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## Isolated lymph nodal recurrence after 10 years in FIGO Stage IA1 cervical adenocarcinoma treated with conization: case report and review of the literature

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### ABSTRACT

**Background.** Cervical cancer (CC) represents the fourth most common cancer in women. Since about 25% of women with CC has 40 years or less, more and more women choose fertility-sparing surgery (FSS). FSS, such as conization, represents valid and safe procedures for patients with IA1 tumours without lymph-vascular involvement (LVSI). It has been established that, for this very early stage, the risk of node involvement is negligible (~ 1 %), that is why nodal staging can be skipped and definitive conization can be considered a curative treatment. The issue is that a wide consensus regarding the most appropriate follow-up protocols after FSS has not been achieved.

**Case presentation.** It is reported a very unusual recurrence of cervical adenocarcinoma that is characterized by the site of metastasis that occurred at nodal level, instead of the most common recurrence site that is the cervix, and for the “time to recurrence” that was astonishing long because it occurred at 10 years after conization. Only English studies and those performed in humans were considered to compare the case study to the actual literature. 10 eligible studies were found.

**Conclusions.** Undoubtedly, because of the rarity of the event, it is not possible to reach a clear conclusion. However, the analysis of this case report could be an opportunity to generate new hypothesis about natural history of the disease and to question the safety of FSS when applied outside the actual indications. It is of paramount importance to never lower our guard even on the very early stages, focusing on oncological secondary prevention. It reflects the importance of build a stricter follow up for these patients until new strong medical evidence will be showed.

### INTRODUCTION

Cervical cancer (CC) represents the fourth most common cancer in women, and it is an important public health problem affecting middle-aged women [1]. According to international guidelines,

the standard treatment of early cervical cancer is radical surgery [2, 3]. However, considering that more than 25% of women with CC have 40 years or less [4] and that the mean age of the new mother is advancing, it has become mandatory to consider fertility-sparing surgery (FSS) in this very peculiar

population. Undeniably, according to international guidelines, FSS may be proposed in selected women with FIGO [5] stage IA or stage IB1 lesions (less than 2-cm diameter) who desire preserving their fertility [2, 3]. A recent review of the literature showed that, after FSS, the mean recurrence rate was 3.2% while the mean cancer death rate was 0.7% [6].

Among FSS procedures, conization represents a valid and safe procedure for patients with IA1 tumours without lymph-vascular involvement (LVSI); moreover, since the risk of lymph node involvement is negligible (~ 1 %) in this subset of patients, nodal staging can be skipped and definitive conization with negative resection margins can be considered a curative treatment in almost 100% of cases [7].

After FSS, there has not been achieved a wide consensus regarding the most appropriate follow-up protocols because the case numbers remain low, and no prospective randomized trial are carried out. Following we report a case of an unusual, isolated lymph node-relapse of FIGO Stage IA1 cervical adenocarcinoma at 10 years after conization. A review of the literature was conducted by combing disease-specific terms (uterine cervix neoplasms AND adenocarcinoma AND microinvasive) with treatment-specific terms (conservative therapy, fertility sparing surgery, conization) in MEDLINE and Embase up to March 2022. Our research particularly focused on recurrence ratio after conization. We found 10 studies.

## CASE PRESENTATION

### *Past medical history*

In July 2010, a 36-year-old woman with a diagnosis of FIGO IA1 cervical adenocarcinoma G1 was submitted to FSS (conization). Negative LVSI and margin of resection resulted to the definitive pathological finding; subsequently, she underwent to a regular clinical follow-up every six months during the subsequent 5 years. In 2013, she conceived spontaneously but, unfortunately, she had a miscarriage. Subsequent routine gynaecological screening was negative.

### *Suspected diagnosis of disease recurrence*

In September 2020, at 46-years-old, after a negative HPV and Pap-test, the gynaecological clinical visit

highlighted a right parauterine mass; the magnetic resonance imaging (MRI) and computer tomography scan (CT scan) confirmed a mm 30 × 30 × 37 multilocular mass as suspected metastatic right iliac lymph node (**Figure 1**). After this finding, she was referred to the Gynaecologic Oncology Unit of the AOU "G. Martino" of Messina. Unfortunately, an ultrasound-guided biopsy did not lead to a differential diagnosis. Thus, after a multidisciplinary board discussion and after a dedicated counselling with the woman, surgery was chosen as the best approach to obtain both a histological diagnosis and a curative effort.

### *Surgery*

In October 2020, the patient was submitted to exploratory laparoscopy to exclude carcinosis, intraperitoneal masses and visceral metastases and to perform a biopsy of the suspected metastatic lymph node. Metastatic glandular cells were confirmed at the intraoperative pathological diagnosis using frozen sections. Therefore, in the same surgical session, the patient underwent open abdominal type C1 radical hysterectomy with bilateral salp-



**Figure 1.** Enhanced magnetic resonance image.

An enhanced mass measuring 30 × 30 × 37 mm was detected at the right parametrium.

ingo-oophorectomy, bilateral pelvic lymph node dissection, right distal ureteral resection with its reimplantation. Since the right ureter appeared closely attracted from the bulky lymph-node, the surgeon (AE) decided to sacrifice the distal portion of the ureter in order to obtain clean macroscopic resection margins. The histopathological finding showed a metastatic lymph-node from the cervical cancer, but the cervix was completely negative. In the metastatic lymph node, HPV16 was detected. The patient was discharged uneventfully 1 week after surgery and received subsequent external radiotherapy. The only complication experienced was a urinary infection treated efficiently with oral antibiotics.

### Adjuvant therapy

From the sixth month after the end of the radiotherapy, the patient experienced multiple intestinal sub occlusive episodes treated conservatively and a major depressive disorder, with deterioration of general conditions. In January 2022, due to intestinal occlusion, she was submitted to exploratory laparotomy with no evidence of macroscopic disease and the general surgeon performed adhesiolysis and multiple biopsies. The histopathologic report was negative, but she died in March 2022 due to cachexia (**Figure 1**).

## DISCUSSION

The report describes an unusual case of cervical cancer relapse after FSS whose atypical features include 1) the elapsed time from the first diagnosis to relapse, considering the initial FIGO stage; 2) the negative pathological finding of the cervix after surgical definitive approach.

The latest FIGO classification (2018) defines stage IA1 of cervical cancer as an invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 3 mm. The horizontal dimension is not considered in the 2018 classification as it is subject to many artifactual errors [5]. The FIGO cancer report had indicated that with normal follow-up at 5 years, the patient, treated for FIGO IA cervical cancer, can return to routine screening schedule [5]. FIGO IA1 cervical cancers have an excellent prognosis and literature data reports very few cases of relapses, treated using either FFS or standard surgery. A recent review of the literature

reported a recurrence rate of 0.2% after FSS in FIGO stage IA1 cervical carcinoma [8].

In a systematic review of published literature, Hou *et al.* reported a survival rate of 99% for microinvasive adenocarcinoma of the cervix for FIGO stage IA1 and a survival rate of 98% for IA2 and a recurrence rate after FSS of 3.4% and 2.2%, respectively [9]. Spoozak *et al.* showed survival rate similar for conization and hysterectomy for both FIGO stage IA1 squamous cell carcinomas and adenocarcinomas. The authors analysed 554 cases of stage IA1 adenocarcinoma of the cervix subdivided into 433 women submitted to hysterectomy and 121 to conization: the 5-year survival was 96.9% for hysterectomy compared with 98.8% for conization. The limit of this study is the lack of the recurrence incidence [10]. Lee *et al.* reported no cases of recurrence after conization for IA1 squamous cervical cancer, concluding that conization alone with careful follow-up appears to be an effective and safe treatment for patients with stage IA1 microinvasive carcinoma, regardless of resection margins status or LVS [11]. Likewise, Baalbergen [12], McHale [13], Poynor [14], Reynolds [15] and Yahata [16] did not reported any cases of relapses in their series after conization in stage IA1 cervical adenocarcinoma, highlighting the relevance of clear margins. Also, Baalbergen *et al.* analysed 59 cases of cervical microinvasive adenocarcinoma including 22 patients underwent FSS. In FSS group, no case of recurrence was reported while in the hysterectomies group, the authors recorded 1 case of lymph-nodal relapse after 30 months: a woman with positive LVSI treated by vaginal hysterectomy [12]. Ceballos *et al.* analysed 32 cases of IA1 adenocarcinoma submitted to both standard and FSS treatment and no relapses were reported after a mean follow-up of 54 months [17]. Instead, MacNab *et al.* reported one case of recurrence of stage IA1 cervical cancer after large loop excision of the transformation zone (LLETZ). This woman had negative cytology at 6 and 12-months after treatment. She was admitted for abdominal pain 18 month-after LLETZ and she was diagnosed a large ovarian mass, ascites and pleural effusion. She was submitted to cytoreduction surgery, and the final histology confirmed a metastatic adenocarcinoma of the cervix [18]. Singh *et al.* reported a case of microinvasive cervical adenocarcinoma treated with conization that has developed a large endometrial localization 33 months after FSS and died for metastatic disease 49 months after cone biopsy [19]. Elliot *et al.* analysed 476 cases of stage IA carcinoma of the cervix, highlighting more recurrence in older



patients, in case of glandular cancer and tumours invading > 3 mm, while LVSI didn't seem to impact on prognosis. However, in this last case-series, there was a case of a young women with characteristics like ours: cervical adenocarcinoma invading 0.1 mm with negative LVSI, treated with a conization. After 8 months, she was submitted to extrafascial hysterectomy with lymphadenectomy because of positive smear at follow-up schedule. The final histology revealed a solitary positive pelvic lymphonode; unfortunately, she died 8 years later for upper abdominal and cerebral metastasis [20]. In literature, most recurrences occur within the first 24 months. Few cases of recurrence were reported 5 years after primary FSS, and in almost all cases several factors increase risk of relapse of early cervical cancer: tumor dimension, depth of stromal invasion, grade and presence of LVSI [12, 21]. It is important to consider that our patient did not have any of these risk factors.

Also, usually, the early cervical cancers, especially in case of stage IA1, recur at the level of the cervix after FSS. The depth of invasion is a major risk factor for recurrence in cervical adenocarcinoma. Hirai *et al.* analysed 302 patients with early cervical adenocarcinomas and concluded that invasive cervical adenocarcinoma with a depth of invasion of 3 mm or less and a horizontal spread of 7 mm or less has little potential for nodal metastasis or recurrence. Among 22 patients with IA1 adenocarcinoma cervical cancer treated with radical hysterectomy, they reported one case of recurrence on vaginal wall 45 months after first treatment [22]. Berek *et al.* reported an absence of incidence of lymphonode metastasis in patients with an adenocarcinoma of the cervix that had a depth invasion of less than 2, while positive

lymphonode were found in 11.1% patients with 2-5 mm of invasion [23].

Furthermore, Sopracordervole *et al.* has concluded their manuscript, about a series of microinvasive adenocarcinoma treated by FSS, highlighting that conization can be safe in women with stage IA1 with clear margins and no LVSI. However, women should be informed about the risk of recurrence considering the low reliability of follow-up techniques (cytology, colposcopy, and endocervical curettage). FSS should be indicated only in patients with strongly desire of offspring [24, 25] (Table 1).

The relationship between high-risk HPV subtype infections and cervical cancer development is widely accepted, while the correlation between HPV expression and disease relapse is still unclear. There are 15 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) that are typically associated with cervical cancer [26].

It has been reported in literature, that there is a highly variable prevalence of HPV DNA in pelvic lymph nodes of patients with cervical cancer, ranging between 25% and 80% [27]. In most articles, it is highlighted how metastatic pelvic lymph nodes tend to be HPV positive. In 2019, Chen *et al.* analysed the presence of HPV DNA in cervical tissues and lymph nodes in 88 patients submitted to surgery for invasive cervical cancer with lymphatic metastases. They retrospectively assessed 88 patients with uterine cervical neoplasms with lymph node metastases and in 82 (93.2%) cases, they found HPV DNA in both the cervical tissues and pelvic lymph nodes [28]. A recent meta-analysis highlighted as the use of prophylactic HPV vaccination as an adjunct to surgical excision for CIN 2 or greater reduces the risk of re-

**Table 1.** IA1 adenocarcinoma of the cervix treated with conization.

Author	Year	FIGO Stage	Cone	Relapse	Median DFS (months)
Singh [19], 2008	/	IA1	1	1	33
Reynolds [15], 2010	1983-2008	IA1	7	0	71
McHale [13], 2001	1985-1996	IA1	4	0	48
Ceballos [17], 2006	1985-2002	IA1	1	0	31
Bisseling [25], 2007	1987-2004	IA1	16	0	72
Baalbergen [12], 2011	1987-2006	IA1	15	0	79.9
Yahata [16], 2010	1990-2004	IA1	10	0	75
Poynor [14], 2006	1992-1999	IA1	3	0	30
Sopracordevole [24], 2012	1995-2007	IA1	4	0*	69
MacNab [18], 2017	2007-2011	IA1	10	1	60
This case, 2023	2010-2020	IA1	1	1	120
<b>Total</b>	<b>1983-2020</b>	<b>IA1</b>	<b>72</b>	<b>3 (4.2%)</b>	<b>64.5</b>

No case of invasive cancer or distant localization, one case of adenocarcinoma *in situ* of the cervix 21 months after conization submitted simple hysterectomy as definitive therapy.

current disease (OR 0.36; 95%CI 0.22-0.57;  $p < 0.0001$  [29]). Perhaps if our patient had undergone conization in the vaccination era, it could have reduced her recurrence risk. This is even more true when we look at the recent data regarding the risk of preneoplastic lesion recurrence: the persistence of HPV after FSS is the principal risk factor for recurrence [33] and HPV vaccination after FSS (conization) is associated with a reduce risk of CIN 2 recurrence [34].

In the very early stages, our goal is achieving a definitive oncological cure by surgery only reducing the recurrence risk to an absolute 0%. Although the emerging literature shows that there are therapeutic possibilities to preserve the quality of life and sexual discomfort during and after any adjuvant therapy [30-32], avoiding radiotherapy and chemotherapy by reducing recurrences of disease to 0% remains the main absolute goal.

To our knowledge, this is the first case available in literature of lymph node recurrence 10-years after conization in FIGO IA1 cervical cancer. Because of the rarity of this event, it is impossible to draw definitive conclusions, but it still provides an interesting and cardinal insight: nowadays, in the era of personalized medicine, it should be mandatory in all patients, even in those who seem to have a low recurrence rate, to pursue a very deep investigation of the disease till its molecular factors. These conclusions are in line with a very recent editorial conducted by D'Orta *et al.* where it is reported that an accurate prediction of treatment response and survival based on all the personal features of the woman affected by cervical carcinoma including its molecular analysis, will help to implement personalized therapies that may improve the treatment of cervical cancer patients [35].

## CONCLUSIONS

We reported a very unusual recurrence of cervical adenocarcinoma submitted to FSS that is distinguished by the site of metastasis that occurred at nodal level, instead of the most common recurrence site that is the cervix, and for the "time to recurrence" that was astonishing long because it occurred at 10 years after conization. Moreover, we reviewed cases of relapse after conization in cervical adenocarcinoma FIGO stage IA1 submitted to FSS in the literature. Undoubtedly, because of the rarity of this event, it is not possible to come to a clear conclusion. Similarly, this case report shows

that an isolated nodal recurrence of cervical cancer at 10 years after FSS, still rare, is possible and it could cause a domino effect that lead to death. The case reported highlights the importance of never lower our guard even on the very early stages. It could be an opportunity to generate new hypothesis about natural history of this disease. Although we still consider FSS a possible option for very early stages in selected cases, we recommend to build a stricter follow up and to offer a more personalized reproductive counselling for these patients until new strong medical evidence will be showed.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors contribution*

A.E., M.A.: Conceptualization. G.V.: Methodology. C.M., P.F.: Data curation. M.A., C.M.: Formal analysis. A.E., M.A., G.V.: Investigation. A.E., A.M.: Project administration. A.E., S.C.: Supervision. A.E., M.A.: Validation. M.A., G.V.: Writing – original draft. C.M., R.G.: Writing – review & editing.

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### *Study registration*

N/A.

### *Disclosure of interests*

The authors declare that they have no conflict of interests.

### *Ethical approval*

N/A.

### *Informed consent*

The patient provided written informed consent to the collection and analysis of her data for scientific purposes.

### *Data sharing*

All data are presented in the study.

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