A case report of triple primary malignant tumors including breast,cervical and thyroid cancers with CHEK2 and PIK3CA mutation

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Case Report

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Abstract

Introduction

To the best of our knowledge the combination of multiple synchronous primary malignant tumors which involves breast carcinoma, thyroid carcinoma and cervical carcinoma has not been previously reported.

Case report

Herein, we report a 47-year-old female who was diagnosed with multiple synchronous primary malignancies: cervical squamous-cell carcinoma, invasive ductal carcinoma of left breast, papillary carcinoma of the left thyroid gland and had a gene mutation of both CHEK2 and PIK3CA. We adopted a comprehensive treatment approach .

Conclusion

When a cancer patient presents with the clinical manifestation of another tumor, the possibility of synchronous occurrence of multiple primary malignant tumors, as well as tumor metastasis should be considered. In addition, the follow-up time of patients with malignant tumors should be extended, because timely detection and treatment of more primary malignancies may extend the survival time of patients and improve their quality of life.

Introduction

Multiple primary malignant tumors(MPMs) are defined as multiple tumors with different pathogenetic origins in the same individual. Based on the timing of the diagnosis, MPMs are classified as synchronous or metachronous. The frequency of MPMs is reported in the range of 2–17%[1] Dual primary malignancies are the most common type, whereas tri-primary and multiple primary malignancies account for only 0.5% and <0.1% of cases, respectively[2]. Here, we report the case of a 47-year-old female who has diagnosed synchronous primary carcinoma of the thyroid, cervix and breast and had treated successfully in the Affiliated Hospital of Qingdao University, in conjunction with a brief review of related literature.

Patient information

In October 2018, a 47-year-old, premenopausal female with chief complaints of vaginal contact bleeding for 3 months was admitted to her local hospital.There were no relation abdominal pain, nor weight loss or any other specific complaints. The disease was initially diagnosed from the cervical biopsy as squamous-cell carcinoma(SCC). Then the patients admitted to our hospital for further diagnosis and treatment.The patient was healthy prior to diagnosis and the family history was non-contributory.

Clinical Findings

Physical examination showed a well-delimited, elastic-firm, mobile tumor whose diameter is 2 centimeters in the upper outer quadrant of the left breast. No palpable axillary and supraclavicular lymph nodes. Gynecologic examination revealed an enlarged firm cervix, and the left parametrial tissue is firm, thickening reaches the pelvic wall while the right parametrial tissue is thickened and stretchy.

Diagnostic Assessment

Laboratory examinations：Tumor markers tested serum carcinoembryonic antigen (CEA) and CA-125 was elevated to 96 ng/mL (normal range 0-3.4 ng/mL) and 53.95 U/mL(normal range 0-35 U/mL), while CA-199, CA-242,CA-724 and CA-153 were all within the normal range. TSH reduced to 0.072 mIU/L(normal range 0.35-4.94 mIU/L). Human papillomavirus (HPV) DNA testing was negative.

Biopsy and imaging examinations：At the local hospital, there had a cervix punch biopsy which histological diagnosis documented a squamous cell carcinoma. Then the patient visited our hospital, the histological diagnosis from left breast biopsy turned out to be an invasive ductal carcinoma and the left thyroid gland showed a papillary carcinoma. Subsequent 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT revealed high FDG uptake by the tumor (the normal value of standardized uptake value max is generally lower than 2.0): 1. The very-low-density nodules with clear boundaries were detected in the left upper lobe of the thyroid gland. (Figure. 1B) 2. The left breast's upper left quadrant showed uneven density, with associated punctuate calcified foci. (Figure. 1C) 3. Cervix thickened and formed soft tissue mass which upward invasion uterine body and the posterior boundary is unclear demarcation from the anterior rectal wall. Enlarged lymph nodes were found in both running area of the left iliac common vessel and bilateral external iliac vessels. (Figure. 1D)

Figure 1 18F-FDG-PET/CT (MIP and axial images) Scans

a MIP. **b** high FDG uptake by the thyroid gland nodules (SUVmax=29.7: arrow) . **c** high FDG uptake by the nodules of the left breast(SUVmax=6.8: arrow). D high FDG uptake by the cervix(SUVmax=20.6), uterine body(SUVmax=8.7) and the running area of the left iliac common vessel and bilateral external iliac vessels(SUVmax=6.3). MIP, maximal intensity projection. FDG, 2-[18F]-fluoro-2-deoxy-D-glucose. PET, position emission tomography. CT, computed tomography. SUVmax, standardized uptake value max.

Final diagnosis： The patient was diagnosed with MPMs including endocervical squamous-cell carcinoma(SCC), thyroid papillary carcinoma(TPC) and breast invasive carcinoma(IDC).

Therapeutic Intervention

After a comprehensive multidisciplinary consultation, two courses of taxol/cisplatin chemotherapy were administered first because of the later stage of cervical carcinoma which is not suitable for surgery. The chemotherapy process went smoothly. Then the following procedures were performed after one month: left breast modified radical mastectomy and left lobar thyroid plus isthmus resection with lymphadenectomy and recurrent laryngeal nerve anatomy. Concurrent radio-chemotherapy for pelvic lesions: pelvic IMRT（intensity-modulated radiation therapy） with the dose of 50Gy/2Gy/25f (Figure 2A)

and point A based cervical cancer brachytherapy with the dose of 6Gy/2Gy/3f (Figure 2B), combined with one course of taxol/cisplatin chemotherapy was applied after the surgery. However due to grade 2 granulocytopenia during radiotherapy, the fourth、fifth and sixth cycle of chemotherapy(TC) was performed delayed after radiotherapy. Finally, we jointly applied endocrine therapy（Anatrazol tablets）and targeted therapy（trastuzumab）until now.

Figure 2 Radiotherapy

a The target area and dose distribution of IMRT in cervical cancer. **b** The target area and dose distribution of brachytherapy in cervical cancer.

Histopathological examination of the surgical specimens with immunohistochemistry confirmed the diagnosis of MPMs, with observations including:(1) a 2.5cm * 1.5cm * 1.5cm invasive ductal carcinoma(IDC) of the rootectomy breast tissue(not otherwise specified,*NOS*) with the nuclear grade of III, with a 1.5cm basal cell papilloma on the skin. (Figure. 3A) All surgical margins were negative, left lymphovascular invasion was not to be observed (0/34). Pathological staging was pT2N0M0. The tumor stained strongly positive for all ER, PR and Her2 but negative for CK5/6 and CK14, showed a Ki-67 proliferation index of 40%. (2) a 1.7cm*1.5cm*1.0cm papillary thyroid carcinoma (PTC) of the rootectomy tissue from the left thyroid gland and the isthmus. (Figure. 3B) A group of metastatic lymph nodes was discovered in the sixth and seventh group of the left neck. Pathological staging was pT1N1M0. CK19, Galectin-3（+）and TTF-1 resulted positive while CD56 and HBME-1 resulted weakly positive. Comprehensive genomic profiling revealed the presence of CHEK2 Gene mutation and PIK3CA Gene mutation with a microsatellite-stable (MSS) phenotype.

Figure 3 Pathology Image

Histological examination by surgery of the breast（**a**） showed invasive ductal carcinoma,thyroid tissue（**b**） showed papillary thyroid carcinoma by hematoxylin and eosin stain. Magni cation, x100.

Follow-up and Outcomes

The patient remained under endocrine therapy（Anatrazol tablets）plus targeted therapy（trastuzumab） after six cycle chemotherapy and visited our hospital regularly for examinations. After a follow-up period of 2.5 years, the patient is alive and well with no evidence of tumor recurrence, metastatic disease, or any more MPMs.

Discussion

There are three notable aspects of this case. First, to the best of our knowledge, the special combination of tumors (SCC of the cervix, IDC of the breast, and PTC) has not been reported previously. Second, the patient had a gene mutation of both CHEK2 and PIK3CA. Third, we adopted a comprehensive treatment approach including radical resection, chemotherapy, radiotherapy, endocrinotherapy and targeted

therapy.In addition to reporting this case, we decided to conduct an adequate literature review to analyze this case as well as identify new cases.

The State of MPMs

Currently, MPMs(multiple primary malignant tumors) diagnostic criteria still continue to use the 1932 diagnostic criteria proposed by Warren and Gates[3]：each tumor must be confirmed by histology and cytology as a malignant tumor with its unique pathological morphology; the possibility of mutual metastasis must be ruled out; tumors occur in different parts, and the two are not continuous with each other. Moertel divides MPMs into synchronous and metachronous multiple primary malignant tumors according to the chronological order of their appearance:≥ 2 types of malignant tumors occur at intervals of ≤ 6 months as synchronous MPMs while >6 months as metachronous MPMs.

Although the underlying mechanisms responsible for the development of MPMs are yet to be fully elucidated, frequently implicated factors can be collated into three broadly defined categories：genetic factors, living environment factors (smoking, alcoholism, obesity, etc.), and iatrogenic factors (radiation therapy, chemotherapy, etc.).

At present, there is no uniform standard for the selection of MPMs treatment options. Whether in patients with synchronous MPMs or metachronous MPMs, the lesions should be completely removed at the same time or sequentially. If the lesion cannot be removed, comprehensive treatment such as immunotherapy, targeted therapy, and chemotherapy can be considered, and the possible impact on second primary cancer treatment during primary tumor treatment should be avoided, such as the accumulation of drug toxicity and the accumulation of radiation dose in the same area.

In our case, the patient’s malignancy occurred simultaneously in the thyroid, cervix, and breast. The pathological types of these three tumors are significantly different from each other; all three tumors were diagnosed at the same time, consistent with the diagnostic criteria for multiple primary malignant tumors. The cervix, breast, and thyroid glands have certain commonalities in hormone metabolism pathways and have the potential to interact to produce MPMs. On the other hand, the genetic test showed gene mutations of CHEK2 and PIK3CA. She did not use tobacco or alcohol and her family history was unremarkable. The existing treatment guidelines were followed. Radical resection of breast and thyroid cancers was performed. Because cervical cancer has metastasized, we applied palliative care. No tumor progression was found in the patient until today.

Progress of the relationship between thyroid tumor，breast cancer and cervical cancer

The relationship between thyroid cancer and breast cancer has attracted widespread attention as early as the 19th century. The study found that patients with a history of thyroid cancer have an increased risk of

recurring breast cancer, and breast cancer patients also have an increased risk of recurring thyroid cancer[45]. Kim's research found that breast cancer recurrence ranked first in patients' second-largest primary tumor[4]. A study from Seoul national university found that 4.3 percent of patients with thyroid cancer had recurrent breast cancer, and 2.6 percent of patients with breast cancer had recurrent thyroid cancer[5]. In addition, the surveillance, epidemiology, and end-result database (http://seer.cancer.gov/) reported that premenopausal women ages 20 to 49 with a history of thyroid cancer had a significantly increased risk of subsequent breast cancer, compared with women without a history of thyroid cancer[6].

But so far, there is no clear conclusion about whether there is a connection between thyroid cancer and breast cancer, and by what way. At present, it is generally believed that hormones play an important role in the occurrence and development of thyroid cancer and breast cancer, as well as genetic susceptibility, autoimmunity, radiation exposure and other factors. Since both the breast and thyroid are hormone-dependent endocrine organs, some researchers have suggested that estrogen, thyroid hormone, or related receptors may play a vital role in the MPMs of breast and thyroid cancer. Studies[7] have shown that beta-estradiol can significantly stimulate the proliferation of thyroid cancer cells in a time and concentration-dependent way, and this effect is inhibited by the estrogen antagonist tamoxifen. Meanwhile, the expression of ER in thyroid cancer tissues is significantly higher than that in para-cancer tissues. Under normal circumstances, the thyroid can continuously express the sodium-iodide symporter(NIS), while only the breast during pregnancy or lactation has functional NIS expression, which can mediate the absorption of iodine. However, the expression of the NIS gene can be detected in 80% of breast cancers and 90% of thyroid cancers, suggesting that NIS may play a large role in the co-occurrence of thyroid cancer and breast cancer. Genetic susceptibility has also been studied between the two types of cancer the activation of the protein kinase B PKB gene and the variation of the cell cycle checkpoint kinase CHEK2) gene may be one of the pathogenic factors. In the setting of breast cancer, PIK3CA mutations are extremely common, second only to TP53 mutations. PIK3CA mutation can occur in thyroid cancer but does not seem to be a major genetic event in thyroid cancer in general.

The MPMs of cervical cancer with thyroid cancer cases are rarely reported in clinic, and its main mechanism may be related to the expression of estrogen. Lee et al.[8] found that the incidence of multiple primary cancers in breast cancer patients was 10.5%, among which the incidence of breast cancer combined with gynecological tumors was the second, only second to thyroid cancer.

The causes of both breast and cervical cancers are unknown, but both are associated with long-term oral contraceptives. Chung et al. [9]reported that long-term oral contraceptives and fertility increase the risk of cervical cancer in HPV infected individuals. At the same time, cervical cancer and breast cancer co-existence of estrogen and progesterone receptor may also be carcinogenic factors.

For this patient, the woman has no history of the application of estrogen and progesterone drugs, considering that the patient's multiple primary cancers are associated with mutations in both CHEK2 and PIK3CA. The research results of Chen et al suggest that CHEK2 mutations predispose to familial aggregations of breast and thyroid cancer and to double primary malignant tumors of the breast and

thyroid[10]. In the setting of breast cancer, PIK3CA mutations are extremely common, second only to TP53 mutations [11]. PIK3CA mutation can occur in thyroid cancer but does not seem to be a major genetic event in thyroid cancer in general[12]. The carcinogenicity of CHEK2/PIK3CA mutation in cervical cancer has not been reported.

Patient Perspective

During the treatment, the patient said that although the chemotherapy drugs and surgery caused her short-term discomfort, however the benefits were long-lasting.

Informed Consent

The patient gives informed consent to this case-report.

Conclusion

Multiple primary malignant tumors are thought to be on the increase due to recent advances in diagnosis and treatment. When a cancer patient presents with the clinical manifestation of another tumor, the possibility of synchronous occurrence of multiple primary malignant tumors, as well as tumor metastasis should be considered. In addition, the follow-up time of patients with malignant tumors should be extended, because timely detection and treatment of more primary malignancies may extend the survival time of patients and improve their quality of life.

Abbreviations

Multiple primary malignant tumors=MPMs; FDG-PET= 2-[18F]- fluoro-2-deoxy-D-glucose positron emission tomography; SCC=squamous cell carcinoma; SUVmax=standardized uptake value max.

Declarations

Acknowledgements

Not applicable.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

RX and SW acquired the data, performed the literature review and edited the manuscript. LS and YZ substantially contributed to the concept and design of the study. HL, Gongjun, W and ZL acquired the data and provided clinical advice. WQ revised the manuscript. Guanqun, W evaluated the specimens and provided histopathological advice. WQ played a major role in preparation of the manuscript. All authors read and approved the nal manuscript.

Ethics approval and consent to participate

The report was submitted for ethical review to the Ethics Committee of the Affiliated Hospital of Qingdao University (Qingdao, China), who waived the requirement for review per institutional protocol owing to the study not containing content that requires ethical approval. The Ethics Committee approved the submission and publication of the manuscript.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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Figures

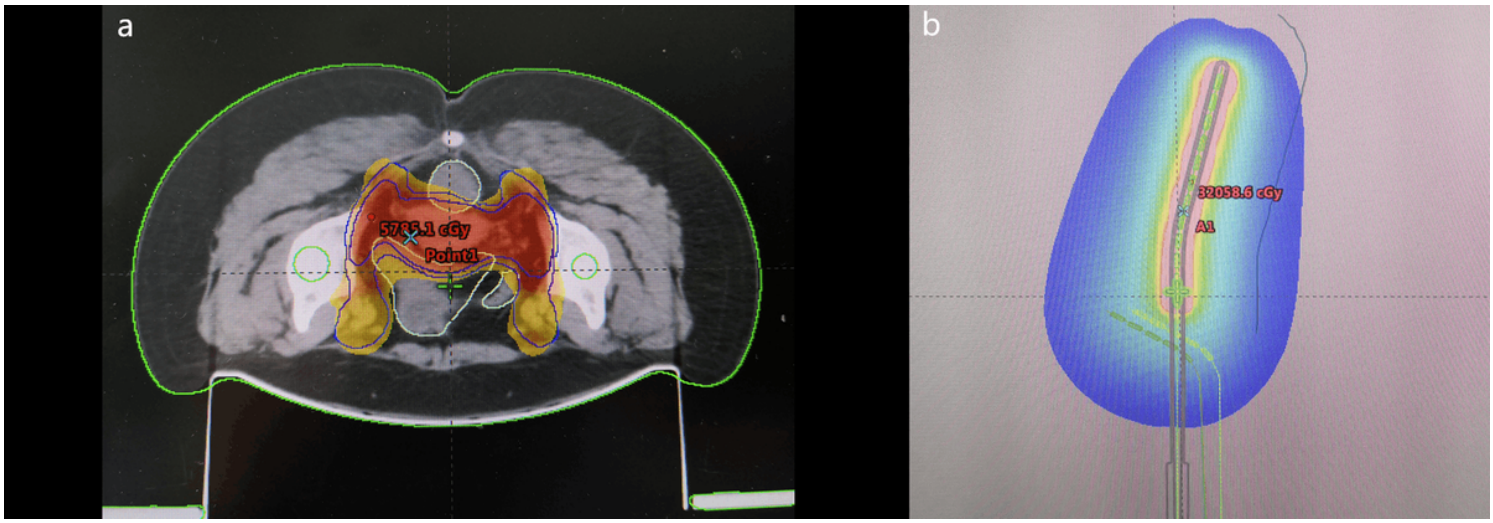

Figure 1

18F-FDG-PET/CT (MIP and axial images) Scans a MIP. b high FDG uptake by the thyroid gland nodules (SUVmax=29.7: arrow) . c high FDG uptake by the nodules of the left breast(SUVmax=6.8: arrow). D high FDG uptake by the cervix(SUVmax=20.6), uterine body(SUVmax=8.7) and the running area of the left iliac common vessel and bilateral external iliac vessels(SUVmax=6.3). MIP, maximal intensity projection. FDG, 2-[18F]-fluoro-2-deoxy-D-glucose. PET, position emission tomography. CT, computed tomography. SUVmax, standardized uptake value max.

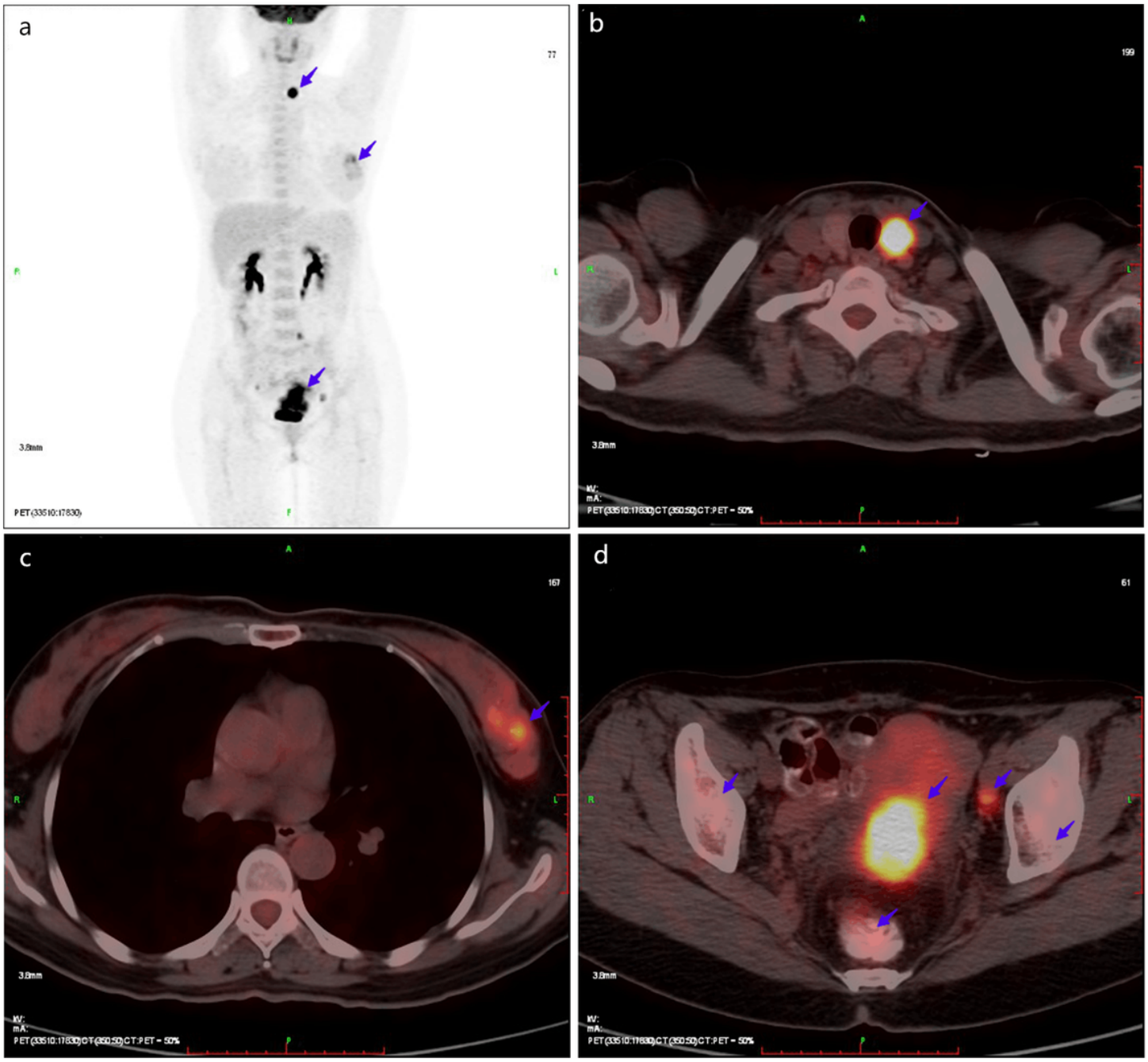

Figure 2

Radiotherapy a The target area and dose distribution of IMRT in cervical cancer. b The target area and dose distribution of brachytherapy in cervical cancer.

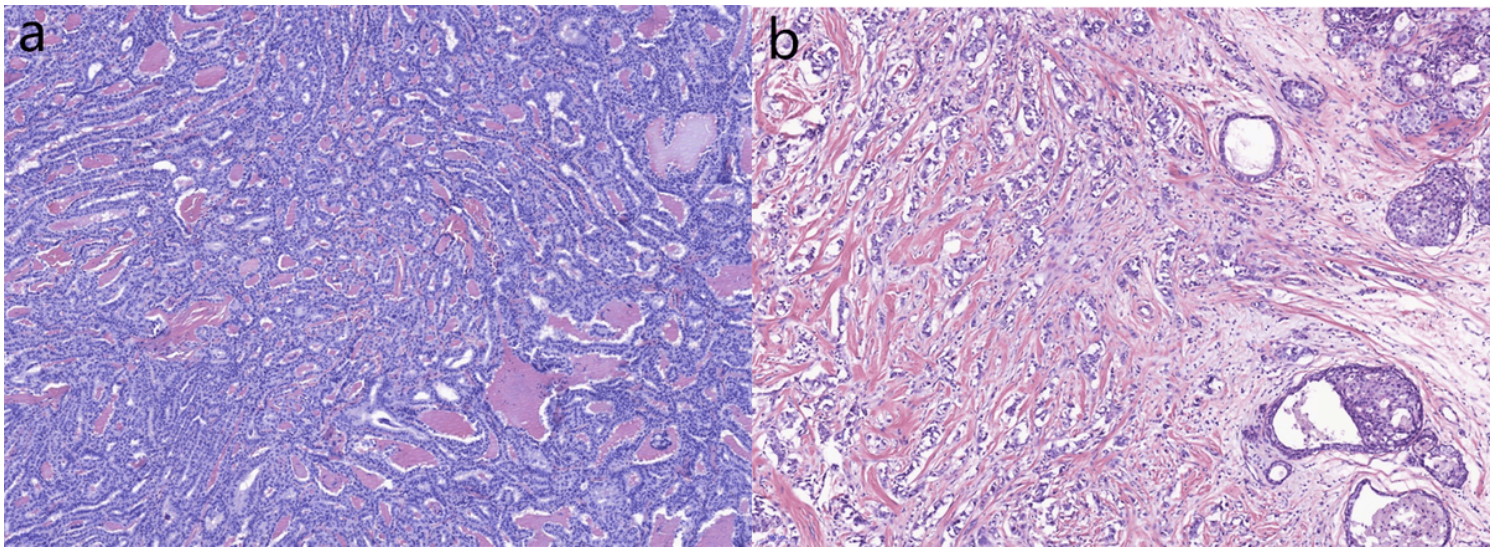

Figure 3

Pathology Image Histological examination by surgery of the breast（a） showed invasive ductal carcinoma,thyroid tissue（b） showed papillary thyroid carcinoma by hematoxylin and eosin stain. Magni cation, x100.

Supplementary Files

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