A RETROSPECTIVE STUDY ON SECOND PRIMARY MALIGNANCIES INCIDENCE IN REGIONAL CANCER INSTITUTE

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ABSTRACT: BACKGROUND: The cancer patients have a life time risk from developing another de novo malignancy, depending on various risk factors like inherited, iatrogenic, infective, and environmental. The malignancy patients could survive longer due to settling treatment modalities, and then likely develop a new metachronous malignancy. The purpose of this study was to investigate clinically useful information for effective screening for synchronous and metachronous second primary cancers and to identify a potential surveillance protocol. **METHODS:** The study has conducted over a 5 years period from 2008 to 2013. A hospital based retrospective gathering of data among the patients that have diagnosed with second malignancy. All patients that have diagnosed with a histological (HPE) second cancer as per warren and gates criteria have included. Various details like age, sex, site, stage, diagnosis of tumor, and synchronous or metachronous of tumor treatment have recorded. **RESULTS:** Out of 52 cases 10(19.23%) were synchronous and 42(80.7%) were metachronous. 35 (67.30%) were females and 17(32.69%) were males. the most common site of primary tumor was head and neck (16 cases 30.76%) followed by breast cancers (11 case 21.15%), among the second cancer most common site was gynecological cancer (12 cases 23.07%) and gastrointestinal tract (11 cases 21.15%) as for as the primary cancer is concerned 34 patients (65.38%) were diagnosed in advanced stages (stage III and IV). The stage of the second tumors was also advanced 32 cases (61.53%) being in stage III, IV. Squamous cell carcinoma represented the most frequent histo pathological type in primary cancer 28 cases (53.84%) and also in the second tumor. 19 cases (36.53%). **CONCLUSION:** The incidence of double primary malignancy is not very rare, could occur synchronously or metachronously. After the recent diagnostic and staging modalities as well as progress in the management of common cancer, the detection of second primary malignancy has increased. Each patient must be informed about the risk of developing secondary malignancies after the first treatment and about the importance of reporting any new symptom which might occur. Careful monitoring ensures an early detection for secondary tumors, and, subsequently, an appropriate management.

KEYWORDS: Second Primary cancers, Synchronous, Metachronous, Multiple primary malignancies.

INTRODUCTION: The incidence of double primary malignancy is not very rare ⁽¹⁻⁴⁾ one of the earliest statistical analyses of double primary malignancy has carried out by burgher in 1934. Who derived an equation for the probability of death from cancer during a specified period of a age with a coincidental second malignancy.⁽⁵⁾

Double primary malignancies (Multiple primary) can be divided in to two categories depending on the interval between tumor diagnosis.⁽⁶⁾ Synchronous malignancies were second tumors have accruing either simultaneously or within 6 months after the first malignancy while Metachronous malignancies were second cancers that have developed after 6 month or even more

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than that from the first malignancy. The criteria have used for the diagnosis of double primary malignancies, have primarily given by warren and gates (table 1) and refined later.⁽⁷⁻¹⁰⁾

1.	Histological confirmation of malignancy in both the index and secondary 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 five years.
3.	Probability of one being the metastasis of the other must be excluded.

Table 1: Warren and Gates Criteria for Diagnosis of Double primary malignancies

The aim of this study was the report of our observation about increasing incidence of multiple primary malignancies.

There is no enough information about a causal relationship between a risk factor and each of the two cancers. May be the presence of a dysplastic changes in the second primary site strongly has suggested a new primary.

Improving of survival rate for patients with malignancies are due to either by early diagnosis screening tools and also with the recently improved more sophisticated diagnostic tools such as Positron Emission Tomography (PET) and tumor markers,⁽¹¹⁻¹²⁾ that amount of picking up indolent tumors have increased contributing further to the obvious increase of multiple primary malignancies (MPM) incidence. With recent treatment modalities, cancer patients have survived much longer to be able to develop Metachronous new primary which might partly related to the treatment of early malignancy.

MATERIALS AND METHODS: This Retrospective study analyzed data from record sheets of patients admitted between Jan. 2008 and Dec. 2014 at this institute of oncology.

The inclusion criteria of patients in this study were the presence of at least two neoplastic locations that confirmed by histopathological examination with distinct histopathology in the two locations.

The time interval to differentiate between synchronous or Metachronous has taken as 6 months as reported by several authors.^(6,10,13)

All patients that have diagnosed with a histological proven second malignancy as per warren and gates criteria have included.

EXCLUDED PATIENTS: Without a clear histological confirmation of each tumor.

The patients whom the second tumor has suspected to be a metastasis of the first location (Suspected brain, bone, liver, lung, metastasis were excluded from the study).

METHODS: Various details like patient age, sex, time and date of first tumor diagnosis, site and stage of the tumor, histopathology grade and treatment regimen have been recorded. Second tumor details like site of origin stage, synchronous or Metachronous, diagnosis method histopathology grade of the tumor treatment modalities have been recorded.

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RESULTS: More than 5 years period, between January 2008 and December 2013, total 46, 608 Cancer patients have registered in our institute of oncology and regional cancer center. Out of which 52 cases (0.11%) of multiple primary malignancies have observed.

Six months (180 days) was considered to be the maximum period for the occurrence of synchronous tumors. Out of 52 cases 10(19.23%) were synchronous and 42(80.7%) were Metachronous. The occurrence intervals of Metachronous tumor have ranged from 1 year to 16 years with an average of 3.01 years for the entire group.

Out of 52 patients 35 (67.30%) were females and 17(32.69%) were males. The average age of the entire group was 50years (ranges 30 to 70 year).

No. of patient	Age	Sex	Date	Diagnosis	Histopathology	Hpe grade	Stage	Treatment	Time gap
1	50	F	22-07-10	Ca cervix	Squamouscell	II	IIIB	Rt+ct	5months
2	60	F	04-07-13	Caesophagus	Squamouscell	III	III	Rt	5months
3	56	M	15-03-11	Ca thyrioid	Papillary carcinoma	II	II	Surgery	2months
4	62	F	16-12-13	Ca endometrium	Adenocarcinoma	II	III	Surgery+rt	1months
5	60	M	14-12-13	Ca gejunction	Adenocarcinoma	II	III	Rt+ct	2months
6	49	M	03-08-11	Ca rectum	Adenocarcinoma	II	III	Surgery+rt+ct	2months
7	62	M	26-04-12	Ca prostate	Adenocarcinoma	II	III	Surgery+rt	2months
8	55	M	03-08-10	Ca thyroid	Papillary carcinoma	II	II	Surgery	6months
9	49	F	26-09-11	Ca stomach	Adenocarcinoma	II	III	Surgery+rt	3months
10	40	F	03-11-12	Ca ovary	Adenocarcinoma	II	III	Surgery+ct	4months

Table 2: summary of synchronous malignancies

No. of patient	Age	Sex	Date	Diagnosis	Histopathology	Hpe grade	Stage	Treatment	Time gap
1	65	F	29-04-13	ca cervix	squamouscell	II	IIB	Radiotherapy+ chemo therapy	1
2	70	F	28-07-13	ca valut	squamouscell	III	II	radiotherapy	1.8
3	65	F	10-11-13	ca soft palate	squamouscell	II	II	radiotherapy	1.5
4	45	F	30-03-13	ca lung(rt)	squamouscell	III	III	chemotherapy	2.5
5	50	M	03-11-13	ca alvelous	squamouscell	III	II	radiotherapy	5.6
6	45	F	22-04-12	ca breast(rt)	Idcc	III	PT2N1MO	surgery+chemo therapy+radiotherapy	4.1
7	30	M	15-01-13	ca hyphophrynx	squamouscell	III	III	radiotherapy	1.7
8	45	F	24-12-12	ca vulva	squamouscell	III	II	surgery	1.5
9	50	F	14-06-12	soft tissu sarcoma	Fhs	III	II	surgery+chemo therapy+radiotherapy	4.2
10	38	F	14-09-13	soft tissu sarcoma	ewingsarcoma	III	III	surgery+chemo therapy+radiotherapy	3.1
11	30	F	27-08-13	ca urrinary bladder	tcc	II	II	surgery+chemo therapy+radiotherapy	5.4

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12	62	F	17-10-13	ca breast(lt)	idcc	II	III	surgery+chemo therapy+radiotherapy	1.1
13	37	F	12-12-13	ca check(rt)	squamouscell	II	I	surgery	5.2
14	48	M	14-08-12	ca tongue	squamouscell	III	III	radiotherapy+chemo therapy	2.1
15	55	F	21-01-13	ca breast(rt)	idcc	II	IV	radiotherapy+chemo therapy	3.4
16	48	F	14-03-13	ca lung(lt)	adenocarcinoma	II	III	radiotherapy+ chemotherapy	2.5
17	50	F	25-04-12	ca hyphoparynx	squamouscell	II	III	radiotherapy+chemo therapy	3.2
18	52	M	15-06-13	ca colan	adenocarcinoma	II	III	surgery+chemotherapy	3.3
19	48	M	18-07-13	ca bladder	tcc	II	III	surgery+chemo therapy+radiotherapy	2.1
20	52	F	18-04-13	ca pancreas	poorly diff carcinoma	II	II	surgery+chemotherapy	2.1
21	52	F	13-12-11	sarcoma thigh (rt)	leiomyosarcoma	I	I	surgery	1.6
22	50	F	16-04-12	liver	hcc	II	III	chemotherapy	1.7
23	44	F	06-06-13	urinary bladder	tcc	II	III	surgery+radiotherapy	2.1
24	50	M	25-06-13	ca kidney(lt)	clearcell	III	III	surgery+chemotherapy	3.5
25	55	M	02-04-13	ca oesophogus	squamouscell	II	II	radiotherapy+chemo therapy	1.1
26	55	M	26-05-12	ca urinarybladder	tcc	II	III	surgery+chemotherapy	2.1
27	45	F	30-01-12	ca pancries	adenocarcinoma	III	II	surgery+chemotherapy	1.1
28	39	F	05-10-11	cacarvix	squamouscell	II	III	radiotherapy+chemo therapy	1.4
29	55	F	15-10-12	ca vulva	squamouscell	III	II	surgery+radiotherapy	3.8
30	60	M	26-08-12	ca lung(rt)	adenocarcinoma	II	III	radiotherapy+chemo therapy	3.5
31	50	F	06-02-13	ca cervix	squamouscell	III	II	radiotherapy+chemo therapy	1.7
32	45	F	25-02-13	ca oesophagus	squamouscell	II	II	radiotherapy+chemo therapy	2
33	50	M	25-09-13	colan	nhl	III	III	surgery+radiotherapy	2.3
34	49	F	28-09-13	thyiroid	papillary carcinoma	II	III	surgery	3.6
35	45	F	25-12-13	ca lung(lt)	adenocarcinoma	III	III	radiotherapy+chemo therapy	2.9
36	50	M	15-12-13	ca urinary bladder	tcc	III	II	surgery+radiotherapy	1.6
37	60	F	02-10-13	ca vulva	squamouscell	III	III	surgery+radiotherapy	10
38	55	F	09-01-10	ca colan	adenocarcinoma	III	II	surgery+chemotherapy	3.2
39	60	M	02-08-13	ca parotid	adenocarcinoma	II	II	surgery+radiotherapy	2.5
40	55	F	05-09-13	ca ovary	adenocarcinoma	II	III	surgery+chemotherapy	9
41	40	F	02-06-12	ca ovary	adenocarcinoma	II	III	surgery+chemo therapy	3.4
42	50	F	04-02-13	ca brest	idcc	II	III	surgery+chemo therapy+radiotherapy	5

Table 3: Summary of Metachronous Malignancies.

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The most common site of primary tumor was head and neck (16 cases 30.76%) followed by breast cancers (11 case 21.15%), cervical cancer (9 cases 17.30%), gastrointestinal tract (8 cases 15.38%) and then other tumors (8 cases 15.38%).

Fig. 1

Among the second cancer most common site was gynecological cancer (12 cases 23.07%) and gastrointestinal tract (11 cases 21.15%) followed by head and neck (7 cases 13.46%) Urology (7 case 13.45%) lung (4 case 7.69%) breast (4 cases 7.69%) and other cancer (14 cases 26.92%).

Fig. 2

Out of the total number of cases with double location 24 tumors (46.15%) have belonged to the gynecological cancers out of which 12 (23.07%) have represented first locations and (12.23.07%) were second locations. Both locations belonged to the gynecological cancers in 6 patients (11.53%) in 4 cases (7.6%) we have observed association of cervix, breast and 3 cases (5.7%) breast, soft tissue sarcoma.

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As for as the primary cancer concerned 34 patients (65. 38%) were diagnosed in advanced stages (stage III and IV). and second tumors also presented in advanced stage, 32 cases (61. 53%) being in stage III, IV.

Squamous cell carcinoma represented the most frequent histopathological type in primary cancer 28 cases (53.84%) type in primary cancers 28 cases (53.84%) and also in the second tumor. 19 cases (36.53%) other various types were found in the second tumors as compared with the first group.

Fig. 3

Fig. 4

DISCUSSION: Among the total cancer patients who were admitted in our Institute of oncology & Regional Cancer center between 2008 and 2013, female to male ratio was 2: 1, while the analysis of patients with double neoplastic locations have revealed a 2: 1 female-male ratio; that has reversed. Most of the patients belonged to the 4th to 5th decades (39 of 52;75%). Most diagnosed tumors were metachronous in comparison to synchronous (42 compared with 10).

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With regard to tumor stage and treatment, there was no difference between first primary and second primary malignancies of same anatomical sites. However, primary and secondary tumors have tended to be in an advanced stage and the treatment, depending on the location, involved surgery, radiotherapy and chemotherapy. The advanced stage of secondary malignancies was unusual, in comparison to other studies. It should explained either by the low compliance of patients to follow-up, or by their tendency to neglect symptoms. The results have underscored the importance of a good communication between patients and doctors, whereby the doctors should give warnings regarding the risk of developing secondary malignancies after the primary treatment, and then also about the occurrence of any new symptoms.

Although the responsible mechanisms for the multiple primary cancers appearance have not been fully explained, but among the most frequent factors that have involved, we could mention: the genetic susceptibility, the immune system of patients, and the intensive exposure to carcinogens including chemo- and/or radiotherapy used in the treatment of tumors.

A secondary malignancy could be defined as a new cancer that has occurred as a result of previous treatment with radiation or chemotherapy. Depending on the schedule of treatment, the most common secondary cancers were skin cancer, breast cancer, acute leukemia, colorectal, lung and stomach cancer, the risk of second cancer developing have been 10% at 20 years and 26% at 30 years after the Hodgkin disease treatment,⁽¹⁴⁾ and 3.8% at 10 years versus 7% at 15 years for patients receiving a doxorubicin-based regimen for breast cancer.⁽¹⁵⁾

Genetic susceptibility, and also the carcinogenic effects of radio/chemotherapy have been largely proposed for the secondary malignancies development. First, it has known, that people with a cancer family would inherit genetic cancer susceptibility as a risk factor, and then moreover, patients whom have treated, and the survivors of earlier cancers with genetic susceptibility, all have an increased risk of multiple primary malignancies. In addition, the treatment used for the first malignancy has resulted in damage to specific regions of DNA with chromosome rearrangement or loss, responsible for tumorigenesis.⁽¹⁶⁾ The new technologies available could analyze various genetic changes such as punctiform mutations, loss of heterozygosity or genetic instability. Microsatellite instability (MSI) has been noticed that occur more frequently in cases of multiple primary malignancies than in sporadic cancers.⁽¹⁷⁾ The percentage of MSI tumors was similar in patients with synchronous or colorectal metachronous tumors. The mechanisms such as trigger microsatellite instability have differed in mentioned two categories.

Patients with Head and Neck Squamous Cell Cancer (HNSCC) have known for 36% cumulative life time risk of developing second primary malignancy over 20 years.⁽¹⁸⁾ This has attributed to field carcinogenesis related to exposure to common risk factors like tobacco chewing, smoking and alcohol consumption.^(10,18) Also In our study head and neck cancers were the most common group to harbor of develops a new primary (10 of 33 cases) . Among the head and neck cancer survivors, the cases whom have developed lung cancer were 50% (5 of 10 cases). As a part of preventive strategy, the patients particularly with HNSCC should be encouraged to stop use of alcohol and tobacco in any form, adopt healthy diet and exercise regularly. At present there is no evidence to recommend use of chemo preventive agents such as beta carotenoids and antioxidants in the prevention of second primary malignancies.⁽¹⁹⁾

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The possibility of multiple primary malignancies existence should always be considered during pretreatment evaluation. Screening procedures are especially useful for the early detection of associated tumors, preferably before clinical manifestations occurrence.

There are some evidences that screening would improve outcomes among patients who might develop second malignancies, although the data were limited. The optimal screening modalities and strategies for reducing mortality from second malignancies remained to be defined for most tumor sites.⁽²⁰⁾

The early diagnosis of secondary malignancies should not be neglected in patients treated for a primary malignancy, especially when the long clinical period before the diagnosis of subsequent tumors has been taken for management. With careful monitoring, secondary tumors could be detected earlier, and, with appropriate intervention, might be better managed, without compromising survival.

Our data could guide oncologists towards a closer follow-up strategy in the management of patients treated for common tumors.

CONCLUSION: In conclusion, second primary malignancy was not uncommon, could occur synchronously or Metachronous. After the recent diagnostic and staging modalities as well as progress in the management of common cancer, the detection of second primary malignancy has increased. Our study result could be explained by the low compliance to follow-up and underscores the importance of communication between patients and medical care team. Each patient must be informed about the risk of developing secondary malignancies after the first treatment and about the importance of reporting any new symptom which might occur. Careful monitoring ensures an early detection for secondary tumors, and, subsequently, an appropriate management.

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