Ossifying Skeletal Muscle Metastases from Colon Cancer: A Case Report and Literature Review

Yu Guo
the second hospital of jilin university https://orcid.org/0000-0002-4403-8647
Shuang Wang
the second hospital of Jilin university
Wangsheng Xue
the second hospital of Jilin university
Jiannan Li
the second hospital of Jilin university
Zeyun Zhao
the second hospital of Jilin university
Mingwei Zhang
the second hospital of Jilin university
An Shang
the second hospital of Jilin university
Donglin Li
the second hospital of Jilin university
Min Wang (jdeywangmin@163.com)
the second hospital of Jilin university https://orcid.org/0000-0002-1288-016X

Case report

Keywords: soft tissue metastases, skeletal muscle metastases, ossification, colon cancer, BRAF mutation

Posted Date: December 31st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-136504/v1

Title page

Ossifying skeletal muscle metastases from colon cancer: A case report and literature review

Authors:

Yu Guo†: The Second Hospital of Jilin University, China. Guoyu126344@163.com

Shuang Wang†: The Second Hospital of Jilin University, China. jdeywangshuang@163.com

Wangsheng Xue: The Second Hospital of Jilin University, China. imsurgeon@163.com

Jiannan Li: The Second Hospital of Jilin University, China. jnli@jlu.edu.cn

Zeyun Zhao: The Second Hospital of Jilin University, China. dearzhaoyun@163.com

Mingwei Zhang: The Second Hospital of Jilin University, China. Zhangmw12345@163.com

An Shang: The Second Hospital of Jilin University, China. 1724302294@qq.com

Donglin Li: The Second Hospital of Jilin University, China.846763584@qq.com

Min Wang*: The Second Hospital of Jilin University, China. jdeywangmin@163.com

†**The author has similar contribution**

* **Corresponding author**: Min Wang

Department of the General Surgery, Jilin University Second Hospital, Changchun, Jilin, China No.218, Ziqiang Street, Nanguan District, Changchun City, Jilin Province, China

E-mail: jdeywangmin@163.com Tel:(+86)18135435372

Abstract:

Background:

Colon cancer is a common malignant disease of the gastrointestinal tract and usually occurs at the junction of the rectum and sigmoid colon. Lymphatic and hematogenous metastases occur frequently in colon cancer and the most common metastatic sites include the regional liver, lung, peritoneum, bone, and lymph nodes. As a manifestation of advanced tumor spread and metastasis, soft tissue metastasis, especially skeletal muscle metastasis ossification caused by colon cancer, is rare, accounting for less than 1% of metastases.

Case presentation:

In this study, we report a rare case of a 43-year-old male patient who developed an ossifying skeletal muscle metastasis of the right proximal thigh with severe pain at 5 months after colon cancer was diagnosed, who subsequently from the developed metastasis. The patient was admitted to the hospital because of pain caused by a local mass on his right thigh. Positron emission tomography-computed tomography showed multiple lymphadenopathy metastases around the abdominal aorta without lung or liver metastases. Color ultrasound revealed a mass located in the skeletal muscle and the results of histological biopsy revealed a poorly differentiated adenocarcinoma suspected to be distant metastases from colon cancer and immunohistochemistry showed small woven bone components that were considered to be ossified.

Conclusion:

Although ossifying skeletal muscle metastases is rare, its potential malignancy is

high. With advances in examinations and treatment modality, Positron emission tomography-computed tomography, collagen gel droplet culture drug-sensitivity test and genetic tests are recommended to optimize comprehensive and individual treatment modality to prolong patient survival.

Key word :

soft tissue metastases, skeletal muscle metastases, ossification, colon cancer, BRAF mutation

Introduction:

With the improvement of people's living standards and changes in dietary structure, the incidence of colon cancer has increased year by year.[1]

Colon cancer, as a kind of malignant tumor, can also metastasize to many other parts of the body. Lymphatic and hematogenous metastases occur frequently in colon cancer and the most common metastatic sites include the regional liver, lung, peritoneum, bone, and lymph nodes[2]. In the case presented here, we demonstrated a solitary metastasis in the skeletal muscle of the thigh, with ossifying metaplasia, but no sign of metastases to common sites, such as the liver or lung. Reviewing the English language literature, only 13 cases, (Table 1) including our case, of skeletal muscle metastasis (SMM)from colon carcinoma have been reported and none of them were from China.

Case report

In January 2018, a 43-year-old male patient presented at our hospital with a right lower abdominal mass of 4 × 5 cm that had been present for 2 months without any abdominal pain or other symptoms. The patient had no special medical history. A colonoscopy revealed a mass in the ascending colon and the biopsy result revealed adenocarcinoma with infiltration in the vessels. The levels of tumor biomarkers CEA (carcinoembryonic antigen) and CA19-9 (carbohydrate antigen 19-9) were 10.18 μg/L (normal range:< 3 μg/L) and 289.24 μg/L (normal range:< 37 μg/L), respectively. Abdominal computed tomography (CT) revealed an ileocecal mass with multiple peripheral lymphadenopathies, but no distant metastasis. The preoperative stage was evaluated as T3N2M0 and a laparoscopic extended right hemicolectomy was performed. The postoperative pathology results indicated poorly differentiated adenocarcinoma infiltrating the entire layer, particularly the subserosa and muscularis propria (Fig. 1a). In addition, the appendix and ileocecal valve were infiltrated by the tumor.

The harvested lymph nodes presented the following positivity: Posterior mesenteric lymph nodes (1/6), middle colonic vascular root lymph nodes (4/12), ileocecal vascular root lymph nodes (6/8), right colonic vascular root lymph nodes (4/6), lymph nodes around cecum (4/ 4), and lymph nodes around the colon (8/9). The pathological TNM stage was then assessed as pT4N2bMo and the patient's postoperative recovery was uneventful.

To reduce the tumor recurrence rate and kill tumor cells throughout the body, the patient underwent four cycles of chemotherapy with the CapeOX regimen (Capecitabine and Oxaliplatin). The patient's CEA and CA19-9 levels increased after

receiving four cycles chemotherapy. Positron emission tomography-computed tomography (PET-CT) was then performed and the result showed multiple lymphadenopathy metastases around the abdominal aorta, without lung or liver metastases (Fig. 2). The patient was recommended for radiotherapy with a total of 50 Gy in five regimens. However, after finishing the second radiotherapy regimen, the patient found a 4 × 4 cm mass in his right thigh that caused intolerable pain. Color ultrasound revealed a mass located in the skeletal muscle (Fig. 1c). A histological biopsy revealed poorly differentiated adenocarcinoma, suspected to be distant metastases from colon cancer, and immunohistochemistry showed small woven bone components that were considered to be ossified (Fig. 1d). A complete resection was suggested, but was refused by patient.

Soon, the patient developed bone metastases to the tibial vertebral bodies and a collagen gel droplet-embedded culture drug sensitivity test (CD-DST) were performed. The result proved that the patient was not sensitive to the chemotherapy regimens of Compound Tegafur Capsules (TS-1), Docetaxel, Gemcitabine, Etoposide (VP-16), or FOLFIRI. Next, the one cycle chemotherapy regimen was changed to Bevacizumab, Irinotecan, and Capecitabine and a gene test was performed. The result showed a mutation of the BRAF gene and wild-type KRAS and NRAS genes (Fig. 3). Furthermore, the tumor mutation burden (TMB) of the blood and tumor tissue DNA was moderate (4.15 Muts/Mb) and low (2.00 Muts/Mb), respectively. Using multi-disciplinary treatment (MDT), the following two cycles chemotherapy were changed to the regimen of Vemurafenib, Irinotecan, and Capecitabine. The regimen

seemed to be effective, with a reduced level of tumor biomarkers and a smaller thigh mass. Although no liver or lung metastases occurred, the patient had been suffering from thigh pain and the side effects of chemotherapy (such as nausea, vomiting) and unfortunately, the patient died in October,2018.

Discussion

The prevalence of SMM ranges from 0.03 to 5.6% in autopsy series of cancer patients [3]. In fact, skeletal muscle comprises about 50% of total body mass. However, metastatic spread to skeletal muscles from colorectal carcinomas are rare, and is usually an indication of systematic spread. Hasegawa et al.[4]reported that 0.028% of patients with colorectal cancer developed SMM. Meanwhile, SMM implies poor prognosis, with a mean survival duration from diagnosis to death of 5.4 months (range: 1–12 months)[5]. Araki et al.[6] reported a patient with SMM in right teres major muscle who survived for 2 years, but died of carcinoma after a complete resection of metastatic lesions and other therapies. However, patients with SMM mostly develop generalized metastases, which soon results in death.

Metastasis to the musculature from colorectal carcinomas are rare, with only 18 cases being reported in recent English language literature, and among them colon carcinoma was the primary site for only 13 cases. In these case reports, the sites of primary carcinomas and metastatic lesions in SMM are diverse, and the interval from resection of the primary carcinoma to the development of SMM ranged from 5 to 60 months. However, Laurence et al.[7] reported that a 51-year male patient who visited

the hospital for the painful mass in the right forearm, which proved to be an SMM, after which a transverse carcinoma was found. Although there are few reports of SMM, possibly because of its asymptomatic nature and undetected characteristics, it is possible that the true incidence is underestimated. The possible mechanism of metastatic spread of adenocarcinoma of the colon to the skeletal muscles could be by via the lymphatics, the hematogenous route, direct extension of primary disease, or from manipulation during surgery. In the case reported by Tunio, they found two sites of muscular metastasis in the gluteus maximus and rectus abdominis muscles in a 28-year-old man with known colon adenocarcinoma. They hypothesized that the possible mechanism for metastasis in this patient implantation of tumor cells during surgery.

Usually, most patients with SMM present with painful masses, which might be important to discriminate SMMs from soft tissue sarcoma, which present as painless masses. There is no specific diagnostic approach for soft tissue metastases and magnetic resonance imaging (MRI) and PET-CT have been recommended as the optimal techniques. For example, the CT of the patient in the present case only reported multiple abnormal signals in the lumbar 5, sacral 1,2,3 cones, bilateral iliac bones, and abnormal signals on the outside of the right iliopsoas muscle, which could only indicate lesions and cannot be used as a basis for diagnosis. Furthermore, PET-CT is not only able to exclude metastatic sites, but also could be used to evaluate the patient's treatment response[8]. Although there is a high risk of regional seeding or implantation of carcinoma cells, needle aspiration biopsy is still highly recommended as a valuable diagnostic approach, with a low incidence of 0.03% of needle metastases reported by

Kline et al[9].

Noticeably, our patient's pathological outcome of needle biopsy revealed adenocarcinoma with ossification. Ossification refers to the formation of heterotopic bone, which occurs occasionally in colorectal polyps, Barrett's esophagus, and mucocele of the appendix[10], but rarely in metastatic tumor deposits. According to the literature, the ossification of SMM has only been observed in three case reports of metastatic colonic adenocarcinoma[6, 11, 12]. The mechanism and pathogenesis of ossification of SMM remain unclear. However, some scholars hypothesized that the potential mechanisms include local hemorrhage, musculature metastases-related biochemical transformations, and tumor implantations. In addition, a recent study[8] revealed that pluripotent mesenchymal cells might differentiate from osteoblasts to cause ossification in SMM.

Although the potentially malignancy of heterotopic ossification from colon carcinoma is unclear, it indicates high tumor malignancy, because the ossification is commonly induced by tumor progression in a tumor microenvironment[13]. The lack of capsule or pseudo-capsule formation of mass infiltrative borders, makes it hard to achieve complete excision. For most distant soft tissue metastases, Stabler et al.[11] recommended that they should be treated with radiotherapy instead of surgery, and SMM accompanied by disseminated metastases should be treated palliatively. In our study, the patient continued to receive radiotherapy after finding the SMM. and during radiotherapy, the mass shrank, which might indicate its potential sensitivity to radiotherapy.

Compared with left-sided primary tumors, right-sided primary tumors seem to be associated with worse survival. Prasanna et al.[14] reported that patients with BRAF mutations have a higher incidence of peritoneal metastases, rather than lung and liver limited metastases, leading to poor prognosis. Right-sided colon carcinomas have higher rates of peritoneal metastases (relative risk (RR)) = 0.6, $p < 0.001$) than left colon carcinomas. In our study, the patient had multiple lymphadenopathy metastases around the abdominal aorta and bone metastases was found 2 months later, which indicated the high malignancy and rapid progression of the tumor. Further study on the association between the BRAF mutations and SMM are warranted.

The TMB is defined as the total number of nonsynonymous mutations per coding area of a tumor genome. The number of mutated genes in the genome will significantly increase in patients with an elevated TMB. As a response, a large number of non-self-antigens will be generated and are more likely to be recognized by the immune system, leading to a strong immune response and higher sensitivity to immunosuppressive agents[15]. Based on a patient's genomic profile and molecular phenotypes, optimal therapy should be selected.

CD-DST is an in vitro tumor sensitivity testing technique for chemotherapeutic drug sensitivity, which requires a small number of specimens. As a simple, rapid, sensitive, and clinically relevant in vitro sensitivity test, it can help clinicians to select effective drugs scientifically and reasonably, optimize drug combinations, improve clinical efficacy, and reduce toxicity in the practical application of individualized treatment.

Compared with irinotecan with Cetuximab, Kopetz et al. [16] reported that the Vemurafenib combined with Irinotecan and Cetuximab significantly prolonged progression-free survival and induced a higher disease control rate, from 2 months to 4 .4 months, which indicated that this combination is the best treatment for colorectal cancer with BRAF mutations. The latest research[17] revealed that about 14% of patients with primary colorectal cancer have mutations in BRAF, as assessed using Next generation sequencing (NGS) and the BRAF V600E mutation, as activating an mutation in exon 15, is the most common single mutation, representing approximately 40.0% of detected mutations[18].

Recent advances in radiological examinations and treatment modalities might result in more frequent diagnosis of SMM. Although it is generally accepted that the prognosis associated with SMM is poor, especially when combined with BRAF mutations, a comprehensive therapy strategy and multidisciplinary treatment might benefit patients.

Conclusions:

In summary, we described a case of skeletal muscle metastases with ossification from a colon adenocarcinoma in a patient from China. Although the potential malignancy has not been determined, ossification of SMM might suggest a high tumor malignancy. Examinations such as PET-CT, CD-DST, and gene testing are recommended to optimize a comprehensive and individualized treatment modality to prolong the patient’s life expectancy in such intractable cases.

Abbreviations

SMM: skeletal muscle metastases; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

Declarations:

Ethics approval and consent to participate

This study conforms to the Declaration of Helsinki. The ethics committee of the Second Affiliated Hospital of Jilin University obtained the consent of the patient.

Consent for publication

Written consent was obtained from the patient for publication of this study and accompanying images.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Authors' contributions

YG wrote the first draft of the manuscript. WSX collected the files. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Benson, A.B., et al., *NCCN Guidelines Insights: Colon Cancer, Version 2.2018.* J Natl Compr Canc Netw, 2018. **16**(4): p. 359-369.
2. Damron, T.A. and J. Heiner, *Distant soft tissue metastases: a series of 30 new patients and 91 cases from the literature*. Ann Surg Oncol, 2000. **7**(7): p. 526-34.
3. Nocun, A. and B. Chrapko, *Multiple and solitary skeletal muscle metastases on 18F-FDG PET/CT imaging*. Nucl Med Commun, 2015. **36**(11): p. 1091-9.
4. Hasegawa, S., et al., *Metastasis to the forearm skeletal muscle from an adenocarcinoma of the colon: report of a case.* Surg Today, 2000. **30**(12): p. 1118-23.
5. Plaza, J.A., et al., *Metastases to soft tissue: a review of 118 cases over a 30-year period.* Cancer, 2008. **112**(1): p. 193-203.
6. Araki, K., et al., *Colorectal carcinoma metastatic to skeletal muscle.* Hepatogastroenterology, 1994. **41**(5): p. 405-8.
7. Laurence, A.E. and A.J. Murray, *Metastasis in skeletal muscle secondary to carcinoma of the colon--presentation of two cases*. Br J Surg, 1970. **57**(7): p. 529-30.
8. Doroudinia, A., et al., *Rectal adenocarcinoma presenting with thigh muscle metastasis as the only metastatic site.* BMJ Case Rep, 2019. **12**(1).
9. Kline, T.S. and H.S. Neal, *Needle aspiration biopsy: a critical appraisal. Eight years and 3,267 specimens later.* JAMA, 1978. **239**(1): p. 36-9.
10. Liberatore, M., et al., *Multiple metastases of soft tissue visualized by technetium-99m-methylene diphosphonate scintigraphy: a case report.* J Med Case Rep, 2014. **8**: p. 459.
11. Stabler, J., *Case report: ossifying metastases from carcinoma of the large bowel demonstrated by bone scintigraphy.* Clin Radiol, 1995. **50**(10): p. 730-1.
12. Yoshikawa, H., et al., *Ossifying intramuscular metastasis from colon cancer: report of a case.* Dis Colon Rectum, 1999. **42**(9): p. 1225-7.
13. Huang, R.S., R.E. Brown, and J. Buryanek, *Heterotopic ossification in metastatic colorectal carcinoma: case report with morphoproteomic insights into the histogenesis*. Ann Clin Lab Sci, 2014. **44**(1): p. 99-103.
14. Prasanna, T., et al., *The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern.* Acta Oncol, 2018. **57**(11): p. 1438-1444.
15. Pai, S.G., et al., *Correlation of tumor mutational burden and treatment outcomes in patients with colorectal cancer.* J Gastrointest Oncol, 2017. **8**(5): p. 858-866.
16. Kopetz, S., et al., *Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer.* N Engl J Med, 2019. **381**(17): p. 1632-1643.
17. Sepulveda, A.R., et al., *Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology.* J Clin Oncol, 2017. **35**(13): p. 1453-1486.
18. Gong, J., et al., *Molecular profiling of metastatic colorectal tumors using next-generation sequencing: a single-institution experience*. Oncotarget, 2017. **8**(26): p. 42198-42213.

Figures

Fig. 1 a. In the resected specimen, the red arrow points to the tumor location and the white arrow points to the appendix; b. H&E staining of the resected specimen; c. the white arrow points to the skeletal muscle metastases on a color ultrasound; d. H&E Staining of an SMM biopsy; the red arrows points to the adenocarcinoma region and the blue arrow points to the ossification region.

Fig. 2 Multiple lymphadenopathy metastases around the abdominal aorta, as assessed using PET-CT

Fig. 3 BRAF gene mutation detected using gene test.

Table1

Table 1. Clinical characteristics of patients with skeletal muscle metastases from colon carcinoma reported in English language literature

Table1

Author	Age/Sex	Country	Primary carcinoma	Surgery	Metastases site	Ossification	Interval (months)	Enbloc resection	Outcome
Laurence *et al*.[9]	70/F	Argentina	Caecum	Right colectomy	Right calf	N	24	Y	Died Soon for generalized metastases
Laurence *et al*.[9]	51/M	Argentina	Transverse colon	Right colectomy	Right forearm	N	0	Y	Died Soon for generalized metastases
Stulc *et al*.[22]	74/M	USA	Ascending colon	Right hemicolectomy	Left buttock	NS	30	Y	NS
Torosian *et al*.[23]	68/M	USA	Transverse colon	Right colectomy	Left thigh	N	60	Y	NS
Caskey *et al*.[24]	62/M	USA	Transverse colon	NS	Left gluteus	NS	6	NS	NS
Caskey *et al*.[24]	71/F	USA	Colon	NS	Right psoas	NS	NS	NS	NS
Araki *et al*.[8]	66/M	Japan	Colon	Colectomy	Right teres major	NS	6	NS	Died after 2 years and 7 months from carcinoma
Stabler *et al*.[13]	65/M	UK	Sigmoid cancer	Sigmoid colectomy	Left psoas	Y	24	NS	Died 2 years after surgery

Table1

Avery *et al.* [25]	71/M	UK	Sigmoid cancer	Sigmoid colectomy	Left psoas	NS	48	NS	NS
Yoshikawa *al*.[14]	54/M	Japan	Sigmoid cancer	Partial sigmoid colectomy	Right buttock	Y	24	Y	Died after 8 months from multiple metastases
Naik *et al*.[26]	56/M	Malay	Right colon	Right hemicolectomy	Recuts abdominis	Y	60	Y	NS
Takada*et al*.[27]	71/M	Japan	Sigmoid colon	Hartmann	Left iliopsoas	N	60	N	NS
Our present case	43/M	China	Ascending colon	Laparoscopic extended right hemicolectomy	Right thigh	Y	5	N	Died 9 months after surgery.

(N, no resection; Y, en bloc resection; NS, not specified; a Time interval from the resection of the primary carcinoma to the skeletal muscle metastases)

Figure1

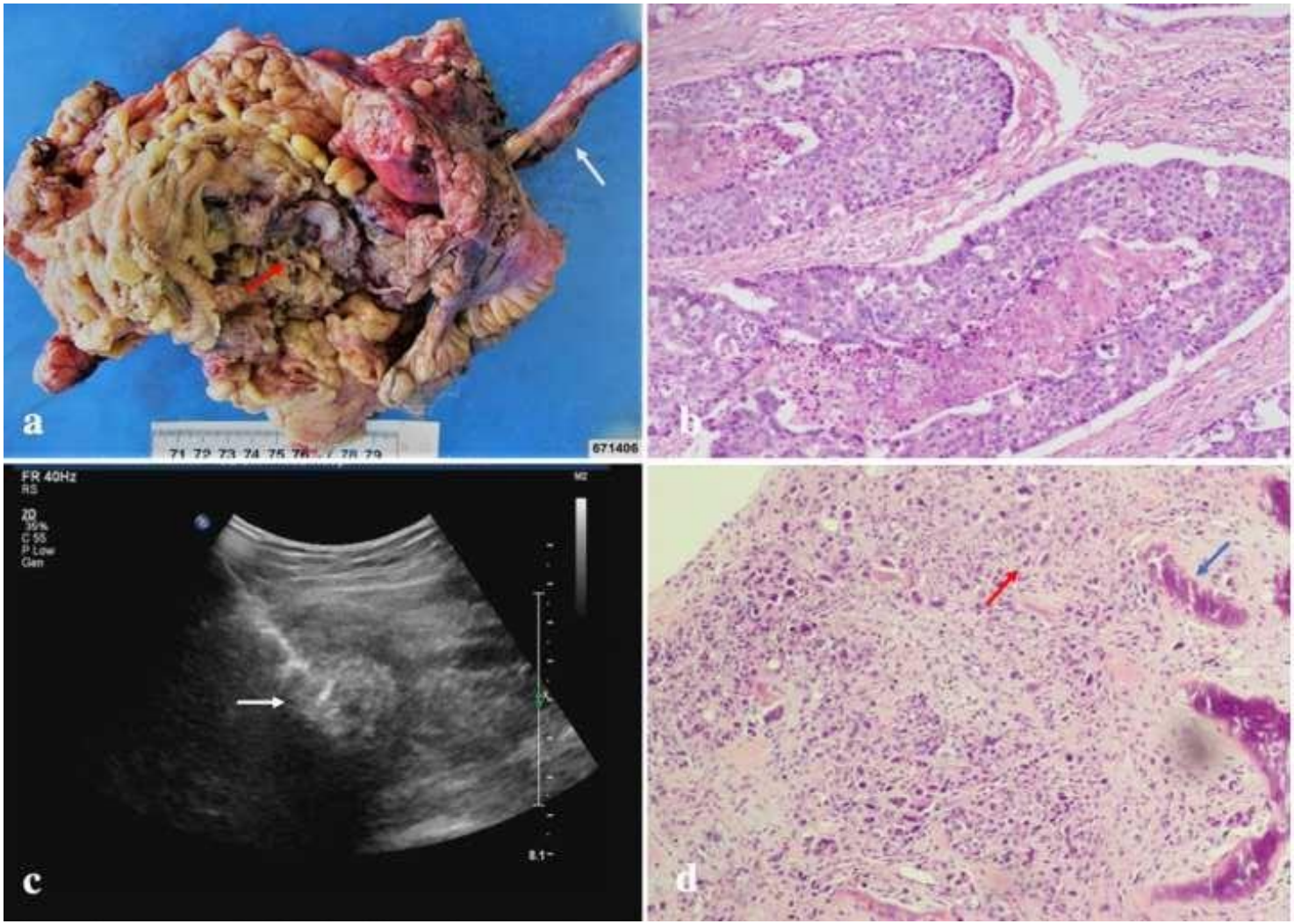


Figure2

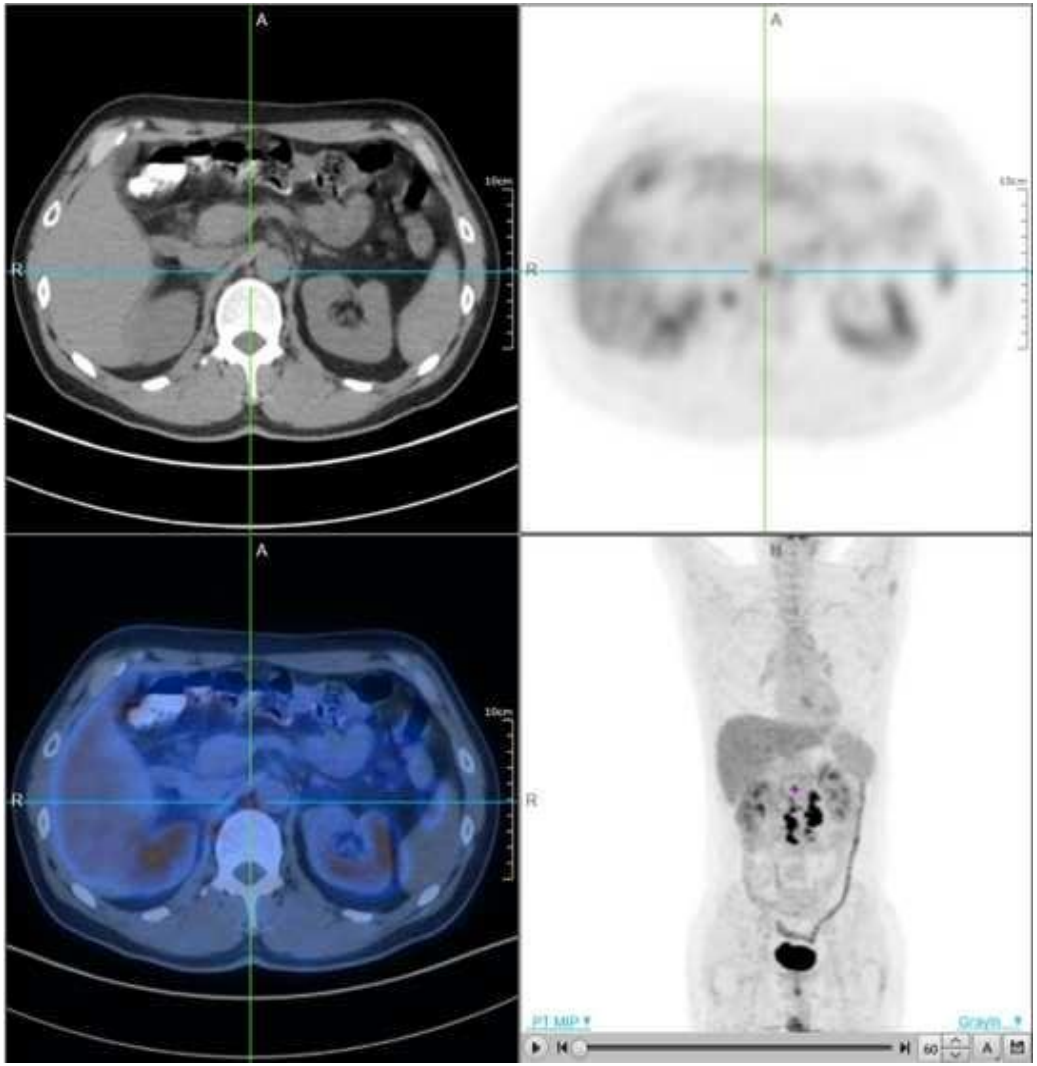
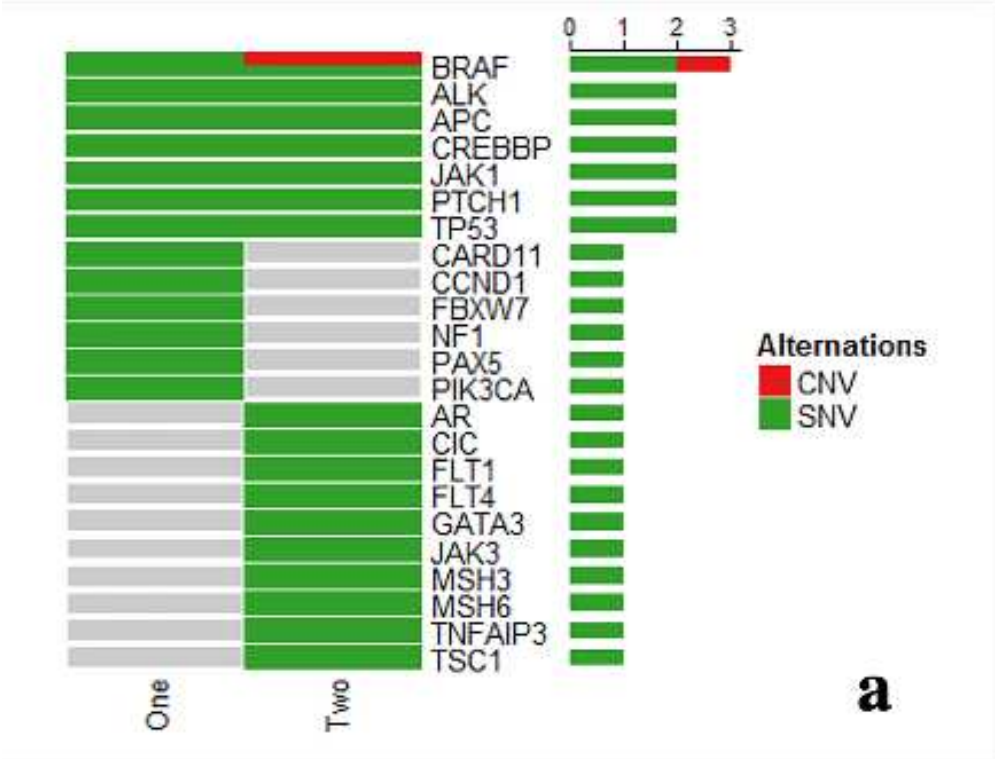
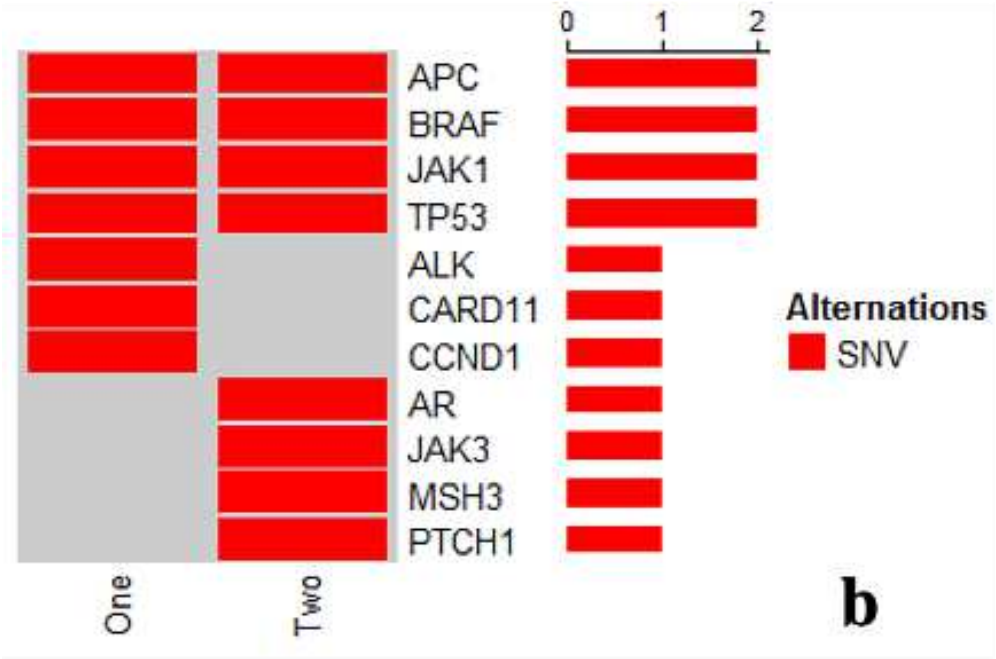


Figure3


0
1
2
3
BRAF
ALK
APC
CREBBP
JAK1
PTCH1
TP53
CARD11
CCND1
FBXW7
NF1
PAX5
PIK3CA
AR
CIC
FLT1
FLT4
GATA3
JAK3
MSH3
MSH6
TNFAIP3
TSC1
Alternations
CNV
SNV
One
Two
a


0
1
2
APC
BRAF
JAK1
TP53
ALK
CARD11
CCND1
AR
JAK3
MSH3
PTCH1
Alternations
SNV
One
Two
b

309

Figures

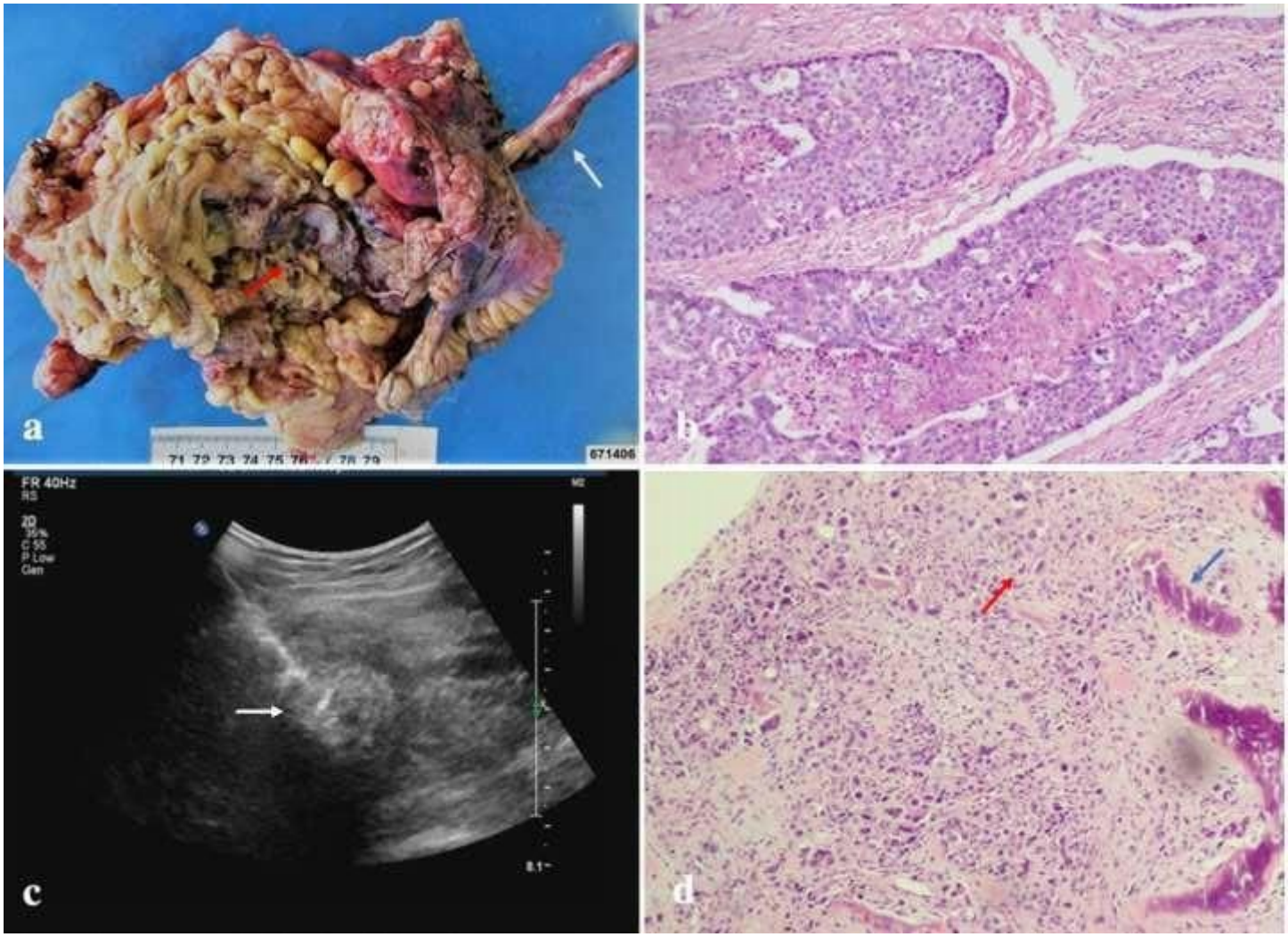


Figure 1

In the resected specimen, the red arrow points to the tumor location and the white arrow points to the appendix; b. H&E staining of the resected specimen; c. the white arrow points to the skeletal muscle metastases on a color ultrasound; d. H&E Staining of an SMM biopsy; the red arrows points to the adenocarcinoma region and he blue arrow points to the ossification region.

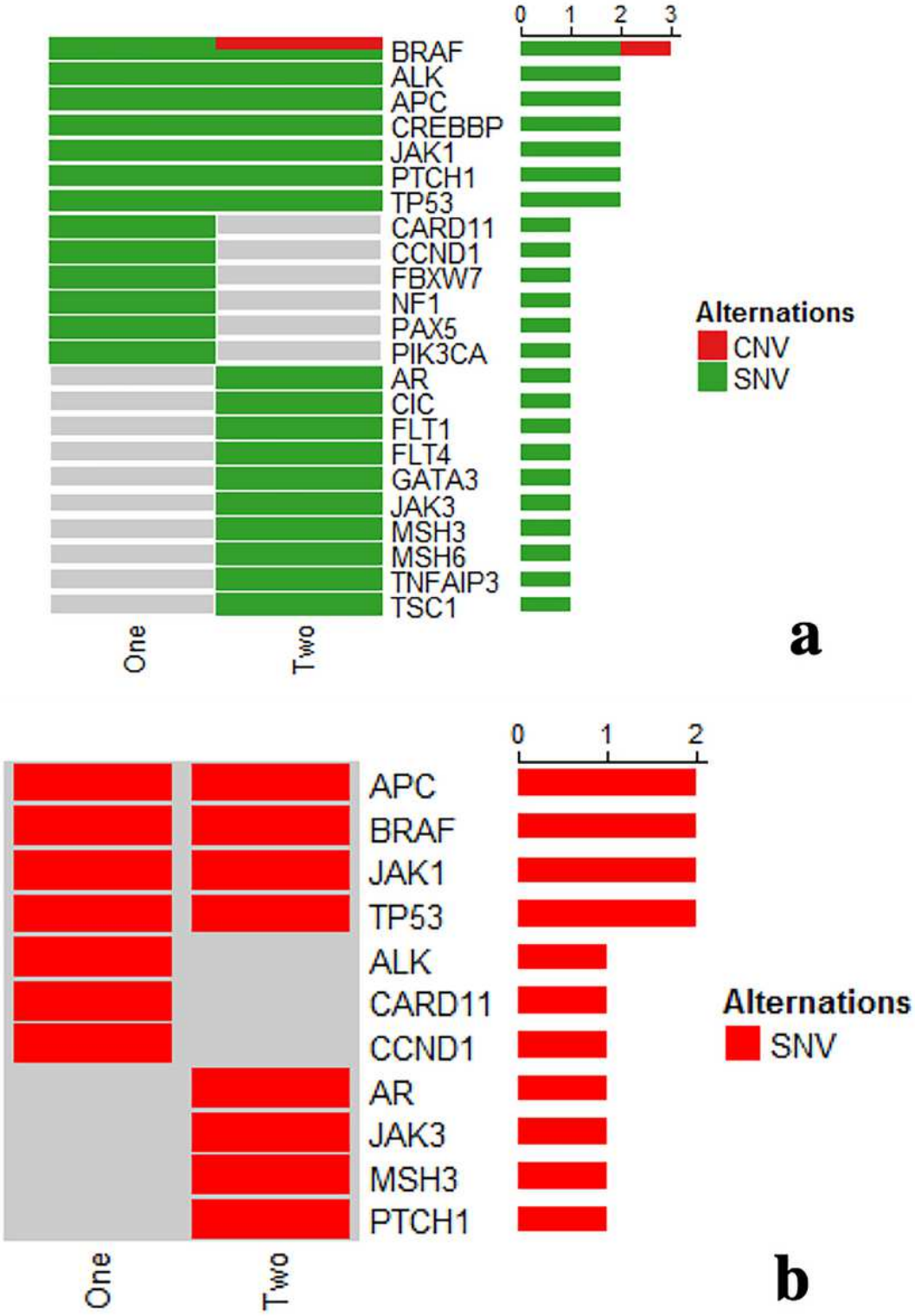


Figure 2

Multiple lymphadenopathy metastases around the abdominal aorta, as assessed using PET-CT

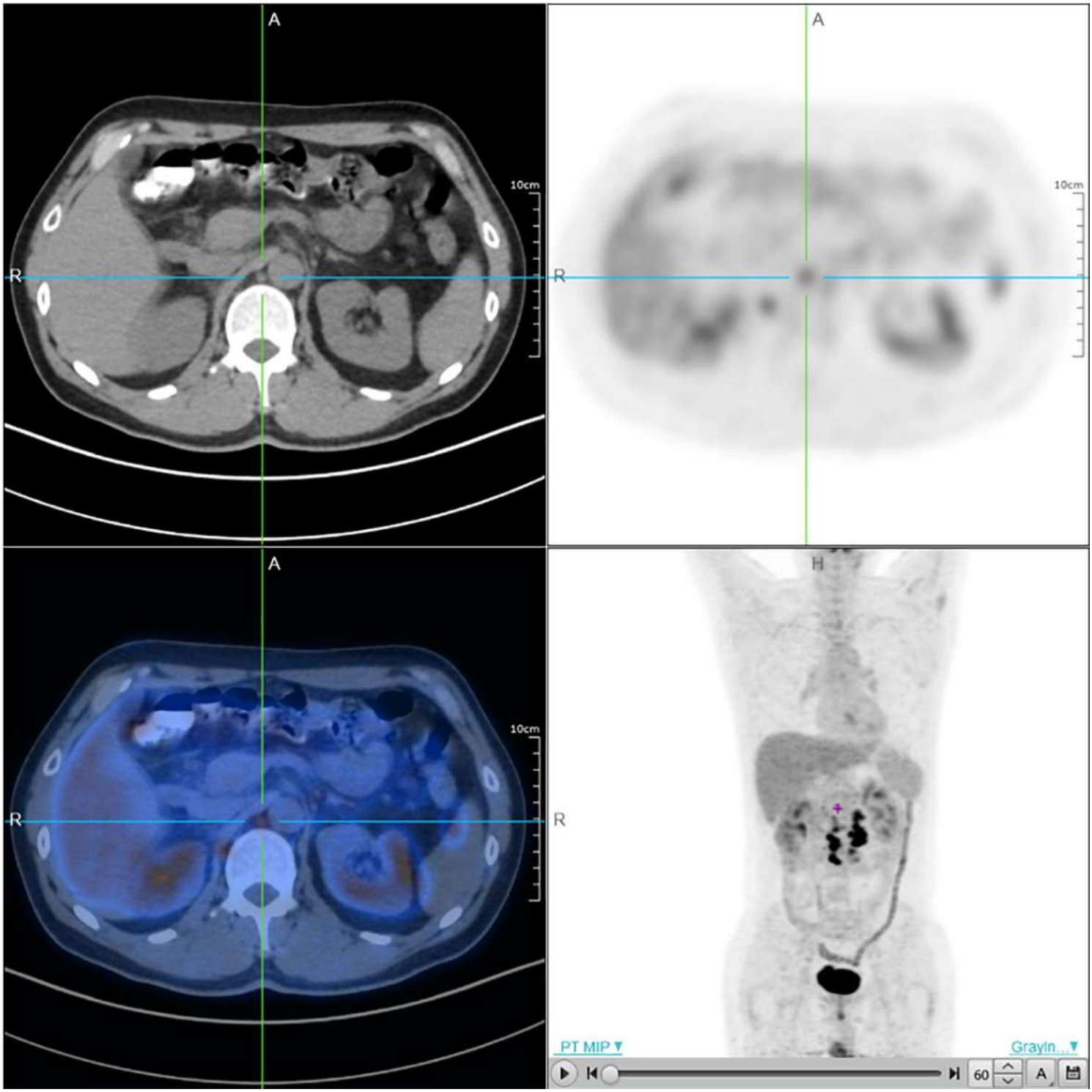


Figure 3

BRAF gene mutation detected using gene test.