The clinical outcome of patients with Stage Ia₁ and Ia₂ squamous cell carcinoma of the uterine cervix: A Cooperation Task Force (CTF) study

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Summary

Purpose of investigation: The objective of this retrospective multicenter study was to assess the clinical outcome of patients with microinvasive squamous cell carcinoma of the uterine cervix.

Methods: The hospital records of 166 patients with microinvasive squamous cell carcinoma of the uterine cervix were reviewed. All cases were retrospectively staged according the 1994 International Federation of Gynecology and Obstetrics (FIGO) nomenclature. One hundred and forty-three cases were in Stage Ia₁ and 23 in Stage Ia₂ disease. Surgery consisted of conization alone in 30 (18.1%) patients, total hysterectomy in 82 (49.4%), and radical hysterectomy in 54 (32.5%). All patients in whom conization was the definite treatment had Stage Ia₁ disease and had cone margins negative for intraepithelial or invasive lesions.

Results: None of the 67 patients submitted to pelvic lymphadenectomy had histologically proven metastatic lymph nodes. Of the 166 patients, eight (4.8%) had an intraepithelial recurrence and four (2.4%) had an invasive recurrence. With regard to FIGO substage, disease recurred in nine (6.3%) out of 143 patients with Stage Ia₁ and three (13.0%) out of 23 with Stage Ia₂ cervical cancer. With regard to type of surgery, disease recurred in three (10.0%) out of the patients treated with conization alone, four (4.9%) out those who underwent total hysterectomy, and five (9.3%) out of those who underwent radical hysterectomy. It is worth noting that none of the 30 patients treated with conization alone had recurrent invasive cancer after a median follow-up of 45 months. However three (10%) of these patients developed a cervical intraepithelial neoplasia (CIN) III after 16, 33, and 94 months, respectively, from conization.

Conclusions: Conization can represent the definite treatment for patients with Stage Ia₁ squamous cell cervical cancer, if cone margins and apex are disease-free. For patients with Stage Ia₂ cervical cancer extrafascial hysterectomy with pelvic lymphadenectomy might be an adequate standard therapy, although the need for lymph node dissection is questionable.

Key words: Microinvasive cervical cancer; Pelvic lymph nodes; Conization; Childbearing ability; Hysterectomy; Recurrence.

Introduction

The pathologic definition of "microinvasive carcinoma of the cervix" has been long debated in the last decades. Several definitions have been proposed that differ mainly for the depth and width of stromal invasion and for vascular space status, and that partly explains the differences in lymph node involvement and recurrence rates reported in the literature [1-17]. The diagnosis should be based on microscopic examination of a cone biopsy, which must include the entire lesion. In 1973 the American Society of Gynecologic Oncologists (SGO) defined microinvasive carcinoma of the cervix as a lesion in which neoplastic epithelium invades the stroma in one or more places to a depth of 3 mm or less below the basement membrane of the epithelium and in which lymphatic or vascular involvement is not demonstrated. In 1985 the International Federation of Gynecology and Obstetrics (FIGO) attempted to quantify the histologic definition of Stage Ia carcinoma of the cervix, which was subdivided in two substages: Stage Ia₁, defined as a lesion with minimal

microscopically evident stromal invasion, and Stage Ia₂, defined as a lesion detected microscopically that can be measured [18]. The upper limit of the measurement should not show a depth of invasion of more than 5 mm taken from the base of the epithelium from which it originates, and the horizontal spread must not exceed 7 mm .

Larger lesions should be staged as Ib. In 1994 the new FIGO staging classification defined Stage Ia₁ as a tumor with a measured stromal invasion of not > 3 mm in depth and not > 7 mm in horizontal spread, and Stage Ia₂ as a tumor with measured stromal invasion of > 3 mm and not > 5 mm in depth and not > 7 mm in horizontal spread [19]. The involvement of vascular, venous or lymphatic spaces, should not change the stage allotment. On the other hand, vascular space involvement correlates with the depth of stromal invasion [6, 8, 12].

The prognosis of microinvasive cervical cancer is very satisfactory. According to Annual report n. 24, the 5-year survival was 97.8% for 638 women with Stage Ia₁ cervical cancer and 97.3% for 213 with Stage Ia₂ disease [19]. The clinical outcome is also excellent for microinvasive adenocarcinoma of the cervix. In a population-based study including 301 cases with this disease identified

from the Surveillance, Epidemiology, and End Results (SEER) Public-Use Database, after a mean follow-up of 46.5 months the censored survival rate was 99.2% for Stage Ia$_1$ and 98.2% for Stage Ia$_2$ cervical adenocarcinoma [20].

Different treatments, including conization alone, total hysterectomy, radical hysterectomy and radical trachelectomy, have been employed in microinvasive carcinoma, and no definite conclusions have been drawn about the optimal management, particularly in young patients who strongly wish to preserve childbearing ability [6, 8, 9, 13-17, 21-27].

The aim of this retrospective Italian study was to assess the risk of recurrence in patients with microinvasive squamous cell carcinoma of the uterine cervix treated with different therapeutic modalities, and in particular in those treated with conization alone.

Materials and Methods

We reviewed the hospital records, including surgical notes and pathologic reports, of 166 patients with microinvasive squamous cell carcinoma of the uterine cervix treated at the Departments of Obstetrics and Gynecology of the University of Brescia, Milano-Bicocca, Padua, Pisa and Turin between 1984 and 1998. Only cases with a depth of invasion lower than 5 mm taken from the base of the epithelium and with horizontal spread lower than 7 mm were included in this study. All cases were retrospectively staged according to the 1994 FIGO nomenclature.

Surgery was performed according to the strategies of treatment of each Department in different periods of time. The patients were followed until December 2001.

Statistical analysis of the data was carried out with the χ^2- test or two-tailed Fisher's exact test when appropriate.

Results

The median age of patients was 45 years (range, 24-84 years). In detail, the age was < 30 years in 12 patients, between 30 and 40 years in 53, and > 40 years in 101. The depth of stromal invasion was < 1 mm in 86 patients, between 2 and 3 mm in 57, and between 3 and 5 mm in 23. Therefore 143 tumors were in Stage Ia$_1$ and 23 in Stage Ia$_2$. Stromal invasion was not related to patient age (data not shown). Table 1 shows the type of surgery performed in the 166 patients.

All patients in whom conization was the definite treatment had Stage Ia$_1$ disease and had cone margins negative for intraepithelial or invasive lesions.

Pelvic lymphadenectomy was carried out in 67 (40.4%) of the 166 patients; 13 of the 82 patients who underwent total hysterectomy and all the 54 patients who underwent radical hysterectomy. No histologically proven lymph node metastasis was detected. Disease recurred in 12 (7.2%) of the 166 patients (Table 2).

With regard to age, disease relapsed in four (6.2%) out of the 65 patients 40 years old or younger and in eight (7.9%) of the 101 patients over 40 years (p = ns).

Table 1. — *Type of surgery in patients with microinvasive cervical cancer.*

Conization	30 (18.1%)
Total hysterectomy (abdominal or vaginal)	82 (49.4%)
Radical hysterectomy	54 (32.5%)

Table 2. — *Type of recurrence in patients with microinvasive cervical cancer.*

	No. of cases (%)
Intraepithelial recurrence	8*
Invasive recurrence on the vaginal dome	2
Pelvic recurrence	1
Distant recurrence	1

*Three cases of cervical intraepithelial neoplasia (CIN III) and five cases of vaginal intraepithelial neoplasia (VIN II-III).

With regard to FIGO substage, disease recurred in nine (6.3%) out of the 143 patients with Stage Ia$_1$ and three (13.0%) out of the 23 with Stage Ia$_2$ cervical cancer (p = ns).

As for type of surgery, disease recurred in three (10.0%) of the 30 patients treated with conization alone, four (4.9%) of the 82 who underwent total hysterectomy, and five (9.3%) of the 54 who underwent radical hysterectomy (p = ns).

It is worth noting that none of the 30 patients treated with conization alone developed recurrent invasive cancer after a median follow-up of 45 months. However three (10%) of these patients developed a cervical intraepithelial neoplasia (CIN III) after 16, 33, and 94 months, respectively, from conization. Of the 30 patients submitted to conization, five (16.7%) subsequently became pregnant: one patient had a miscarriage, three patients delivered healthy babies by the vaginal route, one patient underwent cerclage and delivered a healthy baby by cesarean section.

Of the 82 patients who underwent total hysterectomy, one patient had a vaginal intraepithelial neoplasia (VIN II), (after an interval of 114 months), one had a VIN III (after an interval of 6 months), one had an invasive recurrence on the vaginal dome (after an interval of 36 months), and one had distant recurrence (after a median of 3 months).

Of the 54 patients who underwent radical hysterectomy, three patients developed VIN III (after an interval of 4, 6 and 19 months, respectively), one patient had an invasive recurrence on the vaginal dome (after an interval of 13 months), and one patient had a pelvic relapse (after a median of 23 months).

Discussion

The diagnosis of microinvasive carcinoma of the cervix relies on conization, which requires an adequate surgical technique and thorough histological evaluation of the surgical samples by a skilled pathologist [28]. There has been great debate about the risk of lymph node spread in patients with microinvasive cervical carcinoma. A large review of the literature carried out by Benedet and Ander-

son [13] revealed that the frequency of lymph node metastasis was 1.3% in the 706 patients with a depth of invasion up to 2.9 mm and 7.8% for the 219 patients with a depth of invasion of 3 to 5 mm submitted to lymphadenectomy. However, the study by Sevin *et al.* [11] demonstrated the importance of horizontal measurements, because the only patients who had positive lymph nodes when the depth of invasion was less than 5 mm had lateral spread greater than 7 mm and therefore these patients really had Stage Ib₁ disease. A retrospective review by Copeland *et al.* [10] including 180 patients with squamous cell cervical carcinoma with invasion to a depth of 5 mm or less detected pelvic lymph node metastases in 1% of cases. Rakar [16] reported that lymph nodes were histologically free of disease in all the 214 patients with cervical microcarcinoma, of whom 75 with Stage Ia₂ disease submitted to operations including pelvic lymphadenectomy. Nam *et al.* [17] detected no pelvic lymph node metastasis among 100 patients with Stage Ia₁ cervical cancer submitted to pelvic lymphadenectomy. A Gynecologic Oncology Group (GOG) study reviewed 51 squamous cell carcinoma patients who had conization with 3 to 5 mm of invasion measured, who afterwards underwent radical hysterectomy with pelvic and paraaortic lymphadenectomy, and who had no residual disease identified in the hysterectomy specimen [14]. Vascular space involvement was detected in almost one fourth of these cases but none of the patients had lymph node metastasis. In the population-based study of FIGO Stage Ia₁₋₂ cervical adenocarcinoma based on the SEER Public-Use Database, only one of the 140 women who underwent lymphadenectomy had a single positive lymph node [20]. In our series none of the 67 patients submitted to pelvic lymphadenectomy had histologically proven metastatic lymph nodes. Therefore women with microinvasive cervical carcinoma, even those with depth of invasion of 3 to 5 mm seem to have a low risk of lymph node involvement. Only collected data from many institutions using the current FIGO staging criteria will allow the determination of the true incidence of lymph node metastases in patients with Stage Ia₂ cervical cancer.

The outcome of patients with microinvasive carcinoma is excellent. Kolstad [8] found that three (1.3%) of the 232 patients with Stage Ia₁ cervical cancer developed a local recurrence, whereas of the 411 Stage Ia₂ patients 16 (3.9%) relapsed, and in detail 12 (2.9%) had a local recurrence and four (1.0%) had a pelvic recurrence. In the series by Copeland *et al.* [10] including 180 patients with stromal invasion up to 5 mm, after a median follow-up of 6.5 years four (2.2%) patients had an intraepithelial relapse and four (2.2%) progressed to invasive carcinoma. In the review by Benedet and Anderson [13], the rate of recurrence was 0.8% among the 2,369 patients with a depth of invasion up to 2.9 mm, and 4.3% among the 422 patients with a depth of invasion of 3 to 5 mm. Creasman *et al.* [14] reported that none of the 51 patients with Stage Ia₂ cervical cancer of their selected series had a relapse. Nam *et al.* [17] found that after a median follow-up of five years, only one (0.6%) of the 149

patients with Stage Ia₁ cervical cancer developed a recurrence. Our data are in agreement with the literature: among 166 patients with microinvasive cervical carcinoma, eight (4.8%) had an intraepithelial recurrence and four (2.4%) had invasive recurrence.

The optimal management of microinvasive cervical cancer has not yet been established [6, 8, 9, 13-17, 20-27]. Total or radical abdominal hysterectomy has been long used, but in recent years a better knowledge of the natural history of the disease and the more frequent detection in young women who strongly wish to preserve their fertility have enhanced the tendency to adopt conservative surgical approaches for these patients [16, 21-26, 28-31]. Morris *et al.* [21] used conization as definitive therapy for 14 patients with squamous cell cervical carcinoma that invaded the stroma to a depth less than or equal to 3 mm with no lymphatic or vascular space involvement and negative margins. After a median follow-up of 26.5 months, 13 patients retained their uteri and none had developed recurrent preinvasive or invasive lesions, whereas one patient underwent subsequent hysterectomy and was found to have mild dysplasia. Andersen *et al.* [23] used conization as the definite therapy in 41 patients with microinvasive cervical carcinoma with invasion of 3 mm or less, horizontal spread of 7 mm or less, and no lymphovascular involvement. After a mean follow-up of 81 months, only one case of adenocarcinoma in situ was detected. Winter [22] reviewed the histologic specimens of 494 patients who underwent conization for microcarcinoma of the cervix and who were classified according to the 1994 FIGO nomenclature. After a mean follow-up of 14 years, two patients with Stage Ia₁ tumors and two patients with Stage Ia₂ tumors died of disease. This author suggested that conization alone is indicated for patients with a depth of invasion up to 3 mm without lymph vascular space involvement. Additional pelvic lymphadenectomy can be considered for patients with Stage Ia₁ lesions and lymph vascular space involvement, and removal of the tumor and pelvic lymphadenectomy is indicated for all patients with Stage Ia₂ lesions. In the experience of Marchionni *et al.* [31] including 66 patients with Stage Ia₁ cervical cancer, 34 patients were treated with conization alone, two with cervix amputation, ten with total hysterectomy, and 20 with abdominal or vaginal radical hysterectomy. After a mean follow-up of 58 months, only two (3%) patients developed a central pelvic recurrence, and both had undergone vaginal radical hysterectomy. In our series, of the 30 patients with Stage Ia₁ disease treated with conization, three developed a CIN III but none developed invasive recurrence. Quality of life has become a very important issue in deciding the extent of surgical procedures for patients with a variety of cancers [26]. As cancer treatment has improved survival in several neoplasias, cancer survivors are becoming more interested in preserving their childbearing ability. Conization can represent the definite treatment for patients with Stage Ia₁ squamous cell cervical cancer, if cone margins and apex are disease-free. For patients with Stage Ia₂ cervical cancer extrafas-

cial hysterectomy with pelvic lymphadenectomy might be adequate standard therapy, whereas radical hysterectomy can represent overtreatment because the risk of parametrial involvement with these early lesions appears to be very low [13, 22]. However, the need of lymph node dissection is questionable, because recent data seem to show a low rate of positive pelvic nodes even in patients who have a stromal invasion of 3-5 mm. The indication for demolitive surgery may be modified in accurately selected patients who strongly wish to preserve their fertility potential. Experts in gynecologic oncology and infertility together with a fully informed patient and her family should make treatment decisions [32]. Therefore conization as the definite treatment could be taken into account also for accurately selected patients with Stage Ia_2 cervical cancer.

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