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Second Primary Neoplasms: A Clinico-Pathological Analysis from a Sub Himalayan Cancer Centre in India

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Abstract

Background: There is a lifetime risk of developing another de novo malignancy in diagnosed cancer patients. Detection of new primary has increased due to advances in both diagnostic and treatment modalities. This article aims to analyze the pattern of presentation of second primary neoplasm and to review the relevant literature.

Materials and Methods: We analyzed patients presenting with histologically proven synchronous or metachronous second primaries from July 2011 to July 2016. Warren and Gate's criteria have been used to designate a case as second primary neoplasm. Various details such as age at diagnosis, sex, whether synchronous or metachronous, site, stage, histopathology, treatment were collected.

Results: Over a period of 5 years total 40 cases were observed, out of which 13 were synchronous (33%) and 27 (67%) were metachronous. The median age at the diagnosis of primary malignancy was 65.5 years (range 27-84). Out of the 40 patients, 28 (70%) were males and 12 (30%) were females. The most common site of primary tumor was head and neck and genito-urinary, 11 cases each. Among the second malignancy most common site was gastrointestinal tract (11 cases), followed by genitourinary (10 cases) and lung (9 cases).

Conclusion: The likelihood of diagnosis of second malignancy has increased with the advent of newer diagnostic modalities as well as increased compliance to follow up and progress in the management. Appearance of new signs and symptoms should raise a suspicion and early detection of the disease leads to appropriate management.

Keywords: Neoplasms; Malignancy; Cancer; Treatment

Introduction

According to the reports of National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results Program in 2003 the number of patients with second primary neoplasms is growing rapidly, with independent malignancies comprising of 16% (or 1 in 6) incident cancers [1]. The entity of second primary neoplasms (SPN) is not very rare and is a serious and lethal event in cancer survivors [2-4].

Improved survival either due to early diagnosis or to advances in cancer treatment allow patients to survive long enough to develop subsequent second primary, whereas the development of more reliable and sophisticated diagnostic tools such as PET made possible the detection of synchronous occult neoplasms, for a long time overlooked contributing further to the apparent increase in incidence of second primary neoplasms [5-6].

A SPN can arise either synchronously or metachronously depending on the interval between tumor diagnosis [7]. Synchronous neoplasms are second tumors occurring simultaneously or within 6 months after the first malignancy while metachronous are secondary cancers that developed after more than 6 months from the first malignancy.

Second cancers can reflect the late sequelae of cytotoxic treatment as well as the effect of lifestyle factors, environmental exposures, host factors, genetic predisposition, and gene environment interactions [8]. The criteria used for the diagnosis of second primary neoplasms were first given by Warren and Gates and refined later [9-11].

Data regarding the occurrence and outcome of such second primary neoplasms particularly from the Indian subcontinent are limited. Hence we came up with this retrospective compilation of the pattern of occurrence of SPNs after an index primary and review of the relevant literature.

Materials and Methods

A retrospective analysis was done for the patients presenting to cancer research institute, Dehradun with histologically proven synchronous or metachronous second neoplasms over a period of 5 years from July 2011 to July 2016. It is the only tertiary cancer centre of this sub Himalayan region. The profile of patient visiting the centre is approximately 85% hilly population and remaining from neighbouring plains.

Electronic database of hospital was searched for the patient details and paper records were retrieved from medical record department. Institutional ethical committee clearance was taken beforehand.

Warren and Gate's criteria as described below have been used to designate a case as second primary neoplasm. The time interval to differentiate between synchronous or metachronous neoplasms was taken as 6 months.

Warren and Gates criteria for diagnosis of multiple primary malignancies

- Histological confirmation of malignancy in both the index and secondary tumors.
- Each must be geographically separate and distinct and the lesions should be separated by normal mucosa.
- Probability of one being the metastasis of the other must be excluded.

The inclusion criteria of patients in the study were the presence of two malignant locations, confirmed by histopathological examination. When the second cancer was also of same histology and developed in the same region as the index cancer, it was considered only if the time interval was more than 5 years without any evidence of metastatic disease. We excluded patients without a clear histopathological confirmation of each tumor and also the patients in whom the second tumor was suspected to be a metastasis of the first location.

Various details such as age at diagnosis of index tumor, sex, whether synchronous or metachronous, site of origin index tumour, histopathology, treatment; data regarding the second primary (site, time of diagnosis, stage, histopathology, treatment), metastases, date of the last follow-up and death, if applicable were collected.

Statistical analysis used

A database was created using above mentioned information and basic statistical tools have been used for analyzing the data.

Results

Over a period of 5 years total 40 cases of second primary neoplasms were observed out of which 13 were synchronous (33%) and 27 (67%) were metachronous. The median age at the diagnosis of primary malignancy was 65.5 years (range 27-84 years). The most common age group was between 61-70 years (Figure 1).

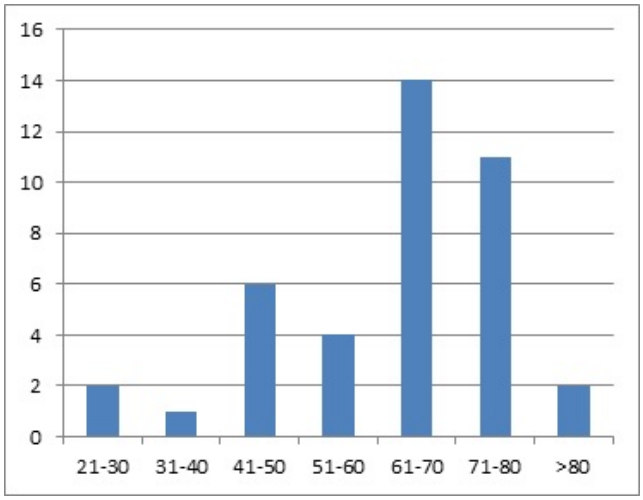

Figure 1: Age distribution in primary malignancy.

Out of the 40 patients, 28 (70%) were males and 12 (30%) were females. Over 92% of cases occurred in patients older than 40 years. Most of the patients were diagnosed in advanced stage with seven patients presenting with a metastatic disease. Bone was the most common site of metastatic disease in 5 patients followed by lung and liver 1 case each.

The most common site of primary tumor was head and neck and genito- urinary (11 cases each), followed by gynecological cancer (7 cases), gastrointestinal tract (3 cases), breast and sarcoma (2 cases each) (Figure 2). The age range for the second primary was 28-88 years. Among the second malignancy most common site was gastrointestinal tract (11 cases), followed by genitourinary (10 cases), lung (9 cases) head & neck 6 cases (Figure 3).

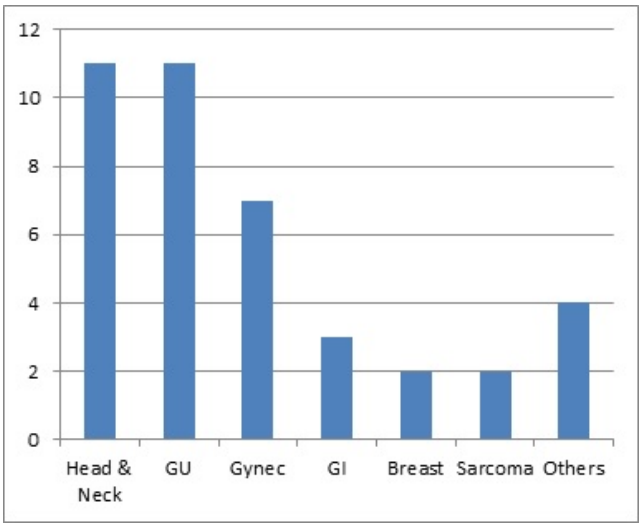

Figure 2: Site distribution of the primary malignancy.

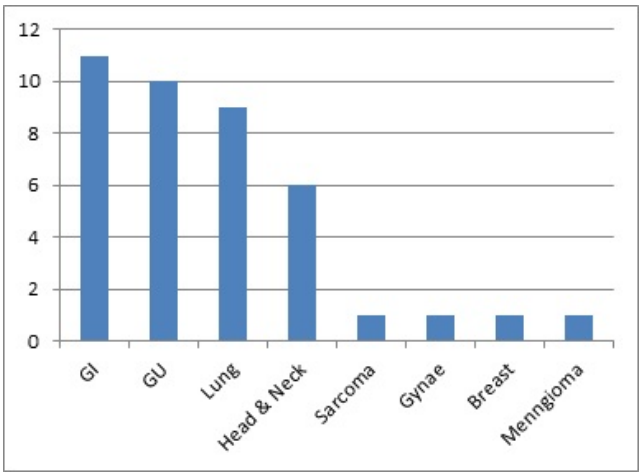

Figure 3: Site distribution of the second malignancy.

Out of the total number of cases with double location, 17 patients (42.5%) belonged to the genitourinary system, out of which 7(17.5%) represented first locations and 6(15%) were second locations. Both locations belonged to the genitourinary system in 4 patients (10%).

The time interval between appearance of primary and secondary in the metachronous group varied from 8 months to 22 years.

The treatment modality in all the patients was determined primarily on the basis of performance status. Among synchronous neoplasms four patients underwent surgery for both the primary and secondary tumor followed by adjuvant treatment if any depending on the final histopathology report. Two patients refused and one defaulted for treatment. Three patients received palliative treatment in view of metastatic disease.

Among metachronous neoplasms, for primary tumor 25 patients were treated with radical intent (14 with surgery, 10 with EBRT, 1 with chemotherapy). For secondary malignancy 16 patients were treated with radical intent, 11 with EBRT and 5 with surgery followed by adjuvant treatment if required. 11 patients were treated by palliative intent either due to old age or poor performance status.

Tables 1 and 2 present the characteristics of patients with synchronous and metachronous neoplasms.

Age /Sex	Primary site	Histopathology	Treatment	Secondary site	Histopathology	Treatment
50/F*	Breast	IDC	Surgery, Hormonal therapy	Kidney	RCC(clear cell)	Surgery,T.sunitinib
74/M	Prostate	Adenocarcinoma	Default	Urinary bladder	Urothelial carcinoma	Default
72/M	Alveolus	SCC	refused	Anorectum	Adenocarcinoma	Refused
65/M	Penis	SCC	Surgery ,EBRT	Lung	SCC	Default
81/M	Prostate	Adenocarcinoma	Hormonal t/t	Lung	SCC	Chemotherapy
76/M	Prostate	Adenocarcinoma	Hormonal t/t	Soft palate	SCC	EBRT
61/F*	Endometrium	Adenocarcinoma	Surgery	Breast	IDC	Surgery
38/F	Thigh	Liposarcoma	Surgery ,EBRT	Colon	Neuroendocrine carcinoma	Surgery
65/M	Leukemia	CLL	Refused	Urinary bladder	Urothelial carcinoma	Refused
54/M	Kidney	RCC(clear cell)	Surgery	Urinary bladder	Urothelial carcinoma	TURBT, EBRT
70/M	Urinary bladder	Urothelial carcinoma	Chemotherapy	Kidney	RCC	Refused
56/F	Ovary	Adenocarcinoma	Surgery, chemotherapy	Stomach	Gist	Surgery
62/M	Lung	SCC	EBRT	Urinary bladder	Urothelial carcinoma	Chemotherapy

*Surgery for both primary and secondary carried out in same sitting. SCC: Squamous cell carcinoma, IDC: Infiltrating duct carcinoma, RCC: Renal cell carcinoma

Table 1: Summary of synchronous neoplasm (N=13).

Age /Sex	Primary Site	Histopathology	Treatment	Secondary Site	Histopathology	Time Interval	Treatment
27/M	Tongue	SCC	Surgery, EBRT	Vallecula	SCC	9 Months	Chemotherapy
50/F	Colon	Adenocarcinoma	Surgery, Chemotherapy	Base Of Tongue	SCC	8 Months	EBRT
64/F	Endometrium	Adenocarcinoma	Surgery	Colon	Adenocarcinoma	4.5 Years	Surgery, Chemotherapy
48/M	Lip	SCC	Rt(Brachytherapy)	Tonsil	SCC	1 Year	Chemoradiation
74/M	Sweat Gland	Carcinoma	Surgery	Urinary Bladder	Urothelial carcinoma	1 Year	EBRT
73/M	Larynx	SCC	Chemoradiation	Lung	Adenocarcinoma	11 Years	EBRT
72/F	Cervix	SCC	EBRT, Brachytherapy	Ovary	Adenocarcinoma	2 Years	Surgery, Chemotherapy
84/M	Prostate	Adenocarcinoma	Hormonal Therapy	Urinary Bladder	Urothelial carcinoma	7.5 Years	EBRT
43/M	Urinary Bladder	Urothelial Carcinoma	Surgery, Chemoradiation	Lung	Small cell cacinoma	3 Years	Chemoradiation, Chemotherapy

68/M	Arm	Spindle Cell Sarcoma	Surgery, EBRT	Prostate	Adenocarcinoma	4 Years	EBRT, Hormonal Therapy
62/M	Tongue	SCC	Chemoradiation	Buccal Mucosa	SCC	2 Years	Surgery, EBRT
78/M	Urinary Bladder	Urothelial Carcinoma	EBRT	Stomach	Adenocarcinoma	6.5 Years	EBRT
60/M	Tongue	SCC	Surgery	Esophagus	SCC	1.5 Years	Chemoradiation
73/M	Larynx	SCC	Surgery	Urinary Bladder	Urothelial Carcinoma	3 Years	Chemotherapy
70/M	Prostate	Adenocarcinoma	Hormonal Therapy	Stomach	Adenocarcinoma	1 Year	Chemotherapy
75/M	Lymphoma	DLBCL	Chemotherapy	Forearm	Synovial Sarcoma	2.5 Years	Surgery, EBRT
57/M	Vallecula	SCC	EBRT	Hypopharynx	SCC	5 Years	EBRT, Chemotherapy
66/F	Ovary	Leiomyosarcoma	Surgery, EBRT	Spinal Cord	Meningioma	3 .5 Years	Surgery, EBRT
50/F	Colon	Adenocarcinoma	Surgery, Chemotherapy	Liver	HCC	22 Years	T.Sorafenib
43/F	Ovary	Adenocarcinoma	Surgery, Chemotherapy	Lung	Adenocarcinoma	5 Years	Chemotherapy, EBRT
68/M	Hypopharynx	SCC	Chemoradiation	Lung	Small Cell Cacinoma	2.5 Years	Chemtherapy
64/M	Buccal Mucosa	SCC	Surgery, EBRT	Esophagus	SCC	3 Years	Chemoradiation
75/F	Breast	IDC	Surgery, EBRT, Chemotherapy	Esophagus	SCC	7 Years	EBRT
30/F	Cervix	SCC	EBRT, Brachytherapy	Lung	Small Cell Cacinoma	9 Months	Chemotherapy
66/M	Cups	SCC	Surgery, EBRT	Lung	SCC	1.5 Years	EBRT, Chemotherapy
80/M	Esophagus	SCC	Chemoradiation	Lung	Adenocarcinoma	1.5 Years	EBRT
66/M	Urinary Bladder	Urothelial Carcinoma	EBRT	Esophagus	SCC	4 Years	Chemoradiation. Chemotherapy
SCC: Squamous cell carcinoma, EBRT: External beam radiotherapy							

Table 2: Summary of metachronous neoplasm (N=27).

Discussion

The analysis of patients with second primary neoplasms between July 2011 to July 2016 presenting to cancer research institute revealed a male-female ratio (2.3:1) with a male predominance which may be due to gender bias seeking the treatment. Most patients belonged to the 7th to 8th age decades. In our study less than 8% patients were younger than 40 years.

Most tumors were diagnosed in the advanced stage, more often metachronous than synchronous (27 compared with 13). Most common site for primary malignancy was head and neck and genitourinary, and for second malignancy was gastrointestinal tract, all accounting for 28% of cases, respectively. Most of the synchronously diagnosed second tumors in our study were incidentally diagnosed. They were detected during the staging evaluation of the primary tumor. Only 4 patients had symptoms attributable to their second primary.

Etiology of occurrence of SPM is multifactorial and has not been fully explained. Travis et al recently grouped second primary into three major categories according to predominant etiologic influences (i.e. syndromic, those due to shared etiologic factors and treatment related), emphasizing the nonexclusivity of these groups [12]. Various syndromes associated with the DNA microsatellite instability such as Lynch I and II syndromes are associated with the development of multiple primary tumors in different organs. Mutation in multiple tumor suppressor genes such as p16, p53, PTEN and Rb gene are linked to development of tumors in breast, soft tissue, esophagus and other sites.

Patients with Head and Neck Squamous Cell Cancer (HNSCC) are known to have 36% cumulative life time risk of developing SPM over 20 years. This is attributed to field carcinogenesis related to exposure to common risk factors like tobacco smoking and alcohol consumption [11]. Another factor to be considered particularly among

metachronous neoplasms is prior intensive exposure to carcinogens including chemotherapy and radiotherapy used in treatment.

The treatment related SPNs may arise in the setting of use of certain chemotherapeutic agents such as alkylating agents, topoisomerase II inhibitors or therapeutic irradiation of the index primary [13-14]. Such treatment induced tumors after radiation and chemotherapy manifest usually after a latent period of 15-20 years [15].

Hence a close clinical follow up is recommended for long periods to detect SPN at the earliest and a strong clinical suspicion and thorough evaluation is needed to differentiate between metastatic disease and a SPN.

According to the literature, the prognosis of patients with SPN could be determined independently in function of the stage of each cancer. The treatment of choice, depending on the tumor location, can involve curative surgical resection of each cancer, radiotherapy and chemotherapy [16-18].

In case of synchronous neoplasms, each tumor should be evaluated and staged as independent tumors. They should be treated aggressively with the curative intent depending on the stage of each disease to achieve maximum therapeutic benefit. If surgery is needed for both the tumors, it can be done in a single stage in majority of the cases with low rates of morbidity and mortality [19]. In our study we have done safely TAH + BSO with modified radical mastectomy and modified radical mastectomy with radical nephrectomy as single stage procedures.

Treatment of the primary tumor should be kept in mind while planning the management of second neoplasm. Prior radiation fields, doses, radiation techniques, chemotherapy should be taken into account. Appropriate dose constraints have to be assigned to the previously irradiated organs. Previously, re irradiation was associated with high rates of treatment related toxicity, but emerging data support the safety and feasibility of conformal delivery techniques in cases of re irradiation.

Further, it could be a difficult task to educate patient and his relatives regarding the occurrence of two primary tumors. A considerable proportion of these patients, on detection of the second primary refuse any further treatment due to psychological distress, socioeconomic and other reasons.

The possibility that SPNs exist must always be considered during pretreatment evaluation. Screening procedures are especially useful for the early detection of associated tumors, preferably before clinical manifestations occur. As observed in our series, 13 patients had synchronous neoplasm and most patients have been diagnosed in advanced stages. The optimal screening modalities and strategies to reduce mortality from second malignancies remain to be defined for most tumor sites [20].

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 SPNs [21,22].

This study is a unique presentation of dual malignancy in sub Himalayan population. Discrete studies from various centers of country are present but not from this region. However, study has limitation of being short time frame of 5 years. The number of cases noted were also less to conclude for a particular pattern or time gap in diagnosis. An elaborated and preferably multicentric data pooling with a large sample size is being advocated to draw a conclusive result.

In conclusion, SPN is not uncommon and can occur synchronously or metachronously. With the advent of newer diagnostic and staging modalities as well as progress in the management, the detection of second primary neoplasms has increased.

Each patient must be counseled about the risk of developing secondary malignancies after the treatment of primary neoplasm. Modifiable risk factors should be addressed with preventive strategies. A regular follow up with careful monitoring and early detection of the disease leads to appropriate management.

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