http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v9i9.26

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Dual malignancies: A Clinico Pathological study in a Regional Cancer Centre of North East India

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Abstract
Introduction: *Incidence of multiple primaries is increasing on account of exposure to common carcinogen, inherent genetic predisposition and increasing surveillance of cancer survivors.*
Materials and Methods: *This was a retrospective study of 48 patients with histologically proven double malignancy attending OPD at RCC, Imphal Manipur during a period 2015 to 2019. We had categorized the malignancies as synchronous if the interval between the first and second malignancy was 6 months or less and metachronous if interval was more than 6 months. Cases in whom the possibility of the second malignancy being metastatic deposit from first primary which was not completely ruled out were excluded.*
Results: *Out of forty-eight dual malignancies twenty-nine were synchronous and nineteen were metachronous. Most common first cancer was head and neck cancer and most common second cancer was gastrointestinal cancers.*
Conclusion: *Thorough evaluation of patients presenting with a primary malignancy and long-term surveillance of cancer survivors should be emphasized in view of increasing incidence of synchronous and metachronous malignancy.*
Keywords: *Clinicopathological study, dual malignancy, metachronous, synchronous.*

Introduction

The occurrence of another unrelated primary malignant tumor in a different organ at the same time or one after another is termed dual malignancy.[1] It can be classified as synchronous if time interval of onset of second malignancy is less than 6 months and metachronous if more than 6 months.[2] The global burden of multiple primary is 14.1 million new cases and 8.2million cancer deaths as reported by IARC 2012 and estimated to rise upto 21.7 million new cases and 13 million deaths by 2030.[3] Frequency of dual malignancy is reported to be as high as 17%.[4] There is also probability of three or four primary tumor with frequency being 0.5% and 0.1% respectively.[5] There are various theories of occurrence of multiple primaries – cancer predisposition syndrome, continued exposure to the carcinogen, field cancerization and toxic effects of chemotherapy, radiotherapy or hormone therapy.[6] The rise in incidence of multiple primaries can also be attributed to advances in

treatment leading to improved survival outcome and also improved screening and surveillance of patients with cancer. Moreover, improved diagnostic tools like PET scan have led to increase diagnosis of indolent cancers which further increased incidence of multiple primary.[7] Till date, the data regarding multiple primaries is scanty. And in view of increasing incidence of multiple primaries we want to emphasize on the possibility of multiple primaries in a patient diagnosed with a primary malignancy and hence need of thorough screening and surveillance in a patient presenting with a primary malignancy.

Materials and Methods

The study was a retrospective study of 48 patients with histologically proven double malignancy attending OPD at RCC, Imphal Manipur during a period of 5 years. We have categorized the malignancies as synchronous if the interval between the first and second malignancy is 6 months or less and metachronous if interval is more than 6 months. We have not included those cases in whom the possibility of the 2nd malignancy being metastatic deposit from first primary is not completely ruled out. PET scan was not done in any of the cases.

Results

A total of forty-eight patients were studied, out of which twenty-eight were males and twenty-three were females. Age at presentation for primary malignancy ranged from 20 to 84 years and for second malignancy age ranged from 22 to 84 years with maximum being in 5th decade. Interval of development of second malignancy ranged from 1 year to a maximum of 11 years. Based on the interval twenty-nine were grouped as synchronous and nineteen were grouped as metachronous. Most common first primary malignancy was head and neck (13 cases; 27.08%) followed by lungs (7 cases; 14.58%), gastrointestinal tract (GIT) (7cases; 14.58%), ovary (4cases; 8.33%), non-Hodgkin's lymphoma (NHL) (3 cases; 6.25%), thyroid (3 cases; 6.25%), breast (3 cases; 6.25%), bladder (2 cases; 4.16%) and others (5 cases; 10.42%). And most common second primary was GIT (12 cases; 25%) followed by head and neck (9 cases18.75%), lungs (9 cases; 18.75%), thyroid (4 cases;8.33%), ovary (3 cases; 6.25%), endometrium (2 cases; 4.16%), vulva(2 cases; 4.16%), soft tissue sarcoma(2 cases; 4.16%) and others (3 cases 6.25%).Out of thirteen head and neck cases, ten patients had synchronous and three had metachronous malignancy. All the three patients who developed metachronous primary and four out of those who presented with synchronous malignancy, site of malignancy was at other subsites of aero digestive tract. One case of ca alveolus had synchronous hepatocellular carcinoma (HCC) which was found to be associated with hepatitis B virus infection. In another case of squamous cell carcinoma (SCC) of pinna, a synchronous primary was detected in vulva. Out of forty-eight patients, there were three cases of primary breast cancer. They developed metachronous malignancy at lungs, colon and esophagus. We had seven cases of carcinoma lungs out of which six had synchronous primaries. Two of the synchronous primaries were at stomach and others were at thyroid, floor of mouth, ovary, brain. Only one case developed metachronous malignancy in thyroid. There were three cases of thyroid malignancy. One had synchronous multiple myeloma and another carcinoma supraglottis. One developed metachronous malignancy of tonsil. There were three cases of primary esophagus. One developed metachronous malignancy in supraglottis and another at vulva. In another case a synchronous primary was detected at maxilla. There were four cases of primaryovarian malignancy, out of which two had synchronous primary at lung and one at rectum. One patient developed metachronous malignancy of endometrium. We had three cases of NHL out of which one developed metachronous malignancy at pyriform sinus (PFS) and another developed soft tissue sarcoma (STS). One patient had synchronous carcinoma lung.

Table 1: Summary of Dual Malignancy

Sl. no.	Age/ sex	1st primary and Histology	Type	Treatment	Time interval	2nd primary and histology	Treatment
1.	44/M	Base of tongue (SCC)	Synchronous	CT, CCRT	-	Ca lower1/3 esophagus (SCC)	CT, CCRT
2.	56/M	Esophagus upper third (SCC)	Metachronous	CT, RT	1 year	Vulva (SCC)	No
3.	53/F	Anorectum(Adenocarcinoma)	Synchronous	Surgery, CT	--	Ovary (Serous)	CT
4.	45/F	Gall Bladder (Adenocarcinoma)	Synchronous	CT	4 months	Ovary (Mucinous)	CT
5.	30/F	Germ Cell Tumor Ovary	Synchronous	No	---	Lung (Adenocarcinoma)	No
6.	65/F	Lung (SCC)	Synchronous	CT	---	Floor of mouth (SCC)	CT
7.	40/F	Ovary (Adenocarcinoma)	Metachronous	Surgery	1 year	Endometrium (Adenocarcinoma)	CT
8.	70/M	Lung (Anaplastic)	Synchronous	----	----	Stomach (Adenocarcinoma)	CT
9.	32/F	Ovary (Endodermal sinus)	Synchronous	CT	----	Rectum (Adenocarcinoma)	CT
10.	48/F	Breast (IDC)	Metachronous	Surgery	8 years	Lung (NSCLC)	RT
11.	54/M	Nasopharynx (SCC)	Synchronous	CT, RT	----	Hypopharynx (SCC)	CT, RT
12.	50/F	Larynx (SCC)	Metachronous	CTRT	----	NSCLC(SCC)	CT
13.	76/M	Thyroid (papillary)	Metachronous	Surgery, RT	9 years	Tonsil (SCC)	RT
14.	38/F	Breast (IDC)	Metachronous	Surgery,RT	11 years	Esophagus (SCC)	CCRT
15.	38/F	Colon (Adenocarcinoma)	Metachronous	CT	4 years	Endometrium (Adenocarcinoma)	Surgery, RT
16.	60/M	Lower Alveolus (SCC)	Synchronous	Surgery, RT	----	Hepatocelluar Carcinoma	CT
17.	58/M	Base of tongue (SCC)	Synchronous	CT	-----	Floor of mouth (mucoepidermoid)	CT
18.	54/F	Larynx(SCC)	Metachronous	NACT, CCRT	1 year	Lung (SCLC)	CT
19.	55/M	NHL (DLBCL)	Synchronous	CT, IFRT	-----	NPC (Undifferentiated)	SCC
20.	61/F	Lung (SCC)	Metachronous	NACT,CCRT	2 years	Thyroid (Follicular)	CT
21.	65/M	Bladder (TCC)	Synchronous	CCRT	-----	Anorectum (Adenocarcinoma)	CT
22.	57/M	Esophagus (SCC)	Synchronous	NACT, RT	-----	Maxilla (SCC)	CCRT
23.	65/M	Lung (SCLC)	Synchronous	CT	------	Thyroid (Papillary)	-
24.	46/M	Tonsil (SCC)	Metachronous	Surgery	1 year	Esophagus (SCC)	NACT,RT
25.	65/F	Lung (NSCLC)	Synchronous	CT	----	Ovary (Adenocarcinoma)	CT
26.	57/M	Maxilla (SCC)	Synchronous	NACT,CCRT	----	Esophagus (SCC)	NACT,CCRT
27.	59/M	Nasopharynx (Undifferentiated)	Synchronous	NACT,RT	-----	Thyroid (Papillary)	NACT,RT
28.	52/M	Renal Cell Ca	Synchronous	Surgery	----	GBM	RT
29.	70/F	Thyroid (Follicular)	Synchronous	Surgery	-----	Multiple Myeloma	CT
30.	45/M	Thyroid (Papillary)	Synchronous	Surgery	----	Supraglottis (SCC)	NACT,RT
31.	52/M	PFS (SCC)	Synchronous	NACT,RT	----	Bladder (TCC)	--------
32.	64/M	Prostate (Adenocarcinoma)	Metachronous	Surgery	1 year	Pancreas (Adenocarcinoma)	CT
33.	76/F	Glottis (SCC)	Synchronous	RT	----	Thyroid(Papillary)	RT
34.	53/M	Esophagus (SCC)	Metachronous	NACT, ICRT,CCRT	5 years	Supraglottis (SCC)	RT
35.	41/F	Breast (Colloid)	Metachronous	Surgery,CT,RT	11 years	Colon (Adenocarcinoma)	CT
36.	65/F	NHL (Thyroid)	Synchronous	Surgery, CT	----	Lung(SCLC)	CT
37.	76/M	Lung	Synchronous	CT	----	Glioma	-
38.	71/M	NHL (DLBCL)	Metachronous	CT	4 years	PFS (SCC)	NACT,CCRT
39.	42/F	Pancreas (Adenocarcinoma)	Synchronous	CT	-----	Breast (IDC)	CT,RT
40.	20/M	NHL (DLBCL)	Metachronous	CT	2 years	Rhabdomyosarcoma	Palliative RT
41.	21/M	CML	Metachronous	CT	7 years	Soft tissue sarcoma	--
42.	71/M	Epiglottis (SCC)	Synchronous	RT	-----	Esophagus (SCC)	RT
43.	65/M	Bladder (TCC)	Metachronous	TURBT, IV BCG	1 year	Lung (SCC)	----
44.	63/F	Vulva (SCC)	Metachronous	RT,CT	2 years	Lung (Adenocarcinoma)	CT
45.	58/F	Ovary (Serous)	Synchronous	-----	-----	Lung (Adenocarcinoma)	CT
46.	84/M	Lung (SCC)	Synchronous	Supportive care	----	Ca Stomach (adenocarcinoma)	Supportive care
47.	55/F	Cervix (SCC)	Metachronous	Surgery, CCRT	5 years	Lung (SCLC)	CT
48.	62/F	SCC Pinna	Synchronous	Excision & grafting	----	Ca Vulva (SCC)	NACT,WLE + LN dissection, RT

SCC: squamous cell carcinoma; CT: chemotherapy; CCRT: concurrent chemoradiotherapy; RT: radiotherapy; IDC: invasive ductal carcinoma; NSCLC: non-small cell lung cancer; NACT: neoadjuvant chemotherapy; DLBCL: diffuse large B cell lymphoma; IFRT: involved field radiotherapy; NPC: nasopharyngeal carcinoma; TCC: transitional cell carcinoma; SCLC: small cell lung cancer; GBM: glioblastoma multiforme; CML: chronic myeloid leukemia; TURBT: transurethral resection of bladder tumor; WLE: wide local excision; LN: lymph node

Discussion

Advances in diagnosis and treatment has led to increase detection rate of indolent cancers and better survival outcome of patients with cancer. However, patient survive with increased risk of a second malignancy as a result of patient's genetic predisposition, personal habits like smoking, chewing tobacco and alcohol consumption and environmental causes. Moreover, treatment of primary malignancy with chemotherapy and radiation therapy is also known to induce chromosomal aberration responsible for tumorigenesis.[8,9] Patients with head and neck cancer is reported to have around 36% life time cumulative risk of developing second primary malignancy over 20 years.[10] The most common site of second primary being in other subsites of aero digestive tract. In our study too, patient with head and neck cancer had the highest incidence of second primary. And 7 case (53.85%) had second primary at other sub sites of head and neck. This can be attributed to exposure to common carcinogens like tobacco both smoking and smokeless form and alcohol. In literature, patients with breast cancer are reported to develop a second primary mostly in opposite breast, endometrium and ovary. And development of endometrial carcinoma was related to hormone therapy. But, in our study, sites of second primary were lungs, colon and esophagus. All the three were metachronous which may probably be due to late effects of treatment.

Conclusion

More emphasis on primary disease leads to increase likelihood of missing co-incidental primary malignancy. The possibility of a 2nd or 3rd malignancy should always be considered for patients with primary cancer. Since diagnosis of multiple primaries has impact on treatment decision as both primaries has to be covered by treatment without adding much toxicity or undesired interactions, thorough evaluation of patient should be emphasized. Patients and their care giver should be warned of the possibility of development of a second malignancy and hence the need for modification of high-risk behavior and long-term surveillance.

Acknowledgement

We would like to express our sincere gratitude to the Head of the Department of Radiation Oncology, RIMS, Imphal, Manipur, respected faculties and above all our patients for their kind cooperation and participation in the study.

Conflicts of interest: No conflicts of interest

References

1. Xu LL, Gu KS. Clinical retrospective analysis of cases with multiple primary malignant neoplasms. Genet Mol Res.2014;13:9271-84.
2. Moertel CG. Multiple primary malignant neoplasms: Historical perspectives. Cancer.1977;40:1786-92.
3. Ferlay J, Steliarova- Foucher E, Lortet-TieulentJ, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe:estimates for 40 countries in 2012. Eur J Cancer.2013;49:1374-403.
4. 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;2:e000172.doi:10.1136/esmoopen-2017-000172.
5. Campbell LV Jr., Watne AL. Multiple primary malignant neoplasms. Arch Surg.1969;99:401-5.
6. Ng AK, Kenney LB, Gilbert ES, Travis LB. Secondary malignancies across age spectrum. Semin Radiat Oncol. 2010;20:67-78.
7. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2.

International RET mutation consortium analysis. JAMA.1996;276:1575-9.

8. Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M,et al. Second neoplasms in survivors of childhood Cancer: Findings from the Childhood Cancer Survivor Study Cohort. J Clin Oncol.2009;27:2356-62.
9. Jeremic B, Shibamoto Y, Acimovic L, Nikolic N, Dagovit A, Aleksandrovic J, et al. Second cancers occurring in patients with early non small cell lung cancer treated with chest radiotherapy alone. J Clin Oncol.2001;19:1056-63.
10. Morris LG, Sikora AG, Hayes RB, Patel SG, Ganly I. Anatomic sites at elevated risk of second primary cancer after an index head and neck cancer. Canc Causes contr.2011;22:671-9.