A Retrospective Clinicopathological Analysis for Cases of Double Primary Malignancies

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Abstract:

Background and objectives: Double primary malignancies is challenging in management. Incidence of double primaries is increasing overtime. This study aims to review clinical, pathologic and treatment outcomes of our observed cases with double primary tumors. Our primary objective was to measure the frequency of double primary either synchronous or metachronous and the secondary objective was to identify demographical data, histopathological types, survival and treatment used in cases presented at Clinical Oncology Department in Helwan University hospital, Eldoah Hospital and Health Insurance Hospital from January 2012 till August 2022.

Methods: The study included Fifty-three cancer patients treated in our centers. Prospective data of patients were retrospectively analyzed. Data analysis was done using Statistical package for Social Science (SPSS 25.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Kolmogorov–Smirnov's test was used to evaluate normal distribution of continuous data, Quantitative non-parametric variables were expressed as mean and SD, Median and Interquartile range (IQR) according to the distribution of data. Qualitative variables were expressed as frequencies and percent. Survival rates were estimated and graphed using the Kaplan-Meier method.

Results: Twenty four case (45.3%) were males, 29 (54.7 %) were females. Ten cases (18.9%) were synchronous and 43 case (81.1%) were metachronous. Commonest site of first tumor was breast (32.1%) followed by kidney and prostate each represented 7.5%. Most common site of second malignant tumor was colon (17%) of cases followed by lung (11.3%). Breast cancer cases represents the most common malignant tumor in19 case (35.8%) where in 17 case (32.1%) was the primary malignancy and in 2 cases was the second malignancy. Most common second diagnoses with breast was thyroid (4 cases) followed by colon (3 cases). Median overall survival from first diagnosis was 41 months and 12 months from the second diagnosis.

Conclusion: Diagnosis of malignancy increases risk of second malignancies due to multiple etiologic factors. Proper follow up of cancer patients enables early diagnosis of second malignancy, improves cure rate and survival. Meticulous reporting of data of double primaries could identify screening strategies for patients at high risk.

Key words: Double primary malignancy, synchronous primary tumors, metachronous primary tumors.

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Introduction:

Double primary tumors are not uncommon [1]. A report done by Owen et al at 1921 included 3000 cases diagnosed with cancer 141 of them had multiple tumors [2]. The criteria used for the diagnosis of double primary malignancies, have primarily given by Warren and Gates and refined later which include; Histological confirmation of malignancy in both the primary and secondary tumors; 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; Probability of one being the metastasis of the other must be excluded [3]. Multiple primary tumors may be synchronous or metachronous. Synchronous tumors occur at the same time or within 6 months from the primary tumor according to the International Associ¬ation of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) [4]. But according to SEER database 2

months is the cutoff for synchronous and metachronous tumors [5].

The incidence of 2nd primary synchronous or metachronous tumor is increasing and reported as high as 10%. Meta analyses show the frequency of second tumor (SPT) as 3-5%, a third tumor (TT) as 0.5%, and a fourth tumor (QT) as 0.3% [6, 7].

Increasing incidence of double primary malignancies is due to multiple etiological factors; Environmental factors as exposure to radon gas, arsenic and asbestos; Lifestyle as tobacco smoking, alcohol and obesity; Genetic factors as Ashkenazi Jewish ancestry; BRCA mutations and Li-Fraumeni syndrome; Longer survival of cancer patients due to development of new drugs and effective treatment strategies; Consequence of cancer treatment as alkylating agents, vinca alkaloids and radiotherapy example is development of AML after treatment of breast cancer as late side effect of chemotherapy [8], breast cancer occurring many years after treatment of lymphoma with mantle field radiotherapy. Proper follow up of cancer patients and new imaging modalities as PET CT has led to accidental detection of indolent tumors, in a large study done by Ishimori T et al 4.1% of 1912 patients which had malignant tumors and scanned by PET CT had secondary suspicious lesions of which 1.2% was histologically confirmed secondary primary [9]. It is often observed that the second malignant tumor is more aggressive with difficult treatment manipulation and with high incidence for metastases. This may be due to tumor genetic factors or a fact that these tumors arise in a host with a compromised hematologic, renal, or hepatic reserve [10].

Patients and Methods:

Our study is a retrospective analysis of prospective data. It included 53 cancer patients treated from January 2012 till August 2022 at Clinical Oncology Department Helwan University Hospital, Eldoah Hospital and Health Insurance Hospital.

The protocol was submitted to the Faculty of Medicine, Helwan University research ethics committee for revision and approval before conduction. All data of the patients were scored in codes to protect their privacy and confidentiality. Request for waiving consent was asked due to difficulty to reach the patients. The study was approved by the institutional Review Board (IRB no. 116-2022).

Patients with histologically proven synchronous or metachronous double primaries were included according to Warren and Gates criteria [3]. Time interval to differentiate synchronous and metachronous was identified as 6 months as by IACR/IARC [4]. Data for each patient: age at time of each tumor diagnosis, sex, synchronous or metachronous, site of origin, diagnosis method, histology, detection clinical stage, and treatment regimen used for each tumor have been recorded.

Statistical analyses:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 25.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Kolmogorov–Smirnov's test was used to evaluate normal distribution of continuous data Quantitative non-parametric variables were expressed as mean and SD, Median and Interquartile range (IQR) according to the distribution of data. Qualitative variables were expressed as frequencies and percent. Survival rates were estimated and graphed using the Kaplan-Meier method.

Results:

Twenty-nine (54.7%) of cases were females, 81.1% of cases had metachronous presentation, breast was the most common 1st primary representing 32.1% followed by kidney and prostate each of them represented 7.5%. Adenocarcinoma was the most common pathology of 1st primary representing 32.1% of cases, GII represented 46.6% of 1st primary tumors, T2 represented 49.1% of 1st primary, N0 represented 59.6%, M0 83%, most common first stage was stage II representing 35.8% of cases as shown in (Table1).

For treatment of the first primary; 66% of cases underwent radical surgery, 9.4% of cases received chemoradiation, 41.5% of cases received chemotherapy, 11.3% of cases received targeted therapy,34% of cases received hormonal treatment, 28.3% of cases received radiation therapy and 1.9% of cases underwent active surveillance, 1.9% underwent TACE and 3.8% underwent TURBT+BCG as shown in (Table 2).

Table 2: Description of mode of treatment of first primary tumor among all cases.

Treatment modality	no	%
Radical surgery	35	66.0%
Chemoradiation	5	9.4%
Chemotherapy	22	41.5%
Targeted therapy	6	11.3%
Hormonal treatment	18	34.0%
Radiotherapy	15	28.3%
Active surveillance	1	1.9%
TACE	1	1.9%
TURBT+BCG	2	3.8%

Mean time for diagnosis of second primary was 40.38 months. Cancer colon was the most common 2nd primary representing 17%, Adenocarcinoma was the most common pathology of second primary representing 49.1%of cases, each of GII, GIII represented 37.7% of 2nd primary tumors, each of T2, T3 represented 26.4%% of 2nd primary, N0 represented 45.3%, M0 64.2%, most common second primary stage was stage IV representing 32.1% of cases as shown in (Table 3).

For treatment of the second primary 50.9% of cases underwent radical surgery, 9.4% of cases received

chemoradiation, 39.6% of cases received chemotherapy, 18.9% of cases received targeted therapy,11.3% of cases received hormonal treatment, 11.3% of cases received radiation therapy and 1.9% of cases underwent metastatectomy, 1.9% underwent bone marrow transplantation (BMT) and 5.7% underwent Radioactive Iodine (RAI), 1.9% underwent transurethral resection bladder tumor (TURBT)+BCG and 1.9% received immunotherapy as shown in (Table 4).

Table 4: Description of mode of treatment of Second primary tumor among all cases

Treatment modality	**no**	**%**
Radical surgery	27	50.9%
Chemoradiation	6	11.3%
Chemotherapy	21	39.6%
Targeted therapy	10	18.9%
Hormonal treatment	6	11.3%
Radiotherapy	6	11.3%
metastatectomy	1	1.9%
BMT and	1	1.9%
RAI	3	5.7%
TURBT+BCG	1	1.9%
immunotherapy	1	1.9%

Most common primary tumor in the synchronous group was prostate which represented 30% of cases (figure 1), while most common second primary was lung which represented 30% of cases followed by colon (20%) (Figure 2). Mean time of second primary diagnosis was 1.7 months. Most common primary tumor in the metachronous group was breast cancer representing 37.2% of cases (figure 3). Mean time of second primary diagnosis was 49.37 months, most common 2nd primary is cancer colon representing16.3% of cases (figure 4).

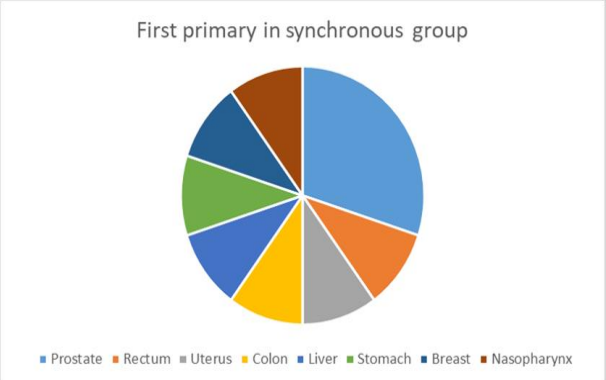

Figure 1: first primary distribution in synchronous group.

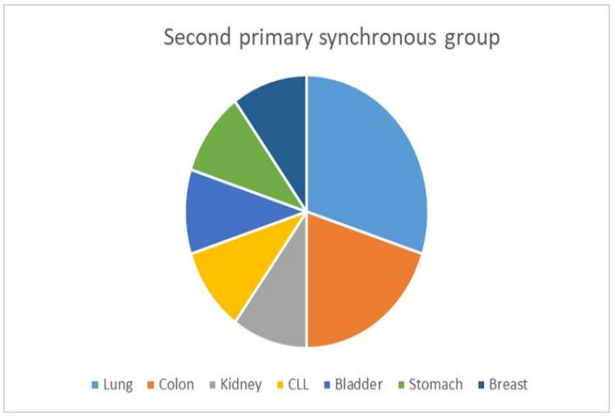

Figure 2: Second primary distribution in synchronous group.

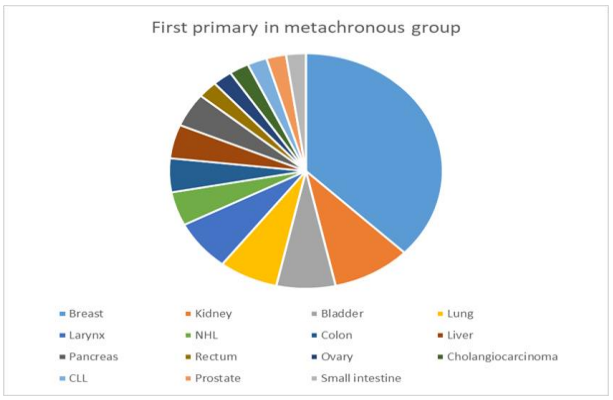

Figure 3: first primary distribution in metachronous group.

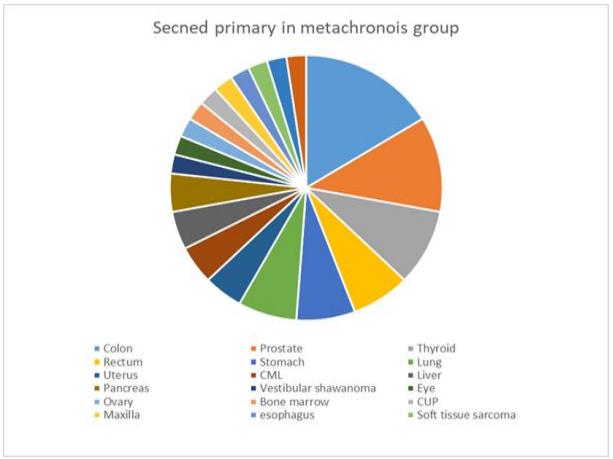

Figure 4: second primary distribution in metachronous group.

Table 1: Description of personal and clinical characteristics of first primary tumor among all cases

		Mean	±SD	Minimum	Maximum
Age (years)		61.53	11.65	31.00	84.00
Sex	**Male**	24	45.3%		
	Female	29	54.7%		
Timing	**Synchronous**	10	18.9%		
	Metachronous	43	81.1%		
First primary	**Breast**	17	32.1%		
	Kidney	4	7.5%		
	Prostate	4	7.5%		
	Bladder	3	5.7%		
	Colon	3	5.7%		
	Liver	3	5.7%		
	Lung	3	5.7%		
	Larynx	3	5.7%		
	Rectum	2	3.8%		
	NHL	2	3.8%		
	Pancreas	2	3.8%		
	Ovary	1	1.9%		
	Uterus	1	1.9%		
	Cholangiocarcinoma	1	1.9%		
	CLL	1	1.9%		
	Small intestine	1	1.9%		
	Stomach	1	1.9%		
	Nasopharynx	1	1.9%		
First pathological type	**Adenocarcinoma NOS**	17	32.1%		
	IDC	16	30.2%		
	Squamous cell carcinoma	5	9.4%		
	Clear cell	4	7.5%		
	HCC	3	5.7%		
	DLBCL	3	5.7%		
	TCC	3	5.7%		
	CLL	1	1.9%		
	Mucinous adenocarcinoma	1	1.9%		
First Grade	**Grade I**	2	3.8%		
	Grade II	30	56.6%		
	Grade III	14	26.4%		
	NA	7	13.2%		
First T	**T0**	0	0.0%		
	T1	14	26.4%		
	T2	26	49.1%		
	T3	7	13.2%		
	T4	2	3.8%		
	Tx	1	1.9%		
	NA	3	5.7%		
First N	**N0**	31	59.6%		
	N1	12	23.1%		
	N2	4	7.7%		
	N3	1	1.9%		
	Nx	1	1.9%		
	NA	3	5.8%		
First M	**M0**	44	83.0%		
	M1	4	7.5%		
	Mx	1	1.9%		
	NA	4	7.5%		
First Stage	**Stage I**	18	34.0%		
	Stage II	19	35.8%		
	Stage III	12	22.6%		
	Stage IV	4	7.5%		

Table 3: Description of personal and clinical characteristics of second primary tumor among all cases.

		Mean	±SD	Minimum	Maximum
Time interval (months)		40.38	45.60	.00	192.00
Second primary	Colon	9	17.0%		
	Lung	6	11.3%		
	Prostate	5	9.4%		
	Stomach	4	7.5%		
	Thyroid	4	7.5%		
	Rectum	3	5.7%		
	Uterus	2	3.8%		
	CML	2	3.8%		
	Liver	2	3.8%		
	Pancreas	2	3.8%		
	Breast	2	3.8%		
	Vestibular schwannoma	1	1.9%		
	Eye	1	1.9%		
	Ovary	1	1.9%		
	Kidney	1	1.9%		
	Bone marrow	1	1.9%		
	CUP	1	1.9%		
	Maxilla	1	1.9%		
	esophagus	1	1.9%		
	Soft tissue sarcoma	1	1.9%		
	NHL	1	1.9%		
	CLL	1	1.9%		
	Bladder	1	1.9%		
Second pathological type	Adenocarcinoma NOS	26	49.1%		
	Neuroendocrine tumor	4	7.5%		
	CML	3	5.7%		
	Papillary	3	5.7%		
	Squamous cell carcinoma	3	5.7%		
	HCC	2	3.8%		
	Mucinous adenocarcinoma	2	3.8%		
	IDC	2	3.8%		
	CLL	1	1.9%		
	plasma cell myeloma	1	1.9%		
	DLBCL	1	1.9%		
	Angiosarcoma	1	1.9%		
	Signet adenocarcinoma	1	1.9%		
	Clear cell	1	1.9%		
	TCC	1	1.9%		
	Follicular	1	1.9%		
Second Grade	Grade I	3	5.7%		
	Grade II	20	37.7%		
	Grade III	20	37.7%		
	NA	10	18.9%		
Second T	T0	0	0.0%		
	T1	11	20.8%		
	T2	14	26.4%		
	T3	14	26.4%		
	T4	7	13.2%		
	Tx	2	3.8%		
	NA	5	9.4%		
Second N	N0	24	45.3%		
	N1	12	22.6%		
	N2	8	15.1%		
	N3	2	3.8%		
	Nx	2	3.8%		
	NA	5	9.4%		
Second M	M0	34	64.2%		
	M1	14	26.4%		
	NA	5	9.4%		
Second Stage	Stage I	15	28.3%		
	Stage II	8	15.1%		
	Stage III	11	20.8%		
	Stage IV	17	32.1%		
	NA	2	3.8%		

Median overall survival from first diagnosis was 41 months. While median overall survival from second diagnosis was 12 months. Among group 1 cases (Synchronous) median overall survival was 10.5 months from the first diagnosis and 10 months from second diagnosis, mortality rate was 20%. However median overall survival among group 2 cases (metachronous) was 55 months from the first diagnosis and 13 months from the second diagnosis.

Discussion:

New advances in diagnosis and treatment of cancer have led to higher cure rates and prolongation of survival. Accumulation of mutations, cancer syndromes such as Lynch and Li Fraumeni syndromes lead to development of multiple primary malignancies, also use of chemotherapeutic agents and radiotherapy have late side effects: one of them is carcinogenesis.

Our study aimed to define clinicopathological parameters of cases diagnosed with double primary and classify them to synchronous and metachronous trying to identify most common tumors that occur in association which each other.

Identifying associations of tumors may allow us to identify some genetic mutations or cancer syndromes that may lead to development of screening schedules that allows us to early diagnose second primary tumors hence allowing increased cure rates.

Treatment of either synchronous or metachronous primary tumors is always a challenge to define a plan of treatment. No guidelines are available for treatment of such cases so we need reporting of these cases, management plans and outcomes so as to find a guide for management.

The study was conducted on cancer patients treated in our center from January 2012 till August 2022. Data of patients diagnosed with double primary were retrospectively analyzed.

Fifty-three patients were enrolled, among them 45.3% were males, 54.7 % were females. 10 cases (18%) were synchronous and 43 cases (81%) were metachronous.

Most common site of 1ry malignant tumor was breast which represented 32.1% of cases followed by kidney and prostate each of them represented 7.5%.

Most common site of 2ry malignant tumor was colon which represented 17% of cases followed by lung which represented 11.3%.

Mean time interval between primary and secondary tumors of 40.38 months in metachronous group.

Similar study was done in India by Bagri PK et al11. It included 41 cases 19% of them were synchronous, 80% were metachronous which was going with our study. The most common sites of primary tumor were head and neck followed by gynecological cancer, breast cancer, while the most common site of second malignancy was breast and gastrointestinal followed by lung. These results differ from our study may be due to environmental and genetic differences.

Long good follow up is required for cancer patients also using least toxic effective treatment protocols and minimizing use of radiation therapy unless indicated may decrease development of second malignancies.

Testing for genetic mutations such as BRCA1, 2 in breast, ovarian and prostate cancer patients also MSI, MMR testing in GIT, uterine malignancies may lead to identification of cancer patients at risk of developing second primaries, also may lead to applying risk reduction strategies as prophylactic surgeries as prophylactic mastectomy or salpingo oophorectomy which is supposed to decrease risk of developing second primary tumors.

Conclusion:

Diagnoses of malignancy increases risk of second malignancies due to multiple etiologic factors. Proper follow up of cancer patients is mandatory for early diagnosis of second malignancy to improve cure rate and hence survival. Efforts should be done for meticulous reporting of data of double primary so that we could identify screening strategies for patients at high risk. Second primary should be always put in mind either synchronous or metachronous. Biopsy from metastatic site should be always considered whenever accessible. Genetic profiling for cancer patients is mandatory as second primary tumors could confirm the theory of genetic bases of cancer etiology.

Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

Haytham Abdelkader data collection, statistics, Aalaa Gamil data collection and writing.

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References:

1. Irimie A, Achimas-Cadariu P, Burz C, et al. Multiple primary malignancies–epidemiological analysis at a single tertiary institution. J Gastrointestin Liver Dis. 2010;19:69-73.
2. Owen LJ. Multiple malignant neoplasms. JAMA 1921; 76:1329–1333.
3. Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and statistical study. Am J Cancer. 1932; 16:1358–414.
4. Amer MH. Multiple neoplasms, single primaries, and patient survival. Cancer Manag Res 2014; 6:119–34.
5. Ferreti Sea. Airtum cancer registration handbook, 2009.
6. Bittorf B, Kessler H, Merkel S, et al. Multiple primary malignancies: An epidemiological and pedigree analysis of 57 patients with at least three tumors. Eur J Surg Oncol. 2001: 27; 302-13.
7. SEER Program Code Manual, Third Edition. Bethesda (MD): National Cancer Institute. January

1998.

8. Ricceri F, Fasanelli F, Giraudo MT, et al. Risk of second primary malignancies in women with breast cancer: results from the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2015; 137:940–8.
9. Ishimori T, Patel PV, Wahl RL. Detection of unexpected additional primary malignancies with PET/CT. J Nucl Med 2005; 46:752–7.
10. Mehdi I, Shah AH, Moona MS, et al. Synchronous and Metachronous Malignant Tumours expect the un-expected. J Pak Med Assoc. 2010: 60(11):905-9.
11. Bagri PK, Singh D, Singhal MK, et al. Double primary malignancies: a clinical & pathological analysis report from a regional cancer institute in India. Iran J Cancer Prev. 2014 Spring;7(2):66-72. PMID: 25250152; PMCID: PMC4142942.