

Synchronous primary carcinoma of uterine cervix and endometrium - single-center retrospective study

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Summary

Background and objectives: Synchronous malignant tumors of the uterine body and the cervix are extremely rare. The stage of both malignancies at diagnosis has prognostic significance and there are only occasional reports in the literature. **Materials and Methods:** We performed a retrospective study of all cases, where surgery for synchronous primary cervical and endometrial cancers was done at the Clinic of Oncogynaecology, University Hospital – Pleven, Bulgaria for an 8-year period. Patients were followed-up until December 2019. We analyzed some clinico-pathological characteristics of both malignant conditions as demographical data and menopausal status of the patients, as well as the histological type and TNM 8 stage of both cancers; we tried to correlate them with the rates of overall survival. **Results:** We explored 1460 patients' files and identified 6 cases of synchronous cervical and endometrial cancers. The mean age of the patients was 58 years (range 47-65). 5 of them (83.3%) were diagnosed in menopause. In 1 case (16.7 %) the size of the cervical cancer (CC) was > 4 cm (locally advanced disease), in 3 cases (50%) it was below 2 cm, and in the remaining 2 cases (33.3%) the CC was only microinvasive. The CC histology was squamous cell carcinoma without keratinization in 5 women (83.3%) and in 1 case (16.7%) - adenosquamous. The histology of all endometrial cancers (EC) was endometroid adenocarcinoma and all of them were stage I. **Conclusions:** Co-existence of synchronous cancers of the uterine cervix and endometrium does not seem to worsen the prognosis of the patients and may even be beneficial: the symptoms of the EC may lead to earlier diagnosis of the synchronously existing malignant conditions.

Key words: Multiple primary malignancies; Synchronous multiple primary malignancies endometrial cancer; Cervical cancer; Treatment; Survival.

Introduction

Multiple primary malignancies (MPM) have been first described in 1879 by Billroth [1]. MPM may originate from a single or from multiple anatomical organs [2]. As per North American Association of Central Cancer Registries (NAACCR) MPM could be subdivided into two categories: (1). Synchronous MPM, where cancers occur at the same time or maximum within 6 months the first primary cancer and (2). Metachronous MPM, where cancers follow in sequence, occurring more than six months apart [1]. As per IACR/IARC and many other classifications a primary tumor originates in a primary site or tissue and is neither an extension, nor a recurrence, nor a metastasis. Synchronous tumours are diagnosed in an interval of less than 6 months if arising in different sites [3].

It is frequently reported that synchronous diagnosis of different cancers introduces additional difficulties and sometimes a delay in the diagnosis. It may thus introduce

a delay in the subsequent treatment of both tumor localizations. Cancers from different anatomical regions may necessitate different initial approaches, e.g. surgery, neoadjuvant systemic treatment or radiotherapy. It seemed interesting to assess whether the same would be valid for synchronous tumors in close anatomical or functional proximity (e.g. gynecological cancer). A second co-existing primary gynecological cancer, occurring in a patient with EC, may be earlier diagnosed due to early symptoms of the EC. Thus the co-existence of MPM within one organ or system may even be beneficial, leading to an earlier diagnosis of an otherwise diagnosed at a later stage and more aggressive tumor that is still asymptomatic.

Synchronous MPM are generally rare and their frequency is not well described in the literature. Synchronous MPM from the female reproductive system are even rarer and there are a few case reports published [4]. Occasional retrospective analyses report a rate of 0.7 % [5]. The most

common combination consisted of EC and ovarian cancer [6]. Synchronous MPM from different parts of one organ as the uterus are even more infrequent. Stage of both malignancies at diagnosis is considered of prognostic significance in MPM [7]. We analyzed a series of 1460 patients, who underwent surgery in our clinic for either endometrial or cervical cancer, or both.

Materials and Methods

Retrospective analysis of all patients, who underwent surgery for synchronous primary CC and EC at the Clinic of Oncogynaecology, University Hospital – Pleven, Bulgaria between 01.01.2008 and 31.12.2015 was done. 6 patients were identified for an 8-year period. The histological results of both EC and CC were centrally reviewed to reconfirm both oncological conditions. The following clinical data were collected from the medical files: demographic data (age at diagnosis, vital status), date and volume of surgery, clinical staging as per TNM 8 and FIGO classification 2002 as well as postoperative management and follow-up. As the analysis period included patients' stages per TNM 7 or the previous version of FIGO 2002 we revised the data and classified according to the newer version of TNM 8 and FIGO 2018. Pathological data that were collected included details about the histology and staging of both tumors. These parameters were assessed and correlated with the rates of overall survival (OS). Follow-up visits were performed every 3 months during the first 2 years and annually ever since. They consisted of clinical examination, blood work-up and an annual whole body CT. Date of last follow up was December 2019.

Results

During the study period 550 patients with CC with FIGO I stage and 910 with endometrial cancer were operated in our clinic. 6 patients with synchronous EC and CC were identified (0.4%); the synchronous EC and CC were diagnosed preoperatively only in 2 women. 5 of all 6 patients were diagnosed in menopause due to symptoms of bleeding. Only one patient was premenopausal and the triggering symptom was intermenstrual bleeding. Median age of the patients with synchronous EC and CC was 58 years (range 47-65). The histology of the EC in all cases was endometrioid adenocarcinoma, whereas for the CC, it was squamous cell carcinoma without keratinization in 5 women (83.3%) and in 1 case (16.7%) - it was adenosquamous. The analysis of the stages of both conditions revealed CC above 4 cm (locally advanced disease) in 1 case (16.7%), in 3 cases (50%) it was less than 2 cm, and in the remaining 2 cases (33.3%) the CC was only microinvasive. As for the EC, there was invasion in the myometrium above 50% (pT1b) in only one case (16.7%) where the histological grade of the tumor was G3 poorly differentiated. In the remaining 5 cases, the invasion was less than 50% (pT1a). Typically, the most common grade amongst EC was G1 - 3 cases (50%). The patient with high risk EC

had a microinvasive CC, but due to the high risk EC, she had a more extensive surgery, comprising of modified radical hysterectomy (RH) with pelvic lymph node dissection (PLND) as the CC was microinvasive. In all remaining 5 patients surgery consisted only of RH with PLND. All patients were subjected to postoperative radiotherapy and their data are briefly represented in Table 1.

Discussion

Multiple primary malignancies (MPM) rarely occur synchronously. Their diagnosis preoperatively is not typical, especially if they originate from different parts of one organ for example the uterus. In our case series, synchronous EC and CC were diagnosed preoperatively in only 2 patients (33%) as a result of dilatation and curettage. Most patients were diagnosed due to symptoms of EC, that occur relatively early in the evolution of the disease: bleeding in menopause. The management of EC is initial surgery. Thus, a second primary that is relatively more aggressive as a CC would be detected at an earlier stage, due to symptoms of the EC. In this case, the co-existence of a more aggressive CC most probably does not influence or worsen the prognosis of the patient as it is diagnosed at an earlier stage. The only case where the EC presented with invasion in the myometrium above 50% had a more aggressive biology with G3 differentiation. As this was a preoperative finding, the high risk EC led to a more extensive surgery, comprising of modified radical hysterectomy with pelvic lymph node dissection. The co-existing microinvasive CC was still asymptomatic and did not also worsen the prognosis of the patient. In all remaining 5 patients, surgery was guided by the EC and consisted of radical hysterectomy with pelvic lymph node dissection.

According to Warren Gates, to diagnose MPM the following criterias should be fulfilled: (a) each tumor should present a definite picture of malignancy (b) each tumor should be histologically distinct (c) the possibility that one is a metastasis of the other must be excluded [8]. Synchronous MPM occur at the same time or maximum within six months of time as per definition of the Surveillance Epidemiology and End Results Programme (SEER) [2] and IARC/IACR [3]. Differentiation between the two tumors is relatively easy when their histologies are different (e.g. squamous and adenocarcinoma) [9]. Synchronous EC and CC are extremely rarely described in the literature and there are only several case reports published [10]. In our series the most common histology of EC was endometrioid adenocarcinoma, whereas in the cervix - it was squamous cell carcinoma and these concur with data from large pathological studies. Patients with synchronous EC and CC are usually post-menopausal with median age at presentation 50-60 years. The most frequent triggering the diagnosis symptom was bleeding in menopause and vaginal discharge [9]. The management of both oncological conditions should be guided by the stage of both diseases [11]. Typically, the prognosis of these patients is not worse as the diagnosis is

Table 1. — Clinical and pathological features of the patients, outcome and survival.

N	Age, years	Dx procedure	Preop Dx	Pathologic stage, CC	Size in cm, CC	Pathologic stage, EC	Surgical treatment	OS, months
1	65	D&C	CC	pT1b2 pNo Mo;G2	> 4	pT1a pNo Mo/G1	RH + PLND	134
2	58	D&C	EC,CC	pT1b1pNoMo; G3	< 2	pT1a pNMo/ G1	RH + PLND	117
3	62	D&C	CC	pT1a2pNoMo	microinvasive	pT1a pNoMo; G2	RH + PLND	90
4	47	biopsy	CC	pT1b1pNoMo; G3	< 2	pT1a NoMo ; G1	RH + PLND	80
5	60	biopsy	CC	pT1b1pN0Mo; G2	< 2	pT1a pNoMo; G2	RH + PLND	79
6	56	D&C	EC, CC	pT1a1pNoMo	microinvasive	pT1b pNoMo; G3	MRH+ PLND	71

D&C- dilation and curettage; Dx – diagnosis; CC – cervical cancer; EC – endometrial cancer; RH – radical hysterectomy; PLND – pelvic lymph node dissection; MRH – modified radical hysterectomy; OS – overall survival; RT - radiotherapy.

triggered by early symptoms of a less aggressive condition (bleeding in menopause from the EC), leading to a diagnosis of a more aggressive condition (CC) in its earlier asymptomatic phase. As all patients, included in our analysis, had an early stage disease, surgery was the initial management modality used in all our cases.

Synchronous primary genital cancers are rare, comprising of only 1-6% of all genital tract neoplasms [12]. The most common combinations consist of ovarian cancer and some other genital tumors, most frequently endometrial cancer [13, 14]. Despite the fact that the etiology and pathogenesis of this phenomenon is still unclear, it is known that if subjected to certain irritation, the embryologically common tissues in the female genital system could synchronously develop tumors [12, 15]. A possible motivation for the occurrence of multifocal lesions could be epithelial metaplasia, that is common for the genital tract and the peritoneum [15]. This could at least partially be the explanation why according to some publications, patients with malignancy of the lower genital tract remain at an increased risk of development of a second primary [16].

Despite the small sample of only 6 patients, 5 of them were diagnosed due to common symptom - menopausal bleeding. In 4 women the diagnosis was preoperatively confirmed histologically via dilatation and curettage. This procedure also diagnosed the co-existing CC in two cases whereas in the remaining 2 cases a further biopsy was done due to the clinical data of a pathologic structure in the uterine cervix, established by the gynecological examination. In the remaining one patient, the diagnosis was menopausal bleeding, that originated from a very locally advanced CC above 4 cm with adenosquamous histology, which was diagnosed at an advanced stage. The EC invaded the myometrium above 50% in only 1 of all 6 cases with synchronous EC and CC, which may also be attributed to the more aggressive biology and poor differentiation of the tumor – G3.

Our case series concur with other pathological studies that most common histology of the endometrium malignancy is endometrioid adenocarcinoma; in the cervix - it is squamous cell carcinoma. As per all international specialized guidelines for early stage CC and EC, the radical

surgical treatment, followed by radiotherapy was the management in all cases and until present with 7 years of follow-up there are no oncologically related deaths registered. This also confirms the fact that the prognosis of two synchronous gynecological tumors is no worse than the prognosis of the more aggressive entity. It is of course better than the prognosis of a gynecological tumor with secondary metastasis even only in the gynecological system [9]. The management of synchronous tumors is largely guided by the recommendations for the treatment of the more aggressive one.

Conclusions

Despite its rarity, synchronous primary tumours in the female genital tract exist and their management includes common surgical techniques. Diagnosis and staging of both tumors preoperatively are largely beneficial as they determine accordingly the extent of the surgery. Radical oncological surgery provides the basis for better outcomes in all early-stage gynecological tumors. Despite the common symptoms in menopausal women, synchronous tumor should be considered in the diagnostic and treatment strategy. The co-existence of two malignancies is not an incurable condition, but mandates precise diagnosis and staging. The curative intent remains the ultimate goal.

Authors' contributions

Conceptualization A.Y.; Methodology S.K., A.Y.; Formal Analysis S.S. (Stanislav Slavchev); Investigation A.Y.; Resources S.K.; Data Curation S.S. (Strahil Strashilov); Writing Original & Draft Preparation A.Y., M.V; Writing Review & Editing A.K; Visualization S.S. (Strahil Strashilov); Supervision A.K., M.V.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee (approval number: 414-КЕНИД/31.03.2016).

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Conflict of Interest

The authors declare no competing interests.

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