Microinvasive carcinoma of the cervix. Analysis of prognostic factors

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Summary

Introduction: Superficially invasive neoplasias of the uterine cervix are a matter of controversy in terms of their definition, prognostic factors and selection of treatment to minimize the risk of recurrences. We reviewed our treatment to determine whether any factors affect this risk.

Patients and methods: The present study was conducted on 59 patients seen at our service, 22 of them with early stromal invasion (IA1) and 37 with microinvasive carcinoma (IA2) according to FIGO criteria (1995). Ten patients were submitted to conization as definitive treatment, although for three of them treatment was complemented with Wertheim-Meigs surgery due to recurrence in the remaining cervix. The other 49 patients were submitted to total abdominal hysterectomy.

Results: Forty-four patients underwent diagnostic or therapeutic conization, and 14 of them presented involvement of the endocervical margin. Seven patients presented recurrence with involvement of the endocervical margin in five. The age of recurrence ranged from 40 to 70 years, with a mean of 52.3 years, as opposed to a general mean of 42.3 ($p<0.05$). Angiolymphatic invasion was positively correlated to recurrence and death ($p<0.01$) as well as depth of invasion.

Conclusions: We conclude that the presence of a cone with an involved endocervical margin represents a high risk of recurrence and that this condition occurs in older patients who are prone to present more extensive lesions. Thus, age should be regarded as an important risk factor. Angiolymphatic invasion and depth of invasion have a poor prognosis in terms of recurrence and death.

Key words: Carcinoma of the uterine cervix; Superficially carcinoma of the cervix; Early stromal invasion; Microinvasive carcinoma; Prognostic factor in cervical cancer; Conization; Treatment of cervical cancer.

Introduction

Superficial neoplasias of the uterine cervix are a matter of controversy in terms of their definition, prognostic factors and selection of treatment to minimize the risk of recurrence [1-6]. The definition of microinvasive carcinoma of the cervix has been a subject of debate for many years. The International Federation of Gynecology and Obstetrics (FIGO) recently changed the definition of stage IA1 cervical carcinoma from a lesion with a degree of invasion so small that it cannot be measured, to a lesion invading into the stroma no greater than 3 mm and with a width no greater than 7 mm [7]. This new definition is more consistent with the definition established by the Society of Gynecologic Oncologists in 1974 (a lesion invading no more than 3 mm into the stroma without lymph-vascular space invasion). There is a sizable quantity of published data confirming that lesions with no more than 3 mm of stromal invasion have a negligible risk of both lymphatic spread and recurrence if no lymph-vascular space invasion is present [1, 2, 4, 5, 8].

Microinvasive cervical carcinoma is a diagnosis made on the basis of cervical conization, and not punch biopsy [9]. Treatment guidelines for women in whom a cervical conization has revealed microinvasive carcinoma should be based on the risk of invasive disease in the residual cervix and the risk for development of new disease. All previous studies which have addressed the management of microinvasive cervical carcinoma on the basis of conization findings have included patients with lesions invading up to 5 mm into the stroma, with or without lymph-vascular space invasion [1, 3, 4, 10]. Many of such patients would not be candidates for conservative therapy on the basis of their conization findings alone. In addition, conization margins are generally classified as negative or positive and no special attention has been paid to this subgroup of patients [1, 3, 4, 10]. The purpose of this study was to determine the risk of residual disease of the cervix when microinvasive carcinoma is diagnosed and to determine whether any factors correlate with this risk for recurrence.

Material and Methods

We retrospectively reviewed 22 cases of early stromal invasion (ESI) classified as IA1 and 37 cases of microinvasive carcinoma (MC) of the cervix classified as IA2, seen at our service from January 1978 to December 1998. We reviewed the charts for clinical details and obtained follow-up from the hospital records and from the treating or referring physicians, with the end point being the last physician-patient contact. ESI and MC are defined in our institution as 0.1 to 3.0 mm (IA1) and 3.1 to 5.0 mm (IA2) in depth according to FIGO (1995) [7] staging and no more than 7 mm in width.

All patients underwent cold-knife conization by well-established techniques described previously [11]. In all conization procedures, careful attention was paid to delineating the internal

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margin. If fertility was not an issue or if the initial conization did not clear the lesion, hysterectomy was performed. Occasionally, a modified radical hysterectomy was performed for recurrence in the remaining cervix. The final diagnosis was accepted as the more severe of the histopathologic diagnoses from the two specimens obtained from biopsy or conization.

All conization specimens were sectioned in their entirety. All specimens containing the endocervical canal were opened longitudinally and sectioned individually. A margin was considered positive when dysplasia or microinvasive carcinoma was present within one high-power field (400x magnification) or approximately within 100 μm of the margin. Depth of invasion was determined in a standard fashion by measuring the leading edge of the invasive focus in relation to the basement membrane of its most likely site of origin. In some instances the site of origin was determined to be the surface epithelium, whereas in others the site of origin was determined to be the base of a gland duct.

For analysis of disease-free survival (DFS) and overall survival (OS), follow-up ranged from 12 to 228 months, with a median follow-up of 50.3 months. Seven patients presented recurrence, and five of them had involvement of the endocervical margins (Table 1).

We studied the following prognostic factors for recurrence: age, histopathologic type, depth of invasion, angiolymphatic invasion, and positive initial conization margin. Multivariate analyses were performed.

Results

Treatment: Ten patients were submitted to conization as the definitive treatment, although for three of them treatment was complemented with Wertheim-Meigs surgery after recurrence in the remaining cervix. The other 49 patients were submitted to total abdominal hysterectomy. Forty-four patients underwent diagnostic or therapeutic conization, and 14 of them presented involvement of the endocervical margin.

Recurrences: Table 1 shows the histopathologic and clinical findings in the final specimen on the basis of the internal conization margin involvement. DFS ranged from 5 to 24 months in this group. Vaginal vault recurrences were treated by cryotherapy, colpectomy and/or radiotherapy. Three of these patients died after recurrence.

Prognostic Factors:

Age: The mean age of the 52 women without recurrence ws 42.3 years, ranging from 24 to 80 years. The mean age of the 22 women with diagnoses of IA1 was 41.6 years, as opposed to 45.4 years for the IA2 group. Fourteen patients with a mean age of 43.2 years had involvement of the endocervical margin. Seven patients presented recurrence, and five of them had involvement of the endocervical margin. The age range of this subgroup with recurrence was 40-70 years, with a mean of 52.3 years ($p<0.05$, compared to the remaining group).

Histopathologic type and depth of invasion: Histopathology showed 51 cases of microinvasive squamous cell carcinomas, six cases of IA2 adenocarcinomas, and two cases of IA2 adenosquamous cell carcinomas. The recurrences occurred in five of the 31 squamous cell IA2, and in one of the 20 squamous cell IA1 ($p<0.01$). Of the two cases of adenosquamous cell IA2, one presented recurrence.

Angiolymphatic invasion: Four patients presented angiolymphatic invasion (6.8%). In this group, one had recurrence treated successfully by cryotherapy in the first step, and another recurrence followed by dissemination and death. The remaining 55 cases without angiolymphatic invasion presented five recurrences with two deaths. Angiolymphatic invasion was positively correlated to recurrence and death ($p<0.01$).

Internal conization margin status: Forty-four patients were submitted to diagnostic or therapeutic conization, and 14 of them presented involvement of the endocervical margin. Seven patients had recurrence, and five of them presented involvement of the endocervical margin.

Discussion

Microinvasive (stage IA1 and IA2) cervical carcinoma accounts for approximately 4-13% of all cases of cervical carcinoma [1, 10]. Because this diagnosis is generally made by conization, the physician must make a treatment recommendation based on the information gleaned from the conization specimen. Treatment options after conization for microinvasive cervical carcinoma range from no further treatment to radical hysterectomy. The nature of further treatment depends on the depth of stromal invasion, the presence or absence of angiolymphatic invasion, and the risk of a more serious lesion in the residual cervix [9].

Previous studies evaluated the risk of residual invasive disease after conization for microinvasive cervical carci-

Table 1. — *Prognostic factors, disease-free survival, and follow-up of seven patients who presented recurrences.*

N	Age (years)	Conization margin (1)	Surgery (2)	FIGO Stage	Type/ lymphvascular invasion	Disease-free survival (months)	Follow-up
1	43	+	WM+	IA2	Squamous cell carcinoma / –	9	Death (3)
2	70	ne	TAH+	IA2	Adenosquamous carcinoma / +	12	Death 7 years after recurrence (4)
3	59	+	TAH+	IA1 (4)	Squamous cell carcinoma / –	8	Death 8 years after recurrence
4	64	ne	TAH+	IA2	Squamous cell carcinoma / –	12	Disease-free 17 years
5	45	+	WM–	IA2	Squamous cell carcinoma / –	5	Disease-free 9 years
6	40	+	TAH+	IA2	Squamous cell carcinoma / +	24	Disease-free 7 years
7	43	+	WM+	IA1 (4)	Squamous cell carcinoma / –	14	Disease-free 2 years (4)

(1) Conization: + endocervical margin with neoplasia; – endocervical margin free: ne-not executed
(2) Surgery: TAH total abdominal hysterectomy; WM Wertheim-Meigs; + residual disease; – disease free
(3) Conization procedure as the initial treatment and WM for the recurrence
(4) Papillomavirus infection associated

noma [1, 3, 9, 10], but no studies about the clinical future of this subgroup of patients were available. In our study population, 23.7% of the women with microinvasive cervical carcinoma in a conization specimen had a positive internal conization margin. Five of them presented recurrence. The risk of recurrence was significantly affected by margin status: 35.7% of the patients with a positive internal margin had recurrence as compared to 4.4% of patients with a negative internal margin. On the other hand, this subgroup of patients who presented recurrence was significantly older than the general group (mean age: 52.3 and 42.3 years), respectively ($p<0.05$). This may be explained by the tendency of the microinvasive cervical carcinoma to be more extensive in older than in younger women, and this group of patients could be eligible for more aggressive initial treatment. On the other hand we know that more in-depth lesions occur in older women than younger ones, like our results: 41.6 years for IA1 and 45.4 years for IA2 carcinomas, but recurrence was an independent factor positively correlated to recurrence in the oldest group - 52.3 years.

Little attention seems to have been paid to microinvasive adenocarcinomas of the cervix and to whether such tumors carry the same favorable prognosis as their squamous counterparts. Only four reasonably sized studies [12-15] have addressed this problem, and these included 100 patients defined as having a depth of invasion up to 5 mm. In our study we had six cases of IA2 adenocarcinomas and two cases of IA2 adenosquamous carcinomas. Although the number of cases was small, of the two cases of IA2 adenosquamous carcinoma one presented recurrence, as opposed to no cases of recurrence in patients with IA2 adenocarcinoma. Microinvasive adenocarcinoma of the cervix is a clinicopathologic entity that appears to have the same prognosis, and should be treated in the same way as its squamous counterpart [14].

Previous studies [1, 3, 9, 10] are in accord that women whose cancers have more than 3 mm of stromal invasion or contain lymphvascular space invasion are not ideal candidates for conservative therapy because of the risk of nodal metastases and recurrence. In a recent review, Benedet and Anderson [8] reported a risk of nodal metastases of 0.8% in squamous carcinomas,with less than 3 mm of stromal invasion and no lymphvascular space invasion, as compared to 8.2% if the vascular spaces are involved. In lesions with 3.1-5.0 mm of stromal invasion, the risk of nodal metastases ranged from 7.5 to 8.3% depending the status of the vascular space. No significant risk was added to this group (IA2) in terms of lymphvascular involvement rather than depth invasion. In our study, we had only four cases of lymphvascular involvement, two of whom presented recurrence. The first was treated successfully and the second died seven years after recurrence, and this case was an adenosquamous IA2 carcinoma. In the group without lymphvascular space invasion there were five recurrences in 55 cases and two deaths. In this way lymphovascular involvement was positively correlated to recurrence and death ($p<0.01$). The depth of invasion in our study was associated with recurrence in five of the 31 squamous cell IA2 carcinomas, and in only one of the 20 cases of IA1 carcinomas. The depth of invasion as well as lymphvascular space involvement and depth of invasion influenced the risk of recurrence.

Further management of women with microinvasive carcinoma of the cervix should depend upon the status of the internal margin post-conization and the recurrence risk which is directly linked to the age of these patients, depth of invasion and lymphvascular space involvement. Older patients who have internal margin conization with neoplasia, or IA2 stage carcinoma with or without lymphvascular space involvement, have a poor prognosis in terms of recurrence and death, and may be selected for more aggressive initial treatment.

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