Report of Two Cases of Quintuple Primary Malignancies and Review of the Literature

MARIA CECILIA CERCATO1, ELVIRA COLELLA2, VIRGINIA FERRARESI3, MARIA GRAZIA DIODORO4 and RICCARDO TONACHELLA2

Departments of 1Epidemiology, 2Geriatric Oncology, 3Medical Oncology A and 4Pathology, Italian National Cancer Institute “Regina Elena”, Rome, Italy

Abstract. Multiple primary malignant neoplasms (MPMN) are not uncommon, however, finding more than three primary malignancies in one individual is unusual. Surviving five malignancies is considered exceptional. Two patients surviving five primary malignant neoplasms for 12 and 18 years are reported: a 55-year-old woman with a squamous cell carcinoma of the larynx, two carcinomas of the breast, a carcinoma of the kidney and an adenocarcinoma of the colon, and a 75-year-old woman with a sarcoma of the myometrium, a carcinoma of the thyroid, an adenocarcinoma of the rectum, a leiomyosarcoma of the colon and a bronchial carcinoid. Only twelve other reported cases with five or more primary infiltrating malignancies involving more than three sites, diagnosed while the patient was alive have been found. Relevant features were that colon cancer was quite often present more than once and survival was longer than expected for the stage (median overall survival, 20 years; 95% confidence interval: 12-28 years).

Multiple primary malignant neoplasms (MPMN) occurring in a patient’s lifetime are not uncommon. Moreover, the number of cancer survivors is growing by 2% each year and a second cancer could represent a leading cause of death (1). Late effects of cancer treatment and lifestyle, as well as the environment and host-related factors, are involved in multiple carcinogenesis (2).

Multiple independent primary malignancies have been reported as case reports, in clinical series and, more recently, have been quantified as incidence rates in population-based series. The proportion of MPMN in clinical and autopsic series reported since 1932 ranges from 0.8% to 16% (3-18).

The population-based systematic studies carried out by long standing Cancer Registries have reported a proportion of MPMN ranging from 2.1% to 6.6% of all incident cases registered from 1935 up to 1995 (19-28). However, as recently reported by the National Cancer Institute, the number of second- or higher-order malignancies is increasing, accounting for approximately 16% of all incident cases registered in 2003 in the Surveillance Epidemiology and End Results (SEER) database (29). Despite this increase, the evidence of triple and quadruple malignancies occurring in the same patient is rare, although some cases have been reported. The occurrence of quintuple or a higher number of carcinomas is an extremely rare event, and, in the very few cases reported, the sites involved are generally no more than three (8, 30-32). We have identified only twelve cases of five or more primary malignancies (nonmelanoma skin cancer and haematological malignancies excluded) arising from at least four different sites, published as case reports in English (32-43).

The aim of this paper was to describe two exceptional cases of women surviving five primary malignancies treated in our Institute and to report an extensive review of the literature on MPMN.

Case 1

In February 1995, a 43-year-old caucasian woman was admitted to the Regina Elena National Cancer Institute for a recently diagnosed breast cancer (first primary). One month before, she had been subjected to a radical mastectomy with axillary nodal dissection for an infiltrating ductal carcinoma of the right breast (pT2 pN1 M0, Stage II) and was referred to our Institute for adjuvant chemotherapy. The patient, a nonsmoker and nondrinker, also experienced dysfonia; furthermore, staging diagnostic abdominal ultrasonography revealed the presence of right ureterohydronephrosis. Clinical and instrumental examinations included a laryngoscopy in which a vegetans lesion of the left vocal cord was documented. A biopsy was obtained and the histological analysis of the specimen showed the presence of an infiltrating squamous cell carcinoma (second...
primary) that was treated by laser colectomy. A thoracic and abdominal CT scan and renal scintigraphy were also performed. The examinations confirmed the presence of severe hydronephrosis of the right renal pelvis resulting in renal autoamputation. No abdominal mass was revealed. The urologists suggested a nephrectomy, which the patient refused.

The patient underwent adjuvant chemotherapy for breast cancer with epirubicin 120 mg/m$^2$ day 1 every 3 weeks for three cycles, followed by CMF (cyclophosphamide, methotrexate, fluorouracil) day 1 and 8 every 4 weeks for 6 cycles, followed by antioestrogenic therapy (tamoxifen 20 mg once a day for five years). Once the chemotherapy was completed, clinical and instrumental follow-up started.

In April 1999, the patient, who was disease-free from the known malignancies, finally agreed to undergo renal surgery as recommended. A right nephrectomy was conducted and the histological analysis showed the presence of a clear cell carcinoma confined to the kidney (third primary). No adjuvant treatment was required and the patient was followed up.

In December 1999, a mammography revealed the presence of a left breast lesion, highly suspicious as being malignant. The patient underwent a left radical mastectomy which revealed a ductal carcinoma of the breast (fourth primary) with multiple microfoci of intraductal carcinoma (pT1 N0 M0, stage I). No standard adjuvant treatment was recommended.

In November 2003, the patient underwent surgery for a fibrous meningioma originating in the pineal region.

Finally, in July 2004, nine years after the onset of the first cancer, the patient was submitted to right hemicolecctomy for the presence of a neoplasia of the ascending colon (fifth primary) which was diagnosed as a poorly differentiated adenocarcinoma (pT3 pN1 M0, Stage III). Adjuvant chemotherapy (FOLFIRI regimen: irinotecan 180 mg/m$^2$ day 1, levo-folinic acid 100 mg/m$^2$ and fluorouracil 400 mg/m$^2$ i.v. continuous infusion for 22 h/day for two days every two weeks for 12 cycles) was administered.

Currently, none of the five malignancies, the first of which was diagnosed 12 years ago, has recurred and follow-up is still ongoing.

**Case 2**

At the end of May 2002, a 70-year-old caucasian woman was referred to our Institute for a neoplasm of the rectum diagnosed at endoscopy. In 1989, at the age of 57, the patient had been subjected to a bilateral hysterectomy for a fibrous tumour of the myometrium that at the histological examination revealed a component of sarcoma (first primary) for which the patient was treated with adjuvant radiotherapy. Eleven years later, in the absence of recurrence of the first cancer, the patient had undergone a total thyroidectomy for a papillary carcinoma (second primary) confined to the thyroid. A staging radiograph and a CT scan of the thorax revealed the presence of two centimetric nodules with a benign appearance, localized in the upper lobe of the left lung and in the middle lobe of the right lung.

In June 2002, the patient was admitted to our Institute and submitted to resection of the rectum for the presence of a poorly differentiated adenocarcinoma (third primary) (pT3, pN0, M0; stageIIA). Staging procedures did not show any sign of distant metastases and confirmed the presence of the known, unmodified lung lesions. In consideration of the stage of the disease and of the age of the patient, no adjuvant treatment was recommended and clinical and instrumental follow-up was continued.

In April 2004, a routine colonoscopy showed a neoplastic lesion of the descending colon that required surgical treatment (right hemicolecctomy). The histological examination revealed a well-differentiated leiomyosarcoma of the colon (fourth primary). Periodical clinical and instrumental evaluations showed no evidence of disease until January 2007, when a CT scan of the thorax revealed an increase in the number and an enlargement of the known lung lesions. A fine-needle aspiration biopsy of one of the lesions was not interpretable, therefore the patient underwent surgery. A diagnostic resection of the upper lobe of the left lung and lingula was performed with histological and immunohistochemical examinations showing the presence of a metastasis from the leiomyosarcoma in addition to a bronchial carcinoid (fifth primary) (Figure 1A, B). Chemotherapy (epirubicin 35 mg/m$^2$/week) for metastatic leiomyosarcoma was administered. The patient is still alive and asymptomatic, 18 years after the diagnosis of the first cancer.

**Literature**


We also searched Cochrane Review (http://www.cochrane.org/reviews/). Reviews were searched for additional references on the topic.

The title and abstract of articles identified were scanned to exclude those not relevant to the topic.

The full text of the remaining articles was read to identify those with pertinent information; the reference lists of the latter were also reviewed to identify additional reports.
Selection criteria. Articles published in English, Spanish or French were selected.

The articles considered for this Review were case reports that describe patients with five or more infiltrating cancers originating from at least four different sites, diagnosed during life. Nonmelanoma skin cancer, haematological malignancies, all cancer diagnosed at autopsy and cases with no more than three different sites involved were excluded.

Results of the search. We found 47 eligible cases published since 1961. Of these, 4 were excluded because of the language of the article (Japanese, Russian and German), 13 for including noneligible neoplasms (noninfiltrating cancer, nonmelanoma skin cancer and haematological malignancies), 14 for the number of the primary sites involved (no more than three), 2 because the cancer was diagnosed postmortem, and 2 for unretrievable data. The remaining 12 cases were considered eligible for our Review and are reported.

Discussion

Multiple primary tumours were first described by Billroth in 1889 (44). In 1932, Warren and Gates, on the basis of reported 1,259 cases, proposed three criteria for the diagnosis of a second primary cancer that are still followed by the majority of authors: each tumour should show specific malignant findings; the tumours should differ in site and one tumour should not be a metastatic focus from another (7). In 1977, Moertel proposed new definitions, including the term “multicentric” if tumours occurring simultaneously in the same anatomical site shared the same histology and “metachronous” if the second tumour was diagnosed more than six months after the diagnosis of the first primary (30).

The wide variation in prevalence of MPMN reported in different clinical and autoptical series could be attributed to several factors, such as the year and criteria of diagnosis of the MPMN, the patients’ characteristics (i.e., age, site of first primary) and the criteria of selection of cases for autopsy (3). Site seems to play an important role, with most MPMN arising in the respiratory, gastrointestinal and genitourinary systems (5, 10, 11, 12, 14, 24, 26, 28). One of the most common malignancies is prostate cancer (33-64% of all MPMN in male patient series) and it is a frequent incidental finding at autopsy in elderly men (3, 13).

Data collected from Italian Cancer Registries series have been used to calculate the incidence of second independent cancer in a cohort of cancer patients aged 15 years or more (19). This report revealed that patients affected by cancer had an approximately 10% statistically significant increase in the risk of cancer of all sites in comparison with the general population (standardized incidence ratio, SIR: 1.08; 95% confidence interval: 1.05-1.12) (19). Furthermore, the observed number of second metachronous malignancies (now defined as tumours diagnosed more than 2 months after the first cancer) according to the site of the first tumour were significantly higher than expected for oral cavity and pharynx, larynx, connective tissue, skin nonmelanoma, ovary and kidney cancer (19).

According to the main aetiological factors, as reported in a recent commentary of the National Cancer Institute, second
Primary neoplasms could be classified into three, not mutually exclusive categories viz syndromic cancer, cancer treatment-related and shared exposure-related (2). Syndromic malignancies are characterized by inherited mutations of genes associated with an increased risk of cancer (45). Although syndromic malignancies represent only a small proportion of all cancer cases and of second primary malignancies, relatives with a germline genetic predisposition are characterized by an increased risk of primary tumours at multiple sites (2). Common clinical features are that the tumours arise at a younger than usual age and several family members are affected (2). Cancer related to antitumour treatments performed in adults, once haematological malignancy has been excluded, are mainly represented by a slight increase in the incidence of lung cancer and sarcoma after postmastectomy radiotherapy (46). Furthermore, five years of antioestrogenic treatment with tamoxifen in breast cancer patients, is associated with a two- to threefold increase in the risk of developing endometrial cancer, while adjuvant chemotherapy is not associated with any detectable increased risk of solid tumours (46). A meta-analysis of 18,000 women enrolled in 47 randomized clinical trials of adjuvant combination chemotherapy for breast cancer showed no significant increase in deaths attributed to other neoplastic causes among all the women allocated to polychemotherapy (47). Several evident associations between cancer sites may be due to the effect of the same risk factor. Exposure to tobacco smoking and alcohol might explain the elevated bidirectional risks observed between various tumours of the upper aerodigestive system as well as the increased cervical cancer risk in women with a smoking-related first cancer, such as oral cavity and bladder cancer (19-22, 24). Moreover women affected by cancer of the cervix are at an increased risk of cancer of the lung and bladder (19, 20, 22, 24).

Limited data are available on cases of more than three multiple primary cancers in one patient. Baigrie in his review concluded that common features in these rare cases were that colon cancer was quite often present more than once, most cases arose in the fifth or sixth decade of life, most were diagnosed at a locally advanced stage, but that they were

<table>
<thead>
<tr>
<th>Author, year (Ref.)</th>
<th>Age (years)*/</th>
<th>Gender</th>
<th>Tumour site: histology</th>
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<td>Szwedk et al., 1988 (38)</td>
<td>n.r./F</td>
<td>Ovary: ADK</td>
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<tr>
<td>Weingartner et al., 1995 (41)</td>
<td>67/M</td>
<td>Bladder: Transitional cell CA</td>
<td>Bladder: Malignant fibrous histiocytoma</td>
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<tr>
<td>Yakushiji et al., 1999 (42)</td>
<td>60/M</td>
<td>Rectum: ADK</td>
<td>Bladder: Transitional cell CA</td>
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<tr>
<td>Mosca et al., 2001 (43)</td>
<td>41/F</td>
<td>Larynx: Squamous CA</td>
<td>Endometrium: ADK</td>
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*Age at diagnosis of first tumour; n.r.: not reported; CA: carcinoma; ADK: adenocarcinoma.
characterized by a relatively low tendency to metastasize and that survival was longer than expected from the stage (40).

Our first case presented all of these features. Of note, the patient was free of metastasis eleven years after the diagnosis of the first malignancy (breast cancer) and more than two years after the diagnosis of the last tumor (colon cancer), even though both of those malignancies were characterized by nodal involvement requiring adjuvant treatment. The second case presented the common features described above, except for the presence of metastatic spread. Survival of both patients has been longer than expected for the locally advanced or metastatic stage of disease at diagnosis of some of their tumors, 12 and 18 years, respectively from the onset of the first cancer.

By searching for case reports published in English, 27 cases of at least five primary malignancies originating from different sites diagnosed within a patient’s lifespan were found. Among these, only twelve cases of quintuple or more infiltrating neoplasms (nonmelanoma skin cancer and haematological malignancies excluded) originating from at least four different sites were identified (32-43) (Table I). Out of these twelve cases, eight were females (67%). The median age at the diagnosis of the first cancer of the eleven evaluable cases was 52 years (range: 37-73 years) and most (43%) of the tumours arose in the fifth or the sixth decade of life. Except for the case reported by Weingartner et al. (41) that included five synchronous primary malignancies, the great majority of the neoplasms reported were metachronous (diagnosed at an interval of more than 6 months). The average interval between the diagnosis of the metachronous neoplasms was 5 years (range: 1-13 years). Overall, among the sixty-seven synchronous and metachronous primary malignancies, colon cancer represented a common finding, often more than once in the same patient. Gastrointestinal neoplasms represented 42% of the involved primary sites, followed by genitourinary neoplasms (34%). The median overall survival of 20 years (95% confidence interval: 12-28 years), comparable to that observed in our two cases, was extremely high for patients affected by infiltrating tumors. This evidence could be partially due to the observed low tendency to metastasize.

The overall excellent prognosis of these patients suggested that long-term follow-up is opportune and adequate treatment of each further tumor is indicated. Furthermore, taking into account the overall improvement in survival achieved in cancer patients in recent years and the late sequelae of cancer treatment, evidence-based long-term management and intervention strategies in order to prevent second malignancies in adult cancer survivors are required.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

References


