

TAILORED APPROACH FOR MULTIPLE PRIMARY NEOPLASMSShailley Arora Sehgal¹, Parul Gupta², Anil Kumar Dhull³, Vivek Kaushal⁴¹Senior Resident, Department of Radiation Oncology, Pt. B. D. Sharma PGIMS, Rohtak, Haryana.²Senior Resident, Department of Radiation Oncology, Pt. B. D. Sharma PGIMS, Rohtak, Haryana.³Senior Medical Officer, Department of Radiation Oncology, Pt. B. D. Sharma PGIMS, Rohtak, Haryana.⁴Head and Senior Professor, Department of Radiation Oncology, Pt. B. D. Sharma PGIMS, Rohtak, Haryana.**ABSTRACT****BACKGROUND**

Due to rarity and inadequate reporting, Multiple Primary Malignant Tumours (MPMTs) still create a perplexing situation in our clinics. However, they are on an increasing trend as result of better investigative work up and treatment modalities leading to prolonged survival. Database maintenance is must to report them. We are hereby reporting a case series to add to the limited literature available and help define investigational and treatment strategy.

MATERIALS AND METHODS

Database of our institute from year 2012 to 2018 was searched for patients with MPMTs and they were categorized in metachronous and synchronous malignant tumours. We also studied the various parameters simultaneously, pertaining to their clinical presentation, work up, performance status, management and outcome.

RESULTS

17 were found to have multiple malignancies out of 15,922 patients. In them 7-patients had synchronous primary malignancies and 10-patients have single primary malignancy at presentation and developed subsequent second malignancies over a period of 4-months to 11-years. Maximum number of first malignancies was of the head and neck region followed by breast.

CONCLUSION

Getting a MPMT diagnosed is a challenge for both patient and treating clinician. Prognosis should not be considered poor in such patients per se but early and meticulous work up and diagnosis is prerequisite for radical treatment. This case series will help in providing insight into the management of such patients, however a tailored approach based on the experience of clinician, patients' performance status and available resources is must.

KEYWORDS

Multiple, Primary, Double Malignancies.

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BACKGROUND

The term 'multiple primary malignancies' was first introduced by Billroth in 1889.¹ They are 'pondered as multiple' if arising in different sites or are of a different assembly of histology and are neither an extension, nor a recurrence or metastasis.² They must be differentiated from multifocal or multicentric tumours. They can be synchronous or metachronous, however, there is no universally accepted categorization for these. The Surveillance Epidemiology and End Results (SEER) database recommends using a 2-month period to distinguish between synchronous and metachronous multiple primaries. International Agency for Research on Cancer (IARC) suggests the registration of

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synchronous tumours diagnosed in an interval of less than 6-months and metachronous if more than 6-months.³

Lifestyle, genetic, hormonal and environmental factors are the key players in causation of these malignancies. Incidence varies between 2.4% and 8%, up to 17% within 20-years of follow-up.⁴⁻⁷ Incidence has increased due to improved screening programs, diagnostic and treatment modalities leading to improved diagnosis and survival advantage.⁸

MATERIALS AND METHODS

Single institution retrospective study conducted on 17-patients with histopathologically proved diagnosis of double malignancies presented in our institute from the year 2012 to 2018. Various parameters pertaining to their clinical presentation, diagnostic work-up, management and outcome were studied. We have used SEER categorization to differentiate between synchronous and metachronous malignancies.

RESULTS

Over a period of 6-years, we observed 17-patients having double malignancies and also found metachronous malignancies more common than synchronous. In our study,

7-patients presented with synchronous malignancies and remaining 10 were metachronous considering 2-month time interval as cut off. Patients were in the age group from 34 to

78-years (Figure 1). Mean age was 55-years. Metachronous malignancies were detected over a period of 4-months to 11-years.

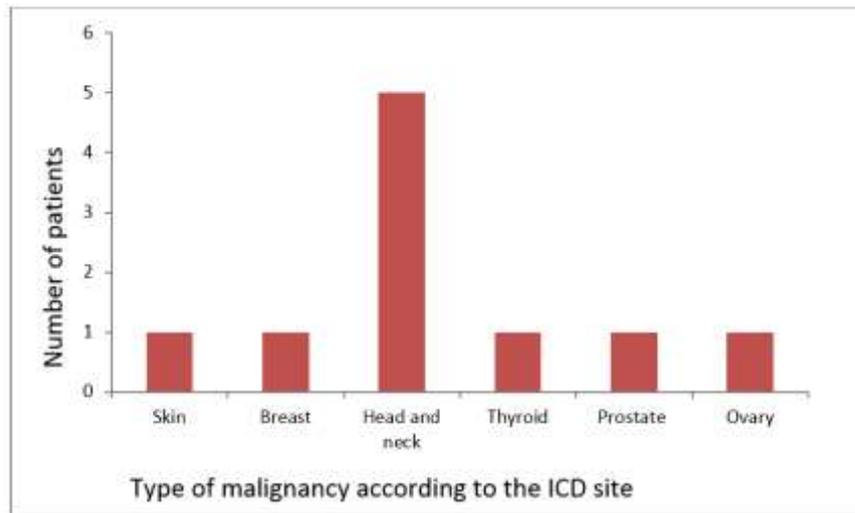


Figure 1. Type of Primary Malignancy Seen in Our Case Series with Number of Patients in Metachronous Malignancies Patients

Sl. No.	First Primary	Histopathology	Treatment	Syn/ Meta*	Second Primary	Treatment	Histopathology	Intent of Treatment
1.	Right foot	SCC [†]	Amputation of Right foot	M	Right tonsil	LFU [†]	SCC [†]	LFU [†]
2.	Right Breast	Infiltrating ductal carcinoma	Right MRM [§] + 6 cycles FEC regimen	M	Ovary	chemotherapy	Serous Cystadenocarcinoma	Radical
3.	Left breast	Infiltrating ductal carcinoma	Left MRM [§]	S	Thyroid	Total thyroidectomy	Micro medullary carcinoma	Palliative
4.	Left lung	Poorly differentiated carcinoma	Palliative EBRT**	S	Abdominal wall	Excision biopsy	Poorly differentiated carcinoma	Palliative
5.	Left tonsil	SCC [†]	Chemotherapy	S	Right lung	Chemotherapy & palliative RT	SCC [†]	Palliative
6.	Base of tongue	Poorly differentiated SCC [†]	NACT (6 cycles) followed by Radical EBRT**	M	Oesophagus	NACT (6 cycles) + concomitant CRT	SCC [†]	Radical
7.	Prostate	Adenocarcinoma	Bilateral orchiectomy followed by hormone therapy	M	Oesophagus	Palliative EBRT+ inj zoledronic acid + bicalutamide	Adenocarcinoma	Palliative
8.	Ovary	Papillary adenocarcinoma	TAH + BSO ⁺⁺ + omental & peritoneal biopsy followed by chemotherapy	M	Right breast	RT MRM [§] + chemotherapy + letrozole	Infiltrating ductal carcinoma	Radical
9.	Buccal mucosa	SCC [†]	Chemotherapy	S	Oesophagus	Palliative EBRT + gefitinib	SCC [†]	Palliative
10.	Thyroid	Papillary adenocarcinoma	Right lobectomy + complete thyroidectomy	M	Right breast	Right MRM [§] followed by chemotherapy followed by Radical EBRT**	Infiltrating ductal carcinoma	Radical
11.	Base of tongue	SCC [†]	NACT (2 cycles) followed by Radical EBRT**	M	Right submandibular gland	Cyclophosphamide	Acinar cell carcinoma	Palliative
12.	Palate	Mucoepidermoid ca	Concurrent chemoradiation	M	Cervix	Concurrent chemoradiation to pelvis	SCC [†]	Radical
13.	Base of tongue	SCC [†]	Concurrent chemoradiation	M	Lung	Chemotherapy	SCC [†]	Radical
14.	Colon	Adenocarcinoma	Chemotherapy	S	Lung	Chemotherapy	SCC [†]	Palliative

15.	Oral cavity	Squamous cell carcinoma	Chemotherapy	S	Larynx	Chemotherapy	SCC [†]	Radical
16.	Right Breast	Infiltrating ductal carcinoma	Right MRM [§]	S	Left Breast	Left MRM [§]	Infiltrating ductal carcinoma	Radical
17.	Sublingual gland	Adenoid cystic carcinoma	Excision	M	Lung	Palliative chemotherapy	Adenocarcinoma	Palliative

Table 1. Data of 17-Patients of Multiple Primary Malignancies with Histopathology and Treatment Modality

Abbreviations Used

*-synchronous/metachronous,

[†]-squamous cell carcinoma,

[‡]-Lost to follow up

[§]- Modified Radical Mastectomy,

^{||} -neoadjuvant chemotherapy,

** - External beam radiotherapy,

^{††}TAH + BSO- total abdominal hysterectomy and bilateral salpingo-oophorectomy.

ICD- International classification of disease.

Case 1- Presented as a case of carcinoma right tonsil after three years of previous history of amputation of right foot for squamous cell carcinoma, but he lost to follow up.

Case 2- Presented earlier with carcinoma right breast, undergone right modified radical mastectomy (MRM) followed by chemotherapy and was on regular follow up. After four years, she subsequently presented with carcinoma ovary and was treated with chemotherapy for the same.

Case 3- Presented with carcinoma thyroid and carcinoma left breast in the same year, underwent total thyroidectomy and left MRM but subsequently developed distant metastasis. In view of severe back pain, she was given palliative radiotherapy to the vertebral metastasis followed by hormone therapy.

Case 4- Presented with carcinoma lung and synchronous another primary in abdominal wall with distant metastasis with poor general condition i.e. Eastern Cooperative Oncology Group (ECOG) 4. He was treated with palliative intent.

Case 5- Presented with synchronous malignancies of carcinoma right tonsil and right lung with distant metastasis. In view of severe pain and locally advanced disease, he was given palliative radiotherapy to face and neck followed by chemotherapy.

Case 6- Presented with carcinoma lower thoracic oesophagus and history of carcinoma base of tongue which was treated radically with neoadjuvant chemotherapy followed by radiotherapy and she was on follow up since then. She was given concurrent chemoradiation for carcinoma oesophagus.

Case 7- Diagnosed with carcinoma prostate and later after 6 months developed carcinoma upper thoracic oesophagus but in view of poor general condition and ECOG 4, he was treated with palliative intent.

Case 8- Carcinoma ovary who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and omental biopsy but within a gap of 2-months, she was diagnosed with another primary of carcinoma right breast for which she underwent right MRM followed by chemotherapy and hormone therapy.

Case 9- Presented with synchronous primary of carcinoma buccal mucosa and cervical oesophagus. He was treated with chemotherapy followed by palliative radiotherapy to cervical oesophagus.

Case 10- Presented with carcinoma thyroid and underwent complete thyroidectomy followed which after 3-years she developed carcinoma right breast and underwent complete radical treatment for the same.

Case 11- Presented with carcinoma right submandibular gland with prior history of carcinoma base of tongue around 7 years back, for which she was treated with radical intent with neoadjuvant chemotherapy followed by radiotherapy. At the time of second primary, her general condition is too poor to tolerate any radical treatment, hence treated with palliative radiotherapy and metronomic chemotherapy.

Case 12- Presented with carcinoma hard palate and was treated with radical intent by concurrent chemoradiation. After 3-years, she presented with carcinoma cervix for which she received concurrent chemoradiation followed by brachytherapy.

Case 13- Presented with carcinoma lung as second primary malignancy and treated with chemotherapy. 3-years back she had been treated for carcinoma base of tongue with radical intent by concurrent chemoradiation and was disease free for carcinoma base of tongue.

Case 14- Presented with synchronous primaries of carcinoma colon and lung and was started on metronomic chemotherapy.

Case 15- Presented with synchronous primaries of carcinoma floor of mouth and larynx and was treated with radical intent with neoadjuvant chemotherapy followed by chemoradiation.

Case 16- Presented with lump in right breast and within a month developed another lump in left breast and diagnosed as bilateral triple negative breast cancer. She was treated with bilateral MRM followed by chemotherapy and radiotherapy and presently on regular follow up.

Case 17- Initially presented with adenoid cystic carcinoma sublingual gland and was treated with wide local excision followed by radical radiotherapy and was on follow up when after 11-years, she was diagnosed with carcinoma left lung. Her general condition was poor with ECOG 3, so was started on metronomic chemotherapy with palliative intent.

Maximum number of first malignancies were of the head and neck region followed by breast. Seven synchronous malignancies constitute Case 3 (carcinoma left breast and thyroid), Case 4 (carcinoma lung and abdominal wall skin), Case 5 (carcinoma tonsil and lung), Case 9 (carcinoma buccal mucosa and oesophagus), Case 14 (carcinoma colon and lung), Case 15 (carcinoma floor of the mouth and larynx) and Case 16 (bilateral breast). In metachronous malignancies, first primary were commonly seen in head and neck region and base of tongue being the most common ICD site. Over a period of 2-months to 11-years, second primary was developed and the most common second malignancy was oesophagus which was found in three cases. Among ten of these except three were treated by standard oncology guidelines. Only in 3 cases, primary was treated with palliative intent in view of age and poor performance status. However, 4 out of 7 synchronous malignancies were treated with palliative intent.

DISCUSSION

In the era of Empress Elizabeth, Billroth was the first man to describe multiple primary malignancies.¹ Since that time oncology have evolved much advances with better treatment modalities and increase survival, leading to increase in frequency of multiple malignancies but still treatment guidelines are yet to be defined. Cancer survivors have a 20% higher risk of new primary cancer in the same or different organs than the general population.⁴ Even the discrepancy in the definition is yet to resolve although Warren and Gates criteria help us to differentiate among the primary versus metastatic disease.⁹ For the diagnosis of multiple primary malignancies, they proposed that each tumour should present a definite picture of malignancy and should be histologically distinct and the possibility about the metastasis must be excluded.

The incidence and the frequency of multiple primaries have underscored mainly because of the loopholes in epidemiological studies and ranges between 2.4-17%.³ The divergences in the definition of metachronous and synchronous malignancies is main contributor for chaotic data. Still we are in penury about causation of multiple

primaries. Although we need to recognize the risk factors e.g. smoking, alcohol, hereditary cancer syndrome which are leading to multiple malignancies.¹⁰ Field cancerization is also a well-known risk factor that implies multifocal development process of cancer at various rates within the entire field in response to a carcinogen. Even if we remove entire tumour but due to this effect there is development of recurrence or second primary.

Due to rarity of multiple malignancies there is no standard protocol defined to cover them. The main concern of these malignancies is to find out a regimen which is beneficial for all the malignancies involved with least toxic effect, especially in synchronous malignancies. In our institute, we have followed the route of treatment modality that is beneficial in both the malignancies. Age, performance status and low immunity are other factors which are troublesome.

CONCLUSION

With prolonged survival and longer follow up, these malignancies are definitely going to increase in incidence. We need standardization of these malignancies in terms of definition, diagnostic modalities, treatment and uniformity throughout the world which will lead to proper notification and reporting of data.

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