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CHALLENGES IN TREATMENT AND THE IMPORTANCE OF RADIOTHERAPY IN A SYNCHRONOUS ENDOMETRIAL AND BREAST CANCER

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Abstract
We report the case of a 69-year-old-female with synchronous endometrial and breast cancer. The imaging and pathology results confirmed the diagnosis. The patient underwent surgery and chemotherapy for endometrial cancer, and surgery followed by external beam radiotherapy for breast cancer. The patient's clinical condition and imaging showed a favorable evolution after 2 months of follow-up.
Keywords: *synchronous endometrial and breast cancer, radiotherapy, complete response.*

Abstract
Raportăm cazul unei femei în vârstă de 69 de ani cu cancer de sân și endometrial sincron. Rezultatele imagistice și histopatologice au confirmat diagnosticul. Pacienta a fost supusă unei intervenții chirurgicale și chimioterapiei pentru cancerul endometrial și intervenției chirurgicale urmată de radioterapie cu fascicul extern pentru cancerul de sân. Starea clinică și imagistică a pacientei au prezentat o evoluție favorabilă după 2 luni de urmărire.
Cuvinte cheie: *cancer endometrial și mamar sincron, radioterapie, răspuns complet.*

INTERNAL MEDICINE

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Introduction

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in women. The most common presentation of endometrial cancer is postmenopausal bleeding[1]. Breast cancer is a major public health problem, being the most common form of cancer in women and the second leading cause of death after lung cancer[2].

The most common sites of metastases are the bone, lungs, and liver[3].

Multiple primary cancers (MPCs) are defined as at least two independent, that are not metastases, but rather new primary tumors with differing histogenesis that can be easily verified by immunohistochemistry examination, that develop within the same or different organs, simultaneously or consecutively.

According to the time criterion, MPCs can be divided into synchronous, i.e., new malignancies that develop within 6 months, and metachronous, i.e., when a new malignancy develops after 6 months[4,5]. Multiple mechanisms such as environmental and genetic factors, host and lifestyle, and treatment-related factors are underlying the pathogenesis for multiple primary cancers[6].

We present a case of a 69-year-old female with synchronous cancer who was treated first for endometrial cancer, through surgery and systemic therapy. She underwent surgery, hormone therapy, and radiotherapy for breast cancer with complete clinical remission. We choose to treat first, endometrial cancer due to related complications.

Case Report

Case history

The following case is a 69 years-old woman who presented to the hospital on 01 March 2020 with postmenopausal bleeding. On scrutiny of the patient's medical history, it resulted that she was previously diagnosed with grade II hypertension and had no family history of cancer.

To establish a complete clinical staging, before the total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy a CT scan was performed, and the results pointed out a tumor mass in the right breast. After surgery, the patient started the systemic treatment. After the six cycles of carboplatin and paclitaxel, at the clinical exam of the breast, the tumor mass was about 7/7, cm in the superior and interior quadrant of the breast, painless, of hard consistency, movable on the profound and superficial planes, without axillary lymph nodes.

The treatment chosen for the tumor mass in the right breast was complete resection of the tumor and the axillary lymph nodes, followed

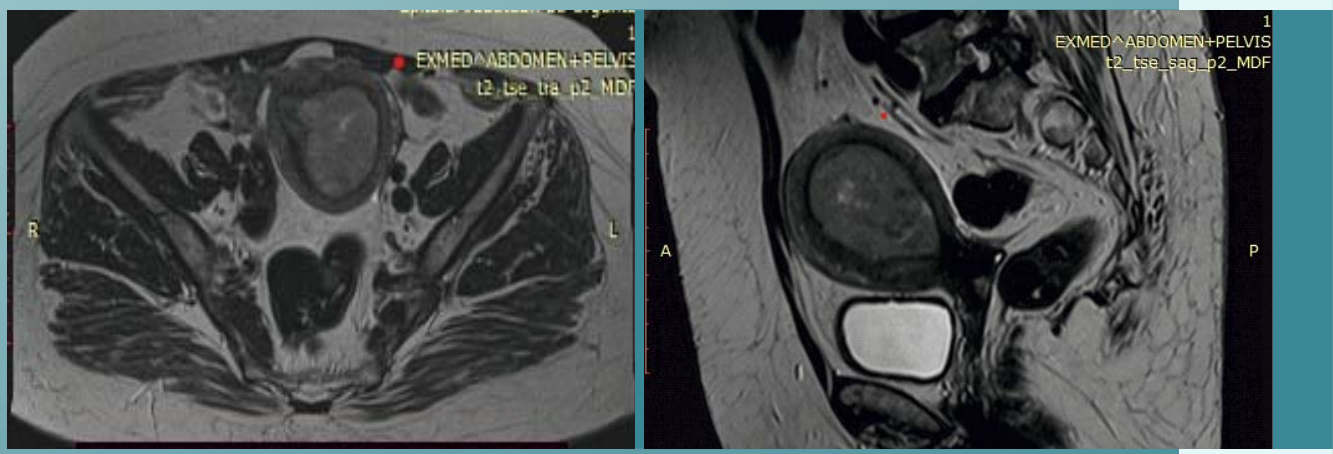


Figure nr. 1. *Magnetic Resonance Imaging axial (A) and sagittal (B) view T2 short tau inversion recovery (STIR) images from diagnosis*



Figure nr. 2. *Computed tomography axial view of the chest before total hysterectomy*

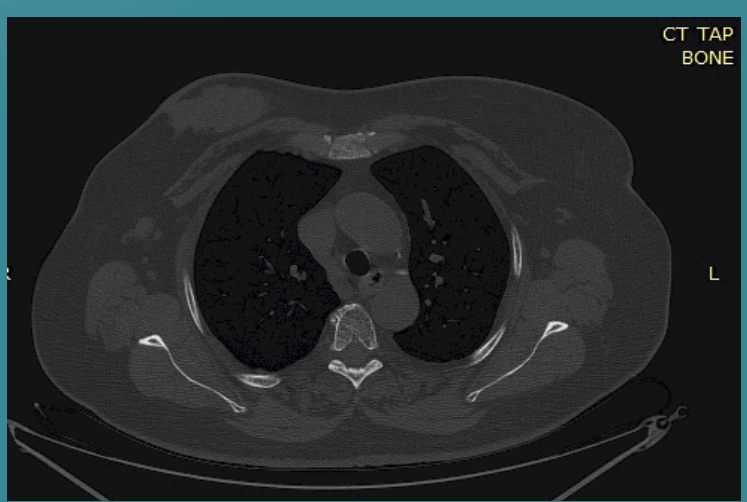


Figure nr. 3. *Computed tomography axial view of the chest in 2021*

by hormone therapy. The radiotherapy treatment was started after the surgery. At the clinical exam, we noticed that the postoperative scar was painless, with normal color, without induration and any secretions.

Investigations and treatment

Due to her postmenopausal bleeding, we decided to perform an MRI of the pelvis that revealed a tumor mass of 6.5/5.7 cm in the body and fundus, in the endometrial layer without invasion of the myometrial layer and with para-aortic pathological lymphadenopathy (Figure 1 A, B). Before surgery, the CT scan of the thorax-abdomen-pelvic regions showed a dimensional progression of the endometrial tumor mass compared to the MRI examination and the appearance of a new tumor mass in the right breast, in the super-intern quadrant with approximate dimensions of 37,5/68/46.5 mm and axillary lymph nodes of 2 cm (Figure 2).

A biopsy from the mass was performed, and endometrial serous carcinoma and para-aortic lymph nodes diagnosis were confirmed. Histopathology study indicated endometrial serous carcinoma, grade of differentiation 3. Immunohistochemistry results from the endometrial mass revealed the presence of proteins p16 and p53 in tumor cells, estrogen receptor 5-10%, and progesterone receptor-negative. She started the treatment for endometrial cancer, so the patient underwent in November 2020 through a total hysterectomy and bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy. The staging after surgery was pT3b pN2a according to the histopathological result. Between December 2020 and May 2021, the patient was treated with 6 cycles of adjuvant Carboplatin and Paclitaxel.

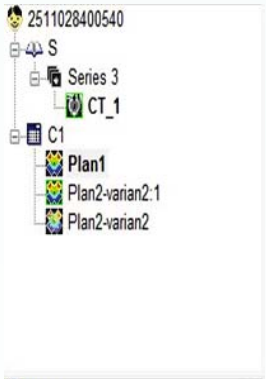
The needle biopsy results from the right breast tumor mass were ductal invasive breast carcinoma, NST, with strongly positive staining (90%) for ER and PgR, negative for Her2 neu, and 5-10% positive Ki67 in tumor cells.

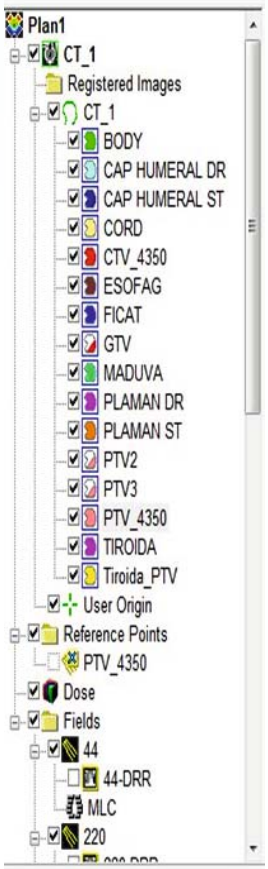
For complete clinical staging in June 2021 the patient performed a CT scan who have revealed a dimensional regression of the tumor mass in the right breast and dimensional regression of axillary lymph nodes; no signs of local pelvic recurrence; without liver and bone metastasis (Figure 3).

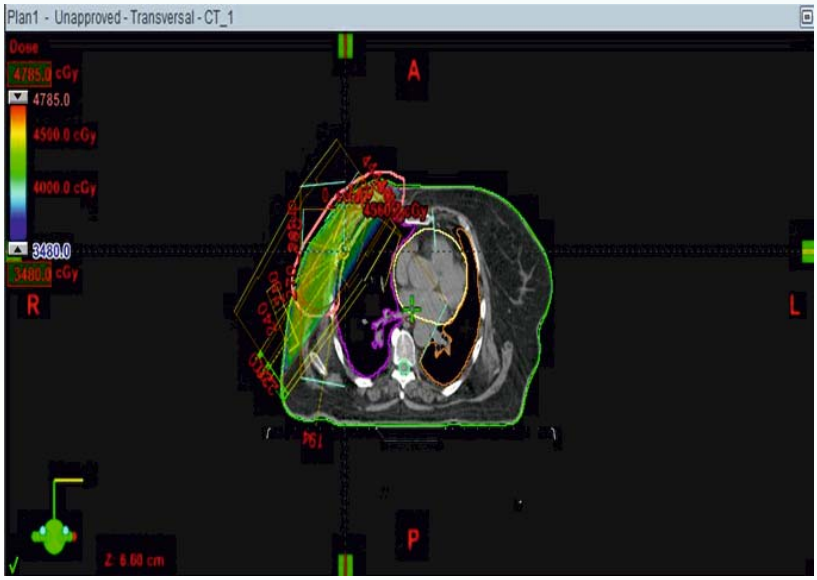
The adjuvant treatment performed for endometrial cancer seam to improve also the clinical aspect of breast cancer.

The patient underwent a radical mastectomy with the following histopathological result, lobular carcinoma, G2, histological score 6, R0, stage pT3 pN2a. After surgery, she started hormone therapy treatment with Letrozole.

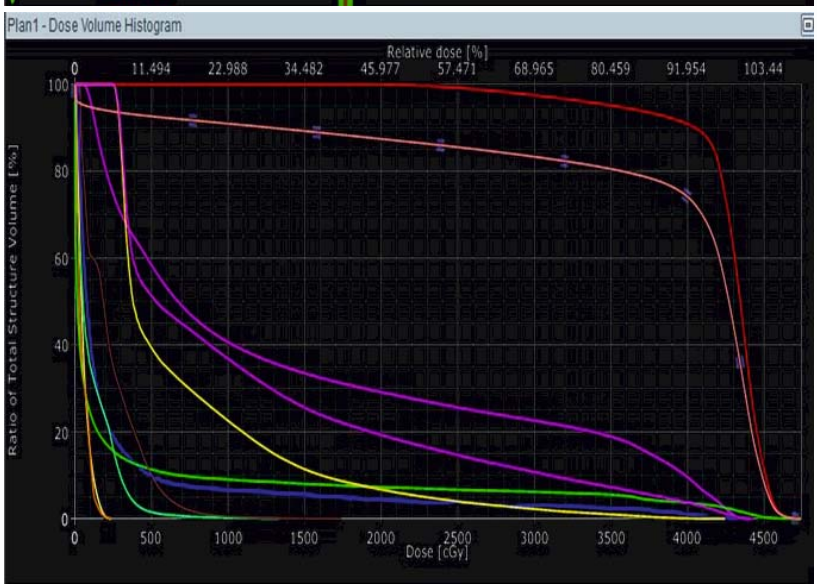
The patient presented at “Prof. Dr. Alexandru Trestioreanu” Oncology Institute from



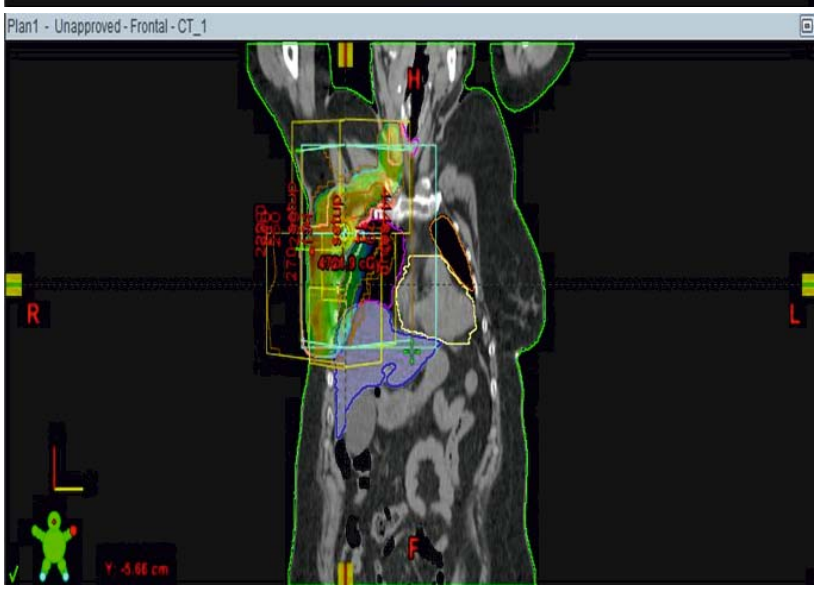




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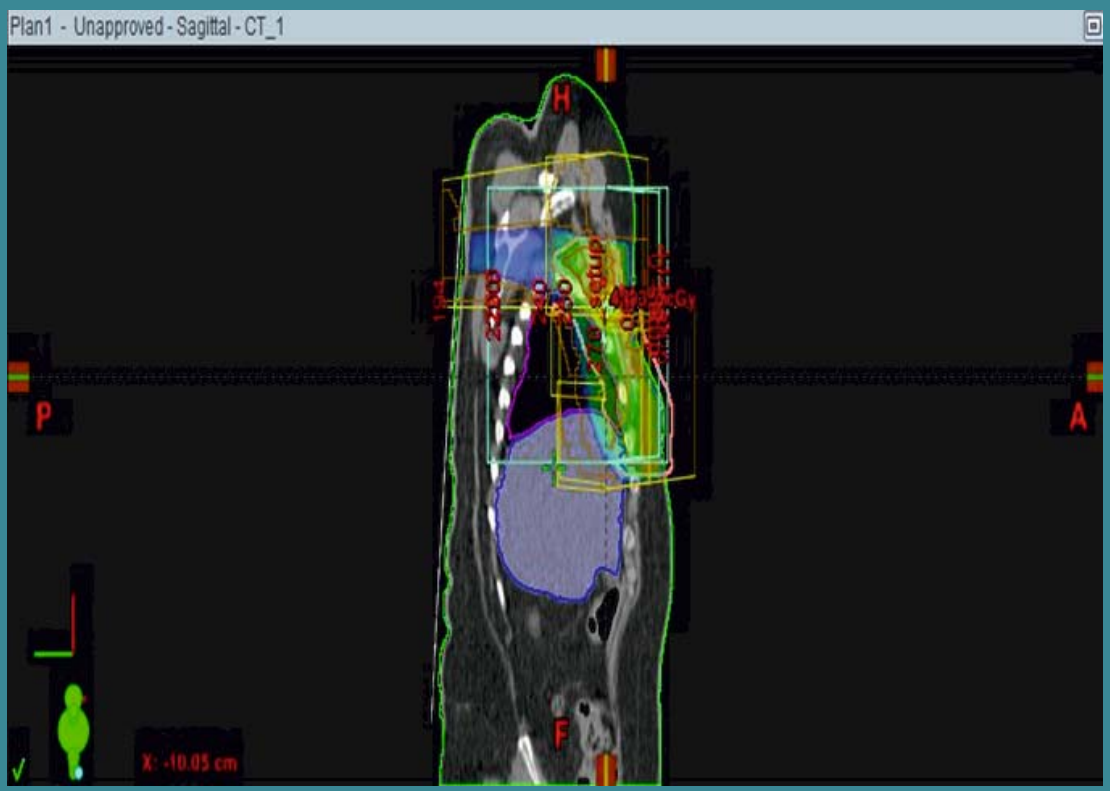


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Figure nr. 4.
EBRT using 3D-CRT with an isodose of 95% and dose-volume-histogram of the treatment plan

Internal Medicine

Clinical Cases



Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		CORD	Approved	Plan1	C1	585.8	100.0	100.0	4.6	239.6	5
☑		ESOFAG	Approved	Plan1	C1	26.4	100.0	100.0	29.9	1739.2	22
☑		PTV_4350	Approved	Plan1	C1	1405.9	100.0	100.0	0.0	4743.0	371
☑		Tiroida_PTV	Approved	Plan1	C1	5.4	100.0	100.2	248.5	4247.7	72
☑		TIROIDA	Approved	Plan1	C1	6.8	100.0	100.1	248.5	4414.1	113

Contouring | External Beam Planning | Brachytherapy Planning | Plan Evaluation

Figure nr. 4. *EBRT using 3D-CRT with an isodose of 95% and dose-volume-histogram of the treatment plan*

Bucharest for starting adjuvant radiation with curative intent. In the upcoming weeks, the patient started EBRT using the three-dimensional conformal radiation therapy technique (3D-CRT) with photons up to a total dose of 43.5 Gy in 15 fractions using a daily 2,9 Gy/ fraction, 1 fraction per day, hypofractionated schedule. The target volume was represented by the right chest wall, right axillary lymph nodes and right supraclavicular lymph nodes. All treatment sessions were done in the supine position, using a lide wire to delimit the postoperative scar (Figure 4).

Follow-up

The treatment was well tolerated with a good clinical response. The follow-up we choose after two months of radiotherapy was the biomarkers CA 15-3, CEA, and CA 125 which were in normal parameters and a CT scan. The CT scan revealed no signs of local breast and uterine recurrence; without liver, brain, and bone metastasis; a pulmonary lymph node in LIS about 3.5 mm- with stationary aspect compared with the previous examinations. The patient's clinical condition and imaging showed a favorable evolution after 2 months of follow-up. She was referred to the medical oncology to continue the follow-up with physical exam four times per year in the first five years and we recommend genetic tests for other cancer due to concomitant cancer.

Discussions

The family history of malignancy, genetic and environmental factors, also the methods of diagnosis, and follow-up information can contribute to the process of developing MPMTs. There are multiple specific mechanisms, but an important role is played by the genes in the occurrence and pathogenesis of MPMTs, including BRCA1/ BRCA2 associated with an increased risk of breast, ovarian, stomach, colorectal, pancreas, and uterus cancer[9].

Many factors increase the risk of developing endometrial and breast cancer, like older age, obesity, family history, early menarche late menopause, and long-term use of estrogen. Radiation exposure, and infertility particularly in the presence of Polycystic Ovarian Syndrome it is correlated with endometrial cancer, on the other hand, alcohol consumption, low parity, and late age at first pregnancy increase the risk of developing breast cancer[10,11]. We noticed in our case some of these risk factors, such as older age, postmenopausal status, and a high body mass index (BMI=32).

Diagnosis of synchronous primary cancers in one patient is a relatively rare event[8] In our case, imaging exams (MRI and CT scans) and pathological evaluations (histopathological and immunohistochemistry) helped us to distinguish the two cancers, to establish a correct diagnosis and to exclude metastasis.

The MRI evaluates the depth of myometrial invasion, cervical extension, and lymph node metastases. The CT scan can be used in the staging evaluation, of endometrial cancer, having high specificity and a positive predictive value for detecting distant metastasis. To improve the prognosis is recommended to perform a multidetector computed tomography is an accurate imaging modality for evaluation of synchronous breast carcinoma and another solid carcinoma[12,13,14].

Using MRI investigation we could see the presence of an endometrial mass and the CT scan helped us to have a complete clinical evaluation, and we noticed the presence of a tumor mass in the right breast without any metastasis. With the help of histopathological and immunohistochemistry exams, we were able to do an individualized therapy because both, breast and endometrial cancer have



more than one molecular subtype with different behavior, response to therapy, and prognosis. Anticancer therapy that can address both active malignancies is problematic because we should choose a treatment that doesn't increase toxicity, create undesirable pharmacological interactions, and decreases the overall outcomes of one or other form of cancer[7]. The presence of synchronous malignant cancers is problematic if each of the cancers is active. The challenge is to find an anticancer therapy that addresses the active malignancies in each patient but does not increase toxicity, create undesirable pharmacological interactions, nor hurt the overall outcomes[7].

In the case of endometrial cancer, some factors raise the risk for distant recurrences, high-grade tumors, deep myometrial penetration, clear cell or papillary serous histologic types and the addition of chemotherapy to radiotherapy seems to be an effective and safe way to treat this subset of endometrial cancer patients[15,16]. Radiotherapy associated with brachytherapy increase the local control, and the prognosis, and can lead to a complete response[17,18,19]. A major challenge is what we should choose to do first, radiotherapy or systemic therapy because both of them have a deadline to keep it efficient, and starting one or the other makes the start of other treatment to be delayed.

In the article of Gordon F. et al., it is recommended for stage III carcinomas of the breast to deliver chemotherapy before the surgery[21]. For the radiotherapy treatment, we choose to follow the Beijing trial who determined that a 3-week schedule of hypofractionated radiotherapy is the same as efficient and safeness as a 5-week schedule of conventionally fractionated radiotherapy[20]. The patient needs to be followed forwards, due to her risk to develop other cancers or metastasis.

Conclusion

The case of endometrial and breast simultaneous cancer is a rare event, which raises issues of diagnosis, treatment, and follow-up, so we must discuss such a case in a multidisciplinary team and have an individualized treatment for the patient. Many factors can contribute to the risk of developing an MPCs, older age, postmenopausal status, family history of malignancy, and gene alteration. We can make a differential diagnosis and confirm simultaneous cancer using imaging and pathological exams.

Treatment of two cancer is a real challenge. The surgery for endometrial and breast cancer improves the local control, and survival and increases the chance of curability. But the situation is not as easy when we speak about adjuvant and neoadjuvant treatment. We decided for our patient to start chemotherapy after surgery for the endometrial mass and seam to function as a neoadjuvant treatment

for breast cancer. Regarding radiotherapy treatment for breast cancer, the hypofractionated schedule has improved the local control, with no signs of local breast and uterine recurrence and without metastasis at the two months CT scan after EBRT.

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