Multiple primary tumors were first described by Billroth at the end of the 19th century.\cite{1,2} He described a patient with stomach cancer who was later found to harbor a malignant tumor of the external ear.\cite{3} Secondary to the significant improvements in the diagnosis and treatment of cancer, a higher proportion of surviving cancer patients are at risk of developing a second, third or even higher number of primary malignancies. The study of multiple primary malignant tumors is of paramount importance since it could unravel clinical associations of certain malignancies, uncover various germ-line and genetic mutations and help tailor follow-up and screening in these patients.\cite{4,5} Even though there is an adequate body of published data describing the epidemiological and clinical characters of patients with two primary malignancies, there is a scarcity of reports addressing patients with three or more malignancies. We present an extremely rare clinical scenario: a patient with eight primary malignant tumors and we reviewed the relevant literature in an attempt to highlight the epidemiological features, pathological characters, therapeutic regimens and disease outcomes of this poorly understood disease entity.

**CASE**

Our patient was a 59-year-old female with Crohn disease with an otherwise non-contributory medical history. At the age of 50 she presented with menorrhagia. Pelvic ultrasound demonstrated endometrial thickening. She underwent total abdominal hysterectomy with preservation of both ovaries. Histopathology revealed International Federation of Gynecology and Obstetrics (FIGO) stage I endometrial adenocarcinoma. At the age of 51 she was found to have a cecal mass on lower gastrointestinal colonoscopy. Computed tomography (CT) of the abdomen showed a 3-cm concentric thickening of the cecum and ascending colon. She underwent right hemicolectomy. Histopathology revealed moderately differentiated papillary adenocarcinoma invading through the musclaris propria into the subserosa, and staging of T3N0M0. No further treatment was offered. At the age of 54 years she presented with hematuria. A CT scan of the abdomen demonstrated a 4-cm T1N0M0 right renal cell carcinoma that was subsequently treated by right nephrectomy. Three months later she presented with bloating and abdominal pain. Magnetic resonance imaging of the abdomen and pelvis showed a matted 8×9 cm right pelvic mass suggestive of an ovarian tumor. She underwent surgical excision and was found to harbor FIGO stage IA right ovarian, moderately differentiated adenocarcinoma with pathological and immuno-histochemical features distinguishing this primary from the previously diagnosed endometrial cancer. She received 4 cycles of adjuvant carboplatin and paclitaxel. At the age of 55 years she presented with invasive lobular carcinoma of the left breast. She underwent modified radical mastectomy. A mastectomy lymph node dissection revealed one of 15 nodes positive for metastatic disease. She was treated with 4 cycles of adjuvant doxorubicin and cyclophosphamide. After 1 year of follow-up she was free of disease.
breast and was treated by surgical excision. She did not receive any further treatment. At the age of 56 years a routine follow-up chest CT scan demonstrated 2×2.5-cm left upper lobe lung nodule. She underwent lobotomy that revealed a T2N0M0 bronchoalveolar adenocarcinoma with free surgical margins. At the age of 57 years she was found to harbor a right ureteric mass on routine follow-up pelvic CT and was subsequently treated by right ureterectomy. Histopathology demonstrated invasive high-grade transitional cell carcinoma with extension to peri-ureteric adipose tissue and free resection margins; stage pT3N0M0. One month later she presented with an ulcer at the right nostril. Surgical excision revealed moderately differentiating squamous cell carcinoma with free surgical margins. At the age of 58 years she presented with a retroperitoneal mass on follow-up CT scan of the abdomen and pelvis. Histopathological examination of an open surgical biopsy specimen revealed findings consistent with recurrent transitional cell carcinoma. She received six cycles of carboplatin and paclitaxel. At the time of writing (108 and 12 months from the time of diagnosis of the first and last primary tumor respectively), she was alive with evidence of residual retroperitoneal disease.

**DISCUSSION**

The exact incidence of patients presenting with at least three primary tumors remains unknown. Rosso et al. extracted data from 69 European cancer registries. Out of a total 2919023 malignant cancers cases; 183683 (6.3%) cases of multiple primary tumors (at least two tumors) were found. It has been estimated that approximately 2% to 12% of patients with two tumors go on to develop a third or fourth neoplasm. In the study by Bittorf and colleagues, 57 (0.1%) of 52398 included patients harbored at least three primary neoplasms. This corresponds to 2.8% of patients with two primary tumors.

For the accurate classification of multiple primary tumors, each tumor must exhibit a definite picture of malignancy, each tumor must represent a distinct clinical entity and the probability that one is a result of metastatic spread from the other must be reliably excluded. However, multiple tumors demonstrating similar histological sub-classification could correctly be labeled as multiple primaries if they arise from different anatomical subsites. A new malignant tumor cannot be classified as a secondary neoplasm if it occurs in the same anatomical location as the first tumor. Nonetheless, tumors arising from the same anatomical site could be considered multiple if they possess varying histologies. Tumors are labeled as simultaneous if both/all are discovered at the same time, synchronous if discovered within 6 months of the first or metachronous if recognized more than 6 months after the discovery of the first tumor.

Risk factors for multiple primary tumors include genetic, constitutional and environmental factors. None were detected in our patient. Unfortunately, our patient did not undergo detailed genetic testing to uncover possible underlying genetic mutations. Even though our patient exhibited at least three primary tumors with direct etiological links to smoking, she said she was a never-smoker.

Some investigators have postulated that the occurrence of a subsequent cancer in surviving cancer patients has probably increased over the past years secondary to the substantially improved treatment, and the subsequent long-term survival expected in patients with this disease. Due to the rarity of occurrence of multiple primary tumors, accurately highlighting such a temporal trend would prove difficult. However, it is well known that the treatment of cancer might result in the development of subsequent malignancies. In like manner, the contribution of radiation treatment against one cancer on the subsequent occurrence of a second or third primary inside the radiation field cannot be dismissed. Radiation-related secondary tumors are typically seen after exposure to high doses of radiation in excess of 10 grays. Chemotherapeutic agents administered for the treatment of brain tumors have been linked to the subsequent development of leukemia. Furthermore, alkylating agents have been related to the development of subsequent malignancies and the potentiation of the carcinogenic effects of radiotherapy on tissues.

The colon is the most common site for multiple primary malignant tumors. In addition, a high incidence of multiple primary tumors has been observed in patients with kidney cancer. Both tumors were found in our case report. Most of the primary malignancies reported in our paper were adenocarcinomas. After an adequate period of follow-up, we report encouraging survival in our patient. Similarly, Hao reported long-term survival in a patient with six primary malignant tumors.
REFERENCES


