

Risk of Second Malignancy in Upper Egypt in the Era of COVID-19: A Multicentric Cancer Experience

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Abstract

Background: The etiology of second cancer is complex and multifactorial, with the variable burden of second malignancy is carried by different types of primary cancers.

Aim of Study: In the current study, we evaluated the incidence of second cancers among cancer survivors during the last 3 years following the outbreak of COVID-19 in three cancer treatment centers of Assiut governorate; clinical oncology department, Assiut Health insurance and south Egypt cancer institute, also their clinicopathologic characteristics and treatment outcomes based on patients' records.

Patients and Methods: We recruited all cases presented to the pre-mentioned centers during the period from the start of 2019 to the end of 2021 with confirmed diagnosis of primary and second new cancers.

Results: We collected ninety-five cases of second malignancies who were still under treatment of their primary tumors, or just under scheduled follow up after finishing their treatments, they had a range of age from 3-86 years. 21.1 % had synchronous and 78.9% had metachronous tumors, the median duration for medical treatments of primary tumors was 12 months, no significant differences in age and sex pattern between synchronous and metachronous, 53.7%, and 46.3% had second hematologic and solid tumors respectively, most hematologic second tumors developed earlier than solid ones ($p=0.023$), there was a female prominence for both primary and second malignant tumors ($p=0.01$ & <0.001 respectively), the overall control rate for second malignant tumors was 78.8%, and the death rate was 34.7%.

Conclusion: Generally, second malignant tumors were not uncommon, their detection had recently increased because of great success in the treatment of primary tumors with prolonged survival and progress in diagnostic and staging modalities. Careful timely surveillance of cancer patients is required especially those who survived COVID-19.

Key Words: Multiple primary malignant tumors – Synchronous tumors – Metachronous tumors – Risk factors.

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Introduction

CANCER'S prominence as a cause of death is rising and reflecting a progressive decline in mortality rates of other causes such as coronary vascular diseases, strokes, and chronic renal failure; also the prognosis of cancer has improved dramatically in the last decades because of great success that has been done in screening programs with early detection of cancers, treatments especially with immunotherapy, and supportive care [1]. Prolonged survival particularly in childhood cancers and aging of population may contribute to appearance of second cancers; approximately one in every six cancers diagnosed among cancer survivors in the United States represent a leading cause of death in these survivors [2].

The etiology of a second cancer is complex and multifactorial, with the variable burden of second malignancy carried by different types of primary cancers. For childhood cancers, genetic predisposition and treatment effects play an essential role in the development of second malignancy, while for adult ones, environmental factors and lifestyles that accumulate over time may result in second cancer development [3].

Suzuki et al. [4] classified double malignancies according to the time interval between both diagnoses into synchronous if second malignancies developed simultaneously or within six months of primary malignancies, and metachronous if they developed more than six months apart.

In a recent study, after 30 years of surveillance following the primary diagnosis of cancer in pediatrics, the overall cumulative incidence of second malignancy was 20.5% (95% CI 19.1%-21.8%), with a cumulative incidence for invasive cancers

was 7.9% (7.2%-8.5%), while 9.1% (8.1%-10.1%) for NMSC, and 3.1% (2.5%-3.8%) for meningioma [5]. For adult cancers, the cumulative incidence of second malignancy at 30 years from breast cancer diagnosis was 21.2% (21.0%-21.4%), 17.8% (17.6%-18.1%) for survivors of colon cancer, and 27.1% (26.7%-27.4%) for survivors of bladder cancer [6].

Extreme pro-inflammatory cytokine release with subsequent organ failure together with impaired immune response, elevated growth factors and chemokines were the hallmark of COVID-19. However, these mechanisms were implicated in tumorigenesis and cancer progression. Furthermore, antigenic stimulation caused by damage-associated molecular pattern and pathogen-associated molecular pattern [7] were similar in both COVID-19 and cancer [8], so in the current study, we evaluated the incidence of second cancers among cancer survivors during the last three years following the outbreak of COVID-19 in three cancer treatment centers of Assiut governorate, also their clinico-pathologic characteristics and treatment outcomes based on patients' records.

Patients and Methods

It was an observational study conducted in Clinical Oncology department, South Egypt Cancer Institute, and Oncology Department of Assiut health insurance. It was approved by the Ethical Committee of Assiut University (IRB=04-2023-300099), we recruited all cases with confirmed diagnosis of primary and second new cancers, presented to the pre-mentioned centers during the period from the start of 2019 to the end of 2021.

Data collection:

Covariates of interest for this study included: Demographic characteristics, family history, cancer characteristics, the time elapsed before the development of second cancers, previous treatments of primary cancers especially exposure to chemotherapy and radiotherapy, new treatments for second cancers, overall response to treatments, genetic profile if available, and death rates as collected from patients' files in these centers. Data regarding their exposure to COVID-19 infection were determined from their records whether they were detected to have positive PCR, positive chest CT findings of COVID-19, or gave a positive history of contact to COVID infected patients.

We excluded multicentric tumors and tumors of the same histology which affected multiple organs or tissues at the same time from being multiple primary cancers; however, multiple can-

cers of different histology developed in the same organ, were considered multiple primary cancers

Data regarding medical treatments such as chemotherapy regimens, tyrosine kinase inhibitors (TKIs), and hormonal therapies were included, patients with other therapies in the results included those with radiofrequency ablation, and trans-arterial chemoembolization.

Statistics:

All data were analyzed using IBM-SPSS ver. 26, descriptive stats and inferential stats were utilized in the form of number, percentages, mean, standard error, median. Using Kolmogorov-Smirnov test, both age and duration of medical treatments were not normally distributed ($p=0.004$ and <0.000 respectively), for association between categorical variables, χ^2 with continuity correction and Fisher's exact tests were used, for association between scale and categorical variables, Mann Whitney U-test was used, data were considered significant at p -value <0.05 .

Results

During the period from January 2019 to December 2021, we collected 95 cases of second malignancies who were still under treatment for their primary tumors, or just under scheduled follow-up after finishing their treatments, they had a range of age from 3-86 years including 19 pediatric cases (Fig. 1), 31 cases were above the age of sixty, and the remaining cases were in between, their characteristics were gathered from their hospital records which were unfortunately defective, especially in their family history and the associated comorbidities, Table (1).

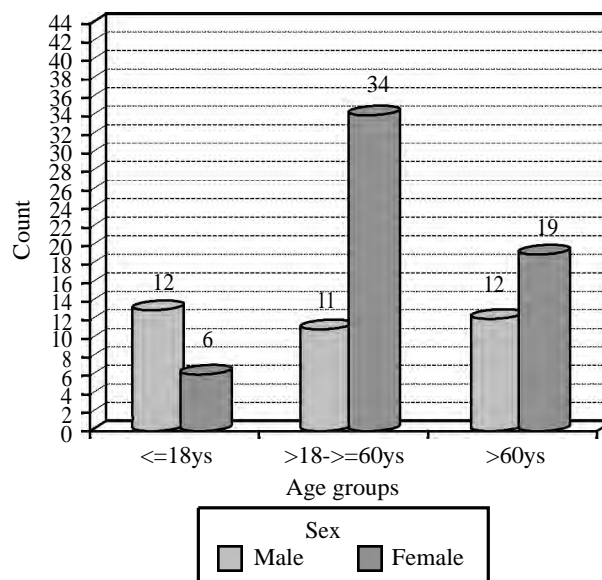


Fig. (1): Distribution of sex according to age groups in ninety-five patients.

Table (1): Demographic characteristics of ninety-five patients.

Demographics	Descriptive
Age	43.7±2.2 3-86 years 49 years
Sex (male/female)	36/59
Family history (%):	
Positive	17 (17.9%)
Negative	32 (33.7%)
Unknown	46 (48.4%)
Degree of relatives (%):	
First degree relative	13 (13.7%)
Second degree and higher	1 (1.1%)
Both first and higher degree	3 (3.2%)
Associated comorbidities (%):	
Unknown	51 (53.7%)
No comorbidities	19 (29%)
One comorbidity	5 (5.3%)
>One comorbidities	20 (21.1%)

Data analyzed as number, percentages, mean ± SE, median.

Twenty patients (21.1%) had synchronous primary and second malignancies which developed simultaneously or at 6-month time intervals, while metachronous primaries were detected in seventy-five patients (78.9%), (Fig. 2). The median age for the synchronous group was slightly larger than that of the metachronous group but without significant difference (55 year vs. 49 years, $p=0.3$), also second primaries had a predilection for female compared to male (59 vs. 36) especially for hematologic cancers (45 females vs. 30 males) without significant differences ($p=0.4$).

Fifty-six patients (58.9%) had solid primaries, of them breast cancers had the lion's share (21 patients), furthermore, forty-four patients had non-metastatic solid cancers and 12 patients had metastatic diseases at the time of presentation (Fig. 3), while the remaining 39 patients (41.1 %) had hematologic cancers with chronic leukemias and NHL represented the main types, Table (2).

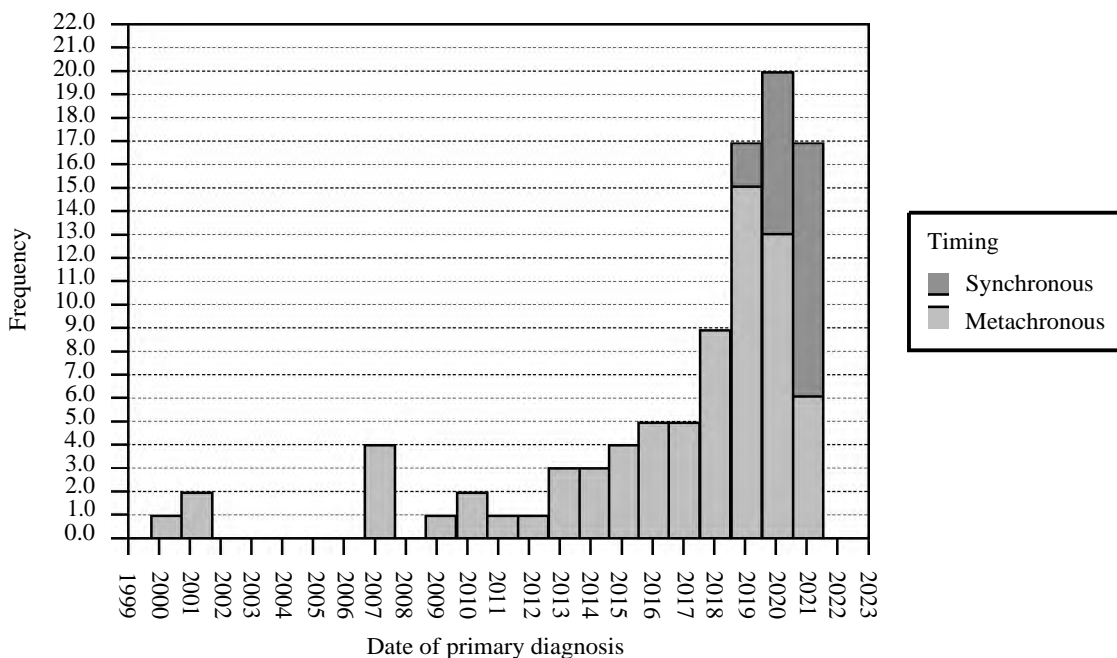


Fig. (2): Distribution of synchronous and metachronous malignancies according to date of diagnosis.

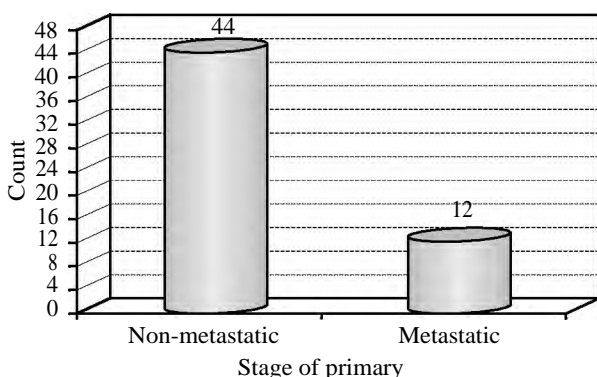


Fig. (3): Stages of solid malignancies.

Table (2): Types of primary tumors.

Hematologic malignancies	N (%)	Solid malignancies	N (%)
NHL	12 (12.6)	Neurogenic tumors	9 (9.5)
HD	6 (6.3)	Breast carcinoma	21 (22.1)
Chronic leukemias	18 (18.9)	Prostatic carcinoma	3 (3.2)
Acute leukemias	1 (1.1)	Ovarian carcinoma	2 (2.1)
Multiple myeloma	2 (2.1)	Colonic carcinoma	5 (5.3)
		Squamous cell carcinoma of head & neck	3 (3.2)
		Others	13 (13.7)
Total	39 (41.1)	Total	56 (58.9)

Data expressed as number and %.

As expected, chemotherapy and TKI were the only modes of treatment for hematologic malignancies, and combined treatments were the main approach for solid tumors, (Figs. 4,5). The mean duration for medical treatment was 26.7 ± 3.3 months (95% CI=20.1-33.4 months) and the median was 12 months as figured below (Fig. 6).

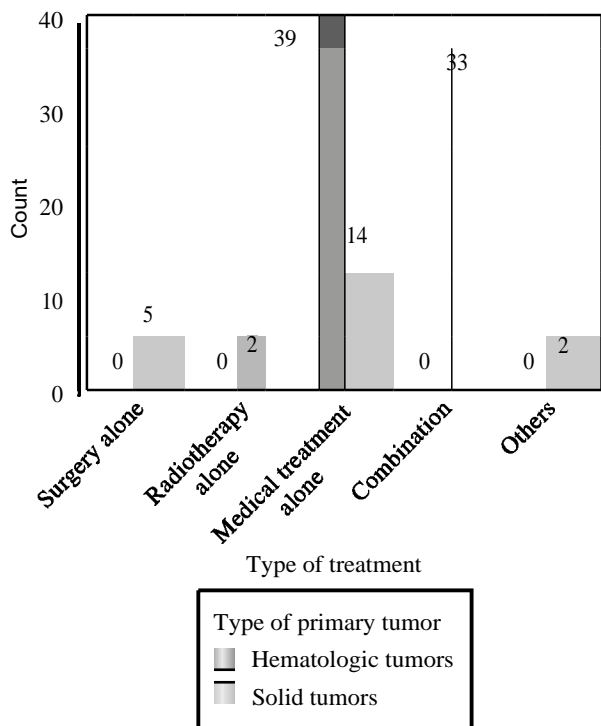


Fig. (4): Types of therapy for primary tumors.

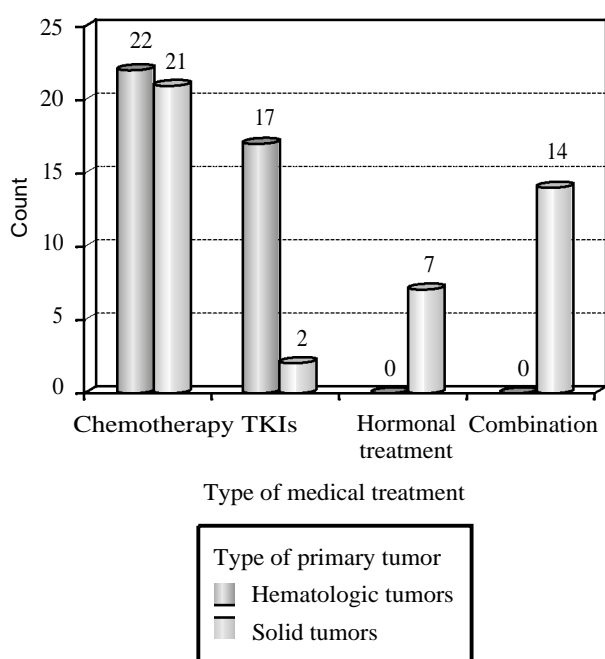


Fig. (5): Types of medical treatment for primary tumors.

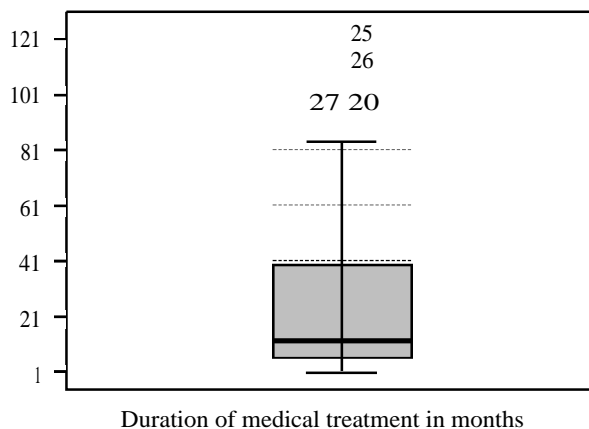


Fig. (6): Duration of medical treatment used for primary cancers.

Sixty-seven (70.5%) patients achieved a complete response to treatment of their primary malignancies, while 15 (15.8%), 7 (7.4%), and 6 (6.3%) of patients achieved partial response, stable disease, and disease progression respectively.

Second hematologic malignancies represented 53.7% (51 patients), and second solid cancers were detected in 46.3% (44 patients), of them 28 patients were non-metastatic while 16 patients had metastatic second solid cancers, contrary to what were expected, the overall control rate was high (76.8%) which was reflected lower death rate (34.7%), Table (3).

Table (3): Characteristic of second cancers.

Second malignancies	N (%)
Hematologic	51 (53.7)
NHL	1 (1.1)
HD	1 (1.1)
MDS	21 (22.1)
Chronic leukemia	6 (6.3)
Acute leukemia	22 (23.2)
Solid malignancies	44 (46.3)
Breast cancer	9 (9.5)
Colorectal cancers	7 (7.4)
Gynecologic cancers	6 (6.3)
Hepatobiliary cancers	7 (7.4)
Thyroid cancers	3 (3.2)
RCC	3 (3.2)
Others	9 (9.5)
<i>Stage of second solid cancers:</i>	
Non-metastatic	28 (29.5)
Metastatic	16 (16.8)
<i>Overall response to treatment:</i>	
Controlled	73 (76.8)
Progressive	22 (23.2)
Median interval between primaries	22 months
Range	7-300 months
<i>Fate of patients:</i>	
Dead	33 (34.7)
Alive	62 (65.3)

Data expressed as number and percentage.

The distributions of sex between hematologic and solid cancers for both primary and second malignancies were significantly different as demonstrated in Table (4).

Table (4): Distribution of sex among primary and second cancers.

Type	Male	Female	p-value
Primary cancers:			
Hematologic	21 (58.3%)	18 (30.5%)	0.01
Solid	15 (41.7%)	41 (69.5%)	
Second cancers:			
Hematologic	29 (80.6%)	20 (33.9%)	<0.001
Solid	7 (19.4%)	39 (66.1%)	

Data expressed as number, & %, and analyzed by Fisher's exact test.

Most second hematologic malignancies developed early within five years from primary malignancies then declined progressively as time passed, while most second solid malignancies developed more than one year after the development of primary ones and increased later on because they were mainly metachronous tumors (LR=9.5, $p=0.023$), (Fig. 7).

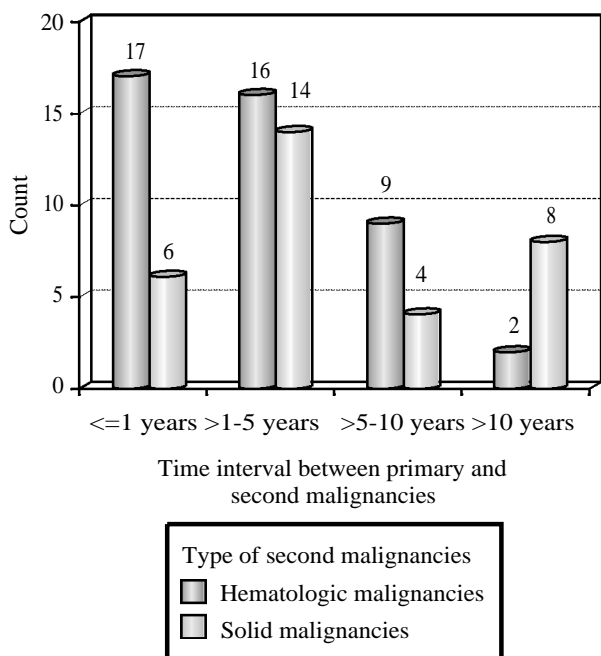


Fig. (7): Type of second malignancies developed related to time interval.

There was a significant difference in the timing of second malignancies, most synchronous tumors were solid ones while most metachronous tumors were hematologic tumors, $p=0.002$, Table (5).

Table (5): Differences in timing between hematologic and solid cancers.

Timing	Hematologic cancers=49	Solid cancers=46
Metachronous	45 (91.8%)	30 (65.2%)
Synchronous	4 (8.2%)	16 (34.8%)
p-value	0.002	

Data as numbers and percentages, analyzed by Fisher's exact test.

The mean duration of medical treatments used for primary cancers was significantly longer before the development of second solid cancers compared to that of second hematologic malignancies (32.03 ± 4.5 months vs. 22.9 ± 4.7 months, $p=0.005$), (Fig. 8).

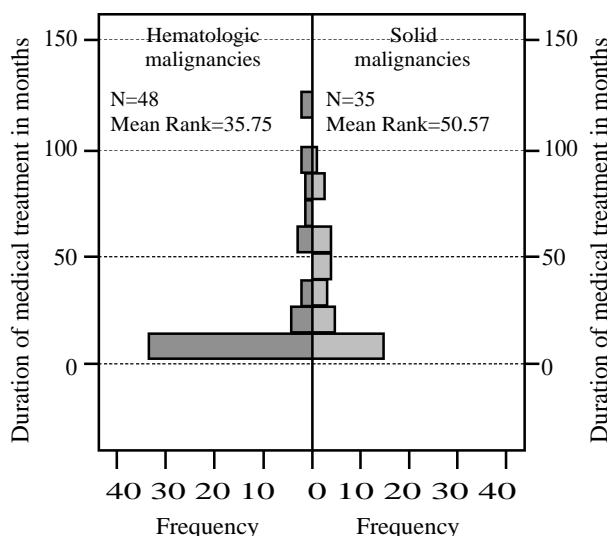


Fig. (8): Differences in the duration of medical treatments between hematologic and solid malignancies, Mann Whitney test, $p=0.005$.

In addition, we found no significant differences in the metastatic or non-metastatic stages between primary and second solid malignancies, $p=0.3$, Table (6). Furthermore, no significant differences in the overall control rate among all primary malignancies and second malignancies, $p=0.9$ (Fig. 9).

Table (6): Differences in stages between primary and second malignant tumors.

Solid tumors	Metastatic	Non-metastatic
Primary (%)	12 (21.4%)	44 (78.6%)
Second (%)	16 (36.4%)	28 (63.6%)
p-value	0.3	

- Data expressed as number and % and analyzed by Chi² test with continuity correction.

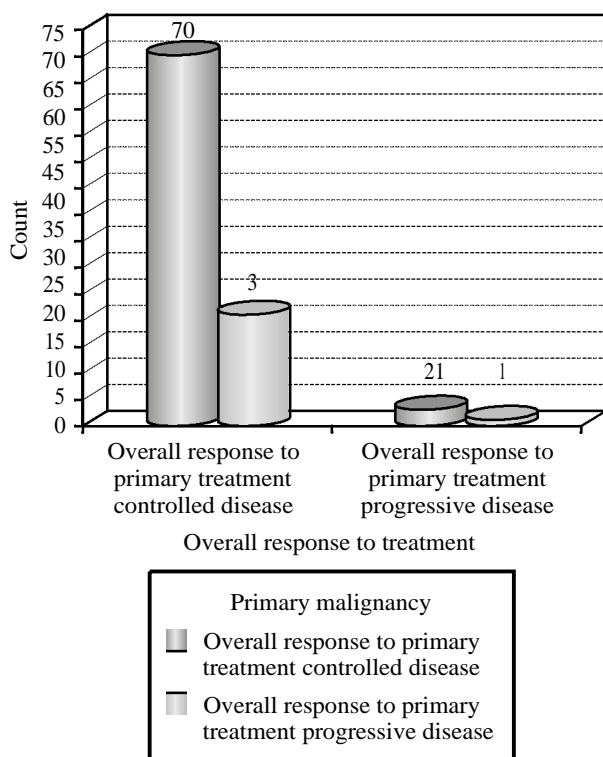


Fig. (9): Differences in the overall response rate to treatments between primary and second malignancies, likelihood ratio, $p=0.9$.

Discussion

A long time ago, Warren and Gates had put criteria defining double primary malignancies which were refined later on, including the presence of histologic confirmation of both primary malignancies and there should be at least 2cm or more of normal mucosa in between, and if they were in the same location, they should be separated by at least 5-year time intervals, both of these definitions were considered after prompt exclusion of being remote metastases [9-11].

Regarding our results, we detected significant differences in the number of synchronous and metachronous states concerning second primary cancers, also in the duration of medical treatments of primary cancers that could be accused of the development of second primaries between hematologic and solid malignancies, moreover, most hematologic second primaries developed earlier than solid cancers. On the other side, we did not find any significant differences regarding the median ages, the stages, and the response rates between primary and second cancers.

In a Chinese observational study [12] involving 15,683 patients with cancers, 161 (1%) had multiple primary cancers, of these, 48.4% had synchronous

tumors and 51.6% had metachronous tumors with a median age for the former 64 years, and for the later was 57 years, also the median time interval between metachronous tumors was 60 months, our results deviated from the previous study where synchronous tumors represented 21.1% and 78.9% for metachronous tumors, the median age for synchronous and metachronous were 55 and 49 years respectively, and a much lower median time interval of 22 months was detected.

The distribution of synchronous second tumors varied between previous studies from 30%-55% [12-14], the current results did not match with the previous studies where we reported 21.1% of patients had synchronous tumors, and 78.9% had metachronous tumors that could be attributed to different population characteristics, and different hospital registries of cancers.

The current results demonstrated a significant female predominance for both primary and second cancers, a finding that was comparable to Bagri et al., [15] but inconsistent with other reports [12,16,17] and could be explained by the high frequency of breast cancers. Patients who were still under treatment or close follow had second malignancies that were detected early and in the curable stage, this was why hematologic malignancies were discovered earlier than solid ones also these results were in alignment with Bagri et al.

Although the risk of second primary cancer is rising, however the responsible mechanisms for development are not fully explained, genetic susceptibility and exposure to DNA damaging agents such as radio/chemotherapy have been largely proposed, also exposure to common risk factors like tobacco smoking, and alcohol consumption is responsible for field carcinogenesis with increased risk for second primaries. Patients with cancer are considered at high risk for infectious diseases particularly COVID-19 with noted similar manifestations between SARS-CoV-2 and cancer, especially cytokine storm [18], in addition, type I interferon responses are pivotal for immunogenic responses against cancer and infectious diseases with subsequent immunosuppression that occurs in both cancers and COVID-19 [19], so the clinical relevance between primary cancers and COVID-19 infection commonly depends on cytokine storm, INF-I, androgen receptors, and immune checkpoint signaling disturbances that could be attributed to the development of second malignancies.

All our study patients had a history of COVID-19 infection as defined in their medical records by

either positive PCR, chest CT findings characteristic for COVID-19, or contact with an infected relative before the discovery of second tumors, we proposed that immunogenic crosstalk between primary cancers and COVID-19 infection had occurred to result in second primaries. Furthermore, the low compliance of patients for follow-up, and the tendency to neglect new symptoms or be misdiagnosed as late effects of previous primary therapies could partially explain the advanced stages for both primary and second cancers.

Collectively, we tried to emphasize that meticulous screening of patients with cancer is required especially in the era of an infectious viral outbreaks to improve the outcomes among patients who will develop second tumors, not only those who have a family history or risk factors for second tumors but also the risk of second tumors should not be underestimated among survivors of primary tumors. Furthermore, comprehensive analysis of second tumors requires observation of a considerable number of patients from multiple centers and hospitals in Egypt for more than 10 years considering variable genetic, environmental, and personal risk factors.

Conclusion:

Our study revealed that 21.1% and 78.9% of patients had synchronous and metachronous tumors, most synchronous tumors were solid and most metachronous tumors were hematologic, female patients were significantly associated with multiple primary malignant tumors compared to males, and the duration of medical treatments had a significant impact on the type of second tumors, generally, second malignant tumors was not uncommon, their detection had recently increased because of great success in the treatment of primary tumors with prolonged survival and progress in diagnostic and staging modalities. Careful timely surveillance of cancer patients is mandatory especially those who survived COVID-19.

Conflict of interest: The authors declared that they do not have no conflict of interests.

Authors contribution: AR is the first author of the manuscript analyzed and interpreted all data and. DA made contributions to the protocol design, and all authors drafted the manuscript. DA, AZ and provided support regarding the statistical analysis and discussion. KF performed all methodological procedure and was responsible for data analysis and manuscript revision. All authors have reviewed and approved the final version of the manuscript.

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Data availability statement: All data generated or analyzed during this study were included within the submitted article.

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خطر الإصابة بورم خبيث ثان في صعيد مصر في عصر COVID-19 : تجربة سرطان متعددة المراكز

الخلفية والهدف : مسببات السرطان الثانى معقد ومتعدد العوامل مع عبء متغير من الورم الخبيث الثانى يحمله أنواع مختلفة من السرطانات الأولية، لذلك فى الدراسة الحالية، قمنا بتقييم حدوث السرطانات الثانية بين الناجين من السرطان خلال السنوات الثلاث الماضية تفشى مرض كوفيد فى ثلاثة مراكز لعلاج السرطان بمحافظة أسيوط. قسم الأورام السريرية جامعة أسيوط والتأمين الصحى بأسيوط ومعهد جنوب مصر للسرطان، وكذلك الخصائص السريرية المرضية ونتائج العلاج بناءً على سجلات المرضى.

الطريقة : قمنا بتجنيد جميع الحالات المعروضة على المراكز المذكورة مسبقاً خلال الفترة من بداية عام ٢٠١٩ إلى نهاية عام ٢٠٢١ مع تشخيص مؤكد للسرطان الأول والثانى الجديد.

النتائج : جمعنا خمسة وتسعين حالة من الأورام الخبيثة الثانية الذين كانوا لا يزالون يخضعون لعلاج أورامهم الأولية ، أو تحت المتابعة المجدولة بعد الانتهاء من العلاج، وكان لديهم نطاق من ٣ إلى ٨٦ عاماً. ٢١.١٪ لديهم أورام متزامنة و ٧٨.٩٪ لديهم أورام سرطانية، وكان متوسط المدة للعلاجات الطبية للأورام الأولية ١٢ شهراً، ولا توجد فروق ذات دلالة إحصائية فى نمط العمر والجنس بين متزامن ومتغير الزمن، ٥٣.٧٪، و ٤٦.٣٪ لديهم أورام دموية وأورام صلبة ثانية على التوالي، معظم الأورام الدموية الثانية تطورت فى وقت أبكر من الأورام الصلبة ($p=0.023$)، كان هناك بروز أنتى لكل من الأورام الخبيثة الأولية والثانية ($p=0.001$ & $p=0.01$ على التوالى)، كان معدل التحكم العام للأورام الخبيثة الثانية ٧٨.٨٪، وبلغت نسبة الوفيات ٣٤.٧٪.

الخلاصة : بشكل عام، لم تكن الأورام الخبيثة الثانية شائعة، فقد زاد اكتشافها مؤخراً بسبب النجاح الكبير فى علاج الأورام الأولية مع البقاء على قيد الحياة لفترات طويلة والتقدم فى طرق التشخيص والتدريب. مطلوب مراقبة دقيقة فى الوقت المناسب لمرضى السرطان خاصة أولئك الذين نجوا بعد COVID-19.