

# Intensity Modulated Radiotherapy of Two Simultaneous Neoplasms - Cervical Carcinoma and Breast Carcinoma: A Case Report with a Review of the Literature

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**Abstract:** Concomitant expression of two neoplasms- cervical carcinoma (CC) and breast carcinoma (BC) is a relatively rare pathology. The manifestation of synchronous primary neoplasms is a challenge for the treating team as it puts a number of questions about the healing strategy.

We present a 57-year-old patient after total laparohysterectomy with lymphatic pelvic dissection on the local advanced CC/IIIB clinical stage. Intensity-modulated radiotherapy (IMRT) in the small pelvis and the upper 2/3 of the vaginal cuff with daily dose (DD) 1.8 Gy up to total dose (TD) 50.4 Gy combined with Cisplatin (50 mg/m<sup>2</sup>) once a week, was conducted. After 4 months from the diagnosis and complex treatment of CC, PET/CT establishes a second neoplasm-invasive ductal carcinoma in the left mammary gland. After the breast-conserving surgery of BC, we are currently conducting Deep Inspiration Breath-Hold (DIBH) Radiation Technique on the left breast with DD 2 Gy up to TD 50 Gy. After 1 month of pelvic RT completion, RT on the paraaortic lymph nodes with DD 1.8 Gy up to TD 50 Gy should be conducted.

The discussion focuses on the simultaneous expression of two or more neoplasms, their relationship with genetic and other unfavorable predisposing factors, as well as the expected survival after the complex treatment of the two invasive carcinomas, involving IMRT.

For the treatment of multiple malignancies, each case must be considered individually, ideally by a multidisciplinary team. If it is necessary to apply radiotherapy, the use of high-tech radiotherapeutic apparatus with the ability to perform modern radiotherapy techniques such as IMRT is required.

**Keywords:** Synchronous primary neoplasms, unfavorable predisposing factors, prognosis, complex treatment, intensity-modulated radiotherapy.

## INTRODUCTION

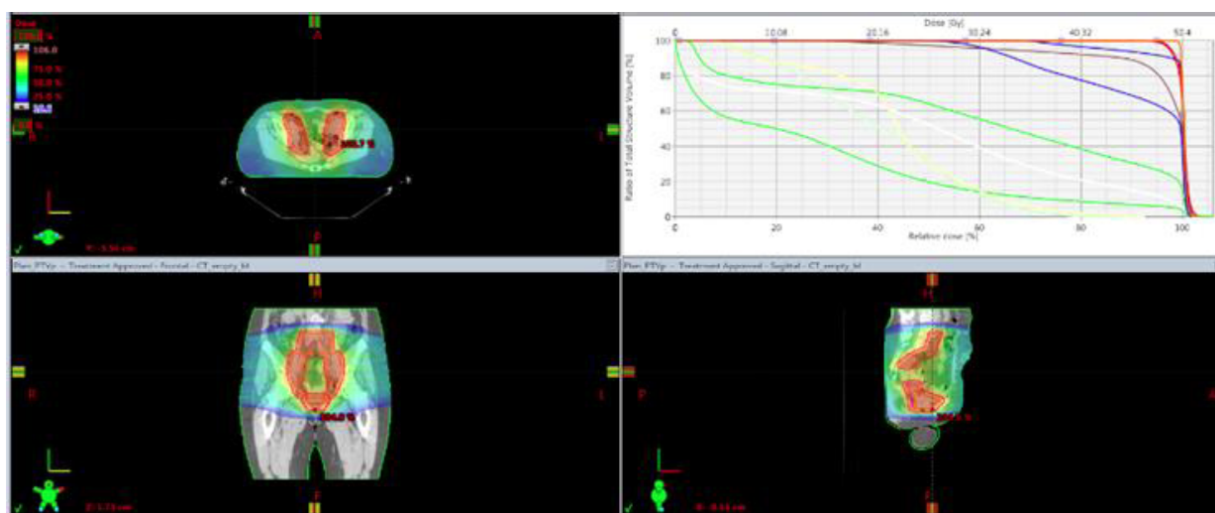
Cervical carcinoma (CC) is the fifth most common cancer in women and the third leading cause of cancer mortality in women globally [1]. It is the leading cause of lethal outcome in women in developing countries and the third most common gynaecological carcinoma in the United States [2]. In Bulgaria the morbidity of 2017. reaches 13.1/100,000 and the mortality is 5.1/100,000 [3]. Multiple primary malignancies (MPMs) are present when a patient is diagnosed with more than one primary malignancy and when each tumor is histologically unrelated to the others [4]. Concomitant expression of two neoplasms- cervical carcinoma and carcinoma of the mammary gland is a relatively rare pathology. The appearance of synchronous primary neoplasms is a challenge for the treating team as it puts a number of questions about the patient's healing strategy.

## CLINICAL CASE

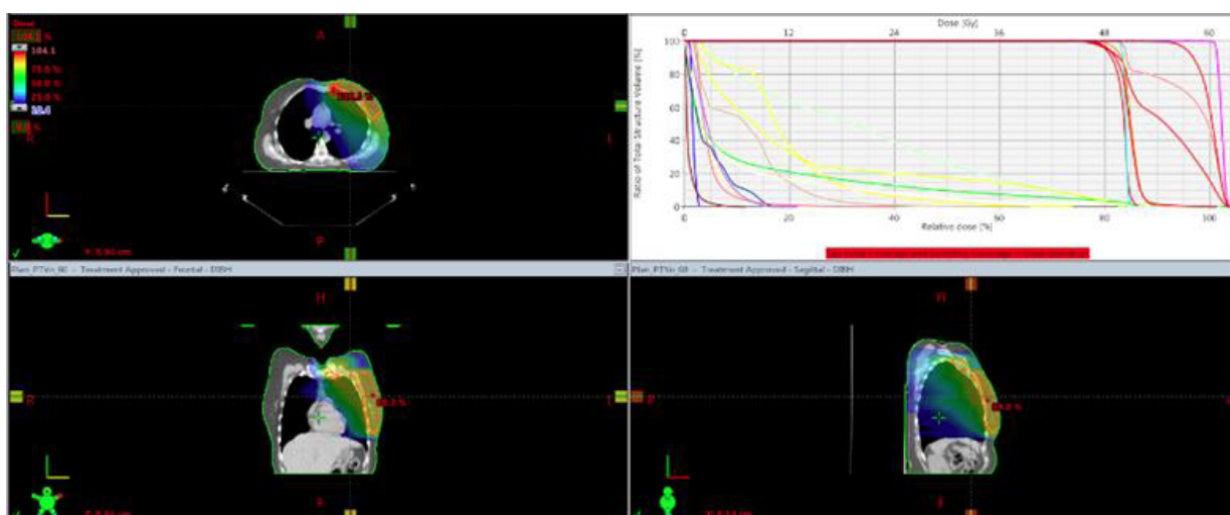
This clinical case presents a 57 years old patient, after radical laparohysterectomy with pelvic lymph node dissection for cervical carcinoma (IIIB clinical stage in FIGO), with histological results moderately differentiated (G2) squamous carcinoma, extensive necrosis areas, multiple tumors embolis in lymph and blood vessels, perineural invasion; isthmus and uterine body with massive infiltration from the abovementioned carcinoma; without serosal infiltration; 12 non-metastatic left pelvic lymph nodes, right pelvic lymph nodes-3 metastatic lymph nodes of 12 dissected lymph nodes. On 26.07.2021. the patient started postoperative intensity-modulated radiotherapy (IMRT) with VMAT technique in the pelvis and the upper 2/3 of the vaginal cuff with daily dose (DD) 1.8 Gy up to total dose (TD) 50.4 Gy combined with Cisplatin (50 mg / m<sup>2</sup>) once a week (Figure 1) The patient experienced very well postoperative simultaneous radio-chemotherapy (RT-Ch).

After 4 months from the diagnosis and complex treatment of CC, PET/CT establishes a second neoplasm in the left mammary gland. Quadrantectomy with axillary lymph nodes dissection of I and II levels

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**Figure 1:** Postoperative intensity-modulated radiotherapy (IMRT) with VMAT technique in the pelvis and the upper 2/3 of the vaginal cuff with daily dose (DD) 1.8 Gy up to total dose (TD) 50.4 Gy combined with Cisplatin (50 mg / m<sup>2</sup>) once a week.



**Figure 2:** Deep Inspiration Breath-hold (DIBH) radiation technique by using volumetric modulated arc therapy (VMAT) with DD 2 Gy up to TD 50 Gy.

was carried out which revealed the following histological and immunohistochemical results-moderately differentiated invasive ductal carcinoma (G2); tumor with a maximum diameter of 16 mm, 10 axillary lymph nodes without metastasis; estrogen receptor (ER) 2+; Progesterone receptor (PR) negativ; HER2 (1+) negativ. After breast-conserving surgery of BC, the left mammary gland was irradiated with deep inspiration breath-hold (DIBH) radiation technique by using volumetric modulated arc therapy (VMAT) with DD 2 Gy up to TD 50 Gy (Figure 2). After 1 month of pelvic RT completion, RT on the paraaortal lymph nodes with DD 1.8 Gy up to TD 50 Gy should be conducted.

The pelvic and left breast radiotherapy was conducted with a weekly assessment of traceability of

paraclinical indicators and strict monitoring of early radiation toxicity expression. The patient showed very good therapeutic tolerance without early radiation reactions from normal tissues and organs.

## DISCUSSION

In the 1930s Warren and Gates [5] proposed the first working definition of multiple primary neoplasms (MPNs): (1) both tumors should be confirmed histologically as malignant; (2) each cancer must be anatomically separate and distinct; and (3) the second tumor must not be a recurrence or metastasis of first cancer. This means that tumours arise in other organs than the independent primaries, each tumour has to be histologically distinctive and the possibility of metastasis or recurrence must be excluded [6,7]. The

mechanism of development of MPNs is unclear and likely multifactorial; identified risk factors include previous cancer treatment, smoking, diet, and genetic mutations [8]. The synchronous expression of breast and cervical carcinoma is a rare event, due to various unfavorable predisposing factors [9]. With the active application of the PET/CT scanners in order to strictly define the stage of the malignant tumors, the possibilities for detecting synchronous neoplasms have risen sharply [10]. The appearance of synchronous primary neoplasms is a challenge for the treating team as it puts a number of questions about the patient's healing strategy. This is a therapeutic dilemma in everyday clinical practice [11]. Causal mechanisms of their development include the following: (i) host factors – genetic (BRCA mutations, Li-Fraumeni syndrome), hormonal, prior cancer diagnosis and treatment exposures, (ii) lifestyle factors such as alcohol and tobacco use (risk factors for several cancer types), and (iii) environmental influences – geography (areas of increased radon exposure), pathogens (human papilloma virus or Epstein-Barr virus infections) and occupational factors [12-17]. Patients with multiple primaries have less aggressive malignancies, present at earlier stages, frequently have a strong family history of similar cancer, and their cancers tend to have indolent clinical behavior with longer survival rates, possibly related to genetic predisposition [14]. Synchronous genital tract neoplasms are rare but cause more clinical problems than a single neoplasm [18,19]. In the publication of Kenji Goto *et al.*/2005, there are two synchronous cervical carcinomas with a different histological results (exocervical squamous cell carcinoma and endocervical clear cell adenocarcinoma), in which Human Papilloma Virus (HPV) 18 only in the squamous cell carcinoma was found [20]. 4-17% of patients with breast cancer (BC) develop multiple primary neoplasias. The most frequent type of synchronous malignancy in patients with BC is contralateral breast cancer (63.3% of cases) followed by female genital organ cancer (13.4% of cases) [6]. In the publication of L. Marinova *et al.* / 2015, an interesting and extremely rare clinical case of two synchronous tumors in the breast, namely invasive ductal carcinoma and primary breast osteosarcoma has been presented [21]. Most often diagnosed synchronous neoplasms are contralateral breast cancer and genital cancers, of which most common is cervical cancer [22]. Genetic factors (e.g., BRCA1, BRCA2) are seen as habitual risk factors for multiple primary tumors [23]. Published data indicate that age, as well as menopausal status at breast cancer diagnosis, are risk factors for the development of

second cancer [24-26]. Studies in Japan and Italy estimated that 9%-11% of early gastrointestinal carcinomas develop other malignancies [27,28]. Five-year survival rates were higher for metachronous cancers (95%) than for synchronous primaries (59%) and single primaries (59%) [14]. For the treatment of multiple malignancies, each case must be considered individually, ideally by a multidisciplinary team, accounting for the type and stage of each tumor, response to treatment, and the patient's overall health status [8]. In the present case, the familial history of the patient implies a high risk of malignant neoplasms as her mother had uterine cancer. Breast cancer is a socially significant, most commonly diagnosed neoplasm in women. In the current clinical case, as it is a I clinical-stage BC after a conservative breast surgery, no chemotherapy is required. For stage IIA BC, the decision was to treat her with chemotherapy followed by postmastectomy radiation therapy due to multiple risk factors, including focal lymphovascular space invasion and 2 positive lymph nodes [29]. Breast-preserving surgery with subsequent high-tech radiotherapy has a great contribution to achieving very good therapeutic and cosmetic results [30]. Adjuvant left breast radiotherapy (ALBRT) for breast cancer can result in a significant radiation dose to the heart [31]. As the number of BCs survivors has increased, chronic sequelae of breast cancer RT has become more important [32]. Heart-sparing can be performed in three different ways in breast cancer radiotherapy: by seeking to keep the heart out of treated volumes (i.e. by prone position or specific breathing techniques such as deep inspiration breath-hold (DIBH) and/or gating), or by using modern radiation techniques like IMRT, volumetric modulated arc therapy (VMAT) or protons [33]. Deep Inspiration Breath-hold (DIBH) is a well-established radiation technique to achieve a significant cardiac dose reduction during adjuvant radiotherapy (RT) in left-sided breast cancer (Figure 2). A new linac system with an integrated surface scanner (SS) for DIBH treatments could easily be incorporated into the daily routine and is associated with significant dose reduction to the heart and ipsilateral lung [34].

## CONCLUSIONS

Concomitant expression of two neoplasms- cervical carcinoma (CC) and breast carcinoma (BC) is a relatively rare pathology. The manifestation of synchronous primary neoplasms is a challenge for the treating team as it puts a number of questions about the healing strategy. The forecast is dependent on the histological results of the corresponding primary

tumors, accounting for the type and stage of each tumor and the adequate complex treatment. For the treatment of multiple malignancies, each case must be considered individually, ideally by a multidisciplinary team. If it is necessary to apply radiotherapy, the use of high-tech radiotherapeutic apparatus with the ability to perform modern radiotherapy techniques such as IMRT is required.

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