Clinical Case Report

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# Metachronous triple primary neoplasms with primary prostate cancer, lung cancer, and colon cancer

## A case report

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**Abstract**

**Rationale:** Multiple primary neoplasms (MPNs) are rare. Most MPNs are double, and triple primary neoplasms are extremely rarer. Here, we describe a case of a 66-year-old man diagnosed with metachronous triple primary neoplasms with primary prostate cancer, lung cancer and colon cancer.

**Patient concerns:** The patient complained of dysuria in January 2015, and he underwent transurethral resection of the prostate. The pathological results showed acinar adenocarcinoma of prostate with a Gleason score of 3+3. In January 2017, he complained of lower abdominal pain, then he took an enteroscopy examination, found a mass in the sigmoid colon, and positron emission tomography/computed tomography examination showed masses in the sigmoid colon and right upper lobe of the lung. Biopsy of the colon showed moderately differentiated adenocarcinoma with Kirsten rat sarcoma viral oncogene homolog exon 2 mutation, and biopsy of the lung showed moderately differentiated adenocarcinoma with epidermal rowth factor receptor exon 21 mutation.

**Diagnoses:** Metachronous triple primary neoplasms with primary prostate cancer, lung cancer and colon cancer.

**Interventions:** The patient underwent surgical resection of the right upper lobe of the lung, postoperative stage was T1bN0M0 (stage IA). After 8 cycles of chemotherapy with modified FOLFOX6 regimen (oxaliplatin 85 mg/m$^2$, leucovorin 400 mg/m$^2$, 5-fluorouracil 400 mg/m$^2$ on day 1, followed by 5-fluorouracil 2400 mg/m$^2$ intravenous infusion over 46 hours every 2 weeks), the patient underwent radical resection of colon cancer, and he finished the remaining 4 cycles of modified FOLFOX6 regimen chemotherapy in November 2017.

**Outcomes:** The patient takes examination every three months, and the results show no recurrence.

**Lessons:** When considering MPNs, thorough surveillance by new screening methods is required to detect a second or even third neoplasm at an early stage.

**Abbreviations:** DNMT3A = DNA methyltransferase 3A, EGFR = epidermal rowth factor receptor, KRAS = Kirsten rat sarcoma viral oncogene homolog, MPNs = multiple primary neoplasms, NGS = next-generation sequencing, SEER = surveillance epidemiology and end results, TERT = telomerase reverse transcriptase.

**Keywords:** colon cancer, lung cancer, metachronous triple primary neoplasms, multiple primary neoplasms, prostate cancer

## 1. Introduction

Multiple primary neoplasms (MPNs) were not recognized by most people until the 1890s. In 1889, MPNs were defined by Billroth as development of ≥2 tumors in the same person with different histological characteristics, arising from different organs, and presenting with their own metastatic deposits.[1] In 1932, the definition was modified by Warren and Gates. According to them, these ≥2 malignancies have different histological characteristics, and the possibility of one being a metastasis of the other must be ruled out.[2] Some studies have defined MPNs as ≥2 malignancies arising from different organs, or the same organ but with different histological characteristics.[3]

MPNs are divided into 2 groups: synchronous and metachronous. Synchronous MPNs are ≥2 tumors diagnosed within 6 months, while metachronous MPNs are ≥2 tumors diagnosed with a time interval >6 months.[4]

With the improvement of diagnostic methods, MPNs have become the third most common cancer diagnosis and now constitute 18% of all cancers according to the US surveillance epidemiology and end results (SEER) program.[5] Most MPNs are double primary neoplasms, and triple primary neoplasms are extremely rare. This paper reports a rare case of metachronous

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The authors declare no conflicts of interest.

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triple primary neoplasms with primary prostate cancer, lung cancer, and colon cancer.

## 2. Case report

The case was a 66-year-old man with unremarkable family and previous disease histories. He complained of dysuria in January 2015. Pelvic magnetic resonance imaging suggested a malignant mass in the prostate, and he underwent transurethral resection of the prostate in February 2015. The pathological results showed acinar adenocarcinoma of the prostate with a Gleason score of 3 +3. In subsequent years, radiological examination showed no recurrence and his prostate-specific antigen level was normal.

The patient complained of lower abdominal pain in January 2017. A mass was found in his sigmoid colon by enteroscopy examination. Positron emission tomography/computed tomography examination showed a mass in the sigmoid colon with local lymph nodes invasion and a mass in the right upper lobe of the lung. In March 2017, the patients underwent biopsy of the 2 masses. Biopsy of the colon showed moderately differentiated adenocarcinoma with Kirsten rat sarcoma viral oncogene homolog exon 2 mutation, and biopsy of the lung showed moderately differentiated adenocarcinoma with epidermal rowth factor receptor exon 21 mutation. In April 2017, the patient underwent surgical resection of the right upper lobe of the lung, and postoperative staging showed T1bN0M0 (stage IA). Since the colon cancer presented as unresectable stage III, from May 2017, we gave him 8 cycles of chemotherapy with modified FOLFOX6 regimen (oxaliplatin 85 mg/m$^2$, leucovorin 400 mg/m$^2$, 5-fluorouracil 400 mg/m$^2$ on day 1, followed by 5-fluorouracil 2400 mg/m$^2$ intravenous infusion over 46 hours every 2 weeks) to convert it to resectable colon cancer. After 8 cycles of chemotherapy, the patient underwent radical resection of colon cancer in September 2017. Figure 1 shows all the pathological tissues. The patient finished the remaining 4 cycles of modified FOLFOX6 regimen chemotherapy in November 2017. Now the patient takes examination every 3 months, and the results show no recurrence.

To find out whether genetic factors were involved in carcinogenesis, the patient's plasma was examined using next-generation sequencing (NGS), which showed DNA methyltransferase 3A (DNMT3A) and telomerase reverse transcriptase (TERT) mutations.

## 3. Discussion

MPNs are rare, when considering, the possibility of one being a metastasis of the other must be excluded. Identifying the differences between MPNs and metastatic tumors is important, the differences include the following points: most metastatic tumors are consist of multiple masses with uniform density and clear outline; tumors should be considered as MPNs when the first primary tumor presented without relapse.

Multiple factors may contribute to the carcinogenesis of MPNs, such as treatment exposures, lifestyle behaviors, and genetic factors.[6] It is reported that radiotherapy associates with 8% MPNs, and the remaining MPNs are correlated with lifestyle behaviors (e.g., smoking), and genetic factors.[5] In this case, the patient had not received any radiotherapy and had no remarkable lifestyle behaviors, but DNMT3A and TERT mutations were discovered by NGS examinations. DNMT3A is involved in DNA methylation.[7] DNMT3A is frequently mutated in cancer, and is one of the 127 frequently mutated genes identified in the Cancer Genome Atlas project.[8] DNMT3A mutation mainly occurs in acute myelogenous leukemia, and may predict poor prognosis.[9–12] Kim et al[13] have reported a low frequency of

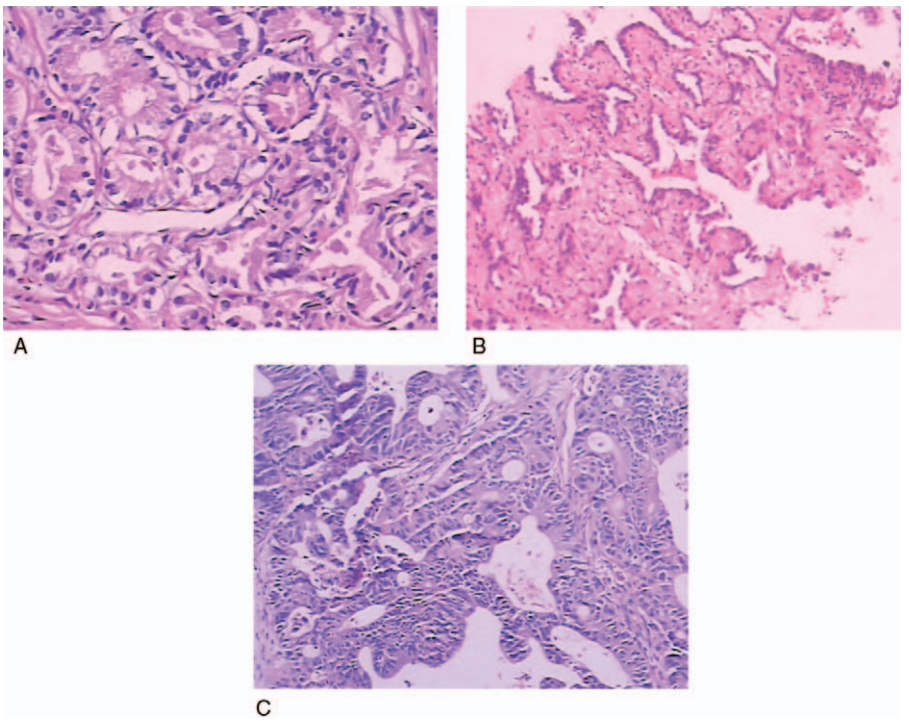


**Figure 1.** A. Acinar adenocarcinoma of prostate (HE, 200×); B. Moderately differentiated adenocarcinoma of lung (HE, 100×); C. Moderately differentiated adenocarcinoma of colon (HE, 100×). HE = hematoxylin-eosin.

DNMT3A mutation in lung cancer that may play a role in carcinogenesis. TERT is a catalytic subunit of the enzyme telomerase, and it is involved in catalyzing the addition of nucleotides in a TTAGGG sequence to the telomere ends of chromosomes.[14] Over 200 combinations of TERT polymorphisms and cancer development have been found, and there is a strong correlation between TERT polymorphisms and lung cancer.[15] The exact genetic factors associated with MPNs are not clear, and genome-wide association studies are recommended to discover common genetic variants in different individuals to evaluate their association with a specific trait.[16] In summary, for this patient, genetic factors are likely the largest contributor to the carcinogenesis of his MPNs.

Treatment of MPNs depends on the time interval of diagnosis. For synchronous MPNs, one should first treat the tumor with life-threatening or poorer prognosis, whereas for metachronous MPNs, one can treat the cancers one at a time.[17] In the present case, the patient was diagnosed with metachronous MPNs, he underwent resection of prostate cancer in 2015, and resection of lung cancer in April 2017. While the colon cancer was unresectable when diagnosed, he received 8 cycles neoadjuvant chemotherapy to convert it to resectable colon cancer, and received resection of colon cancer in September 2017, the remaining 4 cycles of chemotherapy were finished after surgery.

We highlight a rare case of metachronous MPNs consisting of primary prostate cancer, lung cancer, and colon cancer, which has not been reported in the literature. We described the treatment, and performed NGS on the patient, which helped us understand the contribution of genetic factors to MPN carcinogenesis.

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## Author contributions

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**Writing – original draft:** Yuhua Feng, Yiping Liu.
**Writing – review and editing:** Meizuo Zhong, Shan Zeng.

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