

# Synchronous and Metachronous Malignant Tumours expect the un-expected

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## Abstract

**Objective:** To evaluate occurrence of synchronous and metachronous malignant tumours, to find tumour types, age group, and relationship to treatment received.

**Methods:** Previously diagnosed 1st primary tumour cases experiencing a synchronous or metachronous tumour, seen at AOI from February 2003 to August 2009 (78 months) were included. The cases were analyzed for morphology/histology of 1st primary tumour, age and gender of patient, treatment received for first tumour, time interval between the 1st and 2nd primary tumour, morphology/histology of second tumour, and the treatment conferred for 2nd tumour.

**Results:** The 2nd synchronous and metachronous tumours were 46/4025 (1.14%), in 18 males and 28 females (M:F 1:1.6). The age range was 16-75 years (median 43 years). The follow up time was 24-150 months. The time to 2nd primary tumour was 2-132 months. The 1st primary tumours were breast, ovary, GIT and urinary bladder. The patients received surgery, radiotherapy, chemotherapy, and hormonal therapy alone or as multi-modality treatment for the 1st tumours. The frequent 2nd tumours were breast, ovary and Gastro Intestinal tumours.

**Conclusion:** It is imperative that patients with a primary malignant tumour should be thoroughly, closely, and regularly followed. Genetic counseling, risk estimation, cancer screening and chemoprevention must be emphasized. Every subsequent occurring tumour should be biopsied. The effect of 1st tumour on the 2nd or vice versa are still not fully understood and need exploration. The 2nd primary tumour is usually more aggressive, treatment resistant, and metastasizes early requiring a more aggressive treatment strategy (JPMA 60:905; 2010).

## Introduction

The incidence of 2nd primary synchronous or metachronous tumour is increasing and reported as high as 10%. Meta analyses show the frequency of second tumour (SPT) as 3-5%, a third tumour (TT) as 0.5%, and a fourth tumour (QT) as 0.3%.<sup>1,2</sup> Persistent environmental carcinogenic influence, genetic instability, field cancerization, increasing use of systemic chemotherapy or radiotherapy, hormonal manipulation, targeted/genetic therapy, immune suppression, tissue transplantation, and improved survival after 1st primary are implicated.

Synchronous (within 2-6 months of diagnosis of 1st primary tumour) and metachronous (more than 6 months after 1st primary) subsequent malignant tumours are an increasingly frequent phenomenon in clinical oncology practice globally, irrespective of geographic and environmental influence suggesting a genetic predisposition or treatment related factors in malignant disease.<sup>1-18</sup> It is an important survivor issue in oncology management and long term follow up of these cases. The tumours encountered in less than 2 months are often termed as simultaneous tumours. BILLROTH first reported multiple primary tumours of different histology, in different organs, at different time interval in same individuals in 1860.<sup>1,7,11</sup> Incidence of 2nd

primary and subsequent tumours is increasing due to clinical awareness. In SEER analysis<sup>2</sup> (1973-99/2.7 million cases) 10% had reported second tumour. A second (SPT - second primary tumour), third (TT - third tumour), and fourth (QT - quartant tumour) primary tumor is reported as 3-5%, 0.5%, and 0.3% in general population; in a different organ of a different histogenesis.<sup>7</sup> About 2-12% of cases who have two synchronous or metachronous tumors tend to develop a third or fourth primary malignant tumour.<sup>1,19</sup> The etiologic implicating factors are a first primary tumour itself, field cancerization (Head and Neck),<sup>17</sup> persistent environmental carcinogenic influence,<sup>7</sup> genetic predisposition,<sup>4</sup> chemotherapy,<sup>9,11,20-22</sup> radiation therapy,<sup>6</sup> hormonal therapy, targeted therapy or genetic manipulation,<sup>1,11,14,23</sup> Immune suppression<sup>4</sup> and increasingly frequent tissue/organ transplant. Ozone depletion and continuous exposure to ionizing radiation are also implicated. A better overall survival achieved in different tumour types is also an important factor to manifest a second or subsequent tumour in an individual's life span, due to increasing survival in many tumours. The first primary tumour in these situations is called the Index tumour. The subsequent tumours should have a distinct histology, and a metastasis from first primary must be excluded.<sup>2,5</sup> There, however, are some grey areas in this respect<sup>3,5,10,20</sup> like tumours of same histology in different

organs, existence of paired organs, tumours of different histology in the same organ, time interval elapsed between these tumours, and coding of these tumours.<sup>5</sup> The common synchronous and metachronous tumours seen are lymphoid, haematologic, breast, lung, bone, melanoma, thyroid and soft tissue sarcomas.<sup>10-12,21-25</sup> Tumour bed edges and radiation infield areas are risk areas in those who received radiation therapy for the 1st primary tumour. The chemotherapy related tumours usually develop at site of contact (aero-digestive mucosa), site of absorption (GIT), site of metabolism (liver) and excretion (Kidney, lung).<sup>11,23</sup> These tumours are usually smaller in size, more aggressive, less nodal but higher and early systemic metastasis. They are usually resistant to therapeutic manipulations probably due to resistant clonal expansion, chemo radio resistant gene activation, immune compromised and poor physiological status of the patient. The latent time interval between the first primary and subsequent tumour may be as high as 15 years in some cases.<sup>3,6</sup>

This study was carried out to assess the occurrence of synchronous and metachronous tumours in the given population over a specified period of time. It was also intended to look into the age group vulnerability, the

CT in 14/46, bone scintigraphy) means were used to exclude a metastasis from first primary tumour.

The data was collected and analyzed with respect to age, gender, location of first primary tumour; location of second or subsequent synchronous or metachronous tumour, the time elapsed between the two tumours, the treatment received for the first tumour with outcome, and treatment offered for the second tumour. The results were presented in the form of tables, figures, or in descriptive mode.

## Results

The cases of biopsy proven synchronous or metachronous tumours (second or third primary tumour) seen at African Oncology institute during the aforesaid period were 46/4025 (1.14%). There were total 18 male and 28 female cases, with a male to female ratio of 1:1.6. The youngest patient was 16 years while the highest age seen was 75 years, with a mean age of 43 ± 4.3 years. The duration of follow up of these cases was 24-150 months from the diagnoses of first tumour. The minimum time to have a second tumour was 2 months while the maximum was 11 years. The number of synchronous tumours was 11, with 4 males and 7 female cases (Table-1). The first primary in the

**Table-1: Synchronous Second tumours.**

Demographic Data	Male 04	Female 07	Age Range 38-58 years	Average Age 46.2 years	M:F ratio 01:01.8
First Tumour	Breast 07	GBM 01	SCLCA 01	Adeno Ca Pancreas 01	TCC Bladder 01
Treatment Received	Surgery 07	Chemotherapy 09	Radiotherapy 07	Hormonal 03	Multi-modality 09
Time Elapsed	Minimum 02 months	Maximum 05 months	Average 3.4 months		
Second tumour	Breast 05	Colon 03	NHL 01	TCC ureter 01	CML 01
Treatment Received	Surgery 07	Chemotherapy 08	Radiotherapy 04	Hormonal 03	Multi-modality 05

CA: Cancer, CT: chemotherapy, RT: radiotherapy, TCC: transitional cell carcinoma: HRT: hormonal therapy, GBM: glioblastoma multiforme, NHL: Non Hodgkin's lymphoma, CS: clinical stage, TAM: tamoxifen, CML: chronic myeloid leukemia, Neoadj: neoadjuvant.

histology and morphologic sites of these tumours, to see any relationship between 1st and the subsequent tumour, and any potential impact of treatment received for the first tumour.

## Patients and Methods

The cases seen at African Oncology Institute Sabratha Libya from February 2003 to August 2009 (78 months), having a biopsy proven first primary tumour, were included in this study. The other inclusion criteria was a biopsy proven second or third primary synchronous (within 2-6 months of 1st tumour) or metachronous (after 6 months from the diagnosis of 1st tumour) malignant tumour in a different organ in the same individual. A thorough histopathology (aided by immunocytochemistry wherever feasible and available, in 38/46 cases), serologic (serum tumour markers in all the cases), and radiologic (ultrasonography, Computerized tomogram, magnetic resonance imaging, PET-

majority was breast Cancer of female. The second tumour was also breast most commonly in female patients. Table-1 gives the detail of these cases with respect to age, sex, first primary, treatment of 1st tumour, time elapsed between the two tumours, the type of second tumour, and treatment given for this second synchronous tumour.

Table-2 shows the similar data of metachronous second tumours found in the male patients. There were 14 male cases in total, having a second primary metachronous tumour. The minimum time to second tumour was 8 months and the maximum time to development of this second tumour was 11 years. The commonest second tumour encountered was colorectal cancer. The analysis of all these cases is elaborated in depth in Table-2. There was only one case that has a third tertiary tumour (first as Larynx, second as Tongue and then third as maxillary sinus).

There were 21 cases of metachronous second primary

**Table-2: Metachronous Second Tumours.**

Demographic Data	Minimum Age 16 years	Maximum Age 75 years	Average Age 45.2 years		
<b>MALES 14</b>					
First Tumour	TCC Bladder 03	CA Prostate 02	Head and Neck 02	Lung CA 02 (SCLC+NSCLC)	GBM 01 MFH 01 Pancreas 01 RCC Renal 01 NHL 01
Treatment Received	Surgery 09	Chemotherapy 08	Radiotherapy 09	Hormonal 02	Multi-modality 10
Time Elapsed	Minimum 8 Months	Maximum 11 years	Average 41.1 months		
Second Tumour	Colo-rectal 05	HL 02 MM 01	CBD 01 NSCLC 01	TCC ureter 01 Tongue 01 Stent 01	PNET jejunum 01 Thyroid 01 Multi-modality 08
Treatment Received	Surgery 10	Chemotherapy 09	Radiotherapy/Iodine 04		
<b>FEMALES 21</b>					
Demographic Data	Minimum Age 33 years	Maximum Age 55 Years	Average Age 44.6 years		
First Tumour	Breast 03	Ovary 05	Colo-rectal 03	CAGB 03	Astrocytoma 01 Vulva 01 TCC U. bladder 02 Thyroid 02 NPC 01
Treatment Received	Surgery 17	Chemotherapy 11	Radiotherapy 07 Iodine 01	Hormonal 02 Intra-vesical 02	Multi-modality 15
Time Elapsed	Minimum 7 months	Maximum 72 months	Average 24.2 months		
Second Tumour	Colo-rectum 06 Stomach 02 Oesophagus 01 CAGB 01	Ovary 03 Breast 01 Endometrium 01 Vulva 01	NHL 03 CML 01	Thyroid 01	
Treatment Received	Surgery 14	Chemotherapy 13	Radiotherapy 07	Stent 01 ASCT 01	Multi-modality 12

ASCT: autologous stem cell transplant, CML: chronic myeloid leukemia, NHL: non-Hodgkin's lymphoma, NPC: nasopharyngeal carcinoma, RT: radiotherapy, BCG: bacilli-calmette Guerin, CAGB: carcinoma gall bladder: BSC: Best support care, MFH: malignant fibrous histiocytoma, PNET: peripheral neuroectodermal tumor, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, CS: clinical stage, TCC: transitional cell carcinoma, CBD: common bile duct, HL: Hodgkin's lymphoma, RCC: renal cell carcinoma.

**Table-3: First Ten 1st primary, 2nd synchronous, and 2nd metachronous Tumours.**

Site	1st tumour	2nd Synchronous tumour	2nd Metachronous tumour
Colon/Rectum/GIT	3	3	15
Lymphoma, Leukaemia, Myeloma	1	2	7
Head and Neck (Larynx, tongue, NPC, Thyroid)	5	0	3
Ovary	5	0	3
Hepatobiliary, Pancreas	5	0	2
Breast	10	5	1
Lung	3	0	1
Urinary bladder, Ureter	6	1	1
GBM, Astrocytoma	3	0	0
Prostate	2	0	0

tumour seen in females during this aforesaid period of time (Table-2). The common first primary was CA ovary or breast, while the commonest second tumour was colorectal CA. The time interval between the two tumours varied between 8 months to 72 months. The detailed analysis of these cases is provided in Table-2.

The majority of cases in all three sub groups received multi-modality treatment, chemotherapy, radiation therapy,

and hormonal treatment in addition to surgery. All these modalities either alone, or in combination have the potential to induce a second tumour in a favourable environment.

Table-3 shows relationship between the 1st primary, 2nd synchronous, and 2nd metachronous tumours. The common 1st primary tumours were breast, ovary, and head and neck. Breast is the commonest synchronous tumour while GIT is the commonest site of metachronous tumour, independent of 1st primary tumour.

### Discussion

Synchronous and metachronous second, third, or fourth primary distinct tumours are frequently and increasingly encountered in oncology clinical practice of recent time.<sup>1-5</sup> A current day modern and sophisticated life style may be responsible in some cases.<sup>7</sup> A better overall and prolonged cancer survivorship due to improved treatment and early diagnosis are obviously one of the known possible reasons.<sup>7,8,10</sup> An increased and frequent use of cytotoxic chemotherapy drugs in many lines as patient is chemo eligible,<sup>6,11-13</sup> and higher or repeated radiation therapy exposure due to better techniques and delivery systems are also implicated.<sup>6,12</sup> Frequent and increased organ transplant,

immune modulation,<sup>4</sup> field cancerization, continuous carcinogen exposure from environment, progressive ozone depletion, and multitude of genetic factors may also be implicated as possible causal factors.<sup>6,8,12,17,21</sup> The use of newer moieties like hormonal manipulations, target therapies, genetic manipulation, and immune modulators may also be involved.<sup>4</sup> The criteria to have a definite, confirmed, an undoubted second or subsequent tumour has been a matter of debate and strict definite criteria need to be adopted to rule out a metastasis from the first primary tumour.<sup>3,5,9,15</sup>

The frequency of these second synchronous and metachronous tumours is consistently lower in series from the developing World, as also seen from our data.<sup>1-2,4-9</sup> The international data also indicate the prevalence of lymphoid or haematologic malignancies as second tumour, which was not observed in the data presented. This may reflect a presentation at a late advanced stage of first tumour or a sub-optimal survivorship from this tumour. It may well be a reflection of poor follow up of these cases in the long run. There may be yet unexplored genetic or environmental factors playing a role.

The interaction of the two primary tumours with each other in the same individual is also an interesting phenomenon and needs to be studied in further detail. This interaction can range from etiologic influences, pathogenesis, morphologic site predilection, pathobiology, symptom complex, diagnostic testing, treatment decisions, response to treatment in terms of outcome, and survivorship. Second synchronous tumours in the same organ or in paired organs are often a dilemma of diagnosis,<sup>13-14,16,19</sup> and only sophisticated diagnostic aids like molecular genetics can definitely differentiate them as two distinct tumours.<sup>2,5</sup> SEER (Surveillance Epidemiology and End Results) programme is working in this regard to define, re-define, and put diagnostic and differentiation strict yet applicable and reliable criteria.<sup>2</sup> Some tumour types have a high rate of exhibiting a second primary tumour like small cell lung cancer.<sup>6</sup>

There are reported profound differences in the incidence trends and prognostic outlook between synchronous and metachronous bilateral breast cancer diagnosed at different ages. The second or subsequent tumour often exhibits unique features as compared to a first primary tumour.<sup>3,4,7,14,24,25</sup> It is widely believed and often observed that second or subsequent tumour is often more aggressive, resistant to treatment manipulation, and has a more early metastasis. This might be a reflection of tumour genetic factors or a fact that these tumours arise in a host with a compromised haematologic, renal, or hepatic reserve. This often makes the adequate, optimal treatment options a far optimistic reality influencing the final outcome. Adjuvant chemotherapy has a dual effect on metachronous cancer: it reduces the risk, while at the same time it seems to worsen the

prognosis.<sup>11,15-16,19-21,25</sup>

## Conclusion

Syncnchronous and metachronous 2nd, 3rd, or 4th primary tumours are a dreadful reality in an oncologic scenario. This is likely to increase in future in clinical practice due to frequent organ transplant, increasingly complex carcinogenic environment, frequent use of cytotoxic and target molecules in treatment, higher possible dose delivery in radiation therapy, and a far better cancer survivorship. The interaction between two tumours is complex and not yet fully understood. It is imperative to remember this dreadful reality and every cancer patient, whether in complete clinical remission, should be regularly and thoroughly followed through the entire life span. An essential and standard surveillance strategy in this respect is warranted. It is also important that all forms of cancer treatment be evaluated for their potential of mutagenic or transformation capability to induce a cascade of subsequent tumour even as a very late phenomenon. It is at present too optimistic to comment on either the cause or effect relationship between the simultaneous, synchronous or metachronous subsequent tumours. A variety of multi focused and multi dimensional studies are warranted to answer this yet unresolved quest. An appropriate prevention strategy need to be tailor made and incorporated in every national cancer control programme. These tumours, due to their specific biologic behaviour, demand aggressive treatment plan where ever applicable and eligibility permit. This issue is more complicated by the practical observation that they arise in patients whose functional reserves are already compromised, are immune compromised, and often in-eligible to receive further more aggressive treatment.

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