Multiple primary tumours: challenges and approaches, a review

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ABSTRACT

When in a patient more than one tumour in the same or a different organ is diagnosed, multiple primary tumours may be present. For epidemiological studies, different definitions of multiple primaries are used with the two main definitions coming from the project Surveillance Epidemiology and End Results and the International Association of Cancer Registries and International Agency for Research on Cancer. The differences in the two definitions have to be taken into consideration when reports on multiple primaries are analysed. In this review, the literature on multiple primaries is reviewed and summarised. Overall, the frequency of multiple primaries is reported in the range of 2–17%.

Aetiological factors that may predispose patients to multiple primaries can be grouped into host related, lifestyle factors and environmental influences. Some of the most common cancer predisposition syndromes based on a clinical presentation are discussed and the relevant genetic evaluation and testing are characterised. Importantly, from a clinical standpoint, clinical situations when multiple primaries should be suspected and ruled out in a patient are discussed.

Furthermore, general principles and possible treatment strategies for patients with synchronous and metachronous multiple primary tumours are highlighted.

INTRODUCTION

Significant progress has been made in the prevention, diagnosis and treatment of malignant tumours.[1] As a result of screening programmes and improvement in diagnostic procedures, cancer can be detected at an earlier stage. Significant treatment advances have led to increased overall survival in patients with advanced cancer. As of early 2014, nearly 14.5 million people were alive in the USA with a history of cancer. Some of these people are on active anticancer therapy, others have been diagnosed and treated many years ago with no current evidence of tumour. For Switzerland, an estimate reported 2.08% of cancer survivors in 1990 with an expected increase to 3.7% in 2010.[2]

The fact that patients may have multiple primary tumours is not new and already in 1921 a report found in 3000 cases of malignancy '4.7% of cases of multiple growth'.[3] In epidemiological studies, the frequency of multiple primaries is reported to be in the range of 2–17%.[4–8] Many factors can influence the reported numbers of multiple primaries, namely the definition that was applied (see below), the follow-up time since the longer patients are followed up after a primary cancer diagnosis, the higher the likelihood that they may develop a second malignancy and importantly also the patient population studied.[9]

Today, the situation of patients with multiple primaries is of increasing relevance and importance. Apart from many reports in the literature on the frequency of multiple primaries, the practical implications of the management of patients with multiple primaries are rarely discussed. When in a patient two active malignancies are diagnosed at the same time, the challenge is to find an anticancer therapy strategy that covers both cancer types without increased toxicity or relevant pharmacological interactions and without negative impact on the overall outcome. In a patient with a previous cancer history and potentially prior anticancer therapy, it can be difficult to establish the diagnosis of an additional primary because, for example, newly developed metastases could have developed from the first cancer diagnosis but could also be part of a second malignancy. In daily clinical practice, it is important to recognise these situations and to perform the adequate investigations because of relevant implications on subsequent therapeutic management strategies. Multiple primaries also impact enrolment in clinical research protocols because patients with a prior cancer history or with current active secondary malignancy are generally excluded on most clinical trials.

This review will discuss and summarise the topic of multiple primary tumours from an epidemiological viewpoint and will review some of the large cohort studies on multiple primaries. Aetiological factors and genetic syndromes predisposing for multiple primaries will be discussed. Furthermore, clinical situations when a treating physician should

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take the possibility of multiple primaries into consideration will be highlighted.

DEFINITION OF MULTIPLE PRIMARIES

Multiple primaries are defined as more than one synchronous or metachronous cancer in the same individual. For epidemiological studies, tumours are considered multiple primary malignancies if arising in different sites and/or are of a different histology or morphology group. This avoids misclassification of multifocal/multicentric tumours or metastases as multiple primaries. A cancer is classified as index cancer if there has been no prior record of invasive cancer.[10]

The definitions and understanding of a multiple primary have changed over the time and may differ from one study to another. The two most common definitions currently used are provided by the Surveillance Epidemiology and End Results (SEER) project and the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC).[4] One of the main differences is that according to IACR/IARC, several groups of topography codes of International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) are considered one site in the definition of multiple primaries (IARC 2004). For example, the colon is regarded as one site while the SEER considers single tumours of different parts of the colon as single tumours. Further differences are that IACR/IARC apply much broader histological groups and rules not being time dependent. The use of the different guidelines can result in numbers which are different by several percentage points (eg, for breast or colon cancer). European cancer registries generally prefer the use of the IACR/IARC definitions.

The SEER database recommends to use a 2-month period to distinguish between synchronous and metachronous multiple primaries.[11] Rules according to the IARC suggest the registration of synchronous tumours diagnosed in an interval of less than 6 months (or metachronous if more than 6 months) if arising in different sites.[12]

Epidemiology of multiple primaries

The burden of second primary malignancies in a growing and ageing population of first cancer survivors has increased over the last decades.[2] Factors accounting for the increasing frequency of multiple primaries are improved diagnostic tests, increasing and more sophisticated treatment, as well as improved screening and surveillance of patients with cancer, for example, screening for colorectal and breast cancers.[4 9 13–17] Cancer survivors may be susceptible to developing second primary malignancies due to a variety of unique factors, including cancer predisposition syndromes or special tumour characteristics, environmental exposures and late effects of therapies (table 1). Caucasian ancestry, index cancer diagnosed at younger age, lower stage and with generally indolent clinical behaviour with longer survival, as well as positive family history are reported to harbour excess risk for multiple primaries.[11]

The incidence of multiple primaries in a cancer population varies between 2.4% and 8%, up to 17% within 20 years of follow-up (table 2).

The risk of developing a second primary malignancy is varying in different cancer sites and is reported in a range from 1% (primary liver malignancy) up to 16% (primary bladder cancer).[18] Weir *et al* found an incidence of multiple primaries of 19.7% following the SEER guidelines (or 16.9% IACR rules) in colon and 21% (SEER; 19.9% IACR) in patients with lung cancer.[6] Amer *et al* found similar incidences of multiple primaries in patients with colon cancer; however, they only reported 5.6% multiple primaries in patients with lung cancer.[11]

Long-term survival with multiple primaries is variable and is influenced by cancer type and stage at diagnosis. Genetic factors, behavioural influences, lifestyle and comorbidities generally influence patient's outcomes. In

Table 1	Epidemiological factors of multiple primary tumours	
Epidemiological factors of multiple primaries		
Host factors	Genetics	For example, ancestry, Li-Fraumeni and BRCA mutations
	Hormonal factors	For example, hormonal therapy and endometrial cancer
	Prior cancer diagnosis and treatment exposures	The incidence of a second malignancy is higher in a person with a previous cancer diagnosis compared with a person of the same age group without a prior cancer
Lifestyle factors	Alcohol	These are risk factors for several cancer types and are therefore more likely to develop more than one of these predisposed cancer types compared with people without these lifestyle factors
	Tobacco	
Environmental influences	Geography	For example, cancer risk in areas of increased radon exposure
	Pathogens	For example, infections (human papillomavirus, Epstein-Barr virus)
	Occupation	For example, profession-associated cancer types like mesothelioma in workers with asbestos

Table 2 Incidence of multiple primaries over all cancer sites in the literature

Number of patients evaluated	Geographic region	Frequency of multiple primaries	Mean follow-up (years)	Definition used for multiple primary (SEER/IACR/IARC)	Reference
19 252	Italy	2.4%	2.5	IACR	[5]
1 015 564 men	USA	15.8%	NA	SEER	[6]
951 022 women		14.4%		IACR	
		17.2%		SEER	
		14.55		IACR	
334 168	Victoria, Australia	4.3%	5	IACR	[8]
		7.7%	10		
		12.4%	20		
2 919 023	22 European countries	6.3%	NA	IACR	[7]
57 393	West of Scotland	5%	5	IACR	[4]
938	Netherlands	7%	NA	NA	[17]
1873	USA	7.2%	5	SEER	[11]
		11.4%	10		
		13.3%	15		
		14.8%	20		
		17.2%	>20		
1953	USA	2.15%	20	NA	[14]
1 635 060	Italy	6.3%	14	IACR	[16]
82 671	Switzerland	8.17%	6.6	IACR	Authors of this publication

IACR, International Association of Cancer Registries; IARC, International Agency for Research on Cancer; SEER, Surveillance Epidemiology and End Results.

general, black patients have a lower incidence of multiple primaries and also a lower relative survival independent of cancer site or stage at diagnosis (2.37% in black vs 3.41% white women age-adjusted prevalence for cancer survivors in the US population).[19] For an overview of epidemiological studies, see table 2.

The global cancer burden according to IARC in 2012 was 14.1 million new cases and 8.2 million cancer deaths and is estimated to increase by 2030 to 21.7 million new cases and 13 million deaths.[20] With this increase alone, the number of patients with multiple primaries will grow significantly.

In the following short sections, the occurrence of multiple primaries in several common cancer types will be summarised, not in a systematic approach but to provide some ideas of some of the available data on multiple primaries. For details and further reading, several good reviews are referenced.

Multiple primaries in female patients with breast cancer

Coyte *et al* assessed the impact of these different definitions for 8386 women diagnosed with breast cancer. Within 5 years after the diagnosis of primary breast cancer, a total of 98 secondary breast cancers were diagnosed.

When applying the SEER guidelines, 79 of the reported secondary breast cancers qualified as multiple primaries, but according to the IARC/IACR guidelines, it was only one case.[4]

In patients with breast cancer, the incidence of multiple primaries has been reported in the range of 4.1% (Kim *et al* 108 patients, 45.9 months follow-up, guideline not available) to 16.4% (Weir *et al* 301 963 patients, max. 10 years follow-up, SEER, in IACR only 10.4%).[6 11 21] The median time to a second malignancy was between 5 and 8 years.[21 22]

Hormonal treatment of a primary breast cancer increases the risk for endometrial, gastric, colon and ovarian cancers with an excess risk for endometrial cancer observed especially after tamoxifen therapy.[22]

Reproductive/hormonal and genetic factors (eg, BRCA1, BRCA2) as well as obesity are recognised as common risk factors for multiple primaries (table 3).[23]

For the breast cancer genes BRCA1 and BRCA2, there is a strong association with an increased risk for a second breast or ovarian cancer. Furthermore, there is a strong association between hereditary gastric cancer and lobular breast cancer.[9] The risk of a second breast, endometrial or ovarian cancer after breast cancer is inversely associated

Table 3 Common risk factors for multiple primaries in women with breast cancer (adapted from Wood et al[9])

Second cancer	Risk factors		
Second breast cancer	Genetic (BRCA1, BRCA2)	Endocrine/hormonal factors	Obesity
Ovarian	Genetic (BRCA1, BRCA2)	Endocrine/hormonal factors	
Uterine/endometrial		Endocrine/hormonal factors	Obesity
Colorectal cancer		Endocrine/hormonal factors	Obesity
Renal cell carcinoma			Obesity
Pancreatic			Obesity
Thyroid			Obesity
Gallbladder			Obesity

with postmenopausal status and history of full-term pregnancy.[22]

Late toxic effects of radiotherapy and chemotherapy also contribute to the increased risk for a secondary primary tumour after breast cancer. Acute myeloid leukaemia (AML) can be induced during the first 2 years after radiotherapy and is a late effect of adjuvant chemotherapy.[22] In addition, thyroid cancer, second malignancies of breast, bone, connective tissue and lung may arise after radiotherapy.

Multiple primaries in patients with prostate cancer

Rates of multiple primaries in patients with prostate cancer range from 1.14% following radiation therapy (Jin et al Meta-analysis from six references, >10 years follow-up) to 8.7% (Weir et al 335 565 patients, max. 10 years follow-up, SEER and IACR).[6 24] A systematic review with 21 studies evaluating the risk of secondary malignancies in men with prostate cancer who received radiation therapy found an increased risk of bladder cancer (HR 1.67) and colorectal cancer (HR 1.79) with notably an increased risk in patients who were treated with external beam radiation therapy and no increased risk in men who were treated with brachytherapy.[25] Radiation therapy has been shown to increase the risk for urothelial and rectal cancers and sarcomas within the radiation area after a disease-free interval of at least 5 years. Increasingly, genetic factors accounting for secondary primaries in prostate cancer are being recognised, most prominently BRCA2 mutations (see also table 5).[26]

Multiple primaries in patients with Hodgkin's lymphoma

Multiple primaries rates in patients with Hodgkin's lymphoma are reported in the range of 7.5% (Weir et al 13 198 patients, max. 10 years follow-up, SEER and IACR) to 7.8% (Bhuller et al 442 patients, up to 39 years follow-up)[6 27] and are mainly attributed to late toxic treatment effects. Survivors of Hodgkin's lymphoma with a history of radiation therapy have an increased risk for breast, lung, thyroid and colorectal cancers.[27 28] Chemotherapy is associated with an increased risk for secondary leukaemias and lung, gastrointestinal or bladder cancer, as well as soft tissue and bone sarcomas.[9] Secondary malignancies are one of the most relevant causes for

mortality in Hodgkin's lymphoma survivors.[27] Secondary leukaemia and myelodysplastic syndromes are associated with combination chemotherapy, especially etoposide in a dose-dependent manner. Etoposide-related leukaemia is distinguished from other forms of leukaemia that can be induced by alkylating agents by characteristics such as a shorter time from the end of treatment to development of leukaemia and evidence of translocation 11q23 or 21q22.[29]

Multiple primaries in patients with lung cancer

In patients with lung cancer, the incidence of multiple primaries ranges from 13.4% (Rosso et al 2 919 023 patients, follow-up not available, IACR) to 22% (Sánchez et al 1769 patients, 5–23 years follow-up, only patients with survival >3 years (12.3%)).[7] Patients diagnosed with early stage lung cancer have an increased risk for second primaries compared with the general population without a prior cancer diagnosis.[30] Many second malignancies are related to smoking. The rate of second primaries is slightly lower in first primary adenocarcinoma with a rate of 3.36 per 100 person-years than in squamous cell carcinoma with a rate of 3.77 per 100 person-years. It is highest in small cell lung cancer (SCLC) with 4.46 cases per 100 person-years. There is no significant association with radiotherapy.[30]

The most common second cancers are in the lung, especially if the first primary was a SCLC. The most common second lung malignancies are adenocarcinomas (29.9%) followed by squamous cell carcinomas (27.1%). SCLCs represent only 7.9% of the second pulmonary malignancies after a first lung cancer.[31] Also, colorectal and bladder cancers are often found as second malignancies after a primary lung cancer.

Summary on epidemiology of multiple primaries

▶ Multiple primaries are defined as more than one synchronous or metachronous cancer in the same individual.
▶ Synchronous and metachronous multiple primaries are distinguished. Definitions depend on whether SEER or the IACR/IARC rules are applied.
▶ Common risk factors for multiple primaries are as follows: inherited predisposition to cancer; cancer-

promoting aspects of lifestyle, hormonal and environmental factors; treatment of the previous primary cancer and increased surveillance of cancer survivors.[32]

► The incidence of multiple primaries varies in different primary cancer types and treatment that was applied for these cancers.

Cancer predisposition syndromes and genetic testing

Several clinical scenarios should call a clinician's attention towards the possibility of an underlying cancer predisposition, in particular the occurrence of multiple primary cancers, diagnosis at young age and in several family members. For example, metachronous breast and ovarian cancers, especially in younger patients, should prompt evaluation of an underlying hereditary breast and ovarian cancer (HBOC) syndrome associated with germline mutations in the BRCA1/2 genes, likewise prostate cancer in a young male patient with a family history of breast cancer and melanoma. Similarly, colon cancer in a young woman from a colon and endometrial cancer-prone family points towards Lynch syndrome (LS) (see also table 4 for further clinical scenarios).

Also, in the era of novel targeted agents and checkpoint inhibitors, germline and somatic mutations are becoming more important with respect to new treatment options and strategies, such as the use of poly-ADP-ribose polymerase (PARP) inhibitors in patients whose tumours display DNA repair defects (BRCA1/2, ATM) or checkpoint inhibitors in tumours with high mutational load as exemplified by microsatellite instability (MSI). This has opened another field for direct-to-consumer genetic testing, which is increasingly being offered by commercial companies through internet portals and has risen widespread concerns about accuracy, usefulness and interpretation of such tests in the absence of medical supervision and genetic counselling.[29 33] In the following, we will give a short, non-comprehensive overview of the most relevant cancer predispositions in routine oncology care, namely HBOC, LS (formerly known as hereditary non-polyposis colon cancer, HNPCC), multiple endocrine neoplasia type 1 and type 2 (MEN1, MEN2), von Hippel-Lindau (VHL) disease and Li-Fraumeni syndrome (LFS). For a more detailed overview, we recommend the review by Garber and Offit[34] as well as the ESMO guidelines on hereditary cancer syndromes.[35 36]

Hereditary breast and ovarian cancer syndrome

HBOC is a high-penetrance, autosomal-dominant breast and ovarian cancer predisposition caused by germline mutations in the genes BRCA1 and BRCA2. Its prevalence in an unselected population is estimated to be <10% but is markedly increased (up to 35%) in patients with a positive family history of breast and ovarian cancers, young age at first diagnosis, multiple metachronous breast/ovarian tumours or special ethnic groups (Ashkenazi Jews). The average lifetime risk for breast or ovarian cancer in BRCA1 and BRCA2 carriers by age 80 is up to ca. 83% and 76%, respectively;[37] for men with BRCA2 mutation, lifetime risk for breast and prostate cancers is also elevated (up to ca. 8.9%). Criteria for genetic counselling and testing referral vary between countries, but commonly include clinical features (see table 4) as well as predictive models such as BRCAPRO or Manchester Score. However, with higher awareness and apart from surveillance also emerging therapeutic consequences as PARP inhibitors, more widespread testing can be expected.

Lynch syndrome/hereditary non-polyposis colon cancer

In this autosomal-dominantly inherited cancer predisposition, germline loss-of-function mutations in DNA mismatch repair (MMR) genes combined with a second, somatically acquired hit in the tumour lead to MSI and a mutated phenotype resulting in an increased risk for colon and endometrial cancers as well as more rarely to cancers, for example, of the urinary tract, ovary, small intestine, gastric and hepatobiliary tract.[38 39] In the overall colon cancer population, the prevalence for LS is approx. 1–3% and lifetime risk in MMR gene mutation carriers for colon and endometrium cancers amounts to approx. 52–82% and 25–60%, respectively.[40 41] Referral for genetic counselling and testing is generally based on MSI immunohistochemistry results on patient's tumour tissue in conjunction with family history. As with BRCA1/2-associated cancers, MSI (sporadic and germline) recently gained more attention due to possible therapeutic consequences, as was shown, that checkpoint inhibitors seem to be effective almost exquisitely in colon and gastric cancers with MSI high tumours.[42]

von Hippel-Lindau disease

VHL disease is an autosomal dominantly inherited tumour predisposition syndrome, which is associated with an increased risk of developing various benign and malignant tumours, including retinal capillary and central nervous system haemangioblastomas, phaeochromocytomas, renal cysts and clear cell renal cell carcinomas, endolymphatic sac tumours as well as pancreatic cysts, pancreatic neuroendocrine tumours and cystadenomas of the epididymis and the broad ligament.[43] The disease penetrance is high and more than 90% of patients harbouring a *VHL* mutation develop clinical symptoms before the age of 65 years. Disease expression and severity vary considerably within and between families.[44] Preventive screening programmes have improved median overall survival of affected patients.

Li-Fraumeni syndrome

Caused by germline mutations in the 'guardian of the genome', the tumour protein p53 (*TP53)* gene, LFS is characterised by a distinct set of early onset tumours such as sarcoma, breast cancer, brain tumours, leukaemia and adrenocortical carcinoma. Due to the rarity of the syndrome until now, no standard surveillance protocols have been implemented, but recent studies could show

Table 4 Clinical scenarios and potential genetic cancer syndrome

Clinical picture, patient with a history or diagnosis of (synchronous or metachronous)	Familial cancer syndrome to think of	Full picture of familial cancer syndrome
Synchronous bilateral breast cancer or secondary (metachronous) breast cancer	Hereditary breast and ovarian cancer (HBOC) [BRCA1, BRCA2]	•Breast cancer
		•Ovarian cancer
Breast and ovarian cancers	HBOC [BRCA 1/2]	•Male breast cancer
Prostate cancer and pancreatic cancer or melanoma	HBOC [BRCA 2]	•Prostate cancer
		•Melanoma
(Multiple) renal cell carcinomas	VHL	•Renal cell carcinoma <47 years
Renal cell carcinoma and pancreatic cystic lesions	VHL	•Multiple renal cysts
Haemangioblastomas of central nervous system (CNS) and retina	VHL	•Multiple pancreas cysts and pancreatic neuroendocrine tumour
		•CNS and retinal haemagioblastomas
		•Phaeochromocytomas
		•Endolymphatic sac tumours
		•Cystadenomas of epididymis or broad ligament
Breast cancer and sarcoma	Li-Fraumeni syndrome	•Soft tissue sarcoma and osteosarcoma
Breast cancer and leukaemia	Li-Fraumeni syndrome	•Premenopausal breast cancer
		•Leukaemia
		•Brain tumours
		•Adrenocortical carcinoma
		•Lung bronchoalveolar cancer
Colon and endometrial cancers	Lynch syndrome	•Colon cancer
Colon and ovarian cancers	HNPCC	•Endometrial cancer
		•Ovarian cancer
		•Renal pelvis cancers
		•Ureteral cancers
		•Pancreatic and hepatobiliary cancers
		•Stomach and small bowel cancers
Multiple colon polpys and/or colon cancer	Familial adenomatous polyposis	•Colon cancer
		•Duodenal cancer
		•Thyroid cancer
		•Hepatoblastoma
Parathyroid adenomas and pituitary adenomas	MEN1	•Pituitary tumours
		•Parathyroid tumours
		•Endocrine tumours of the gastro–entero–pancreatic tract
		•Carcinoid tumours
Medullary thyroid cancer and phaeochromocytoma	MEN 2	•Medullary thyroid cancer
		•Phaeochromocytoma

Continued

Table 4 Continued		
Clinical picture, patient with a history or diagnosis of (synchronous or metachronous)	**Familial cancer syndrome to think of**	**Full picture of familial cancer syndrome**
		• Parathyroid hyperplasia/adenoma

HNPCC, hereditary non-polyposis colon cancer; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; VHL, von Hippel-Lindau.

long-term survival benefit for patients complying with an intensive surveillance protocol for early tumour detection.[45]

MEN1/MEN2 syndrome

Basis of the autosomal dominantly inherited MEN1 syndrome are germline mutations in the *MEN1* gene, predisposing to parathyroid adenomas, pituitary adenomas and pancreatic islet cell tumours as gastrinomas, vipomas or insulinomas.[46] Surveillance of mutation carriers should start at an early age, usually between 5 and 10 years. MEN2 is associated with medullary thyroid cancer and phaeochromocytoma and in nearly 90% of affected patients a germline *RET-proto-oncogene* mutation can be found.[47]

CLINICAL SITUATIONS WHEN TO SUSPECT MULTIPLE PRIMARIES (SYNCHRONOUS OR METACHRONOUS)

As discussed above, multiple primaries can occur in a synchronous or metachronous pattern. In the situation of a new cancer diagnosis, staging examinations are performed to assess the extent of disease but sometimes also to localise a primary tumour in the situation where a metastatic site is the first presentation of malignancy. In patients with a prior cancer diagnosis, often over the period of several years, follow-up tests and examinations are performed in order to rule out relapse.

With the increasing use of more sophisticated imaging methods, namely positron-emission tomography computed tomography (PET-CT) and whole body MRI, it is not uncommon to find suspicious lesions that might have not been detected by standard CT and/or bone scintigraphy. In a large series of 1912 patients who were scanned with PET-CT scans, lesions suspicious of additional malignant tumour were found in 4.1% of which 1.2% were histologically confirmed.[48] Not surprisingly, these secondary primaries were in the following localisations: thyroid, colon, breast, oesophagus, bile duct and head and neck regions, where even contrast enhanced CT may easily miss small tumours. In a series of 200 patients with oesophageal cancer who underwent PET-CT for staging, a total of 17% patients had synchronous multiple primary tumours, namely in the stomach, head and neck regions, colon and lung.[49]

Several clinical features should alert clinicians to the possibility that a patient may have a second primary tumour both synchronous and in the situation of a prior cancer history:

► Atypical metastatic spread of primary tumour (eg, radiologically lytic bone metastases in prostate cancer).
► High tumour burden relative to tumour marker load (eg, extensive liver metastases with low prostate-specific antigen in prostate cancer).
► New metastatic spread (eg, liver, lung) several years after a primary cancer diagnosis.
► Single new metastatic lesion after a primary cancer diagnosis (eg, single pulmonary nodule in a patient with a prior primary head and neck carcinoma).
► Chronological atypical metastatic spread (eg, relapse 5 years after primary small cell carcinoma of the lung).
► Recurrence in patients with exposure to environmental carcinogens (eg, smoking).
► Suspicion of haematological malignancy after prior chemotherapy (eg, etoposide, anthracyclines).
► Suspicion of secondary malignancy in patients with prior radiation for malignancy and especially if recurrence in prior radiation field.
► Suspicious lesion on imaging (eg, PET-CT) detected at staging or in follow-up.
► Differential standard uptake value (SUV) of suspected lesions on PET-CT (eg, lesions with very high SUV and lesions with low SUV).

In case of a suspected secondary primary, a histological confirmation should be pursued if the patient is considered for active treatment. With the advances in imaging and imaging-guided biopsy techniques, it is in most cases possible to get enough tissue for an adequate diagnosis. Importantly, the primary tissue should always be available for comparison, especially in cases of undifferentiated histologies and clinicians should inform the reporting pathologist about the fact that a primary cancer diagnosis has already been established. In case of a new diagnosis in a patient with multiple metastatic sites, the collection of more than one biopsy has to be considered.

TREATMENT APPROACHES IN PATIENTS WITH MULTIPLE PRIMARIES

Synchronous multiple primaries

The treatment of patients with synchronous multiple primaries is challenging and often a therapeutic dilemma. In table 5, a few examples of patients with synchronous multiple primaries are summarised to illustrate the difficulties that arise in daily clinical practice. Patients with

Table 5 Examples of clinical cases of patients with synchronous advanced multiple primary tumours

Patient characteristics	Malignancy 1	Malignancy 2	Therapeutic dilemma	Current management strategy
60-year-old man, former smoker	Small cell lung cancer (SCLC) Progression: after 6 cycles of cisplatin/ etoposide	Aplastic anaemia Diagnosed 4 months after completion of cisplatin/etoposide	•Chemotherapy at progression of SCLC not possible due to grade 4 neutropenia and thrombocytopenia in the setting of aplastic anaemia •Immunosuppressive therapy for aplastic anaemia with possible negative impact on SCLC	•Supportive treatment with eltrombopag for thrombocytopenia •In case of stabilisation of pancytopenia, evaluation of second line therapy for SCLC
71-year-old man, hereditary haemochromatosis	Castration-resistant prostate cancer with bone and lymph node metastases	Renal cell carcinoma with lung metastases	•Drugs active in for CRPC different than agents in RCC •TKI used for RCC endocrine drugs (abiraterone/ enzalutamide) used for CRPC: combinations not tested, no safety data, possible drug–drug interactions, expensive combinations	•Alternating treatment for the two malignancies: for example, TKI for 3–4 months for mRCC, then interruption and treatment for mCRPC for 3–4 months depending on the most significant tumour
64-year-old man, former smoker	Non-small cell lung cancer (NSCLC) stage IIIB	Rectal cancer stage I	•Chemotherapy regimens active in NSCLC generally not active in rectal cancer •NSCLC stage IIIB prognosis-defining, but untreated rectal cancer bears high risk of local complications (eg, bowel obstruction)	•Curative resection of rectal cancer (node-negative) with protective colostomy •Chemoradiation with curative intent for NSCLC (IIIB)
65-year-old woman, former smoker	NSCLC, metastatic to lymph nodes and bone, KRAS proto-oncogene (KRAS)-mutated, programmed death receptor ligand (PD-L1) expression 0%	Acute myeloid leukaemia (AML) Diagnosed simultaneously with NSCLC	•Chemotherapy for NSCLC not possible due to grade 4 neutropenia in the setting of AML •State-of-the art treatment for AML in the setting of metastatic NSCLC	•Treatment with azacitidin for AML •In case of stabilisation of AML, evaluation of treatment for NSCLC (checkpoint inhibitor rather than chemotherapy due to limited bone marrow reserve)

synchronous multiple primaries should be discussed in multidisciplinary team (MDT) meetings and a consensus on a therapeutic strategy can sometimes take more than one MDT to form. Also, the patient should be informed about the situation and therapeutic challenges and often the uncertainty about the prognosis, because the therapy approach needs to be adapted.

In localised disease, the strategy may be surgery or radiation/chemoradiation therapy covering both malignancies.[50 51]

However, in the situation of advanced disease, the antitumour therapy selection is often difficult and mostly not based on evidence from the literature and clinical trials. In patients where both tumours are likely to respond to the same antitumour regimen as may be the case in patients with synchronous squamous cell carcinoma of the head and a second head and neck or

squamous non-small cell lung cancer, the therapeutic decision will involve a systemic therapy, which is likely to be active in for example, a platinum-based chemotherapy.

In patients with synchronous multiple primaries, the following points should be considered when deciding on an antitumour treatment strategy. Please note that the proposed approaches are individual decisions and not general treatment recommendations. Also, these treatment approaches are not based on prospective trial evidence but rather 'real-world' examples of challenging clinical situations.

▶ What is the most significant tumour in terms of prognosis? Is there any chance of a curative approach or is the situation palliative? If palliative, which tumour is metastasised, what is known about the tumour dynamics (imaging, tumour marker) of

the synchronous multiple primaries? What are the systemic therapy options?

► Should treatment strategy focus on local or systemic therapy? Can one of the synchronous tumours be treated radically and then the second malignancy sequentially?

► Which problems can be anticipated? For example, bowel obstruction in untreated colorectal cancer, liver failure in case of extensive liver metastases.

► If systemic therapy is necessary for, for example, two advanced malignancies, can a regimen be chosen that is active for both diagnoses? If not, what is the potential of interaction between two antitumour regimens (hepatic, eg, cytochrome-P (CYP) or cardiac frequency-corrected QT interval on the ECG)? Is there any literature about the combination (eg, axitinib and enzalutamide (see table 5))? Can systemic chemotherapy for an advanced solid tumour be applied at all (eg, in the case of secondary malignancy in the form of AML)? Can the two malignancies be treated in a cycling manner (eg, systemic treatment for tumour A for 2–3 months, followed by systemic therapy for tumour B)?

► Tumour profiling: Can the tumours be profiled (eg, targeted panel sequencing) and could these tumours have a common genetic background, which allows a common strategy option (eg, synchronous malignancies in BRCA1/2 carriers)?

Importantly, patients with active secondary malignancy are excluded from the vast majority of clinical trials involving novel treatments. For the majority of situations of patients with synchronous multiple primaries, only case reports are available in the literature and these should be applied to an individual clinical situation with caution.

Metachronous multiple primaries

The situation of metachronous multiple primaries can be equally challenging. For the situation when the first malignancy is still active/advanced, the considerations above apply. For the situation where a tumour was treated with curative intent and where a biopsy has confirmed a metachronous second malignancy, several points should be considered:

► Can the second primary cancer be treated with curative intent?

► What prior treatment has the patients had for the prior cancer diagnosis?Prior surgery: For example, in breast cancer? Is a second breast-conserving surgery possible and reasonable? In lung cancer: Is a second lung operation possible?Prior radiation therapy: Is there any overlap with the prior radiation field? Could the second primary be radiation therapy induced? What is the tolerance of the healthy tissue in the previously irradiated area? What is the radiation reserve and does it allow a radiation therapy with curative intent or only a palliative schedule/dose?Prior systemic therapy: What regimen? How long since the last systemic

therapy? What cumulative dose (eg, anthracyclines)? Is there any residual toxicity (eg, neuropathy, bone marrow toxicity)? Is the second primary potentially treatment induced?

► Can any possible complications be anticipated based on the patient's prior anticancer therapy history?

► Are there carcinogenic factors that can be managed? For example, smoking, alcohol, viral infection.

► Could a cancer predisposition explain the multiple primaries?

As discussed in the sections above, the number of multiple metachronous tumours is likely to increase. Currently, the literature on the management of patients with metachronous multiple primaries is scarce, but it will be important to collect the information possibly through cancer registries in order to learn and identify potential rare complications in these situations.

DISCUSSION AND CONCLUSION

Based on a combination of factors (diagnosis, treatment, demographics), it is expected that in the course of the coming years, the prevalence of patients with multiple primaries will increase. In the literature, depending on definition, the frequency of multiple primaries ranges between 2.4% and 17% and it is important to realise that with longer follow-up the number of multiple primaries increases in all studies significantly and also that most of the epidemiological studies are based on data acquired more than 10 years ago and that therefore with longer follow-up or in subsequent studies the percentage of patients with synchronous but mainly metachronous multiple primaries will increase.

Also, it is important to recognise that certain patient populations are at higher risk of developing multiple primaries, namely male patients and patients with a history of smoking or alcoholism but also patients diagnosed with a primary malignancy at an early stage and lower grade and patients with a hereditary cancer syndrome. Also, the number of octogenarians diagnosed with cancer is increasing and at the same time the frequency of multiple primaries in older patients who are potentially fit enough to receive active antineoplastic therapy.

Treatment-related secondary malignancies as observed in patients with germ cell or Hodgkin's lymphoma are well characterised but with novel targeted therapies it is currently unclear whether an increased rate of secondary malignancies needs to be taken into consideration. For the B-RAF (rapidly accelerated fibrosarcoma) inhibitor vemurafenib, an increased rate of secondary cutaneous malignancies was demonstrated and requires careful and regular dermatological evaluation for patients on treatment.[52] Also, for the PARP inhibitor olaparib, cases of myelodysplastic syndromes and AML have been observed and careful monitoring of patients for haematological toxicity is recommended.[53]

With the advances and wider availability of genetic testing (eg, gene panels), patients diagnosed with

multiple primaries will be increasingly investigated for an underlying cancer predisposition. The gain of knowledge on patients with hereditary cancer and cancer survivors will hopefully allow the development of specific management and surveillance measures.

For clinical trials, generally patients with secondary malignancies are very often excluded unless they have been low grade/stage and were successfully treated at least 3-5 years ago. To reflect more of a real life population and to enable patients with a prior cancer history participation in clinical trials, the exclusion criteria, especially for early phase clinical trials could be modified to only exclude patients who currently require active anticancer therapy. Admittedly, this may add marked complexity in assessing efficacy and progression and may therefore not be suitable for phase III clinical trials.

Further research is needed, especially with regards to the areas of the treatment of patients with synchronous or metachronous multiple primary cancers. Also, the impact of prior therapies on prognosis, antitumour efficacy and toxicity needs to be better characterised.

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