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Original Research

Multiple Primary Tumours, How Frequent we can Offer Curative Therapy?

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Background: Patients with Multiple-primary Malignancies are usually excluded from clinical trials. Clinical information re-distribution, associations, response to treatment and prognosis are scared. Collecting information will help us to expect the impact of prior therapies and to teach us how to best treat them. This study aims to report cases in our society and to see if we have a special predilection of certain Multiple-primary Malignancies in our region based on different geographic and environmental risk factors. Our retrospective study aims to collect these cases and follow their prognosis and treatment response as well as looking for any relation to cancer therapy.
Methods: A retrospective study included patients who have two or more histologically diverse primary malignancy, either as synchronous or metachronous malignancy. The study was conducted in King Abdullah Medical City, Saudi Arabia over 7 years period from 2012 to 2019. We collected all patient's clinicopathological information, treatment, and modalities.
Results: We collected 53 cases of multiple primary malignancies 26were synchronous (48%) and 27 were metachronous (52%). Out of 53 patients, 29 (60 %) were females and 14 (40 %) were males. The most common sites for synchronous are breast and endometrial cancer. Curative treatment could be offered in 19 patients (73%). For metachronous tumours, the most common primary tumour was breast cancer, while the most common second malignancy was colorectal cancer. Curative treatment could be offered in 15 patients (53%).
Conclusion: Multiple primary malignancies represent a small proportion of our cases, with no special predilection in our society. Multiple primary malignancies did not signify a poor prognosis; besides nonmetastatic cases showed a good response to therapy. We should not forget the possibility of a second primary tumour as these cases can be reasonably treated with curative intent.

Introduction

Multiple-primary cancers are defined as primary malignant tumours of different histological origins in a single patient. Recently, there has been an increase in the number of patients diagnosed with multiple-primary cancers; attributed to improved diagnostic techniques and prolonged life span of patients with malignancy. Now we are aware that most multiple primary cancers are double primary cancers [1][2][3].

The incidence of Multiple-Primary Malignancies has been common among cancer patients [4]. One of the earliest statistical analyses of Double-Primary Malignancies was carried out by Bugher in 1934, he derived an equation for the probability of death from cancer during a specified period of age with a coincidental Second Malignancy [5]. According to the definition used, the overall reported frequency of Multiple-Primary Cancers ranges from 2% to17% [6].

The criteria used for the diagnosis of Double-Primary malignancies has been primarily given by

Warren and Gates [7]. While, the two most commonly used definitions were provided by the SEER Program (Surveillance, Epidemiology, and End Results) and the IACR/IARC (International Association of Cancer Registries and International Agency for Research on Cancer) [8]. The SEER database considers single tumours at different sites in the same organ (e.g., colon) as multiple sites. The IACR/IARC rules are more limited; only one tumour is recorded for an organ, regardless of time, unless there are histologic differences. Additionally, The SEER database advocates the use of a 2-month period to distinguish between Synchronous and Metachronous Multiple- Primaries, whereas IARC recommends a 6-month period [9-10].

The theory regarding the origin of the majority of Multiple-Primary cancers is that they arise due to random chance, but different mechanisms have been suggested to be involved in Multiple-Primary Cancers, such as the family history, immunologic, genetic defects, exposure to carcinogens, radiation, chemotherapy, and field cancerization [11].

Germline mutations in mismatch repair genes can produce susceptibility to cancers of the colorectum, ovary, stomach, small bowel, upper uroepithelial tract, hepatobiliary tract, and brain. Li-Fraumeni syndrome (LFS), an autosomal- dominant disorder, features the occurrence of breast cancer in young women and of soft tissue sarcomas, osteosarcomas, brain tumours, acute leukaemia, and adrenocortical tumours in children and young adults [12]. Germline mutations in the p53 tumour suppressor gene (also known as TP53) have been identified in approximately one-half of LFS families in the literature [13] and cigarette smoking that affects the risk of several cancer types.

All the information about double malignancy came from case reports with very few centers reporting their experience and none from our region. We needed to collect our experience in treating those cases. Collecting information will aid us in expecting the impact of prior therapies and teach us how to best treat them.

This is a retrospective study with a single medical facility’s experience with Multiple-Primary cancer cases. This study aims to report cases of Double-Primary Malignancy in our society and see if we have a special predilection of certain Double-Primary cancers based on different geographic and environmental risk factors.

Materials and Methods

This was a retrospective observational study carried out at King Abdullah Medical City, Makkah, Saudi Arabia, from January 2012 to December 2019. All Patients with malignant tumors of different histological origins were defines as histologically confirmed Multiple-Primary Malignancy cases. Patients were identified through a retrospective review of medical records excluding patients with insufficient histopathological data.

The data collected were the patients’ characteristics, pathological data, and outcome information. Moreover, this research protocol was approved by the Institutional Review Board Committee. Since the study performed is retrospective, we obtained a waiver of informed consent from IRB.

Results

We collected 53 cases of Multiple-Primary malignancies 26 were synchronous (48%) and 27 were metachronous (52%). Out of 53 patients, 29 (60 %) were females and 14 (40 %) were males.

The most common sites for synchronous, Table 1, are breast and endometrial cancer. Metastasis at diagnosis was present in 7 patients (23%). The median age of diagnosis for synchronous tumours

was 61 years (range: 27 to 83 years), 4 patients were male (26%). CT scan for staging workup resulted in the detection of a second tumour in 21 patients 5 patients of which was diagnosed during pathological examination. Curative treatment could be offered in 19 patients (73%).

Age At diagnosis	sex	Primary	Secondary	Detected by	Treatment	Metastasis at presentation	State of last follow up	Outcome /duration from diagnosis to death
79	F	Stage II breast cancer invasiveductal cancer (IDC)	Stage IV ovarian serous cancer	CT scan	Mastectomy and chemotherapy carboplatin/ Paclitaxel	yes	dead	Refused surgery for the ovary then received paclitaxel weekly then palliative care
68	F	Right breast IDC 11/2017	Stage IIIC high grade serous cancer	CT scan	TAH &BSOO mentectomy. Adjuvant Carbo/ paclitaxelNo surgery for breast	No	Alive	Under follow up
61	F	Right breast IDC stage IIIB	Stage IIA colon cancer	CT scan	BCS ALNDC hemotherapy FEC/ Docetaxel Sigmoidectomy letrozole	No	free	Under follow up
44	F	Right breast cancer IDC	Appendicular mucinous adenocarcinoma stage IV	CT scan	MRM tamoxifen	yes	dead	5 months
52	F	Left breast stage IIIA IDC	Stage IA endometrioid adenocarcinoma of the uterus	CT scan	TAH& BSO omentectomy PLND Left MRM Chemotherapy FEC /docetaxel Radiotherapy Letrozole	No	free	Positive family history of ovarian cancer BRCA mutation positive Under follow-up
63	F	Breast IDC	Endometrial endometrioid adenocarcinoma	CT scan	Neoadjuvant with dual anti-HER 2 therapy. Followed by surgery for both	No	Alive	The patent currently under adjuvant therapy
63	F	Triple negative left breast IDC	Hormone receptor positive right breast cancer	Path exam	Neoadjuvant AC/ docetaxel Bilateral MRM	No	Alive	Currently under adjuvanthormonal therapy
65	F	Right breast IDC	Stage IV Rectal adenocarcinoma	CT scan	Right MRM Chemotherapy for rectal cancer	yes	Yes liver	Still under chemotherapy
75	F	Stage IVB	Stage I	CT scan	Carboplatin	yes	Dead	Refused

		endometrioid adenocarcinoma	mucinous carcinoma of the breast		paclitaxel. But Refused surgery			surgery for the endometrium after very good response to chemotherapy
49	F	Stage IA endometrial endometrioid adenocarcinoma	Stage IA mucinous borderline tumour	Path exam	TAH &BSOinfracolic omentectomy	No	free	Under follow up
36	F	Stage IA endometrial adenosequamus cancer	Papillary thyroid cancer	CT scan	TAH &BSOTotal thyroidectomy	No	free	Underfollow up
64*	F	Stage IA endometrial endometrioid adenocarcinoma NSCLCstage T1bN0	Cancer rectum	CT scan	TAH &BSOOmentectomy + Choleycystectomy Right lung lobectomy and hilar lymphnode excision LAR	No	free	Under follow up
56	F	Stage I Uterine leio myosarcoma	Stage IA Ovarian endometrioid borderline tumour	Path exam	TAH &BSOOmentectomy 7/2018	No	alive	Under follow up
72	F	Stage IA carcinosarcoma of the uterus	Stage I mucinous carcinoma of the breast	CT scan	TAH &BSOFollowed by Adjuvant carboplatin/paclitaxel,Radiotherapy External pelvicRight MRM Adjuvant Letrozole	No	free	Relapsed 6 years later with metastatic carcinosarcoma shifted to palliative care after two cycles of chemotherapy
27	F	Left foot leio myosarcoma	thymoma	CT scan	Surgery for both	No	free	Under follow up
39	F	Low grade brain glioma large infiltrative mass	Abdominal mass GIST	CT scan	Bilateral V/P shunt	No	dead	21 months
78	M	Stage IV nasopharyngeal cancer undifferentiated	Hepatocellular carcinoma Cirrhosis, LCF	CT scan	Radiotherapy incomplete course	yes	dead	6 months
47	F	Colon cancer high grade adenocarcinoma	Hodgkin’s disease classical type stage IV	CT scan	ABVD	yes	dead	9 months
83	M	Rectal moderately differentiated cancer	Metastatic Prostate cancer GS4+4	CT scan	Goserelin / bicalutamide	yes	dead	8 months

69	M	Sigmoid adenocarcinoma T2N1	stageIIB Lung adenocarcinoma Lung carcinoid tumour low grade	CT scan	Surgery for both then adjuvant chemotherapyfor lung carboplatin/ pemetrexed	no	Alive	Under follow up
60	F	Gastric adenocarcinoma T4N3M0	Lung mucinous adenocarcinoma	CT scan	Neoadjuvant chemotherapyECF for gastric cancer, Gastrectomy then Lung lobectomy	N0	Dead	13 months
78	M	Prostate adenocarcinoma	Pleomorphic undifferentiated Sarcoma left femur	CT scan	Orchiectomy radiotherapy	no	Alive	Lost follow up
59	M	Renal cell carcinoma	Metastatic nasopharyngeal cancer	CT scan	Target therapy plus chemotherapy	yes	Alive	localized RCC refused surgery received pazopanib changed to sunitinib metastatic NPC received gemcitabine10 cycles then start 2nd linedocetaxel
68	F	Stage I gastric leiomyosarcoma	Stage I ovarian serous cancer	CT scan	Partial gastrectomy, ovarian cystectomy then Neoadjuvant carboplatin/ paclitaxel then debulking surgery	no	free	Underfollow up
34	F	stage IA high grade ovarian mucinous cancer	Stage IA endometrioid adenocarcinoma	Path exam	TAH&BSO and omentectomy. Chemotherapy carboplatin/paclitaxel	no	free	Under follow up
45	F	Stage IC mucinous ovarian cancer	Stage IB endometrioid adenocarcinoma	Path exam	TAH&BSO and omentectomy. Chemotherapy carboplatin/paclitaxel Followed by radiotherapy	no	free	Under follow up

Table 1: Patients with Synchronous Advanced Multiple Primary Tumours.

For metachronous tumours, Table 2, the median age of diagnosis for the second primary neoplasm was 54years (range: 34 to 82years) 3 patients of which were male. The median interval of six years was observed, the most common sites of a primary tumour were breast, the most common second malignancy was colorectal cancer and Metastasis at diagnosis were present in 7 patients (25%). Curative treatment could be offered in 15 patients (53%).

Age	Sex	Primary	Treatment	Secondary	Treatment	Metastasis at presentation	Interval between primary and secondary	Recurrence
53	F	Stage I Breast IDC	Surgery hormonal letrozole	Stage II Colon cancer	Surgery, FOLFOX	No	7 y	
50	F	Stage III Breast IDC	Neoadjuvant chemotherapy EC/T Surgery, radiotherapy	Coloncancer T4N1M0	SUREGERY Capecitabine / Oxaliplatin	NO	14 Y	Colon cancer recurrence and received chemotherapy HIPEC and on chemotherapy
64	F	Stage II triple negative breast IDC	Surgery chemotherapy radiotherapy	Stage IV pancreatic cancer	Palliative care	yes	6 y	Died after 3 months
39	F	Breast IDC stage II	Surgery FAC Tamoxifen	Endometrium	Surgery radiotherapy	no	11 y	
44	F	Stage II breast IDC	Surgery TEC radiotherapy Tam /letrozole	Stage III Uterine carcinosarcoma	surgery carbo/paclitaxel		6 y	
42	F	STAGE IIA BREAST IDC	RT MRM TE Cradiotherapy Tamoxifen	APL M5	ATRA	no	2 y	
35	F	Stage II breast IDC	Surgery FEC/ Docetaxel Radiotherapy tamoxifen	AML	FLAG then IDC.	no	5 y	In CRUnder FU
51	F	Stage IIIA Breast cancer IDC Her2neu positive disease	Surgery chemotherapy Radiotherapy	Lung squamous cell lung cancer	Chemotherapy	no	2 y	Still under chemotherapy
47	F	ER+ breast cancer	Surgery and adjuvant chemo. Hormonal and radiotherapy	Stage IIA triple negative breast cancer	Surgeryand chemotherapy	Yes	8 y	Under follow up
45	F	Papillary thyroid cancer	Surgery total thyroid ectomy, radioactive iodine	Stage III Follicular lymphoma	FCR		3 y	Under follow up
41	F	Papillary Thyroid Cancer	Surgery radiotherapy	Stage IC Ovarian serous cancer	Debulking surgery Adjuvant chemotherapy	no	9 y	dead
72	M	Papillary	Thyroid	Stage IV	Chemothera	yes	20 y	dead

		Thyroid cancer	surgery and ablation on replacement	NSCLC	py and palliative radiotherapy			
59	F	CML chronic phase	TKI Imatinib, desatinib	Colon cancer	Chemotherapy. Radiotherapy		9 y	Dead
Age	Sex	Primary	Treatment	Secondary	Treatment	Metastasis at presentation	Interval between primary and secondary	Recurrence
35	F	CML	TKI	Tracheal adenocarcinoma	Surgery radiotherapy	no	15 y	In MMRUnder follow up
70	F	Colon cancer	Surgery, XELOX	Breast	Docetaxel trastuzumab	yes	5 y	dead
68*	F	Stage II adenocarcinoma Colon cancer	Surgery radiotherapy chemotherapy	CMLThen developed thyroid cancer	TKIChemotherapy for colon	No	2 y	dead
80	F	HCC	HAchemoembolization	Breast cancer stage IV liver bone	Trastuzumab Hormonal treatment	yes	2y	dead
70	F	Stage IV adenocarcinoma of the gall bladder	Surgery then gemcitabine	Stage colon cancer	Surgery chemotherapy FOLFOX /bevacizumab	yes	1y	dead
66	F	Stage endometrial endometrioid adenocarcinoma	Surgery	Breast DCIS	Surgery Tamoxifen	No	3 y	free
41	F	Stage II granulosa cell tumour of the ovary	Surgery chemotherapy VAC	Stage IV Carcinoid tumour of the pancreas	octreotide	yes	10 y	Under octreotide
82	F	Stage IA endometrial endometrioid Adenocarcinoma	Surgery	Stage I breast IDC	Hormonal and radiotherapy	no	1 y	free
65	F	Stage IIIc serous ovarian cancer	Neoadjuvant chemotherapy carboplatin / paclitaxel Interval debuing Adjuvant chemotherapy	Stage IV high grade neuroendocrine tumour	Refused chemotherapy	No	1y	dead
59	M	Cancer larynx T1N0M0	Radical Radiotherapy	Stage IV gastric cancer	Palliative chemotherapy and radiotherapy	Yes, liver Mets	2 y	dead
64	M	DLBCL stage IV B	Chemotherapy	Stage IIIB Mesothelioma	Chemotherapy	No	4 y	Under Chemotherapy
34*	F	Stage III B	ABVD	Papillary	Surgery	No	12 y	Under follow

		Hodgkin's lymphoma		thyroid cancer And left breast cancer	radioactive iodine			up
55*	F	Stage IIA DLBCL	Chemotherapy and radiotherapy	Breast cancer stage and follicular lymphoma stage IA	Lumpectomy and ALNDChemotherapy Hormonal therapy for the breast Radiotherapy for FL	No	2y	Under follow up
54	F	Stage IIIA NHL follicular GII	Rituximab for 4 weeks and then maintenance	Hodgkin's lymphoma in axillary lymph node	AVD	No	2 y	Under follow up

Table 2: Patients with Metachronous Advanced Multiple Primary Tumours.

*Triple malignancies; IDC, Invasive ductal carcinoma; DLBCL, diffuse large b cell lymphoma; TAH BSO, total abdominal hysterectomy and bilateral salpingoophrectomy; BCS ALND, breast conserving surgery and axillary lymph node dissection; MRM, modified radical mastectomy NSCLC non-small cell lung cancer; ABVD, Adriamycin, bleomycin vinblastine dacarbazine; AML, Acute myeloid leukaemia; APL, Acute promyelocytic leukaemia.

Discussion

Multiple primaries [14] are more than one tumour arising in different sites and or of different histology either synchronous or metachronous depends on the duration between them, 2-month according to SEER data [15] and 6 months according to IARC. In our study, we used the definition of IARC. The burden of multiple tumours is expected to increase due to the use of accurate imaging techniques. In a single facility in Saudi Arabia, we collected 54 cases over 7 years. Multiple-Primary did not always signify a bad prognosis as we treated all non-metastatic cases with curative intent.

It is most imperative to diagnose it early before the patient reaches the metastatic stage. This means that we should have a high degree of suspicion. The role of the radiologist is crucial as usually, radiologists are first to flag for suspicion of multiple tumours. In our study, most of the synchronous tumours were detected initially by CT scan then confirmed pathologically. Examples from our study as CT scan done for a patient with ovarian cancer showed a breast mass or CT scan showed a speculated lung lesion in a patient with breast cancer or showed renal mass in a patient with nasopharyngeal cancer.

The response to therapy is always an alarm for the physician to review his pathology by repeating the biopsy of the metastatic disease. In our study a patient with breast cancer who developed lung nodules treated treated with chemotherapy as. Metastatic breast then the poor response to chemotherapy urged us to biopsy the largest metastatic nodule and to our surprise came to be second primary Lung Cancer.

Cancer patients who survive their primary tumour always have a high risk to develop a second primary and this is due to many reasons like genetic predisposition as one of our patients who has Double Synchronous Primary Breast Cancer and Endometrial Cancer gave a strong family history of ovarian cancer and her BRCA genetic testing came to be positive.

Cancer treatment is carcinogenic. We are reporting leukaemia in ovarian cancer patients treated with chemotherapy, breast cancer patients treated for DLBCL, and breast and thyroid cancer in

Hodgkin’s lymphoma patients treated at a young age.

For patients with breast cancer, the incidence of second primaries studied and has been reported to range from 4.1% to 16.4% [15-16]. An excess risk of endometrial cancer is reported with the use of Tamoxifen [17] Genetic factors as BRCA1 BRCA2 mutations are well-known risk factors for Multiple-Primary [18]. In this study, we reported 7 cases of the Synchronous Second-Primary with breast cancer, 3 cases with ovarian cancer. Also, we reported endometrial cancer in patients with hormone receptor-positive breast cancer with BRCA mutation. AML can be triggered during the first 2 years after radiation therapy and it is also a late effect of chemotherapy. For metachronous tumour in patients with breast cancer, We reported two cases of AML which may be chemotherapy related.

Patients with prostate cancer who received external beam radiotherapy are at increased risk of bladder cancer, rectal cancer and sarcomas within the radiation field after being disease-free for at least 5 years [19]. Second primaries can also occur in patients with prostate cancer owing to genetic factors, especially BRCA mutation [20]. In our study, we reported prostate cancer, rectal cancer, and prostate cancer and sarcoma synchronously.

The most important cause of mortality in Hodgkin’s lymphoma is a Second-Primary cancer [21]. We reported a case of colon cancer synchronously with Hodgkin’s lymphoma and thyroid cancer. Also, breast cancer that occurred 12 years after ABVD for Hodgkin’s lymphoma. Smoking is an important risk factor not only for lung cancer but also for a Second-Primary Cancer. A 7.9%of lung cancer cases who acquire a second primary have SCLC [22]. In this study, we reported colon cancer 1 year after lung cancer and gastroesophageal cancer that was diagnosed 18 months after the lung cancer diagnosis.

The treatment decision of synchronous tumours is not straightforward and usually requires a multidisciplinary approach, one of our patients had a synchronous breast and endometrial cancer. We discussed the case in our tumour board, and we decided to give her neoadjuvant chemotherapy followed by surgery MRM and TAH&BSO in the operating room by two surgeons.

We treated our patients with curative intent in more than 60% of cases so, we should always be aware of the possibility of a second primary cancer. Late metastatic spread in a patient with triple-negative breast cancer led us to suspect second primary and diagnose pancreatic cancer. Also, low tumour marker in ovarian cancer patient which was initially high was found to have a second primary neuroendocrine tumour, continued smoking history should alert us about this possible important carcinogen.

We should inform our patients about the late side effects of their treatment, particularly Second-Primary Malignancies, by including it in the consent form. Such actions would educate patients on the value of continuous surveillance and avoiding all possible carcinogens especially smoking in addition to encouraging them for a healthy lifestyle [23-24].

Patients with multiple primaries are usually excluded from clinical trials and there are no established guidelines to treat these cases. we need clinical trials to study the new histology non-specific medications like (immunotherapy, biologic therapy. etc).

Finally, in our medical facility, we adopted the policy of referring our cases with Multiple-Primary to our genetic oncology clinic for evaluation and genetic testing; this hopefully will help us gain more knowledge about patients with hereditary cancer. we will report these data separately.

In conclusion, we are expecting an increase in the prevalence of Multiple-Primary tumours due to increased accuracy of diagnostic techniques in addition to novel target therapy that may increase the risk. Hereditary cancer syndrome, smoking, cancer therapy are all risk factors. we need to pick these cases as early as possible before the development of metastasis as this has a marked impact

on patient survival. Treatment decisions for these cases should be based on a multidisciplinary approach.

Research on this topic is an unmet need particularly the genetic background for developing second primary cancers. To reflect more of a real-life population, we need clinical trials investigating those patients in detail to increase the physician's awareness that these cases are not rare, and they need to be treated with curative intent in most situations.

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