Synchronous Dual Malignancies: An Observational Study of Clinicopathological Features Done at a Regional Cancer Centre

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Summary

A cancer patient survives for a longer period with current treatment protocols, compared to previously. As a result, patients have a higher chance of developing multiple primary malignancies. The chance of multiple primary malignancies is also exacerbated by common risk factors like addiction, genetic predisposition or environmental risk factors. The aim of this study is to observe the trend of synchronous malignancies, study their management and to review the relevant literature. A retrospective study of data collected prospectively of patients who presented with synchronous dual malignancies. The study was conducted over a period of one year, from January 2019 to December 2019, of patients with histologically proven second primary malignancy which satisfies Warren and Gates criteria. International Agency for Research on cancer (IARC) guidelines have been followed to define synchronous malignancies. Clinico-radiological, pathological and treatment related data were studied. Most common index primary site was the head and neck region followed by breast. Most common method of detection was Computed Tomography of thorax followed by clinical examination. Most common combination of malignancies was head and neck index primary with lung followed by bilateral breast primary.

Conclusions: The clinician needs to be alert to the possibility of a synchronous second malignancy and work up to rule out the same accordingly. Synchronous malignancies can be treated together, according to underlying disease biology and stage, and performance status, after discussion in multidisciplinary tumor board.

Keywords: Synchronous malignancy, second primary malignancy, dual malignancy

Introduction

The incidence of dual malignancies varies greatly among different sites of primary cancers. The incidence is higher for cancers with a genetic or hormonal basis or having a longer survival rate, such as breast or oral cavity.[1]The various epidemiological studies cite an incidence of dual malignancy between 2-17%. [2] The earliest study of dual malignancies was done by Bugher et al in 1934, who derived the equation for the probability of death from cancer during a given age with a coincidental second malignancy.[3]

With improved treatment options, leading to longer cancer survivorship, and more accurate diagnostic techniques, the rate of detection of second primary malignancies has increased[4]. With this, oncologists have to evolve their techniques in an attempt to address the multiple malignancies. Warren and Gates have given the criteria to define second primary malignancy, which was refined subsequently. (Table 1) [5,6]

Materials and Methods

A retrospective analysis of prospectively collected data was done, for patients presenting with pathologically proven double malignancy in a synchronous setting, over the period of one year from January 2019 to December 2019. Warren and Gates criteria [5,6] (Table 1) have been used to define second primary malignancy. International Agency for Research on Cancer (IARC) guidelines have been followed to define synchronous malignancies, which state that two malignancies are to be registered as synchronous if they occur within 6 months of each other.[2,7] The same has been previously used in multiple studies.[8-11] The patients with proven metastasis, or those presenting more than six months after index malignancy were excluded from the study. Also, patients with any one malignancy being hematological malignancy were excluded. Each patient was analyzed for type of malignancies, the time interval between detection of both malignancies, the method of diagnosis, the stage of each malignancy at presentation, histology of each malignancy and the treatment protocol given. Disease free survival and overall survival are not commented upon in the present study owing to the short duration of follow up.

The malignancy with which the patient presented first was considered as the index primary, and the malignancy which was detected subsequently during clinico-radiological evaluation, as the second primary malignancy.

Results

Over a period of one year, 17 cases of synchronous malignancies were included in the study,

Table 1: Warren and Gates Criteria

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 metastasis of the other must be excluded

Table 2: Details of Cases of Synchronous Dual Malignancies

No	Age/ Sex	Index Primary site	Addiction history	Stage of Index primary site	Second primary site	Stage of second primary	Method of detection of second primary	Time interval between detection of both primaries	Treatment	Status
1	67/M	SCC tongue	Tobacco chewing	pT2N1	Adenoca Left lung	pT1bN0	CT Thorax	Simultaneous	Hemiglossectomy+ MND + Left apicoposterior segmentectomy Adjuvant RT to head and neck region	Alive
2	65/M	SCC tongue	Tobacco chewing	pT2N0	SCC Right lung	cT3N2	CT Thorax	1 month	Hemiglossectomy+ MND + Palliative chemotherapy to lung	Alive
3	73/M	SCC Buccal mucosa	Nil	pT2N0	Adenoca Right lung	pT1b	CT Thorax	Simultaneous	Composite resection + Flap + Right upper lobectomy + Adjuvant RT to head and neck region	Alive
4	59/M	SCC Nasopharynx	Nil	cT2N2	Adenoca Prostate	cT2N1	Clinical examination	Simultaneous	Nasopharynx- Curative + RT + Chemotherapy to Nasopharynx + Hormonal therapy to prostate	Expired
5	41/F	SCC maxilla	Nil	pT4aN3b	SCC Tonsillo lingual sulcus	pT1	Intraoperative finding	Intra-operative finding	WLE of maxilla+ WLE of Tonsillo lingual sulcus growth +MND II Pt deferred adjuvant treatment.	Alive
6	54/M	Mucoepi-dermoid carcinoma Buccal mucosa	Tobacco chewing	pT2N1	Carcinoid Right Lung	pT1a	CT Thorax	4 months	Composite resection + Flap + Adjuvant RT to head and neck region + Right middle lobectomy	Alive
7	52/F	IDC breast Right	Nil	ypT4bN2	Papillary carcinoma thyroid	pT1a	Clinically	Simultaneous	Chemoport insertion + NACT + MRM + Total thyroidectomy +Post-operative RT to chest wall+ Hormonal therapy	Alive
8	60/F	IDC breast Left	Nil	pT2N0	Papillary ca breast Right	pT1N0	Mammography	Simultaneous	Bilateral Mastectomy+ Bilateral SLNB + Chemoport insertion + Adjuvant chemotherapy	Alive
9	39/F	IDC left breast	Nil	ypT4bN1	IDC breast right	ypT2N0	Mammography	Simultaneous	Chemoport insertion + NACT + Bilateral MRM + Adjuvant RT to right chest wall + Adjuvant chemotherapy	Alive
10	60/F	IDC breast Right	Nil	pT2N1	Tubular carcinoma breast Left	pT1N0	Mammography	Simultaneous	Right MRM + Left Mastectomy + Left SLNB + Chemoport insertion + Adjuvant chemotherapy + Adjuvant RT to right chest wall	Alive
11	48/F	IDC left breast	Nil	ypT3N3	Serous papillary ovarian	Stage Ib	USG Abdomen	Simultaneous	NACT + Debulking surgery for carcinoma ovary + left MRM +	Alive

No	Age/ Sex	Index Primary site	Addiction history	Stage of Index primary site	Second primary site	Stage of second primary	Method of detection of second primary	Time interval between detection of both primaries	Treatment	Status
					carcinoma				Adjuvant chemotherapy + Adjuvant RT to left chest wall + Hormonal therapy	
12	55/F	Serous papillary adenoca-ovary	Nil	Stage IIIA2	Squamous cell carcinoma cervix	Stage IB	Clinical examination	Simultaneous	Staging laparotomy + Adjuvant RT + Adjuvant chemotherapy	Alive
13	58/F	Serous papillary adenoca ovary	Nil	Stage IC1	ILC breast Left	pT2N0	Clinical examination	Simultaneous	Staging laparotomy + left Mastectomy + SLNB+Adjuvant chemotherapy	Alive
14	65/M	SCC lung Right	Cigarette smoker	ypT2bN0	Adenoca esophagus	ypT2N1	CT Thorax	Simultaneous	NACT + Right Middle+lower lobectomy + 3 stage esophagectomy	Expired
15	80/M	SCC lung Left	Cigarette smoker,	cT2N2	SCC esophagus	not feasible	CT Thorax	Simultaneous	Patient refused treatment	Lost to follow up
16	62/F	Clear cell RCC	Nil	pT2N0	Adenoca endometrium	stage IB	Contrast Enhanced CT(A+P)	Simultaneous	Left radical nephrectomy + Staging laparotomy For endometrial cancer	Alive
17	63/M	Adenocarcinoma esophagus	Nil	cT4Nx	Conventional RCC	cT2N0	CT Thorax	Simultaneous	Inoperable disease	Expired

Abbreviations used in table
1. SCC- Squamous Cell Carcinoma
2. CT scan- Computed Tomography
3. MND- Modified Neck Dissection
4. RT- Radiotherapy
5. WLE- Wide Local Excision
6. IDC- Invasive Ductal Carcinoma
7. ILC- Invasive Lobular Carcinoma
8. NACT- Neoadjuvant Chemotherapy
9. MRM- Modified Radical mastectomy
10. TAH- Total Abdominal Hysterectomy
11. BSO- Bilateral Salpingo-oopherectomy
12. RCC- Renal Cell Carcinoma

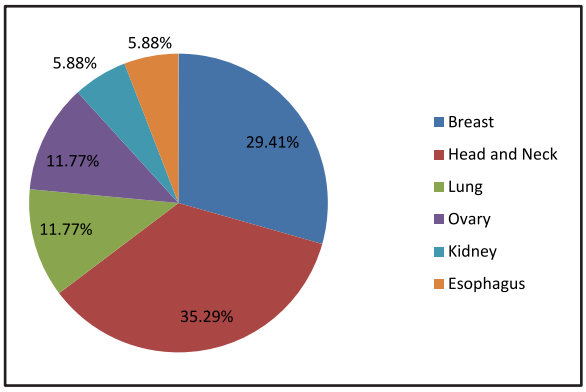

Figure 1: Distribution of Index primary

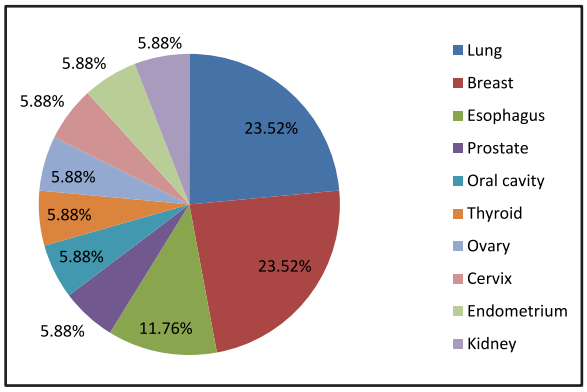

Figure 2: Distribution of second primary malignancy

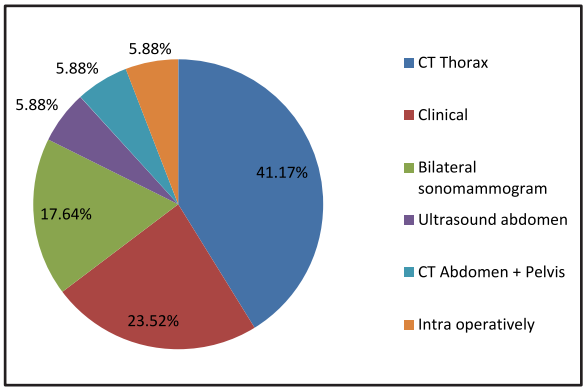

Figure 3: Methods of detection of second primary malignancy

according to the inclusion and exclusion criteria. (Table 2). The age range was 39-80 years, with median age of 60 years. There were eight male (47.05%) and nine female (53.94%) patients. In the region-wise distribution of index malignancy (Figure 1), the highest cases were of head and neck malignancy (6/17, 35.29%) followed by carcinoma of breast (5/17,29.41%). The region wise distribution of second primary malignancy (Figure 2), the most common sites were lung and breast (23.5%). Out of 17 patients in our study, five patients had significant history of addiction to tobacco chewing (three) and cigarette smoking (two). All three patients with

history of tobacco chewing had index primary in oral cavity. Two patients who had history of cigarette smoking had lung as index primary and esophagus as second primary.

Different diagnostic techniques were used to detect the second primary malignancy (Figure 3). In seven cases out of 17 (41.17%), the second primary malignancy was detected by Computerized Tomography (CT scan) of Thorax. In one case out of these seven, with index primary in tongue, CT scan of thorax was not done as a part of initial work up, but done after one month, when patient complained of persistent cough and hemoptysis, and the second primary malignancy in lung was detected. Four cases out of 17 (23.52%) were detected by clinical examination. Other methods of detection included bilateral sonomammogram (N=3), Ultrasound of abdomen (N=1) and CT of Abdomen and Pelvis (N=1). One case was detected intraoperatively.

Among the head and neck cancers, the site of second malignancy was lung in four cases out of six (66.67%). In one patient, with synchronous malignancy of maxilla and Tonsillolingual (TL) sulcus, the latter was detected intraoperatively. The lesion over TL sulcus was not seen on pre-operative magnetic resonance imaging, and missed on clinical examination due to the small size and posterior location. Endoscopic examination under general anesthesia was not done in the patient. One patient with index malignancy of nasopharynx had a second primary malignancy of prostate, detected clinically by per rectal examination while evaluating urological symptoms of the patient.

There were five patients with an index primary malignancy involving the breast (29.41%). Out of these five, three patients had the malignancy in bilateral breasts. Both lesions had different histopathology and receptor status in all three cases. One patient had synchronous breast and ovary cancer, with index primary in the breast. One patient had a second primary malignancy in thyroid. No patient had a significant family history. Genetic testing could not be done in the patients due to logistic issues.

Two patients had index primary malignancy in the ovary, and a second primary in breast and cervix, respectively. Two patients had synchronous malignancy in lung and esophagus, with lung as index primary. One patient had index primary in kidney, and a second primary in endometrium. One patient had index primary in esophagus and second primary in kidney.

In 14 patients out of 17 (82.35%), both primaries were detected simultaneously by clinical examination or radiological investigations during work up of index primary. Two cases were detected after the treatment of the index primary, within six months. One case was detected intra-operatively. Most common combination of malignancies was head and neck with Lung, with four cases out of 17 (23.52%).

Out of 17 patients, 10 underwent upfront surgery for both malignancies (58.82%). Three patients underwent neoadjuvant chemotherapy followed by definitive therapy. In one patient, the index primary was Carcinoma of tongue, which underwent upfront surgery, and the second malignancy in lung was detected after one month, and it was managed by palliative chemotherapy. One patient underwent non operative management, with curative radiation given to nasopharynx and hormonal therapy given for carcinoma of prostate since patient was not fit for surgery. One patient was inoperable and given palliative chemotherapy. One patient refused treatment. Out of 17 patients, three patients expired in the follow up (17.64%).

Discussion

With increasing survival of cancer patients, and increased prevalence of various addictions such as tobacco, or alcohol, incidence of multiple primary malignancies is increasing. Improved detection techniques such as Positron Emission Tomography with CT fusion (PET CT) or improved CT/MRI scans are also picking up multiple primary malignancies at an increasing rate. Genetic factors play an important role in synchronous malignancies as these patients are at an increased risk of cancer in multiple organs. Environmental factors such as exposure to asbestos, or long term radon exposure can also contribute to the same.[2]

The risk of development of second primary malignancy differs from site to site. In head and neck cancers, where there is 36% cumulative risk of a second primary malignancy over 20 years [11]. The oft-quoted reason for the same is the field cancerization theory [12] by Slaughter, where he observes, "From the foregoing observations it would appear that epidermoid carcinoma of the oral stratified squamous epithelium originates by a process of field cancerization, in which an area of epithelium has been preconditioned by an as-yet-unknown carcinogenic agent." In a study by Krishnatreya et al,[13] the incidence of a synchronous dual malignancy in a head and neck cancer is found to be 1.33%. The most common site of the second primary is lung with a 20 year cumulative risk of 13%. It was reflected in our study too, where four cases of synchronous malignancy involving head and neck region had lung as second primary. In a study by Morris et al [11], which was a population based study of head and neck cancer patient registered in SEER database, the risk of a second primary malignancy differed by subsite. It was highest in squamous cell carcinoma of hypopharynx, followed by oropharynx, oral cavity and larynx. The study also showed an

increase in incidence of esophageal cancer. Our study correlated with the above findings, as the highest incidence of synchronous dual malignancies is seen with head and neck cancer, with six cases out of 17 demonstrating index primary malignancy in head and neck region (35.29%).

As elucidated in a study by Warnakulasuriya et al that addiction plays a strong role in causation of head and neck cancer, particularly tobacco.[14] It was further supported by Muwonge et al[15] who studied the role of tobacco and alcohol in causation of oral cancer. Our study reflects these findings, as five patients were found to have a significant history of tobacco chewing and cigarette smoking. Notably, all three patients with tobacco addiction had a primary lesion in head and neck region and both the patients with cigarette smoking had synchronous malignancy in lung and esophagus.

Keeping the increased incidence of synchronous malignancy in head and neck cancers, the initial evaluation of a head and neck cancer should include a through clinical examination, supported by an office procedure like nasal endoscopy or an indirect laryngoscopy, especially in smokers. These patients have an increased rate of detection of "silent" second primary malignancies, and curative therapy can be attempted in a single sitting in such patients.[16] In a study by Loh et al, [17] CT Thorax was shown to have a detection rate of 10.8% of synchronous lung malignancy or pulmonary metastasis in head and neck malignancies. CT thorax should be added to imaging of head and neck. When the primary lesion is locally advanced, PET-CT can be considered instead of CT thorax, if logistically feasible to detect synchronous second primary as well as distant metastases. If detected early, these cases can be taken up for upfront surgery, if operable, or can be planned for neoadjuvant treatment followed by definitive surgery, or definitive chemo-radiation, based on patient's performance status and associated co morbidities, after planning the same in a multi-disciplinary tumor board discussion.

Another common site for synchronous malignancy is the breast. Owing to multiple genetic factors, such as BRCA or p53 gene mutation, or common risk factors, there is a high prevalence of synchronous breast cancers. In a study by Londero et al, [18] the prevalence of synchronous breast cancers was 3%. The meta-analysis in the study demonstrated a lower overall survival (OS) for patients of synchronous and metachronous breast cancers, compared to unilateral breast cancers. Synchronous breast and ovary cancers need to be differentiated from breast cancers metastasizing to ovary. A metastatic breast cancer is positive on immunohistochemistry for gross cystic disease fluid protein 15 (GCDFP15), Mammaglobin and GATA 3 and negative to PAX 8, CA125 and WT1. A serous cystadenocarcinoma is positive for PAX 8, CA 125 and WT1, and negative for Mammaglobin, GATA 3 and GCDFP15.[19] Present study demonstrated two patients with synchronous malignancy of breast and ovaries, and three patients with synchronous breast cancers. Due to common risk factors between breast and ovarian cancer, and increased incidence of bilateral breast cancers, screening should always be done to rule out these synchronous malignancies. A simple and cost-effective method for screening of ovarian malignancies in a carcinoma breast is an ultrasound of abdomen. Similarly, bilateral sonomammogram should be a standard practice in a carcinoma ovary patient, to detect synchronous breast cancer. For other sites, the incidence of genitourinary synchronous tumors has been reported to be 2.8-6.3% in different studies [20-22] In our study, we reported two patients having synchronous malignancies with genitourinary cancers, both diagnosed incidentally.

Management of such patients with synchronous malignancies requires discussion in a multidisciplinary tumor board, taking into consideration the underlying disease biology. If two malignancies are present with different disease biology, the more aggressive disease is managed first. As in present series, one patient had a index malignancy involving breast, which was locally advanced, and a second primary in the form of a papillary carcinoma of thyroid. Neoadjuvant chemotherapy of breast was given first, keeping in mind the aggressive biology of breast carcinoma relative to thyroid malignancy, and later both sites were operated simultaneously. If a preoperative chemotherapy is planned, it should be planned to be effective against both the malignancies. Before planning treatment, the underlying co-morbidities and performance status also needs to be taken care of, especially when dealing with a major organ resection, such as esophagectomy. As shown in the current study, dual malignancies with esophagus as one primary had a poor outcome (Table 2), and hence, a judicious approach needs to be taken for consideration of surgery in such cases.

Conclusion

With rising incidence of synchronous malignancies, it is important to diagnose them early. A through clinical examination is a must, especially in malignancies with a high incidence of second primary, such as oral cavity and breast. The radiological investigations are supplementary to clinical examination and should be ordered according to the site of index primary. For head and neck malignancies, we recommend a screening CT scan of thorax to rule out synchronous lung or esophageal malignancies. Similarly, for breast malignancies, we recommend

bilateral mammosonography and an ultrasound of abdomen in all. These methods are easily available, easy to interpret and are not as resource and cost-intensive as a PET-CT scan, which is limited by availability and cost.

The treatment decisions should be undertaken by a multidisciplinary tumor board in accordance with tumor biology, stage of the disease and patient's performance status. Aggressive and locally advanced primaries should be given priority for treatment. Chemotherapeutic agent, which is effective in both malignancies should be used if feasible, for neoadjuvant or adjuvant therapy.

Conflicts of interest: None
Work is attributed to: Department of Surgical Oncology

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