

Conservative therapy in cervical and nasopharyngeal synchronous tumours: case report

Terapêutica conservadora em tumores síncronos do colo do útero e nasofaringe: caso clínico

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Abstract

Introduction: A 68-year-old patient was diagnosed with stage II invasive cervical squamous cell carcinoma (SCC). **Case report:** During staging examinations, a stage II non-keratinizing invasive nasopharyngeal SCC was identified. The patient underwent pelvic external beam radiotherapy (EBRT), followed by an external boost to the uterus, parametria, and cervical tumor and margin. Concurrently, EBRT was performed with the simultaneous integrated boost to the nasopharyngeal tumor and nodal regions. During radiotherapy, the patient received weekly chemotherapy with cisplatin, which was suspended due to hematological toxicity. Following this treatment, intrauterine and vaginal brachytherapy was performed. After 2 years of follow-up, there were not any visible lesions on both sites. Imaging studies revealed only one left cervical lymphadenopathy, with a favorable response to treatment. **Conclusion:** This clinical case illustrates the feasibility and efficacy of simultaneous treatment of primary cervical and nasopharyngeal stage II tumors, utilizing concurrent chemoradiotherapy, as recommended for both tumors at locally advanced stages.

Keywords: Synchronous tumors. Radiotherapy. Squamous cell. Case report.

Resumo

Introdução: Uma doente de 68 anos foi diagnosticada com um carcinoma espinhocelular invasivo do colo do útero (estádio II). **Relato de caso:** Durante o estadiamento, identificou-se um carcinoma espinhocelular invasivo não queratinizante da nasofaringe (estádio II). A doente realizou radioterapia externa pélvica, seguida de boost dirigido ao útero, paramétrios e tumor com margem. Concomitantemente, efetuou radioterapia externa com boost integrado simultâneo dirigido ao tumor nasofaríngeo e regiões ganglionares. Durante a radioterapia, a doente cumpriu quimioterapia semanal com cisplatina, suspensa por toxicidade hematológica. Posteriormente, realizou braquiterapia intrauterina e vaginal. Aos 2 anos de seguimento, nenhum dos locais apresentava lesões observáveis. **Conclusão:** Este caso clínico ilustra a viabilidade e a eficácia do tratamento simultâneo de tumores primários do colo uterino e da nasofaringe em estágio II, utilizando quimiorradioterapia concomitante, conforme recomendado para ambos os tumores em estádios localmente avançados.

Palavras chave: Tumores síncronos. Radioterapia. Espinhocelular. Caso clínico.

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Introduction

The diagnosis of two or more primary tumors within a time frame of up to 6 months designates them as synchronous tumors, and their incidence has been increasing globally¹. However, the identification of synchronous squamous cell carcinomas (SCC) of the cervix and nasopharynx remains rare^{2,3}.

Cervical cancer is one of the most commonly diagnosed cancers in women and still represents a major public health concern. It can be associated with the human papillomavirus (HPV), particularly the oncogenic subtypes HPV-16 and 18⁴. HPV vaccination could potentially eradicate the infection, therefore largely decreasing the incidence of these tumors. In Portugal, the estimated 5-year survival was 91% in 2020, probably due to populational screening and HPV vaccine⁵. The most common symptoms include abnormal vaginal bleeding, mainly after coitus, vaginal discharge, pelvic pain, and dyspareunia. The diagnosis is confirmed by biopsy with SCC being the most frequent histological type, followed by adenocarcinoma. The clinical staging is based on the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and the Union for International Cancer Control tumor, Node, and Metastasis Staging Classifications (8th edition)⁴.

Nasopharyngeal cancer has a higher incidence in Asian countries but is declining worldwide. In low-incidence areas, it has a bimodal age distribution, with a higher incidence in adolescents and young adults and a second peak after 65 years of age. In higher incidence countries the peak is between 40 and 59 years of age. Survival rates are higher in women, Asian people, and younger patients. The diagnosis is made by endoscopic-guided biopsy of the primary tumor, which can be divided into keratinizing, non-keratinizing (differentiated or undifferentiated), and more rarely basaloid carcinoma. The presence of Epstein-Barr virus (EBV) is associated with nasopharyngeal carcinoma, especially the non-keratinizing type. In endemic areas, positivity for p16 and HPV has been reported in up to 8% of non-keratinizing undifferentiated carcinoma, with a better prognosis than the EBV-related cases. In other geographic areas, this association is less pronounced, with HPV being more related to keratinizing carcinoma. Despite current data, the role of HPV in carcinogenesis and cancer progression remains unclear. The clinical staging relies on the American Joint Committee on Cancer Staging Classification 8th edition. The most accurate examinations are magnetic resonance imaging (MRI) and positron emission tomography with the



Figure 1. Cervical stage IIB cancer diagnosis in magnetic resonance imaging (top), and positron emission tomography computed tomography with the fludeoxyglucose F18 (below).

Fludeoxyglucose F18 radiotracer (PET-CT 18F-FDG) for local and distant involvement, respectively⁶.

The clinical case described below illustrates the feasibility and efficacy of simultaneous treatment for primary tumors of the cervix and nasopharynx at stage II. As stated before, for both, treatment at locally advanced stages is based on a combination of radiotherapy and concurrent chemotherapy with cisplatin as the first-line treatment^{2,3,7}.

Clinical case

Patient, female, 68 years old, previously healthy, presented with a 2-month history of vaginal bleeding, initially only during intercourse. On the physical examination, it was identified as a vegetating, friable, and very hemorrhagic lesion on the cervix. A tamponade needed to be performed. On the laboratory results, both CA125 and SCC tumoral markers were elevated.

A biopsy of the lesion was done, which revealed an HPV-positive, moderately differentiated SCC. The staging was completed with a pelvic MRI and a PET-CT 18F-FDG (Fig. 1). The tumor had 35 mm of maximum diameter, invaded the upper third of the vagina, and

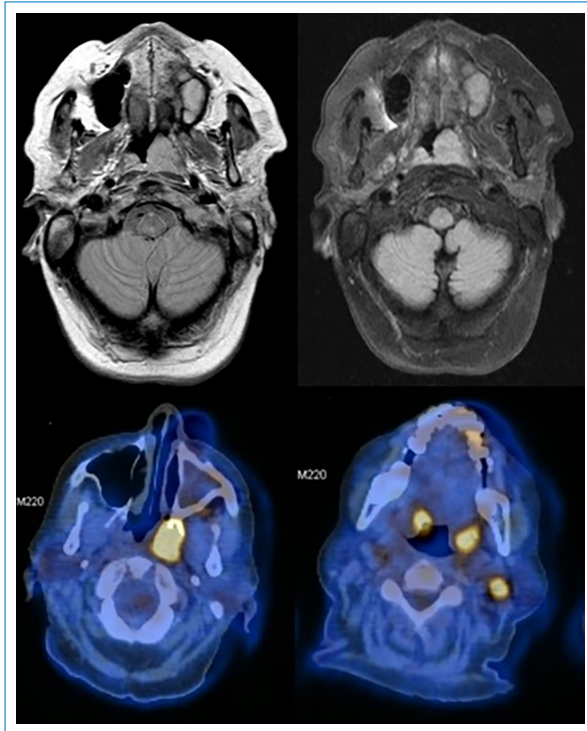


Figure 2. Nasopharyngeal stage II cancer diagnosis in magnetic resonance imaging (top), and positron emission tomography computed tomography with the fludeoxyglucose F18 (below).

extended to the anterior and inferior parametrium and paracolpos. The lesion was therefore classified as a cT2bN0M0, Stage IIB (FIGO 2018).

As a useful staging tool for these types of tumors, a PET-CT 18F-FDG was performed and identified a suspicious lesion in the nasopharynx along with left cervical lymphadenopathy (level IIa) (Fig. 2). It had a maximum diameter of 19 mm and a maximum standardized uptake value (SUVmax) of 20.0. The adenopathy was 10mm and had an SUVmax of 7.1. An evaluation from otorhinolaryngology was asked and at observation, it was identified a left nasopharyngeal mass. A biopsy was performed and was compatible with an EBV-positive non-keratinizing SCC. Finally, a cranioencephalic and nasopharyngeal MRI was performed to assess locoregional staging (Fig. 2). It showed a lesion centered on the mucosal planes, without any apparent invasion of the deep muscular planes. This second tumor was therefore clinically staged as a cT1N1M0 (Stage II). The case was discussed in a multidisciplinary meeting involving gynecology, head and neck surgery, oncology, and radiation oncology attending specialists.

The patient underwent pelvic external beam radiotherapy (EBRT) with a total dose of 50.4 Gy delivered in 28 fractions (1.8 Gy / fraction), followed by a boost to

the uterus, parametria, and cervical tumor and margin with an additional 9 Gy in 5 fractions (1.8 Gy/fraction).

Concurrently, EBRT was performed with a simultaneous integrated boost in 33 fractions: 69.96 Gy (2.12 Gy / fraction) to the nasopharyngeal tumor and margin, 66 Gy (2 Gy / fraction) to the left cervical lymphadenopathy (level IIa), and 59.4 Gy (1.8 Gy / fraction) to the nasopharynx, cranial base, parapharyngeal spaces, inferior part of the sphenoidal sinus, posterior part of the nasal fossae and of the maxillary sinuses, and bilateral cervical lymph nodes (levels Ib-V and VIIa). Both treatments were planned using volumetric-modulated arc therapy (VMAT).

The patient received concurrent chemotherapy with a dose of weekly cisplatin 40 mg/m², which was suspended after 4 cycles due to hematological toxicity with G2 anemia, G3 leukopenia, thrombocytopenia, and G1 neutropenia, according to CTCAE v5.0⁸.

On the 6th and 14th days following the completion of EBRT, intrauterine and vaginal brachytherapy (BT) was performed, delivering 14 Gy in 2 fractions (7 Gy / fraction).

Due to G2 weight loss, oral mucositis, and G3 anorexia, the patient underwent nasogastric intubation. Furthermore, the patient presented with radiation G2 dermatitis and xerostomia, and G1 diarrhea.

Approximately 3 weeks after treatment, mucositis had been resolved, and the nasogastric tube was removed. The patient experienced hypoacusia from 6 weeks to 8 months after treatment. Body weight started to gradually improve 1 year after treatment, with 48 kg by this time. The main symptoms remaining are xerostomia and anorexia, G2. Moreover, the patient presented a fungal infection in the left maxillary sinus, which was surgically treated 10 months after our treatment, with complete recovery.

After 2 years of follow-up, the patient exhibited a favorable clinical response. On physical examination, no lesions were observed in the cervix or nasopharynx. The follow-up imaging studies have been conducted with PET-CT 18F-FDG (Fig. 3) and MRI (Fig. 4), starting 2 months after the treatment. These exams showed only one left cervical lymphadenopathy, without other expansive formations, but presenting favorable morphological and metabolic responses. Consequently, the multidisciplinary team has decided not to perform a biopsy of this remaining adenopathy.

Discussion

In the absence of international guidelines, the therapeutic decision was based on the combination of the



Figure 3. Post-treatment positron emission tomography-computed tomography with the fludeoxyglucose F18 (pelvis).

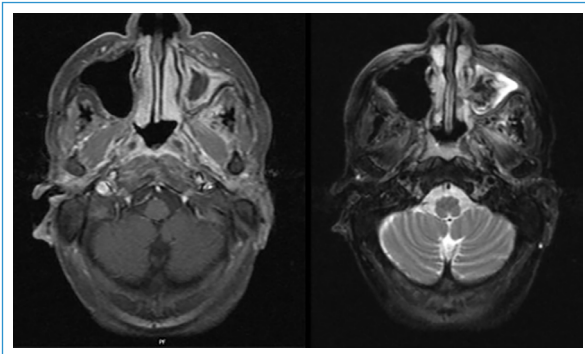


Figure 4. Post-treatment magnetic resonance imaging (nasopharynx).

protocols for each tumor, considering their characteristics and clinical experience. However, the simultaneous treatment of both tumors can be challenging to manage due to the risk of cumulative toxicity.

For both tumor locations, the use of advanced radiotherapy technologies such as VMAT and image-guided radiation therapy is essential to ensure target coverage and minimize toxicities^{2,3}. Regarding the pelvic area, VMAT is useful in minimizing the dose to the bowel, bladder, rectum, femoral heads, kidneys, and spinal cord and to reduce hematologic toxicity³. On the nasopharynx, the use of VMAT has shown to be superior to conventional EBRT techniques in 5-year overall survival and 5-year local control. Moreover, less late toxicity has been reported with VMAT, such as xerostomia, trismus, and temporal lobe injury, favoring a better quality of life in long-term survivors².

In local advanced cervical cancer, definitive treatment with concurrent chemoradiotherapy has been shown to improve both disease-free survival and overall survival compared to other treatment modalities.

Definitive EBRT with a dose of 40-50 Gy is applied to the primary tumor, parametria, uterosacral ligaments, 3 cm of vaginal margin, and regional lymphatics at risk. In this case, with clinically negative nodes, the targets should cover the entirety of the external iliac, internal iliac, obturator, and presacral nodal basins. An additional boost can be administered to the primary tumor and/or involved nodes, as it was done in this case. BT is preferentially performed during the latter part of treatment to enable enough tumor regression. It is usually performed using an intracavitary approach, with an intrauterine tandem and vaginal colpostats³. In this case, BT was performed by introducing an intrauterine catheter into the uterine cavity, and two vaginal catheters at the level of the fornix and using a microSelectron high dose-rate Iridium-192 source.

EBRT is an essential part of the curative treatment of nasopharyngeal carcinoma. EBRT is commonly directed at the primary tumor, involved nodes, and nodal regions at risk of microscopic spread bilaterally. A total dose of 70 Gy is recommended for the eradication of macroscopic disease and a dose of 50-60 Gy for the regions at risk, delivered with conventional or hypofractionated dose schemes with a total of 33-35 fractions. VMAT can be applied with a simultaneous integrated boost, or with a sequential boost with similar clinical outcomes and toxicities².

In cervical cancer, concurrent chemotherapy is administered using a dose of weekly cisplatin 40 mg/m^{2,3}. In nasopharyngeal stage II disease, it is recommended to associate concurrent chemotherapy with high-dose cisplatin of 100 mg/m² every 3 weeks (1st, 22nd, and 43rd days of treatment) with a cumulative dose above 200 mg/m². However, if there are particular concerns regarding toxicity, a weekly dose of cisplatin 40 mg/m² has also an impact on overall survival; however, with inferior results compared to the first dose scheme^{2,7,9}. In this case, there was an indication for using cisplatin as the first line of treatment, but, at the same time, there were special concerns regarding toxicity on both sites. Therefore, we adopted the weekly cisplatin scheme.

During follow-up, clinical examinations should be performed periodically to assess late toxicities. In our case, the use of special planning techniques, such as VMAT, enabled the appliance of highly conformal dose distributions to the target volume. Therefore, we were able to ensure the sparing of normal tissues and the management of adverse effects. Regarding evaluation of tumoral response, nasopharyngeal and skull MRI should be performed every 6 months for the first 3 years after treatment.

Regarding the limitations of this clinical case, it should be mentioned that EBV was only identified in the histological study of the cervical tumor. Therefore its values were not controlled on peripheral blood tests.

Conclusion

The described case illustrates the efficacy of chemoradiotherapy in the approach to two synchronous primary tumors. However, given the scarcity of literature in this clinical context, the need for discussion in a therapeutic decision-making meeting is emphasized, to allow the development of a personalized treatment plan.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's

confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence.

The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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