.1097/00000658-196611000-00001.
Vogt A, Schmid S, Heinimann K, et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open. 2017;2(2):e000172. Published 2017 May 2. https://doi.org/10.1136/esmoopen-2017-000172.

Wells M, King E. Patient adherence to swallowing exercises in head and neck cancer. Curr Opin Otolaryngol Head Neck Surg. 2017;25(3):175–81. https://doi.org/10.1097/MOO.0000000000000356.

Williamson CW, Paravati A, Ghassemi M, Lethert K, Hua P, Hartman P, Sanghvi P. Five simultaneous primary tumors in a single patient: a case report and review of the literature. Case Rep Oncol. 2015;8:432–8. https://doi.org/10.1159/000440799.

Wood ME, Vogel V, Ng A, Foxhall L, Goodwin P, Travis LB. Second malignant neoplasms: assessment and strategies for risk reduction. J Clin Oncol. 2012;30(30):3734–45. https://doi.org/10.1200/JCO.2012.41.8681.

Xiong Z, Yang L, Deng G, Huang X, Li X, Xie X, et al. Patterns of occurrence and outcomes of contralateral breast cancer: analysis of SEER data. J Clin Med. 2018;7:pii: E133. https://doi.org/10.3390/jcm7060133.

Xu LL, Gu KS. Clinical retrospective analysis of cases with multiple primary malignant neoplasms. Genet Mol Res. 2014;13(4):9271–84. https://doi.org/10.4238/2014.March.12.19.

Yamamoto S, Yoshimura K, Ri S, Fujita S, Akasu T, Moriya Y. The risk of multiple primary malignancies with colorectal carcinoma. Dis Colon Rectum. 2006;49(Suppl 10):S30–6. https://doi.org/10.1007/s10350-006-0600-8.

Yun HR, Yi LJ, Cho YK, et al. Double primary malignancy in colorectal cancer patients: MSI is the useful marker for predicting double primary tumors. Int J Color Dis. 2009;24:369–75.

Zhai C, Cai Y, Lou F, Liu Z, Xie J, Zhou X, Zhanggui W, Fang Y, Pan H, Han W. Multiple primary malignant tumors - a clinical analysis of 15,321 patients with malignancies at a single Center in China. J Cancer. 2018;9:2795–801. https://doi.org/10.7150/jca.25482.

Zheng G, Sundquist K, Sundquist J, Försti A, Hemminki A, Hemminki K. Rate differences between first and second primary cancers may outline immune dysfunction as a key risk factor. Cancer Med. 2020;9(21):8258–65. https://doi.org/10.1002/cam4.3454.

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