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Synchronous Anal Canal Cancer and Cervical Cancer: Report of a Case and Management Implication

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Abstract. *Background: This is the case report of a synchronous anal canal cancer and cervical cancer in a patient who underwent definitive chemoradiotherapy (CRT) and radical surgery for anal canal and cervical carcinoma, respectively. Case Report: A 55-year-old woman was diagnosed with cT4a cN1 Mx anal canal squamous cell carcinoma and stage IA2 cervical squamous cell carcinoma, based on biopsy and imaging. Definitive CRT consisted of radiotherapy (total dose of 59.4 Gy) and concomitant mitomycin (10 mg/m^2) and 5-fluorouracil (750 mg/m^2/5 daily continuous infusion) during the first and last week of radiation. The patient exhibited a complete clinical and radiological response. A radical hysterectomy with pelvic lymphadenectomy was then performed. At the last follow-up (30 months), the patient is still disease-free without any treatment-associated complications. Conclusion: There is limited information in the literature regarding treatment strategy and outcome of patients with synchronous anal canal and cervical cancer. A two-step treatment, including CRT and radical hysterectomy, is likely to be accepted as valid option.*

Synchronous cancer is a secondary independent cancer occurring simultaneously or within six months of the first primary cancer diagnosis (1). Although virtually all anal canal and cervical cancers are HPV-induced, suggesting host susceptibility to HPV-induced oncogenesis, there is no evidence of increased risk of synchronous diagnosis of anal canal and cervical primaries – while it is evident that uterine cervix cancer patients have an increased risk of synchronous urinary tract carcinomas, with a standardized incidence ratio of 1.41 (1).

In this context, we describe a case of a patient with synchronous carcinomas of both the anal canal and uterine cervix. We consider the reported case noteworthy. The hope is to help clinicians to identify high-risk patients more readily and design more effective cross-screening programs, as well as treatment strategies, and guide researchers to elucidate the underlying molecular mechanisms of pathogenesis.

Case Report

A 55-year-old Caucasian postmenopausal woman presented to our department with palpable inguinal lymphadenopathy and changes in stool caliber. She had a histologically confirmed diagnosis of HPV16-positive moderately differentiated squamous cell carcinoma of the anal canal. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (App 6452). Written informed consent was obtained from the patient. The patient was referred to a multidisciplinary gastrointestinal tumor board before treatment. Clinical examinations, including complete medical history, careful digital ano-rectal examination and inguinal node palpation, as well as gynecological evaluation, were combined with imaging to assess the local (T), regional nodal (N), and distant (M) extent of the tumor. Radiological imaging consisted of chest-abdomen contrast-enhanced computed tomography (CT) and pelvic magnetic resonance with diffusion-weighted imaging (DW-MRI). The pelvic DW-MRI examination demonstrated a malignant 7 cm lesion in the anal canal involving the vagina with metastasis in the inguinal and mesorectal lymph nodes (cT4 cN1a) and an

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Table I. *Synchronous cancer of the anal canal and cervix.*

Author	Stage		Treatment		Follow-up	Outcome
	Anal canal cancer	Cervical cancer	Anal canal cancer	Cervical cancer		
Kawamoto (5)	cT3 cN3 M0^	IB1	CRT (59.4 Gy/33 fr)*		15 months	NED
Our case	cT4a cN1 M0^^	IA2	CRT (59.4 Gy/33 fr)**	Radical hysterectomy with SLN	30 months	NED

^7th edition. ^^8th edition. *With S-1, an oral fluoropyrimidine 60 mg/m^2/day twice daily on days 1-14 and 29-42. **With mitomycin 10 mg/m^2 (days 1 and 29) and 5-fluorouracil 750 mg/m^2/5 daily continuous infusion (days 1-5 and 29-33). CRT: Chemoradiotherapy; Gy: Gray; fr: fraction; NED: no evidence of disease; SLN: sentinel lymph node mapping.

isolated 5 mm cervical lesion suspicious for carcinoma. No distant metastases were reported (Mx). A gynecological exam was performed and a HPV16-related high grade squamous intraepithelial lesion with features suggestive of endocervical gland involvement was confirmed. The case was then discussed in a gynecological multidisciplinary team meeting. Management of the anal canal primary was considered to have higher priority than the cervical lesion. Patient was treated with definitive concurrent CRT (2). Radiation therapy was delivered with an intensity modulated technique (IMRT). The prescription dose was 45 Gy (1.8 Gy/fraction) to the whole pelvis plus 5.4 Gy (1.8 Gy/fraction) to the anal canal and pathological lymph nodes and additional 9 Gy (1.8 Gy/fraction) to the tumor volume. Concomitant chemotherapy consisted of mitomycin (10 mg/m^2, days 1 and 29) and continuous infusions of 5-fluorouracil (750 mg/m^2, days 1-5 and 29-33). The patient was seen weekly during CRT and then regularly until acute toxicity resolution. Treatment was well tolerated. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events, Version 5.0 (3). The patient experienced neutropenia G2, anemia G1, nausea G2, diarrhea G2, local pain G2, cystitis G1, and perianal radiodermatitis G2. Two months after completion of CRT, clinical examination demonstrated complete regression of the anal canal tumor. Due to synchronous cervical lesion diagnosis, formal assessment of tumor response was made 8 weeks after CRT completion with pelvic MRI and chest-abdomen CT. As a complete clinical and radiological remission of anal canal carcinoma was confirmed, according to the patient, to treat cervical lesion, a non-fertility sparing approach was chosen and a radical hysterectomy with pelvic lymphadenectomy was then performed (4). The final histopathological findings confirmed the presence of a HPV16-related invasive cervical squamous cell carcinoma (IA2) with no lymph vascular invasion and tumor-free surgical margins.

Currently, the patient is well and there are no signs of disease. Following both primary treatments, no tumors were detected by imaging studies and pathological examination. At 30 months from initial diagnosis, the patient continues to have no clinical or radiographic evidence of disease recurrence and remains on close follow-up, including ano-rectal digital examination and gynecological examination with imaging exams every 6 months.

Discussion

Our case is the second case of synchronous cancer of the anal canal and cervix reported in literature (Table I) (5). It is the first treated with CRT (for the anal canal lesion) and radical surgery (for the cervical lesion) and thus management itself can be questioned. The patient had synchronous HPV16-related squamous cell carcinomas. The anal canal cancer was clinically advanced at the time of diagnosis (the patient had significant lesion when she presented for initial evaluation) and screening for second cancers was not a priority for planning treatment for such invasive cancer. Diagnosis of an early-stage cervical lesion at the time of the anal canal cancer diagnosis raises the following questions: i) before recommending CRT for anal canal cancer, would you consider a second-look surgical planning to assess the cervix and its regional lymph nodes, including common iliac nodes?; ii) after definitive CRT for anal canal cancer, would you recommend an external beam or brachytherapy boost for the cervical lesion?; iii) what is the best follow-up strategy?

Treatment strategy for synchronous cancer of the anal canal and the cervix is unclear. For sure, appropriate evaluation of the clinical stage is crucial for determining the optimal therapeutic strategy and predicting the patients' prognosis. Both anal canal and cervical cancers are generally radiosensitive. Independently of stage disease, definitive CRT with a total dose of 50.4-59.4 Gy (1.8 Gy per fraction) is the standard of care for patients suffering from squamous anal canal cancer (6). Whereas exclusive radiation therapy using a dose up to 80 Gy without chemotherapy can be accepted as a curative option in early-stage squamous cell cervical cancer (7). In case of synchronous cancers, it is expected to use medical judgment in the context of

individual clinical circumstances to determine patient's treatment. The prognosis and curative potential of each cancer should be considered. The aim should be to achieve the highest efficacy, while maintaining a reduction in toxicity burden. In our case, top priority was given to anal canal cancer treatment: considering the non-metastatic scenario, we chose to maximize survival time. The standard curative CRT treatment was proposed, postponing the cervical treatment plan after CRT, once clinical response evaluation for the anal canal lesion was performed. Because of a complete clinical/radiological response, a definitive treatment for the synchronous cervical cancer was recommended. Radical hysterectomy was not mandatory: a fertility-sparing surgical approach was proposed and discussed. The patient was informed of the risk of pathological factors that warranted the use of adjuvant treatment and the impossibility to be submitted to it because the CRT received for anal canal cancer precluded an adequate dose coverage. With respect to the patient's discretion, the most adequate procedure for the synchronous cervical cancer was considered to be a radical hysterectomy with pelvic lymphadenectomy.

A critical comparison in term of treatment strategy is difficult because of the lack of literature data.

Kawamoto *et al*. (5) reported a case in which CRT was used to treat synchronous cancer of the anal canal and cervix. Radiation therapy was delivered with IMRT technique at a total dose of 36 Gy (1.8 Gy per fraction) to the whole pelvis, plus 23.4 Gy (1.8 Gy per fraction) to both primary lesions. No additional boost to cervical target volume was planned. One can argue if external radiotherapy to a total dose of 59.4 Gy in 33 fractions (without uterovaginal endocavitary brachytherapy) is an option that offers equivalent efficacy to surgery (8, 9). Kawamoto *et al*. (5) referred no evidence of disease at 15-month follow-up. However, it should be considered that the vast majority of patients who recur do so within two years of completion of treatment. Therefore, the 15-month follow-up is relative short to adequately evaluate clinical outcome. We believe that our two-step management is a successful treatment that assures a long-term outcome and gives the patient an opportunity to better control psychological distress resulting from the synchronous diagnosis.

Finally, the important question of follow-up modalities for patients submitted to definitive CRT and radical hysterectomy remains unanswered. It is tempting to consider a stricter follow-up, although the increased relative risk of recurrence remains hypothetical and needs confirmation. We agree to follow-up our patient with a clinical examination, routine cytology, and an anoscopy and colposcopy every 3 months for the first year and every 6 months thereafter. We decided to perform a pelvic DWI-MR with contrast every 6 months and chest-abdomen contrast-enhanced CT annually.

What lesson can be drawn from this case report? For sure that screening is strictly recommended. It is generally accepted that HPV infection plays an important role in both anal canal and cervix carcinogenesis and thus, these two types of cancer potentially share similar molecular mechanisms for pathogenesis. For instance, we recently observed two cases of locally advanced anal canal cancer and concomitant high grade squamous intraepithelial lesion. These two patients had a definitive CRT for anal canal cancer and a conization with negative margins for precancerous cervical lesion thereafter.

From a practical standpoint, primary prevention with vaccination against HPV could effectively reduce the incidence of these HPV-related cancers. HPV-related lesions of the anogenital tract – including cervix, vagina, anus, vulva, penis – are typically associated with high-risk HPV types 16 and 18 (10). To note, three prophylactic HPV vaccines are currently available: i) a bivalent vaccine designed to prevent HPV type 16 and 18 infections; ii) a quadrivalent vaccine targeting HPV subtypes 6, 11, 16, and 18; iii) a nonavalent vaccine targeting HPV subtypes 6, 11, 16, 18, 31, 33, 45, 52, and 58. Despite the fact that there is no direct evidence, we made the assumption that the vaccination coverage would be effective even in anal canal disease.

Our case stressed the importance of an accurate multidisciplinary team management. The hope is to streamline the decision-making process, in order to help clinicians to identify high-risk patients, and design more effective cross-screening programs and treatment strategies in patients with synchronous HPV-related cancer.

Conclusion

The optimal therapeutic approach has not yet been clearly defined. An international register is on the verge of being opened and radiation oncologists who have any experience in synchronous anal canal and cervical cancers are invited to participate.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

DM, FDF, CGC: Conceptualization; CGC, IP: Data curation; CGC, FDF: Writing - original draft; IP, FT, GG: Writing – review & editing; DM, FDF, CGC, IP, FT, GG, VT: final approval.

References

1 Hayat MJ, Howlader N, Reichman ME and Edwards BK: Cancer statistics, trends, and multiple primary cancer analyses from the

Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist *12(1)*: 20-37, 2007. PMID: 17227898. DOI: 10.1634/theoncologist.12-1-20

2 De Felice F, Martinetti MT, Orelli S, Bulzonetti N, Musio D and Tombolini V: Definitive chemoradiotherapy for anal carcinoma: Long-term results based on consistent time-to-event endpoints. Oncology *94(1)*: 25-30, 2018. PMID: 28918425. DOI: 10.1159/000479971

3 Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, version 5.0 2017. Available at: http://ctep.cancer.gov [Last accessed on May 29, 2022]

4 Marchetti C, De Felice F, Di Pinto A, Romito A, Musella A, Palaia I, Monti M, Tombolin V, Muzii L and Benedetti Panici P: Survival nomograms after curative neoadjuvant chemotherapy and radical surgery for Stage IB2-IIIB cervical cancer. Cancer Res Treat *50(3)*: 768-776, 2018. PMID: 28724282. DOI: 10.4143/crt.2017.141

5 Kawamoto T, Ito K, Shimizuguchi T, Kito S, Nihei K, Sasai K and Karasawa K: Intensity-modulated radiotherapy for synchronous cancer of the anal canal and cervix. Oncol Lett *16(4)*: 4512-4518, 2018. PMID: 30197673. DOI: 10.3892/ol.2018.9229

6 National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: anal carcinoma version 1.2022. Available at: https://www.nccn.org [Last accessed on June 8, 2020]

7 National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: cervical carcinoma version 1.2022. Available at: https://www.nccn.org [Last accessed on June 8, 2020]

8 Chargari C, Peignaux K, Escande A, Renard S, Lafond C, Petit A, Lam Cham Kee D, Durdux C and Haie-Méder C: Radiotherapy of cervical cancer. Cancer Radiother *26(1-2)*: 298-308, 2022. PMID: 34955418. DOI: 10.1016/j.canrad.2021.11.009

9 Uno A, Yamamoto S, Iihara H, Fujii H, Makita C, Hayasaki Y, Ueda Y, Ito M, Takenaka M, Kumano T, Mori M, Yasue M, Kato-Hayashi H, Kobayashi R, Morishige KI, Matsuo M, Hayashi H and Suzuki A: Control and risk factors of nausea and vomiting in patients with cervical cancer receiving radiotherapy. Anticancer Res *42(6)*: 3117-3123, 2022. PMID: 35641271. DOI: 10.21873/anticanres.15800

10 Yang EJ, Kong CS and Longacre TA: Vulvar and anal intraepithelial neoplasia: terminology, diagnosis, and ancillary studies. Adv Anat Pathol *24(3)*: 136-150, 2017. PMID: 28398952. DOI: 10.1097/PAP.0000000000000149

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